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ORIGINAL RESEARCH

Complement Components C1r and C8 Serve as Potential Inflammatory Biomarkers for Coronary Heart Disease Severity: The Mediating Role of C-Reactive Protein

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Purpose: Inflammation plays an important role in the occurrence and development of coronary heart disease (CHD). We investigated serum complement C1r, C1s, C7, C8, C9 as potential biomarkers and the mediating role of C-reactive protein (CRP) in CHD severity. The severity of coronary artery stenosis was quantified using the validated Gensini score.

Patients and Methods: In this prospective cross-sectional study (n=314), patients were categorized into a control group (n=102) and a CHD group (n=212) via coronary angiography. CHD severity was quantified by the Gensini score (mild ≤31; moderate-to-severe >31). The study incorporated multiple known pathogenic factors such as demographic characteristics, underlying diseases, and metabolic indicators for comprehensive analysis. Serum complement levels were measured by ELISA. Spearman correlation, multivariate logistic regression, ROC analysis, and mediation modeling assessed associations and CRP's role.

Results: Serum C1r and C8 were significantly elevated in CHD and severe stenosis groups. While C1s showed a slight increase in the severe stenosis group, it, along with C7 and C9, showed limited overall diagnostic utility for CHD. Spearman analysis revealed that C1r and C8 were positively correlated with both Gensini score and cTnT levels. In the fully adjusted model (Model 4), C1r remained a robust independent predictor of moderate-to-severe stenosis (continuous OR=2.10, 95% CI: 1.41–3.12; Q4 vs Q1 OR=5.61, 95% CI: 2.12–14.89). C8 also maintained statistical significance as a continuous variable (OR=1.98, P=0.004). Furthermore, mediation analysis indicated that CRP mediated 31.6% and 46.2% of the effects of C1r and C8 on disease severity, respectively. The combined AUC of C1r and C8 for predicting CHD was 0.769.

Conclusion: C1r is an independent predictor of CHD severity, while C8 exhibits a dose-dependent association modulated by systemic status. Integrating anatomical and physiological markers confirms the complement-CRP axis's pivotal role in CHD risk stratification, providing evidence for inflammatory biomarkers in lesion assessment.

Keywords: complement activation, Gensini score, mediation analysis, coronary heart disease, risk stratification

Introduction

Coronary heart disease (CHD), also known as coronary atherosclerotic heart disease, refers to the narrowing or occlusion of the coronary arteries due to atherosclerosis, leading to myocardial ischemia, hypoxia, or necrosis, and subsequently causing heart disease.[1] Emerging evidence has shown that inflammation plays a pivotal role in the initiation and progression of CHD. Unstable atherosclerotic plaques, prone to rupture, trigger platelet aggregation and thrombosis, which are central to the

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occurrence of acute cardiovascular events.[2] Atherosclerosis (AS), the primary pathological process underlying CHD, is driven by a complex interplay of inflammatory processes and lipid metabolism disturbances.[3] The accumulation of lipids in the arterial wall induces local inflammation, which recruits immune cells, such as monocytes/macrophages, neutrophils, T lymphocytes, and B lymphocytes, through various immune response mechanisms. These inflammatory cells contribute to the pathological processes, thereby exacerbating disease progression.[4]

The complement system, a key component of the innate immune and inflammatory response, plays an important role in the development of atherosclerosis.[5] Studies have confirmed the presence of various complement components, receptors, and regulatory factors in the atherosclerotic vascular wall.[6] Additionally, substances released from damaged and necrotic tissue can trigger complement activation via the classical and alternative pathways.[7] Much research on the complement system in AS and CHD has focused on the initiator molecule complement C1q,[8] the central component complement C3,[9] and the key effector molecule complement C5.[10] Other studies have also highlighted the involvement of molecules such as complement C2,[11] complement C4,[12] and complement C6,[13] which participate in classical pathway activation and contribute to the inflammatory processes driving AS and CHD development.However, the specific roles and relationships of the early executors of the classical pathway, C1r and C1s, and the terminal complement components C7, C8, and C9, in AS and CHD, particularly in relation to coronary artery stenosis, remain unclear.

C-reactive protein (CRP), primarily produced by hepatocytes and endothelial cells under the influence of interleukin (IL)-6, IL-1β, and tumor necrosis factor (TNF), induces endothelial activation and dysfunction by altering endothelial vascular reactivity.[14] Elevated CRP levels are not only closely associated with various acute and chronic inflammatory conditions but also serve as clinical biomarkers of inflammatory diseases and infections. CRP can directly activate the complement system, amplifying and synergizing with its pro-atherosclerotic effects, which are closely related to the development of adverse cardiovascular events associated with plaque rupture.[15] In this study, we hypothesize that serum CRP mediates the relationship between complement components and coronary artery stenosis through modulation of inflammatory pathways. We aim to investigate the associations between serum levels of complement components C1r, C1s, C7, C8, and C9 and the occurrence and severity of CHD, as well as to assess the potential mediating role of serum CRP in this relationship.

Materials and Methods

Study Population

This prospective cross-sectional study included patients who presented with chest tightness and chest pain as their primary complaints at the Department of Cardiovascular Medicine, First Affiliated Hospital of Nanchang University, and who were suspected of having CHD and underwent coronary angiography (CAG) between January and May 2025. All participants were consecutively enrolled and met the following inclusion and exclusion criteria, as shown in Figure 1. Inclusion criteria: (1) Diagnosis according to the updated CHD treatment guidelines,[16] (2) Age > 18 years. Exclusion criteria: (1) Presence of malignant tumors, schizophrenia, or psychiatric disorders, (2) Cardiomyopathies, acute or chronic endocarditis, and myocarditis due to various causes, (3) Pulmonary heart disease, congenital heart disease, acute or chronic infections, hematological diseases, or autoimmune disorders, (4) Patients unable to comply with the study.Based on the diagnostic criteria for CHD, participants were assigned to either the CHD group or the control group. This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University (Ethical Approval No. ITT2024849). The informed consent process is standardized and performed at the time of patient admission. Before any study-related procedures, members of the research team provided a comprehensive oral and written explanation to each eligible patient, detailing the study's objectives, the voluntary nature of participation, and the confidentiality of their biological samples and clinical data. Subsequently, written informed consent was obtained from all participants prior to their enrollment, blood sampling, and data collection. The study has been registered with the Chinese Clinical Trial Registry. (https://www.chictr.org.cn/index.html, ID: ChiCTR2500106574).

Diagnosis and Classification of CHD Severity

Coronary angiography (CAG) is the gold standard for diagnosing coronary heart disease (CHD). If CAG results show that one or more coronary arteries (including their branches) have a stenosis of ≥50%, the patient is classified into the

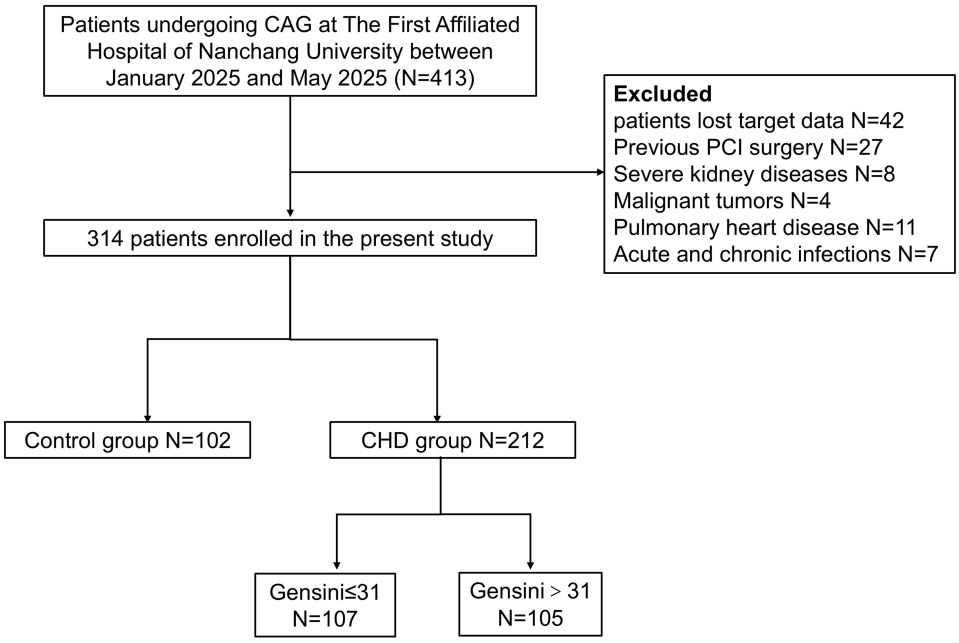

Figure 1 Flow chart of the study.

CHD group, while patients without CHD are assigned to the control group. The Gensini score is a validated quantitative method used to assess the severity of CHD. The score is calculated based on the anatomical location and the percentage of luminal stenosis. For each coronary lesion, the Gensini score is determined by multiplying the anatomical site score (across seven predefined coronary artery segments) by the stenosis grade score (six levels of stenosis severity).[17] The total Gensini score is the sum of the scores for all individual lesions, with higher scores indicating more severe and extensive disease. Based on the median Gensini score, the CHD group was further subdivided into the mild coronary artery stenosis group (Gensini ≤ 31) and the moderate-to-severe coronary artery stenosis group (Gensini > 31).

Serum Levels of Complement Proteins C1r, C1s, C7, C8, and C9 Were Measured

On the second day of hospitalization, venous blood samples were collected after an 8-hour fasting period. The samples were centrifuged at 1200 rpm for 10 minutes, and the serum was stored at −80°C until analysis. The levels of complement C1r (BP01129), C1s (BP00896), C7 (BP02804), C8 (BP04619), and C9 (BP03350) were determined using ELISA kits (Shanghai Biopack Biotechnology Co., Ltd., Shanghai, People's Republic of China), according to the manufacturer's instructions. All patient samples were tested in duplicate, and the same batch of reagents was used for all measurements to ensure consistency.

Baseline Information Collection

General clinical data related to the patients were collected, including: age, gender, height, weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), smoking history, alcohol consumption history, hypertension history, and diabetes history. Hypertension was defined as SBP ≥140 mmHg and/or DBP ≥90 mmHg or the current use of antihypertensive medications.[18] The diagnosis of diabetes was based on one or more of the following criteria:[19] (1) self-reported history of diabetes; (2) use of antidiabetic medications; (3) fasting blood glucose (FBG) ≥7.0 mmol/L; (4) 2-hour blood glucose ≥11.1 mmol/L during an oral glucose tolerance test (OGTT). Body mass index (BMI) was calculated as weight (kg) / height (m^2). In this study, we categorize BMI into three groups: Underweight (BMI <18.5 kg/m^2), Normal (18.5 ≤ BMI < 24.0 kg/m^2), and Overweight/Obesity (BMI ≥24.0 kg/m^2).

Laboratory test indicators were also collected, including glycated hemoglobin (HbA1c), blood glucose (Glu), white blood cell count (WBC), hemoglobin (HGB), platelet count (PLT), neutrophil count (NE), neutrophil percentage

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(NEUT), lymphocyte count (LY), monocyte count (Mo), C-reactive protein (CRP), D-dimer (D-Dimer), alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine (Scr), uric acid (UA), creatine kinase (CK), creatine kinase-MB (CK-MB), lactate dehydrogenase (LDH), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), cardiac troponin T (cTnT), and N-terminal pro B-type natriuretic peptide (NT-proBNP). Fasting venous blood samples were collected the morning after admission, and all indicators were measured and analyzed by the hospital laboratory. Additionally, echocardiographic parameters, including left ventricular ejection fraction (LVEF), left atrial diameter (LAD), and left ventricular end-diastolic diameter (LVEDD), were recorded.

Statistical Analysis

Data analysis and graphical representations were performed using R software (version 4.5.1), SPSS software (version 26.0), and GraphPad Prism (version 9.5). The Kolmogorov–Smirnov test (K–S test) was used to assess the normality of continuous variables. Continuous variables with normal distribution were expressed as means±standard deviation (SD), while those with non-normal distribution were expressed as median (interquartile range, IQR). Independent-sample t-tests and Mann–Whitney *U*-tests were used for comparisons of normally and non-normally distributed continuous variables, respectively. Categorical variables were presented as frequencies (percentages) and compared using chi-square tests. Spearman correlation analysis was used to assess the relationship between Gensini scores, cTnT, and serum complement levels. To investigate the association between complement C1r, C8, and the degree of coronary artery stenosis, four logistic regression models were constructed: Model 1, the unadjusted crude model; Model 2, adjusted for sex and age; Model 3, further adjusted for traditional cardiovascular risk factors including hypertension, diabetes, BMI, smoking, alcohol consumption, TG, HDL-c, and LDL-c; and Model 4, further adjusted for metabolic, inflammatory, and myocardial injury markers including WBC, Scr, UA, and cTnT. Results were presented as odds ratios (OR) with 95% confidence intervals (95% CI). Subgroup analyses were also conducted to evaluate the association between complement C1r, C8, and coronary artery stenosis across different population characteristics. Receiver operating characteristic (ROC) curve analysis and the area under the curve (AUC) value were used to evaluate the predictive ability of complement C1r, C8, and their combined markers for coronary heart disease. Finally, the SPSS PROCESS macro was used to perform bootstrap sampling (5000 iterations) to validate the mediating effect of CRP. Direct, indirect, and total effects, along with their 95% confidence intervals, were calculated to assess the mediating role of CRP in the relationship between complement C1r, C8, and Gensini scores. A p-value of <0.05 was considered statistically significant.

Results

Comparison of Clinical Features

Comparison of Clinical Characteristics and Baseline Data Between the Control Group and CHD Group

A total of 413 patients underwent coronary angiography, of whom 314 met the inclusion criteria and were included in the study. Based on the diagnostic criteria for CHD, the patients were divided into two groups: the CHD group (n = 212) and the control group (n = 102). Compared with the control group, the CHD group had significantly higher proportions of males, elderly individuals, a history of diabetes, smoking, and a higher BMI. Laboratory tests showed that in the CHD group, HbA1c, Glu, WBC, NE, Mo, CRP, D-Dimer, Scr, UA, TG, cTnT, and NT-proBNP levels were significantly elevated (all $P < 0.05$), while HDL-c levels were significantly lower ($P < 0.05$).Regarding echocardiographic parameters, the CHD group had significantly higher LAD and LVEDD compared to the control group, while LVEF was significantly lower in the CHD group, with all differences being statistically significant (all $P < 0.05$).A comprehensive summary of the demographic and clinical characteristics is presented in Table 1.

Comparison of Clinical Features and Baseline Data of CHD Patients with Different Gensini Scores

To analyze the correlation between various clinical indicators and the severity of CHD, Table 2 divides 212 CHD patients into two groups based on the median Gensini score. Compared to the mild coronary artery stenosis group (Gensini≤31), the moderate-to-severe coronary artery stenosis group (Gensini>31) had significantly higher proportions of males and individuals with a history of smoking, with statistically significant differences ($P < 0.05$).Laboratory tests revealed that in the Gensini >31

Table 1 Clinical and Laboratory Characteristics of Patients

Characteristics	Control Group (n=102)	CHD Group (n=212)	$Z/X^2/t$	P
Sex, male (n%)	57(55.9)	143(67.5)	3.987	0.046
Age (year)	62.5(55.75, 69)	66(57, 72)	−2.012	0.044
Diabetes n (%)	11(10.8)	60(28.3)	12.077	0.001
Smoking n (%)	31(30.4)	99(46.7)	7.547	0.006
Alcohol n (%)	20(19.6)	53(25.0)	1.122	0.289
Hypertension n (%)	54(52.94)	131(61.79)	2.229	0.135
SBP(mmHg)	128.12±1.71	131.11±1.48	1.325	0.186
DBP(mmHg)	73.43±1.19	73.75±1.01	0.202	0.840
HR(bpm)	79(71.75, 89.25)	81(72, 88)	−0.495	0.620
BMI (%)	23.72±0.37	24.22±0.23	1.184	0.237
HbA1c (%)	6.20(5.88, 6.41)	6.38(6.10, 7.00)	−4.436	<0.001
Glu (mmol/L)	5.65 (5.0, 6.88)	6.13(4.98, 8.68)	−2.081	0.037
WBC ($\times10^9$/L)	5.94(4.70, 7.01)	6.38(5.40, 7.83)	−3.120	0.002
HGB (g/L)	136(127, 151)	134(121, 147)	−1.372	0.170
PLT ($\times10^9$/L)	210.05±6.38	219.71±4.73	1.19	0.235
NE ($\times10^9$/L)	3.78(2.99, 4.67)	4.49(3.38, 5.34)	−3.391	0.001
NEUT (%)	64.70(58.78, 70.83)	67.40(60.8, 72.85)	1.357	0.176
LY ($\times10^9$/L)	1.53(1.15, 2.03)	1.54(1.16, 1.91)	−0.369	0.712
Mo ($\times10^9$/L)	0.36(0.28, 0.46)	0.41(0.32, 0.53)	−3.087	0.002
CRP (mg/L)	0.80(0.30, 2.38)	2.18(0.98, 4.50)	−5.372	<0.001
D-Dimer (mg/L)	0.23(0.14, 0.43)	0.27(0.19, 0.50)	−2.491	0.013
ALT (U/L)	20.05(14.60, 27.13)	19.55(14.81, 28.30)	−0.071	0.943
AST (U/L)	22.05(18.10, 27.80)	21.35(18.35, 26.75)	−0.463	0.643
Scr (μmol/L)	64.50(55.85, 80.20)	74.55(62.30, 90.65)	−3.939	<0.001
UA (μmol/L)	305.07±8.73	345.42±7.67	3.472	0.001
CK (U/L)	102.80(74.00, 132.14)	96.55(71.35, 148.35)	−0.033	0.974
CK-MB (U/L)	16.75(14.18, 21.53)	17.45(14.50, 23.05)	−0.857	0.392
LDH (U/L)	214.4(196.25, 242.13)	222.76 (193.95, 262.73)	−0.825	0.409
TC (mmol/L)	4.42±0.11	4.34±.082	−0.545	0.586
TG (mmol/L)	1.4(0.95, 2.02)	1.50(1.18, 2.32)	−2.270	0.023
HDL-c (mmol/L)	1.13(0.97, 1.38)	1.01(0.86, 1.18)	−4.263	<0.001
LDL-c (mmol/L)	2.41±0.08	2.43±0.07	0.152	0.880
cTnT (pg/mL)	6.52(3.22, 10.98)	11.32(6.18, 29.85)	−5.013	<0.001
NT-proBNP (ng/L)	72(70, 129.23)	124.1(70, 726.7)	−4.297	<0.001
LVEF (mm)	61.5(60, 65)	60(58, 63)	−2.694	0.007
LAD (mm)	32(29, 35)	34(31, 37)	−3.594	<0.001
LVEDD (mm)	45(41.75, 48)	46(44, 49)	−2.774	0.006

Notes: For categorical variables, data are presented as n (%). For continuous variables with a normal distribution, data are expressed as mean ± standard deviation (±SD). For continuous variables with a non-normal distribution, data are presented as median (IQR).

Abbreviations: CHD, Coronary Heart Disease; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; HR, Heart Rate; BMI, Body Mass Index; HbA1c, Glycated Hemoglobin; Glu, Glucose; WBC, White Blood Cell; HGB, Hemoglobin; PLT, Platelet; NE, Neutrophil; NEUT (%), Neutrophil Percentage; LY, Lymphocyte; Mo, Monocyte; CRP, C-Reactive Protein; D-Dimer, D-Dimer; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; Scr, Serum Creatinine; UA, Uric Acid; CK, Creatine Kinase; CK-MB, Creatine Kinase-MB; LDH, Lactate Dehydrogenase; TC, Total Cholesterol; TG, Triglyceride; HDL-c, High-Density Lipoprotein Cholesterol; LDL-c, Low-Density Lipoprotein Cholesterol; cTnT, Cardiac Troponin T; NT-proBNP, N-terminal pro-B-type Natriuretic Peptide; LVEF, Left Ventricular Ejection Fraction; LAD, Left Atrial Diameter; LVEDD, Left Ventricular End-Diastolic Diameter.

group, WBC, NE, CRP, Scr, UA, LDH, cTnT, and NT-proBNP levels were significantly higher compared to the Gensini ≤31 group (all $P < 0.05$).Regarding echocardiographic parameters, the Gensini >31 group showed an increasing trend in LVEDD and a decreasing trend in LVEF, with both differences being statistically significant ($P < 0.05$).

Table 2 Comparison of Clinical Characteristics of CHD Patients with Different Gensini Scores

Characteristics	Gensini≤31 (n=107)	Gensini>31 (n=105)	$Z/X^2/t$	P
Sex, male (n%)	63(58.88)	80(76.19)	7.235	0.007
Age (year)	66(59, 73)	67(55.5, 72.00)	−0.557	0.578
Diabetes n (%)	26(24.30)	34(32.38)	1.706	0.192
Smoking n (%)	41(38.32)	48(45.71)	6.096	0.014
Alcohol n (%)	23(21.50)	30(28.57)	1.415	0.234
Hypertension n (%)	63(58.88)	68(64.76)	0.777	0.378
SBP (mmHg)	129.00±1.76	133.27±2.38	−1.445	0.150
DBP (mmHg)	72.64±1.22	74.88±1.62	−1.110	0.268
HR (bpm)	80.61±1.27	81.51±1.33	−0.492	0.623
BMI (%)	24.06±0.32	24.39±0.34	−0.701	0.484
HbA1c (%)	6.31(6.00, 6.90)	6.4(6.20, 7.11)	−1.182	0.237
Glu (mmol/L)	6.09(4.94, 7.74)	6.15(4.98, 9.42)	−0.805	0.421
WBC (×109/L)	6.18(4.97, 7.48)	6.85(5.83, 8.08)	−2.758	0.006
HGB (g/L)	135(124, 146)	132(120, 149.5)	−0.228	0.819
PLT (×109/L)	207(173, 248)	219(181.5, 254.5)	−1.243	0.214
NE (×109/L)	4.14(3.12, 5.06)	4.59(3.61,5.52)	−2.434	0.015
NEUT (%)	66.50(59.50,70.60)	68.10(61.85,74.90)	−2.096	0.036
LY (×109/L)	1.56(1.22,1.85)	1.49(1.13,1.97)	−0.713	0.476
Mo (×109/L)	0.39(0.30,0.48)	0.45(0.34,0.71)	−3.108	0.002
CRP (mg/L)	1.41(0.59,2.88)	3.43(1.46,11.10)	−5.255	<0.001
D-Dimer (mg/L)	0.26(0.19,0.44)	0.30(0.19,0.71)	−1.240	0.215
ALT (U/L)	18.70(13.80,27.30)	20.80(15.75,28.50)	−1.178	0.239
AST (U/L)	21.00(18.40,26.80)	22.30(18.05,26.75)	−0.771	0.440
Scr (μmol/L)	70.30(57.70,85.00)	80.50(68.25,104.50)	−3.978	<0.001
UA (μmol/L)	328.83±9.55	362.32±11.87	−2.199	0.029
CK (U/L)	92.00(70.80,138.00)	106.80(71.55,152.90)	−0.838	0.402
CK-MB (U/L)	17.20(14.80,22.40)	18.00(14.20,23.55)	−0.310	0.756
LDH (U/L)	218.90(192.10,252.40)	229.90(197.33,278.06)	−2.034	0.042
TC (mmol/L)	4.38±0.12	4.30±0.12	0.470	0.639
TG (mmol/L)	1.54(1.18,2.22)	1.44(1.18,2.40)	−0.122	0.903
HDL-c (mmol/L)	1.10±0.05	1.00±0.02	1.719	0.088
LDL-c (mmol/L)	2.41±0.09	2.44±0.10	−0.193	0.847
cTnT (pg/mL)	7.93(2.09,14.53)	16.62(8.83,64.71)	−4.939	<0.001
NT-proBNP (ng/L)	101.00(70.00,221.00)	229.60(70.00,1034.00)	−3.825	<0.001
LVEF (mm)	60.00(60.00,63.00)	60.00(55.00,62.00)	−2.977	0.003
LAD (mm)	34.00(31.00,37.00)	34.00(31.00,37.00)	−0.651	0.515
LVEDD (mm)	46.00(43.00,49.00)	47.00(44.00,50.50)	−2.268	0.023

Notes: For categorical variables, data are presented as n (%). For continuous variables with a normal distribution, data are expressed as mean ± standard deviation ($\overline{X}$±SD). For continuous variables with a non-normal distribution, data are presented as median (IQR).

Abbreviations: CHD, Coronary Heart Disease; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; HR, Heart Rate; BMI, Body Mass Index; HbA1c, Glycated Hemoglobin; Glu, Glucose; WBC, White Blood Cell; HGB, Hemoglobin; PLT, Platelet; NE, Neutrophil; NEUT (%), Neutrophil Percentage; LY, Lymphocyte; Mo, Monocyte; CRP, C-Reactive Protein; D-Dimer, D-Dimer; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; Scr, Serum Creatinine; UA, Uric Acid; CK, Creatine Kinase; CK-MB, Creatine Kinase-MB; LDH, Lactate Dehydrogenase; TC, Total Cholesterol; TG, Triglyceride; HDL-c, High-Density Lipoprotein Cholesterol; LDL-c, Low-Density Lipoprotein Cholesterol; cTnT, Cardiac Troponin T; NT-proBNP, N-terminal pro-B-type Natriuretic Peptide; LVEF, Left Ventricular Ejection Fraction; LAD, Left Atrial Diameter; LVEDD, Left Ventricular End-Diastolic Diameter.

Expression Levels of Serum C1r, C1s, C7, C8, and C9

Table 3 presents an evaluation of the serum levels of C1r, C1s, C7, C8, and C9 in the control group and CHD group to assess their potential as biomarkers for coronary heart disease (CHD). As shown in Figure 2, serum C1r and C8 levels

Table 3 Comparison of Serum Complement Levels Between Patients with Coronary Heart Disease and Healthy Controls

Characteristics	Control Group (n=102)	CHD Group (n=212)	Z	P
C1r (pg/mL)	10985.0(5317.5, 19,380.0)	29,955.0(14,305.0, 71,542.5)	−7.021	<0.001
C1s (pg/mL)	90870.0(81,902.5, 103,167.5)	92,415.0(83,650.0, 102,312.5)	−0.816	0.415
C7 (pg/mL)	67510.0(34,602.5, 111,945.0)	60,760.0(31,630.0, 116,010.0)	−0.333	0.739
C8 (pg/mL)	621.0(389.0, 1207.0)	1342.0(630.5, 3489.5)	−5.272	<0.001
C9 (pg/mL)	33557.5(20,297.5, 47,470.0)	31,337.5(20,503.75, 44,982.5)	−0.582	0.561

Notes: data are presented as median (IQR).

were significantly higher in the CHD group compared to the control group ($P < 0.05$). Table 4 divides the CHD group into mild coronary artery stenosis and moderate-to-severe coronary artery stenosis groups based on the median Gensini score, to assess the expression of these markers as biomarkers for evaluating the degree of coronary artery stenosis. Compared with patients with mild coronary artery stenosis (Gensini ≤31), serum levels of C1r and C8 were significantly elevated ($P < 0.05$). While C1s also showed a statistically significant increase ($P = 0.017$), its elevation was less pronounced compared to C1r and C8 (Figure 3).

Correlation Analysis Between Serum Complement C1r, C1s, C7, C8, C9, cTnT and Gensini Scores

To further explore the relationship between serum complement components and the severity of CHD, we performed Spearman correlation analysis between serum C1r, C1s, C7, C8, C9, cTnT levels and Gensini scores, a validated index for quantifying CHD severity (Figure 4). Spearman correlation analysis showed that in CHD patients, serum complement C1r (r=0.497, P<0.001) and C8 (r=0.349, P<0.001) were positively correlated with Gensini scores, and similarly, serum cTnT also demonstrated a significant positive correlation with Gensini scores (r=0.436, P<0.001), whereas C1s (r=0.055, P=0.331), C7 (r=0.015, P=0.797), and C9 (r=−0.078, P=0.167) showed no statistically significant correlation with Gensini scores.

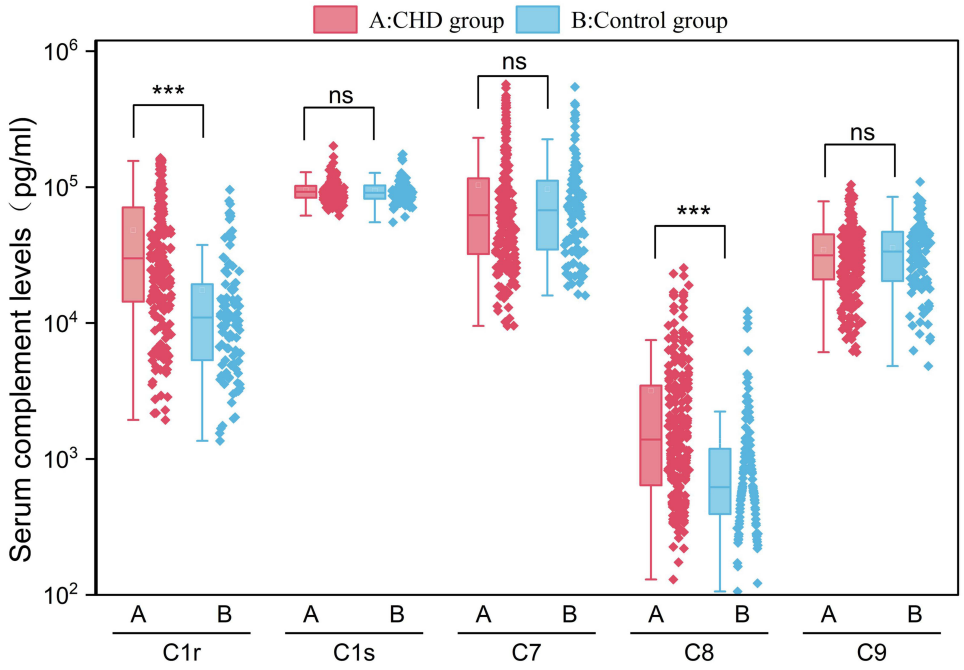

Figure 2 Boxplot Comparison of Serum Complement C1r, C1s, C7, C8, and C9 Levels Between the CHD and Control Groups.
Notes: Data are presented as median with interquartile range (box plot) and individual data points.*** indicates P < 0.001, ns indicates no significant difference.

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Table 4 Comparison of Complement Concentration in Patients with Different Gensini Score Groups

Characteristics	Gensini≤31 (n=107)	Gensini>31 (n=105)	Z	P
C1r (pg/mL)	19500.0(7740.0, 48,760.0)	44,960.0(20,715.0, 104,260.0)	−5.105	<0.001
C1s (pg/mL)	90560.0(83,330.0, 99,560.0)	93,860.0(84,510.0, 107,495.0)	−2.387	0.017
C7 (pg/mL)	54930.0(30,280.0, 114,200.0)	65,970.0(33,030.0, 142,675.0)	−1.484	0.138
C8 (pg/mL)	1018.0(540.0, 2366.0)	1882.0(720.0, 5822.0)	−3.240	0.001
C9 (pg/mL)	33690.0(22,160.0, 46,805.0)	28,690.0(16,705.0, 44,382.50)	−1.617	0.106

Notes: data are presented as median (IQR).

Furthermore, to evaluate the potential link between complement activation and myocardial injury, we analyzed the correlation between these complement components and cTnT levels (Figure 5). The results revealed that serum C1r and C8 were also significantly and positively associated with cTnT (r=0.447, P<0.001 and r=0.310, P<0.001). Spearman correlation analysis confirmed the differential expression of serum complement C1r and C8 in CHD and their role in reflecting the severity of CHD. The close association of C1r and C8 with both Gensini scores and cTnT levels further suggests that these complement components are not only potential biomarkers for coronary artery stenosis severity but are also closely linked to the degree of clinical myocardial damage.

Relationship Between Serum Complement C1r, C8 and the Severity of CHD

Multivariable binary logistic regression analysis was performed to assess the associations of serum C1r and C8 levels with the severity of coronary heart disease (CHD) (Table 5). In the unadjusted model (Model 1), serum C1r levels were positively correlated with CHD severity; each standard deviation (SD) increase in C1r was associated with a significantly higher risk of more severe CHD (OR: 3.99; 95% CI: 2.39–6.66; P < 0.001). After progressive adjustment for demographics (Model 2), traditional cardiovascular risk factors (Model 3), and further adjustment for metabolic, inflammatory, and myocardial injury markers (Model 4), the association between serum C1r and CHD severity remained

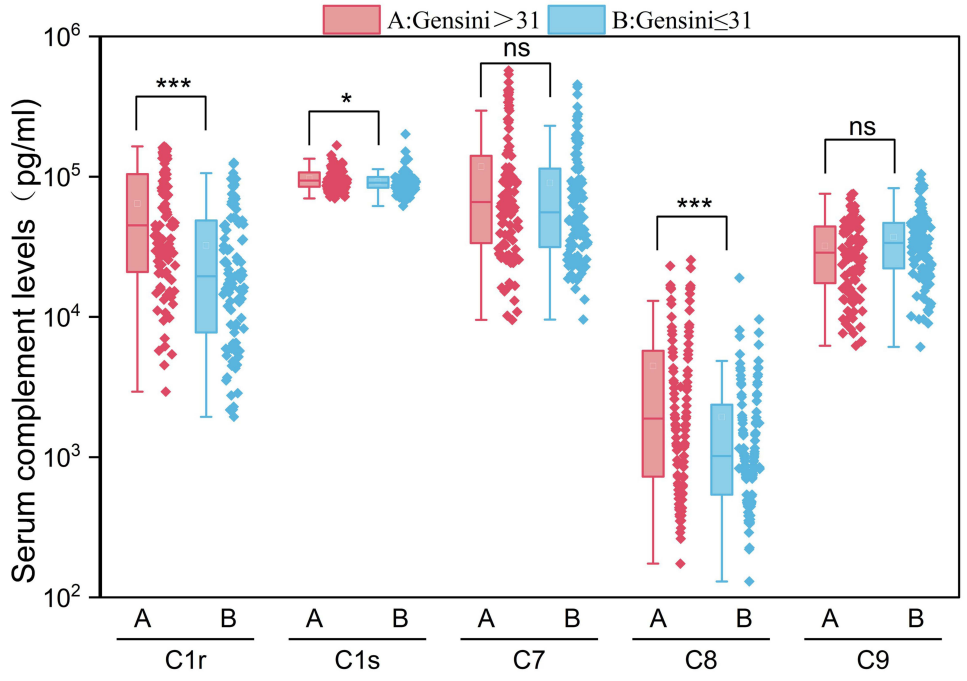

Figure 3 Boxplot Comparison of Serum Complement C1r, C1s, C7, C8, and C9 Levels Among Patients with Different Gensini Scores.
Notes: Data are presented as median with interquartile range (box plot) and individual data points. * indicates P < 0.05, *** indicates P < 0.001, ns indicates no significant difference.

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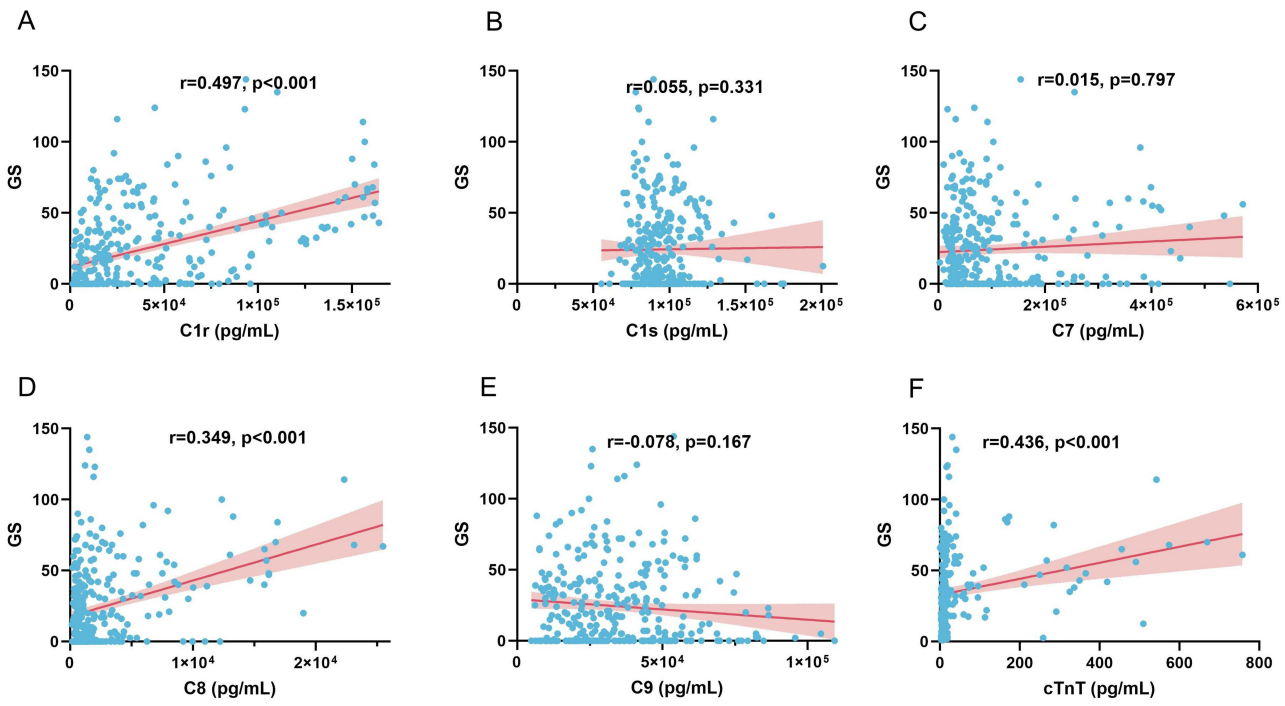

Figure 4 Correlation Analysis Between Serum Complement C1r, C1s, C7, C8, C9 and Gensini Scores.
Notes: (**A**) Correlation Analysis Between Serum C1r and Gensini Scores; (**B**) Correlation Analysis Between Serum C1s and Gensini Scores; (**C**) Correlation Analysis Between Serum C7 and Gensini Scores; (**D**) Correlation Analysis Between Serum C8 and Gensini Scores; (**E**) Correlation Analysis Between Serum C9 and Gensini Scores. (**F**) Correlation Analysis Between Serum cTnT and Gensini Scores.
Abbreviation: GS, Gensini Scores.

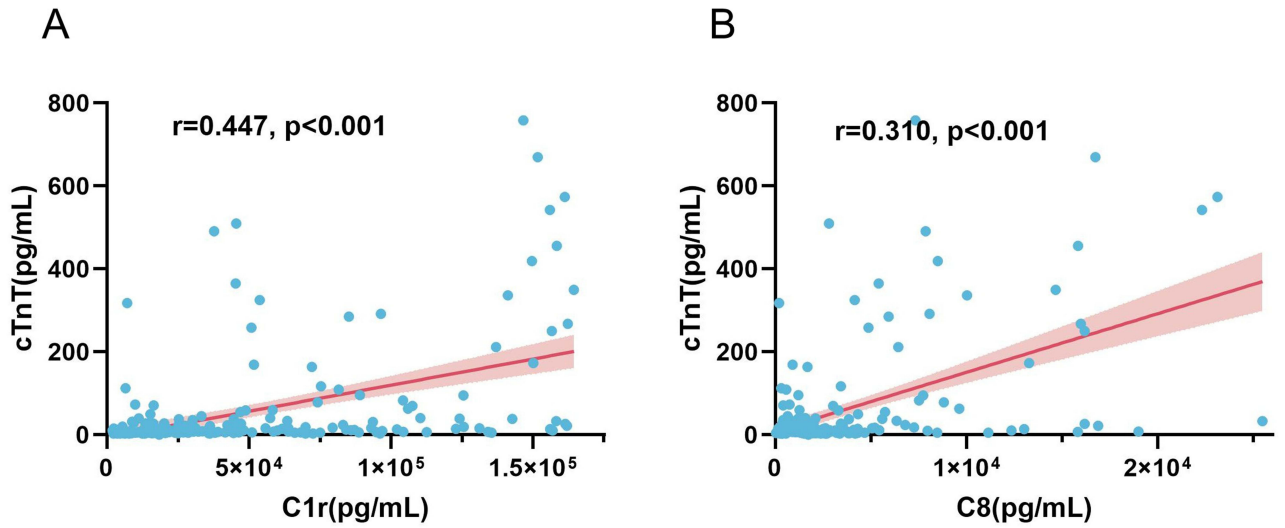

Figure 5 Correlation Analysis Between Serum Complement C1r, C8 and cTnT Levels.
Notes: (**A**) Correlation Analysis Between Serum C1r and cTnT Levels; (**B**) Correlation Analysis Between Serum C8 and cTnT Levels.

statistically significant. In the fully adjusted Model 4, serum C1r persisted as an independent predictor of CHD severity (OR per SD increase: 2.10; 95% CI: 1.41–3.12; P < 0.001). Furthermore, compared with the lowest quartile (Q1: ≤12,350 pg/mL), participants in the highest quartile (Q4: ≥96,071 pg/mL) in Model 4 exhibited a markedly elevated risk (OR: 5.61; 95% CI: 2.12–14.89; P < 0.001). A significant linear dose-response relationship was observed across all models (P for trend < 0.001).

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Table 5 Multivariate Logistic Regression Analysis of the Association Between C1r, C8 and the Severity of CHD

Characteristic	Model 1a		Model 2b		Model 3c		Model 4d	
	OR (95% CI)	p-Value	OR (95% CI)	p-Value	OR (95% CI)	p-Value	OR (95% CI)	p-Value
C1r (pg/mL)								
Continuous	3.99(2.39–6.66)	<0.001	3.85(2.32–6.38)	<0.001	2.35(1.64–3.39)	<0.001	2.10(1.41–3.12)	<0.001
Q1	1(Ref)		1(Ref)		1(Ref)		1(Ref)	
Q2	1.94(0.87–4.36)	0.11	1.95(0.86–4.43)	0.11	1.96(0.84–4.56)	0.12	2.06(0.87–4.85)	0.10
Q3	2.84(1.27–6.35)	0.011	2.87(1.26–6.54)	0.012	3.23(1.36–7.67)	0.008	2.88(1.19–6.98)	0.019
Q4	7.06(3.00–16.59)	<0.001	6.95(2.92–16.52)	<0.001	7.63(3.02–9.32)	<0.001	5.61(2.12–14.89)	<0.001
P for trend		<0.001		<0.001		<0.001		<0.001
C8 (pg/mL)								
Continuous	2.36 (1.43–3.90)	<0.001	2.41(1.46–3.96)	<0.001	2.29(1.48–3.55)	<0.001	1.98(1.25–3.14)	0.004
Q1	1(Ref)		1(Ref)		1(Ref)		1(Ref)	
Q2	0.68(0.31–1.47)	0.32	0.66(0.29–1.46)	0.30	0.65(0.29–1.49)	0.31	0.57(0.25–1.33)	0.19
Q3	1.16(0.54–2.49)	0.69	1.16(0.53–2.53)	0.71	1.19(0.53–2.64)	0.67	1.11(0.49–2.51)	0.80
Q4	2.56(1.16–5.64)	0.02	2.69(1.19–6.01)	0.017	2.79(1.20–6.48)	0.017	1.83(0.74–4.49)	0.19
P for trend		0.009		0.008		0.007		0.10

Notes: a Model 1: no covariates were adjusted. b Model 2: adjusted for Sex, Age. c Model 3: adjusted for Sex, Age, Hypertension, Diabetes, BMI, Smoking, Alcohol, TG, HDL-c, LDL-c. d Model 4: adjusted for Sex, Age, Hypertension, Diabetes, BMI, Smoking, Alcohol, TG, HDL-c, LDL-c, WBC, Scr, UA and cTnT.
Abbreviation: Ref, Reference.

When analyzed as a continuous variable, serum C8 levels were significantly and positively associated with CHD severity across all models, underscoring its predictive value independent of traditional risk factors and clinical parameters. Quartile analysis revealed a significant dose-response relationship between serum C8 levels and CHD severity in Models 1 through 3 (P for trend < 0.01 for all); compared with the lowest quartile (Q1: ≤630 pg/mL), the risk of more severe disease was significantly elevated in the highest quartile (Q4: ≥4,297 pg/mL). However, in Model 4, the associations across C8 quartiles attenuated significantly. The risk increase in Q4 was no longer statistically significant compared with Q1 (OR: 1.83; 95% CI: 0.74–4.49; P = 0.19), and the linear trend also lost statistical significance (P for trend = 0.10). These findings suggest that the association between C8 and CHD severity may be partially modulated by systemic inflammatory or metabolic status.

Subgroup and Interaction Analysis

To further investigate whether the association between serum complement C1r, C8, and the severity of CHD differs among various populations, we conducted subgroup analyses based on age, sex, hypertension, diabetes, smoking, alcohol and BMI. For serum complement C1r (Figure 6) and C8 (Figure 7), the results suggest that the relationships between serum C1r, C8 and CHD severity are consistent across all subgroups, with no significant interactions observed between stratified variables (p for interaction > 0.05), indicating no significant heterogeneity in these associations within the subgroups. In summary, the relationships between serum C1r, C8, and CHD severity are consistent across different population subgroups and are not influenced by the aforementioned stratified clinical characteristics. This further strengthens their potential as reliable biomarkers for assessing CHD severity.

ROC Curve Analysis of Serum Complement C1r and C8 for the Severity of CHD

ROC curve analysis was performed to evaluate the diagnostic performance of serum complement C1r and C8 in predicting CHD and moderate-to-severe coronary artery stenosis. As shown in Figure 8, the ROC analysis results indicated that the area under the curve (AUC) for serum complement C1r and C8 in the CHD group were 0.745 and 0.684, respectively, with a combined AUC of 0.769, sensitivity of 0.660, and specificity of 0.804. For the moderate-to-severe coronary artery stenosis group (Gensini > 31), the AUC for serum complement C1r and C8 were 0.703 and 0.629, respectively, with a combined AUC of 0.731, sensitivity of 0.667, and specificity of 0.692. Overall, serum complement C1r and C8 demonstrated good diagnostic value in both scenarios, supporting their potential role as biomarkers for CHD and its severity (Table 6).

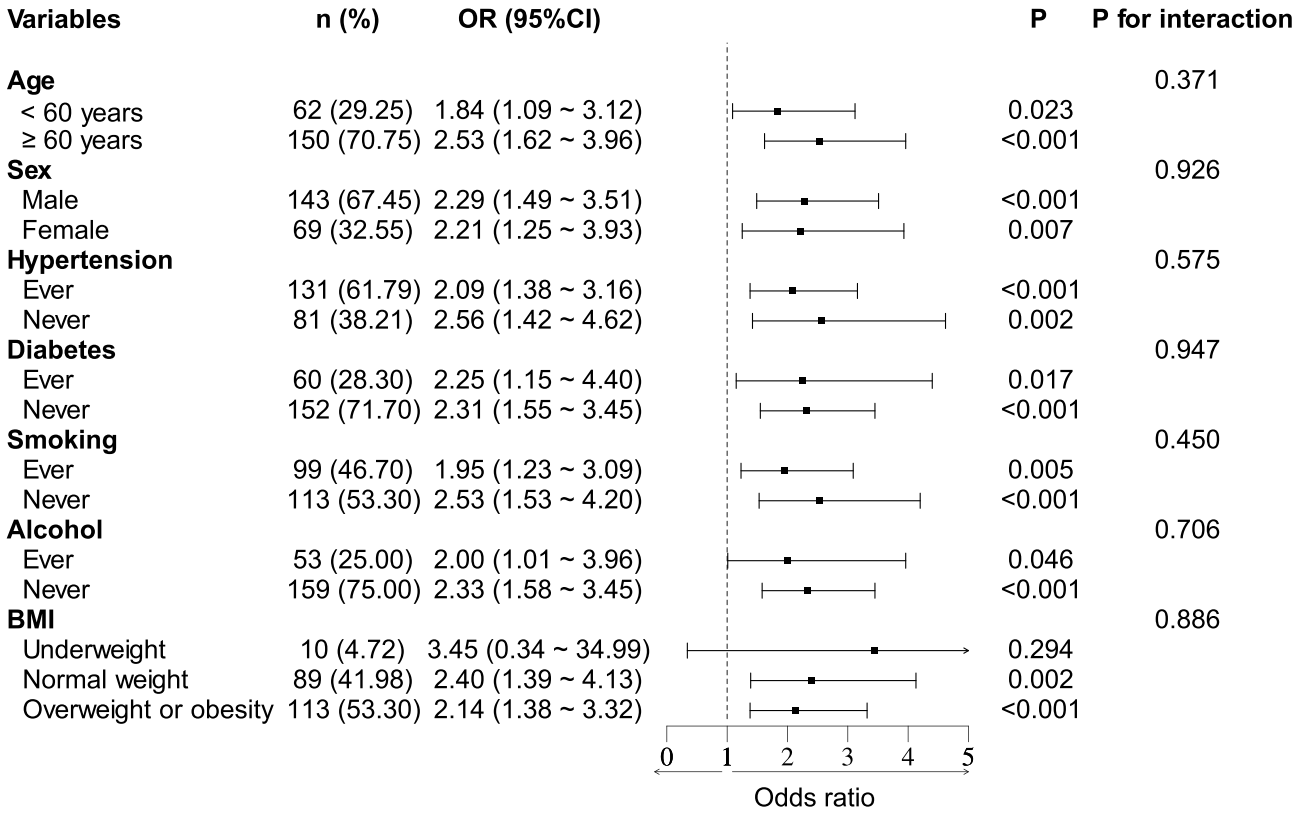

Figure 6 Subgroup Analysis of the Relationship Between Serum Complement C1r and the Severity of CHD.

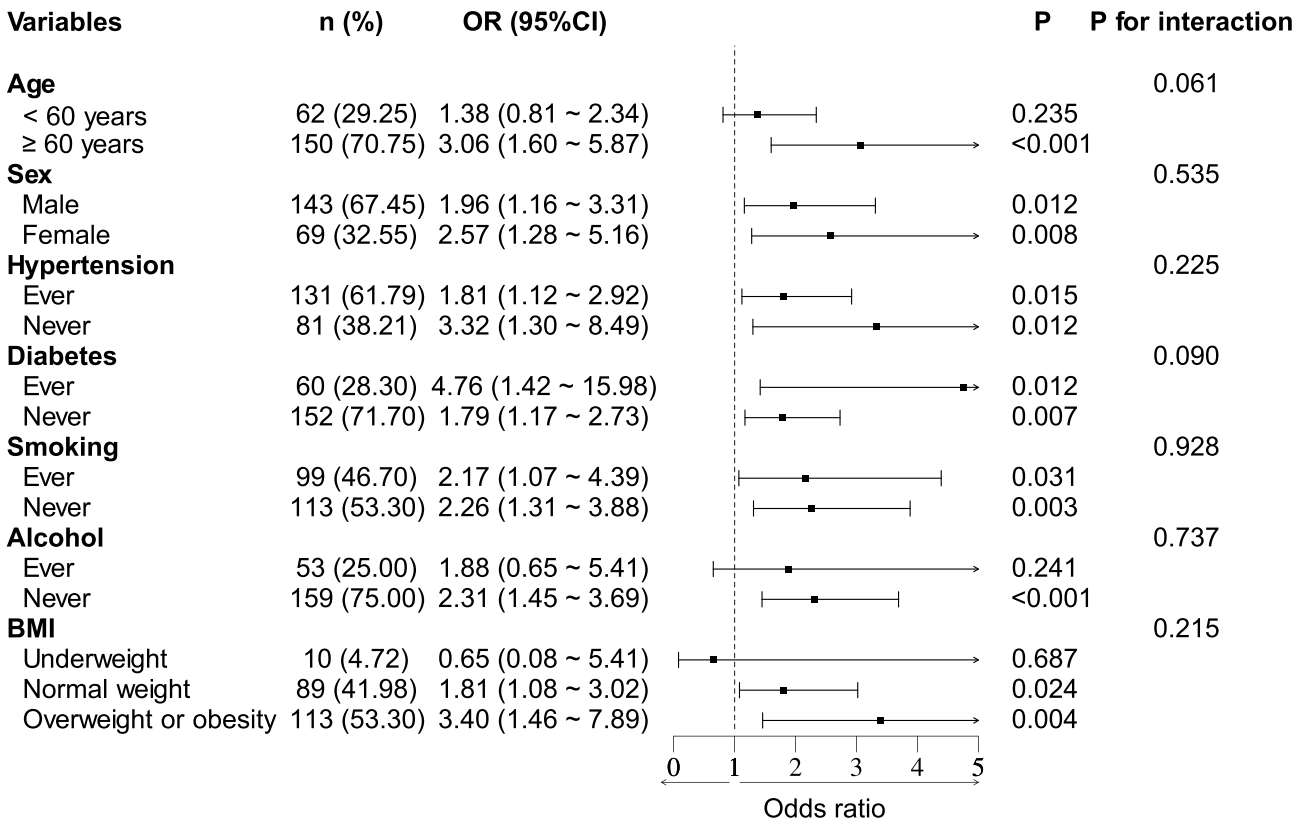

Figure 7 Subgroup Analysis of the Relationship Between C8 and the Severity of CHD.

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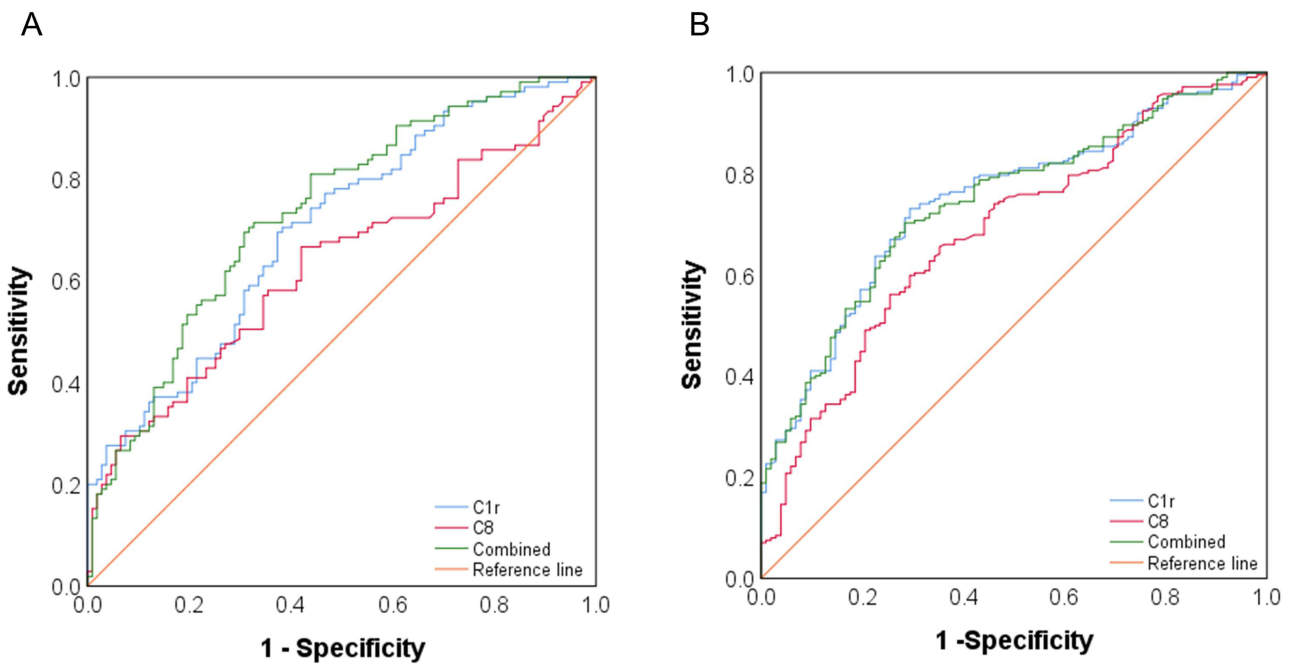

Figure 8 ROC Curve Analysis of Serum Complement C8 and the Severity of CHD.
Notes: ROC Curves for Predicting CAD and Severe Coronary Artery Stenosis. (**A**) ROC Curve for Predicting CAD; (**B**) ROC Curve for Predicting Moderate-to-Severe Coronary Artery Stenosis.

Mediating Role of CRP

In our study, we identified the mediating role of CRP in the association between serum complement C1r, C8, and Gensini scores. Figure 9 illustrates the specific effect sizes of these relationships, while Table 7 provides more detailed data. The indirect effect of serum complement C1r on Gensini score risk through CRP was 0.1151, and this was significant according to the Bootstrap test. After adjusting for the mediating variable CRP, the direct effect of C1r on Gensini score risk was 0.2488 (P = 0.0042). The total effect of C1r on Gensini score was 0.3639 (P < 0.001). Similarly, the indirect effect of serum complement C8 on Gensini score risk through CRP was 0.1777, and this was also significant according to the Bootstrap test. After adjusting for CRP, the direct effect of C8 on Gensini score risk was 0.2068 (P = 0.0426). The total effect of C8 on Gensini score was 0.3845 (P < 0.001). Mediation analysis confirmed that CRP partially explained the association between serum complement C1r, C8, and the risk of coronary artery stenosis, accounting for 31.6% and 46.2% of the total effect, respectively.

Discussion

CHD is the most common cardiovascular disease worldwide, with high incidence, disability, and mortality rates. Although revascularization therapies, such as percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG), have become standard treatments for CHD, their mortality and disability rates remain high globally.[20]

Table 6 Comparative Analysis of Area Under the Receiver Operating Characteristic Curves

Group	Indicators	AUC	Cut Off	Sensitivity	Specificity	95% CI	P
CHD	C1r	0.745	0.437	0.731	0.706	(0.689,0.800)	<0.001
	C8	0.684	0.306	0.561	0.745	(0.622,0.745)	<0.001
	Combined	0.769	0.464	0.660	0.804	(0.716,0.822)	<0.001
Gensini>31	C1r	0.703	0.322	0.705	0.617	(0.634,0.772)	<0.001
	C8	0.629	0.246	0.667	0.579	(0.553,0.704)	0.001
	Combined	0.731	0.365	0.673	0.692	(0.664,0.798)	<0.001

Notes: AUC, Area Under Curve.

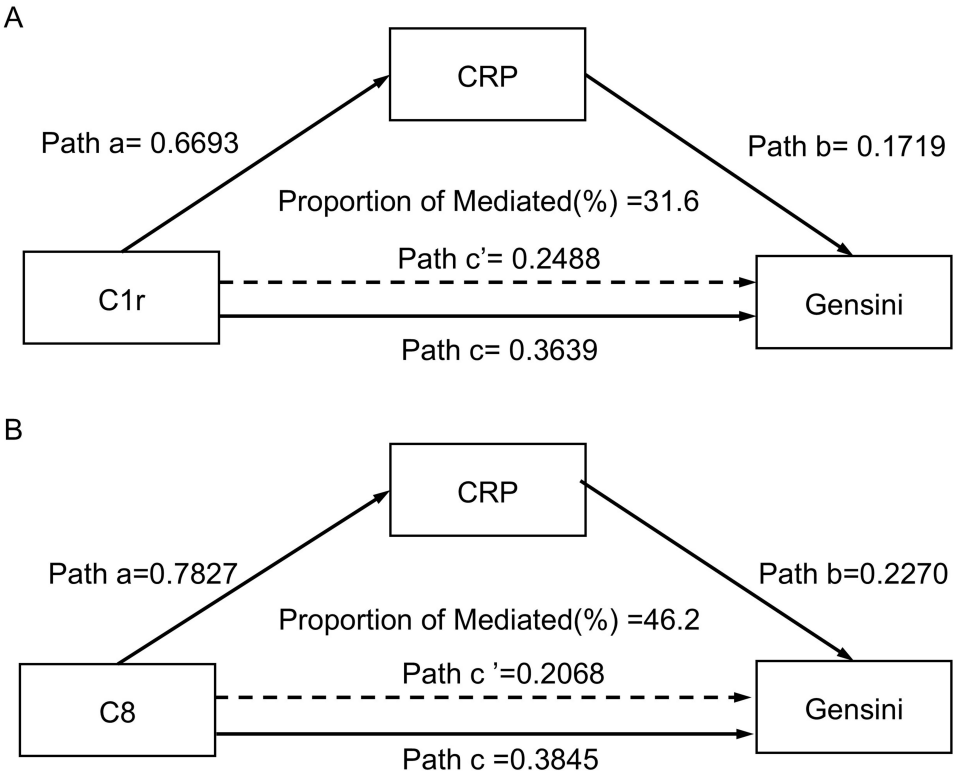

Figure 9 Mediated Analysis Model Path Diagram.

Notes: Serum complement C1r and C8 are defined as independent variables; Gensini score is the dependent variable; CRP is the mediating variable. Path a represents the regression coefficient for the association between the independent variable and CRP. Path b represents the regression coefficient for the association between CRP and Gensini score. Path c represents the overall effect of serum complement C1r and C8 on Gensini score. Path c' represents the direct effect of serum complement C1r and C8 on Gensini score, after controlling for CRP. (**A**) Path Diagram of the Mediation Analysis Model for Serum Complement C1r as the Independent Variable. (**B**) Path Diagram of the Mediation Analysis Model for Serum Complement C8 as the Independent Variable.

Studies have shown that inflammation plays an important role in the pathogenesis of CHD, not only promoting the progression of atherosclerosis but also exacerbating plaque instability, significantly increasing the risk of cardiovascular events.[21] Traditional cardiovascular risk factors, psychological stress, aging, and other factors can induce endothelial dysfunction, promote lipoprotein deposition and oxidation, recruit monocytes to differentiate into macrophages, and release cytokines, driving plaque formation through an imbalance of pro-inflammatory and anti-inflammatory responses. Inflammation can degrade the fibrous cap of plaques, induce microcalcification, and stimulate the secretion of matrix metalloproteinases, exacerbating plaque instability and increasing the risk of rupture.[22,23] Anti-inflammatory therapies are crucial throughout the treatment of CHD. Identifying novel early blood biomarkers that reflect inflammation activity is essential for achieving convenient, non-invasive diagnosis and early risk stratification of CHD.[24–27]

In the complement activation process of atherosclerosis, the formation of the C1 complex ($C1q\text{-}C1r_2\text{-}C1s_2$) is crucial.[28] C1r, as the first protease activated in the classical complement pathway, is a key component of the innate immune system. Its core function is to activate the complement cascade of the classical pathway through interaction with C1q and C1s.[29] Early in atherosclerosis, C1q plays a protective role by promoting cholesterol efflux from macrophages, reducing foam cell formation, and inhibiting pro-inflammatory signals. In the later stages of atherosclerosis, circulating substances including serum

Table 7 Mediation Analysis of CRP in the Association Between Serum Complement C1r, C8, and Gensini

Independent Variable	Mediator	Total Effect Coefficient (95% CI)	P	Direct Effect Coefficient (95% CI)	P	Indirect Effect Coefficient (95% CI)	Proportion Mediated, %
C1r	CRP	0.3639 (0.2372, 0.4906)	<0.001	0.2488 (0.0795, 0.4182)	0.0042	0.1151 (0.0164, 0.2402)	31.6%
C8	CRP	0.3845 (0.2590,0.5101)	<0.001	0.2068 (0.0069, 0.4067)	0.0426	0.1777 (0.0292, 0.3903)	46.2%

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complement C1r, C1s, help form and activate the C1 complex, thus promoting disease progression via the classical pathway.[30,31] The complement membrane attack complex C5b-9 is the final common product of the classical, lectin, and alternative pathways of complement activation. It can also mediate inflammatory responses. As the terminal effector complex of the complement system, C5b-9 induces endothelial dysfunction, increases vascular permeability, and promotes the expression of pro-inflammatory mediators, destabilizing plaques. Moreover, it stimulates smooth muscle cell proliferation and migration, inhibits apoptosis, and, in collaboration with C5a, recruits monocytes and other inflammatory cells to exacerbate local inflammation, further promoting plaque progression and instability.[32,33]

Our study systematically explored the associations between serum complement components (C1r, C1s, C7, C8, and C9) and the severity of coronary heart disease, while further elucidating the potential mediating role of CRP. As a hallmark of systemic inflammation,[34,35] CRP is synthesized not only by hepatocytes under IL-6 stimulation but also locally by vascular endothelial cells. It accelerates the progression of AS by promoting monocyte adhesion and activating the complement system. Notably, CRP serves as a critical mediator of the classical pathway, co-localizing with terminal C5b-9 complex deposits in the atherosclerotic intima.[36,37]

For the first time, we linked serum C1r and C8 levels not only to the Gensini score but also to clinical myocardial injury. cTnT remains the gold-standard biomarker for evaluating myocardial damage and prognosis in CHD.[38] In our cohort, both C1r and C8 exhibited significant positive correlations with Gensini scores and cTnT levels ($P < 0.001$), suggesting their involvement in coronary lesion progression and myocardial injury, particularly during phases of plaque instability and heightened vascular inflammation. Mechanistically, C1r initiates the classical pathway, leading to C3 convertase formation and the subsequent amplification of the inflammatory response and subsequent CRP production, thereby establishing a pro-atherogenic positive feedback loop.[39,40] Meanwhile, as a key component of the membrane attack complex (MAC), C8 triggers vascular inflammation and plaque rupture by promoting cytokine release and apoptosis of vascular smooth muscle cells.[41,42] Multivariate ordered logistic regression analysis showed that C1r and C8 are positively correlated with the severity of coronary artery stenosis, and this correlation is independent of traditional cardiovascular risk factors. In Model 4, it was found that the highest quartile (Q4) of serum C1r is still significantly associated with an increased risk of moderate to severe stenosis, exhibiting a clear dose-response relationship; there is no statistically significant difference between the highest quartile (Q4) and Q1 of serum C8, but there is a linear trend among the quartiles. This suggests that serum C1r may lead to plaque instability and myocardial injury by amplifying the inflammation-complement positive feedback loop. Conversely, although serum C8 does not have independent predictive significance in Model 4, it suggests that the pathological impact of serum C8 may not be simply driven by linear concentration. Subgroup analysis further showed that the association between serum complement C1r, C8, and coronary artery stenosis remained consistent across different population characteristics, with no significant interaction observed. Additionally, mediation analysis revealed a partial mediating effect of CRP in the relationship between serum complement C1r, C8, and coronary artery stenosis, suggesting that serum complements C1r and C8 may activate or amplify both local and systemic inflammatory responses, leading to elevated CRP levels and further promoting the progression of CHD. This suggests that targeting complement activation or CRP-related pathways may serve as a future therapeutic strategy. ROC curve analysis further highlighted that the combined detection of serum complement C1r and C8 could enhance sensitivity and specificity in predicting CHD, providing experimental evidence for the development of new biomarker combinations to assist in risk stratification and early identification of coronary artery lesions.

This study also has some limitations. First, it is a single-center, prospective cross-sectional design with a relatively small sample size, and the population consisted of patients suspected of having CHD who underwent coronary angiography, which may introduce selection bias. Second, serum complement components were measured using ELISA, which, although standardized, did not verify their functional activity. Third, while we measured serum levels of serum complement C1s, C7, and C9, their specific biological roles in CHD pathogenesis remain unclear, particularly why serum complement C1s showed a categorical increase in severe stenosis groups but failed to demonstrate a linear correlation with the continuous Gensini score. This discrepancy suggests that C1s may only increase once a certain threshold of coronary damage is reached, rather than progressing linearly with disease severity. Additionally, the reasons behind the lack of diagnostic utility for serum C7 and C9 remain to be further elucidated. Furthermore, while the mediation analysis suggests a partial mediating effect of CRP, the specific molecular mechanisms, particularly the interactions between serum complement C1r, C8, and CRP, require further validation through basic experimental studies. Fourth, although we adjusted for traditional risk factors in our regression

models, several other potential determinants of CHD severity were not accounted for, including dietary habits, mental status, genetic background, and environmental exposures. These unmeasured factors may act as residual confounders that influence both complement activation and the progression of coronary stenosis. For instance, specific dietary patterns or chronic psychological stress are known to modulate systemic inflammation.[43,44] Furthermore, since the study was conducted at a single center and focused on an ethnically homogeneous population of Chinese Han individuals, the findings may not be fully generalizable to other ethnic groups with different genetic predispositions or environmental influences. Future prospective cohort studies with broader data collection protocols are warranted to validate the independent predictive value of C1r and C8 across more diverse populations.

Conclusion

In conclusion, this study confirms that serum complement C1r is an independent risk factor for the severity of coronary heart disease, while serum complement C8 shows a dose-dependent association, crucially, both relationships are significantly mediated by CRP. This finding not only strengthens the understanding of the role of the complement system in the inflammatory mechanisms of coronary heart disease but also provides new theoretical and experimental support for incorporating serum complement C1r, C8, and CRP into CHD risk assessment and pathophysiological research. Future studies should include larger sample sizes and prospective cohort studies to further elucidate the potential value of related complement components in the progression of CHD.

Data Sharing Statement

The datasets used and analyzed in this clinical study are available from the first author upon reasonable request.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the principles of the Declaration of Helsinki. All participants in the study gave their consent and signed the informed consent form. The study was approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University (Ethical Approval No. ITT2024849) and has been registered with the Chinese Clinical Trial Registry. (https://www.chictr.org.cn/index.html, ID: ChiCTR2500106574). All participants provided written informed consent prior to enrollment, allowing the use of their clinical data and blood samples for research purposes.

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Author Contributions

Xia Feng: Conceptualization, Methodology, Formal analysis, Writing – Original Draft; Xiaoting Jiang: Validation, Investigation, Writing – Original Draft; Shaolin Gong: Software, Formal analysis, Data curation, Visualization, Writing – Original Draft; Wen Liu: Investigation, Data curation, Writing – Original Draft; Qiong Yan: Methodology, Investigation, Data curation, Writing – Review and Editing; Hongmei Qi: Methodology, Validation, Data curation, Writing – Review and Editing; Ling Yu: Investigation, Resources, Data curation, Writing – Review and Editing; Xiang Wang: Conceptualization, Supervision, Project administration, Funding acquisition, Writing – Review and Editing. Xiaoping Peng: Conceptualization, Supervision, Project administration, Funding acquisition, Writing – Review and Editing. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that there are no conflicts of interest in this article.

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