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Association of plasma C1q/TNF-related protein 9 levels with disease severity and prognosis in patients with coronary atherosclerotic heart disease

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C1q/tumor necrosis factor-related protein 9 (CTRP9) has been recognized as a factor associated with cardiovascular disease. Nevertheless, research regarding its relationship with the severity of coronary artery disease and the occurrence of adverse clinical events in coronary atherosclerotic heart disease (CAD) remains limited. A total of 302 patients were divided into mild lesion group and moderate-severe lesion group according to coronary artery complexity, determined by the SYNTAX scores. Major adverse cardiovascular events (MACEs) were assessed during a total follow-up of 21 months. The relationships of plasma CTRP9 levels with the severity of coronary artery stenosis and adverse prognosis were assessed in patients with CAD. Compared with the mild lesion group, the CTRP9 was significantly lower in the moderate-severe lesion group. In the receiver-operating characteristics (ROC) curve analysis, a cut-off CTRP9 value of 266.95 ng/mL was identified for predicting moderate-severe lesions. A total of 97 MACEs (32.12%) were documented after 21 months of follow-up. Multivariable Cox regression analysis revealed that decreased plasma CTRP9 levels independently predicted MACEs (HR: 0.996, 95% CI: 0.994–0.998, P < 0.001) after adjustment for potential confounding factors. Kaplan–Meier survival curves illustrated a significantly higher incidence of MACEs in patients with decreased CTRP9 levels compared with those with higher levels. Plasma CTRP9 levels were associated with the severity of coronary artery disease. Lower plasma CTRP9 levels were indicative of moderate-severe coronary lesions and an increased risk of MACEs in patients with CAD.

Keywords Coronary Atherosclerotic Heart Disease, CTRP9, MACEs, Coronary Artery Stenosis, Prognosis

Abbreviations

CTRP9	C1q/tumor necrosis factor-related protein 9
CAD	Coronary artery disease
MACEs	Major adverse cardiovascular events
CAG	Coronary arteriography
SYNTAX	Synergy between percutaneous coronary intervention with taxus and cardiac surgery
PCI	Percutaneous artery intervention
CABG	Coronary artery bypass grafting
ANOVA	Analysis of variance
SD	Standard deviation
IQR	Interquartile range
ELISA	Enzyme-linked immunosorbent assay
T2DM	Type 2 diabetes mellitus
ROC	Receiver-operating characteristics
BMI	Body mass index
UA	Uric acid

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HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
TG	Triglyceride
TC	Total cholesterol
Lp (a)	Lipoprotein-a
ApoA1	Apolipoprotein A1
ApoB	Apolipoprotein B
LDH	Lactate dehydrogenase
FIB	Fibrinogen
D-D	D-Dimer
CK-MB	Creatine kinase-MB
eGFR	Estimated glomerular filtration rate
Scr	Serum creatinine
FBG	Fasting blood glucose
LVDD	Left ventricular end-diastolic diameter
EF	Ejection fraction
CRP	C-reactive protein
ACEI	Angiotensin-Converting Enzyme Inhibitor
ARB	Angiotensin II Receptor Blocker
AUC	Area under the curve
OR	Odds ratio
HR	Hazard ratio
CI	Confidence interval
AMPK	AMP-activated protein kinase
Nf-kB	Nuclear factor-k-gene binding
MCP-9	Monocyte chemoattractant protein-9
TNF-α	Tumor necrosis factor-α
VCAM-1	Vascular cell adhesion molecule 1
ICAM-1	Intercellular cell adhesion molecule 1
MDA	Malondialdehyde

Coronary atherosclerotic heart disease, a highly prevalent cardiovascular disorder, is characterized by the accumulation of atherosclerotic plaques within the coronary arteries, leading to progressive narrowing or obstruction of the vessel lumen and resulting in myocardial ischemia, hypoxia, and potentially necrosis[1]. Associated risk factors include inflammatory processes, hypertension, insulin resistance, disorders of lipid and glucose metabolism, cigarette smoking, and vascular endothelial dysfunction[2–4]. Cardiovascular adverse events constitute the principal cause of mortality among patients with coronary artery disease[5]. Thus, novel and straightforward screening biomarkers are urgently needed to evaluate early-stage CAD severity and prognosis.

CTRP9, a member of the adiponectin superfamily, is predominantly secreted by epicardial adipose tissue, as well as by the liver, skeletal muscle, and various other organs tissues[6,7]. CTRP9 has attracted increasing attention due to its significant role in antioxidative stress, anti-atherosclerosis, immune inflammation regulation, energy and glycolipid metabolism, and vascular endothelial function[8]. Notably, CTRP9 exhibits cardioprotective effects and has emerged as a novel factor for cardiovascular protection in development of CAD[9,10]. Hence, CTRP9 shows promise as a novel biomarker for predicting CAD progression and prognosis.

This study aims to explore and analyze the correlation between plasma CTRP9 levels and the complexity as well as the prognosis of CAD. This provides valuable evidence to support the early diagnosis, risk stratification, and prediction of adverse events during the progression of CAD.

Methods

Target population

Between February 2022 and July 2022, a total of 436 consecutive patients with suspected stable CAD who underwent coronary angiography were screened at the First Affiliated Hospital of Anhui Medical University. Based on clinical presentation, laboratory findings, medical history, coronary angiographic results, and predefined inclusion and exclusion criteria, 134 patients were excluded from the study. The detailed exclusion process is illustrated in Fig. 1. In accordance with the specified exclusion and inclusion criteria, a total of 302 patients were enrolled in this study. Inclusion criteria for cases involved meeting the diagnostic criteria set forth by the United States College of Cardiology Heart Association in 2020; Secure informed consent from the study participants and obtain approval from the medical ethics committee. Exclusion criteria: patients with severe organic heart diseases such as congestive heart failure, valvular heart disease, myocarditis, etc.; patients underwent CABG or PCI; patients with severe hepatic or renal dysfunction; patients older than 80 or younger than 18 years of age; patients with incomplete clinical data. (Fig. 1)

Data collection

Fasting venous blood was collected the day after admission and the levels of fasting blood glucose (FBG), creatine kinase-MB (CK-MB), lactate dehydrogenase (LDH), estimated glomerular filtration rate (eGFR), serum creatinine (Scr), uric acid (UA), fibrinogen (FIB), D-dimer (D-D), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), lipoprotein-a (Lp (a)), apolipoprotein A1 (ApoA1), and apolipoprotein B (ApoB), were measured using the standard laboratory analyzer. Age, gender, body mass index (BMI), history of hypertension, Type 2 diabetes mellitus (T2DM), smoking

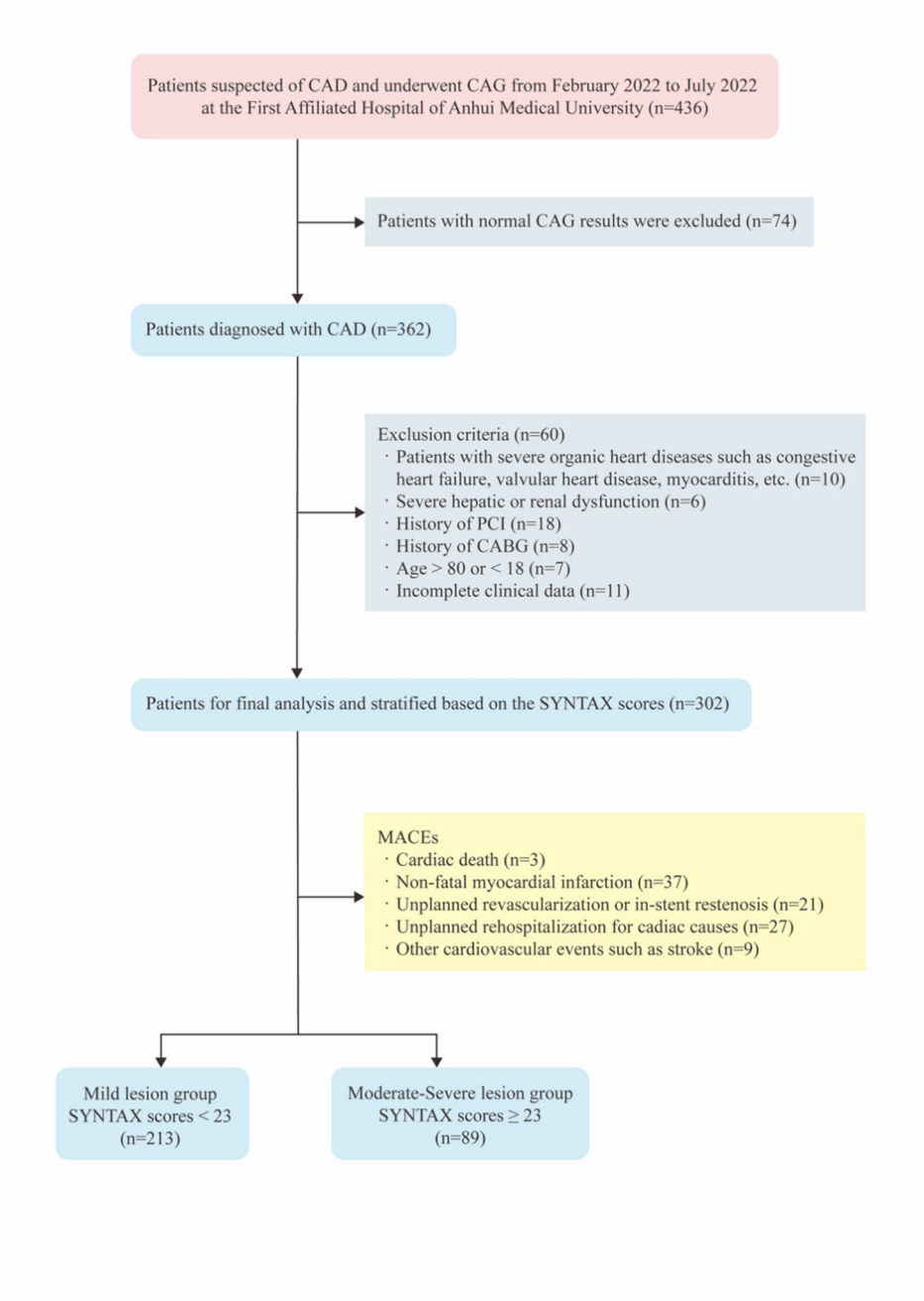

Fig. 1. Flow chart of study participants. Patients with coronary atherosclerotic heart disease (CAD) who were enrolled in the study were categorized into two groups based on their severity of coronary artery disease. CAD: Coronary atherosclerotic heart disease. CAG: Coronary arteriography. PCI: Percutaneous artery intervention. CABG: Coronary artery bypass grafting. SYNTAX: Synergy between percutaneous coronary intervention with taxus and cardiac surgery. MACEs: Major adverse cardiovascular events.

and drinking, were obtained through the clinical electronic medical record system. Simpson ultrasonography was utilized to acquire data on ejection fraction (EF) and left ventricular end-diastolic diameter (LVDD). Prior to CAG, fasting venous blood was obtained from the study subjects. After centrifugation, the supernatant was extracted for testing. It was then divided into two parts, sub-packaged in EP tubes, and subsequently stored at -80℃. ELISA was employed for the detection of plasma CTRP9 levels. The ELISA kit was provided by Shanghai Aibo Biotechnology Company and utilized in strict adherence to the reagent's guidelines.

Coronary angiography

Coronary angiography and percutaneous coronary intervention were conducted in accordance with the prevailing guidelines[11]. The SYNTAX scores evaluate the severity of coronary artery lesions by integrating factors

Variables	Total ($n=302$)	Mild lesion ($n=213$)	Moderate-Severe lesion ($n=89$)	t/X²	P
Demographic data					
Age (years)	62.50 ± 11.48	61.55 ± 11.96	65.06 ± 9.86	2.413	0.017
Male, n (%)	205 (67.90%)	146 (68.50%)	59 (66.30%)	0.694	0.405
BMI (kg/m²)	24.89 ± 3.47	24.50 ± 3.02	25.01 ± 2.76	1.369	0.172
Medical history					
Drinking, n (%)	83 (27.50%)	61 (28.60%)	22 (24.70%)	0.137	0.711
Smoking, n (%)	135 (44.70%)	94 (44.10%)	41 (46.10%)	0.814	0.367
Hypertension, n (%)	168 (55.60%)	113 (53.10%)	55 (61.80%)	0.067	0.796
T2DM, n (%)	76 (25.20%)	41 (19.20%)	35 (39.30%)	4.645	0.031
Laboratory measurement					
CTRP9 (ng/mL)	325.85 (247.06,442.52)	385.07 (303.54,516.72)	216.06 (177.97,261.94)	11.265	< 0.001
TC (mmol/L)	4.99 ± 1.12	4.77 ± 1.00	5.48 ± 1.25	5.296	< 0.001
TG (mmol/L)	1.46 (1.03,2.04)	1.23 (0.94,1.61)	2.21 (1.82,3.01)	10.213	< 0.001
HDL-C (mmol/L)	1.23 ± 0.51	1.37 ± 0.51	0.91 ± 0.32	9.359	< 0.001
LDL-C (mmol/L)	3.06 ± 1.21	2.72 ± 0.96	3.84 ± 1.36	7.174	< 0.001
Lp (a) (mg/L)	148.00 (63.25,315.75)	127.00 (59.00,299.50)	194.00 (74.50,358.00)	2.089	0.037
ApoA1 (g/L)	1.21 (1.11,1.35)	1.21 (1.12,1.36)	1.20 (1.10,1.32)	1.239	0.215
ApoB (g/L)	0.80 ± 0.24	0.78 ± 0.24	0.83 ± 0.24	1.73	0.085
FBG (mmol/L)	5.31 (4.83,6.03)	5.20 (4.73,5.71)	5.88 (5.11,7.34)	5.698	< 0.001
CK-MB (U/L)	12.00 (10.00,17.00)	12.00 (10.00,16.00)	14.00 (10.00,21.00)	2.92	0.003
eGFR (ml/ (min.1.73m²))	92.77 ± 18.59	93.51 ± 19.19	90.92 ± 16.98	1.12	0.263
Scr (μmol/L)	76.72 ± 25.50	77.08 ± 26.66	75.37 ± 22.52	0.39	0.697
UA (μmol/L)	355.89 ± 101.43	348.23 ± 97.23	374.93 ± 112.46	2.154	0.032
LDH (U/L)	184.00 (161.75,217.25)	182.00 (160.50,210.50)	198.50 (163.00,236.75)	2.371	0.018
FIB (g/L)	3.07 (2.65,3.60)	2.99 (2.57,3.48)	3.27 (2.72,3.90)	3.099	0.002
D-D (μg/mL)	0.25 (0.16,0.43)	0.22 (0.15,0.40)	0.32 (0.23,0.58)	4.705	< 0.001
CRP (mg/L)	3.74 ± 1.95	3.88 ± 1.99	3.42 ± 1.82	0.363	0.547
LVDD (cm)	4.97 ± 0.55	4.95 ± 0.55	5.02 ± 0.56	0.949	0.343
EF (%)	60.00 (57.00,62.25)	61.00 (57.50,63.00)	58.00 (52.50,61.00)	3.484	< 0.001
SYNTAX scores	14.00 (8.00,23.00)	10.00 (7.00,15.00)	29.00 (23.75,36.50)	13.488	< 0.001
Vessel involvement					
1	176 (58.30%)	175 (82.20%)	1 (1.10%)	189.965	< 0.001
2	83 (27.50%)	36 (16.90%)	47 (52.80%)		
3	43 (14.20%)	2 (0.90%)	41 (46.10%)		
Medication history					
Anti-plat, n (%)	38 (12.60%)	27 (12.70%)	11 (12.40%)	0.006	0.940
Statins, n (%)	37 (12.30%)	24 (11.30%)	13 (14.60%)	0.651	0.420
ACEI/ARB, n (%)	27 (8.60%)	16 (7.50%)	11 (12.40%)	1.812	0.178
Beta-blockers, n (%)	18 (6.00)	11 (5.20%)	7 (7.90%)	0.817	0.366
Hypoglycemic drugs, n (%)	32 (10.60%)	18 (8.50%)	14 (15.70%)	3.511	0.061

Table 1. General information of enrolled patients. *Notes*: BMI: Body mass index. T2DM: Type 2 diabetes mellitus. CTRP9: C1q/tumor necrosis factor-related protein 9. TC: Total cholesterol. TG: Triglyceride. HDL-C: High-density lipoprotein cholesterol. LDL-C: Low-density lipoprotein cholesterol. Lp(a): Lipoprotein-a. ApoA1: Apolipoprotein A1. ApoB: Apolipoprotein B. FBG: Fasting blood glucose. CK-MB: Creatine kinase-MB. Scr: Serum creatinine. eGFR: Estimated glomerular filtration rate. UA: Uric acid. LDH: Lactate dehydrogenase. FIB: Fibrinogen. D-D: D-Dimer. CRP: C-reactive protein. EF: Ejection fraction. LVDD: Left ventricular end-diastolic diameter. SYNTAX: Score, synergy between percutaneous coronary intervention with taxus and cardiac surgery. ACEI: Angiotensin-Converting Enzyme Inhibitor. ARB: Angiotensin II Receptor Blocker

such as the location of coronary lesions, the degree of calcification, the degree of stenosis, and the presence or absence of collateral circulation. According to the score, coronary lesions were divided into three grades: (1) mild lesions: ≤22 points; (2) Moderate lesions: 23–32 points; (3) Severe lesions: ≥33 points[12]. In view of the relatively small number of patients in the severe disease group ($n = 34$), together with the imbalance in subgroup sample sizes, the need to preserve the robustness of statistical analyses, and the clinical relevance of coronary

lesion complexity, the moderate and severe SYNTAX score categories were subsequently combined into a single cohort (SYNTAX ≥ 23) for all subsequent analyses in this study. Based on the SYNTAX scores, patients were categorized into two groups: mild lesions group (scores ≤ 22) and moderate-severe lesions group (scores ≥ 23). The cardiac catheterization procedures were performed by two experienced interventional cardiologists.

Endpoint event assessment

A clinical follow-up study was conducted on all research subjects, with the primary endpoint being the occurrence of MACEs, including cardiac death, non-fatal myocardial infarction, coronary revascularization, readmission for heart failure and non-fatal stroke[13]. The median follow-up duration for these events was 21 months (median, 21 months; interquartile range, 4–21months).

Data analysis

Statistical analyses were conducted using SPSS version 26.0. Prior to analysis, the normality of all continuous variables was assessed using the Kolmogorov–Smirnov test. Continuous variables conforming to a normal distribution were expressed as mean ± standard deviation (SD), whereas non-normally distributed variables were presented as median with interquartile range (IQR). Comparisons between two groups were performed using independent-samples t-tests for normally distributed variables and Mann–Whitney U tests for non-normally distributed variables. Comparisons between two groups were conducted using independent-samples t-tests for normally distributed variables (with variance homogeneity confirmed by Levene's test) and Mann–Whitney U tests for non-normally distributed variables. Correlations between continuous variables were assessed using Spearman rank correlation due to the non-normal distribution of several key variables. A logistic regression model was employed to investigate whether the study indications were risk factors for the severity of CAD. ROC curves were generated to illustrate the diagnostic performance of plasma CTRP9 levels for MACEs and mid/high SYNTAX scores. MACE-free survival curves, based on plasma CTRP9 levels, were constructed using Kaplan-Meier survival estimates. Survival rate disparities were evaluated using the log-rank test. Prognostic risk factors were analyzed through univariate and multivariate analyses using the Cox regression model. All tests were two-tailed, and $P < 0.05$ was considered statistically significant.

Results

Baseline information

Table 1 displays the general information of the target population. No statistically significant differences were observed between the two groups in the following variables: sex, BMI, drinking, smoking, ApoA1, ApoB, eGFR, Scr, CRP, LVDD and medication history ($P > 0.05$). However, significant disparities were observed in age, T2DM, plasma CTRP9 level, TC, TG, HDL-C, LDL-C, Lp (a), FBG, CK-MB, UA, LDH, FIB, D-D, EF, vessel involvement and SYNTAX scores ($P < 0.05$).

Correlation between plasma CTRP9 level and other variables

In Table 2, an analysis is presented regarding the association between plasma CTRP9 levels and other variables in patients. The results indicate that plasma CTRP9 levels are positively related to HDL-C but inversely related to TG, TC, LDL-C, UA, FBG, and SYNTAX scores. Figure 2 shows that with the increase of CTRP9, the SYNTAX scores gradually decrease, indicating a reduction in the degree of coronary stenosis.

Logistic regression analysis of risk factors for moderate-severe lesions

Figure 3 illustrates the results of the association between CTRP9 and the degree of coronary stenosis, taking into account various confounding factors through adjustment. Univariate logistic regression analysis identified age, T2DM, UA, FIB, D-D, FBG, LDL-C, TC, TG, and Lp-a as potential risk factors, while CTRP9, HDL-C, and LVEF were recognized as protective factors. In multivariate logistic regression analysis, CTRP9 consistently manifests itself as an independent protective factor, even after accounting for various confounding factors (Fig. 3, OR: 0.987, 95% CI: 0.980–0.993, $P < 0.001$).

Diagnostic value of plasma CTRP9 level in ROC curve for moderate-severe lesions

The diagnostic value of plasma CTRP9 levels for identifying moderate-severe coronary artery lesions was evaluated using receiver operating characteristic (ROC) curve analysis. The optimal cut-off value of CTRP9

	CTRP9	
Variables	***r***	***P***
TC	− 0.325	< 0.001
TG	− 0.686	< 0.001
LDL-C	− 0.404	< 0.001
HDL-C	0.440	< 0.001
FBG	− 0.382	< 0.001
UA	− 0.192	0.001
SYNTAX scores	− 0.768	< 0.001

Table 2. The correlation between CTRP9 and risk factors for CAD.

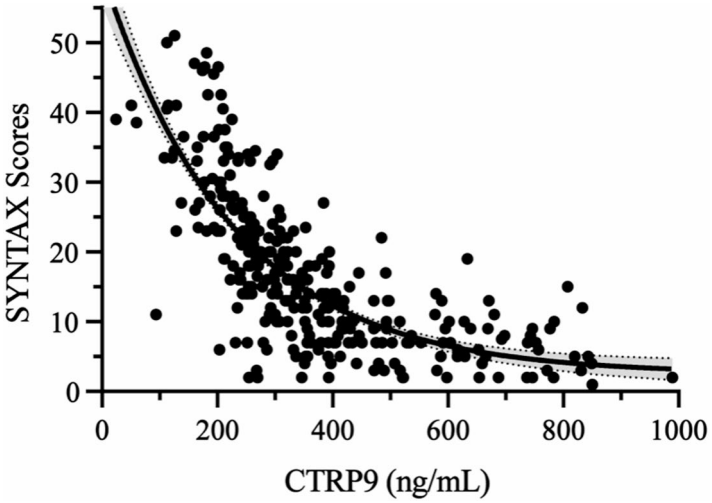

Fig. 2. Correlation between plasma CTRP9 levels and the SYNTAX scores.

Variables	OR	95% CI	Forest Plot
Age	1.035	0.991–1.080	0.117
T2DM	0.652	0.164–2.600	0.545
FIB	1.078	0.700–1.661	0.733
D-D	1.369	0.394–4.756	0.621
LDH	#	#	#
CK-MB	#	#	#
UA	0.996	0.991–1.001	0.126
FBG	1.871	1.109–3.158	0.019
TC	0.098	0.025–0.387	0.001
TG	5.37	2.524–11.428	<0.001
HDL-C	1.658	0.217–12.651	0.626
LDL-C	14.049	3.479–56.730	<0.001
Lp(a)	#	#	#
EF	0.991	0.993–1.052	0.762
CTRP9	0.987	0.980–0.993	<0.001

Fig. 3. Logistic regression analysis of risk factors for moderate-severe lesions. OR: Odds ratio. CI: Confidence interval. #: There were no statistically significant variables in the univariate analysis.

was determined using the Youden index and identified as 266.95 ng/mL, yielding an AUC of 0.911 (95% CI: 0.876–0.946, sensitivity: 86.90%, specificity: 80.90%, $P < 0.001$). (Fig. 4)

Univariate and multivariate Cox regression model in MACEs

The incidence of MACEs was determined through a follow-up survey in different sub-groups. Throughout the median follow-up duration of 21 months (median: 21 months; range: 4–21 months), a total of 97 cases of MACEs, constituting 32.12%, were documented. This comprised 3 instances of cardiac death, 37 occurrences of non-fatal acute myocardial infarction (AMI), 21 incidents of coronary revascularization, 27 cases of heart failure, and 9 occurrences of ischemic stroke. Variables with potential clinical relevance and those showing significance in univariate analyses were entered into the multivariate Cox proportional hazards model using a forward selection approach. In the multiple Cox regression model, CTRP9 was identified as an independent predictor of MACEs, maintaining statistical significance even after adjustment for potential confounders. Lower plasma CTRP9 levels

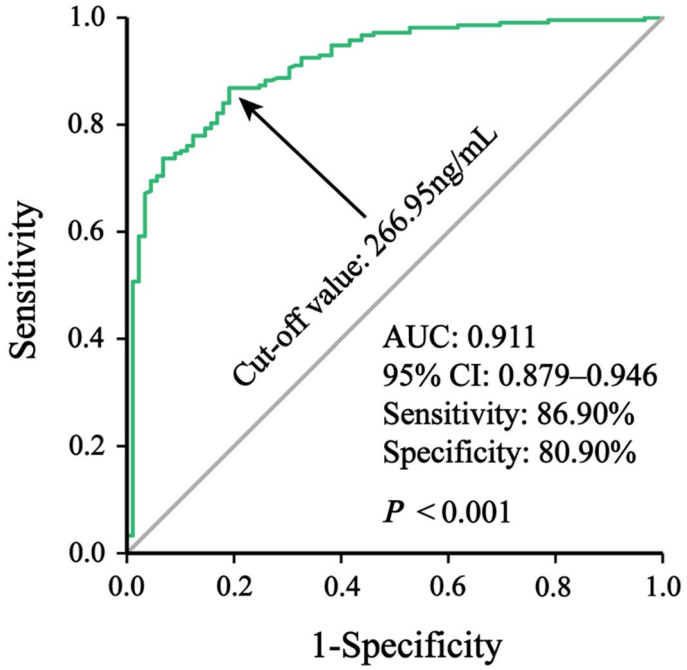

Fig. 4. Diagnostic value of plasma CTRP9 level in ROC curve for moderate-severe lesions. AUC: Area under the curve. CI: Confidence interval.

were independently associated with an increased risk of MACEs. Notably, the HR reflects the effect of a per-unit (per ng/mL) decrease in CTRP9 concentration, indicating that for each 1 ng/mL reduction in CTRP9, the risk of MACEs increases by approximately 0.4%. (Table 3).

Kaplan–Meier survival curves

Based on the cut-off value of CTRP9 derived from the ROC analysis, patients were stratified into different groups, and those with lower plasma CTRP9 levels exhibited a significantly higher risk of MACEs. Furthermore, when CTRP9 was entered into the Cox proportional hazards model as a continuous variable, lower plasma CTRP9 levels were independently associated with an increased risk of MACEs. Notably, the hazard ratio reflects the effect of a per-unit (per ng/mL) decrease in CTRP9 concentration. (Fig. 5, $P < 0.001$).

Discussion

CTRP9 is a protein, the closest paralog of adiponectin, and is predominantly expressed in adipose tissue. It exerts a wide range of metabolic functions across multiple organ systems, including adipose tissue, liver, cardiac myocytes, hypothalamus, and skeletal muscle[14,15]. Previous studies have confirmed that CTRP9 has a protective effect in diabetes, CAD, lung diseases, and other fields[9,16]. With the advancement of research, CTRP9 has attracted considerable attention in the cardiovascular field due to its beneficial effects in cardiovascular protection[17].

This study demonstrated the correlation between CTRP9 levels and the complexity of coronary artery lesions, while also highlighting its prognostic value in assessing adverse cardiovascular risks in patients with CAD. Plasma CTRP9 levels exhibited a significant decrease in patients with moderate-severe vascular disease compared to those with mild lesions. Lower CTRP9 levels were associated with higher SYNTAX scores, indicating increased complexity of coronary artery lesions. Even when accounting for multiple confounding factors, CTRP9 retained its status as an independent protective factor for coronary artery lesions. The explanation for the negative correlation between CTRP9 levels and coronary artery stenosis that we have found may be attributed to the fact that CTRP9 can increase the stability of the plaques. To further investigate the clinical significance of CTRP9, ROC curve analysis was performed to evaluate its diagnostic performance. The optimal cut-off value was determined to be 266.95 ng/mL based on the Youden index. Since reduced CTRP9 levels correlate with coronary lesion complexity, this optimal cut-off value provides a practical means of identifying patients predisposed to advanced coronary atherosclerosis.

Such patients could benefit from closer clinical monitoring and more intensive therapeutic interventions, thereby enabling earlier risk stratification and more targeted management in clinical practice.

Dysregulated lipid metabolism and oxidative stress can impair endothelial function and accelerate the progression of atherosclerotic plaques, ultimately leading to coronary lumen narrowing. Previous studies have demonstrated that CTRP9 exerts multiple vasoprotective effects during the development and progression of atherosclerosis[2,18]. Li et al. reported that, in apolipoprotein E–deficient mice, overexpression of CTRP9 enhanced carotid plaque stability by reducing the levels of pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α) and monocyte chemoattractant protein-9 (MCP-9)[19]. In addition, CTRP9 suppresses inflammation-related signaling pathways such as nuclear factor-k-gene binding (NF-κB), leading to decreased

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Age	1.022	1.004–1.040	0.018	1.006	0.986–1.026	0.569
Male	1.193	0.769–1.851	0.432	#	#	#
BMI	0.996	0.932–1.065	0.914	#	#	#
Drinking	1.106	0.713–1.717	0.652	#	#	#
Smoking	1.245	0.836–1.855	0.280	#	#	#
Hypertension	1.028	0.688–1.536	0.893	#	#	#
T2DM	1.575	1.013–2.405	0.036	1.010	0.556–1.834	0.975
CTRP9	0.994	0.992–0.996	< 0.001	0.996	0.994–0.998	< 0.001
FIB	1.061	1.009–1.116	0.021	1.012	0.947–1.082	0.715
D-D	1.143	1.047–1.248	0.003	1.028	0.903–1.170	0.677
LDH	1.001	1.000–1.002	0.009	1.001	0.999–1.002	0.348
CK-MB	1.008	1.000–1.016	0.039	1.001	0.989–1.013	0.844
UA	1.004	1.002–1.006	< 0.001	1.001	0.999–1.004	0.221
eGFR	0.994	0.984–1.005	0.274	#	#	#
Scr	1.004	0.997–1.011	0.232	#	#	#
FBG	1.278	1.146–1.425	< 0.001	1.011	0.846–1.208	0.901
TC	1.327	1.116–1.579	0.001	0.765	0.445–1.314	0.331
TG	1.586	1.343–1.873	< 0.001	1.255	0.954–1.651	0.104
HDL-C	0.441	0.275–0.707	0.001	1.785	0.784–4.064	0.167
LDL-C	1.422	1.213–1.667	< 0.001	1.392	0.816–2.375	0.225
Lp (a)	1.001	1.000–1.001	0.005	1.000	1.000–1.001	0.205
ApoA1	0.919	0.342–2.469	0.866	#	#	#
ApoB	1.390	0.622–3.107	0.422	#	#	#
EF	0.939	0.918–0.961	0.001	0.956	0.919–0.995	0.027
LVDD	1.510	1.092–2.088	0.013	0.864	0.507–1.473	0.592

Table 3. Univariate and Multivariate Cox regression analysis of MACEs. HR: Hazard ratio. CI: Confidence interval. #: There was no statistical significance in univariate Cox analysis. MACEs: Major adverse cardiovascular events.

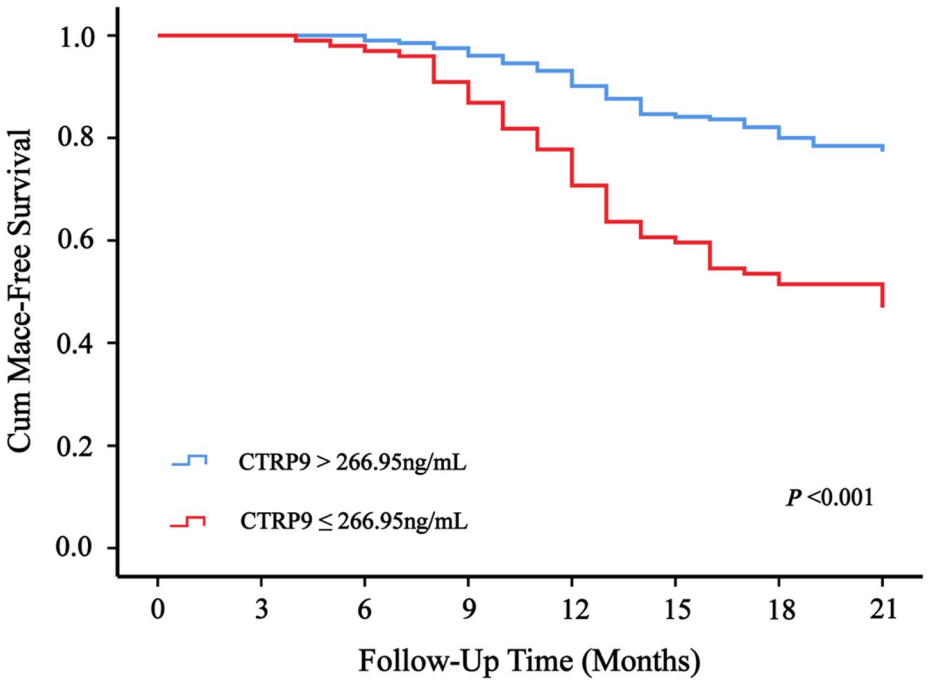

Fig. 5. Kaplan–Meier survival curves.

expression of adhesion molecules, including vascular cell adhesion molecule 1 (VCAM-1) and intercellular cell adhesion molecule 1 (ICAM-1), and promotes endothelium-dependent vasodilation through activation of the AMP-activated protein kinase (AMPK) pathway. CTRP9 also reduces reactive oxygen species production and attenuates high-glucose-induced oxidative stress[20–22]. These studies provide evidence that CTRP9 may contribute to inhibiting the release of inflammatory cytokines and adhesion molecules, thereby preserving the integrity and function of blood vessels and mitigating the progression of atherosclerosis.

CTRP9 has been shown to play a significant role in enhancing insulin sensitivity and regulating lipid metabolism[16]. This study further investigated the relationship between CTRP9 and blood lipids lipid profiles and glycemic parameters in patients. Plasma CTRP9 levels revealed a significant negative correlation with LDL-C, FBG, and TG, while a positive correlation was observed with HDL-C. These relationships were also partially reflected in a study of Huang et al.[23]. These findings suggest that plasma CTRP9 levels may serve as a valuable biomarker for evaluating glucose and lipid metabolism, as well as the severity of atherosclerosis. Gao et al. demonstrated that CTRP9 was exclusively associated with well-developed coronary collateral circulation in non-diabetic participants, but not in diabetic participants[24]. These findings suggest that CTRP9 has the potential to promote vascular revascularization in the event of ischemic events. In a study of 416 patients with T2DM, plasma CTRP9 concentrations were found to be significantly correlated with atherosclerosis[25]. Previous experiments have indicated that circulating CTRP9 was associated with coronary stiffness, and the plasma CTRP9 levels in patients with CAD were reduced[26]. Lei S et al. found that CTRP9 enhanced cholesterol efflux by reducing foam cell apoptosis[27]. CTRP9 plays a crucial role in attenuating cardiac dysfunction associated with high-fat diet-induced metabolic stress[28]. Based on these studies, we hypothesized that differences in CTRP9 expression levels may be related to its compensatory response to insulin resistance and inflammatory environments in different study subjects, such as CAD and T2DM.

The protective effect of CTRP9 on CAD has been reported, but its relationship with the prognosis of CAD remains unclear. The incidence of MACEs is commonly used as a major outcome indicator to evaluate the effectiveness of interventions in clinical trials[29]. In this study, lower plasma CTRP9 concentrations were associated with a higher risk of MACEs compared with higher levels. From a statistical perspective, CTRP9 was analyzed as a continuous variable in the Cox regression model; therefore, the observed HR reflects the incremental change in risk associated with each 1 ng/mL decrease in plasma CTRP9 levels. CTRP9 is an anti-inflammatory protein that improves endothelial function, and a reduction in its levels represents a state of chronic adverse biological exposure. Consequently, although the hazard ratio per unit decrease appears numerically small, the wide range of CTRP9 levels observed in clinical practice suggests that cumulative decreases across multiple units may have substantial clinical significance. These results indicate that CTRP9 may serve as a reliable biomarker for predicting the prognosis of CAD. Emerging research indicates that CTRP9 has the capacity to confer cardioprotective benefits through promoting the secretion of angiogenic factors in endothelial cells, inhibiting intimal hyperplasia, and reducing myocardial fibrosis[30,31]. Numerous other studies have indicated that the administering a specific concentration of CTRP9 to wild-type mice prior to ischemia-reperfusion reduces the myocardial infarction area[32,33]. Li et al. revealed a significant reduction in circulating CTRP9 levels among patients with myocardial infarction, irrespective of the stage of the infarction. These findings may indicate that CTRP9 is a unique predictor of myocardial infarction. Further experiments indicated that administration of certain concentrations of CTRP9 to mice modeled with myocardial infarction could improve left ventricular systolic function[34]. This is also consistent with our experimental results, which revealed that further multivariate Cox regression analysis indicated that CTRP9 and EF retained their independent predictive capacity for MACEs in CAD, even after adjusting for confounding factors. Liu et al. demonstrated that CTRP9 has the potential to ameliorate fibrosis, atrial inflammation, and susceptibility to atrial fibrillation in rats following myocardial infarction[35]. CTRP9 could attenuate cardiac remodeling after myocardial infarction and the reduction of CTRP9 level was directly proportional to the morbidity, mortality, and severity of heart failure[36]. These consequences also suggested that CTRP9 exerted a unique protective role in cardiac prognosis.

Based on current evidence, plasma CTRP9 levels may have clinical value for risk stratification in patients with coronary artery disease. Lower CTRP9 concentrations are associated with more complex coronary lesions and an increased risk of long-term major adverse cardiovascular events, independent of confounders. Given its inverse relationship with adverse metabolic profiles and atherosclerosis severity, CTRP9 may complement traditional risk markers to identify high-risk CAD patients. Combined with prior evidence of its anti-inflammatory, anti-atherosclerotic, and cardioprotective effects, CTRP9 represents a promising biomarker for improving prognostic evaluation in CAD. Therefore, future clinical strategies for managing CAD should extensively investigate the functions of CTRP9, emphasizing the necessity for additional research to fully understand the clinical implications of CTRP9 within the CAD context.

Limitation

Nonetheless, several inherent limitations of this study should be recognized. First, the observational and single-center design may introduce potential bias, and the findings may not be generalizable to other populations. Second, the study lacks external validation, which could further strengthen the robustness of the results. Third, the relatively short follow-up duration may limit the ability to capture long-term clinical outcomes comprehensively. Additionally, the modest sample size may reduce the statistical power of certain analyses. Finally, while this study provides valuable clinical associations, the underlying mechanisms through which CTRP9 regulates the progression of coronary artery disease remain to be fully elucidated. Comprehensive experimental studies, including animal models, are warranted to investigate these mechanisms in detail.

Conclusion

In general, plasma CTRP9 levels were found to be low in the moderate-severe group, and these reductions in CTRP9 levels may aid in identifying individuals at an increased risk of MACEs. It can be preliminarily inferred that CTRP9 serves as a significant risk factor for assessing the degree of coronary artery stenosis and predicting the prognosis of patients with CAD. In the future, it is expected to guide the treatment of patients with CAD.

Data availability

Data is provided within the manuscript or supplementary information files. Please contact Shimei Shang to request the research data.

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Author contributions
Shimei Shang was responsible for the experimental design, data collection, and analysis, and played a key role in revising the initial draft of the manuscript. Lin Jia was in charge of image editing and contributed to the revision of the initial draft. Xianhe Lin was responsible for experimental design and provided funding support. All authors reviewed the manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

Institutional Review Board Statement
The study was conducted in accordance with the Declaration of Helsinki, and approved by the ethics committee of The First Affiliated Hospital of Anhui Medical University. (Reference number: Quick-PJ 2023-14-45).

Informed consent statement
All patients provided written informed consent to participate in this study, and we concealed information related to patient identity. Included populations agreed to have information published in the journal.

Additional information
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