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ORIGINAL RESEARCH

Elevated Serum Fibulin-5 Levels Correlate with Coronary Artery Disease Progression

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Background: This study aimed to assess the association between serum fibulin-5 levels and the progression of coronary artery disease (CAD) and its potential role as a diagnostic biomarker.

Methods: This study was conducted by the Department of Cardiology at Shanghai Pudong Hospital, enrolling 186 patients diagnosed with CAD and 150 healthy controls. Clinical and biochemical parameters were compared between the groups using Student's *t*-test. ELISA was used to quantify serum fibulin-5 levels. Pearson's correlation and logistic regression analyses were conducted to assess the relationship between fibulin-5 levels and CAD-related indicators.

Results: Compared to healthy individuals, patients with CAD exhibited significantly higher levels of body mass index (BMI), systolic blood pressure (SBP), fasting blood glucose (FBG), white blood cell (WBC) count, high-sensitivity C-reactive protein (hs-CRP), triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), intima-media thickness (IMT), brachial-ankle pulse wave velocity (baPWV), and fibulin-5, along with reduced flow-mediated dilation (FMD) and high-density lipoprotein cholesterol (HDL-C) (all $P<0.05$). Patients with CAD involving >2 vessels showed significantly elevated SBP, hs-CRP, TG, TC, LDL-C, IMT, baPWV, and fibulin-5, and lower HDL-C and FMD than those with CAD involving ≤2 vessels ($P < 0.05$). ELISA results demonstrated significantly increased fibulin-5 levels in patients with CAD, with the highest levels in the >2 vessels group. ROC analysis identified a fibulin-5 cutoff value of 64.2 ng/mL, achieving 93% sensitivity and 72% specificity (AUC = 0.950) for differentiating CAD progression from healthy controls. Fibulin-5 levels were positively correlated with age, hs-CRP, TC, LDL-C, IMT, and baPWV, and negatively correlated with FMD. Multivariate logistic regression identified SBP, IMT, baPWV, and fibulin-5 as independent risk factors for CAD involving >2 vessels ($P < 0.05$).

Conclusion: Serum fibulin-5 levels were significantly elevated in patients with CAD involving >2 vessels compared to healthy subjects and were positively correlated with disease progression.

Keywords: fibulin-5, coronary artery disease, intima-media thickness, disease progression, biomarkers

Introduction

Coronary artery disease (CAD) remains one of the leading causes of morbidity and mortality worldwide, characterized by the accumulation of atherosclerotic plaques in the coronary arteries, leading to reduced blood flow and ischemic heart disease.[1] The pathophysiology of CAD involves complex interactions between endothelial dysfunction, inflammation, and extracellular matrix (ECM) remodeling, which contribute to plaque formation, progression, and instability.[2] Among the various biomarkers associated with CAD, extracellular matrix proteins have gained increasing attention for their role in vascular integrity and disease progression.

Fibulin-5, a secreted ECM protein, plays a critical role in maintaining vascular integrity by promoting elastic fiber assembly and regulating endothelial cell functions. It is predominantly expressed in vascular tissues and has been implicated in modulating vascular remodeling, oxidative stress, and inflammation, which are key processes involved in the pathogenesis of CAD.[3,4] CAD is characterized by progressive atherosclerosis, in which endothelial dysfunction and ECM degradation contribute to plaque formation and vascular stiffening.[5] Studies suggest that fibulin-5 may act as

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a protective factor by inhibiting abnormal vascular smooth muscle cell proliferation and promoting elastogenesis, thereby stabilizing the vascular wall.[6]

Recent investigations have explored the expression levels of fibulin-5 in patients with atherosclerosis and related vascular disorders. For instance, decreased fibulin-5 expression has been observed in atherosclerotic lesions and is associated with increased matrix metalloproteinase (MMP) activity and vascular stiffness.[7] Conversely, some studies have reported elevated circulating levels of fibulin-5 in response to vascular injury or remodeling, potentially reflecting a compensatory mechanism.[6] Furthermore, fibulin-5 has been shown to interacts with inflammatory pathways, suggesting its potential role in CAD progression.[3] Fibulin-5 has emerged as a potential therapeutic target in chronic obstructive pulmonary disease (COPD) due to its crucial role in elastogenesis and extracellular matrix remodeling.[8] Fibulin-5 suppresses lung cancer invasion by downregulating the expression of matrix metalloproteinase-7 (MMP-7), thereby inhibiting extracellular matrix degradation and tumor progression.[9] However, the clinical relevance of serum fibulin-5 levels in CAD, particularly in relation to disease progression, is unclear. Prior studies have largely focused on experimental models or small patient cohorts, leaving a gap in our understanding of the potential of fibulin-5 as a biomarker for CAD progression.[10]

Serum fibulin-5 is a particularly important biomarker for assessment compared to other markers because of its pivotal role in maintaining vascular and ECM integrity, as well as its involvement in pathological processes such as inflammation, fibrosis, and tumor progression. Unlike many conventional markers that provide general indications of inflammation or tissue injury, fibulin-5 is directly involved in elastogenesis and ECM remodeling, which are key processes implicated in vascular diseases, COPD, and certain cancers. Elevated or dysregulated fibulin-5 levels have been associated with endothelial dysfunction, atherosclerotic plaque stability, and tumor invasiveness, making it a more disease-specific and mechanistically informative biomarker than traditional inflammatory or metabolic markers.[4,11,12] Additionally, fibulin-5 modulates the activity of matrix metalloproteinases (MMPs), such as MMP-7, further emphasizing its role in pathological ECM degradation and remodeling processes.[9]

This study aimed to investigate the association between serum fibulin-5 levels and CAD progression, hypothesizing that increased fibulin-5 may serve as a biomarker for advanced atherosclerosis and adverse cardiovascular outcomes. Understanding this relationship could enhance risk prediction and identify novel therapeutic targets for CAD.

Methods

Study Population

In this study, we consecutively collected 186 CAD patients admitted to the Department of Cardiology in Shanghai Pudong Hospital between January 2022 and June 2024. All patients underwent coronary angiography and were confirmed to have CAD. Additionally, 150 age- and sex-matched individuals without coronary heart disease (non-CHD), who also underwent coronary angiography and were ruled out for CAD, were included as controls. The severity of coronary lesions in the CAD group was assessed based on the number of major coronary arteries with significant stenosis, and all 186 patients were categorized into two groups: ≤2-vessel disease (n = 125) and >2-vessel disease (n = 61). Extensive exclusion criteria were implemented to minimize potential confounding factors that might influence the study outcomes. Participants with a history of myocardial infarction, infections, inflammatory bowel disease, chronic obstructive pulmonary disease (COPD), autoimmune disorders, liver disease, renal failure, cancer, or recent use of anti-inflammatory drugs, steroids, or immunosuppressants were excluded from the study. This study was approved by the Ethics Committee of Guangming Traditional Chinese Medicine Hospital of Pudong New Area (Approval No. GTCM202401-WMKT-BED). Informed consent was obtained from participants or nearest relatives.

Data Collection

Upon admission, clinical data were collected, which included demographic information (age, sex, smoking or alcohol intake history), comorbidities (hypertension and diabetes mellitus), and blood pressure (SBP). Following an overnight fast, 10 mL of venous blood samples were acquired to assess various biochemical indices, including fasting blood sugar (FBS), white blood cells (WBC), high-sensitivity C-reactive protein (hs-CRP), triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C).

Measurement of Intima-Media Thickness (IMT)

The IMT of the carotid artery was measured using carotid ultrasound.[13] The ultrasound images were obtained from the posterior wall of both the left and right carotid arteries. The carotid IMT value was calculated as the average of five measurements for each subject.

Measurement of Flow-Mediated Dilation (FMD)

FMD was conducted by measuring the diameter of the brachial artery to assess endothelial function.[14] Patients were positioned supine for no less than 15 minutes. An automated sphygmomanometer (Dinamap device) was placed on the forearm to monitor blood pressure and pulse at 5-minute intervals- a standard blood pressure cuff measured arterial pressure two inches below the antecubital fossa. After acquiring baseline images, reactive hyperaemia was induced by inflating the cuff. Images of both the baseline and maximum diameters of the brachial artery were captured.

Measurement of Brachial-Ankle Pulse Wave Velocity (BaPWV)

BaPWV was utilized to measure the conduction velocity of the brachial-ankle pulse wave in order to evaluate arterial wall compliance and stiffness. Patients were rested in the supine position, and their baPWV was measured using an automatic waveform analyzer (VP-1000; Omron, Tokyo, Japan). The cuffs were applied to both the upper arm and ankle. BaPWV was calculated automatically through time-phased analysis, which is normalized to the distance between the upper arm and ankle.[15]

ELISA Detection of Serum Fibulin-5

Serum fibulin-5 levels in non-CAD and CAD patients were measured using the Human FBLN5 (fibulin-5) ELISA Kit (EH0772, Feien Biotechnology Co., Ltd, Wuhan, China), with absorbance recorded at 450 nm on a microplate reader. Fibulin-5 concentrations were determined based on the standard curve and expressed as ng/mL.

Statistical Analysis

SPSS 20.0 statistical software was employed for data processing. Continuous variables are presented as the mean ± standard deviation (SD) and analyzed using a *t*-test or Mann–Whitney *U*-test to compare two groups. Categorical variables are reported as frequency (percentage) and analyzed with the chi-square test. The Pearson correlation test examined the correlation between fibulin-5 and continuous variables. The ROC curve established the cutoff point of serum fibulin-5 for CAD subjects with vessels > 2 compared to those with vessels. Univariate and multivariate logistic regression analyses assess the impact of serum fibulin-5 on CAD disease progression. A P-value of <0.05 was regarded as the threshold for a significant difference.

Results

Baseline Characteristics

The investigation employed a comprehensive approach to compare subjects with coronary artery disease (CAD) to a healthy control group. The results from the Student's *t*-test revealed that subjects with CAD showed significantly higher levels of various health indicators, including body mass index (BMI), hypertension, systolic blood pressure (SBP), fasting blood glucose (FBG), white blood cell (WBC), high-sensitivity C-reactive protein (hs-CRP), triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), intima-media thickness (IMT), brachial-ankle pulse wave velocity (baPWV), and fibulin-5, while subjects with CAD exhibited significantly lower levels of flow-mediated dilation (FMD) and high-density lipoprotein cholesterol (HDL-C) (Table 1). However, there were no significant differences between the CAD group and the healthy controls in terms of age, sex, smoking, drinking, and diabetes mellitus (P > 0.05).

Additionally, we conducted a Student's *t*-test analysis to compare patients with CAD in the vessel ≤ 2 group (n=125) with those in the vessel > 2 group (n=61). The results indicated that patients with CAD in the vessel > 2 group exhibited significantly elevated levels of various health indicators, including SBP, hs-CRP, TG, TC, LDL-C, IMT, baPWV, and fibulin-5. In comparison, patients with CAD in the vessel > 2 group demonstrated significantly lower levels of HDL-C

Table 1 Baseline Characteristics of the Healthy Controls and Subjects with of CAD

Parameters	Non-CAD (n=150)	CAD (n=186)	P-value
Age (years)	61.81±8.10	62.20±8.38	0.683
Sex (male, %)	59 (49.2%)	102 (54.8%)	0.332
BMI (kg/m^2)	23.58±2.51	24.38±2.38	0.005
Smoking, n (%)	27 (22.5%)	55 (29.6%)	0.173
Drinking, n (%)	29 (24.2%)	62 (33.3)	0.087
Hypertension, n (%)	32 (26.7%)	71 (38.2%)	0.038
Diabetes mellitus, n (%)	19 (15.8%)	44 (23.7%)	0.098
SBP (mmHg)	124.87±6.29	128.46±6.11	<0.001
FBG (mmol/L)	4.89±1.02	5.62±1.15	<0.001
WBC (10^9/L)	5.92±1.38	6.32±1.25	0.009
hs-CRP (mg/L)	0.93±0.22	1.13±0.22	<0.001
TG (mmol/L)	1.41±0.20	1.52±0.20	<0.001
TC (mmol/L)	4.54±0.44	4.87±0.46	<0.001
LDL-C (mmol/L)	2.58±0.39	3.12±0.46	<0.001
HDL-C (mmol/L)	1.23±0.22	1.07±0.20	<0.001
IMT (mm)	0.81±0.06	0.98±0.13	<0.001
FMD (%)	7.41±1.29	6.82±1.14	<0.001
baPWV (cm/s)	1489.98±246.37	1645.62±243.28	<0.001
Fibulin-5 (ng/mL)	57.38±9.34	86.52±15.27	<0.001

Notes: Continuous variables are expressed as mean ± SD, and analyzed using *t* test or Wilcoxon-Mann–Whitney test. Categorical variables are expressed as frequency (percentage), and analyzed using the chi-square test.

Abbreviations: CAD, coronary artery disease; BMI, body mass index; SBP, systolic blood pressure; FBS, fasting blood sugar; WBC, white blood cell; hs-CRP, high-sensitivity C-reactive protein; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; IMT, intima-media thickness; FMD, flow-mediated dilation; baPWV, brachial-ankle pulse wave velocity.

and FMD (Table 2). Nevertheless, there were no significant differences between patients with CAD in the vessel ≤ 2 groups and those in the vessel > 2 group concerning age, sex, BMI, smoking, drinking, hypertension, diabetes mellitus, FBG, and WBC (P > 0.05).

Serum Fibulin-5 Levels are Elevated in CAD Patients

ELISA testing was employed to measure the serum levels of fibulin-5 in the control group (n = 150), CAD with vessels ≤ 2 (n = 125), and CAD with vessels > 2 (n = 61). The results demonstrated that fibulin-5 levels were higher in the CAD with vessels ≤ 2 group compared to the healthy controls (Figure 1A). We also noted that fibulin-5 serum levels were significantly elevated in the CAD with vessels > 2 group (Figure 1A). Furthermore, the Receiver Operating Characteristic (ROC) curve analysis revealed that the optimal cutoff value for serum fibulin-5 is 64.2 ng/mL, with a sensitivity of 93% and a specificity of 72%, resulting in an Area Under the Curve (AUC) of 0.950 (Figure 1B). Consequently, the ROC curve was used to ascertain the optimal cutoff value (64.2 ng/mL) for serum fibulin-5, distinguishing CAD from healthy controls.

Correlation Between Serum Fibulin-5 and Clinical Indicators Associated with CAD

In a study involving 186 patients with CAD, serum levels of fibulin-5 were positively correlated with several factors, including age (r=0.176, P=0.016), hs-CRP (r=0.237, P=0.001), TC (r=0.215, P=0.003), LDL-C (r=0.227, P=0.002), IMT (r=0.194, P=0.008), and baPWV (r=0.159, P=0.030). Conversely, the level of fibulin-5 was negatively associated with FMD (r=−0.178, P=0.015) (Table 3). Furthermore, a Pearson correlation test revealed that serum levels of fibulin-5 had a positive correlation with IMT and baPWV while showing a negative correlation with FMD (Figure 2).

Table 2 Baseline Characteristics of CAD with Vessels ≤ 2 and with Vessels > 2

Parameters	CAD with Vessels ≤ 2 (n = 125)	CAD with Vessels > 2 (n = 61)	P-value
Age (years)	61.50±7.91	63.66±9.16	0.099
Sex (male, %)	64 (51.2%)	38 (62.3%)	0.153
BMI (kg/m^2)	24.17±2.46	24.82±2.17	0.078
Smoking, n (%)	32 (25.6%)	23 (37.7%)	0.089
Drinking, n (%)	40 (32.0%)	22 (36.1%)	0.581
Hypertension, n (%)	44 (35.2%)	27 (44.3%)	0.232
Diabetes mellitus, n (%)	28 (22.4%)	16 (26.2%)	0.564
SBP (mmHg)	127.46±6.23	130.49±5.51	0.001
FBG (mmol/L)	5.52±1.18	5.83±1.05	0.089
WBC (10^9/L)	6.21±1.20	6.53±1.34	0.106
hs-CRP (mg/L)	1.09±0.19	1.19±0.25	0.010
TG (mmol/L)	1.50±0.20	1.57±0.18	0.030
TC (mmol/L)	4.79±0.42	5.04±0.50	<0.001
LDL-C (mmol/L)	3.04±0.45	3.29±0.46	0.001
HDL-C (mmol/L)	1.08±0.21	1.03±0.19	0.094
IMT (mm)	0.95±0.11	1.04±0.14	<0.001
FMD (%)	6.96±1.17	6.55±1.04	0.021
baPWV (cm/s)	1590.75±232.29	1758.07±227.71	<0.001
Fibulin-5 (ng/mL)	83.46±14.60	92.79±14.82	<0.001

Abbreviations: CAD, coronary artery disease; BMI, body mass index; SBP, systolic blood pressure; FBS, fasting blood sugar; WBC, white blood cell; hs-CRP, high-sensitivity C-reactive protein; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; IMT, intima-media thickness; FMD, flow-mediated dilation; baPWV, brachial-ankle pulse wave velocity.

Logistic Regression Analysis for CAD with Vessels > 2 Patients

Univariate and multivariate logistic regression analyses were conducted to identify independent risk factors for CAD with vessels > 2 patients. The results of the univariate logistic regression analysis revealed that SBP (OR=1.074, 95% CI=1.004–1.149; P=0.038), IMT (OR=43.961, 95% CI=1.317–1467.054; P=0.035), baPWV (OR=1.002, 95% CI=1.001–1.004; P=0.010), and fibulin-5 (OR=1.031, 95% CI=1.003–1.059; P=0.027) (Table 4). Furthermore, the

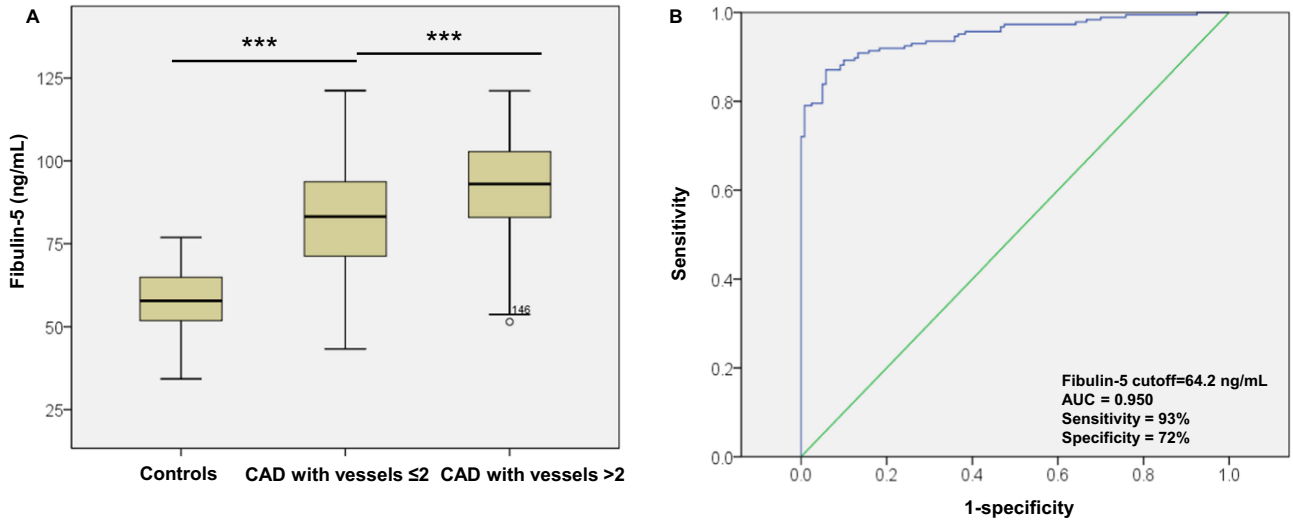

Figure 1 Serum Fibulin-5 levels are higher in CAD patients. (**A**) Comparison of serum Fibulin-5 levels between the non-CAD (n = 150), CAD with vessels ≤ 2 (n = 125), and CAD with vessels > 2 (n = 61). (**B**) The ROC curve was used to obtain the optimal cut-off value of serum Fibulin-5 that distinguishes the CAD subjects with vessels > 2 from CAD subjects with vessels. *T* test was applied. ***P<0.001.

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Table 3 Correlation Between Serum Fibulin-5 and Clinical Indicators

Parameters	All CAD Subjects (n=186)	
	r	P
Age (years)	0.176	0.016
BMI (kg/m^2)	0.093	0.207
SBP (mmHg)	0.116	0.115
FBS (mmol/L)	0.053	0.469
WBC (10^9/L)	0.140	0.056
hs-CRP (mg/L)	0.237	0.001
TG (mmol/L)	0.049	0.510
TC (mmol/L)	0.215	0.003
LDL-C (mmol/L)	0.227	0.002
HDL-C (mmol/L)	−0.072	0.330
IMT (mm)	0.194	0.008
FMD (%)	−0.178	0.015
baPWV (cm/s)	0.159	0.030

Notes: The correlation between serum Fibulin-5 and continuous variables was analyzed using the Pearson correlation test.

multivariate logistic regression analysis results indicated that SBP (OR=1.073, 95% CI=1.008–1.142; P=0.028), IMT (OR=105.532, 95% CI=4.715–2362.211; P=0.003), baPWV (OR=1.002, 95% CI=1.001–1.004; P=0.003), and fibulin-5 (OR=1.036, 95% CI=1.010–1.063; P=0.006) (Table 5).

Discussion

In this study, we explored the relationship between serum fibulin-5 levels and CAD disease progression. Our findings revealed that fibulin-5 levels were significantly elevated in CAD patients with ≤2 affected vessels and in those with >2 affected vessels compared to healthy controls. Receiver operating characteristic (ROC) curve analysis identified an optimal cutoff value of 69.46 ng/mL for serum fibulin-5 to differentiate CAD patients with >2-vessel disease from those with ≤2-vessel involvement. Furthermore, serum fibulin-5 levels were positively correlated with age, hs-CRP, TC, LDL-C, IMT, and baPWV and negatively correlated with FMD. Multivariate logistic regression analysis further demonstrated that patients with CAD and >2-vessel disease had significantly higher serum fibulin-5, SBP, IMT, and baPWV levels. These findings suggest that elevated serum fibulin-5 levels may be associated with CAD disease progression and could serve as potential biomarker for its progression.

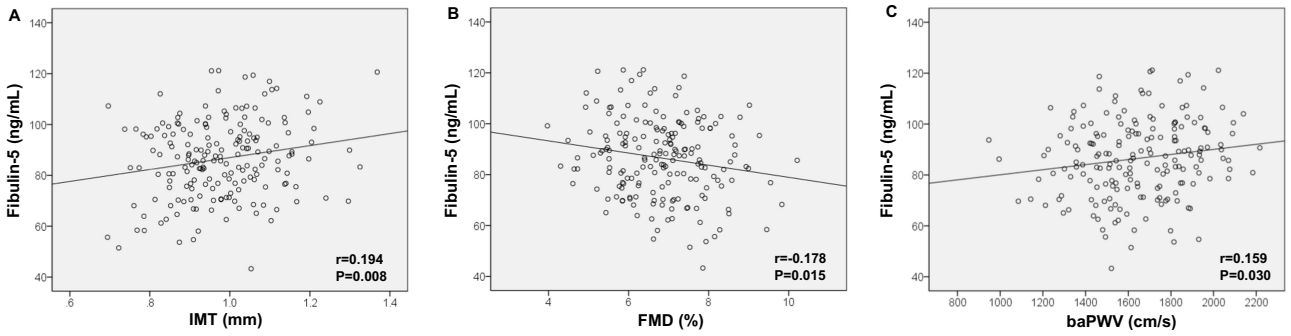

Figure 2 The correlation between serum Fibulin-5 and clinical indicators. Pearson correlation test was performed between Fibulin-5 with (**A**) IMT, (**B**) FMD, and (**C**) baPWV in all CAD patients.

Table 4 Logistic Univariate Regression for CAD with Vessels > 2

Characteristics	Odds ratio	95% CI	P-value
Age (years)	0.979	0.932–1.028	0.390
Sex (male, %)	1.586	0.727–3.459	0.246
BMI (kg/m^2)	1.040	0.883–1.225	0.639
Smoking, n (%)	1.292	0.560–2.983	0.548
Drinking, n (%)	1.208	0.542–2.695	0.644
Hypertension, n (%)	1.531	0.701–3.345	0.285
Diabetes mellitus, n (%)	1.629	0.638–4.160	0.308
SBP (mmHg)	1.074	1.004–1.149	0.038
FBS (mmol/L)	1.022	0.708–1.476	0.906
WBC ($10^9/L$)	1.006	0.737–1.372	0.970
hs-CRP (mg/L)	3.315	0.521–21.093	0.204
TG (mmol/L)	3.243	0.438–24.007	0.249
TC (mmol/L)	1.481	0.507–4.324	0.473
LDL-C (mmol/L)	1.195	0.423–3.377	0.737
HDL-C (mmol/L)	0.391	0.052–2.952	0.363
IMT (mm)	43.961	1.317–1467.054	0.035
FMD (%)	0.924	0.650–1.314	0.661
baPWV (cm/s)	1.002	1.001–1.004	0.010
Fibulin-5 (ng/mL)	1.031	1.003–1.059	0.027

Abbreviations: CAD, coronary artery disease; BMI, body mass index; SBP, systolic blood pressure; FBS, fasting blood sugar; WBC, white blood cell; hs-CRP, high-sensitivity C-reactive protein; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; IMT, intima-media thickness; FMD, flow-mediated dilation; baPWV, brachial-ankle pulse wave velocity; CI, confidence interval.

Table 5 Logistic Multivariate Regression for CAD with Vessels > 2

Characteristics	Odds Ratio	95% Confidence Interval	P-value
SBP (mmHg)	1.073	1.008–1.142	0.028
IMT (mm)	105.532	4.715–2362.211	0.003
baPWV (cm/s)	1.002	1.001–1.004	0.003
Fibulin-5 (ng/mL)	1.036	1.010–1.063	0.006

Abbreviations: CAD, coronary artery disease; SBP, systolic blood pressure; IMT, intima-media thickness; baPWV, brachial-ankle pulse wave velocity.

Our study aligns with previous research highlighting the role of fibulin-5 in vascular remodeling and atherosclerosis. Fibulin-5, an extracellular matrix protein, regulates elastin assembly and vascular integrity.[4] However, its upregulation in pathological conditions such as CAD suggests a compensatory response to vascular injury or chronic inflammation. Consistent with our findings, previous studies have reported elevated fibulin-5 levels in patients with acute intracerebral hemorrhage (ICH), which correlate with disease progression.[16] Similarly, another study found that fibulin-5 levels were significantly higher in patients with stable CAD than in controls,[7] supporting its potential as a biomarker for atherosclerosis progression. Our ROC curve analysis further reinforced the diagnostic utility of fibulin-5, demonstrating a high sensitivity (93%) and specificity (72%) at a cutoff value of 64.2 ng/mL for discriminating multivessel CAD from healthy controls. This finding is particularly significant as it suggests that fibulin-5 could aid in risk stratification, complementing existing biomarkers such as hs-CRP and LDL-C.

The observed positive correlation between fibulin-5 and high-sensitivity C-reactive protein (hs-CRP) ($r = 0.237$, $P = 0.001$) in our study suggests that fibulin-5 may be involved in systemic inflammation, a well-established contributor to atherosclerosis. This finding is consistent with previous research showing that fibulin-5 expression is upregulated in endothelial cells in response to inflammatory cytokines.[17] Furthermore, the strong associations between fibulin-5 and lipid parameters, including total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C), support the earlier evidence that fibulin-5 contributes to lipid retention within the arterial wall,[18] thereby promoting plaque formation. In addition, our study identified significant correlations between fibulin-5 and indicators of arterial stiffness (baPWV) and endothelial dysfunction (FMD). These results align with those of a previous study that reported that the overexpression of fibulin-5 impairs endothelial function in animal models by reducing nitric oxide bioavailability.[19] The negative correlation between fibulin-5 and FMD ($r = -0.178$, $P = 0.015$) further supports the hypothesis that fibulin-5 plays a role in endothelial injury, a key mechanism in the progression of CAD.

Logistic regression is a statistical technique used to estimate the probability of a binary outcome based on one or more predictors. In the context of CAD, it serves as a valuable tool for identifying factors associated with the presence or progression of disease. Multivariate logistic regression identified fibulin-5, along with SBP, IMT, and baPWV, as independent predictors of multivessel CAD. This finding reinforces the notion that fibulin-5 is not merely a bystander but may actively participate in CAD progression. Previous studies have reported that fibulin-5 promotes smooth muscle cell proliferation and vascular calcification,[6] which could explain its association with more severe CAD. Our findings are consistent with research showing that extracellular matrix proteins, including fibulin-5, contribute to plaque instability and adverse cardiovascular outcomes.[20]

While several studies have explored fibulin-5 in vascular diseases, our study provides novel insights into its role in CAD progression stratification. For instance, a previous study reported elevated fibulin-5 in aortic aneurysms, but its association with CAD progression has been less explored.[7] Our results extend these observations by demonstrating that fibulin-5 correlates with multiple atherosclerotic markers and independently predicts multivessel disease. Moreover, the strong diagnostic performance of fibulin-5 (AUC = 0.950) suggests its potential clinical utility, which has not been previously reported in CAD risk stratification.

Limitations

This study had several inherent limitations. First, the relatively small sample size necessitates a cautious interpretation of the findings. Second, its cross-sectional design precludes the assessment of temporal or causal relationships, highlighting the need for prospective longitudinal studies to confirm the prognostic relevance of serum fibulin-5 levels. Third, the study population lacked ethnic diversity, which may limit the generalizability of our results. Future research should involve larger, multiethnic cohorts to enhance the external validity of the findings.

Conclusion

In conclusion, our study demonstrates that serum fibulin-5 levels are significantly elevated in patients with CAD, particularly in those with multivessel disease, and are significantly associated with disease progression (Figure 3). ROC analysis identified fibulin-5 (cutoff: 64.2 ng/mL) as a sensitive and specific biomarker for detecting severe CAD (vessels > 2). Furthermore, fibulin-5 correlated positively with hs-CRP, LDL-C, IMT, and baPWV but negatively with FMD, indicating its potential involvement in vascular dysfunction. Multivariate regression analysis showed that fibulin-5, along with SBP, IMT, and baPWV, was an independent predictor of CAD progression. Collectively, these findings highlight the potential of fibulin-5 as a diagnostic and prognostic biomarker for CAD progression. A larger prospective study encompassing a more diverse population is needed to validate the potential of serum fibulin-5 levels as a prognostic biomarker for CAD progression.

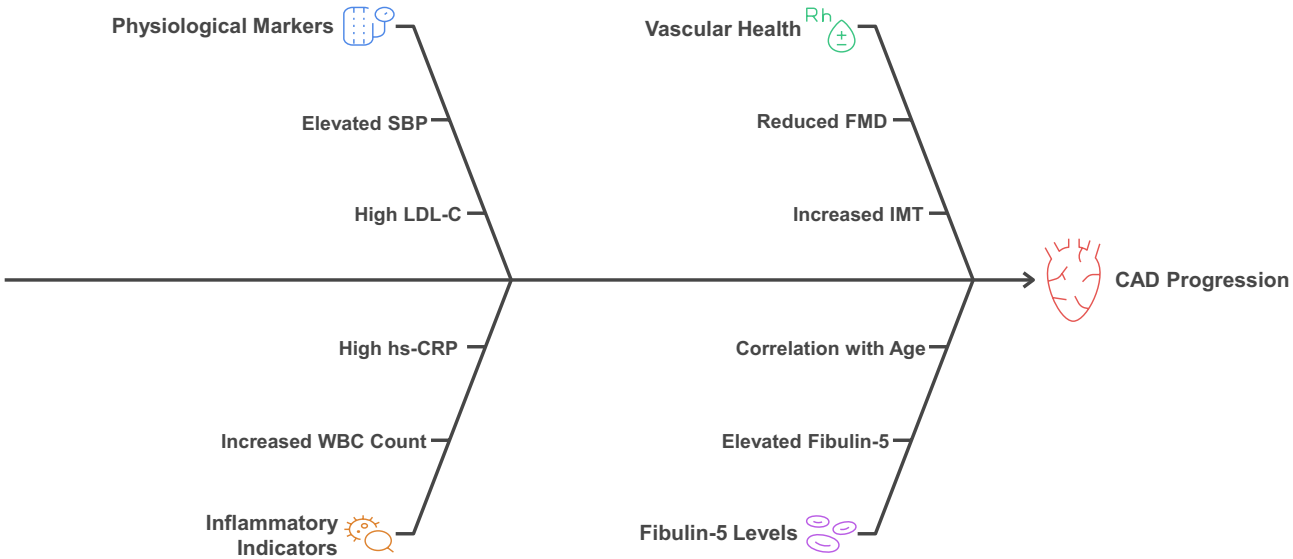

Figure 3 Schematic depiction of the risk factors associated with CAD progression.

Data Sharing Statement

The datasets used/analyzed during the present study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

The study protocol was reviewed and approved by the Ethics Committee of Guangming Traditional Chinese Medicine Hospital, Pudong New Area (Approval No. GTCM202401-WMKT-BED). The study was conducted in accordance with all standard protocols and ethical principles outlined in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all participants prior to their inclusion in the study.

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We have used AI tool (Copilot) to prepare this paper.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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