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Original Article

Beclin 1 level combined with Gensini score and low-density lipoprotein cholesterol correlate strongly with multi-vessel disease

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Abstract: Objective: To investigate the correlation between serum Beclin 1 levels and multi-vessel disease (MVD). Methods: A total of 169 participants were enrolled in this retrospective study. Based on coronary angiographic findings, 106 patients diagnosed with coronary heart disease (CHD) were categorized into single-vessel disease (SVD) and MVD groups, and their Gensini scores were calculated respectively. General demographic data and serum biochemical indicators were collected. Serum Beclin 1 concentration was detected by enzyme-linked immunosorbent assay. The differential expression of Beclin 1 among the three groups was compared and analyzed. Logistic regression models and receiver operating characteristic (ROC) curves were used to explore the association between Beclin 1 level and MVD. Results: Compared to the control group, Beclin 1 levels were significantly decreased in both the groups, with the lowest level observed in the MVD group [2.45 (1.69, 4.17), 2.64 (2.24, 2.89), 1.09 (0.66, 1.78), P<0.001]. Multivariate analysis results demonstrated that Gensini score was an independent risk factor for MVD (OR = 1.045, 95% CI: 1.018-1.090, P<0.001), while Beclin 1 (OR = 0.372, 95% CI: 0.174-0.695, P = 0.001) and low-density lipoprotein cholesterol (LDL-C) (OR = 0.295, 95% CI: 0.128-0.619, P<0.001) served as independent protective factors against MVD The combined model (Gensini score + Beclin 1 + LDL-C yielded an AUC of 0.936, with an optimal predictive probability cutoff of ≥0.664, a sensitivity of 0.911, and a specificity of 0.963. Compared to the basic model (Gensini score + LDL-C), the combined model exhibited a higher AUC, indicating that the addition of Beclin 1 effectively improved the predictive efficacy for MVD. Conclusion: The combination of Beclin 1 level, Gensini score, and LDL-C had good predictive value for MVD.

Keywords: Multi-vessel disease, Beclin 1, Gensini score

Introduction

Coronary heart disease (CHD) is one of the most prevalent cardiovascular diseases and the leading cause of chronic disease-related mortality worldwide. Multi-vessel disease (MVD) is defined as the presence of >50% stenosis in two or more coronary arteries, or left main coronary artery lesions confirmed by coronary angiography, which is frequently accompanied by chronic total occlusion or diffuse severe stenosis of coronary vessels [1]. Approximately 50%-60% of patients undergoing coronary revascularization are diagnosed with MVD. Compared to patients with single-vessel disease (SVD), MVD patients have a higher incidence of postoperative complications such as shock, pulmonary edema and atrioventricular block, along with significantly higher mortality [2]. Therefore, early identification and diagnosis of MVD are of great clinical significance.

The occurrence and progression of CHD are mainly attributed to the formation and development of coronary atherosclerotic plaques [3], involving multiple pathologic mechanisms including endothelial injury, inflammation, oxidative stress, glucose and lipid metabolism disorders, and thrombosis [4-6]. Studies have confirmed that autophagy participates in the for-

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mation and remodeling of coronary atherosclerotic plaques, and its regulatory effect is independent of traditional risk factors such as age, smoking and hypertension [7, 8]. Autophagy dysfunction is closely associated with the progression of atherosclerosis (AS) and the stability of atherosclerotic plaques [9]. Beclin 1, a core regulatory protein of autophagy mainly localized to the endoplasmic reticulum, plays a pivotal role in the autophagy signaling pathway, regulating the initiation, extension and maturation of autophagosomes [10, 11]. Existing studies have shown that Beclin 1 is closely related to AS progression and exerts anti-atherosclerotic effects, thereby delaying the onset and progression of CHD [12-14]. Phosphorylation modification of Beclin 1 can inhibit autophagosome formation in macrophages, further promoting the progression of AS [15]. Feng et al. [16] found that apelin-13 could promote cholesterol efflux from macrophage foam cells by activating the Class III PI3K/Beclin 1-mediated autophagic pathway, thereby alleviating the pathologic progression of atherosclerosis. The above evidence indicates that Beclin 1 possesses anti-atherosclerotic properties. However, the correlation between Beclin 1 and MVD remains unclear. Clarifying this association will provide new insight for the early diagnosis of MVD and the reduction of adverse cardiovascular mortality. Accordingly, this study aimed to explore the correlation between serum Beclin 1 level and MVD.

Materials and methods

Study population

This retrospective cohort study was conducted at Beijing University of Chinese Medicine Third Affiliated Hospital. Patients admitted with chest pain from August 2022 to February 2024 were consecutively enrolled. The inclusion criteria were as follows: (1) aged 18-80 years; (2) underwent coronary angiography; (3) complete clinical and imaging data available. The exclusion criteria were as follows: (1) complicated severe heart failure, rheumatic heart disease or other organic heart diseases; (2) history of malignant tumors; (3) severe hepatic and renal dysfunction; (4) recent severe cerebrovascular accidents; (5) mental disorders; (6) active infectious diseases; (7) incomplete key clinical data. This study was approved by the Ethics Committee of Beijing University of Chinese Medicine Third Affiliated Hospital.

Data collection

Relevant clinical data of enrolled patients were extracted from the hospital electronic medical record system, including general baseline information and laboratory biochemical test results.

Baseline clinical data included gender, age, height, weight, blood pressure, history of diabetes mellitus (DM) and smoking history. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). All participants underwent fasting venous blood collection (3 mL) in the early morning. Serum levels of triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were detected routinely.

Detection of serum Beclin 1 level

During coronary angiography, 15 mL arterial blood was collected after successful right radial artery catheterization, and centrifuged at 3000 r/min for 10 minutes. The supernatant (100 μL) was extracted and stored at -80°C for subsequent detection. Serum Beclin 1 level was measured using a commercial Human BECN1 ELISA Kit (E-EL-H0564, Elabscience, China) in strict accordance with the manufacturer's instructions. Briefly, corresponding antibody and blocking solution were added sequentially for room-temperature incubation, followed by addition of enzyme substrate solution for chromogenic reaction. After termination of the reaction, the absorbance of each well was measured at 450 nm using a microplate reader. The standard curve was plotted to calculate the serum Beclin 1 concentration of each sample.

Gensini score evaluation

The severity of coronary artery stenosis was quantitatively evaluated using the Gensini scoring system based on coronary angiographic results [17]. The basic score was determined by the degree of coronary stenosis: 0 points for no stenosis, 1 point for stenosis ≤25%, 2 points for 25%-50% stenosis, 4 points for 50%-75% stenosis, 8 points for 75%-90% stenosis, 16 points for 90%-99% stenosis, and 32 points for total occlusion (100% stenosis). The basic score was further weighted according to the lesion location: ×5 for left main coronary artery lesions; ×2.5 for proximal anterior descending artery and proximal circumflex artery lesions;

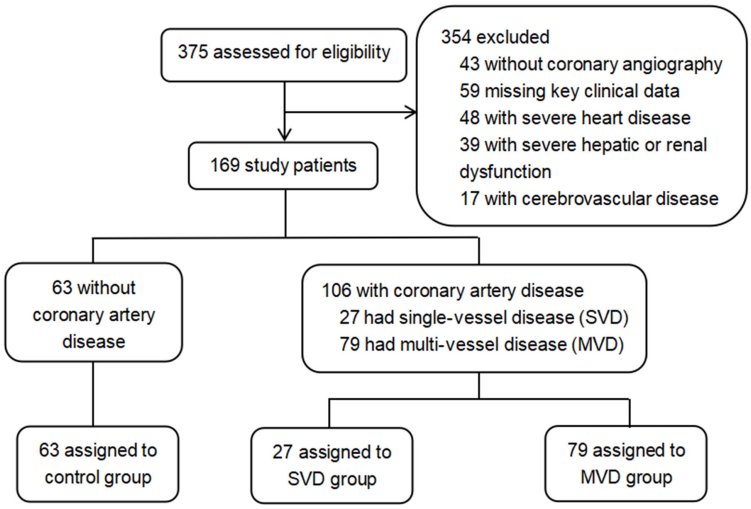

Figure 1. Participant screening flowchart. Abbreviations: MVD, multi-vessel disease; SVD, single-vessel disease.

×1.5 for middle anterior descending artery lesions; ×1.0 for right coronary artery, distal anterior descending artery, diagonal branch, left ventricular posterior branch and obtuse marginal branch lesions; ×0.5 for other minor vascular lesions. The total Gensini score of each patient was the sum of weighted scores of all stenotic vessels.

Statistical analysis

SPSS 22.0 and GraphPad Prism 9.0 software were used for data statistical analysis. Normally distributed quantitative data were expressed as mean ± standard deviation (χ ± sd), and one-way ANOVA was used for inter-group comparison. Non-normally distributed quantitative data were expressed as median (interquartile range) [M (Q1, Q3)], and the Mann-Whitney U nonparametric test was adopted for group comparison. Qualitative data were presented as case numbers and percentages (%), and compared using the χ^2 test or Fisher's exact test as appropriate.

MVD was set as the dependent variable (SVD = 0, MVD = 1). Candidate independent variables included age, BMI, sex, smoking history, drinking history, hypertension, diabetes mellitus, hyperlipidemia, TC, TG, LDL-C, HDL-C, Beclin 1 and Gensini score. First, univariate Firth's penalized likelihood binary logistic regression was performed for all candidate variables to avoid statistical bias caused by data separation. Subsequently, variables with P<0.05 in univariate analysis were included in the multivariate binary logistic regression model, and the backward stepwise method was used for variable screening (elimination criterion: P>0.05). The results were presented as odds ratio (OR) and 95% confidence interval (95% CI), and P<0.05 was defined as statistically significant.

A predictive model for MVD was constructed based on multivariate Firth's binary logistic regression results. ROC curve analysis was performed to evaluate the discriminatory efficacy of single indicators and the combined model for MVD. The area under the curve (AUC), optimal cutoff value, sensitivity and specificity were calculated. The optimal cutoff value was determined based on the maximum Youden index. For indicators negatively correlated with MVD, reverse ROC analysis was conducted, and the cutoff values and judgment criteria were reported based on the original scale of the indicators.

Results

Baseline clinical and biochemical characteristics of participants

A total of 169 participants were enrolled in this study, including 106 CHD patients and 63 participants with normal coronary angiography results (control group). The 106 CHD patients were further divided into an SVD group (n = 27) and a MVD group (n = 79) according to the number of stenotic coronary arteries (the patient screening flowchart is shown in **Figure 1**). Among all participants, 104 were male and 65 were female. The median age was 61 (56, 68) years in the control group, 64 (55, 71) years in the SVD group, and 65 (51, 69) years in the MVD group. The baseline clinical and biochemical characteristics of the three groups are summarized in **Table 1**. There were no significant differences in age, hypertension prevalence, diabetes prevalence, hyperlipidemia prevalence, TG level, or BMI among the three groups.

Table 1. Clinical and biochemical characteristics of participants in the control group, SVD group, and MVD group

	Control (n = 63)	CHD (n =106)		t/ x^2/z/F	P
		SVD (n = 27)	MVD (n = 79)		
Gender (male, %)	25 (39.7%)	16 (59.3%)	63 (79.7%)	23.840	<0.001
Age (years)	61 (56, 68)	64 (55, 71)	65 (51, 69)	0.656	0.720
BMI (kg/m^2)	24.78 (22.34, 28.70)	25.35 (23.44, 28.37)	24.21 (22.49, 26.30)	3.447	0.178
Smoking (n%)	15 (23.8%)	10 (37.0%)	40 (50.6%)	10.682	0.005
Alcohol consumption (n%)	12 (19.0%)	6 (22.2%)	30 (38.0%)	6.778	0.034
Medical history					
Hypertension (n%)	41 (65.1%)	17 (63.0%)	53 (67.1%)	0.168	0.919
DM (n%)	19 (30.2%)	6 (22.2%)	30 (38.0%)	2.535	0.282
Hyperlipidemia (n%)	50 (79.4%)	20 (74.1%)	66 (83.5%)	1.227	0.541
biochemical characteristics					
TC (mmol/L)	4.75 (4.01, 5.53)	4.30 (3.80, 4.94)	3.55 (2.84, 4.35)	31.731	<0.001
TG (mmol/L)	1.56 (1.05, 2.20)	1.40 (1.06, 1.88)	1.58 (1.05, 2.31)	0.440	0.803
LDL-C (mmol/L)	2.69 (2.10, 3.33)	2.25 (1.99, 3.22)	1.84 (1.27, 2.17)	29.089	<0.001
HDL-C (mmol/L)	1.32 (1.06, 1.53)	1.17 (1.03, 1.34)	1.08 (0.91, 1.30)	12.387	0.002

Abbreviations: BMI, body mass index; DM, diabetes mellitus; TC, total cholesterol; TG, serum levels of triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CHD, Coronary Heart Disease; SVD, single-vessel disease; MVD, multi-vessel disease.

Table 2. Beclin 1 level and Gensini scores of participants in the control group, SVD group, and MVD group

	Control (n = 63)	CHD (n = 106)		t/x^2/z/F	P
		SVD (n = 27)	MVD (n = 79)		
Beclin 1 (ng/mL)	2.45 (1.69, 4.17)	2.64 (2.24, 2.89)	1.09 (0.66, 1.78)	47.278	<0.001
Gensini scores		12 (4, 20)	52 (30, 104)	-6.176	<0.001

Abbreviations: CHD, Coronary Heart Disease; SVD, single-vessel disease; MVD, multi-vessel disease.

Compared to the control group, the SVD and MVD groups had significantly higher proportions of male patients, smokers and drinkers (all P<0.05). No significant inter-group differences were observed in the prevalence of hypertension, diabetes or hyperlipidemia (all P>0.05). In addition, CHD patients (both SVD and MVD groups) had lower serum TC and LDL-C levels than healthy controls (both P< 0.05).

Differential expression of Beclin 1 among the three groups

As shown in **Table 2** and **Figure 2A**, serum Beclin 1 levels were significantly lower in CHD patients than in healthy controls (P<0.05). ELISA results showed that the median Beclin 1 level was 2.64 (2.24, 2.89) in the SVD group and 1.09 (0.66, 1.78) in the MVD group, with the MVD group exhibiting the lowest Beclin 1 level.

Gensini score differences among the three groups

Coronary angiography-based Gensini score analysis showed that the median Gensini score was 12 (4, 20) in the SVD group and 52 (30, 104) in the MVD group (**Table 2**; **Figure 2B**), with significantly lower scores in the SVD group.

Correlation between Beclin 1 level and Gensini score

All 106 CHD patients were stratified into three subgroups according to Gensini score: low-score group (Gensini score <11, n = 15), medium-score group (11 ≤ Gensini score ≤38, n = 39) and high-score group (Gensini score >38, n = 52). As shown in **Table 3** and **Figure 3A**, the median Beclin 1 level was 2.64 (2.24, 3.85) in the low-score group, 2.05 (1.38, 2.66) in the medium-score group, and 0.74 (0.60, 1.56) in

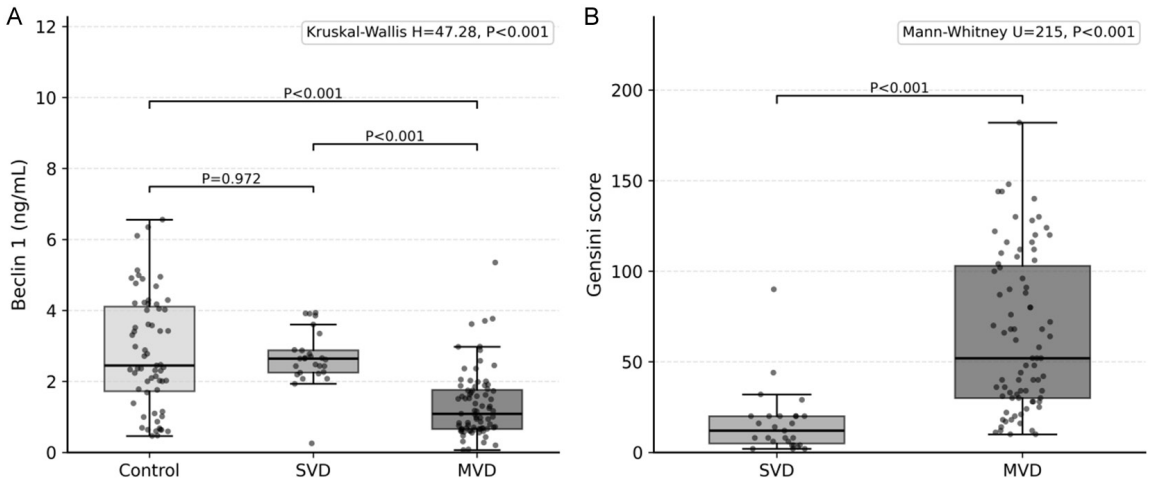

Figure 2. Comparison of Beclin 1 levels and Gensini scores among the three groups. A. Boxplot with error bars showing the distribution of serum Beclin 1 levels in the control, single-vessel disease (SVD), and multi-vessel disease (MVD) groups. The overall difference was assessed using the Kruskal-Wallis test, followed by pairwise Mann-Whitney U tests. B. Boxplot with error bars comparing the Gensini scores between the SVD and MVD groups, assessed by the Mann-Whitney U test. The bold horizontal line in each box represents the median, the lower and upper hinges correspond to the first and third quartiles, and the whiskers extend to the furthest data points within 1.5 times the interquartile range. data points are overlaid to show the underlying distribution.

Table 3. Association between Beclin 1 and Gensini score

	Gensini score			t/x²/z/F	P
	low score (n = 15)	medium score (n = 39)	high score (n = 52)		
Beclin 1 (ng/mL)	2.64 (2.24, 3.85)	2.05 (1.38, 2.66)	0.74 (0.60, 1.56)	47.818	<0.001

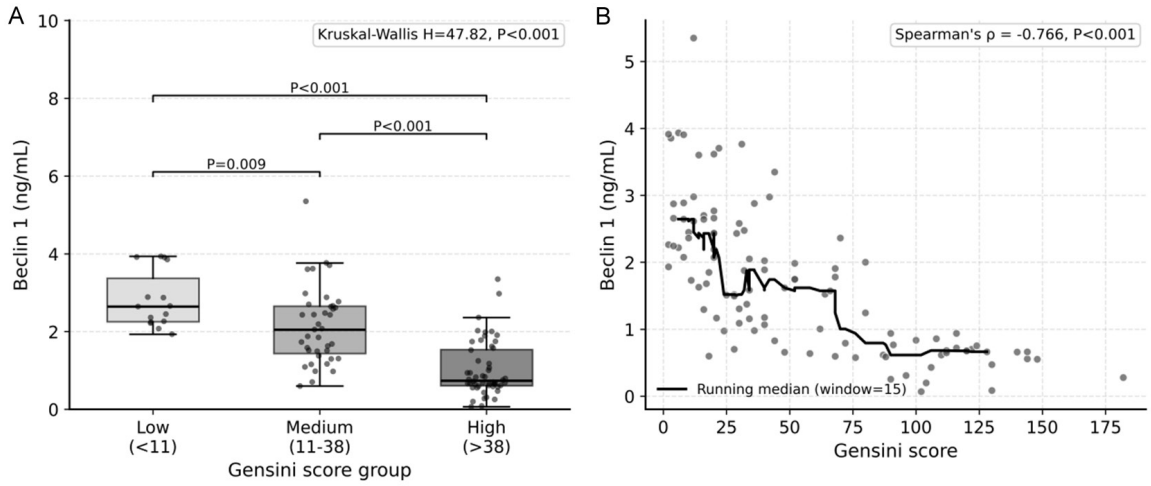

Figure 3. Association between Beclin 1 levels and Gensini scores. A. Boxplot with error bars illustrating Beclin 1 levels across three groups categorized by Gensini score: Low (<11), Medium (11-38), and High (>38). Statistical significance was determined using the Kruskal-Wallis test and subsequent pairwise Mann-Whitney U tests. Boxplot elements are defined as median (horizontal line), interquartile range (box), and 1.5 times the interquartile range (whiskers). B. Scatter plot demonstrating the inverse correlation between continuous Gensini scores and Beclin 1 levels. The solid black line represents a running median smoother (window size = 15) to visualize the non-linear trend. The correlation was evaluated using Spearman's rank correlation coefficient (ρ).

Table 4. Variable assignment for Firth logistic regression analysis of MVD

Variable	Assignment method
Dependent variable	
MVD	1 = Yes (MVD), 0 = No (SVD)
Independent variables	
Gender	1 = Male, 0 = Female
Age (years)	Continuous, as original value
BMI (kg/m^2)	Continuous, as original value
Smoking	1 = Yes, 0 = No
Alcohol consumption	1 = Yes, 0 = No
Hypertension	1 = Yes, 0 = No
DM	1 = Yes, 0 = No
Hyperlipidemia	1 = Yes, 0 = No
TC (mmol/L)	Continuous, as original value
TG (mmol/L)	Continuous, as original value
LDL-C (mmol/L)	Continuous, as original value
HDL-C (mmol/L)	Continuous, as original value
Gensini score	Continuous, as original value
Beclin 1 (ng/mL)	Continuous, as original value

Abbreviations: BMI, body mass index; DM, diabetes mellitus; TC, total cholesterol; TG, serum levels of triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; SVD, single-vessel disease; MVD, multi-vessel disease.

Table 5. Univariate firth logistic regression analysis of factors associated with MVD

Variable	β	OR (95% CI)	P
Gender	0.9867	2.682 (1.052-6.814)	0.039
TC (mmol/L)	-0.4164	0.659 (0.456-0.909)	0.011
LDL-C (mmol/L)	-0.6585	0.518 (0.319-0.787)	0.002
Gensini score	0.0734	1.076 (1.041-1.126)	<0.001
Beclin 1 (ng/mL)	-1.329	0.265 (0.140-0.449)	<0.001
DM	0.712	2.038 (0.792-5.847)	0.143
Alcohol consumption	0.712	2.038 (0.792-5.847)	0.143
BMI	-0.0795	0.924 (0.821-1.030)	0.156
Smoking	0.5358	1.709 (0.716-4.234)	0.229
Hyperlipidemia	0.589	1.802 (0.626-4.936)	0.266
HDL-C	-0.5063	0.603 (0.129-2.930)	0.523
TG	0.0656	1.068 (0.848-1.517)	0.617
Hypertension	0.1917	1.211 (0.484-2.942)	0.676
Age	-0.0064	0.994 (0.957-1.030)	0.728

Abbreviations: BMI, body mass index; DM, diabetes mellitus; TC, total cholesterol; TG, serum levels of triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; β, regression coefficient; OR, odds ratio; CI, confidence interval; MVD, multi-vessel disease.

the high-score group, with significant intergroup differences. Correlation analysis confirmed a significant negative correlation between Gensini score and serum Beclin 1 level (**Table 3**; **Figure 3B**).

Logistic regression analysis of MVD risk factors

Univariate Firth's binary logistic regression analysis showed that Gensini score, Beclin 1, LDL-C, TC and gender were significantly correlated with MVD (all P<0.05). The detailed results were: Gensini score (OR = 1.076, 95% CI: 1.041-1.126, P<0.001); Beclin 1 (OR = 0.265, 95% CI: 0.140-0.449, P<0.001); LDL-C (OR = 0.518, 95% CI: 0.319-0.787, P = 0.002); TC (OR = 0.659, 95% CI: 0.456-0.909, P = 0.011); and sex (male = 1, female = 0) (OR = 2.682, 95% CI: 1.052-6.814, P = 0.039) (**Tables 4** and **5**; **Figure 4**).

All significant variables in univariate analysis were included in the multivariate Firth's binary logistic regression model. The final independent influencing factors for MVD were Gensini score, Beclin 1 and LDL-C. Multivariate analysis results indicated that Gensini score was an independent risk factor for MVD (OR = 1.045, 95% CI: 1.018-1.090, P<0.001), while Beclin 1 (OR = 0.372, 95% CI: 0.174-0.695, P = 0.001) and LDL-C (OR = 0.295, 95% CI: 0.128-0.619, P<0.001) were independent protective factors for MVD (**Table 6**; **Figure 5**).

ROC curve analysis of the predictive value of Beclin 1 for MVD

Based on multivariate regression results, Gensini score, Beclin 1 and LDL-C were combined to construct a predictive model for MVD. Single-indicator ROC analysis showed that the AUC of Gensini

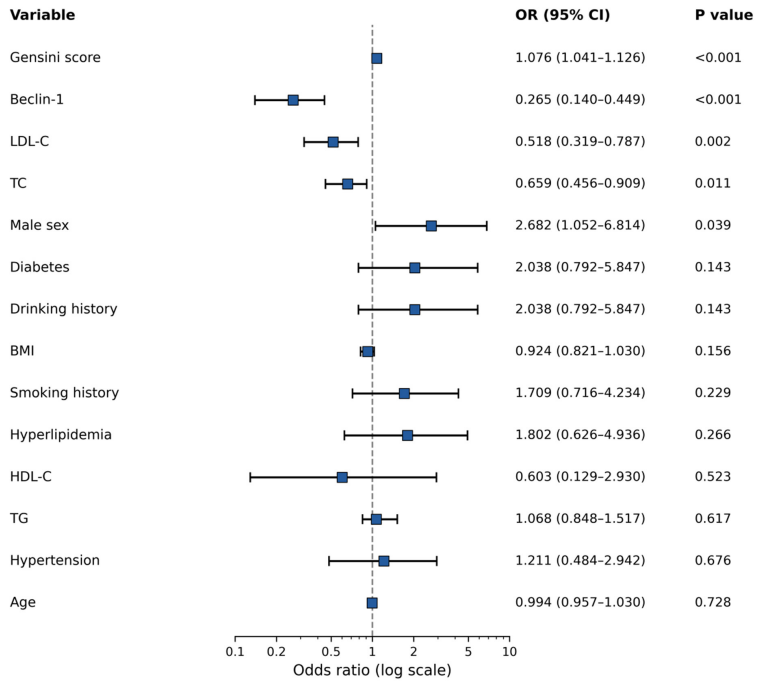

Figure 4. Forest plot of univariate analysis. Abbreviations: BMI, body mass index; TC, total cholesterol; TG, serum levels of triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

Table 6. Multivariate firth logistic regression analysis of factors associated with MVD

Variable	β	OR (95% CI)	P
LDL-C (mmol/L)	-1.2195	0.295 (0.128-0.619)	<0.001
Gensini score	0.0441	1.045 (1.018-1.090)	<0.001
Beclin 1 (ng/mL)	-0.9882	0.372 (0.174-0.695)	0.001

Abbreviations: LDL-C, low-density lipoprotein cholesterol; β, regression coefficient; OR, odds ratio; CI, confidence interval; MVD, multi-vessel disease.

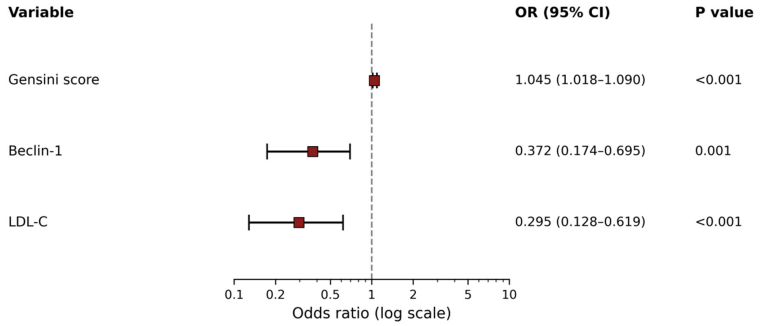

Figure 5. Forest plot of multivariate analysis. Abbreviation: LDL-C, low-density lipoprotein cholesterol.

score was 0.899 (optimal cutoff value ≥21.000, sensitivity = 0.861, specificity = 0.852); the AUC of Beclin 1 was 0.875 (optimal cutoff value ≤2.052, sensitivity = 0.861, specificity = 0.926); the AUC of LDL-C was 0.748 (optimal cutoff value ≤1.880, sensitivity = 0.570, specificity = 0.889). The combined model (Gensini score + Beclin 1 + LDL-C) achieved an AUC of 0.936, with an optimal predictive probability cutoff of ≥0.664, a sensitivity of 0.911 and a specificity of 0.963 (**Figure 6**). The basic model (Gensini score + LDL-C) had an AUC of 0.912, with an optimal cutoff of ≥0.635, a sensitivity of 0.848 and a specificity of 0.889. The higher AUC of the combined model verified that the addition of Beclin 1 significantly improved the predictive efficacy of the model for MVD (**Figure 7**).

Discussion

Coronary heart disease (CHD) is characterized by coronary atherosclerotic lesions that cause luminal stenosis or vascular occlusion. MVD is defined as >50% stenosis in two or more coronary arteries or left main coronary artery lesions on angiography, often accompanied by chronic total occlusion or diffuse severe coronary stenosis. The pathogenesis of MVD is multifactorial, involving systemic atherosclerosis, impaired cardiac function in non-infarcted myocardial regions, and reduced blood flow in severely stenotic non-infarct-related arteries [18]. Compared to SVD, MVD is associated with poorer long-term prognosis. A previous study by Leksto found that the 12-month cumulative incidence of major adverse cardiovascular events reached 32.5% in MVD patients [19], which is consistent with the severe disease phenotype of MVD observed in our study. In this study, we adopted the clinically

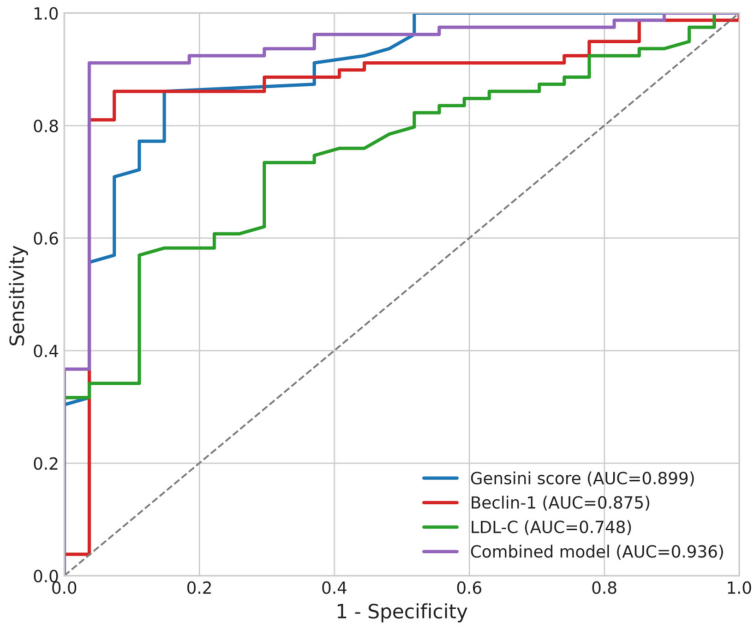

Figure 6. ROC curves. Abbreviation: LDL-C, low-density lipoprotein cholesterol.

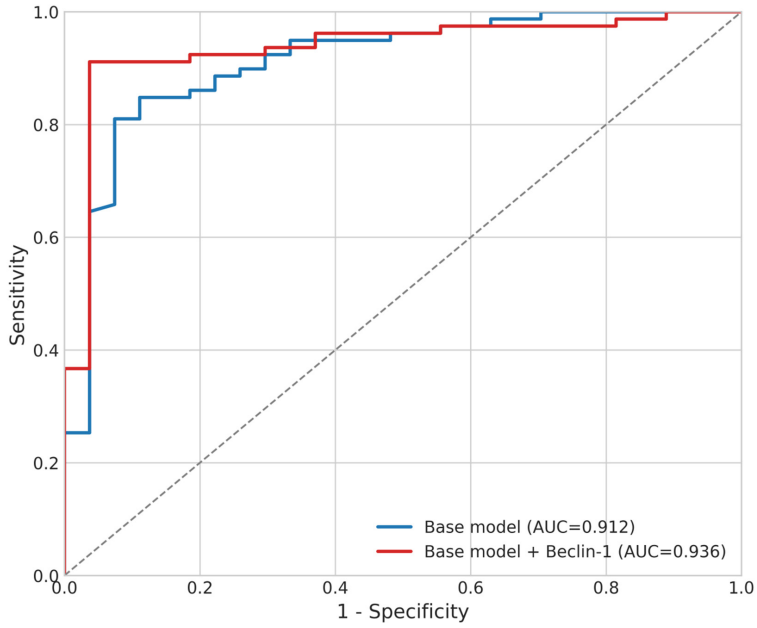

Figure 7. Combined predictive model.

validated Gensini scoring system to evaluate coronary lesion severity, and confirmed that MVD patients had significantly higher Gensini scores than SVD patients [20]. Univariate regression analysis further verified that Gensini score was independently associated with MVD.

The correlation between Gensini score and MVD has solid biological and clinical rationales. Although the Gensini score is an angiography-based evaluation index rather than a tomographic measurement, it comprehensively reflects the severity and distribution of coronary stenosis, and serves as a reliable surrogate indicator of total coronary atherosclerotic burden. Current clinical consensus emphasizes that total plaque burden and diffuse lesion distribution, rather than focal luminal stenosis alone, are core determinants of adverse cardiovascular prognosis. A review in the *European Heart Journal* pointed out that coronary atherosclerotic burden is a powerful predictor of major adverse cardiovascular events, and non-obstructive coronary disease involving more than four vascular segments carries a cardiovascular risk comparable to obstructive CHD [21]. A prospective Danish cohort study by Fuchs also confirmed that both obstructive and extensive diffuse coronary atherosclerosis significantly increased the risk of myocardial infarction, with the highest risk observed in patients with combined obstructive and extensive lesions [22]. Collectively, these findings validate our result that elevated Gensini score was positively correlated with MVD, indicating that angiographic total lesion burden can effectively reflect the complexity and severity of coronary artery disease.

Atherosclerosis is the core pathological basis of CHD progression. Emerging studies have confirmed that Beclin 1, a key autophagy regulatory protein, is closely involved in AS progression [23]. Our study found that serum Beclin 1 levels were gradually decreased in the control group, SVD group, and MVD group in

turn, with significant inter-group differences. In addition, stratified analysis based on Gensini score showed that patients with more severe coronary lesions (higher Gensini scores) had lower Beclin 1 levels. Further logistic regression analysis identified Beclin 1 as an independent protective factor against MVD, which may be attributed to its regulatory effects on autophagy activation and apoptotic inhibition.

Numerous studies have proven that Beclin 1-mediated autophagy plays a critical role in delaying atherosclerosis and alleviating coronary artery damage [7]. A study by Chen demonstrated that Tongxinluo, a traditional Chinese medicine, could inhibit atherosclerotic plaque progression by upregulating Beclin 1-dependent autophagy to reduce lipid accumulation in macrophages [24]. Ye et al. found that Beclin 1 knockdown inhibited vascular re-endothelialization and aggravated neointimal hyperplasia through mediating the crosstalk between autophagy and apoptosis [25]. Appropriate Beclin 1 expression also regulates vascular endothelial cell inflammation, oxidative stress and permeability, maintaining vascular endothelial homeostasis [26, 27]. A recent case-control study by Grazide reported that decreased circulating levels of autophagy-related proteins ATG5 and Beclin 1 were closely associated with acute myocardial infarction, suggesting that reduced peripheral Beclin 1 levels may reflect impaired autophagic flux in advanced coronary artery disease [28]. Our finding of reduced Beclin 1 levels in MVD patients is consistent with this conclusion, indicating that downregulated Beclin 1 may represent a maladaptive autophagic response to severe and diffuse coronary atherosclerotic lesions. Notably, the biological significance of circulating Beclin 1 in stable and unstable CHD remains uncertain. Further mechanistic studies combining plaque imaging, inflammatory phenotyping and long-term clinical outcomes are required to confirm whether Beclin 1 serves as a biomarker of atherosclerotic burden, plaque vulnerability or compensatory autophagic response.

The negative correlation between LDL-C and MVD observed in this study requires cautious and differentiated interpretation. Mechanistically, sustained elevated LDL-C is a well-established causal risk factor for arterial lipid deposition, plaque proliferation, and atherosclerotic cardiovascular events [29], and long-term LDL-C reduction can effectively decrease atherosclerotic burden. Therefore, the inverse association between LDL-C and MVD in our multivariate model does not indicate a protective effect of high LDL-C on diffuse coronary disease. This statistical phenomenon is attributed mainly to the limitations of cross-sectional study design. Single-point LDL-C detection at admission cannot reflect long-term cumulative lipid exposure. Patients with severe MVD usually receive standardized intensive lipid-lowering therapy and lifestyle intervention after symptom onset, resulting in reduced intraoperative LDL-C levels. In addition, traditional lipid risk factors cannot fully explain the heterogeneity of coronary atherosclerotic phenotypes, and residual confounding factors such as unrecorded medication use may affect the statistical results [30].

Several limitations should be considered when interpreting these findings. First, the modest sample size and class imbalance between groups may affect coefficient stability and precision. Second, all biomarkers were measured at a single time point; therefore, dynamic exposure history, particularly for LDL-C, could not be captured. Third, the regression model was developed in an observational setting and may still be influenced by residual confounding, unmeasured medication use, and disease-management history. Nevertheless, the use of Firth logistic regression was appropriate in this small-sample context and helps reduce bias caused by sparse data and separation. Overall, our findings support the view that MVD is best understood as a composite phenotype reflecting both anatomic atherosclerotic burden and underlying biological dysregulation, rather than as a purely angiographic descriptor.

In conclusion, the combined detection of Beclin 1, Gensini score, and LDL-C provides a reliable predictive tool for MVD.

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Disclosure of conflict of interest

None.

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