The Role of Small Dense Low-Density Lipoprotein Cholesterol in the Prediction of Acute Myocardial Infarction

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Research

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Abstract

Background: Acute myocardial infarction (AMI) is a common acute and severe cardiovascular disease. A growing body of evidence suggests that small dense low-density lipoprotein cholesterol (sdLDL-C) is associated with an increased risk of cardiovascular disease. This study aimed to evaluate the predictive value of different lipid indicators, particularly sdLDL-C, in the assessment of AMI.

Methods: We retrospectively reviewed the hospital database for all consecutive participants who underwent coronary angiography due to the experience of chest pain in our hospital from September 2019 to June 2020. The basic demographic and clinical data and laboratory assay results for all participants were collected and evaluated at admission. Statistical analysis was performed using SPSS version 26.0.

Results: A total of 216 patients with AMI, 154 patients with unstable angina pectoris (UAP) and 103 healthy subjects were included. The levels of LDL3-7 were significantly different among the three groups ($P<0.05$). Significant positive correlations were observed between the Gensini score and several variables, including hypertension and levels of glucose, sdLDL-C, TC, and LDL-C ($r > 0.1$, $P < 0.001$). The sdLDL-C level in the AMI group was significantly higher than that in the control group in individuals with normal LDL-C ($P < 0.001$). Based on the receiver operating characteristic (ROC) curves, the area under the curve (AUC) of sdLDL-C for AMI risk was 0.666, which was better than that of other lipids. Multivariate logistic regression analysis demonstrated that the sdLDL-C level was significantly correlated with AMI. A logistic regression model were established based on sdLDL-C and other variables to identify people at high cardiovascular risk, with an AUC of 0.868.

Conclusions: Increased sdLDL-C level was an independent risk factor for AMI. sdLDL-C may be a useful parameter for the assessment of AMI and help clinicians classify high-risk cardiovascular disease.

Introduction

Ischaemic heart disease, specifically acute myocardial infarction (AMI), is a leading cause of mortality and disability worldwide[1]. Hypercholesterolemia is an independent risk factor associated with the development of atherosclerosis and cardiovascular diseases. According to the latest guidelines, lowering levels of low-density lipoprotein cholesterol (LDL-C) to the target has been strongly recommended[2–4]. However, a portion of patients who achieved the appropriate LDL-C targets is still at high risk of incident cardiovascular events[5–7]. Several studies have proven that the residual risk may be related to the heterogeneity of LDL-C[8]. LDL-C represents a heterogeneous group of particles with different densities, apoprotein contents, and physical properties. LDL particles have been classified into two distinct phenotypes: Phenotype A, characterized by a higher proportion of large, more buoyant LDL particles (lbLDL), and pattern B, with a predominance of small dense LDL (sdLDL-C) particles[9, 10]. As a consequence of increased penetration of the arterial wall, lower binding affinity for the LDL receptor, prolonged plasma half-life, and lower resistance to oxidative stress, the particles of sdLDL-C have more

efficient pro-atherogenic effects than lbLDL[11, 12]. A higher sdLDL-C level has been reported to be associated with an increased risk of atherosclerotic cardiovascular disease[13]. The National Cholesterol Education Program (NCEP) has demonstrated that a high level of sdLDL-C is currently regarded as a risk factor for cardiovascular disease (CVD) and is considered to be a better risk predictor of atherosclerosis than LDL-C[14].

Regrettably, at present, very few studies have explored the role of sdLDL-C in the diagnosis and treatment of high cardiovascular risk. The present study aimed to determine the predictive value of different lipid indicators, particularly sdLDL-C, in the assessment of AMI.

Methods

Study Design and Patient Selection

We retrospectively reviewed the hospital database for all consecutive participants who underwent coronary angiography due to the experience of chest pain in the Affiliated Hospital of Chengde Medical University from September 2019 to June 2020. Ultimately, a total of 216 patients with the diagnosis of AMI, 154 with the diagnosis of UAP and 103 healthy subjects were included in the study. The inclusion criteria were as follows: participants underwent coronary angiography after admission. Participants were excluded for the following reasons: (1) renal dysfunction, receiving hemodialysis (2) severe hepatic disease and infectious disease (3) currently treated for malignancy (4) thyroid dysfunction (5) immune and hematopoietic disorders (6) connective tissue with coronary vasculitis (7) aortic dissection or hypertrophic cardiomyopathy. The diagnosis of AMI was based on the ESC Guidelines for the management of acute myocardial infarction: Briefly, acute myocardial infarction (MI) was defined as an elevation of cardiac troponin values with at least one value above the 99th percentile upper references with persistent chest discomfort or other symptoms suggestive of ischemia and ST-segment elevation in at least two contiguous leads as STEMI. In contrast, patients without ST-segment elevation at presentation are usually designated as having a non-ST-segment elevation myocardial infarction (MI) [1]. UAP was defined as the chest pain can also occur at rest, which is more severe and the duration is longer. There is a transient ST segment changed in the ECG when the chest pain occured but myocardial enzymes without changed [15]. Due to the retrospective study design, no informed consent was needed to include patients in the study.

Baseline Examination

The basic demographic, clinical data, and laboratory assays of all participants were collected and evaluated at admission. Hypertension was defined as systolic blood pressure above 140 mm Hg and /or diastolic blood pressure above 90 mmHg for three or more consecutive times [16].The diagnosis of Diabetes mellitus was defined as fasting plasma glucose levels ≥ 126 mg/dL, 2-h or casual glucose levels of at least 200 mg/dL, or currently use of medication for diabetes or insulin. The HbA1c calculated

with the following formula[17]: HbA1c (%) = 1.019×HbA1c(Japan Diabetes Society) (%)−0.25% by a National Glycohemoglobin Standardization Program. Smoking is defined as smoking more than one cigarette a day. The severity of coronary stenosis was evaluated by calculating the Gensini score[18].

Laboratory Tests

Fasting blood samples were obtained by venipuncture after the participants had fasted for at least 10 hours once upon admission and collected into an EDTA-containing tube. After the blood samples were centrifuged immediately at 3000 rpm for 10 min at 4°C to separate the serum. Total cholesterol (TC), triglyceride (TG), HDL-C, and lipoproteins were measured by standard laboratory procedures. The LDL-C subfraction analysis was detected by the Lipoprint LDL system, which including low-density lipoprotein (LDL) 1, 2, 3, 4, 5, 6, and 7 by high-resolution polyacrylamide gel electrophoresis[19]. According to their size and density, LDL 1 and 2 are defined as large LDLs, and LDL 3 to 7 are defined as sdLDLs[20].

Statistical Analysis

Statistical analysis was performed using SPSS Statistics version 26.0 software (IBM Corp. Armonk, New York, USA). Data were tested for normality by making P-P and Q-Q plots. Parametric statistics (t-test) were used for normally distributed data and expressed as median (standard deviation, SD). Nonparametric Mann–Whitney U test was used for non-normally distributed data and expressed as median (interquartile range, IQR)). Categorical variables were compared between the 2 groups using the Pearson $\chi 2$ test, continuity correction, and Fisher's exact 2-tailed test. If the data are not normally distributed, correlation analysis was performed using the Spearman correlation coefficient. Related data were presented as receiver operating characteristics (ROC) curves and area under the curve (AUC). The AUC value > 0.5 indicated better predictive values; the closer the AUC to 1, the better the model performance. The ability of sdLDL-C concentration and multi-index combination concentration to predict the AMI events by ROC curve. The independent variables with a univariate analysis result of $P < 0.05$were included in the Logistic regression analysis. Logistic regression models were constructed for the prediction of AMI. Statistical significance was determined P-value less than 0.05.

Results

Basic demographics, clinical data and laboratory assays

A total of 216 patients were included in the AMI group, 153 patients were included in the UA group, and 103 healthy subjects were included in the control group. Of the 472 participants who qualified for inclusion in this study, 314 were females and 158 were males. Significant differences were observed in gender, history of smoking, diabetes mellitus, levels of glucose, sdLDL-C, LDL-C, TC, and HDL between the AMI group and the control group ($P < 0.05$). There were significant differences in gender, hypertension, diabetes mellitus, and history of smoking between the UAP group and the control group. However, the

levels of sdLDL-C were not significantly different between the UAP group and the control group. Detailed statistics on basic demographics, clinical data and laboratory assay results for all participants are shown in Table 1.

Table 1
Clinical and laboratory characteristics in all subjects

Variables	AMI (n = 216)	UA (n = 153)	Control (n = l03)	Pvalue
Age (years)	57.61 ± 10.9	60.47 ± 8.5	57.9 ± 9.4	0.019
Gender	173 (80.1)**	102 (66.7)**	39 (37.9)	0.003
Hypertension (%)	110 (51.0)	90 (58.8) *	42 (40.8)	0.123
Diabetes mellitus (%)	38 (17.6)**	36 (23.4) **	5 (4.9)	0.164
History of smoking (%)	130 (60.2)**	65 (42.2) **	23 (22.3)	0.001
Family history of CAD (%)	23 (10.6)	6 (3.9)	7 (6.8)	0.019
sdLDL-C(mg/dL)	18 (9,34.75)**	12 (6,22)	12 (7,23)	< 0.001
LDL-C (mmol/L)	2.62 (1.92,3.25) **	2.13 (1.52,2.79)*	2.37 (1.68,2.98)	< 0.002
TC (mmol/L)	4.46 (3.8,5.1)*	4.06 (3.42,4.87)*	4.21 (3.67,4.84)	< 0.003
TG (mmol/L)	1.31 (0.8,2.11)	1.57 (1.03,2.45)	1.52 (0.97,2.21)	< 0.004
HDL (mmol/L)	1.04 (0.9,1.26)*	1.01 (0.9,1.21)**	1.07 (0.96,1.28)	0.116
GLU (mmol/L)	6.63 (5.51,8.71) **	6.19 (5.19,7.61)*	5.82 (5.13,7.03)	< 0.001
Comparison the control group,*p < 0.05**p < 0.001				

Comparison Of The Sdldl-c Subgroups In Different Groups

A comparison of the sdLDL-C subgroups in the different groups is shown in Table 2. The levels of LDL3-7 were significantly different among the three groups (P < 0.05). Notably, the serum levels of LDL3 and LDL4 in the AMI group were higher than those in the other groups. However, there were no significant differences in the levels of LDL-1 or LDL-2 between the different groups.

Table 2
LDL subtractions in difference group

LDLsubclasses	AMI (n = 216)	UA (n = 153)	Control (n = l03)	P-value
LDL-1(mg/dL)	20 (11.3,37.8)	22.5 (16,34)	24 (17,34)	0.258
LDL-2(mg/dL)	24.5 (15,39)	21 (16,31.25)	24 (16,32)	0.245
LDL-3(mg/dL)	14 (8,21)	9 (4,15.5)	10 (6,16)	< 0.001
LDL-4(mg/dL)	4 (1,10)	2 (0,4)	2 (0,6)	< 0.001
LDL-5(mg/dL)	0 (0,3)	0 (0,0)	0 (0,0)	< 0.001
LDL-6(mg/dL)	0 (0,0)	0 (0,0)	0 (0,0)	< 0.001
LDL-7(mg/dL)	0 (0,0)	0 (0,0)	0 (0,0)	0.018

Correlations Of Clinical Characteristics And Gensini Scores

Spearman correlation coefficients were calculated to determine the correlation between the clinical characteristics and Gensini scores of the three groups, and a heatmap was drawn accordingly (Fig. 1). There were significant positive correlations between the Gensini score and several variables, including hypertension and levels of glucose, sdLDL-C, TC, and LDL-C ($r > 0.1$, $P < 0.001$).

Correlation of the sdLDL-C level with other serum lipid parameters

As shown in Fig. 2 and Table 3, the Spearman correlation coefficient was used to assess the correlations of the sdLDL-C concentration with serum lipids. Significant positive correlations were observed between the sdLDL-C level and serum lipids, including TC, TG, LDL-C and HDL-C levels. The sdLDL-C level was found to be positively correlated with TC, TG and LDL-C levels ($r = 0.251$, $P < 0.001$, $r = 0.144$, $P = 0.008$, $r = 0.351$, $P < 0.001$). There was a significant inverse correlation between sdLDL-C and HDL levels ($r=-0.248$, $P < 0.001$).

Table 3
Correlation of sdLDL-C level with serum lipids

Serum lipids	sdLDL-C	
	Pearson R	P-value
TC	0.251	< 0.001
TG	0.144	0.008
LDL-C	0.351	< 0.001
HDL	-0.248	< 0.001

Comparison of sdLDL levels between the AMI and control group in participants with normal LDL-C

As shown in Table 4 and Fig. 3, in participants with a normal LDL-C (LDL-C ≤ 3.36mmol/L), the sdLDL-C level in the AMI group was significantly higher than that in the control group (P < 0.001).

Table 4
Comparison of sdLDL levels between the AMI and control group in participants with normal LDL-C (LDL-C ≤ 3.36mmol/L)

	AMI (n = 137)	Control (n = 112)	Pvalue
sdLDL-C	18 (10.5,41)	14 (7,24)	0.001

Exploration of risk factors for AMI by ROC curve analysis

ROC curve analysis was performed to evaluate the predictive value of sdLDL-C and other serum lipids, including LDL-C and TC, and the results are depicted in Fig. 4. The results indicated that sdLDL-C presented with a higher AUC than other serum lipid parameters [AUC (95% CI): sdLDL-C, 0.666]. The ROC curve of LDL-C and TC levels for AMI was 0.621 and 0.576, respectively. The best cut-off value of sdLDL-C was 24.5 mg/dL, with a sensitivity and specificity of 47.2% and 79.6%, respectively.

Multivariate Logistic Regression Analysis Of Risk Factors For Ami

The independent variables with a univariate analysis result of P < 0.05 were included in the multivariate logistic regression analysis. Eight variables were included in the multivariate analysis, including gender, diabetes mellitus, history of smoking, and levels of sdLDL-C, TC, HDL-C, LDL-C, and glucose, and the results are shown in Table 5. The present study findings indicated that increased sdLDL-C levels were an independent risk factor for AMI [OR (95% CI): 1.029, 1.01-1.048, P = 0.003]. In addition, there were

variables deemed to be risk factors with an odds ratio (OR) greater than 1 and P-values less than 0.05, including gender, LDL-C level and glucose level. No significant differences existed between AMI and other variables.

Table 5
Multivariable Logistic Regression Analysis of Risk Factors for AMI

Variable	OR Value	95% CI	P value
sdLDL-C	1.029	1.010–1.048	0.002 *
TC	0.689	0.406–1.171	0.169
HDL-C	2.145	0.660–6.972	0.204
LDL-C	2.521	1.436–4.424	0.001 *
GLU	1.486	1.268–1.742	< 0.001 *
Gender	5.952	2.705–13.907	< 0.001 *
History of smoking	2.089	0.976–4.471	0.058
sdLDL-C small dense Low density lipoprotein cholesterol, TC total cholesterol, HDL-C high-density lipoproteins cholesterol, LDL low-density lipoprotein, Glu glucose, OR odds ratio, CI confidence interval			
*p < 0.05			

A logistic regression model was performed to assess the AMI and effectively distinguish high-risk from low-risk patients with cardiovascular diseases, with an AUC of 0.868 (Fig. 5). Conventional cardiovascular and lipid risk factors included gender, history of smoking, diabetes mellitus, and levels of glucose, sdLDL-C, TC, HDL-C, and LDL-C.

Discussion

AMI is a serious cardiovascular emergency; thus, screening and early detection of high-risk populations are therefore crucial[1]. Previous reports suggested that sdLDL-C are an independent risk factor and more predictive than LDL-C for the assessment of CVD and metabolic syndrome (MS) [21–26]. A large prospective population-based cohort study performed in 2014 by Hoogeveen et al. indicated that sdLDL-C was positively associated with atherosclerosis[27]. Arain et al.[8] provided evidence for the association of sdLDL-C with the risk of cardiovascular events in the general population. The level of sdLDL-C is significantly elevated in individuals with prediabetes (Pre-DM) and DM[28–30]. A recent study assessed the association of sdLDL levels with major adverse cardiovascular events (MACEs) in DM patients and indicated that sdLDL was a useful biomarker for coronary artery disease (CAD) in DM patients [31].

To date, although sdLDL-C has been considered a better biomarker for predicting CVD,

very few studies have explored the role of sdLDL-C in the assessment of AMI. The results of our study demonstrated that sdLDL-C levels in AMI patients were significantly higher than that in the healthy participants. However, there were no significant differences between the UAP patients and the healthy participants. In a multivariate logistic model, we also found that significantly increased sdLDL-C levels showed a significantly increased risk of AMI. sdLDL-C was an independent risk factor for the development of AMI. Moreover, the sdLDL-C AUC of AMI was superior to that of other lipids, which indicated the prediction value of sdLDL-C is better than other lipids. Of note, in participants with LDL-C within the normal range, the sdLDL-C level in the AMI group was significantly higher than that in the control group. Therefore, sdLDL-C is a critical predictive factor of AMI, especially for individuals with normal LDL-C.

Several previous studies found that sdLDL levels were significantly associated with Gensini scores[32]. Zhao xi et al. [10] indicated that sdLDL-C could be an useful marker for predicting the severity of CAD in untreated Chinese patients. In agreement with previous studies, our results showed a significant positive correlation between sdLDL-C levels and Gensini scores. The sdLDL-C level was associated with an increase in the severity of coronary artery stenosis. LDL3 and LDL4 are subtypes with higher concentrations of sdLDL-C. in our research, we also found a significant positive correlation between LDL3 and LDL4 levels and the severity of coronary artery stenosis. Our study illustrated that the sdLDL-C level was positively correlated with traditional cardiovascular risk factors, including TC, TG, and LDL-C, which is consistent with the results of a previous study[33]. To identify people at high cardiovascular risk, we constructed a model that included the evaluation of clinical variables in cardiovascular risk factors. Compared with the single risk factor model, the multiple risk factor model has better predictive value for CVD.

The main limitations of this study were as follows: First, this was a retrospective study, and it was difficult to assess the relationship between sdLDL-C and AMI progression. Second, our study has a relatively small sample size. Therefore, future research based on a large sample that aims to evaluate the predictive value of the sdLDL-C level for AMI events is needed.

Conclusions

This study indicated that sdLDL-C was an independent risk factor for the development of AMI. Our findings may help clinicians classify high-risk cardiovascular disease. Further study with a large sample size is necessary in the future.

Abbreviations

AIM
Acute myocardial infarction;
sdLDL-C
Small dense Low density lipoprotein cholesterol;

UAP
Unstable angina pectoris
GLU
Glucose;
TC
Total cholesterol;
LDL-C
Low density lipoprotein cholesterol;
TG
Triglyceride;
HDL-C
High-density lipoproteins cholesterol;
LbLDL
Buoyant LDL;
MACEs
Major adverse cardiovascular events;
NCEP III
National Cholesterol Education Program Adult Treatment Panel III;
AUC
Area under the curve;
ROC
Receiver operating characteristic

Declarations

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Authors' contributions

Ke-Lin Ma managed the case and edited the manuscript; Yi-Xiang Liu and Huan Lian collection of the data and assistance in data analysis; Sun LX and Liu Chao contributed to design of the study; Zhang Ying assisted with editing and critical revision of the final manuscript; All authors read and approved the final manuscript.

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Availability of data and materials

The data is dependable in this article and is available from the corresponding authors.

Ethics approval and consent to participate

This study was a retrospective study. No ethics committee certification is required.

Consent for publication

Written informed consent for publication was obtained from all participants

Competing interests

The authors declare that they have no conflict of interest.

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Figures

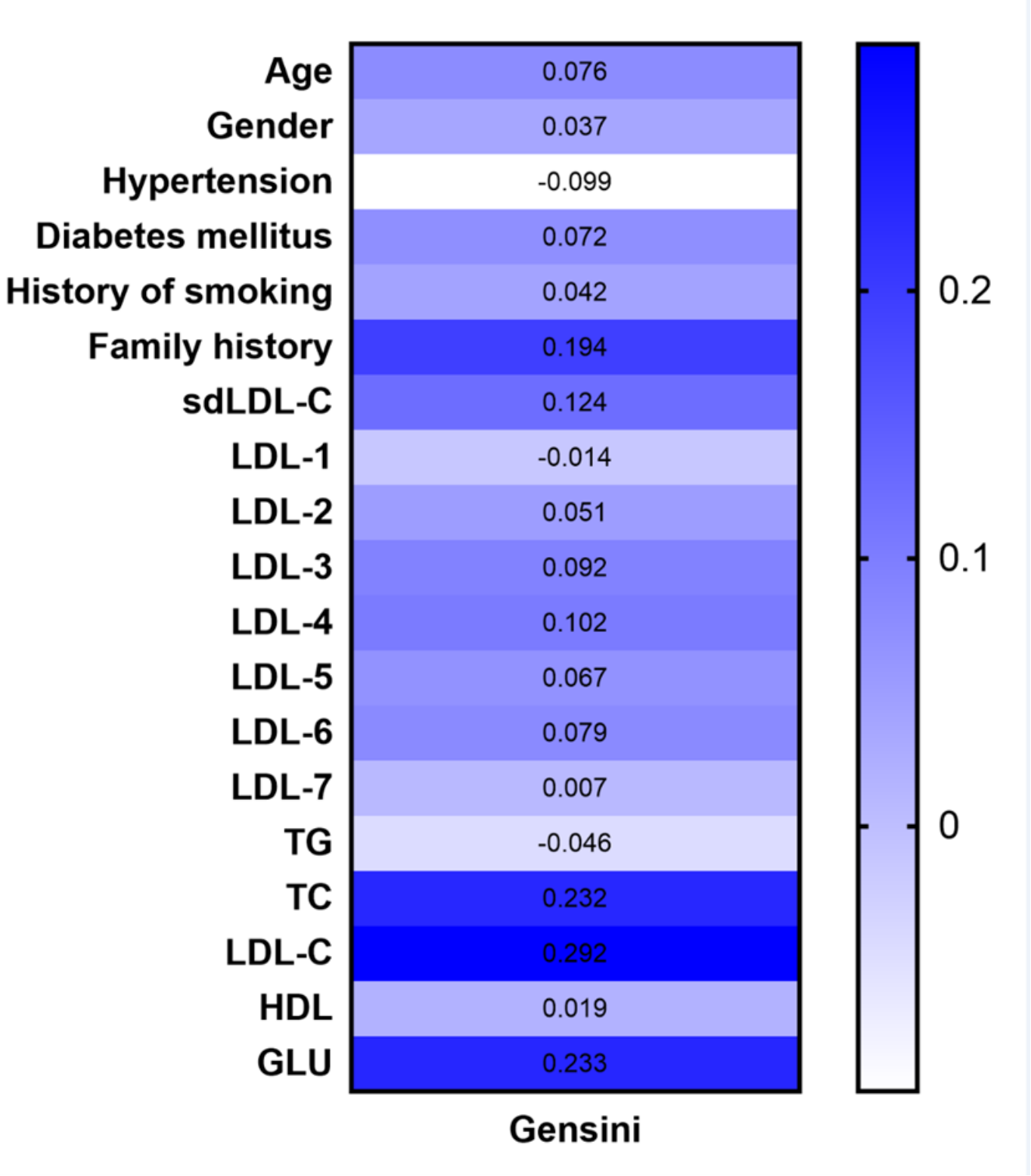

Figure 1

Correlations of clinical characteristics and Gensini scores The heatmap detailed description the correlation between the clinical characteristics and Gensini scores of the three groups. There were significant positive correlations between the Gensini score and several variables, including hypertension and levels of glucose, sdLDL-C, TC, and LDL-C ($r > 0.1$, $P < 0.001$).

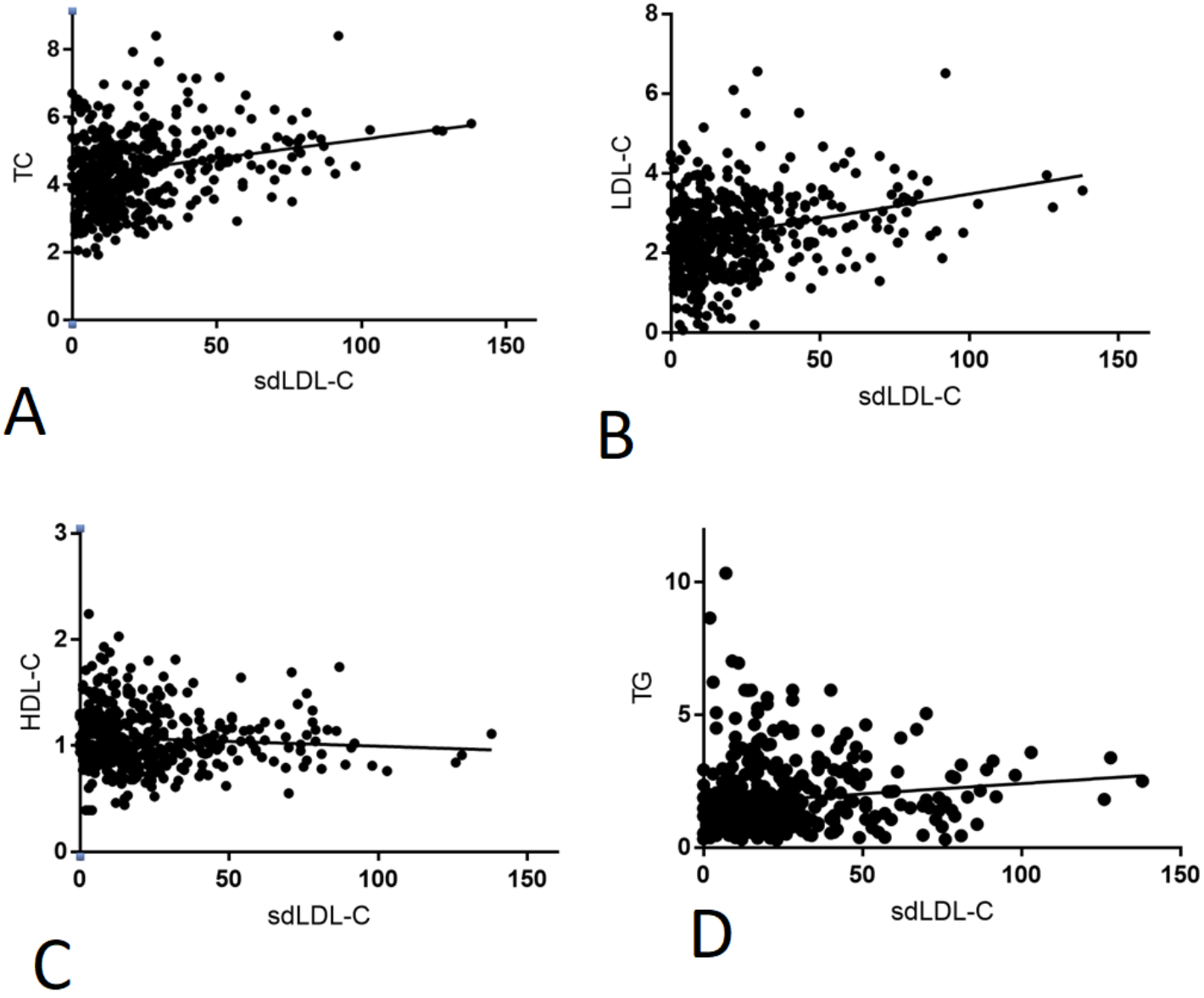

Figure 2

Correlation of sdLDL-C with serum lipids A detailed description the correlations of the sdLDL-C concentration with other serum lipids in a series of illustrations. The sdLDL-C level was found to be positively correlated with TC, TG and LDL-C levels (r=0.251, P<0.001, r=0.144, P=0.008, r=0.351, P<0.001). There was a significant inverse correlation between sdLDL-C and HDL levels (r=-0.248, P<0.001).

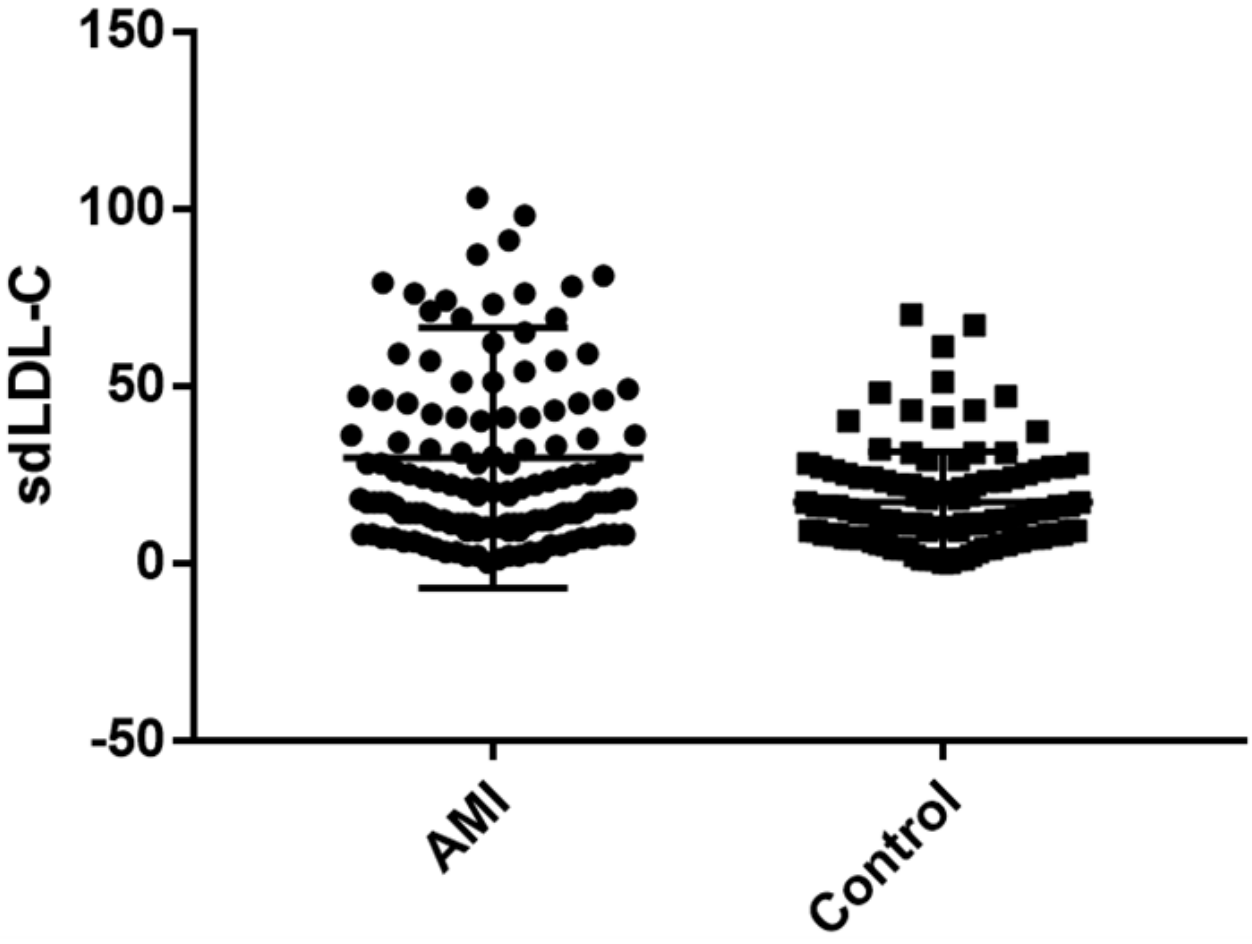

Figure 3

Comparison of sdLDL levels between the AMI and control group in participants with normal LDL-C (LDL-C≤3.36mmol/L)

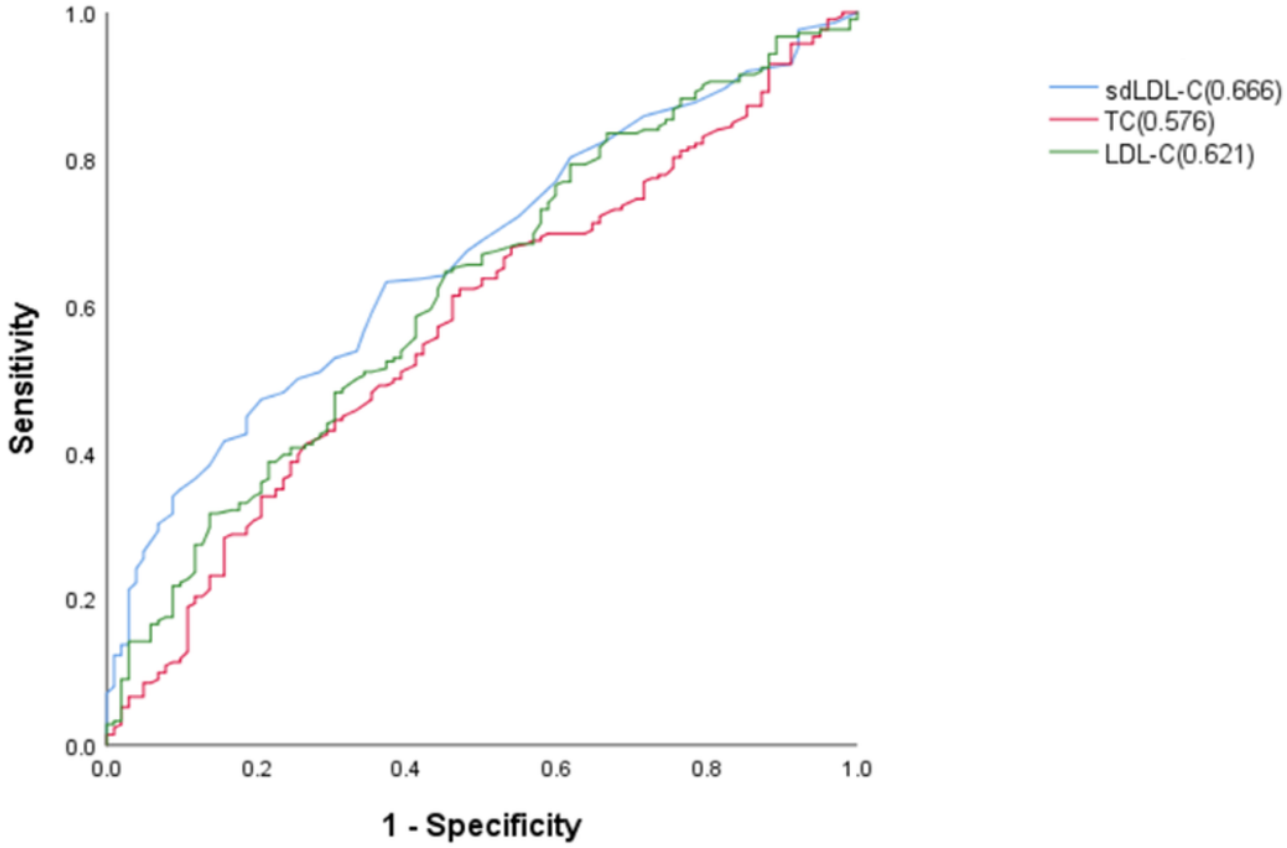

Figure 4

Predictive values of sdLDL-C and traditional lipids risk factors for AMI The ROC curve is to evaluate the predictive value of sdLDL-C and traditional lipid risk factors including LDL-C and TC levels for AMI. The present study revealed that sdLDL-C showed a higher AUC than other serum lipid parameters [AUC (95% CI): sdLDL-C, 0.666].

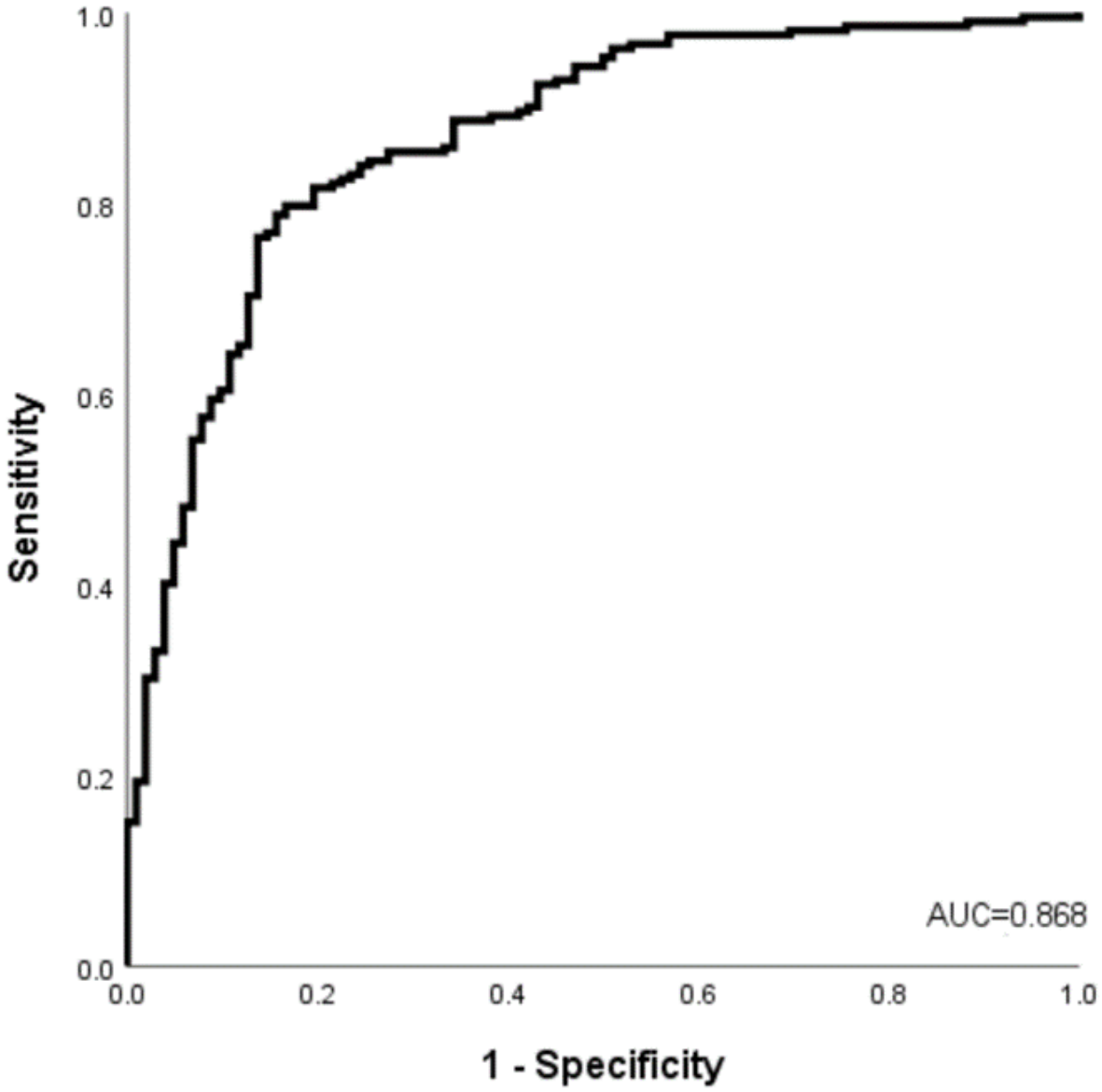

Figure 5

An established model for prediction of AMI risk We constructed a model with an AUC of 0.868 that included the evaluation of clinical parameters in cardiovascular risk factors including gender, history of smoking, diabetes mellitus, and levels of glucose, sdLDL-C, TC, HDL-C, and LDL-C. Compared with the single risk factor model, the multiple risk factor model has better predictive value for CVD.