

RESEARCH ARTICLE

Evaluation of small dense low-density lipoprotein concentration for predicting the risk of acute coronary syndrome in Chinese population

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Abstract

Background: Acute coronary syndrome (ACS) is the leading cause of death in developing and developed countries, yet assessing the risk of its development remains challenging. Several lines of evidence indicate that small, dense low-density lipoproteins (sd-LDL) are associated with increased cardiovascular disease risk. We aim to evaluate sd-LDL concentration for predicting the risk of ACS in Chinese population.

Methods: Baseline characteristics of 121 patients with ACS and 172 healthy controls were obtained. Plasma sd-LDL-C was measured using homogeneous assay, and the proportion of sd-LDL-C in LDL-C was detected.

Results: There was gender and age effect on the sd-LDL-C concentration and sd-LDL-C/LDL-C ratio among healthy subjects. Elevated sd-LDL-C concentrations and sd-LDL-C/LDL-C ratio were observed in ACS patients with unstable angina pectoris (UAP), non-ST-segment elevation myocardial infarction (STEMI), and ST-segment elevation myocardial infarction (NSTEMI) compared with healthy controls ($P < .05$); however, there were no differences among ACS groups. According to Pearson's correlation coefficient analyses, sd-LDL-C concentration and sd-LDL-C/LDL-C ratio were positively correlated with triglyceride (TG) and LDL-C concentrations ($P < .05$) and negatively correlated with high-density lipoprotein (HDL) concentration ($P < .05$). Based on the receiver operating characteristic (ROC) curves, the cutoff values of sd-LDL-C and sd-LDL-C/LDL-C ratio for the prediction of ACS were 1.06 mmol/L and 34.55%, respectively. Multivariate logistic regression analysis demonstrated that the sd-LDL-C/LDL-C ratio, but not sd-LDL-C concentration, was significantly associated with ACS events [OR (95% CI): 1.24, 1.11-1.38, $P < .001$].

Conclusions: The sd-LDL-C/LDL-C ratio may be associated with an increased risk of developing ACS in Chinese population.

Abbreviations: ACS, acute coronary syndrome; AMI, acute myocardial infarction; AUC, area under the curve; CAD, coronary artery disease; CI, confidence intervals; CK-MB, creatine kinase MB fraction; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; hs-cTnI, high-sensitive cardiac troponin I; LDL, low-density lipoprotein; MI, myocardial infarction; MYO, myoglobin; NMR, nuclear magnetic resonance; NSTEMI, non-ST-segment elevation myocardial infarction; OR, odds ratio; ROC, receiver operating characteristic; sd-LDL, small dense LDL; STEMI, ST-segment elevation myocardial infarction; TG, triglyceride; UAP, unstable angina pectoris.

Wu, Yu, and Tong equally contributed to this work.

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KEYWORDS

acute coronary syndrome, Chinese population, risk factor, small dense LDL

1 | INTRODUCTION

Acute coronary syndrome (ACS) is a more severe type of coronary artery disease (CAD), which contributed to a major cause of mortality and morbidity in developed and developing countries. This syndrome consists of unstable angina pectoris (UAP), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI).¹ There is accumulating evidence that ACS is related to recent activation of the immune-mediated inflammatory process associated with atherosclerotic plaques.² Low-density lipoprotein (LDL) is the principal cholesterol-carrying lipoprotein in human plasma and, as such, contributes significantly to the morbidity and mortality of CAD.³ Therefore, European Society of Cardiology (ESC) guidelines for preventing ACS recommend decreasing low-density lipoprotein cholesterol (LDL-C) to a target level of <1.8 mmol/L.⁴ Large prospective cohort studies comparing LDL particle number with LDL-C level have demonstrated that the LDL-C particle number was more strongly associated with the risk of CAD than the LDL-C level.^{5,6} Therefore, evaluation of LDL levels cannot identify all individuals with incident CAD, as many CAD events occur in subjects with normal LDL levels.⁷

Low-density lipoprotein is composed of heterogeneous particles that differ in density, size, and chemical composition. LDL particles are divided into 2 distinct phenotypes: pattern A, with a higher proportion of large, more buoyant LDL particles (Ib-LDL), and pattern B, with a predominance of small dense LDL (sd-LDL) particles.⁸ sd-LDL particles are considered to be highly atherogenic as a result of higher penetration into the arterial wall, lower binding affinity for the LDL receptor, prolonged plasma half-life, and lower resistance to oxidative stress compared with buoyant LDL.⁹ Using LDL-C to evaluate cholesterol-related CAD risk will underestimate actual risk in individuals who have optimal LDL-C levels but high levels of sd-LDL-C.¹⁰ Due to the atherogenic properties of sd-LDL, its measurement may be useful for risk assessment.

Small dense low-density lipoprotein has been found to be associated with increased risk of cardiovascular disease in cross-sectional studies and prospective observational studies using traditional measurement methods.¹¹⁻¹⁵ However, to date, few studies have explored the role of sd-LDL-C in the diagnosis and treatment of ACS. Fukushima et al¹⁶ found that the sd-LDL-C concentration was significantly higher in patients with ACS compared with controls, especially those with metabolic syndrome, in addition, the reduction in sd-LDL-C by atorvastatin was much more greater than LDL-C in patients with ACS, which indicated that sd-LDL-C is a superior therapeutic marker of statin treatment in patients with ACS. In general, Chinese patients typically have lower baseline levels of LDL-C than the patients of western countries.¹⁷ Because of the complication of pathophysiological processes of atherothrombosis and racial differences, whether sd-LDL-C concentration or the sd-LDL-C/LDL-C

ratio is a better predictor of ACS risk than LDL-C concentration or other traditional cardiovascular risk factors in Chinese population remains unknown.

2 | MATERIALS AND METHODS

2.1 | Study population

This study enrolled one hundred and seventy-two healthy subjects who were randomly selected from consecutive subjects visiting the Guangzhou First People's Hospital for an annual health check-up from March 2016 to February 2017. The inclusion criteria of healthy participants were as follows: (a) All participants were native Chinese aged 22-76 years old; and (b) All participants did not have a history of CAD, thromboembolic disease, peripheral arterial disease, malignancy, infectious disease, liver or renal diseases, endocrine diseases, dyslipidemia, or diabetes mellitus. All healthy subjects were divided into groups according to age (20-29, 30-39, 40-49, 50-59, and ≥ 60 years old) and sex (male and female).

Patients with ACS who satisfied all criteria for inclusion were selected. The patients with ACS enrolled in the present study had UAP (31 men and 17 women), NSTEMI (23 men and six women), and STEMI (37 men and seven women). ACS was diagnosed according to criteria established by the European Society of Cardiology^{18,19}: Briefly, acute myocardial infarction (MI) was defined as a typical rise, which was defined as >99% of normal levels [troponin T > 0.05 ng/mL; creatine kinase MB fraction (CK-MB) >10 ng/mL], and gradual fall of troponin, or a more rapid rise and fall of CK-MB, with at least one of the following: acute onset of typical ischemic chest pain; some Q waves in V1-V3, 30-ms Q waves ≥ 1 mm in two contiguous leads; ST-segment elevation or depression in ≥ 2 leads, ≥ 0.2 mV in V1-V3, >0.1 mV in other leads. UAP was defined as a history of new-onset, more frequent, more persistent or resting episodes of chest pain without typical changes in myocardial enzymes but with ECG evidence of myocardial ischemia (transient ST-segment displacement >0.1 mV during chest pain).

This study was carried out in accordance with the principles of the Declaration of Helsinki and was approved by the ethics committees of Guangzhou First People's Hospital.

2.2 | Baseline examination

Fasting blood samples were obtained by venipuncture after the participants had fasted for at least 10 hours and centrifuged immediately. The diagnosis of hypertension was based on a history of hypertension, systolic blood pressure above 140 mm Hg, or diastolic blood pressure above 90 mm Hg. The average of the second and third measurements of blood pressure was used for analysis. Diabetes mellitus was defined as a fasting glucose level ≥ 7.0 mmol/L (126 mg/dL) or a self-reported

TABLE 1 Baseline characteristics of ACS patients and healthy subjects

Characteristics	Healthy subjects	ACS patients			P value
		UAP	STEMI	NSTEMI	
Patients—no. (%)	172	48 (39.7)	44 (36.3)	29 (24.0)	
Age—y	42.3 ± 16.7	65.70 ± 1.60	64.44 ± 2.10	63.93 ± 2.18	NS
Male sex—no. (%)	77 (44.8)	33 (68.8)	33 (75.0)	23 (79.3)	NS
Risk factors					
Hypertension	/	33 (68.8)	22 (50.0)	17 (58.6)	0.048
Diabetes mellitus	/	14 (29.2)	13 (29.5)	9 (31.0)	NS
History of smoking	/	16 (33.3)	17 (38.6)	12 (41.4)	NS
Laboratory values on admission					
Myoglobin—ng/mL	54.7 ± 2.9	134.7 ± 3.6	144.8 ± 28.6	138.1 ± 19.1	0.037
Creatine kinase MB—ng/mL	1.9 ± 0.2	2.4 ± 0.3	19.6 ± 7.6	11.0 ± 2.4	0.015
Creatinine—μmol/L	75.4 ± 4.3	95.3 ± 5.3	105.1 ± 14.6	111.1 ± 20.9	NS
Hs-cTnI—ng/mL	0.031 ± 0.012	0.048 ± 0.020	1.982 ± 0.877	1.184 ± 0.378	0.003
Triglyceride—mmol/L	1.2 ± 0.1	2.0 ± 0.4	1.5 ± 0.1	1.9 ± 0.3	NS
HDL-C—mmol/L	1.1 ± 0.1	1.2 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	NS
LDL-C—mmol/L	1.7 ± 0.1	2.4 ± 0.1	3.0 ± 0.1	2.9 ± 0.2	NS

Note: Values are mean ± SD or percent.

Abbreviation: NS, Not Significant.

history of physician-diagnosed diabetes or treatment for diabetes. Information on smoking status and other medical histories of the patients were obtained through surveys by a well-trained nurse.

2.3 | Laboratory measurements

Plasma fasting blood glucose (FBG), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and LDL cholesterol (LDL-C) concentrations were measured by standard laboratory procedures in an automatic biochemistry analyzer (AU5800; Beckman Coulter) using detection kits (Beckman Coulter). In addition, plasma CK-MB, myoglobin (MYO), and high-sensitive cardiac troponin I (hs-cTnI) were measured by a UniCel Dxl 800 analyzer (Beckman Coulter) with commercial detection kits (Beckman Coulter).

For this study, we used archived plasma samples of healthy controls and patients with ACS that had been frozen at -80°C and never previously thawed. The determination of sd-LDL-C concentrations was performed by a fully automated homogeneous method (Denka Seiken Co., Ltd.) in an automated biochemistry analyzer (AU5800; Beckman Coulter) as previously described.²⁰

The ratio of sd-LDL-C/LDL-C was calculated as measured sd-LDL-C (mmol/L)/ LDL-C (mmol/L).¹⁸ All the laboratory measurements of patients with ACS and healthy subjects were under no treatment after admission.

2.4 | Statistical analysis

Statistical analyses were conducted with SPSSII for Windows (19.0). Continuous data are presented as the mean ± SD and compared with

Student's *t* test. Correlation analyses for non-parametric (Spearman's Rho) data were performed to establish relationships between sd-LDL-C concentration or the sd-LDL-C/LDL-C ratio and traditional cardiovascular risk factors. A one-way analysis of variance (ANOVA) and Fisher's protected least significant difference were used to compare the mean values of sd-LDL-C and the sd-LDL-C/LDL-C ratio among groups. Receiver operating characteristic (ROC) curve analysis was used to determine the ability of sd-LDL-C concentration, sd-LDL-C/LDL-C ratio, and LDL-C concentration to predict ACS events. To examine the association of sd-LDL-C and the sd-LDL-C/LDL-C ratio with ACS events, we performed a multivariate logistic regression analysis; all odds ratios (ORs) are presented with their 95% confidence intervals (CIs). $P < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Baseline characteristics

Baseline characteristics of all patients with ACS and healthy subjects at admission to the hospital are provided in Table 1. The mean ages of the patients in the UAP, STEMI, and NSTEMI groups were 65.70, 64.44, and 63.93 years, respectively. All the study participants were Chinese, and over 60% was male.

3.2 | sd-LDL-C concentrations and sd-LDL-C/LDL-C ratios in healthy subjects

The precision and accuracy of the automated homogeneous assay were evaluated by analyzing 20 replicates of quantitation standard

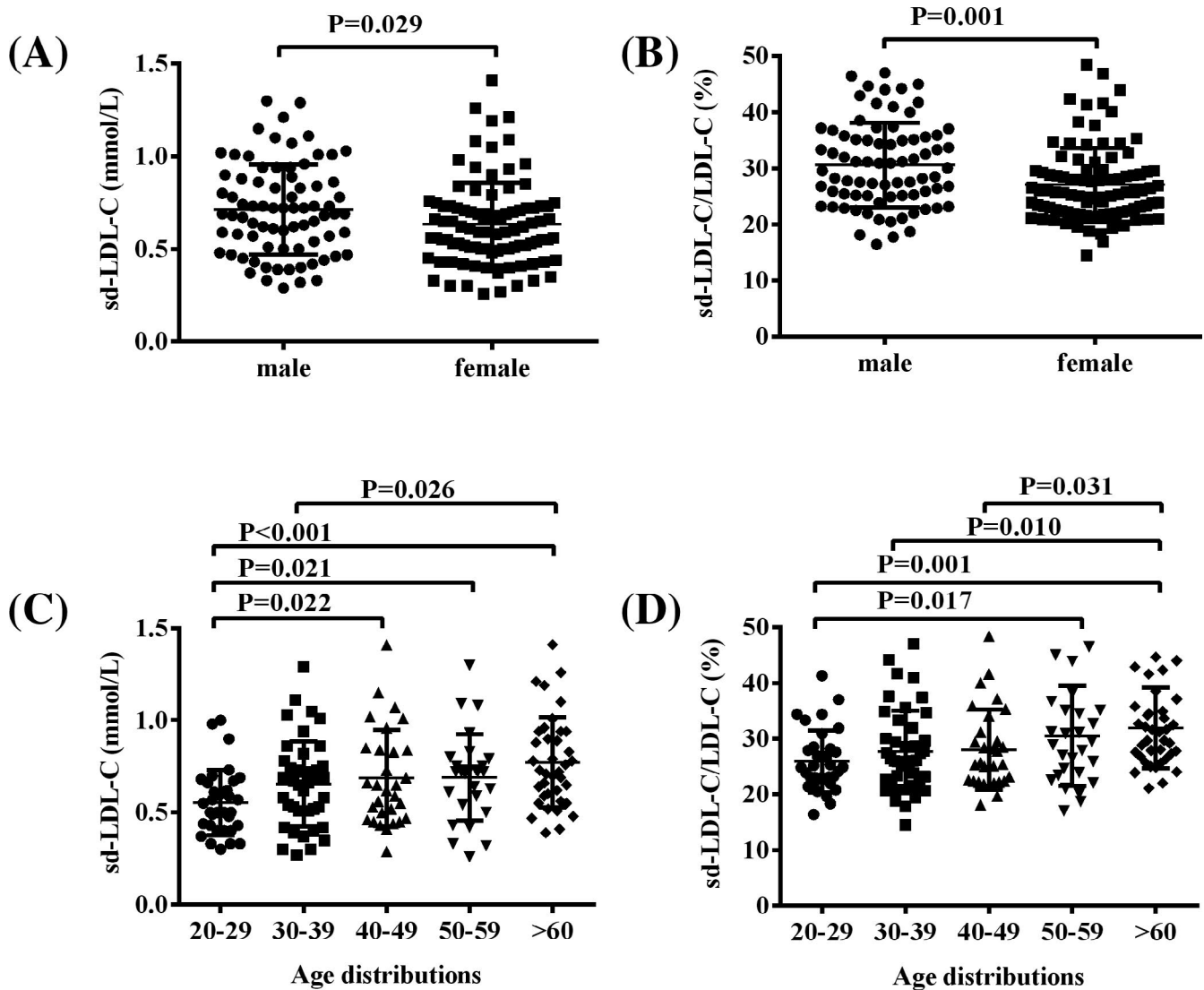


FIGURE 1 The concentration of sd-LDL-C and the sd-LDL-C/LDL-C ratio in healthy subject. A, B, Gender difference between healthy males and females at the concentration of sd-LDL-C and the sd-LDL-C/LDL-C ratio. C, D, Age difference between healthy males and females at the concentration of sd-LDL-C and the sd-LDL-C/LDL-C ratio

samples before this study. The precision (CV %) of this method was 2.1%, and the diagnostic accuracy was 96.9% (data not shown), which showed similar diagnostic performance as previous study.¹⁹

One hundred and seventy-two subjects were classified into the male and female groups. The age of the subjects ranged from 22 to 76 years old, and the mean age was 42.3 ± 16.7 years. To determine whether there was an age or a gender difference, we first compared the sd-LDL-C concentration and sd-LDL-C/LDL-C ratio between females and males (Figure 1A,B) and then separated the healthy female and male participants into five age groups (Figure 1C,D). The sd-LDL-C concentration was significantly higher in males than in females (0.71 ± 0.24 vs 0.63 ± 0.22 mmol/L, $P = .029$); similarly, the sd-LDL-C/LDL-C ratio was significantly higher in males than in females (30.61 ± 7.51 vs $27.08 \pm 6.59\%$, $P = .001$). In addition, the sd-LDL-C concentration was significantly higher in the age groups of 40-49, 50-59, and above 60 years than in the age group of 20-29 years (0.68 ± 0.26 , 0.69 ± 0.23 , and 0.77 ± 0.25

vs 0.55 ± 0.18 mmol/L; $P = .022$, $.021$, and $<.001$, respectively). The sd-LDL-C/LDL-C ratio in the age groups of 50-59 and above 60 years was significantly higher than that in the 20-29-year age group (30.48 ± 9.01 and 31.89 ± 7.27 vs $25.95 \pm 5.58\%$; $P = .017$ and $.001$, respectively). Additionally, the sd-LDL-C/LDL-C ratio in the above-60-years age group was significantly higher than that in the 30- to 39- and 40- to 49-year age groups (27.64 ± 7.40 and 28.00 ± 7.20 vs $30.48 \pm 9.01\%$; $P = .010$ and $.031$, respectively).

3.3 | Association of sd-LDL-C and the sd-LDL-C/LDL-C ratio with cardiovascular risk factors

The correlations of the sd-LDL-C concentration and sd-LDL-C/LDL-C ratio with various traditional cardiovascular risk factors are shown in Table 2. Strong positive correlations of sd-LDL-C concentration and the sd-LDL-C/LDL-C ratio with lipid risk factors, such as log triglycerides ($P < .001$ and $P < .001$, respectively) and LDL-C ($P = .003$ and

$P < .001$, respectively), were observed. In addition, HDL-C concentration showed a negative correlation with sd-LDL-C concentration and the sd-LDL-C/LDL-C ratio ($P = .013$ and $P < .001$, respectively). Additionally, hs-cTnI was not significantly correlated with sd-LDL-C concentration and the sd-LDL-C/LDL-C ratio.

3.4 | sd-LDL-C concentrations and ACS events

To eliminate the effects of gender and age, we selected the group of above 50 years old of healthy subjects as normal control and divided them into male and female groups. Among all the male participants, the mean baseline plasma sd-LDL-C concentration was 0.72 (healthy control), 1.09 (UAP), 1.30 (STEMI), and 1.44 (NSTEMI) mmol/L, and the mean sd-LDL-C/LDL-C ratio was 30.27% (healthy control), 47.26% (UAP), 40.04% (STEMI), and 42.81% (NSTEMI). Among all the female participants, the mean baseline plasma sd-LDL-C concentration was 0.62 (healthy control), 1.03 (UAP), 1.17 (STEMI), and 1.14 (NSTEMI) mmol/L, and the mean sd-LDL-C/LDL-C ratio was 26.71% (healthy control), 41.41% (UAP), 35.25% (STEMI), and 36.87% (NSTEMI) (Figure 2A,B). sd-LDL-C concentrations and sd-LDL-C/LDL-C ratios were significantly higher in ACS patients with UAP, STEMI, and NSTEMI than in healthy controls. In this study, we aimed to determine a cutoff value for sd-LDL-C concentration and the sd-LDL-C/LDL-C ratio that could predict ACS. ROC analysis showed that the area under the curve (AUC) of the sd-LDL-C/LDL-C ratio was highest, demonstrating that the sd-LDL-C/LDL-C ratio was a more valuable predictor of ACS: [AUC (95% CI): sd-LDL-C/LDL-C ratio, 0.89, 0.84-0.93, $P < .001$; sd-LDL-C concentration, 0.85, 0.80-0.90, $P < .001$; LDL-C, 0.66, 0.60-0.72, $P < .001$] (Figure 2C). However, there was no significant difference in the AUC between the sd-LDL-C concentration and sd-LDL-C/LDL-C ratio. Based on the ROC curve, the cutoff values of sd-LDL-C and the sd-LDL-C/LDL-C ratio that could predict ACS were 1.06 mmol/L and 34.55%, respectively, with a sensitivity of 71.9% and 75.2%, respectively, and a specificity of 87.8% and 92.0%, respectively (Figure 2C).

To evaluate the influence of sd-LDL-C concentrations and sd-LDL-C/LDL-C ratios on the occurrence of ACS events, we performed a logistic regression analysis. In the univariate model, a high sd-LDL-C/LDL-C ratio was significantly associated with the risk of ACS [OR (95% CI): 1.24, 1.11-1.38, $P < .001$], while high sd-LDL-C concentrations were not significantly associated with an increased risk of ACS events [OR (95% CI): 0.09, 0.004-1.94, $P > .05$]. In the

multivariate model, after adjustments for age and gender (model 1), the association between the sd-LDL-C/LDL-C ratio and ACS events remained significant [OR (95% CI): 1.24, 1.15-1.35, $P < .001$]. When HDL-C was excluded from the multivariate model (model 2), age, LDL-C concentration, and the sd-LDL-C/LDL-C ratio were significantly associated with ACS events [OR (95% CI): 1.09, 1.04-1.13, $P < .001$; 6.97, 2.23-21.78, $P < .05$; and 1.29, 1.17-1.43, $P < .01$, respectively]. Similarly, when LDL-C was excluded from the multivariate model (Model 3), age, HDL-C concentration, and the sd-LDL-C/LDL-C ratio were significantly associated with ACS events [OR (95% CI): 1.09, 1.04-1.14, $P < .01$; 0.004, 0.000-0.05, $P < .01$; and 1.22, 1.10-1.34, $P < .001$, respectively] (Table 3).

4 | DISCUSSIONS

In the present study, we investigated the relationship between plasma concentrations of sd-LDL-C and risk of ACS using a newly developed automated homogeneous sd-LDL-C assay. Our results showed that elevated concentrations of sd-LDL-C and elevated sd-LDL-C/LDL-C ratios were strongly associated with ACS.

Small dense low-density lipoprotein is traditionally measured by ultracentrifugation²¹ or gradient gel electrophoresis,²² which separates different LDL particles by density and size; however, both methods are laborious and time-consuming and require special equipment. Nuclear magnetic resonance (NMR) imaging can be used to simultaneously determine the size and number of LDL particles, but the instrument required for NMR is too expensive; therefore, NMR is not yet widely available for routine clinical practice, although automated NMR analyzers have already been developed for high-throughput clinical laboratory testing.²³ Heparin sodium salt precipitation followed by centrifugation enables the determination of sd-LDL concentrations; however, this method still requires offline sample pre-treatment, which hinders its integration into general clinical practice.²⁴ Due to the above limitations, the traditional methodologies for the assessment of sd-LDL are not suitable for use in clinical laboratories in large-scale samples. Ito et al²⁰ developed a fully automated homogeneous method for detection of sd-LDL, which showed good agreement with traditional method and high specificity. Then, this method was widely used in understanding the significance of sd-LDL in the following clinical studies.²⁵ Though the homogeneous sd-LDL-automated homogeneous assay is available already for almost 8 years, however, this precise and rapid method for the routine measurement of large numbers of samples was introduced into clinical laboratory of China within 3 years.

We used this method to explore the diagnosis performance of patients with ACS of Chinese population and found that there are gender and age differences in sd-LDL-C concentrations and sd-LDL-C/LDL-C ratios among healthy controls, which is consistent with the data obtained in Western and Chinese populations.²⁶⁻²⁸ As demonstrated in the previous studies, pattern B was reported in approximately 25% of the population but was less frequent in women and younger subjects (40 years old).²⁹ In addition, CAD risk markedly

TABLE 2 Correlation of sd-LDL-C and sd-LDL-C/LDL-C ratio with traditional cardiovascular risk factors

Risk factors	sd- LDL-C		sd-LDL-C/LDL-C	
	Pearson R	P	Pearson R	P
HDL-C	-0.223	.013	-0.325	<.001
LDL-C	0.597	<.001	0.265	.003
hs-cTnI	0.164	.089	0.237	.013
Log triglycerides	0.356	<.001	0.528	<.001

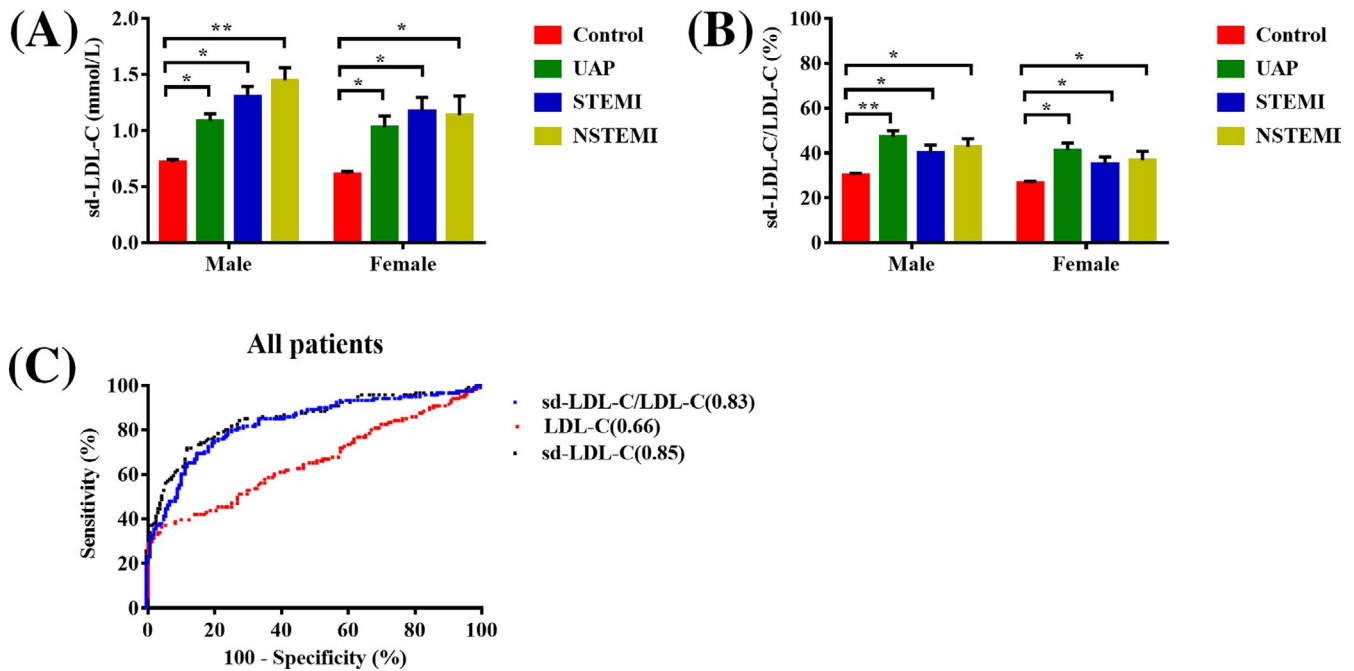


FIGURE 2 The concentration of sd-LDL-C and the sd-LDL-C/LDL-C ratio and ROC curves of ACS patients. A, B, The concentration of sd-LDL-C and the sd-LDL-C/LDL-C ratio in patients with UAP, STEMI and NSTEMI and healthy controls in males and females. C, ROC curves of sd-LDL-C concentration, the sd-LDL-C/LDL-C ratio, and LDL-C level in ACS patients

TABLE 3 Predictors of ACS events according to logistic regression analysis

Variable	Univariate model		Multivariate model					
	OR	95% CI	Model 1		Model 2		Model 3	
			OR	95% CI	OR	95% CI	OR	95% CI
Age	1.08	1.03-1.14**	1.08	1.04-1.12***	1.09	1.04-1.13***	1.09	1.04-1.14**
men	2.47	0.53-10.38	3.71	1.29-10.72*	3.37	0.99-11.42	2.39	0.62-9.25
sd-LDL-C	0.09	0.004-1.94	0.59	0.20-1.79	0.04	0.003-0.58*	0.47	0.09-2.58
LDL-C	3.79	0.95-15.14	-	-	6.97	2.23-21.78**	-	-
sd-LDL-C/LDL-C	1.24	1.11-1.38***	1.24	1.15-1.35***	1.29	1.17-1.43**	1.22	1.10-1.34***
HDL-C	0.01	0.001-0.17**	-	-	-	-	0.004	0.000-0.05**

Note: Model 1 was adjusted for age, men, sd-LDL-C, and sd-LDL-C/LDL-C.

Model 2 was adjusted for age, men, sd-LDL-C, sd-LDL-C/LDL-C, and LDL-C.

Model 3 was adjusted for age, men, sd-LDL-C, sd-LDL-C/LDL-C, and HDL-C.

* $P < .05$.

** $P < .01$.

*** $P < .001$.

increases with age in men and after menopause in women, and alterations in LDL concentration clearly contribute to this increased risk.³⁰ However, the present study did not separate menopausal from premenopausal women to explore the effects of menopause on sd-LDL-C.

Few studies have demonstrated the clinical value of sd-LDL-C in the assessment of ACS risk. Kwon et al³¹ found that sd-LDL-C was an independent risk factor for the development of ACS in the Korean population by using polyacrylamide tube gel electrophoresis method. In addition, Emadzadeh et al³² demonstrated that sd-LDL-C was significantly higher in patients presenting with ACS

than controls and showed no differences between acute myocardial infarction (AMI) and UAP groups. The automated homogeneous sd-LDL-C assay we used in this study can directly detect the plasma concentration of sd-LDL-C in large numbers of samples within a short time. And we also found that the mean sd-LDL-C concentration and sd-LDL-C/LDL-C ratio were significantly higher in the ACS group than in the healthy control group in Chinese population. However, increases in sd-LDL-C concentration did not show a statistically significant trend toward an increased risk of CAD (OR, 1.008), whereas increases in the sd-LDL-C/LDL-C ratio showed a 5.78-fold increased risk for CAD.³³ Similarly, we demonstrated

that a high sd-LDL-C/LDL-C ratio was associated with a 1.25-fold higher risk of ACS ($P < .001$), while sd-LDL-C concentration was not significantly associated with ACS ($P > .05$). Therefore, a high sd-LDL-C/LDL-C ratio might be a more important risk factor for cardiovascular events among patients with ACS than a high sd-LDL-C concentration.

Several previous studies have assessed the associations of sd-LDL-C with traditional cardiovascular risk factors.³ In agreement with previous studies, we also found that plasma sd-LDL-C concentrations and the sd-LDL-C/LDL-C ratio were positively correlated with plasma TG and LDL-C concentrations; however, sd-LDL-C concentrations and sd-LDL-C/LDL-C ratios were negatively correlated with HDL-C concentration. Thus, these data suggest that sd-LDL-C is adversely associated with cardiovascular lipid risk factors and that increased concentrations of sd-LDL-C and high sd-LDL-C/LDL-C ratios may be associated with metabolic disorders.

Our data suggest that the sd-LDL-C/LDL-C ratio is a promising novel parameter for the assessment of ACS risk. The advantage of the automated homogeneous assay for determining sd-LDL-C content is excellent reproducibility, which makes this assay much more user-friendly and more applicable than traditional methods. However, the present study also has some limitations: First, the cohort was relatively small; therefore, additional large cohort studies are required to clarify the predictive value of the sd-LDL-C/LDL-C ratio, as measured by the homogeneous assay, in subjects with ACS. Second, the ACS study population represented a heterogeneous cohort with regards to gender. Third, the plasma we used in our study was previously stored at -80°C ; therefore, whether the results of this study can be extended to fresh plasma samples remains to be determined.

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