Original Article

Association between lipoprotein(a) and atherosclerosis with different diabetic status: a cross-sectional study in a Chinese population

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Background: Lipoprotein(a) [Lp(a)] levels and diabetic status have been recognized as risk factors for atherosclerosis. However, no studies on atherosclerosis have integrated these two indicators. This study aimed to evaluate the relationship between Lp(a) levels, diabetic status, and their combined effects on subclinical atherosclerosis.

Methods: This cross-sectional study included patients presenting with a first episode of chest pain at the First Affiliated Hospital of Chongqing Medical University from June 2018 to February 2022. All participants underwent coronary computed tomography angiography (CCTA) and carotid ultrasound to evaluate subclinical atherosclerosis. Logistic regression analysis was used to examine the associations of Lp(a) levels and diabetic status—both individually and in combination—with coronary artery calcium (CAC) and carotid arteriopathy.

Results: Among 912 patients, 473 (51.9%) had CAC and 637 (69.8%) had carotid arteriopathy. After adjusting the confounding variables, elevated Lp(a) levels associated with CAC [odds ratio (OR) 1.51, 95% confidence interval (CI): 1.02–2.24, P=0.040] and carotid arteriopathy (OR 1.77, 95% CI: 1.10–2.86, P=0.02) were statistically significant. After combining diabetic status, almost all Lp(a) levels were significantly associated with CAC and CAC score categories (CAC scores: 0.1–99.9, 100–399.9, ≥400) in the diabetes mellitus (DM) group. In this group, the highest risk for CAC and the most severe CAC score categories were observed in patients with Lp(a) levels of >300 mg/L. Among patients with DM, in the lower Lp(a) level group, the prevalence and severity of CAC were more pronounced than those in the medium Lp(a) level group. Additionally, in patients with DM only, elevated Lp(a) levels were associated with carotid arteriopathy (OR 3.38, 95% CI: 1.24–9.20; P=0.02), increased carotid intima-media thickness (cIMT; OR 3.67, 95% CI: 1.10–12.30; P=0.04), and stable/vulnerable carotid plaque (OR 3.39, 95% CI: 1.09–10.55; P=0.04; OR 3.21, 95% CI: 1.07–9.65; P=0.04). However, there were no significant differences between prediabetes and CAC or carotid arteriopathy.

Conclusions: In patients with chest pain and DM without cardiovascular disease (CVD), Lp(a) level was significantly associated with subclinical atherosclerosis and had a synergistic effect with DM. Notably, lower Lp(a) levels in patients with DM may lead to an additional subclinical atherosclerosis risk, whereas prediabetes does not show the same association. Therefore, these findings highlight the importance of formulating early preventive strategies for subclinical atherosclerosis based on Lp(a) levels and diabetic status.

Keywords: Lipoprotein(a) [Lp(a)]; prediabetes; diabetes mellitus (DM); coronary artery calcium (CAC); carotid plaques

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Introduction

Cardiovascular disease (CVD) remains one of the leading causes of death worldwide, with atherosclerosis serving as the primary underlying factor, contributing to the development of CVD and stroke in most cases (1,2). Coronary artery calcium (CAC) score, carotid intima-media thickness (cIMT) are surrogate markers of subclinical atherosclerosis. CAC and cIMT can be used to identify atherosclerosis before the manifestation of clinical symptoms and are closely associated with the incidence and mortality of atherosclerotic CVD (ASCVDs) (3,4). A CAC score ≥100 has been associated with increased 10-year ASCVD incidence (5). Additionally, the rupture of vulnerable carotid plaques is involved in the development of arterial embolism and ischemic stroke and is recognized as a noninvasive biomarker of atherosclerotic disease, even in the asymptomatic stage (6,7). Therefore, it is important to accurately identify the risk factors of coronary calcification and carotid arteriopathy to prevent and assess CVDs and stroke.

Lipoprotein(a) [Lp(a)] is a low-density lipoprotein-like particle characterized by the covalent binding of an apoB-100 molecule to apo(a). Elevated Lp(a) levels may promote atherosclerosis through mechanisms such as enhanced oxidative stress, interference with coagulation and fibrinolytic systems, and mediation of the release of inflammatory cells and factors (8). As confirmed by robust evidence from epidemiology, genome-wide association studies, and Mendelian randomization, there is a causal association between elevated Lp(a) levels and an increased risks of coronary artery disease (CAD) and coronary atherosclerosis. According to the "A Beijing Heart Society Expert Scientific Statement", an Lp(a) level greater than 30 mg/dL is considered a risk-enhancing factor in the evaluation of CVD risk (9,10). However, the absence of standardized quantitative methods, variations in expression across races and ethnicities, and limited availability of authorized treatment guidelines and therapeutic options for elevated Lp(a) levels have constrained routine assessment and utilization of Lp(a) levels in clinical practice (11-14).

Diabetes mellitus (DM) is a complex metabolic disorder marked by insufficient insulin production or resistance to its effects. Prediabetes, which includes impaired glucose tolerance and fasting glucose abnormalities, is a precursor to DM (15,16). The "China Chronic Disease and Risk Factors Monitoring Report" highlights an increase in diabetes prevalence, from 10.9% in 2013 to 12.4% in 2018, while prediabetes rates also rose from 35.7% to 38.1% (17). Numerous studies have established a positive correlation between DM and prediabetes, the risk of CVD, and overall mortality (18-20). According to the 2019 European Society of Cardiology (ESC) guidelines on diabetes, prediabetes, and CVD, maintaining low-density lipoprotein cholesterol (LDL-C) levels below 1.4 mmol/L is recommended for patients with diabetes and ASCVD. Although reducing LDL-C can improve cardiovascular outcomes, patients with DM continue to face a higher absolute risk of cardiovascular events compared to those with normal glucose levels (21). This suggests that diabetes may affect cardiovascular health through mechanisms beyond LDL-C levels, warranting further investigation into how different diabetic states

Highlight box

Key findings

- In patients with diabetes, high levels of lipoprotein(a) [Lp(a)] are associated with an increased risk of subclinical atherosclerosis, while lower levels of Lp(a) do not mean a lower risk; prediabetes is not associated with subclinical atherosclerosis.

What is known and what is new?

- Lp(a) and diabetes have been proved to be associated with atherosclerosis risk.
- This study reveals for the first time the different association between Lp(a) and atherosclerosis among different diabetic status in western China.

What is the implication, and what should change now?

- The appropriate prevention and treatment of subclinical atherosclerosis should be based on different diabetic status and Lp(a) levels.

interact with other cardiovascular risk factors.

With the advent of Lp(a)-lowering medicines, a more effective targeted approach that extends beyond current risk-stratification paradigms should be established to implement safer therapies, particularly for patients with high Lp(a) levels. One strategy is to integrate Lp(a) testing with established CVD risks assessment tools, such as diabetic status (22-25). This strategy can improve the effectiveness of risk discrimination and generate a dual risk stratification system for a more precise CVD risk categorization. Nevertheless, few studies have reported consistent findings about the concurrent evaluation of these risk markers. Therefore, this study aimed to examine the independent and joint association of Lp(a) levels and diabetic status with subclinical atherosclerosis in the Chinese population. We hypothesized that elevated Lp(a) levels and DM are independently and jointly associated with subclinical atherosclerosis. We present this article in accordance with the STROBE reporting checklist (available at https://cdt.amegroups.com/article/view/10.21037/cdt-24-410/rc).

Methods

Study population

Overall, 1,066 patients presenting with stable chest pain underwent coronary computed tomography angiography (CCTA) and carotid ultrasonography at the First Affiliated Hospital of Chongqing Medical University, between June 2018 and February 2022. The inclusion and exclusion criteria were as follows: (I) patients with stable chest pain underwent CCTA and carotid ultrasound within 7 days to evaluate CAC and carotid arteriopathy, with images of sufficient quality for accurate analysis. (II) Patients who had no prior diagnosis or confirmed cases of CVD, including CAD, cerebrovascular diseases, severe arrhythmias, valvular heart disease, and New York Heart Association (NYHA) class III or above heart failure; or any related treatments (e.g., revascularization, pacemaker or defibrillator implantation, valve replacement, and nitroglycerin therapy). CAD was defined as ≥50% stenosis in at least one coronary artery on coronary angiography. Cerebrovascular disease was defined by the presence of acute ischemic or hemorrhagic stroke confirmed using neuroimaging techniques such as computed tomography (CT) or magnetic resonance imaging (MRI). Heart failure (NYHA class III or higher) is defined by the NYHA classification in which patients exhibit marked limitations in physical activity and experience symptoms of heart failure even with minimal exertion, as diagnosed via clinical evaluation and echocardiography (26). Severe arrhythmia was defined as the presence of significant arrhythmias, including conditions as ventricular tachycardia or atrial fibrillation with rapid ventricular response, confirmed through 24 h Holter monitoring or event recording. Valvular heart disease was defined by echocardiographic evaluation showing significant valvular stenosis or regurgitation, impacting cardiac function and requiring clinical intervention. (III) Secondary conditions or medication use that may lead to potential fluctuations in Lp(a) levels and blood glucose including severe acute infection, fever, cold, and other symptoms within 2 weeks, or taking antibiotics, malignant tumors (and undertreatment), liver cirrhosis, estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, or a prior diagnosis of end-stage renal diseases (ESRDs) (and undergoing hemodialysis). (IV) Additionally, considering that Lp(a) levels are genetically controlled and racial and ethnic differences, patients were required to present ID card proving they were ≥18 years old, of Han Chinese ethnicity, and residents of Chongqing, China for more than 6 months. (V) Complete clinical data and biochemical indicators were collected using questionnaires in the electronic medical record system. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Ethical Review Board of the First Affiliated Hospital of Chongqing Medical University (No. K2023-575) and individual consent for this retrospective analysis was waived.

Clinical and laboratory values

Following standardized protocols and laboratory procedures, data on hypertension, diabetes, hyperlipidemia, smoking status (no, yes), and alcohol consumption (no, yes) of these patients were collected from medical records by experienced technicians. The height and weight of these patients were also measured to calculate the body mass index (BMI; kg/m^2: the ratio of weight in kilograms to the square of height in meters).

To account for the potential impact of dietary intake on certain parameters, venous blood samples were collected in the morning after >10 h overnight fast. Blood tests were performed using an AU-5, 800 Chemistry Analyzer (Beckman Coulter Inc., Brea, CA, USA), including

LDL-C, high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), total cholesterol (TC), hemoglobin A1c (HbA1c), hypersensitive C-reactive protein (hsCRP), creatinine (Cr), and uric acid (UA). The concentration of Lp(a) was measured using a latex-enhanced turbidimetric immunoassay (the circulating level: mg/L).

Echocardiography was used to evaluate the left ventricular ejection fractions (LVEFs).

CT scans

CCTA was conducted using a Siemens 64-slice multidetector CT scanner (from Siemens, Erlangen, Germany) with the following settings: 120 kV tube voltage, 80 mA tube current, 0.15–0.21 mm pitch, scan duration of 7–11 seconds, 0.62 mm slice thickness, and a rotation speed of 0.25 seconds per rotation. A total of 85–90 mL of Ultravist contrast agent (Bayer HealthCare, Berlin, Germany) was administered intravenously through the elbow using a high-pressure injector at a rate of 4.5–5.5 mL/s, followed by 40 mL of normal saline. After scanning, primary images were transferred to a dedicated workstation for CAC analysis. Calcified lesions were identified as areas with an attenuation of >130 Hounsfield units and a minimum area of 1 mm^2 on each slice. Calcification was defined as lesions with an attenuation >130 Hounsfield units and an area ≥1 mm^2 in each slice. CAC was quantified in Agatston units (AU) (27) and further classified as follows: 0 (normal), 0.1 to 99.9 (mild), 100 to 399.9 (moderate), and ≥400 (extensive) (28).

Carotid ultrasonography

All procedures adhered to the Chinese Stroke Vascular Ultrasound guidelines, performed by at least two professionally trained and experienced technicians (29). After a 15 min rest in the supine position, carotid plaque analysis was performed on patients using carotid artery Doppler ultrasonography with a 6–10 MHz linear-array probe to access atherosclerotic plaques and cIMT in the bilateral common carotid artery, bifurcation, and internal and external carotid arteries. Carotid arteriopathy was defined as the presence of an abnormal cIMT or plaques in any carotid segment. A mean cIMT value ≥1.0 mm indicated increased thickness, while a cIMT >1.5 mm or an atherosclerotic protrusion extending ≥50% into the arterial lumen signified plaque formation. Based on the acoustic and morphological characteristics of the carotid plaques, medium- and strong-echo plaques were classified as stable while low- and mixed-echo plaques were classified as vulnerable plaques. Patients with both stable and vulnerable plaques were classified as having vulnerable plaques (6).

Risk factor definition

According to the International Society of Hypertension guidelines, hypertension was defined as a condition characterized by a persistent elevation in systolic blood pressure (SBP) to >140 mmHg and a diastolic blood pressure (DBP) of at least 90 mmHg (30). Dyslipidemia is defined as the presence of one or more abnormal lipid concentrations, including LDL-C ≥4.14 mmol/L, HDL-C <1.04 mmol/L, TG ≥2.26 mmol/L, TC ≥6.22 mmol/L, or a previous diagnosis of dyslipidemia (31). According to the American Diabetes Association guidelines, prediabetes was defined as an HbA1c level: 5.7% to 6.4%, while DM was defined as an HbA1c level ≥6.5%, a prior DM diagnosis, or current use of antidiabetic medication (32).

Statistical model

As recommended in the Chinese guidelines, an Lp(a) level >30 mg/dL (>300 mg/L) was regarded as the CVD risk threshold following a small-sample population study (10). Therefore, in this study, participants were classified based on Lp(a) levels: <79.5 mg/L (the lower), 79.5–300 mg/L (the medium), and >300 mg/L (the elevated group), and by diabetic status: normal, prediabetes, and DM. After combining Lp(a) levels and diabetic status, nine subgroups were obtained.

Additionally, outcome variables included CAC scores and carotid plaques with Lp(a) level and diabetic status as the primary variables. The Kolmogorov-Smirnov test was used to assess the distribution of these variables. For continuous variables, the values were expressed as the mean ± standard deviation (SD) or median (25^{th}–75^{th} percentile); for categorical variables, the values were expressed as absolute values and proportions. In terms of comparison among groups, normally distributed data were analyzed using the independent samples *t*-test, while skewed data were analyzed using the Mann-Whitney *U* test. Furthermore, categorical variables were analyzed using Pearson's Chi-squared test. Univariate logistic regression analysis was conducted to identify clinical factors significantly associated with CAC scores and carotid plaques. Subsequently, binary and multivariate logistic regression analyses were performed

to identify the independent impact of diabetic status and Lp(a) levels on CAC scores and carotid plaques after the variables were adjusted with P<0.1 in the univariate analysis. The results were expressed as odds ratios (ORs) with corresponding 95% confidence intervals (95% CIs). All statistical analyses were conducted using SPSS (version 26.0; IBM Corp., Armonk, NY, USA), and a P value <0.05 was considered statistically significant.

Results

Baseline characteristics

The demographic characteristics of the population in the cross-sectional study are listed in *Table 1*. In this cross-sectional study, 98 individuals with a prior diagnosis of CAD, 9 individuals with malignant tumors, 12 individuals with an eGFR <30 mL/min/1.73 m^2, and 35 individuals with a lack of complete clinical data were excluded. Overall, 912 participants were included to explore the association between Lp(a) levels and atherosclerosis among different diabetic statuses. Overall, 912 patients with a median age of 67.0 (25^{th}–75^{th} percentile, 57.0, 73.0) years were included in this cross-sectional analysis. Of these, 430 (47.1%) were male, 295 (32.3%) were smokers while 256 (28.1%) consumed alcohol. A total of 569 (62.4%) patients were diagnosed with hypertension and 510 (55.9%) were diagnosed with dyslipidemia. CAC and carotid arteriopathy were diagnosed in 473 (51.9%) and 637 (69.8%) patients, respectively. Furthermore, 337 (37.0%) and 367 (40.2%) patients were diagnosed with DM and prediabetes, respectively. Among patients with CAC, there was a higher prevalence of hypertension, diabetes, and carotid arteriopathy, accompanied by elevated levels of hsCRP, HbA1c, and Cr. Patients with carotid arteriopathy had a

Table 1 Baseline characteristics of CAC and carotid arteriopathy

Characteristics	Total (n=912)	CAC			Carotid arteriopathy		
		Normal (n=439)	CAC (n=473)	P	Normal (n=275)	Carotid atherosclerosis (n=637)	P
Gender				0.047			0.004
Male	430 (47.1)	192 (43.7)	238 (50.3)		110 (40.0)	320 (50.2)	
Female	482 (52.9)	247 (56.3)	235 (49.7)		165 (60.0)	317 (49.8)	
Age, years				<0.001			<0.001
<67	451 (49.5)	288 (65.6)	163 (34.5)		200 (72.7)	251 (39.4)	
≥67	461 (50.5)	151 (34.4)	310 (65.5)		75 (27.3)	386 (60.6)	
Smoking status				0.32			0.046
Yes	295 (32.3)	135 (30.8)	160 (33.8)		76 (27.6)	219 (34.4)	
No	617 (67.7)	304 (69.2)	313 (66.2)		199 (72.4)	418 (65.6)	
Alcohol consumption				0.63			0.19
Yes	256 (28.1)	120 (27.3)	136 (28.8)		69 (25.1)	187 (29.4)	
No	656 (71.9)	319 (72.7)	337 (71.2)		206 (74.9)	450 (70.6)	
Hypertension				<0.001			<0.001
Yes	569 (62.4)	243 (55.5)	326 (68.9)		144 (52.4)	425 (66.7)	
No	343 (37.6)	196 (44.6)	147 (31.1)		131 (47.6)	212 (33.3)	
Dyslipidemia				0.40			0.03
Yes	510 (55.9)	239 (54.4)	271 (57.3)		139 (50.5)	371 (58.2)	
No	402 (44.1)	200 (45.6)	202 (42.7)		136 (49.5)	266 (41.8)	

Table 1 (*continued*)

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Characteristics	Total (n=912)	CAC			Carotid arteriopathy		
		Normal (n=439)	CAC (n=473)	P	Normal (n=275)	Carotid atherosclerosis (n=637)	P
Diabetic status				<0.001			0.03
Normal	208 (22.8)	117 (26.7)	91 (19.2)		73 (26.5)	135 (21.2)	
Prediabetes	367 (40.2)	203 (46.2)	164 (34.7)		117 (42.5)	250 (39.2)	
DM	337 (37.0)	119 (27.1)	218 (46.1)		85 (30.9)	252 (39.6)	
Age, years	67.0 (57.0, 73.0)	62.0 (54.0, 68.0)	70.0 (64.0, 77.0)	<0.001	59.5 (51.0, 67.0)	69.0 (62.0, 76.0)	<0.001
BMI, kg/m^2	24.6±3.5	24.6±3.3	24.7±3.7	0.055	24.8±3.6	24.6±3.5	0.86
Cr, μmol/L	68.0 (58.0, 79.0)	66.0 (56.0, 76.0)	70.0 (60.5, 82.0)	<0.001	66.0 (55.0, 76.0)	70.0 (60, 80)	<0.001
UA, μmol/L	324 (268.3, 386.0)	318.0 (262.0, 381.0)	327.0 (275.0, 389.5)	0.10	318.0 (258.0, 382.0)	326.0 (274.0, 386.0)	0.09
TC, mmol/L	4.2 (3.6, 4.9)	4.3 (3.7, 4.9)	4.2 (3.4, 4.9)	0.051	4.3 (3.8, 4.9)	4.2 (3.5, 4.9)	0.18
TG, mmol/L	1.3 (0.9, 1.8)	1.3 (1.0, 1.8)	1.3 (0.9, 1.7)	0.26	1.3 (1.0, 1.8)	1.3 (0.9, 1.7)	0.051
HDL-C, mmol/L	1.2 (1.0, 1.5)	1.2 (1.0, 1.5)	1.2 (1.0, 1.5)	0.07	1.2 (1.0, 1.5)	1.2 (1.0, 1.50)	0.71
LDL-C, mmol/L	2.6 (2.0, 3.2)	2.6 (2.1, 3.2)	2.5 (1.9, 3.2)	0.06	2.7 (2.0, 3.1)	2.5 (2.0, 3.2)	0.65
Lp(a), mg/L	79.5 (36.0, 218.8)	71.0 (35.0, 195.0)	86.0 (36.0, 251.0)	0.10	61.0 (30.0, 160.0)	92.5 (40.0, 251.0)	<0.001
hsCRP, mg/L	1.0 (0.5, 2.4)	0.8 (0.5, 1.9)	1.1 (0.5, 3.0)	<0.001	0.8 (0.4, 1.9)	1.0 (0.5, 2.5)	0.002
HbA1c, %	6.0 (5.7, 6.6)	5.9 (5.6, 6.3)	6.1 (5.7, 6.9)	<0.001	5.8 (5.6, 6.3)	6.0 (5.7, 6.7)	<0.001
LVEF, %	64.0 (61.0, 67.0)	65.0 (62.0, 67.0)	64.0 (60.0, 66.0)	<0.001	65.0 (62.0, 67.0)	64.0 (61.0, 66.0)	0.004
Medication history							
Antilipidemic use	738 (80.9)	331 (75.4)	407 (86.0)	<0.001	191 (69.5)	547 (85.6)	<0.001
Antihypertensive use	550 (60.3)	222 (50.6)	328 (69.3)	<0.001	135 (49.1)	415 (65.1)	<0.001
CACs, AU	1.5 (0, 96.6)	0	92.5 (17.7, 296.2)	<0.001	0 (0, 1.4)	17.1 (0, 158.3)	<0.001
CAC severity				<0.001			<0.001
0	439 (48.1)	439 (100.0)	0		203 (73.8)	236 (37.0)	
0.1–99.9	249 (27.3)	0	249 (52.6)		47 (17.1)	202 (31.7)	
100–399.9	132 (14.5)	0	132 (27.9)		20 (7.3)	112 (17.6)	
≥400	92 (10.1)	0	92 (19.5)		5 (1.8)	87 (13.7)	
Carotid arteriopathy				<0.001			<0.001
Normal	275 (30.2)	203 (46.2)	72 (15.2)		275 (100.0)		
Increased cIMT	123 (13.5)	67 (15.3)	56 (11.8)		0	123 (19.3)	
Stable plaques	239 (26.2)	99 (22.6)	140 (29.6)		0	239 (37.5)	
Vulnerable plaques	275 (30.2)	70 (15.9)	205 (43.3)		0	275 (43.2)	

Data are expressed as mean ± standard deviation, median (25th–75th percentile) or the number (percentage). CAC, coronary artery calcium; DM, diabetes mellitus; BMI, body mass index; Cr, creatinine; UA, uric acid; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); hsCRP, hypersensitive C-reactive protein; HbA1c, hemoglobin A1c; LVEF, left ventricular ejection fraction; AU, Agatston units; cIMT, carotid intima-media thickness.

Table 2 Univariate logistic regression analysis on CAC and carotid arteriopathy with clinical factors

Characteristics	CAC			Carotid arteriopathy		
	OR	95% CI	P	OR	95% CI	P
Gender (male)	1.32	1.01, 1.71	0.040[a]	1.50	1.13, 2.00	0.006[a]
Age (≥67 years)	3.60	2.73, 4.72	<0.001[a]	4.06	2.98, 5.54	<0.001[a]
BMI	0.97	0.74, 1.25	0.79	1.06	0.80, 1.40	0.71
Hypertension	1.77	1.35, 2.32	<0.001[a]	1.84	1.38, 2.46	<0.001[a]
Dyslipidemia	1.13	0.87, 1.47	0.37	1.38	1.03, 1.83	0.03[a]
Smoking	1.17	0.88, 1.54	0.28	1.36	1.00, 1.86	0.052[a]
Alcohol consumption	1.09	0.82, 1.46	0.56	1.23	0.89, 1.70	0.20
Medication history						
Antilipidemic use	1.96	1.40, 2.75	<0.001[a]	2.61	1.86, 3.67	<0.001[a]
Antihypertensive use	2.19	1.67, 2.87	<0.001[a]	1.92	1.44, 2.56	<0.001[a]
Diabetic status						
Normal	1.00			1.00		
Prediabetes	1.04	0.74, 1.46	0.83	1.13	0.79, 1.62	0.50
DM	2.39	1.68, 3.40	<0.001[a]	1.57	1.08, 2.29	0.02[a]
The level of Lp(a)						
<79.5 mg/L	1.00			1.00		
79.5–300 mg/L	1.14	0.84, 1.53	0.40	1.55	1.11, 2.15	0.009[a]
>300 mg/L	1.41	0.99, 2.00	0.054[a]	1.96	1.31, 2.94	0.001[a]
Cr	1.02	1.01, 1.03	<0.001[a]	1.02	1.01, 1.03	<0.001[a]
UA	1.00	1.00, 1.00	0.21	1.00	1.00, 1.00	0.12
TC	0.91	0.80, 1.04	0.19	0.95	0.82, 1.09	0.45
TG	1.03	0.93, 1.14	0.54	0.89	0.80, 1.00	0.040[a]
HDL-C	0.71	0.50, 1.01	0.06[a]	0.92	0.63, 1.35	0.67
LDL-C	0.89	0.76, 1.03	0.12	1.01	0.86, 1.20	0.87
hsCRP	1.06	1.02, 1.09	0.001[a]	1.04	1.00, 1.08	0.041[a]
LVEF	0.95	0.93, 0.97	<0.001[a]	0.97	0.94, 1.00	0.02[a]

[a], P<0.10. CAC, coronary artery calcium; OR, odds ratio; CI, confidence interval; BMI, body mass index; DM, diabetes mellitus; Lp(a), lipoprotein(a); Cr, creatinine; UA, uric acid; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; hsCRP, hypersensitive C-reactive protein; LVEF, left ventricular ejection fraction.

higher prevalence of hypertension, hyperlipidemia, diabetes, as well as coronary calcification, accompanied by higher levels of Cr, Lp(a), HbA1c, and hsCRP. Moreover, these results revealed that patients with signs of CAC or carotid arteriopathy tended to present a lower LDL-C levels and higher utilization rates of antilipidemic medications.

Lp(a) levels, diabetic status, and CAC

As listed in *Table 2*, the univariate logistic regression analysis results showed that age ≥67 years (OR 3.60; 95% CI: 2.73–4.72, P<0.001), male gender (OR 1.32; 95% CI: 1.01–1.71, P=0.040), hypertension (OR 1.77; 95% CI: 1.35–2.32, P<0.001), DM (OR 2.39; 95% CI: 1.68–3.40,

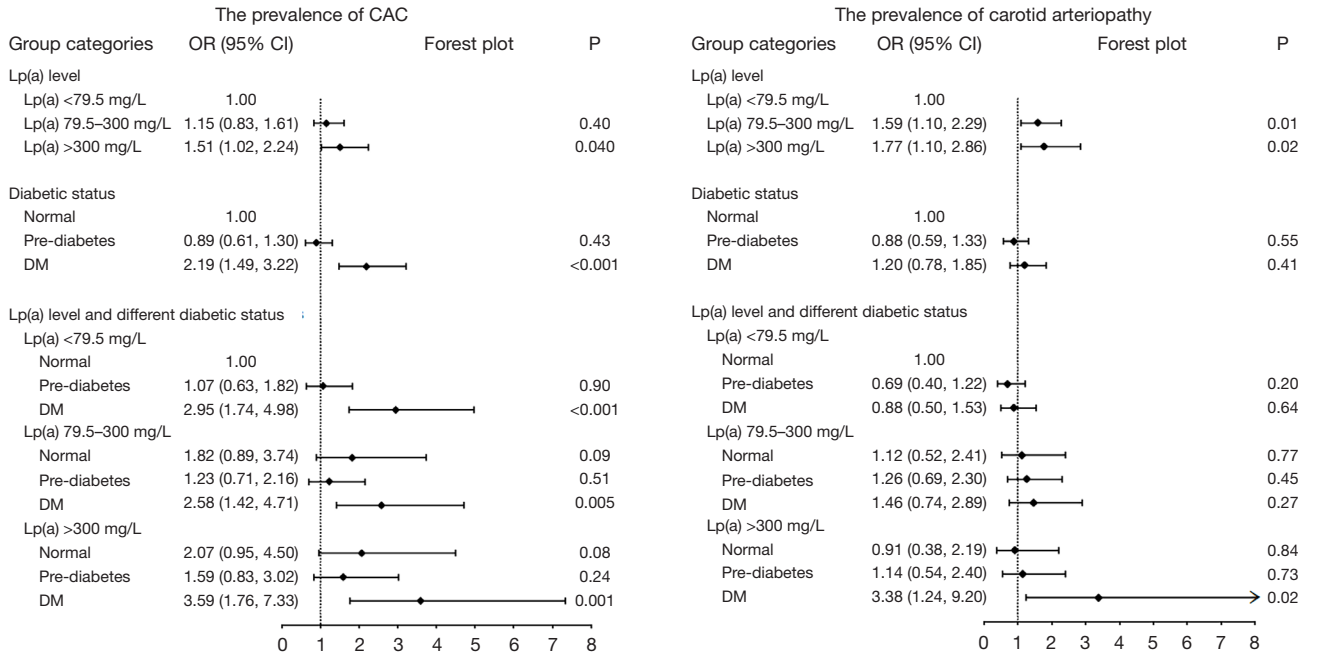

Figure 1 Binary logistic regression analysis of the prevalence of CAC, carotid arteriopathy and Lp(a) levels with different diabetic status. The prevalence of CAC: (I) Group Lp(a) level: adjusted for diabetic status, gender, age, hypertension, antilipidemic use, antihypertensive use, Cr, HDL-C, hsCRP, LVEF. (II) Group diabetic status: adjusted for Lp(a), gender, age, hypertension, antilipidemic use, antihypertensive use, Cr, HDL-C, hsCRP, LVEF. (III) Group Lp(a) level and different diabetic status: adjusted for gender, age, hypertension, antilipidemic use, antihypertensive use, Cr, HDL-C, hsCRP, LVEF. The prevalence of carotid arteriopathy: (I) Group Lp(a) level: adjusted for diabetic status, gender, age, hypertension, dyslipidemia, antilipidemic use, antihypertensive use, smoking, Cr, TG, hsCRP, LVEF. (II) Group diabetic status: adjusted for Lp(a), gender, age, hypertension, dyslipidemia, antilipidemic use, antihypertensive use, smoking, Cr, TG, hsCRP, LVEF. (III) Group Lp(a) level and different diabetic status: adjusted for gender, age, hypertension, dyslipidemia, antilipidemic use, antihypertensive use, smoking, Cr, TG, hsCRP, LVEF. CAC, coronary artery calcium; OR, odds ratio; CI, confidence interval; Lp(a), lipoprotein(a); DM, diabetes mellitus; Cr, creatinine; HDL-C, high-density lipoprotein cholesterol; hsCRP, hypersensitive C-reactive protein; LVEF, left ventricular ejection fraction; TG, triglycerides.

P<0.001), use of antilipidemic medication (OR 1.96; 95% CI: 1.40–2.75, P<0.001), use of antihypertensive medication (OR 2.19; 95% CI: 1.67–2.87, P<0.001), Cr level (OR 1.02; 95% CI: 1.01–1.03, P<0.001), Lp(a) >300 mg/L (OR 1.41; 95% CI: 0.99–2.00, P=0.054), HDL-C (OR 0.71; 95% CI: 0.50–1.01, P=0.06), hsCRP (OR 1.06; 95% CI: 1.02–1.09, P=0.001), and LVEF (OR 0.95; 95% CI: 0.93–0.97, P<0.001) were associated with CAC (*Table 2*, P<0.1). As for carotid arteriopathy, age ≥67 years (OR 4.06; 95% CI: 2.96–5.54, P<0.001), male gender (OR 1.50; 95% CI: 1.13–2.00, P=0.006), hypertension (OR 1.84; 95% CI: 1.38–2.46, P<0.001), dyslipidemia (OR 1.38; 95% CI: 1.03–1.83, P=0.03), DM (OR 1.57; 95% CI: 1.08–2.29, P=0.02), use of antilipidemic medication (OR 2.61; 95% CI: 1.86–3.67, P<0.001), use of antihypertensive medication (OR 1.92; 95% CI: 1.44–2.56, P<0.001), smoking (OR 1.36, 95% CI: 1.00–1.86, P=0.052), Lp(a) from 79.5 to 300 mg/L (OR 1.55, 95% CI: 1.11–2.15, P=0.009), Lp(a) >300 mg/L (1.96, 95% CI: 1.31–2.94, P=0.001), Cr level (OR 1.02; 95% CI: 1.01–1.03, P<0.001), TG (OR 0.89; 95% CI: 0.80–1.00, P=0.040), hsCRP (OR 1.04; 95% CI: 1.00–1.08, P=0.041), and LVEF (OR 0.97; 95% CI: 0.94–1.00, P=0.02) were associated with carotid arteriopathy (*Table 2*, P<0.10). These clinical factors could be regarded as confounding variables and were adjusted in the subsequent logistic regression analysis.

As listed in Table S1, the binary logistic regression crude model indicated that Lp(a) levels were not significantly associated with CAC. As shown in *Figure 1* and Table S1, after adjusting for confounders (diabetic status, gender, age, hypertension, use of antilipidemic medication, use of antihypertensive medication, Cr, HDL-C, hsCRP, and

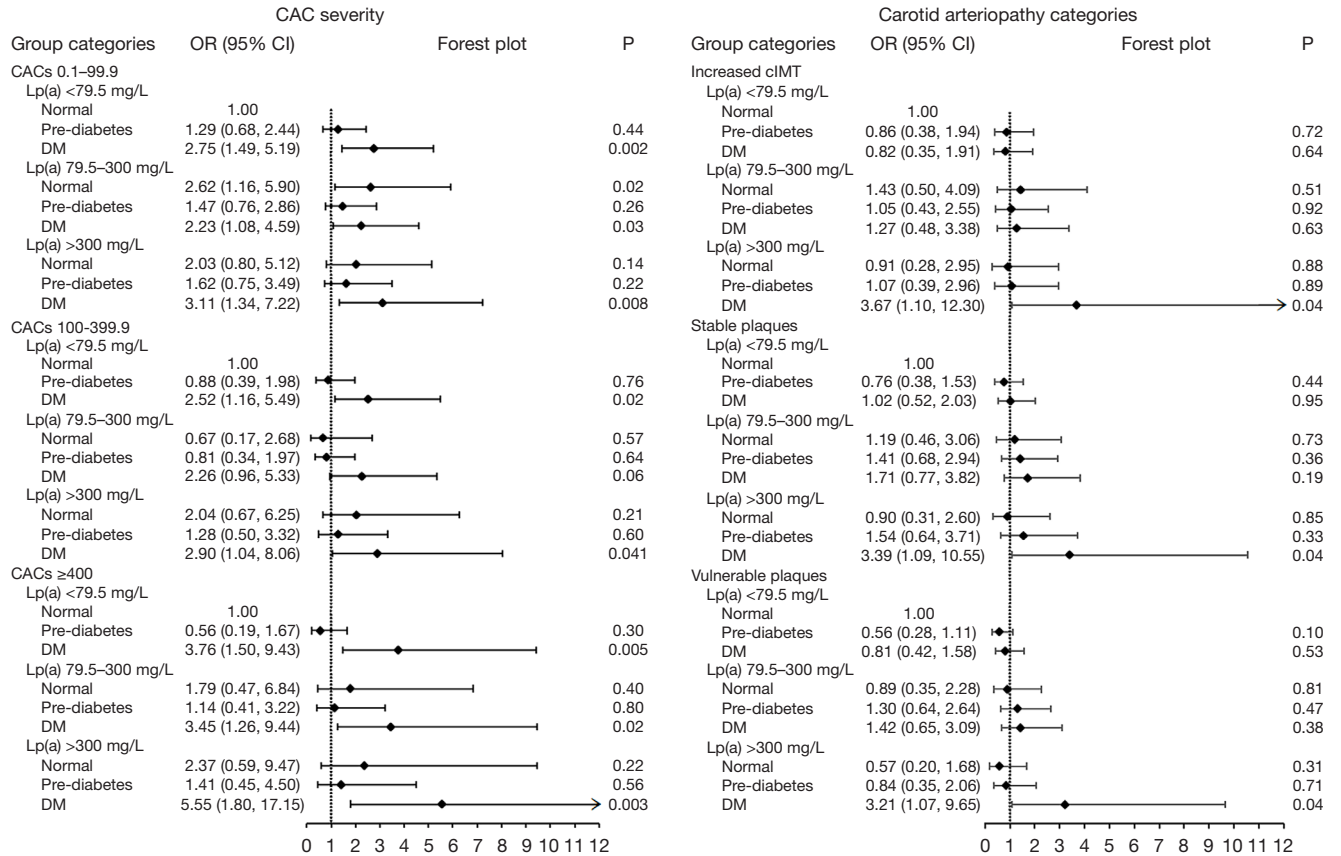

Figure 2 Multivariable logistic regression analysis of CAC, carotid arteriopathy categories and Lp(a) levels with diabetic status. CAC severity group: Model 1 adjusted for gender, age, hypertension, antilipidemic use, antihypertensive use, Cr, HDL-C, hsCRP, LVEF. The carotid arteriopathy categories group: Model 1 adjusted for gender, age, hypertension, dyslipidemia, antilipidemic use, antihypertensive use, smoking, Cr, TG, hsCRP, LVEF. CAC, coronary artery calcium; OR, odds ratio; CI, confidence interval; cIMT, carotid intima-media thickness; Lp(a), lipoprotein(a); DM, diabetes mellitus; Cr, creatinine; HDL-C, high-density lipoprotein cholesterol; hsCRP, hypersensitive C-reactive protein; LVEF, left ventricular ejection fraction; TG, triglycerides.

LVEF), compared with lower Lp(a) levels, the higher Lp(a) levels were associated with the prevalence of CAC (OR 1.51, 95% CI: 1.02–2.24, P=0.040). Additionally, when compared with normal subjects, the difference in the prevalence of CAC in patients with prediabetes was not statistically significant (OR 0.89, 95% CI: 0.61–1.30, P=0.43), whereas the difference in patients with DM was statistically significant (OR 2.19, 95% CI: 1.49–3.22, P<0.001), after adjusting for Lp(a), gender, age, hypertension, antilipidemic use, antihypertensive use, Cr, HDL-C, hsCRP, LVEF. When analyzing combined Lp(a) levels and diabetic status, the binary logistic regression crude model also indicated that patient with DM having Lp(a) levels <79.5 mg/L, 79.5–300 mg/L and >300 mg/L were all associated with the prevalence of CAC (OR 2.85, 95% CI: 1.75–4.61, P<0.001), (OR 2.99, 95% CI: 1.71–5.22, P<0.001), and (OR 3.82, 95% CI: 1.96–7.44, P<0.001), compared to those with lower Lp(a) levels and normoglycemia. After, further adjustment for gender, age, hypertension, use of antilipidemic medication, use of antihypertensive medication, Cr, HDL-C, hsCRP, and LVEF were adjusted, the association was still statistically significant (OR 2.95, 95% CI: 1.74–4.98, P<0.001), (OR 2.58, 95% CI: 1.42–4.71, P=0.005), and (OR 3.59, 95% CI: 1.76–7.33, P=0.001), respectively. However, there was no statistically significant difference in the prevalence of CAC between the normoglycemia and prediabetes groups, regardless of Lp(a) level. As shown in *Figure 2* and Table S2, adjusted for Model 1 (gender, age, hypertension, antilipidemic use, antihypertensive use, Cr, HDL-C, hsCRP, LVEF), there were significant associations

between different Lp(a) levels and almost all CAC score categories in patient with DM (CAC score 0.1–99.9, 100–399.9, and ≥400). Among them, the DM group with Lp(a) level >300 mg/L presented the highest risk for all CAC score categories (OR 3.11, 95% CI: 1.34–7.22, P=0.008; OR 2.90, 95% CI: 1.04–8.06, P=0.041; OR 5.55, 95% CI: 1.80–17.15, P=0.003). Furthermore, patients with normoglycemia having medium Lp(a) levels showed an increased risk of mild CAC (CAC score =0.1–99.9) compared with normal controls (OR 2.62, 95% CI: 1.16–5.90, P=0.02). However, there was still no significant association between CAC scores and patients with prediabetes and Lp(a) levels (P>0.05). Finally, we conducted additional adjustments for Model 2 (dyslipidemia, TC, LDL-C, and HDL-C levels, in addition to Model 1). The final results were consistent with the aforementioned conclusions further reinforcing the robustness of our findings (Table S2).

Regarding the associations with carotid arteriopathy, as shown in *Figure 1* and Table S3, after adjusting for diabetic status and Model 1 (sex, age, hypertension, dyslipidemia, antilipidemic use, antihypertensive use, smoking, Cr, TG, hsCRP, and LVEF), both moderate and high levels of Lp(a) were significantly associated with carotid arteriopathy compared with normal controls (OR 1.59; 95% CI: 1.10–2.29, P=0.01; OR 1.77, 95% CI: 1.10–2.86, P=0.02). However, prediabetes and DM showed no association with the prevalence of carotid arteriopathy compared with the normal controls. Furthermore, *Figure 1* and Table S3 show that when combining Lp(a) levels with diabetic status, the multivariable logistic regression analysis indicated a significant association only in patients with DM having Lp(a) levels >300 mg/L (OR 3.38, 95% CI: 1.24–9.20, P=0.02), after accounting for the aforementioned confounding factors. *Figure 2* and Table S4, further show that after adjusting for confounders (Model 1), increased cIMT, stable plaques, and vulnerable plaques were statistically significant only in patient with DM having elevated Lp(a) levels (OR 3.67, 95% CI: 1.10–12.30, P=0.04; OR 3.39, 95% CI: 1.09–10.55, P=0.04; OR 3.21, 95% CI: 1.07–9.65, P=0.04). There was insufficient evidence linking normoglycemia and prediabetes with the incidence of carotid arteriopathy. Finally, we conducted additional adjustments for Model 2 (TC, LDL-C, and HDL-C levels in addition to Model 1). The final results remained the same (Table S4).

Discussion

This study evaluated the effect of Lp(a) levels on subclinical atherosclerotic risk in patients with different diabetic statuses. First, elevated Lp(a) levels were independently associated with the prevalence of CAC and carotid arteriopathy, even after adjusting for relevant clinical risk factors. However, among the different diabetic statuses, an association with an increased CAC risk was only observed in patients with DM. Second, patients with DM having elevated Lp(a) levels showed a stronger association with both the presence and severity of CAC and carotid arteriopathy than those with only one elevated risk marker. Third, patients with DM having lower Lp(a) levels had a higher CAC risk than those with medium Lp(a) levels. Fourth, no statistically significant differences were observed in CAC scores and carotid arteriopathy between the prediabetes and normal groups.

Lp(a), DM and atherosclerosis

The pathogenic effects of Lp(a) are believed to involve several mechanisms: the deposition of LDL components within atherosclerotic plaques, a prothrombotic effect due to the apo(a) tail's interference with plasminogen activation, the induction of a multi-tiered inflammatory response via oxidized phospholipids (OxPLs), and the facilitation of calcium accumulation in vascular tissues (23,33). Similar to previous studies, this study demonstrated a strong and independent association between elevated Lp(a) levels and atherosclerosis (13,34-36), and these findings were extended to the Chinese population. However, conclusions regarding the relationship between Lp(a) and CAC are inconsistent. For example, the Dallas Heart Study showed that, in white and black people, there was no consistent independent relationship between the size of the Lp(a) or apo(a) subtypes and the plasma level of CAC (37). In contrast, Kaiser *et al.* revealed that Lp(a) is associated with accelerated progression of low-attenuation plaques (necrotic cores) in patients with advanced multivessel coronary artery disease but not with coronary calcification (38). However, these two studies differ from ours in that our study subjects were non-CVD Chinese people with chest pain symptoms, were older, and had a higher proportion of multiple underlying diseases. Additionally, the influence of race-specific factors and genetic polymorphisms related to the Lp(a) gene—

which affect circulating Lp(a) levels—may account for the variability in the relationship between Lp(a) and CAC across different populations (39).

Hyperglycemic damage is one of the most important mechanisms associated with DM. Hyperglycemia induces vascular inflammation and endothelial dysfunction by accumulating free radicals, and further increases oxidative stress by enhancing glucose oxidation (40). DM has been shown to be a risk factor for coronary calcification in many studies (41-44). However, the crude binary logistic regression model in this study showed a significant positive correlation between DM and carotid arteriopathy, and after adjusting for confounding factors, such as sex, age, hyperlipidemia, and medication history, the significant statistical association disappeared. This contrast with some previous studies (45-47). In this study, the proportion of previous cardiovascular interventions in patients with DM was higher than in patients without DM, and the proportion of treatments for hypertension and hyperlipidemia was also greater (48). Multiple studies revealed that elderly patients with type 2 diabetes mellitus (T2DM) treated with statins have lower cIMT values and increased plaque stability, further indicating that patients with T2DM treated with standardized lipid-lowering drugs can not only stabilize and reverse plaques but also significantly improve carotid arteriopathy (49,50). When Lp(a) was subsequently combined, the results showed that patients with DM having high Lp (a) levels were significantly associated with carotid arteriopathy and its severity, and the correlation was significantly higher than that in the high-level Lp(a) group or the DM group alone. In summary, patients with DM having high levels of Lp(a) may benefit from optimized treatment strategies to delay their progression and improve the clinical outcomes (51).

Lower Lp(a) level and atherosclerosis

It is worth noting that this study also suggested that patients with DM and lower Lp(a) levels (OR 2.95, 95% CI: 1.74–4.98, P<0.001) had a higher CAC correlation than DM patients with medium Lp(a) levels (OR 2.58, 95% CI: 1.42–4.71, P=0.005). Similar results were observed in the subgroup analyses of CAC severity. According to existing evidence, low Lp(a) levels are associated with an increased risk of prediabetes, diabetes, insulin resistance (IR), and hyperinsulinemia, and the CVD risk remains elevated (52-54). However, the underlying mechanisms remain unclear. Neele *et al.* showed that high insulin concentrations inhibited apo(a) synthesis at the transcriptional level in monkey liver cells, which may partially explain the phenomenon of lower Lp(a) levels in patients with T2DM and IR (55). Studies have also shown that apo(a) subtypes are significantly larger in individuals with elevated insulin or glucose levels, and it is well known that apo(a) size is negatively correlated with Lp(a) plasma concentration (56-58). Additionally, it has been reported that after Lp(a) treatment, low levels of Lp(a) may increase the risk of T2DM (9). Therefore, for patients with DM, the correlation between low levels of Lp(a) and CAC was higher than that of patients with DM with medium levels of Lp(a). The underlying mechanism is that a low level of Lp(a) leads to an increased risk of DM and high blood sugar damage, though further studies are required.

Prediabetes and atherosclerosis

Prediabetes is a stage of altered glucose metabolism associated with an increased risk of progression to DM and CVDs (59). The results of different studies vary due to the lack of standardized recommendations for the definition of prediabetes. In this study, patients with prediabetes were not found to be associated with subclinical atherosclerosis despite elevated Lp(a) levels. Previous studies have reported a crude association between prediabetes (based on HbA1c and FPG levels) and CAC, but only half of these studies demonstrated a significant association after statistical adjustment for confounding factors (60,61). DM has a detrimental effect on the arterial wall independent of the associated metabolic risk factors (62). In a study by Farhan *et al.*, the risk profile of patients with prediabetes was more similar to that of patients with normal glucose metabolism than that of patients with DM (63). This observation, together with a recent controversial study in *Science* that defined prediabetes as a "dubious diagnosis", has led to the view that prevention and treatment of prediabetes may cause more harm, leading to unnecessary medical interventions and burden (64,65). However, a recent large meta-analysis of 129 studies (involving >10 million participants) found that prediabetes was associated with an increased risk of all-cause mortality and CVDs (66). Given the controversial nature of prediabetes and the risk of progression to DM, efforts should continue to better

identify individuals at risk of altered glucose metabolism and prevent complications such as vascular stenosis and thrombosis (62). Simultaneously, large-scale prospective studies on the relationship between prediabetes and atherosclerosis are warranted.

Over the past decade, Lp(a) has transitioned from being a relatively obscure risk factor for ASCVD to a key target in cardiovascular risk prevention. This change is due to: (I) robust epidemiological and genetic data consistently show that Lp(a) levels exceeding 30 mg/dL (or >75 nmol/L) are associated with an elevated ASCVD risk (67); (II) it has been observed that patients treated with statins continue to increase their Lp(a)-mediated ASCVD risk despite relatively good LDL-C control (68), and there are currently no specific therapeutic drugs for Lp(a) (69); (III) emerging therapies that effectively lower Lp(a) levels, such as proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors, apo(a) antisense oligonucleotide (pelacarsen), and apo(a) small interfering RNA (olpasiran, SLN360), have shown promise in improving cardiovascular outcomes and patients' quality of life. As these treatments continue to evolve, the potential clinical benefits of reducing Lp(a) levels have become a central focus in the prevention and management of CVDs.

This study attempted to confirm that elevated Lp(a) levels help identify individuals with a higher risk of subclinical atherosclerosis in different diabetic statuses through logistic regression analysis. Similarly, if two risk markers are abnormal simultaneously, proper blood glucose control, high-intensity statin therapy, and active lifestyle changes are necessary to help reduce the risk of ASCVD (70). Additionally, in patients with DM, low Lp(a) levels were paradoxically associated with subclinical atherosclerosis, whereas in patients with prediabetes, Lp(a) levels did not stratify the disease. The study findings may provide support for broader testing of Lp(a) in a wider population.

Strengths and limitations

This cross-sectional survey of subclinical atherosclerosis in hospitalized patients with stable chest pain provides latest data that objectively reflects the independent and joint associations between Lp(a) levels and CAC and carotid arteriopathy risk in different diabetic statuses (normal, prediabetes, and DM) in western China. However, there are certain limitations in this observational study, including the selection of only hospitalized patients with chest pain from a single center in China and the fact that all patient data were obtained from the electronic medical record system of a tertiary hospital, which may lead to potential selection bias. These results require further examination and verification in a multicenter study. In addition, we only measured the baseline levels of plasma Lp(a) and diabetic status, as well as the baseline CAC and carotid arteriopathy data at the time of admission. Therefore, the experimental design of this observational, cross-sectional study limits its ability to determine the correlation between the research indicators, as it is affected by unmeasured confounding factors that cannot be ruled out. This design does not allow for establishing the causal relationship between Lp(a), diabetic status, and subclinical atherosclerosis. Finally, this study is also limited by its small sample size; therefore, it is necessary to obtain more evidence through larger prospective studies and follow-ups to explore the impact on the prognosis of cardiovascular adverse events in patients.

Conclusions

In conclusion, Lp(a) level has emerged as an independent risk factor for subclinical atherosclerosis in CVD-negative Chinese patients with chest pain at baseline, demonstrating a synergistic effect with DM. Notably, DM patients with lower Lp(a) levels correlate with an additional risk of subclinical atherosclerosis, while prediabetes patients do not. Therefore, it is necessary to formulate early prevention strategies for subclinical atherosclerosis based on Lp(a) levels and diabetes status.

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Footnote

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Data Sharing Statement: Available at https://cdt.amegroups.com/article/view/10.21037/cdt-24-410/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cdt.amegroups.com/article/view/10.21037/cdt-24-410/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethical Review Board of the First Affiliated Hospital of Chongqing Medical University (No. K2023-575) and individual consent for this retrospective analysis was waived.

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