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Synergistic effects of lipoprotein (a) and fibrinogen on carotid plaque in patients with coronary artery disease

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Abstract

Background Elevated lipoprotein (a) [Lp (a)] and fibrinogen (Fib) are important factors contributing to the pathogenesis of atherosclerosis. Carotid plaque is a manifestation of carotid atherosclerosis, and previous studies have shown that Fib has a synergistic effect on Lp (a)-induced events. However, the effect of the combined action of Lp (a) and fibrinogen on carotid plaque has not been elucidated.

Methods This was a cross-sectional study that screened a total of 3913 patients who attended the First Affiliated Hospital of Xinjiang Medical University with confirmed diagnosis of coronary artery disease (CAD) and carotid ultrasonography during 2019–2024. General clinical information, physical examination data, and laboratory tests were collected from the patients. Based on the results of carotid ultrasonography, the patients were divided into a group with carotid plaque (1123 cases) and a group without carotid plaque (2790 cases). Multifactorial logistic regression analysis was used to explore the correlation between Lp (a) and Fib levels and carotid plaque and the interrelationship between them.

Results A total of 3913 patients were included, including 2666 males and 1247 females, and the incidence of carotid plaque was 28.7%, with significant differences in Lp (a) and Fib levels between the two groups with and without carotid plaque ($P < 0.05$) and a significant interaction effect. Multiple logistic regression analysis showed that for every tenfold increase in plasma Lp (a) levels (i.e., an increase of one logarithmic unit), the incidence of carotid plaque could increase by about 32% or so. After stratified analysis for age and sex, it was observed that carotid plaque was significantly associated with plasma Lp (a) levels in men and in patients aged < 60 years (male: OR = 1.301, 95% CI 1.051–1.611; age < 60 years: OR = 1.373, 95% CI 1.076–1.753). Plasma Fib levels were associated with carotid plaque in patients of different sexes and age groups, and there was a significant synergistic effect of Lp (a) and Fib on carotid plaque ($P_{interaction} < 0.05$).

Conclusions Elevated levels of Lp (a) and Fib are independent risk factors for combined carotid plaque in patients with coronary artery disease, and there is a synergistic effect of both on carotid plaque. Therefore, plasma Lp (a) and Fib levels of patients should be focused on for better treatment of carotid plaque and prevention of ischemic stroke.

Keywords Lipoprotein (a), Fibrinogen, Carotid plaque, Coronary artery disease, Dyslipidemia, Ischemic stroke

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Introduction

Atherosclerosis is a chronic inflammatory vascular disease characterized by the formation of lipid plaques within the walls of the arteries, leading to the narrowing or blockage of blood vessels, which in turn may lead to serious health problems such as heart disease and stroke. The formation of atherosclerosis involves complex processes including endothelial damage, lipid deposition, inflammatory response and thrombosis [1].

Dyslipidemia is a common cause of atherosclerosis, and it is now clear that low-density lipoprotein (LDL) and lipoprotein (a) [Lp (a)] can lead to atherosclerosis [2], and some studies have shown that the atherogenic effect of Lp (a) is 6.6 times that of LDL [3, 4]. Fibrinogen (Fib), a plasma glycoprotein with coagulation function synthesized in the liver, as another important factor contributing to the pathogenesis of atherosclerosis, not only participates in the process of blood coagulation and thrombosis but also is closely related to the progression of atherosclerotic lesions and the stability of plaques through the promotion of the inflammatory response and immune response [5, 6]. Apolipoprotein (a) [Apo (a)] in Lp (a) is highly homologous to plasminogen and can competitively bind to fibrin thereby interfering with plasminogen activation and fibrinolysis, leading to thrombosis [7].

Carotid plaque is a manifestation of carotid atherosclerosis, which can lead to ischemic stroke if intra-plaque hemorrhage, rupture and dislodgement, and wall thrombosis occur. The results of the Copenhagen General Population Study and the Copenhagen City Heart Study showed that high levels of Lp (a) were associated with an increased risk of ischemic stroke [8]. Previous studies have shown that elevated plasma fibrinogen levels are associated with carotid plaque formation and may increase plaque instability, thereby increasing the risk of ischemic stroke [9]. The most specialized structure in Lp (a), Apo (a), shares Kringle IV and V and a protease structural domain with plasminogen, Kringle is present in many proteins in the coagulation and fibrinolytic system and binds to fibrin in the blood clot [10]. Thus Lp (a) can compete with plasminogen for lysine binding sites on fibrinogen through the Kringle structural domain and alter the structure of the fibrin clot [11], reducing the binding and activation of plasminogen and inhibiting the fibrinolytic system. In contrast, the protease structural domain of Lp (a) is inactive and does not promote fibrinolysis, thus leading to the inability of fibrin to be efficiently degraded and removed thus overdepositing in the vasculature [10], which increases the risk of thrombosis and also provides the basis for the formation of atherosclerotic plaques. And some studies have revealed a synergistic effect of Fib on Lp (a)-induced events [12]. However, whether Lp (a) increases the risk of ischemic stroke by promoting carotid atherosclerosis to form carotid plaques remains unclear, and whether there is an interaction between Lp (a) and Fib remains to be explored. The aim of this study was to elucidate the effects of plasma Lp (a) and Fib levels on carotid plaques in patients with coronary artery disease and their interrelationships, to provide a basis for better treatment of carotid plaques and prevention of ischemic stroke, and to provide theoretical support for the use of Lp (a) and Fib as biomarkers of cardiovascular and cerebral vascular disease and as potential therapeutic targets.

Methods

Study population

This was a retrospective case control study, conducted in accordance with the principles of the Declaration of Helsinki. We selected patients with stable conditions and coronary artery disease (≥50% stenosis in at least one coronary artery [13]) diagnosed by coronary angiography who attended the heart center of the First Affiliated Hospital of Xinjiang Medical University between 2019 and 2024, and were on long-term regular oral aspirin antiplatelet therapy and moderate-dose atorvastatin lipid-lowering therapy. Inclusion criteria were as follows: (1) patients aged ≥ 18 years; (2) lipid levels and coagulation function tests were performed in each patient after admission; and (3) complete color Doppler ultrasound examinations of bilateral carotid arteries and vertebral arteries. Exclusion criteria were as follows: (1) incomplete clinical data; (2) patients in acute inflammatory states; (3) patients with combined thyroid function abnormalities, chronic liver disease (hepatitis, cirrhosis), chronic renal insufficiency (uremia), etc.; and (4) patients with a history of malignant tumors. A total of 3913 patients were eventually enrolled in the study. This study was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University (No. 220525-06-2305A-Y1), and the patients voluntarily participated in the trial and signed an informed consent form.

Research methodology

General clinical data of the patients were collected upon admission, including gender, age, past history (e.g., history of hypertension, diabetes mellitus, coronary artery disease), and history of smoking and alcohol consumption, as well as physical examination data (e.g., height, weight, BMI, heart rate, pulse rate, and blood pressure). Venous blood specimens were collected from the median elbow vein after 12 h of fasting and tested for blood counts, liver and kidney functions, blood lipids, blood glucose, coagulation function and other test indices. All specimens were tested

by the clinical laboratory of the First Affiliated Hospital of Xinjiang Medical University using a biochemical analyzer (Dimension AR/AVL Clinical Chemistry System, Newark, NJ, U.S.A). Lipoprotein (a) levels were detected by latex immunoturbidimetric assay using Lipoprotein (a) Assay Kit (Zhejiang Quark Biotechnology Co., catalog number: 180307). Fibrinogen levels were quantified by the Clauss method using an STA-R fully automated hemagglutination instrument (Stago, France) and accompanying reagents (catalog number: 00673).

Relevant definitions and diagnostic criteria

Carotid plaque: Carotid plaque detection was performed using a GE Vivid E9 color Doppler diagnostic ultrasound instrument (General Electric Company, Fairfield, Connecticut, USA) equipped with a high-frequency line-array probe with a frequency of 7–13 MHz. All ultrasound examinations were performed independently by two experienced sonographers (both with over 10 years of experience). Inter-operator reproducibility was assessed using the ICC, which showed an ICC of 0.88 (95% CI 0.82–0.92), indicating good reproducibility. With the patient lying down and the head rotated 45°to the contralateral side, the transverse and longitudinal sections of bilateral carotid arteries were examined, the common carotid artery (CCA) was swept from the medial side of the clavicle in turn, and the bifurcation of the common carotid artery and the internal carotid artery (ICA) and external carotid artery (ECA) were examined along the vascularization pathway on both sides. The intima media thickness (IMT) at the carotid bifurcation and whether there is plaque formation in the carotid arteries bilaterally, as well as the size, number, morphology, and echo intensity of the plaques were recorded. IMT is calculated as the distance from the edge of the first echo line to the edge of the second echo line. According to the latest version of Mannheim carotid intima media thickness and plaque consensus [14], atheromatous plaque is defined as a localized structural change projecting into the lumen of an artery that is greater than the intima-media thickness (IMT) of the surrounding carotid artery by at least 0.5 mm or 50%, or IMT > 1.5 mm in any of the above arterial segments. Those who did not meet these criteria were judged to be plaque free.

Dyslipidemia: Dyslipidemia was diagnosed when ≥ 1 of the following fasting venous plasma test indices were met: Total cholesterol (TC) ≥ 6.2 mmol/L; Low-density lipoprotein cholesterol (LDL-C) ≥ 4.1 mmol/L; Triglycerides (TG) ≥ 2.3 mmol/L; and high-density lipoprotein cholesterol (HDL-C) < 1.0 mmol/L [15].

Statistical analysis

Statistical analysis was performed using SPSS version 27.0. The Kolmogorov–Smirnov test of normality was applied, and for normally distributed measures, they were expressed as mean ± standard deviation, and the independent samples t-test was used to analyze the data between the two groups. For skewed distribution measures, expressed as M (IQR), the Mann–Whitney *U* rank sum test was applied for analysis. Considering the skewness of Lp (a) level, Log_{10} logarithmic transformation was used for regression analysis. Enumeration data were presented as n (%), and the chi-squared (χ^2) test or Fisher's exact test was used to determine differences between groups. Logistic regression analysis was used for multifactor analysis, and variables that were statistically significant in the univariate analysis were included in the regression model. A multiplicative interaction model was used to analyze the relationship between Lp (a) and fibrinogen. $P < 0.05$ was considered a statistically significant difference.

Results

Baseline characteristics of the study population

A total of 3913 patients with coronary artery disease were included in this study, including 2666 men and 1247 women, with an overall incidence of carotid plaque of 28.7% and 2790 patients without carotid plaque. Of 2,666 male patients, 835 had carotid plaque, representing 74.4% of all patients with carotid plaque ($n = 1123$). The 1831 male patients were free of carotid plaque, representing 65.6% of all patients without carotid plaque ($n = 2790$), and baseline information is shown in Table 1. Carotid plaques were more likely to occur in men and patients aged > 60 years, and the differences between the two groups in the prevalence of risk factors such as smoking, alcohol consumption, and history of hypertension and diabetes, as well as renal function, lipid levels, and glycemic indices were statistically significant ($P < 0.05$).

Correlation of Lp (a) and Fib levels with carotid plaque

Patients were grouped according to the presence or absence of carotid plaque, and comparing the lipid and fibrinogen levels between the two groups, it was found that patients with carotid plaque had lower HDL-C levels as well as higher Lp (a), ApoB, and Fib levels (Table 2). Because age, gender, history of smoking, alcohol consumption, history of hypertension, history of diabetes mellitus, and hyperlipidemia are important risk factors for carotid plaque formation, they were included as adjusting variables in multivariate analyses using logistic regression models. It was observed that Lp (a), ApoB, and Fib levels in patients with and without carotid

Table 1 Clinical characteristics of subjects

Characteristics	Overall (n = 3913)	With carotid plaque (n = 1123)	Without carotid plaque (n = 2790)	P value
Age, y	56.19 ± 11.71	60.62 ± 10.5	54.41 ± 11.7	**< 0.001**
Male (n,%)	2666 (68.13)	835 (74.35)	1831 (65.63)	**< 0.001**
BMI, kg/m2	26.91 ± 9.54	26.74 ± 3.97	26.97 ± 10.85	0.58
Medical history				
Smoking (n,%)	1579 (40.35)	516 (45.95)	1063 (38.10)	**< 0.001**
Drinking (n,%)	1156 (29.54)	369 (32.86)	787 (28.21)	**0.004**
Hypertension (n,%)	1457 (37.23)	534 (47.55)	923 (33.08)	**< 0.001**
Diabetes (n,%)	735 (18.78)	301 (26.80)	434 (15.56)	**< 0.001**
Surgical (n,%)	1855 (47.41)	549 (48.89)	1306 (46.81)	0.24
Laboratory tests				
SBP, mmHg	127.77 ± 25.13	131.48 ± 37.47	**126.28 ± 17.7**	**< 0.001**
DBP, mmHg	77.67 ± 11.43	77.36 ± 11.63	77.8 ± 11.34	0.28
Height, cm	168.47 ± 8.37	168.42 ± 7.79	168.49 ± 8.57	0.85
Weight, kg	76.28 ± 13.68	76.53 ± 13.12	76.18 ± 13.9	0.48
BSA, m^2	2.54 ± 0.16	2.54 ± 0.16	2.54 ± 0.16	0.84
ALT, U/L	29.02 ± 31.66	27.51 ± 21.79	29.63 ± 34.88	0.06
AST, U/L	23.85 ± 25.26	23.14 ± 17.76	24.14 ± 27.74	0.27
Scr, umol/L	73.3 ± 24.08	76.08 ± 22.73	72.17 ± 24.51	**< 0.001**
Bun, mmol/L	5.42 ± 1.68	5.67 ± 1.77	5.32 ± 1.63	**< 0.001**
TC, mmol/L	4.12 ± 1.19	4.14 ± 1.24	4.11 ± 1.17	0.40
TG, mmol/L	2.09 ± 1.93	2.03 ± 1.8	2.11 ± 1.98	0.22
HDL-C, mmol/L	1.05 ± 0.32	1.03 ± 0.32	1.06 ± 0.32	**0.01**
LDL-C, mmol/L	2.6 ± 0.88	2.64 ± 0.94	2.58 ± 0.86	0.06
Lp (a), mg/L	29 (54.83)	34.75 (71.5)	28.1 (49.31)	**< 0.001**
Glu, mmol/L	6 ± 2.37	6.38 ± 2.74	5.84 ± 2.19	**< 0.001**
HbA1c, %	6.46 ± 1.41	6.78 ± 1.6	6.33 ± 1.3	**< 0.001**

Table 2 Comparison of lipid levels and coagulation in patients with and without carotid plaque

Overall	With carotid plaque (*n* = 1123)	Without carotid plaque (*n* = 2790)	Before adjustment	After adjustment	
			P value	OR (95% CI)	*P* value
HDL-C, mmol/L	1.03 ± 0.32	1.06 ± 0.32	**0.01**	0.780 (0.571–1.067)	0.121
Log_{10} (Lp (a)), mg/L	1.59 ± 0.53	1.52 ± 0.5	**< 0.001**	1.318 (1.097–1.584)	**0.003**
ApoB, g/L	0.88 ± 0.3	0.85 ± 0.28	**0.01**	2.231 (1.580–3.150)	**< 0.001**
APTTR	1.04 ± 0.12	1.05 ± 0.14	**0.01**	0.376 (0.165–0.854)	**0.019**
Fib, g/L	3.23 ± 0.82	3.03 ± 0.72	**< 0.001**	1.327 (1.170–1.506)	**< 0.001**

HDL-C High-density lipoprotein cholesterol, *Lp (a)* Lipoprotein (a), *ApoB* Apolipoprotein B, *APTTR* Activated partial thromboplastin time ratio, *Fib* Fibrinogen.
Adjustment variables: age, sex, smoking, dringking, hypertension, diabetes mellitus, systolic blood pressure, creatinine, urea, HDL-C, Glu, HbA1c

plaque remained statistically different between the two groups after multifactorial adjustment ($P < 0.05$). For every tenfold increase (i.e., one log unit increase) in Lp (a) levels, the prevalence of carotid plaque increased by 31.8% (OR = 1.318, 95% CI 1.097–1.584), and similarly, elevated levels of fibrinogen led to an increased risk of carotid plaque development (OR = 1.327, 95% CI 1.170–1.506). And there was a significant interaction between Lp (a) and Fib (OR = 1.103, 95% CI 1.070–1.136, $P_{\text{interaction}} < 0.001$) (Table 5).

Effect of Lp (a) and Fib levels on carotid artery plaque by gender

In this study, male and female gender groups were performed to observe the correlation between Lp (a) and Fib levels and carotid plaque and their interrelationships in different genders, respectively. TG, Lp (a) and APTTR, D-dimer, and Fib levels in male patients were significantly different between the two groups with and without carotid plaques. Elevated levels of Lp (a) and Fib were still found to be associated with an increased risk of carotid plaque disease after multifactorial adjustment (Log_{10} (Lp (a)): OR = 1.301, 95% CI 1.051–1.611; Fib: OR = 1.273, 95% CI 1.104–1.468) (Table 3). In contrast, a correlation between plasma Lp (a) levels and carotid plaque was not observed in female patients; instead, patients with carotid plaque were found to have higher levels of TC, LDL-C, ApoB, and Fib, and this correlation persisted after multivariable adjustment ($P < 0.05$) (Table 3). However, a significant interaction between the effects of Lp (a) and Fib on carotid plaque was observed in both male and female patients (male: OR = 1.101, 95% CI 1.064–1.139, $P_{interaction} < 0.001$; female: OR = 1.107, 95% CI 1.040–1.179, $P_{interaction} = 0.001$) (Table 5).

Correlation analysis of Lp (a) and Fib levels with carotid plaque in different age groups

Since age > 60 years is a risk factor for carotid plaque formation, this study further compared age in groups. In patients aged < 60 years, all lipid indices except TG and Fib levels were statistically different between the two groups, and after multifactorial adjustment, it was observed that LDL-C, Log_{10} (Lp (a)), ApoB, and Fib levels were still associated with carotid plaque, and all are risk factors for increased carotid plaque development (Table 4). Whereas the association of HDL-C and Fib levels with carotid plaque was observed in patients aged ≥ 60 years ($P < 0.05$), this association was no longer present after multifactorial adjustment (Table 4). However, a synergistic effect of Lp (a) and Fib levels on carotid plaque could be found in patients of different age groups, this interaction was stronger in patients aged < 60 years (OR = 1.148, 95% CI 1.102–1.196, $P_{interaction} < 0.001$) (Table 5).

Discussion

According to researchers' statistics and projections, about 21.1% of the global population (30–79 years old) will have carotid plaque in 2020 [16]. The presence of carotid plaque significantly increases the risk of myocardial infarction, stroke, and peripheral vascular disease such as atherosclerosis of the lower extremities. Studies

Table 3 Comparison of lipid levels and coagulation function in patients with and without carotid plaque by gender

Male	With carotid plaque (*n* = 835)	Without carotid plaque (*n* = 1831)	Before adjustment	After adjustment	
			P value	OR (95% CI)	*P* value
TG, mmol/L	2.1 ± 1.96	2.34 ± 2.23	**0.01**	0.951 (0.895–1.010)	0.104
Log_{10} (Lp (a)), mg/L	1.61 ± 0.54	1.52 ± 0.52	**< 0.001**	1.301 (1.051–1.611)	0.016
APTTR	1.05 ± 0.12	1.06 ± 0.14	**0.03**	0.349 (0.130–0.936)	0.036
D-Dimer, ng/mL	159.01 ± 230	107.96 ± 173.27	**< 0.001**	1.001 (1.000–1.002)	0.006
Fib, g/L	3.2 ± 0.86	3.01 ± 0.75	**< 0.001**	1.273 (1.104–1.468)	< 0.001
Female	**With carotid plaque (*n* = 288)**	**Without carotid plaque (*n* = 959)**	**Before adjustment**	**After adjustment**	
			***P* value**	**OR (95% CI)**	***P* value**
TC, mmol/L	4.39 ± 1.28	4.16 ± 1.07	**0.003**	1.302 (1.094–1.550)	0.003
LDL-C, mmol/L	2.76 ± 0.98	2.61 ± 0.85	**0.01**	1.396 (1.131–1.724)	0.002
Log_{10} (Lp (a)), mg/L	1.55 ± 0.51	1.52 ± 0.46	0.35	1.376 (0.947–2.000)	0.094
ApoB, g/L	0.89 ± 0.31	0.83 ± 0.27	**0.01**	2.316 (1.200–4.468)	0.012
TT, s	20.55 ± 1.73	20.91 ± 3.43	**0.02**	0.951 (0.857–1.055)	0.342
PT, s	11.07 ± 1.01	11.36 ± 1.65	**0.01**	0.806 (0.680–0.955)	0.013
APTT, s	30.71 ± 3.06	31.26 ± 3.4	**0.02**	0.976 (0.924–1.032)	0.393
APTTR	1.02 ± 0.11	1.04 ± 0.12	**0.01**	0.399 (0.086–1.844)	0.240
Fib, g/L	3.29 ± 0.68	3.07 ± 0.64	**< 0.001**	1.563 (1.185–2.063)	0.002

TG Triglycerides, *Lp (a)* Lipoprotein (a), *APTTR* Activated partial thromboplastin time ratio, *Fib* Fibrinogen, *TC* Ttotal cholesterol, *LDL-C* Low-density lipoprotein cholesterol; *ApoB* Apolipoprotein B, *TT* Thrombin time; *PT* Prothrombin time, *APTT* Activated partial thromboplastin time. Adjustment variables: age, smoking, dringking, hypertension, diabetes mellitus, systolic blood pressure, creatinine, urea, HDL-C, Glu, HbA1c

Table 4 Comparison of lipid levels and coagulation function in patients with and without carotid plaque in different age groups

Age < 60	**With carotid plaque (*n* = 531)**	**Without carotid plaque (*n* = 1867)**	**Before adjustment**	**After adjustment**	
			***P* value**	**OR (95% CI)**	***P* value**
TC, mmol/L	4.33 ± 1.37	4.19 ± 1.19	**0.02**	1.121 (0.999–1.259)	0.052
HDL-C, mmol/L	0.98 ± 0.32	1.04 ± 0.3	**< 0.001**	0.743 (0.483–1.143)	0.176
LDL-C, mmol/L	2.78 ± 0.98	2.64 ± 0.84	**0.002**	1.261 (1.087–1.464)	0.002
Log_{10} (Lp (a)), mg/L	1.64 ± 0.53	1.52 ± 0.5	**< 0.001**	1.373 (1.076–1.753)	0.011
ApoA1, g/L	1.15 ± 0.25	1.18 ± 0.23	**0.03**	0.737 (0.392–1.386)	0.344
ApoB, g/L	0.93 ± 0.31	0.87 ± 0.27	**< 0.001**	2.046 (1.305–3.208)	0.002
Fib, g/L	3.26 ± 0.84	3 ± 0.71	**< 0.001**	1.454 (1.233–1.715)	< 0.001
Age ≥ 60	**With carotid plaque (*n* = 592)**	**Without carotid plaque (*n* = 923)**	**Before adjustment**	**After adjustment**	
			***P* value**	**OR (95% CI)**	***P* value**
HDL-C, mmol/L	1.07 ± 0.32	1.11 ± 0.34	**0.03**	0.833 (0.534–1.301)	0.422
Log_{10} (Lp (a)), mg/L	1.54 ± 0.53	1.51 ± 0.49	0.23	1.197 (0.910–1.574)	0.198
APTTR	1.04 ± 0.12	1.05 ± 0.12	**0.03**	0.291 (0.087–0.975)	0.045
Fib, g/L	3.2 ± 0.79	3.09 ± 0.72	**0.01**	1.139 (0.937–1.384)	0.193

TC Total cholesterol, *HDL-C* High-density lipoprotein cholesterol, *LDL-C* Low-density lipoprotein cholesterol, *Lp (a)* Lipoprotein (a), *ApoA1* Apolipoprotein A1, *ApoB* Apolipoprotein B; *Fib* Fibrinogen, *APTTR* Activated partial thromboplastin time ratio. Adjustment variables: sex, smoking, dringking, hypertension, diabetes mellitus, systolic blood pressure, creatinine, urea, HDL-C, Glu, HbA1c

Table 5 Synergistic effect of Lp (a) and Fib on carotid plaque

Log_{10} (Lp (a))*Fib	Groups	With carotid plaque	Without carotid plaque	*β*	OR (95% CI)	*P* for interaction
	Overall	5.26 ± 2.6	4.7 ± 2.22	0.098	1.103 (1.070–1.136)	**< 0.001**
	Male	5.28 ± 2.7	4.68 ± 2.33	0.096	1.101 (1.064–1.139)	**< 0.001**
	Female	5.21 ± 2.28	4.75 ± 2.01	0.102	1.107 (1.040–1.179)	**0.001**
	Age < 60	5.46 ± 2.55	4.67 ± 2.21	0.138	1.148 (1.102–1.196)	**< 0.001**
	Age ≥ 60	5.08 ± 2.63	4.78 ± 2.26	0.052	1.054 (1.008–1.101)	**0.020**

Lp (a): Lipoprotein (a); Fib: Fibrinogen. The interaction term effect values and whether they were statistically significant were obtained by including the product term of Log_{10} (Lp (a)) and Fib as an interaction term in the logistic regression model

have shown that every 0.1 mm increase in carotid intima-media thickness increases the risk of myocardial infarction by 10% to 15% and the risk of stroke by 13% to 18% [17], so early prevention of carotid atherosclerotic plaque formation and delaying its progression effectively reduces the risk of cardiovascular and cerebrovascular diseases.

Lp (a) is mainly produced in the liver by covalent binding of LDL-like particles containing apolipoprotein B100 and apolipoprotein (a) via disulfide bonds [18]. Lp (a) particles contain triglycerides, cholesteryl esters, and oxidized phospholipids and may be involved in pathophysiological processes in several systems by promoting atherosclerosis, inducing inflammation, and prothrombotic effects [19, 20]. Genomic, epidemiological, and Mendelian randomization studies have shown that elevated Lp (a) is an independent risk factor for a variety of cardiovascular diseases including coronary heart disease, ischemic stroke, and calcific aortic stenosis [21]. Previous studies have shown that Lp (a) and TG/HDL-C have some value in assessing the stability of carotid atherosclerotic plaques in patients with acute ischemic stroke, and that elevated levels of Lp (a) and TG/HDL-C significantly increase the risk of unstable plaques in patients' carotid arteries [22]. In the present study, we found a significant correlation between patients' plasma Lp (a) and ApoB levels and carotid plaque after correction for risk factors, a result consistent with those reported in related studies [23], and for every tenfold increase (i.e., one log unit increase) in Lp (a) levels, the risk of carotid plaque prevalence increased by 31.8% (OR = 1.318, 95% CI 1.097–1.584). When we stratified the analysis by sex we found that Lp (a) levels were associated with the development of carotid plaques in male patients, whereas this result was not observed in female patients, probably because the prevalence of carotid plaques is much lower in women than in men. Previous studies have found gender differences in the relationship between Lp (a) and carotid atherosclerosis [24], and our findings extend

the knowledge of gender differences in the relationship between Lp (a) and carotid plaque, but due to the small sample size of the stratified populations and differences in the prevalence of carotid plaques between the genders, a larger study may be needed to further validate this result. Next, by subgrouping patients by age, the results of the study showed that carotid plaque was significantly associated with plasma LDL-C, Lp (a), and ApoB levels in patients < 60 years of age, whereas no correlation between lipid levels and carotid plaque was found in patients ≥ 60 years of age. This may be influenced by the use of lipid-lowering drugs in patients with coronary artery disease. Taking lipid-lowering drugs does not significantly affect plasma Lp (a) levels, but may slow the development of atherosclerosis by lowering LDL-C levels; however, the risks associated with elevated Lp (a) levels will not be completely eliminated by the use of lipid-lowering drugs, such as statins, and the attainment of LDL-C. Therefore, this study also reminds us to pay more attention to the importance of controlling lipid levels and early prevention of carotid plaque development in young and middle-aged patients.

Fibrinogen is a class II acutely glycosylated protein with a relative molecular weight of 340 kDa, synthesized by the liver and free in plasma, and is an important reaction substrate for thrombosis. In the case of atherosclerosis, the lining of the blood vessel is damaged and fibrinogen is deposited in the damaged area, promoting thrombosis. In turn, fibrinogen and its degradation products can also stimulate the proliferation and migration of vascular smooth muscle cells, promoting the formation and development of atherosclerotic plaques [5, 6]. Previous studies on the correlation between fibrinogen and carotid plaques are few, Huijun Wen et al. [25] found that the D-dimer to fibrinogen ratio was positively correlated with carotid plaque grading, which could predict the severity of carotid plaques in patients with acute cerebral infarction. In this study, plasma Fib levels were found to be associated with carotid plaque in patients with coronary artery disease, and this correlation persisted after multivariate adjustment. Comparison of age and gender subgroups revealed a significant effect of Fib levels on carotid plaque, with elevated Fib levels increasing the risk of carotid plaques. Since patients with coronary heart disease have been taking anticoagulant or antiplatelet drugs regularly for a long time, anticoagulant drugs mainly prevent blood coagulation by inhibiting the activity of coagulation factors, and antiplatelet drugs usually inhibit the activation and aggregation of platelets to reduce the formation of thrombus, and therefore do not directly affect the level of fibrinogen. In contrast, this correlation disappeared in patients aged ≥ 60 years after adjustment for multifactoriality, which was considered to be possibly due to the altered coagulation status of elderly patients.

Lp (a) is a specialized lipoprotein that contains an apolipoprotein (a) molecule that is partially homologous to plasminogen. Lp (a) competes with plasminogen for the binding site of fibrinogen, which promotes fibrin deposition in the arterial wall and participates in thrombus formation, which then initiates the onset and progression of atherosclerosis [26]. Cheng Yang et al. [27] found that high levels of Lp (a) and Fib were associated with a significantly increased risk of ischemic stroke, and that Lp (a) and Fib had a synergistic effect on ischemic stroke in statin-treated patients with stable CAD. Given the link between the two, this study continued to explore the effects of Lp (a) and Fib on carotid plaque in patients with coronary heart disease, and found that plasma Lp (a) levels and Fib elevation were independent risk factors for carotid plaque, with a significant interaction between the two. The combined carotid plaque-causing effect of Lp (a) and Fib is greater than the product of their individual effects. Analysis of different age and sex subgroups still yielded consistent results, suggesting that Lp (a) and Fib have a synergistic effect on carotid plaque formation in patients with coronary artery disease, which may contribute to their increased risk of ischemic stroke. Therefore, more attention should be paid to patients' plasma Lp (a) and fibrinogen levels, and continued clarification of the mechanisms behind this synergistic effect may be needed in the future to provide a theoretical basis for better prevention and treatment of carotid plaques and reduction of the risk of ischemic stroke.

Plasma Lp (a) concentration levels are mainly regulated by the LPA gene and are less influenced by factors such as diet and living environment [21]. Globally, the number of people with Lp (a) levels above 50 mg/dL is estimated to be over 1.4 billion [28]. However, to date there is a lack of therapies that effectively reduce Lp (a) levels. The efficacy and safety of traditional lipid-lowering tools such as statins, niacin, PCSK9 inhibitors, and plasma replacement methods in lowering Lp (a) levels remain to be explored. Various new types of investigational lipid-lowering drugs aimed at significantly reducing Lp (a) levels, such as antisense oligonucleotide drugs, small interfering RNA drugs, and other RNA-targeted therapies, have entered phase II and III clinical trials [29]. Therapeutic approaches and medications for Lp (a) will evolve as medicine advances, and the core principle of the current management of patients with clinically elevated Lp (a) levels is to reduce the overall risk of ASCVD, including control of concomitant clinically significant dyslipidemias. Patients with elevated Lp (a) may benefit from lifestyle interventions, more aggressive statin LDL-C-lowering therapy, and other control of other

modifiable cardiovascular risk factors. Therefore, at present, prevention and treatment of carotid plaque through lifestyle improvement and rational use of statins is an effective way.

This study also has some limitations. First, the results of this study should be cautiously generalized to other populations because the patients were selected from a database established by a single health care provider and because plasma Lp (a) concentrations are race-specific. Second, there may be potential confounders in the study design, such as the fact that certain possible risk factors were not considered or interventions were used. In addition, since this was a retrospective study and causality could not be established, only correlations were analyzed in this study, and further validation may be needed in the future with prospective cohort studies or randomized controlled trials. Finally, some other factors such as lifestyle and genetic factors may influence the interpretation of the relationship between Lp (a) and Fib and carotid plaque, and more studies are needed to explore the mechanisms of this association.

Conclusions

In summary, plasma Lp (a) and Fib levels in patients with coronary artery disease are associated with the occurrence of carotid plaque, and there is a synergistic effect between the two on carotid plaque, and the active control and improvement of other modifiable cardiovascular risk factors in patients with high Lp (a) levels may become an important measure for the prevention and treatment of carotid plaque and ischemic stroke.

Abbreviations

Lp (a)	Lipoprotein (a)
Fib	Fibrinogen
CAD	Coronary artery disease
IMT	Intima-media thickness
TC	Total cholesterol
TG	Triglycerides
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
LDL	Low density lipoprotein
Apo (a)	Apolipoprotein (a)
ApoB	ApolipoproteinB
ApoA1	ApolipoproteinA1

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Author contributions

F ZY and W MW conceived and supervised the study and performed statistical analysis of the data. L ZY was involved in the procedure and wrote the main body of the manuscript. W MY participated in the discussion on the interpretation of the research content and took part in the procedure. L S revised this paper. All authors critically revised and approved the final version of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University (No. 220525-06-2305A-Y1) and was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from each participant.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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