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RESEARCH ARTICLE

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Lp-PLA2 evaluates the severity of carotid artery stenosis and predicts the occurrence of cerebrovascular events in high stroke-risk populations

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Abstract

Background: Lipoprotein-associated phospholipase A2 (Lp-PLA2) is an independent risk factor for cardiovascular disease. However, relationship between carotid artery stenosis and cerebrovascular events in high stroke-risk populations is still unclear.

Methods: A total of 835 people at a high risk of stroke were screened from 15,933 people aged >40 years in April 2013 and followed at 3, 6, 12, and 24 months. Finally, 823 participants met the screening criteria, and the clinical data and biochemical parameters were investigated.

Results: Among the 823 participants, 286 had varying degrees of carotid artery stenosis and 18 had cerebrovascular events. The level of Lp-PLA2 in the carotid artery stenosis group was higher than that in the no stenosis group, and the level in the event group was higher than that in the no event group ($p < 0.05$). Spearman correlation analysis showed that Lp-PLA2 was positively correlated with the degree of carotid artery stenosis ($r = 0.093$, $p = 0.07$) and stenosis involvement ($r = 0.094$, $p = 0.07$). The correlation coefficient between Lp-PLA2 and lipoprotein was the highest on the levels of sdLDL ($r = 0.555$, $p < 0.001$), followed by non-HDL, LDL, TC, and TG. Cox multivariate regression analysis revealed that, compared with the first quantile of Lp-PLA2 level (Q1, low level), the risk of cerebrovascular events in the fourth quantile of Lp-PLA2 was 10.170 times that of the first quantile (OR = 10.170, 95% CI 1.302–79.448, $p = 0.027$).

Conclusions: Lp-PLA2 levels can evaluate carotid artery stenosis and predict the occurrence of cerebrovascular events in high stroke-risk populations and provide scientific guidance for risk stratification management.

KEYWORDS
cerebrovascular events, high-risk population, lipoproteinassociated phospholipase A2, stroke

1 | INTRODUCTION

Cerebrovascular disease (CVD) has become a major social and public health problem worldwide,[1,2] including stroke, abnormal cerebrovascular, and malformations, and other disorders of cerebral blood circulation.[3] The mortality rate of cerebrovascular diseases in urban and rural areas is 125.78 per 100,000 and 151.91 per 100,000, respectively.[4,5] Given the high morbidity, high mortality,

high disability, and high recurrence rates of CVD,[6] it places a very heavy burden on families and society. Therefore, the prevention and treatment of cardiovascular diseases are urgently needed.

Hypertension, dyslipidemia, heart disease, diabetes, smoking, being overweight, and lack of physical activity are common risk factors for CVD.[7] Among these risk factors, blood biomarkers play a critical role in the formation and rupture of atherosclerotic plaques.[8] However, currently available evidence is insufficient to predict CVD events. To identify a sufficient method for the occurrence of cerebrovascular disease in populations at a high risk of stroke, research of new biomarkers to predict CVD events early has attracted wide attention. Recently, researchers have explored biomarkers associated with atherosclerosis (AS) and CVD. Among these studies, lipoprotein-associated phospholipase (Lp-PLA2) was found to significantly promote AS.[9]

Atherosclerosis is a disorder of lipid metabolism and chronic inflammatory diseases.[10,11] Endothelial dysfunction is a pathological basis for cerebrovascular diseases and is one of the major factors in the formation of carotid artery stenosis.[12] This eventually leads to cardiovascular and cerebrovascular events.

Lp-PLA2 is mainly secreted by macrophages, T lymphocytes, monocytes, and mast cells.[13] Lp-PLA2 plays a key role in the development of inflammation and AS, mainly including the aggregation and activation of leukocytes and platelets, vascular smooth muscle cell proliferation and migration, endothelial dysfunction, expression of adhesion molecules and cytokines, and the core of plaque necrosis. The formation of Lp-PLA2 downregulates the synthesis and release of nitric oxide in endothelial cells, enhances oxidative stress response, and promotes endothelial cell apoptosis.[14]

This study mainly aimed to explore the relationship between Lp-PLA2 levels and carotid artery stenosis and the value of early prediction of CVD events in stroke-risk populations and to provide a scientific basis for risk stratification management and early prevention of stroke-risk populations in order to reduce the heavy burden of cardiovascular disease on families and society.

2 | METHODS

2.1 | Ethics statements

This study was approved by the Ethics Committee of Zhejiang Provincial People's Hospital (No. 2020QT286), which waived the requirement of informed consent.

2.2 | Study population

In April 2013, the study subjects were screened from 15,933 residents aged >40 years in Zhaohui Street, Xiacheng District, Hangzhou, Zhejiang Province. For those at a high risk of stroke, 835 candidates were selected, and members of the research team conducted telephone follow-ups of people at a high risk of stroke at the 3rd, 6th, 12th, and 24th months from April 2013, and 823 eventually met the criteria, including 473 women and 350 men. (Study flow was shown on Figure 1).

The inclusion criteria were as follows: aged >40 years; a history of stroke; a history of transient ischemic attack; a history of hypertension (≥140/90 mm Hg) or taking antihypertensive drugs; atrial fibrillation and valvular disease; smoking; dyslipidemia or unknown; diabetes; rarely performed physical exercise (standard frequency of physical exercise is ≥3 times a week, each ≥30 minutes, for more than 1 year; those engaged in moderate to severe physical labor are regarded as having regular physical exercise), obesity (body mass index [BMI] ≥ 26 kg/m^2); and a family history of stroke. Those who have lived or worked outside the study areas for more than half a year; have severe liver or kidney disease or malignant tumors, mental illness, or systemic immune disease; or have 2-year follow-up period, incomplete data, or lost to follow-up were excluded. The screening of the above at-risk population is in line with national clinical guidelines for stroke.[15]

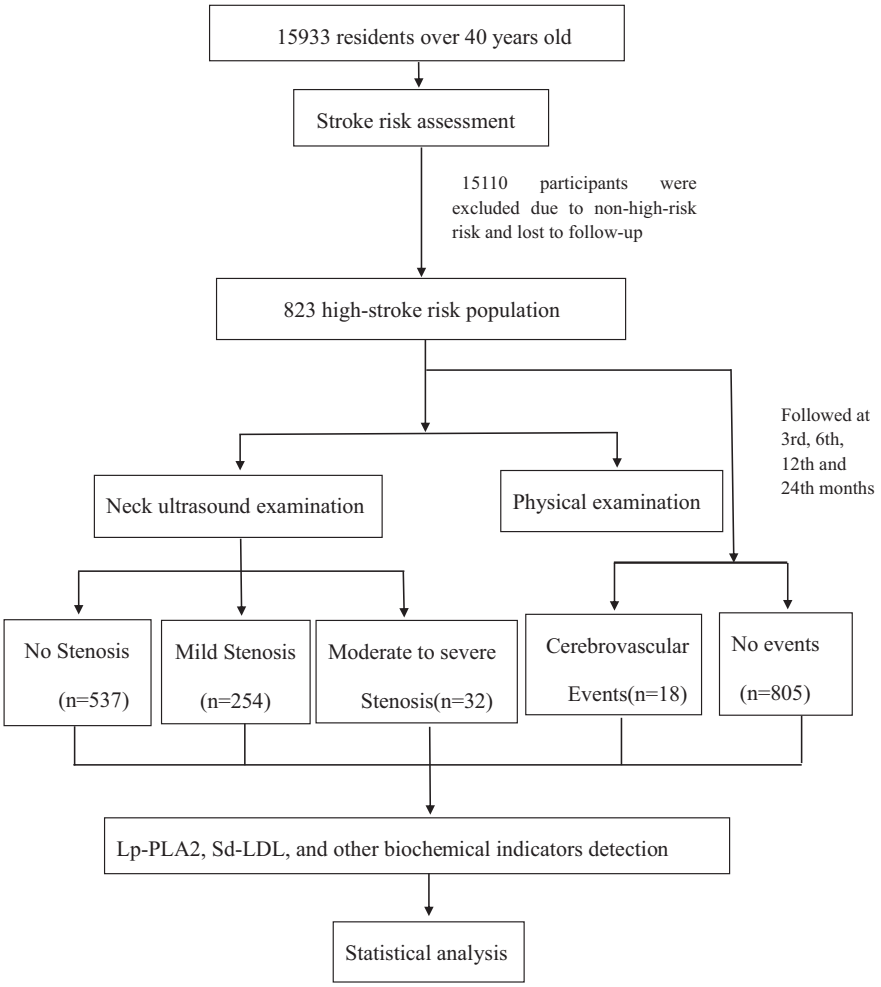
2.3 | China stroke prevention project committee (CSPPC) stroke program

Stroke is a chronic disease that seriously threatens the health of the Chinese population. The incidence of stroke across the country is rising at an annual rate of 8.7%. The annual cost of treating cerebrovascular diseases is more than 10 billion yuan, and the indirect economic losses cost nearly 20 billion yuan every year. To address the various challenges caused by stroke, the Chinese Ministry of Health established the CSPPC in April 2011. CSPPC formulates policies, issues clinical guidelines, and organizes community hospitals to carry out stroke-risk factor screening and risk assessment for permanent residents over 40 years old in high-incidence areas and to conduct health education and regular physical examinations for selected low-risk populations, intervention guidance for the middle-risk population based on individual characteristics, further inspections for the high-risk population, and comprehensive intervention. During regular follow-up of the middle-risk and high-risk groups, patients identified to have cervical vascular disease or suspected stroke will be referred to the hospital for further diagnosis and treatment.

2.4 | Carotid ultrasound and physical examination

The neck ultrasound examinations of all subjects were performed using ultrasound diagnostic apparatus S2000 (Siemens, Germany) according to the guidelines established by the European Stroke Conference. The blood vessels examined included the bilateral common carotid artery, carotid sinus, internal carotid artery, subclavian artery, and vertebral artery. Carotid artery stenosis[16] is then divided into (i) mild stenosis, in which the inner diameter is reduced by 1%–49%, the ultrasound image shows local plaques, and there is no

FIGURE 1 Study flowchart



significant change in blood flow; (ii) moderate stenosis, in which the inner diameter is reduced by 50%–69%, the blood flow is accelerated at the plaque stenosis, and the pathological vortex is formed at the distal end of the stenosis; and (iii) severe stenosis, in which the inner diameter is reduced by 70%–99%, the plaque is aggravated, the blood flow is further accelerated at the plaque stenosis, and pathological vortex and turbulent mixed signals are formed at the distal end.

All relevant measurements such as weight, height, waist circumference, and blood pressure (BP) were measured by trained medical personnel in strict accordance with the corresponding standards. After verification and verification, data were entered into the database of the China Stroke Data Center.

2.5 | Data collection and blood biochemistry

All subjects fasted for at least 8 hours, and 3 mL of cubital venous blood was drawn into a separating gel-accelerating vacuum blood collection tube and left for approximately 15 minutes after the plasma was precipitated. The serum was separated by centrifugation at relative centrifugal force of 560 *g* for 15 minutes, and one part was sent to the laboratory biochemistry room. Blood glucose (GLU), triglycerides (TG), total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), homocysteine (HCY), uric acid (UA), and free fatty acid (FFA) tests were completed on the same day. One portion was immediately stored in the refrigerator at −80°C. Small and dense low-density lipoprotein (sdLDL), Lp-PLA2, high-sensitivity C-reactive protein (hs-CRP), cystatin C (Cys C), and lipoprotein a (LPa) completed the test on the day of the experiment.

Demographic parameters such as age; sex; waist circumference; BMI, systolic blood pressure; diastolic blood pressure; medical history of all subjects, such as heart disease history, diabetes history, hypertension history, dyslipidemia history, smoking history, family history of hypertension, family history of diabetes data such as stroke, family history of coronary heart disease, family history of stroke; carotid artery ultrasound results; and cardiovascular and cerebrovascular events were all collected from the China Stroke Data Center database.

2.6 | Statistical analysis

SPSS 20.0 was used to analyze the data, and GraphPad Prism 5 (GraphPad Software Inc., La Jolla, CA) was used to draw graphs.

Count data were expressed as a percentage, and the comparison between groups was analyzed using the chi-square test. Measurement data with normal distribution were expressed as mean ± standard deviation (±s). The comparison between two groups was performed using the t test, and the comparison of multiple groups was performed by single-factor analysis of variance. Measurement data of non-normal distribution are expressed as median (interquartile range), and the rank-sum test was used for comparison between groups. Correlation analysis was performed using Spearman correlation analysis or Pearson correlation analysis. Regression analysis was performed using logistic multivariate regression analysis. Survival analysis uses the proportional hazards regression model (Cox regression analysis) method, and $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Lp-PLA2 levels in groups with different degrees of carotid artery stenosis

According to the neck ultrasound findings, there were 537 patients in the no stenosis group, 254 patients in the mild stenosis group, and 32 patients in the moderate to severe stenosis group. As the

TABLE 1 Demographic characteristics and clinical biochemical parameters in different carotid artery stenosis groups

Variables	Degree of carotid artery stenosis			*p* Value
	No Stenosis	Mild Stenosis	Moderate to severe Stenosis	
Total number, n	537	254	32	
Males, n (%)	202 (37.6%)	128 (50.4%)	20 (62.5%)	0.000
Age (y)	66.46 ± 8.38	70.6 ± 7.84	75.03 ± 7.5	0.000
BMI (kg/m²)	24.84 (22.82–27.01)	24.77 (22.84–26.87)	24.12 (19.92–25.88)	0.186
SBP (mm Hg)	135 (128–146)	143 (133–154)	143 (129–152)	0.000
DBP (mm Hg)	81.67 ± 10.28	81.93 ± 11.25	82.78 ± 10.54	0.822
Heart Disease, n (%)	111 (20.7%)	54 (21.3%)	11 (34.4%)	0.185
Diabetes, n (%)	207 (38.5%)	114 (44.9%)	22 (68.8%)	0.002
Hypertension, n (%)	485 (90.3%)	234 (92.1%)	31 (96.9%)	0.357
Dyslipidemia, n (%)	332 (61.8%)	149 (58.7%)	24 (75%)	0.188
Smoking, n (%)	80 (14.9%)	37 (14.6%)	4 (12.5%)	0.931
History of stroke, n (%)	138 (25.7%)	72 (28.3%)	6 (18.8%)	0.451
TC (mmol/L)	5.43 ± 1.17	5.37 ± 1.08	5.27 ± 1.33	0.645
TG (mmol/L)	1.70 (1.22–2.41)	1.73 (1.31–2.52)	1.92 (1.26–2.67)	0.695
LDL (mmol/L)	3.09 ± 0.89	3.14 ± 0.87	(3.07 ± 0.99)	0.736
HDL (mmol/L)	1.22 (1.05–1.49)	1.20 (1.05–1.42)	1.19 (1.01–1.33)	0.285
nonHDL(mmol/L)	4.13 ± 1.14	4.11 ± 1.01	4.06 ± 1.24	0.920
Glucose (mmol/L)	5.57 (5.00–6.66)	5.81 (5.04–6.89)	6.41 (5.39–9.30)	0.002
HOMA-IR	2.49 (1.69–3.65)	2.34 (1.69–3.91)	2.64 (1.61–4.47)	0.921
HOMA-IS	0.40 (0.27–0.60)	0.43 (0.26–0.59)	0.39 (0.22–0.62)	0.918
UA(μmol/L)	337 (279–402)	350 (292–407)	389 (352–441)	0.002
HCY(μmol/L)	11.9 (10.3–14.8)	12.8 (11.0–15.2)	16.5 (12.8–20.8)	0.000
FFA(μmol/L)	584 (449–785)	609 (424–805)	604 (471–789)	0.947
Cystatin C (mg/L)	0.93 (0.81–1.07)	0.98 (0.85–1.11)	1.10 (0.97–1.45)	0.000
hs-CRP (mg/L)	0.73 (0.34–1.88)	0.72 (0.34–1.91)	0.95 (0.37–3.19)	0.629
LP(a) (mg/L)	117.4 (58.3–221.0)	123.7 (66.9–247.6)	95.9 (42.8–245.8)	0.216
SdLDL (mg/dL)	35.42 (25.15–47.42)	36.25 (26.00–47.97)	41.09 (28.08–53.95)	0.496
Lp-PLA2 (IU/L)	554.04 ± 127.32	574.16 ± 132.55	601.94 ± 154.44	0.027

Abbreviation: BMI, body mass index; DBP, diastolic blood pressure; FFA, Free Fat Acid; HCY, homocysteine; HDL, High-density lipoprotein; HOMA-IR, Homeostasis model assessment for insulin resistance; HOMA-IS, Homeostasis model assessment for insulin sensitivity; hs-CRP, High-sensitivity C-reactive protein; LDL, Low-density lipoprotein; LP(a), Lipoproteins(a); LP-PLA2, Lipoprotein-associated phospholipase A2; nonHDL, Non–high-density lipoprotein cholesterol; SBP, systolic blood pressure; sdLDL, small dense low-density lipoprotein; TC, Total cholesterol; TG, Triglycerides; UA, uric acid.

severity of carotid artery stenosis increased, the age, systolic BP, male ratio, and diabetes history ratio increased, and the difference among the three groups was statistically significant ($p < 0.05$) (Table 1). The level of Lp-PLA2 was higher in the moderate to severe stenosis group than in the no stenosis group ($p < 0.05$), and the level in the mild stenosis group was higher than that in the non-stenosis group ($p < 0.05$). No statistically significant differences in sdLDL and other parameters were found among the three groups ($p > 0.05$). Then, the correlation between Lp-PLA2 and other parameters was analyzed. Studies have shown that Lp-PLA2 is positively correlated with the degree of carotid artery stenosis and the range of stenosis. In these high-risk groups, the clinical biochemical indicators TG, TC, LDL, nonHDL, GLU, Homeostatic Model Assessment for Insulin Resistance, UA, HCY, FFA, CYS C, hs-CRP, and sdLDL were positively correlated with Lp-PLA2 ($r > 0$, $p < 0.05$), and the correlation coefficient between Lp-PLA2 and other lipoproteins was in this order sdLDL > non-HDL > LDL > TC > TG. sdLDL showed the strongest correlation with Lp-PLA2 ($r = 0.555$), and HDL was negatively correlated with Lp-PLA2 ($r = -0.145$, $p < 0.001$).

3.2 | Association between Lp-PLA2 level and occurrence of cerebrovascular events

We followed the patients for 2 years and found that 18 had cerebrovascular events, and the remaining 805 had no cerebrovascular events. The level of Lp-PLA2 was higher in the group with cerebrovascular events than in the group without cerebrovascular events (662.81 ± 111.25 vs 559.86 ± 130.05, $p < 0.001$) (Table 2 and Figure 2). The levels of some parameters that can reflect renal function, such as Cys C, HCY, and UA, were also higher in the event group than in the no event group (Table 2, $p < 0.05$). The level of hs-CRP, an inflammatory marker, was also higher in the event group than in the no event group (Table 2, $p < 0.05$). No statistical difference was found between the other parameters of the event group, such as HDL, LDL, and the no event group (Table 2, $p > 0.05$). The levels of Lp-PLA2 were then divided into four groups (Q1–Q4). As the quartile of Lp-PLA2 levels increases, the incidence of cerebrovascular events increases. In the cerebrovascular event group, the incidence of cerebrovascular events increased with the increase in Lp-PLA2

TABLE 2 Comparison of demographic characteristics and clinical biochemical parameters of cerebrovascular events

Variables	Cerebrovascular events		*p* Value
	No events	Events	
Total number, n	805	18	
Males, n (%)	343 (42.6%)	7 (38.9%)	0.475
Age (y)	67.96 ± 8.52	73 ± 6.75	0.013
BMI(kg/m²)	24.80 (22.77–26.95)	25.12 (24.00–26.34)	0.547
SBP (mm Hg)	138 (129–150)	142 (136–149)	0.138
DBP (mm Hg)	81.74 ± 10.58	84.11 ± 11.04	0.348
Heart Disease, n (%)	169 (21%)	7 (38.9%)	0.068
Diabetes, n (%)	335 (41.6%)	8 (44.4%)	0.495
Hypertension, n (%)	732 (90.9%)	18 (100%)	0.184
Dyslipidemia, n (%)	492 (61.1%)	13 (72.2%)	0.242
Smoking, n (%)	118 (14.7%)	3 (16.7%)	0.507
History of stroke, n (%)	211 (26.2%)	5 (27.8%)	0.531
TC (mmol/L)	5.4 ± 1.15	5.64 ± 1.11	0.389
TG (mmol/L)	1.71 (1.24–2.45)	1.97 (1.23–2.47)	0.583
LDL (mmol/L)	3.1 ± 0.89	3.33 ± 1.04	0.271
HDL (mmol/L)	1.21 (1.04–1.46)	1.28 (1.04–1.47)	0.920
Glucose (mmol/L)	5.64 (5.01–6.80)	6.08 (5.48–6.52)	0.229
HOMA-IR	2.47 (1.67–3.71)	3.00 (1.85–5.20)	0.211
HOMA-IS	0.41 (0.27–0.60)	0.34 (0.19–0.55)	0.212
UA(μmol/L)	341 (286–405)	431 (313–496)	0.023
HCY(μmol/L)	12.4 (10.5–15.0)	14.8 (13.2–21.4)	0.003
FFA(μmol/L)	588 (445–793)	609 (468–834)	0.613
Cystatin C (mg/L)	0.94 (0.83–1.08)	1.19 (0.96–1.32)	0.002
hs-CRP (mg/L)	0.72 (0.34–1.86)	1.68 (0.47–4.22)	0.030
LP(a) (mg/L)	120.0 (60.1–230.4)	114.5 (44.4–220.0)	0.687
SdLDL (mg/dL)	35.54 (25.40–47.49)	50.76 (40.36–56.18)	0.002
Lp-PLA2 (IU/L)	559.86 ± 130.05	662.81 ± 111.25	0.0007

quantile (Table 3, p = 0.027). In the group with cerebrovascular events, the fourth quartile had a higher incidence of cardiovascular and cerebrovascular events than the first quartile (Table 3, $p < 0.05$).

3.3 | Cerebrovascular events are positively correlated with the degree of carotid artery stenosis

The incidence of cerebrovascular events in the stenosis group was higher than that in the no stenosis group (Table 4, p = 0.17), but no statistically significant difference was noted. As regards progression of stenosis, that is, from no stenosis to severe stenosis, increases in the degree of stenosis likely lead to an increase in the incidence of cerebrovascular events (Table 4). Furthermore, the greater the number of stenoses, the greater the probability of cerebrovascular events (Table 4).

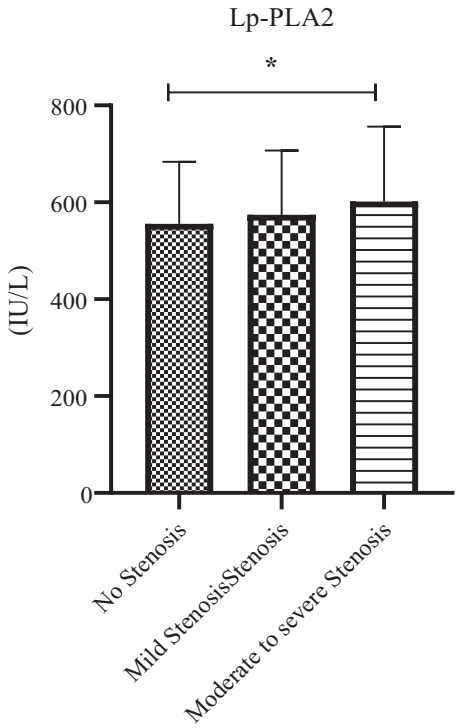


FIGURE 2 Differences in Lp-PLA2 levels among people with different degrees of stenosis. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

3.4 | Effects of Lp-PLA2 levels on cerebrovascular events and mortality

Participants were followed for 2 years. In the subsequent analysis using Cox regression to analyze the forward LR method, the occurrence of cerebrovascular events was used as the value indicating that the event had occurred, the follow-up time was used as the time variable, the Lp-PLA2 level quartile was used as the classification covariate, and the first quantile was used as the reference group. The results suggest that Lp-PLA2 is a risk factor for cerebrovascular events (Figure 3, p = 0.046). Compared with the first quartile, the risk of cerebrovascular events increased as the quartile increased. Compared with the first quantile, the risk of cerebrovascular events in the fourth quantile was 10.170 times that of the first quantile (OR=10.170, 95%CI 1.302–79.448, p = 0.027) (Table 5 and Figure 4).

4 | DISCUSSION

In this study, the association between CVD and Lp-PLA2, a novel plasma biomarker involved in the development of carotid artery stenosis and cerebrovascular events in populations at a high risk of stroke, was investigated. The results showed that the level of Lp-PLA2 in the carotid artery stenosis group was significantly higher than that in the no stenosis group, and its level was positively correlated with the degree of carotid artery stenosis. Cox regression analysis showed that Lp-PLA2 was an independent factor in the risk prediction of cerebrovascular events. All findings demonstrated the possible clinical application of Lp-PLA2 to predict the occurrence of cerebrovascular events and assess the degree of carotid artery stenosis.

Lp-PLA2 is a biomarker produced by inflammatory cells, which can break down oxidized phospholipids and release products that promote inflammation and further aggravate AS.[17] Some previous studies have referred to the role of Lp-PLA2 in the formation of carotid AS and carotid stenosis. Charniot et al.[18] showed that the level of Lp-PLA2 in patients with carotid artery stenosis increased significantly with the severity of atherosclerotic lesions, and the level of Lp-PLA2 in the severe stenosis group was the highest. A group of researchers investigated 111 patients with chronic coronary artery disease confirmed by angiography and reported that Lp-PLA2 was positively correlated

TABLE 3 Relationship between the incidence of cerebrovascular events after grouping Lp-PLA2 quartiles

Quartiles of Lp-PLA2 (IU/L)					
	Q1	Q2	Q3	Q4	*p* Value
No events	205 (99.5%)	202 (98.5%)	202 (98.1%)	196 (95.1%)	0.027
Events	1 (0.5%)	3 (1.5%)	4 (1.9%)	10 (4.9%)	

Note: The difference between the events and no evens group of Lp-PLA2 with varying level.
First quantile (Q1): Lp-PLA2 ≤ 473.10 IU/L; second quantile (Q2): 473.10 IU/L < Lp-PLA2 < 560.70 IU/L; third quantile (Q3): 560.70 IU/L ≤ Lp-PLA2 < 643.90 IU/L; fourth quartile (Q4): Lp-PLA2 ≥ 643.90 IU/L.
$p < 0.05$ is considered statistically significant.

TABLE 4 Relationship between carotid artery stenosis and the incidence of cerebrovascular events

	Cerebrovascular Events		
	No events	Events	*p* Value
Carotid artery stenosis			
No stenosis	528 (98.3%)	9 (1.7%)	0.170
Stenosis	277 (96.9%)	9 (3.1%)	
Degree of carotid artery stenosis			
No stenosis	528 (98.3%)	9 (1.7%)	0.156
Mild stenosis	247 (97.2%)	7 (2.8%)	
Moderate to severe stenosis	30 (93.8%)	2 (6.2%)	
Carotid artery stenosis range			
No stenosis	528 (98.3%)	9 (1.7%)	0.149
<3 blood vessels	176 (97.8%)	4 (2.2%)	
≥3 blood vessels	101 (95.3%)	5 (4.7%)	

Note: The diference between the cebrovascular events and no events in the carotid artery stenosis group and no stenosis,with varying degrees of stenosis and stenosis range.

$p < 0.05$ is considered statistically significant.

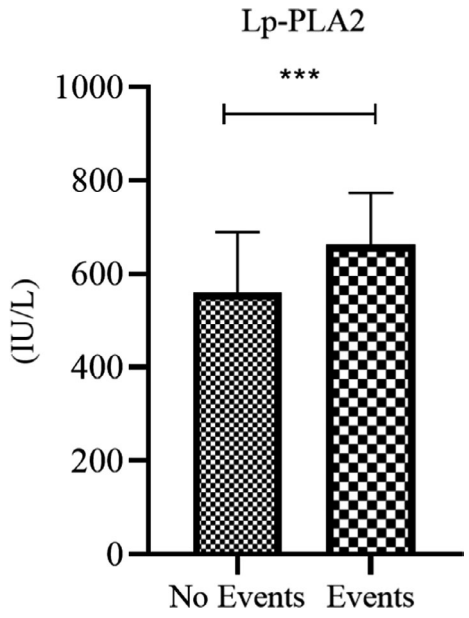


FIGURE 3 Differences in Lp-PLA2 levels between groups with cerebrovascular events and without cerebrovascular events. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

with carotid intima-media thickness. In addition, the carotid artery stenosis of the Lp-PLA2 high-level group was severe and the thickness of the intima-media was higher than those in the control group,[19] which implies that Lp-PLA2 may be the main factor for carotid artery thickening. Another researcher recruited 678 patients diagnosed with coronary artery disease by angiography. Multivariate regression analysis showed that Lp-PLA2 is an independent risk factor for AS. A cross-sectional study measured Lp-PLA2 levels in the blood of people aged >40 years and proved that this new marker is inextricably linked to carotid AS and carotid artery stenosis. However, this study cannot prove the role of high levels of Lp-PLA2 in carotid plaque formation.[20] The above results suggest that increased expression of Lp-PLA2 is highly associated with atherosclerotic lesions. Therefore, it plays a very important role in risk assessment of carotid artery stenosis. However, most research samples are relatively small and may not be able to prove the clinical value of Lp-PLA2 in these blood circulation diseases.

Lp-PLA2 plays a role in CVD, as it can aggravate atherosclerotic lesions and easily rupture complex and vulnerable plaques, leading to CVD events. Several recent studies have shown that plasma Lp-PLA2 levels are associated with the risk of subsequent coronary heart disease and ischemic stroke.[19,21–23] In a multi-ethnic cohort study, high levels of Lp-PLA2 and activities were associated with an increased incidence of cardiovascular disease and coronary heart disease in people without a baseline clinical cardiovascular disease.[24] In this study, the patients who were at a high risk for stroke were followed for 2 years, and the level of Lp-PLA2 in the cerebrovascular event group was significantly higher than that in the no event group. Moreover, we grouped Lp-PLA2 levels into quartiles and found that the high-level group (Q4) had a much higher risk of cerebrovascular events than the low-level group, with an increase in the Lp-PLA2 quartile, and the incidence of cerebrovascular events increased. In addition, the risk of cerebrovascular events in the fourth quantile is 10.170 times that of the first quantile. The results suggest that Lp-PLA2 is a risk factor for the occurrence of cerebrovascular events, and as the level of Lp-PLA2 increases, the risk of cerebrovascular events increases. Lp-PLA2 level has a predictive value for the occurrence of cerebrovascular events in populations at a high risk of stroke.

The limitations of this study are as follows. First, the sample size was not large, the follow-up time was only 2 years, and the number of cerebrovascular events that eventually occurred was relatively small. Second, this study was conducted at a single center and the study population mainly included people aged >40 years at a high

TABLE 5 Cox regression analysis for cerebrovascular events and death by Lp-PLA2 (UI/L) Levels

Variables	*B*	*SE*	*Wals*	*OR*	95% CI		*p* Value
					Upper bound	Lower bound	
Q1			8.015				0.046
Q2	1.113	1.155	0.929	3.044	0.317	29.264	0.335
Q3	1.392	1.118	1.550	4.022	0.450	35.985	0.213
Q4	2.319	1.049	4.891	10.170	1.302	79.448	0.027

Abbreviations: CI, confidence interval; OR, odds ratio.

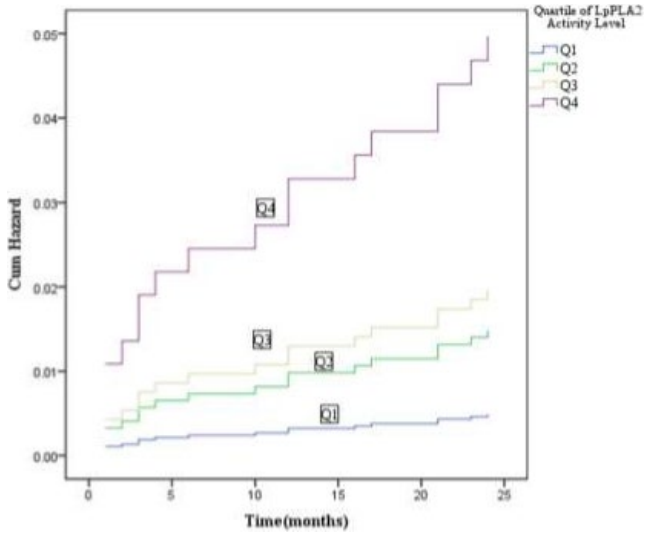


FIGURE 4 Cox cumulative hazard for people with various Lp-PLA2 levels. The Lp-PLA2 level was grouped as follows: Q1, Lp-PLA2 ≤ 473.10 IU/L; Q2, 473.10 IU/L < LpPLA2 < 560.70 IU/L; Q3, 560.70 IU/L ≤ LpPLA2 < 643.90 IU/L; Q4, Lp-PLA2 ≥ 643.90 IU/L

risk of stroke, so the results of the study only represented a small part of the population. Finally, we only analyzed the correlation between other demographic parameters and clinical biochemical indicators and Lp-PLA2. However, we did not combine these indicators with Lp-PLA2 to assess carotid artery stenosis and cerebrovascular events. In the future, we will increase the sample size and follow patients for a longer period of time. We will further explore the clinical value of multiple indicators in cerebrovascular events and carotid artery stenosis.

In conclusion, the level of Lp-PLA2 was positively correlated with the degree of carotid artery stenosis and predicted cerebrovascular events. Our results suggest that Lp-PLA2 may be a tool for evaluating the prognosis of the development of cardiovascular and cerebrovascular diseases.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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