

Correlation between plasma levels of Lp-PLA2, Hcy, CRP, Lp(a), AT-III, and TEG parameters and carotid atherosclerosis in patients with combined hypertension and cerebral infarction

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Abstract

Background: To observe the correlation between Lp-PLA2, Hcy, CRP, Lp(a), AT-III, and TEG parameters and carotid atherosclerosis with combined hypertension and cerebral infarction and evaluate their value in risk determination.

Methods: Patients with primary hypertension were selected as subjects and divided into 2 groups based on cerebral infarction: simple hypertension group and hypertension combined with cerebral infarction group. The differences of Lp-PLA2, Hcy, CRP, Lp(a), AT-III, and TEG were compared. Spearman correlation and multivariate logistic regression model were used to analyze the correlation. A ROC curve was used to analyse the value of a single item and their combination for the determination of carotid AS risk.

Results: The levels of single item and CIMT in the hypertension combined with cerebral infarction group were higher, and the values of R, EPL, and LY30 were lower than corresponding indicators in the simple hypertension group. Furthermore, it was found that Lp-PLA2 and Hcy were risk factors. The AUC for Hcy and Lp-PLA2 for the determination the carotid AS risk were larger.

Conclusions: The increase or decrease of Lp-PLA2, Hcy, and TEG were important factors influencing the development of carotid AS with combined hypertension and cerebral infarction. The levels of Lp-PLA2, Hcy, and TEG with combined hypertension and cerebral infarction were significantly different from those with simple hypertension and could be used as independent predictive factors for determining carotid AS risk.

Background

Cerebral infarction has become a common cardiovascular and cerebrovascular disease in recent years (1). Compared with that in western countries, the incidence of cerebral infarction in the Chinese population is higher (~ 15 to 50%) (2) (3). Cerebral infarction involves progressive stenosis or even blood vessel obstruction caused by carotid and/or vertebral atherosclerosis (AS). The insufficient blood supply in the brain causes hypoxia, ischaemia, and even necrosis of brain cells. Cerebral infarction can also result in long-term cardiac insufficiency and a reduced left ventricular ejection fraction, which can eventually affect cardiac function (4). The consequences of progression of this disease cannot be ignored (5).

The development and progression of cerebral infarction are associated with various indicators, such as hypertension, AS, dyslipidaemia, obesity, diabetes mellitus, and smoking (6–8). Hypertension is an important traditional risk factor in the progression of cerebral infarction (9). A reduction in blood pressure in patients with hypertension reduces the incidence of cerebral infarction (10–12); however, it is still higher than that in the healthy population (13). A persistent increase in blood pressure results in vascular endothelial injury and haemodynamic changes that promote platelet activation in the blood (14), causing AS under the joint actions of multiple factors such as dyslipidaemia, obesity, and inflammation (15). AS plaques and thrombosis are major pathological bases of cerebral infarction (16). Inflammation and platelet aggregation are considered the trigger mechanisms and key links that participate in the development of AS plaques and thrombosis. Changes in the levels of some factors in patients with combined hypertension and cerebral infarction may have a certain association with disease progression.

Looking for risk factors and disease-associated factors has become a focus of scientific research and clinical diagnosis and treatment. Exploration of novel markers is very important for predicting the development of cerebral infarction, evaluating the disease condition of patients, and scientifically selecting treatment regimens. Some recent studies have shown that several mediators such as lipoprotein-associated phospholipase A2 (Lp-PLA2), homocysteine (Hcy), C-reactive protein (CRP), and lipoprotein(a) (Lp(a)) might be risk factors for AS (17–19).

Carotid intima thickening is an early sign of AS, therefore, it is selected as a predictive indicator of cardiovascular and cerebrovascular events. Carotid intima-media thickness (CIMT) is detected by colour Doppler ultrasound as the standard, to screen for plasma inflammation and coagulation-related indicators (Lp-PLA2, Hcy, CRP, Lp(a), AT-III, and TEG) that participate in AS plaques and thrombosis to investigate the correlation between each indicator and CIMT in order to provide bases for the prevention of AS and treatment of patients with combined hypertension and cerebral infarction.

Methods

1 Material and methods

1.1 General data Patients with primary hypertension who were admitted to the Affiliated Hospital of Nanjing University of Traditional Chinese Medicine for treatment between January 2018 and May 2019 were used as subjects. The Medical Ethics Committee of our hospital approved the study, and patients who participated the research were informed and signed a consent form. The inclusion criteria were ☒ patients who met the diagnostic criteria of primary hypertension in the Chinese Guidelines for Prevention and Treatment of Hypertension (2010 revised edition); blood pressure at admission indicated stage 2-3 hypertension; systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 100 mmHg; no previous history of peripheral arteriosclerosis and cardiovascular and cerebrovascular diseases; and no positive sign during the physical examination; ☒ patients who met the diagnostic criteria of cerebral infarction revised during the Fourth National Cerebrovascular Disease Conference and in whom the diagnosis was confirmed by magnetic resonance imaging (MRI) or brain computed tomography (CT); and ☒ healthy individuals who received a physical examination, did not have previous history of peripheral arteriosclerosis and cardiovascular and cerebrovascular diseases after inquiry of the medical history, did not have diseases that caused increased levels of Lp-PLA2, Hcy, CRP, and Lp(a), and had not recently taken any medication. The exclusion criteria were ☒ patients who had secondary hypertension, atrial fibrillation, diabetes mellitus, coronary heart disease, and malignant tumours; ☒ patients who had kidney and coagulation diseases and thyroid dysfunction; ☒ patients who had haematopoietic diseases, rheumatic and immune system diseases, tissue necrosis, and acute and chronic inflammation diseases combined with infection and fever; ☒ patients with a history of surgery, trauma, deep vein thrombosis, and organ transplantation; ☒ patient who took medication that affected Lp-PLA2, Hcy, CRP, and Lp(a) levels (such as diuretics, folic acid, vitamin B complex, and statins); ☒ patients with a history of long-term smoking and drinking; and ☒ pregnant or lactating women. The simple hypertension group had 193 patients (106 males and 87 females) whose ages ranged from 23 to 91 years (average age, 64 ± 14 years). The hypertension combined with cerebral infarction group had 192 patients (117 males and 75 females) whose ages ranged from 34 to 90 years (average age, 69 ± 12 years). In addition, a healthy population who received a physical examination was used as the control group. In the control group, there were 151 patients (105 males and 46 females), whose ages ranged from 31 to 85 years (average age, 65 ± 13 years). These people of control group had never had a stroke or a history of high blood pressure.

1.2 Detection methods

1.2.1 Bilateral carotid ultrasound A PHILIPS iu-22 multi-functional colour Doppler ultrasound diagnostic apparatus (Philips, Netherlands) was used; the probe frequency was 5 to 12 MHz. CIMT of the subjects was measured separately. The following were the determination standards for CIMT: CIMT <1.0 mm and normal carotid ultrasound suggested smooth arterial intima; $1.0 \text{ mm} \leq \text{CIMT} \leq 1.5$ mm suggested intimal thickening and rough arterial intima; and CIMT >1.5 mm and localized eminences suggested by ultrasound indicated carotid intimal plaque formation. Carotid AS was diagnosed when there was intimal thickening and/or plaque formation in either side of the carotid artery.

1.2.2 Measurement of Lp-PLA2, Hcy, CRP, Lp(a), AT, and TEG levels The blood from each subject was obtained for testing. The levels of Lp-PLA2 were measured by a Model 680 enzyme-labeled instrument (Bio-Rad, America) with a functional assay sensitivity of 10 ng/ml. The levels of Hcy were measured by an ARCHITECT i2000SR immunoanalyzer (Abbott, America) with a functional assay sensitivity of $1.0 \mu\text{mol/L}$. The CRP levels were detected by a QuikRead go immunity analyzer (Orion Diagnostica Oy, Finland) with a functional assay sensitivity of 1.0 mg/L. The levels of Lp(a) were measured by an OLYMPUS AU5800 biochemical analyzer (Beckman Coulter, America). The levels of AT were measured by a STA-R Evolution coagulation analyzer (STAGO, France). Simulation of the coagulation process in the body and dynamic monitoring of coagulation system functioning are used to detect various indicators such as the coagulation factor activity, platelet function, and fibrinolytic activity. The detection parameters in this study included coagulation reaction time (R), clot formation time (K), clot formation rate (α -angle), maximum clot strength or hardness (MA), estimated percent lysis (EPL), clot amplitude reduction rate (LY30), coagulation comprehensive index (CI), clot mechanic strength (G), and platelet aggregation function (A). We detected TEG with a Thrombelastograph 5000 analyzer (Haemonetics, America). In addition, blood lipids parameters were detected using an OLYMPUS AU5800 biochemical analyser. The instruction manual was referenced for specific protocols.

1.3 Statistical analysis

Normally distributed data were expressed as median plus or minus standard deviation and one-way anova was performed between groups. Percentage data were expressed as percentage (%) and χ^2 test was performed between groups. The p-values were corrected for the number of comparisons using the Bonferroni method, and all tests were two-tailed. Spearman correlation and multivariate logistic regression model were selected to analyze the correlation between each index and CIMT. Receiver operating characteristics (ROCs) were analyzed to determine the optimal cut-off values, and the area under the curve (AUC) values were compared to select the variables that predict the differentiation. $P<0.05$ was considered statistical significant. All statistical analysis was performed using the Statistical Package for Social Sciences software, version 20.0 (SPSS, Chicago, IL, USA).

Results

2.1 Comparison of body mass index (BMI), cigarette, sex and age as well as TC, TG, HDL-C, LDL-C, Lp-PLA2, Hcy, CRP, Lp(a), AT-III, CIMT, and TEG among the 3 groups

The differences in age, sex, cigarette and BMI as well as TC, TG, HDL-C, and LDL-C among the 3 groups were not statistically significant ($p>0.05$). The levels of Lp-PLA2, Hcy, Lp(a), CIMT, and the TEG-related parameters MA, A, G in the hypertension combined with cerebral infarction group were significantly higher, whereas the R, EPL, and LY30 values were significantly lower than corresponding indicators in the simple hypertension group (Lp-PLA2: $p<0.001$; Hcy: $p<0.001$; Lp(a): $p=0.020$; CIMT: $p=0.001$; MA: $p<0.001$; A: $p<0.001$; G: $p=0.015$; R: $p=0.038$; EPL: $p=0.029$; LY30: $p=0.007$) (Table 1 and Figure 1).

2.2 Detection of carotid AS in the 3 groups

In the hypertension combined with cerebral infarction group, 80 patients had carotid intima thickening, and 51 patients had plaque formation; therefore, there were 131 patients with carotid AS, accounting for 68.23% of the group. In the hypertension group, 80 patients had carotid intima thickening, and 23 patients had plaque formation; therefore, there were 103 patients with carotid AS, accounting for 53.37% of the group. In the control group, 23 patients had carotid intima thickening, and 13 patients had plaque formation; therefore, there were 36 patients with carotid AS, accounting for 23.84% of the group. Analysis using the χ^2 test showed that among the 3 groups, those with normal carotid intima, intima thickening, and plaque formation differed significantly ($\chi^2=16.162$, $p<0.001$). The percentage of AS increased significantly in the hypertension combined with cerebral infarction group ($\chi^2=67.702$, $p<0.001$) (Table 2).

2.3 Correlation analysis between plasma Lp-PLA2, Hcy, CRP, Lp(a), AT-III, and TEG and CIMT of patients in the hypertension combined with cerebral infarction group

Correlation analysis showed that the plasma levels of Lp-PLA2 and Hcy positively correlated with CIMT of patients in the hypertension combined with cerebral infarction group (Lp-PLA2: $r=0.413$, $p<0.001$; Hcy: $r=0.510$, $P<0.001$). The level of the TEG-related parameter R negatively correlated with CIMT (R: $r=-0.211$, $p=0.003$). After adjusting for age, sex, smoking and blood lipid, the correlation was still found (Table 3 and Figure 2). The results showed that Lp-PLA2, Hcy, R were linearly correlated with CIMT after gradual correction of age, sex, smoking and blood lipid by stepwise linear regression analysis of multiple factors. In addition, the VIF (Variance Inflation Factor) values of each variable in the model are less than 2, indicating that there is no collinearity among the variables (Table 4).

Analysis of the correlation among plasma Lp-PLA2, Hcy, CRP, Lp(a), AT-III, and TEG parameters in all enrolled subjects showed that Lp-PLA2 positively correlated with Hcy, α -angle, MA, A, CI, and G and negatively correlated with AT-III and K. Hcy positively correlated with CRP, Lp(a), α -angle, MA, A, CI, and G and negatively correlated with AT-III, R, K, and EPL (Table 5).

2.4 Logistic regression analysis between plasma Lp-PLA2, Hcy, CRP, Lp(a), AT-III, TEG and CIMT

The results showed that Lp-PLA2 and Hcy were risk factors for carotid atherosclerosis after adjusting for age, sex, smoking and blood lipid. The OR values (95% CI) were 1.019 (1.012-1.027) and 1.190 (1.110-1.277), respectively (Table 6).

2.5 Diagnostic value of Lp-PLA2, Hcy, CRP, Lp(a), AT-III, or TEG alone and in combination for the determination carotid AS risk.

The ROC curve showed that in the evaluation of carotid AS risk using Lp-PLA2, the AUC was 0.677, the 95% CI was 0.632 to 0.722, and the threshold value was 140.01 ng/ml; in the evaluation of carotid AS risk using Hcy, the AUC was 0.707, the 95% CI was 0.663 to 0.750, and the threshold value was 12.79 µmol/L; in the evaluation of carotid AS risk using Lp(a), the AUC was 0.557, the 95% CI was 0.509 to 0.606, and the threshold value was 12.50 mg/L; and in the evaluation of carotid AS risk using AT-III, the AUC was 0.555, the 95% CI was 0.506 to 0.604, and the threshold value was 94.5%. The TEG-related parameters that were significant in the evaluation of carotid AS risk were R, K, α-angle, MA, Cl, and G; their AUCs were 0.600, 0.621, 0.624, 0.562, 0.555, and 0.562, respectively, and the threshold values were 6.95 min, 1.65 min, 65.95°, 56.75 mm, 1.75, and 6551 d/sc, respectively. For the determination of carotid AS risk using the combination of all TEG parameters, the AUC was 0.663, and the 95% CI was 0.617 to 0.708. For the determination of carotid AS risk using the combination of Lp-PLA2, Hcy, CRP, Lp(a), and AT-III, the AUC was 0.747, and the 95% CI was 0.706 to 0.787. For the determination of carotid AS risk using the combination of all items, the AUC was 0.759, and the 95% CI was 0.719 to 0.798; the AUC was the largest (Table 7 and Figure 3).

Conclusions

Hcy and Lp-PLA2 were better diagnostic indicators in the prediction of carotid AS risk

The pathology of AS involves chronic inflammation with slow progression. Various inflammatory mediators and chemokines participate in its development and progression (20, 21). The stability of AS plaques is key to determining disease prognosis (22). The rupture of AS plaques can cause a series of serious life-threatening consequences such as cerebral infarction or myocardial infarction. The development and progression of AS is closely associated with oxidative stress, inflammation, and dyslipidaemia (23). The formation of foam cells from mononuclear macrophages through a series of pathological processes involving the phagocytosis of lipids under the arterial intima has been recognized as a marker of the development and progression of AS plaques (24). Abnormal autophagy in macrophages and macrophages themselves play a pivotal role in the progression of AS plaques (25). After autophagy, macrophages can release Lp-PLA2 to promote foam cell formation, which is closely associated with plaque instability (26). Abnormal autophagy in macrophages is also closely associated with the process of inflammation (27). Autophagy can directly regulate the production and secretion of inflammatory factors such as IL-1β. In addition, inflammatory factors released by mononuclear macrophages also play an autophagy regulatory role (28, 29).

In mediators associated with carotid AS, Lp-PLA2 can hydrolyse oxidized LDL in the arterial wall to produce lysophosphatidylcholine and oxidized free fatty acids. These 2 inflammatory mediators have very strong AS-promoting functions (30). Earlier studies considered that elevated LP-PLA2 levels were associated with cardiovascular events (31). Hcy is a cytotoxic sulfur-containing amino acid and is an intermediate metabolite produced by the demethylation of methionine. Through oxidative stress, Hcy can attenuate endothelial system functions, promote vascular smooth muscle proliferation, and increase the incidence of thrombotic diseases (32). CRP is not only a highly sensitive inflammation marker but also a component of the non-specific immune system in the body. It activates complements that participate in inflammation and promote thrombosis (33). Lp(a) is a lipoprotein containing specific antigens. It is involved in the development and progression of coronary AS (34). Some researchers have reported that plasma Lp(a) has a very close relationship with AS (35, 36). It indicated that there were differences in the percentage of carotid AS and the levels of Lp-PLA2, Hcy, Lp(a) between the hypertension combined with cerebral infarction group and the simple hypertension group. Furthermore, we found that CIMT was positively correlated with Lp-PLA2 and Hcy. It was hypothesized that Lp-PLA2 and Hcy correlated with carotid AS of patients with combined hypertension and AS. We found that the AUCs of Hcy and Lp-PLA2 in the ROC analysis were larger (0.707 and 0.677, respectively), suggesting that Hcy and Lp-PLA2 were also better diagnostic indicators in the prediction of carotid AS risk.

R value was also a better diagnostic indicator for the prediction of carotid AS

In the development of AS, deregulation the coagulation and anti-coagulation system in the body also plays a very important role. The human body as a whole relies on the collaboration among multiple systems and multiple tissues. Mediators and systems never work in isolation. The complement system, inflammatory system, and coagulation system influence and regulate one another during the development of AS. AT-III is closely associated with the hypercoagulable state, and a reduction in its activity

suggests thrombosis. It has been shown that a reduction in AT-III activity might predict the progression of acute coronary events in patients with coronary artery disease; in addition, the level of reduction in AT-III activity positively correlated with coronary artery stenosis (37, 38). This study showed that the AT-III levels in the hypertension combined with cerebral infarction group and the simple hypertension group were not statistically different and that the AT-III levels in the two groups were much lower than corresponding indicators in the control group. These results indicated that patients with hypertension were already in a thrombophilic state whether or not they had combined cerebral infarction. The correlation analysis results showed that AT-III did not correlate with AS. The ROC curve analysis showed that AT-III was not suitable for the diagnosis of carotid AS.

Blood flow status, vascular wall injury, and blood component changes are 3 elements of thrombosis. During hypertension, high fluid shear stress can easily damage the vascular intima. Injured endothelial cells release various types of cytokines that increase the levels of many coagulation factors and adhesion between platelets, exposed collagen under the endothelium, and fibres; subsequently, platelets are activated and release active substances that cause vasoconstriction and induce adhesion and aggregation of more platelets (39–41). Therefore, the body of patients with hypertension is in a hypercoagulable state. TEG can monitor dynamic changes in coagulation during the diagnosis and treatment of common cerebral infarction complications in patients with hypertension and analyse the types of abnormal coagulation. Compared to conventional coagulation detection, TEG can detect abnormal coagulation earlier (42). The coagulation reaction time R mainly reflects the activity of coagulation factors; the K value and α -angle reflect the clot formation rate and fibrinogen function; MA reflects platelet function; the CI value reflects the coagulation comprehensive index; the G value reflects the mechanical strength of clots; and the amplitude value A reflect the aggregation function of platelets. Through our correlation analysis, we found that the R value decreased as CIMT increased, suggesting that the R value was negatively correlated with carotid AS. The ROC analysis result showed that the AUC of the R value in the determination of carotid AS risk was 0.600, suggesting that the R value was also a better diagnostic indicator for the prediction of carotid AS. Meanwhile, we found that the α -angle, MA, A, and CI values increased, the R and K values decreased in both of the hypertension groups compared with the control group. These results suggested that patients with hypertension, whether or not combined with cerebral infarction, had increased fibrinogen activity, increased platelet activity and coagulation factor activity, and increased CI compared to the normal population; in addition, their bodies tended to remain in a hypercoagulable state.

In summary, in patients with combined hypertension and cerebral infarction, an increase or decrease in plasma levels of Lp-PLA₂, Hcy, and TEG-related parameters influenced the formation of carotid AS. The levels of Lp-PLA₂, Hcy, and TEG indicators in patients with combined hypertension and cerebral infarction could be used as independent predictive factors for determining carotid AS risk. Analysis using a combination of indicators could help increase the reliability of carotid AS risk determinations.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethical Committee of Affiliated Hospital of Nanjing University of Traditional Chinese Medicine. All subjects agreed the study and signed informed consent letters.

Consent to publish

The manuscript is approved by all authors for publication.

Availability of data and materials

The data and materials are available.

Competing interests

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Authors' Contributions

Dr Gu and Dr Yang conceived and designed the study. Dr Ji and Dr Wang performed the experiments. Dr Zhu provided the mutants. Dr Ji and Dr Gu wrote the paper. Dr Zhuo and Dr Gu reviewed and edited the manuscript. All authors read and approved the manuscript.

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Abbreviations

AS: atherosclerosis; Lp-PLA2: lipoprotein-associated phospholipase A2; Hcy: homocysteine; CRP: C-reactive protein; Lp(a): lipoprotein(a); AT $\ddot{\text{a}}$: antithrombin $\ddot{\text{a}}$; TEG: thrombelastograph; CIMT: Carotid intima-media thickness; MRI: magnetic resonance imaging; CT: computed tomography; R: coagulation reaction time; K: clot formation time; α -angle: clot formation rate; MA: maximum clot strength or hardness; EPL $\ddot{\text{a}}$ estimated percent lysis $\ddot{\text{a}}$ LY30 $\ddot{\text{a}}$ clot amplitude reduction rate $\ddot{\text{a}}$ CI: coagulation comprehensive index; G: clot mechanic strength; A: platelet aggregation function; ROC: Receiver operating characteristics; AUC: area under the curve; BMI: body mass index; TC: total cholesterol; TG: triglyceride; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; VIF: Variance Inflation Factor

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Tables

Tables

Tab.1 Comparison of the levels of Lp-PLA₂·Hcy·CRP·Lp(a)·AT-III·TEG and CIMT in three groups

groups	n	age	gender	cigarette	BMI	TC	TG	HDL·C	LDL·C
		(year)	(m/f)	(yes/no)		(mmol/L)	(mmol/L)	(mmol/L)	(mmol/L)
Group A	192	69±12	117/75	73/119	24.1±2.5	4.85±1.17	1.55±0.97	1.46±0.37	2.86±0.97
Group B	193	64±14	106/87	67/126	23.8±2.4	4.91±1.16	1.47±0.91	1.53±0.43	2.96±0.89
Group C		151	65±13	105/46	58/93	23.9±2.7	4.78±1.08	1.58±1.13	1.43±0.45
									2.91±0.93
p Value ^a		0.088		0.761	0.591	0.467	0.432	0.579	
p Value ^b		0.094	0.306	0.306	0.835	0.896	0.511	0.531	0.867
p Value ^c		0.125		0.566	0.791	0.768	0.487	0.399	

groups	Lp-PLA2 (ng/ml)	Hcy (μmol/L)	CRP (mg/L)	Lp(a) (mg/L)	AT-II (%)	CIMT (mm)
Group A	140.09±29.43	15.92±8.05	13.28±28.13	202.35±267.17	94.35±11.22	1.16±0.37
Group B	119.66±29.29	12.20±4.06	9.45±18.45	144.45±178.96	93.97±13.30	1.03±0.33
Group C	100.12±30.81	9.13±1.90	5.36±3.35	113.28±152.58	99.88±6.93	0.83±0.35
p Value ^a	<0.001	<0.001	0.191	0.020	1.000	0.001
p Value ^b	<0.001	<0.001	0.192	0.511	<0.001	<0.001
p Value ^c	<0.001	<0.001	0.001	<0.001	<0.001	<0.001

groups	R (min)	K (min)	α-Angel (°)	MA (mm)	EPL (%)	LY30 (%)	A (mm)	CI (d/sc)	G
Group A	6.33±1.47	1.63±0.59	66.61±5.42	60.01±4.88	4.53±4.75	3.23±3.76	56.11±6.47	1.79±1.22	7930±1945
Group B	6.69±1.12	1.61±0.37	66.09±4.56	57.62±5.70	6.53±8.69	4.79±5.25	52.79±8.06	1.62±1.06	7281±1903
Group C	7.48±0.86	1.93±0.28	62.11±5.12	55.94±7.88	6.56±8.76	4.79±6.06	50.61±9.75	1.27±1.20	7073±2939
p Value ^a	0.038	1.000	0.934	<0.001	0.029	0.007	<0.001	0.406	0.015
p Value ^b	<0.001	<0.001	<0.001	0.036	1.000	1.000	0.039	0.017	1.000
p Value ^c	<0.001	<0.001	<0.001	<0.001	0.042	0.014	<0.001	<0.001	0.002

Group A: the hypertension combined with cerebral infarction group; Group B: the hypertension group; Group C: control group. p Value^a Group A versus Group B||p Value^b Group B versus Group C||p Value^c Group A versus Group C

Tab.2 Analysis of the detection of carotid atherosclerosis in three groups

groups	n	CIMT <1.0	1.0≤ CIMT ≤1.5	CIMT >1.5	Carotid AS
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Group A 192 61±31.77± 80±41.67± 51±26.56± 131±68.23%±

Group B 193 90±46.63± 80±41.45± 23±11.92± 103±53.37%±

Group C 151 115±76.16± 23±15.23± 13±8.61± 36±23.84%±

χ^2 16.162 67.702

p Value <0.001 <0.001

Group A: the hypertension combined with cerebral infarction group; Group B: the hypertension group; Group C: control group.

Tab.3 Analysis of the correlation of Lp-PLA2±Hcy±CRP±Lp(a)±AT-±TEG and CIMT

	Spearman's r	p Value	Partial's r	p Value
Lp-PLA2	0.413	<0.001	0.397	<0.001
Hcy	0.510	<0.001	0.434	<0.001
CRP	0.063	0.385	0.015	0.836
Lp(a)	0.139	0.054	0.136	0.060
AT-±	0.111	0.124	0.166	0.121
R	-0.211	0.003	-0.217	0.003
K	-0.099	0.171	-0.189	0.109
α -Angel	0.102	0.160	0.188	0.099
MA	-0.012	0.864	0.032	0.664
EPL	0.145	0.054	0.076	0.299
LY30	0.095	0.192	0.106	0.144
A	-0.032	0.659	-0.041	0.571
CI	-0.031	0.671	-0.110	0.132
G	-0.038	0.603	0.045	0.537

Tab.4 The multiple stepwise linear regression analysis of Lp-PLA2±Hcy±CRP±Lp(a)±AT-±TEG and CIMT

	Unstandardized Coefficients		Beta	t	p Value	Collinearity Statistics	
	B	Std. Error				Tolerance	VIF
(Constant)	0.502	0.153		3.291	<0.001		
HCY	0.019	0.003	0.419	7.269	<0.001	0.999	1.001
lpPLA2	0.005	0.001	0.390	6.768	<0.001	0.999	1.001
R	-0.049	0.014	-0.194	-3.372	<0.001	0.998	1.002

Tab.5 Analysis of the correlation of Lp-PLA2-Hcy-CRP-Lp(a)-AT-TEG

	Hcy	CRP	LPa	AT3	R	K	α -	MA	EPL	LY30	A	CI	G
Angel													
LpPLA2	r	0.308	-0.010	0.079	-0.109	-0.074	-0.220	0.234	0.117	-0.065	-0.021	0.097	0.194
	p	0.000	0.818	0.067	0.012	0.085	0.000	0.000	0.007	0.132	0.620	0.025	0.000
Hcy	r		0.158	0.148	-0.130	-0.182	-0.347	0.375	0.236	-0.207	-0.041	0.263	0.154
	p		0.000	0.001	0.002	0.000	0.000	0.000	0.000	0.349	0.000	0.000	0.000
CRP	r			0.151	-0.117	-0.035	-0.133	0.116	0.121	-0.075	-0.067	0.134	-0.001
	p			0.000	0.007	0.425	0.002	0.007	0.005	0.081	0.123	0.002	0.980
LPa	r				-0.019	-0.003	-0.154	0.151	0.088	-0.028	0.013	0.063	0.109
	p				0.659	0.948	0.000	0.000	0.041	0.514	0.772	0.145	0.012
AT3	r					0.207	0.165	-0.200	-0.069	0.092	0.043	-0.119	-0.037
	p					0.000	0.000	0.000	0.110	0.033	0.317	0.006	0.394
R	r						0.467	-0.408	-0.177	-0.062	-0.128	-0.102	0.180
	p						0.000	0.000	0.000	0.149	0.003	0.018	0.000
K	r							-0.765	-0.426	0.061	-0.066	-0.311	0.026
	p							0.000	0.000	0.159	0.126	0.000	0.551
α -Angel	r								0.451	-0.115	-0.027	0.372	-0.058
	p								0.000	0.008	0.539	0.000	0.180
MA	r									-0.277	-0.223	0.714	-0.037
	p									0.000	0.000	0.000	0.957
EPL	r									0.777	-0.562	-0.157	-0.252
	p									0.000	0.000	0.000	0.000
LY30	r										-0.577	-0.058	-0.230
	p										0.000	0.179	0.000
A	r											-0.026	0.707
	p											0.554	0.000
CI	r												0.030
	p												0.483

Tab.6 The logistic regression analysis of Lp-PLA2-Hcy-CRP-Lp(a)-AT-TEG and CIMT

	B	S.E.	p Value	OR (95%CI)
lpPLA2	0.019	0.004	0.000	1.019 (1.012-1.027)
Hcy	0.174	0.036	0.000	1.190 (1.110-1.277)
CRP	0.002	0.005	0.729	1.002 (0.992-1.012)
LPa	0.000	0.000	0.373	1.000 (0.999-1.001)
AT3	0.002	0.009	0.818	1.002 (0.985-1.020)
R	-0.199	0.102	0.052	0.820 (0.670-1.002)
K	0.052	0.357	0.884	1.054 (0.524-2.119)
Angel	0.043	0.031	0.174	1.044 (0.981-1.110)
MA	-0.043	0.042	0.306	0.958 (0.882-1.040)
EPL	-0.010	0.018	0.555	0.990 (0.956-1.024)
LY30	0.045	0.037	0.220	1.047 (0.973-1.125)
A	0.018	0.031	0.566	1.018 (0.958-1.081)
CI	0.093	0.102	0.362	1.097 (0.899-1.339)
G	0.000	0.000	0.660	1.000 (1.000-1.000)
Constant	-5.253	3.121	0.092	0.005

Tab.7 The use of cut-off values of individual biomarker or in combination for discrimination carotid atherosclerosis.

	cut-off value	p Value	AUC(95%CI), %	Sensitivity, %	Specificity, %	PPV/NPV, %	Accuracy, %
Lp-PLA2 (ng/ml)	140.01	<0.001	0.677 (0.632-0.722)	42.2	84.6	33.6/59.1	63.2
Hcy ($\mu\text{mol/L}$)	12.79	<0.001	0.707(0.663-0.750)	45.6	84.6	35.3/60.5	64.9
CRP (mg/L)	12.50	0.076	0.544(0.495-0.593)	22.2	89.1	20.2/53.0	55.4
Lp(a) (mg/L)	71	0.021	0.557(0.509-0.606)	62.6	47.7	57.1/55.7	55.2
AT- \square (%)	94.5	0.027	0.555 (0.506-0.604)	51.1	64.7	44.5/56.6	57.8
R (min)	6.95	<0.001	0.600(0.552-0.648)	75.6	47.4	61.8/65.6	61.6
K (min)	1.65	<0.001	0.621 (0.573-0.668)	75.6	47.4	61.8/65.6	61.6
α -Angel ($^{\circ}$)	65.95	<0.001	0.624(0.577-0.672)	74.8	46.6	62.0/64.6	60.8
MA (mm)	56.75	0.014	0.562 (0.513-0.610)	76.7	36.8	67.9/60.9	56.9
EPL (%)	4.55	0.601	0.513(0.464-0.562)	51.9	55.6	48.6/53.2	53.7
LY30(%)	3.25	0.599	0.487(0.438-0.536)	59.3	46.2	56.5/52.8	52.8
A(mm)	55.85	0.054	0.548(0.499-0.597)	48.5	65.4	43.0/55.6	56.9
CI	1.75	0.028	0.555(0.506-0.604)	43.3	71.1	38.2/55.3	57.1
G(d/sc)	6551	0.014	0.562 (0.513-0.610)	77.4	36.5	68.3/61.4	57.1
Combined-a		<0.001	0.663(0.617-0.708)	73.7	52.6	58.7/66.4	63.2
Combined-b		<0.001	0.747(0.706-0.787)	47.0	91.0	34.4/62.9	68.8
Combined-c		<0.001	0.759(0.719-0.798)	41.9	95.9	30.7/61.9	68.7

Combined-a combined the parameters of R \square K \square α -Angel \square MA \square EPL \square LY30 \square A \square CI \square G \square Combined-b combined the parameters of Lp-PLA2 \square Hcy \square CRP \square

Lp(a) \square AT- \square Combined-c combined the parameters of Lp-PLA2 \square Hcy \square CRP \square Lp(a) \square AT- \square R \square K \square α -Angel \square MA \square EPL \square LY30 \square A \square CI \square G \square .

Figures



Figure 1

Comparison of the levels of Lp-PLA2-Hcy-CRP-Lp(a)-AT-and TEG and CIMT in three groups Group A: the hypertension combined with cerebral infarction group; Group B: the hypertension group; Group C: control group.



Figure 2

Analysis of the correlation of Lp-PLA2-Hcy-CRP-Lp(a)-AT-and TEG and CIMT



Figure 3

3 The ROC analysis of combined biomarkers and individual biomarker in the evaluation of carotid AS Combined-a-combined the parameters of R-K α -Angel-MA-EPL-LY30-A-Cl-G Combined-b-combined the parameters of Lp-PLA2-Hcy-CRP-Lp(a)-AT- Combined-c-combined the parameters of Lp-PLA2-Hcy-CRP-Lp(a)-AT-R-K α -Angel-MA-EPL-LY30-A-Cl-G.