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Original Article

Prognostic value of color Doppler ultrasound, D-dimer, and Lp-PLA2 levels in carotid atherosclerotic stenosis

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Abstract: Background: This research mainly explored the prognostic value of color Doppler ultrasound combined with D-dimer and Lp-PLA2 levels in carotid atherosclerotic stenosis. Methods: From January 2018 to August 2020, 67 patients (patient group) who were diagnosed as cerebral infarction by neurology and carotid atherosclerotic stenosis by digital subtraction angiography (DSA) were recruited in this research. Fifty healthy people served as controls and were brought into this research. PI (pulsatility index), RI (resistance index), Vd (end diastolic velocity), and Vs (peak systolic velocity) were obtained by color Doppler ultrasound vascular wall imaging. The levels of D-dimer and Lp-PLA2 in serum were examined. The receiver operating characteristics (ROC) curve was employed to analyze the diagnostic efficacy of color Doppler ultrasound imaging parameters, serum D-dimer, and lipoprotein-associated phospholipase A2 (Lp-PLA2) levels on the prognosis of patients with carotid atherosclerotic stenosis. Results: The levels of PI, RI, serum D-dimer, and Lp-PLA2 in the patient group were higher than those in the control group ($P < 0.05$). Levels of Vd and Vs were lower. PI, RI, serum D-dimer, and Lp-PLA2 levels were positively correlated with mRS scores ($P < 0.05$). Vd and Vs were negatively correlated ($P < 0.05$). The measurement of VD and Lp-PLA2 levels was more effective in predicting the prognosis of patients with carotid atherosclerotic stenosis. Conclusion: Vd parameters and Lp-PLA2 levels have high clinical values in carotid atherosclerotic stenosis, and are worthy of clinical application.

Keywords: Color Doppler ultrasound, D-dimer, Lp-PLA2, carotid atherosclerotic stenosis, prognosis

Introduction

Cardio-cerebrovascular diseases have always been a common and extremely harmful disease among the elderly, with high morbidity, disability, and mortality [1]. With the rapid aging population, the number of elderly patients aged 80 and above has increased. There are many basic diseases in elderly patients. Cardio-cerebrovascular events still occur even under the condition of regulating second-level prevention drug. Atherosclerosis is one of the vital basic pathologies [2, 3]. Elderly patients are often accompanied with symptoms such as hypertension, their blood pressure is in a high state for a long time, the vascular endothelial cells are damaged, and the tension of the vascular wall is gradually changed. Higher blood pressure will also cause monocytes, lymphocytes, and some macrophages to be in the intima, which reduce the elasticity of the arterial wall and gradually harden the vascular wall. As a result, carotid atherosclerosis has become the most familiar disease in elderly patients [4-6].

Research has shown that carotid artery stenosis caused by carotid atherosclerotic plaque is one of the most crucial reasons for ischemic cerebral infarction [7]. Recent investigations reveal that more than 90% of carotid artery stenosis is caused by atherosclerosis [8]. Prevention and treatment measures mainly include controlling risk factors, drug treatment, carotid endarterectomy, and carotid stent implantation [9]. Although the treatment of carotid artery stenosis has made progress, patients still have a relapse after treatment [10]. There is no clinical index to predict the prognosis of carotid atherosclerotic stenosis. Color Doppler ultrasound is a common imaging method in diagnosing carotid atherosclerotic

stenosis clinically. D-dimer and Lp-PLA2 are clinical detection indexes for atherosclerosis [11, 12].

The purpose of this research is to investigate the predictive value of color Doppler ultrasound indicators, D-dimer, and lipoprotein-associated phospholipase A2 (Lp-PLA2) levels in the prognosis of carotid atherosclerotic stenosis, and to provide reference indicators for clinical determination of prognosis.

Methods and data

Clinical data

Patients with cerebral infarction and carotid atherosclerotic stenosis diagnosed by neurology from January 2018 to January 2021 were enrolled in this retrospective analysis. Sixty-seven cases were regarded as the patient group. All of them (40 male and 27 female patients) were treated with carotid stent implantation, with an average age of 65.4±7.7 years. There were 50 healthy controls (35 male and 15 female patients), with an average age of 62.4±6.2 years. This research was approved by the Medical Ethics Committee of our hospital. Ethics batch number: LL0410 (05).

Inclusion and exclusion criteria

Inclusion criteria: All patients were diagnosed as carotid atherosclerotic stenosis. Patients were diagnosed as carotid atherosclerotic stenosis by digital subtraction angiography (DSA). All the symptoms met the standard of Chinese Guidelines for Diagnosis and Treatment of Acute Ischemic Stroke 2018 [13]. Patients and their families knew about this research and signed informed consent forms.

Exclusion criteria: Patients who were complicated with tumors; those with congenital organ dysfunction, or consciousness disorder; those who did not cooperate with treatment and follow-up.

Color Doppler ultrasound detection

PHILIPS-EPI Q7 color Doppler ultrasound diagnostic instrument was applied in this research. The probe frequency was 4-6 MHz. Patients were routinely in the supine position without a pillow, with their heads tilted to the opposite side of the examined blood vessel with necks fully exposed. The probe was adjusted to clearly display the long axis image of carotid artery. The carotid artery was observed by color flow imaging. In the measurement of blood flow spectrum, the sampling volume is placed on the axis of the blood vessel. The Doppler angle must be ≤ 60 degrees. PI (pulsatility index), RI (resistance index), Vd (end diastolic velocity), and Vs (peak systolic velocity) were tested.

D-dimer and Lp-PLA2 detection

A total of 3 mL venous blood was collected by anticoagulation blood collection vessel containing sodium citrate on an empty stomach in the morning. It was stored at 2-10°C and centrifuged within 30 min. The D-dimer concentration was determined by latex immunoturbidimetry assay. Three mL venous blood was collected by common vacuum blood collection tube (including coagulant), stored at 2-8°C, and centrifuged within 30 min. The concentration of Lp-PLA2 was measured by fluorescein enhanced immunochemistry. Blood samples were collected from healthy controls on an empty stomach in the early morning of the same day. The collection method was the same as that of cerebral infarction patients. All tests were completed within 2 h.

Outcome measures

Main outcome measures: The difference of imaging parameters, D-dimer, and Lp-PLA2 levels between both groups were observed. The correlation of mRS scores with imaging parameters, D-dimer, and Lp-PLA2 was explored.

Secondary outcome measures: Patients were divided into a good prognosis group (0-1) and a poor prognosis group (2-5) according to mRS scores after 6 months of treatment. The differences of imaging parameters, D-dimer, and Lp-PLA2 were compared, and the ROC curve was drawn to analyze its predictive value.

Statistical analysis

The collected data were processed and analyzed by SPSS20.0 software package, and the relevant pictures were drawn through the GraphPad Prism 8 software package. The measurement data were processed through the t

Table 1. Comparison of baseline data of patients

Factors	Patient group (n=67)	Control group (n=50)	*P* value
Age (years)			0.764
≥ 65	30	21	
< 65	37	29	
Gender			0.251
Male	40	35	
Female	27	15	
BMI (kg/m^2)			0.529
≥ 23	44	30	
< 23	23	20	
History of smoking			0.424
Yes	45	37	
No	22	13	
History of alcoholism			0.390
Yes	15	8	
No	52	42	
Past medical history			
Hypertension	50	40	0.495
Hyperlipidemia	44	32	0.851
Diabetes	29	21	0.890
mRs score on admission			
0-1	43		
2-5	24		
Stenosis severity			
Moderate	55		
Severe	12		
Stenosis site			
Unilateral	50		
Bilateral	17		

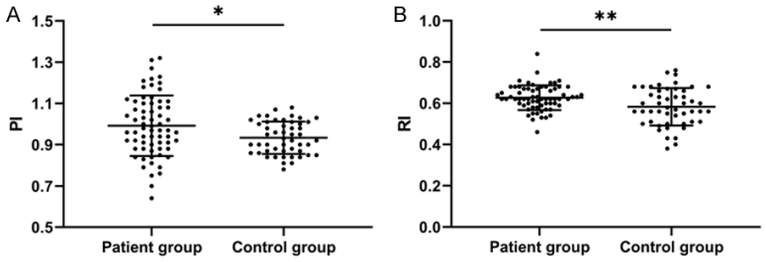

Figure 1. Comparison of PI and RI parameters between the two groups. A. Comparison of PI parameters between control group and patient group. B. Comparison of RI parameters between control group and patient group. Compared with control group, * means $P < 0.05$, ** means $P < 0.01$ and ***$P < 0.001$.

test. The comparisons between the groups were assessed through independent-sample t test, and that within groups was under paired t test, expressed by t. The counting data were examined by Chi-square test, represented as x^2. Rank-sum test was applied in ranked data, which was marked by Z. The predictive value was analyzed by receiver operating characteristic (ROC) curve. The correlation between imaging parameters, D-dimer and Lp-PLA2, and mRs scores was assessed by the Spearman test. The differences were statistically marked ($P < 0.05$).

Results

Comparison of clinical data

It was found that there was no significant difference in age, gender, BMI, smoking, alcoholism, and past medical history between the two groups ($P > 0.05$, **Table 1**).

Imaging parameters, D-dimer, and Lp-PLA2 in patients

We compared the imaging parameters, D-dimer, and Lp-PLA2 between the two groups. Compared with the control group, the levels of PI, RI, serum D-dimer, and Lp-PLA2 in the patient group increased, and those of Vd and Vs decreased ($P < 0.05$, **Figures 1**-**3**).

Correlation of mRs scores with imaging parameters, D-dimer, and Lp-PLA2 on admission

We analyzed the correlation of mRs scores with imaging parameters, D-dimer, and Lp-PLA2 on admission. In view of the Spearman test analysis, PI, RI, serum D-dimer, and Lp-PLA2 levels were positively correlated with mRS scores. Vd and Vs parameters were negatively correlated with it ($P < 0.05$, **Figure 4**).

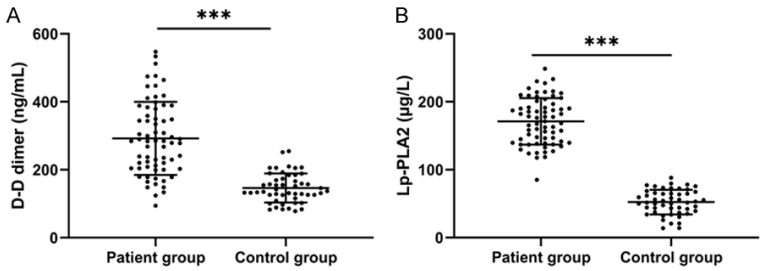

Figure 2. Comparison of the levels of D-dimer and Lp-PLA2 between the two groups. A. Comparison of D-dimer levels between control group and patient group. B. Comparison of Lp-PLA2 levels between control group and patient group.

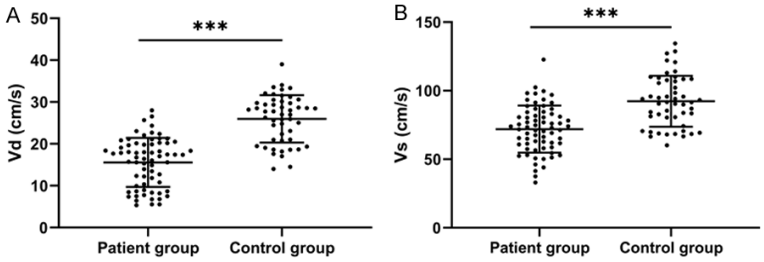

Figure 3. Comparison of Vd and Vs parameters between the two groups. A. Comparison of Vd parameters between control group and patient group. B. Comparison of Vs parameters between control group and patient group.

Association of prognosis with imaging parameters, D-dimer, and Lp-PLA2

To understand the association of prognosis with imaging parameters, D-dimer, and Lp-PLA2, we evaluated the mRs scores of patients after 6 months. Among them, 18 scored 0, 22 scored 1, and 27 > 2. Patients were divided into a good prognosis group (n=40) and a poor prognosis group (n=27). We analyzed the imaging parameters, D-dimer, and Lp-PLA2 in both groups. The results manifested that compared with the poor prognosis group, the levels of PI, RI, and serum Lp-PLA2 in the good prognosis group were lower before treatment. Those of Vd and Vs were higher ($P < 0.05$, **Figure 5**). The D-dimer showed no difference between the two groups ($P > 0.05$).

Prognostic value of imaging parameters, D-dimer, and Lp-PLA2 in patients

In this research, we found that there were differences in imaging parameters and Lp-PLA2 indexes after grouping patients according to prognosis. This showed that these indicators may have predictive value in the prognosis of patients. To determine their value, we drew ROC curves. Through analysis, we identified that the areas under the horizontal curves of PI, RI, serum Lp-PLA2, Vd, and Vs were 0.676, 0.708, 0.730, 0.797, and 0.648, respectively (**Figure 6** and **Table 2**).

Discussion

The epidemiological survey in 2015 found that stroke was the primary reason for death among the major causes of death among urban and rural residents in China [14]. The proportion of Chinese male patients dying from stroke was much higher than that of female patients [15]. More than 80% of stroke patients are ischemic stroke, and 30% of them are related to carotid artery stenosis [16]. Great progress has been made in the treatment of carotid atherosclerotic stenosis. Studies have shown that early intervention can improve the prognosis of patients with carotid artery stenosis [17]. There is a lack of clinical prognostic indicators for carotid atherosclerotic stenosis.

D-dimer is a stable and specific degradation product of cross-linked fibrin. Studies have shown that the change of D-dimer level in a human body can directly reflect the hypercoagulable state and fibrinolysis degree in vivo. This was also the main reason why D-Dimer was used in thrombolytic monitoring of thrombotic diseases [18, 19]. Lp-PLA2, as a new clinical inflammatory marker, is a kind of pro-inflammatory enzyme secreted by lymphocytes and mature macrophages [20]. It can be combined with low-density lipoprotein (LDL), high-density lipoprotein (HDL), and lipoprotein (a). The produced substances can induce the formation of proinflammatory substances such as cytokines and adhesion factors. These can aggravate the inflammation of the body and promote atherosclerosis [21]. Carotid ultrasound has a high diagnostic value for atherosclerotic plaque.

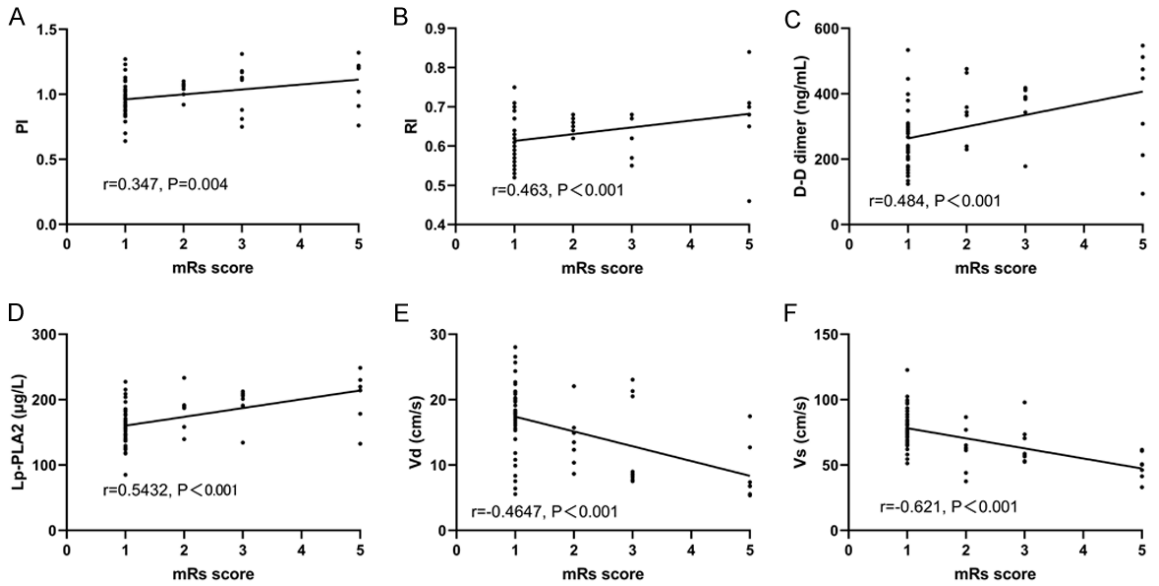

Figure 4. Correlation of mRs score with imaging parameters, D-dimer, and Lp-PLA2. A. Correlation between PI parameters and mRs scores. B. Correlation between RI parameters and mRs scores. C. Correlation between D-dimer levels and mRs scores. D. Correlation between Lp-PLA2 levels and mRs scores. E. Correlation between Vd parameters and mRs scores. F. Correlation between Vs parameters and mRs scores.

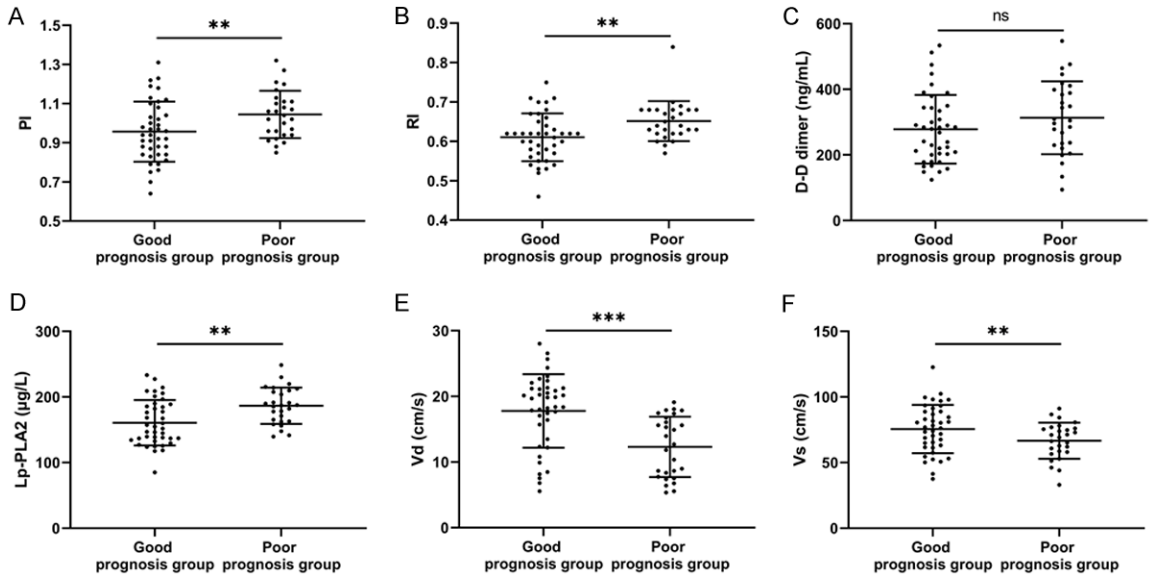

Figure 5. Imaging parameters, D-dimer and Lp-PLA2 in good and poor prognosis groups. A. Comparison of PI parameters between patients in both groups. B. Comparison of RI parameters between patients in both groups. C. Comparison of D-dimer levels between patients in both groups. D. Comparison of Lp-PLA2 levels between patients in both groups. E. Comparison of Vd parameters between patients in both groups. F. Comparison of Vs parameters between patients in both groups. Compared with the control group, ns indicates $P > 0.05$, ** indicates $P < 0.01$ and ***$P < 0.001$.

Carotid artery ultrasound can effectively evaluate the intima-media thickness of extracranial artery, whether there is stenosis in lumen, the severity of stenosis, and the hemodynamic state of stenosis, which can accurately predict intracranial artery stenosis [22]. PI and RI reflect vascular resistance. The rise of PI indicates diastolic blood flow and vascular resistance increase. RI indicates terminal vascular resistance increase. Vd and Vs are the reference indexes reflecting intravascular blood flow velocity. Observing the changes of the two can

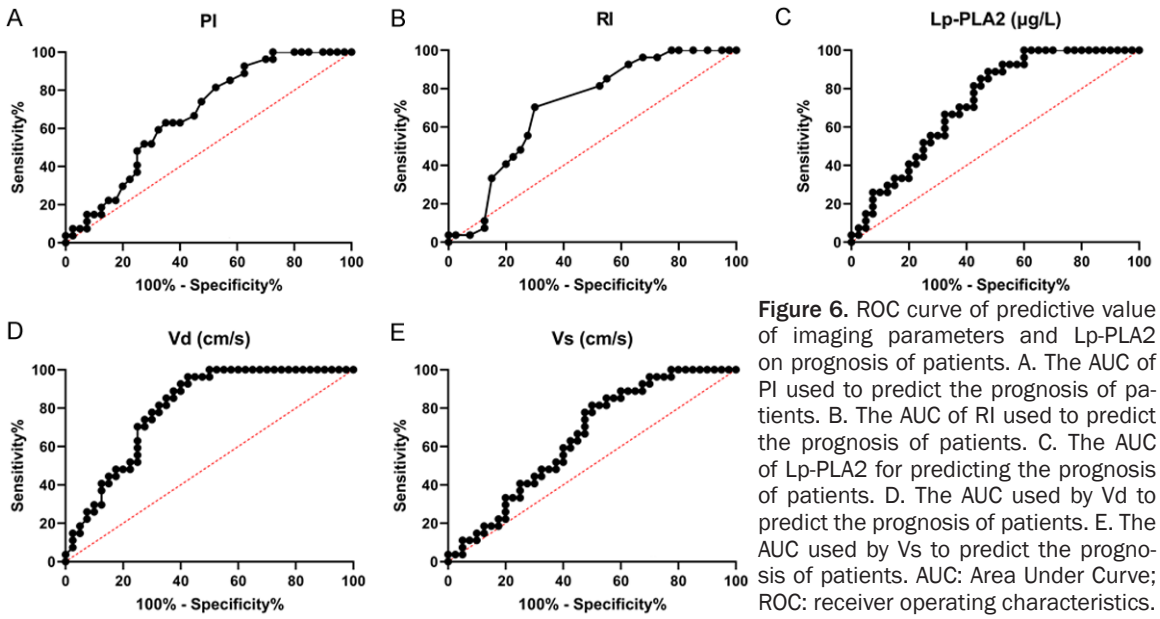

Figure 6. ROC curve of predictive value of imaging parameters and Lp-PLA2 on prognosis of patients. A. The AUC of PI used to predict the prognosis of patients. B. The AUC of RI used to predict the prognosis of patients. C. The AUC of Lp-PLA2 for predicting the prognosis of patients. D. The AUC used by Vd to predict the prognosis of patients. E. The AUC used by Vs to predict the prognosis of patients. AUC: Area Under Curve; ROC: receiver operating characteristics.

Table 2. ROC parameters

Factor	AUC	*P* value	Specificity	Sensitivity	Yorden Index	Cut-off
PI	0.676	0.015	92.59%	37.50%	30.09%	0.89
RI	0.708	0.004	70.37%	70.00%	40.37%	0.63
Lp-PAL2	0.730	0.002	88.89%	52.50%	41.39%	115.61
Vd	0.797	< 0.001	96.29%	57.50%	53.79%	18.14
Vs	0.648	0.040	81.48%	50.00%	31.48%	76.93

Note: AUC: Area Under Curve; ROC: receiver operating characteristics.

be used as a direct reference for patients with vascular stenosis [23]. In this study, we analyzed the predictive value of imaging parameters, D-dimer, and Lp-PLA2 on the prognosis of patients with carotid atherosclerotic stenosis. We compared the difference of indexes between common people and those with carotid atherosclerosis stenosis. We found that compared with the control group, the levels of PI, RI, serum D-dimer, and Lp-PLA2 in the patient group increased, those of Vd and Vs decreased. Early studies have demonstrated that Lp-PLA2 is a new risk factor for high-risk coronary and carotid artery disease [24]. Other studies have shown that CT parameters can be used as an indicator for the diagnosis of carotid plaque [25], which is similar to our results. This showed that the above indexes can be used as clinical reference for judging carotid atherosclerotic stenosis. We analyzed the relationship between influencing parameters, serum D-dimer, Lp-PLA2, and mRs scores before admission. The mRs score is a famous scale for the outcome of stroke, which can evaluate the independent living skills of patients [26]. The Spearman correlation analysis found that PI, RI, serum D-dimer, and Lp-PLA2 levels were positively correlated with mRS scores, Vd and Vs parameters were negatively correlated with it. These results can explain the influencing parameters, and serum D-dimer and Lp-PLA2 can be used as clinical reference indexes for patients with carotid atherosclerotic stenosis.

In this study, we determined the clinical value of the above indexes in patients with carotid atherosclerosis stenosis, to observe their predictive value in prognosis. We followed them for 6 months and evaluated their prognosis by mRs scores. They were divided into a good prognosis group and a poor prognosis group based on scores. By comparison, we discovered that before treatment, the levels of PI, RI, and serum Lp-PLA2 were lower in the former group than in the latter group. Those of Vd and Vs were higher, suggesting that these benchmarks are expected to become the prognostic indicators of patients with carotid atherosclerotic stenosis. To verify their effectiveness, we analyzed them by ROC curve, and found that PI, RI, serum Lp-PLA2, Vd and Vs all have certain clinical predictive value. The changes of

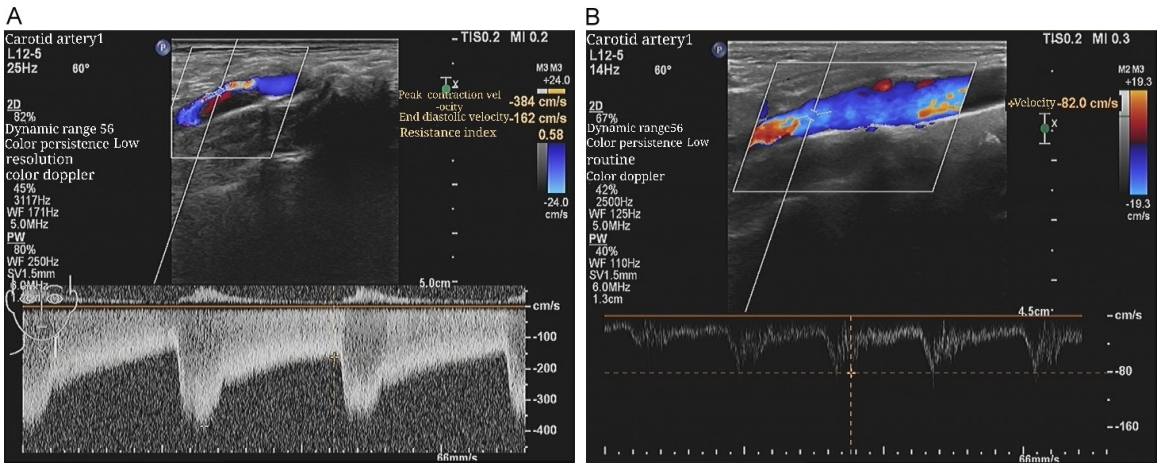

Figure 7. Doppler ultrasound induction of carotid artery pain in patients and normal people. A. Carotid artery cross-carotid Doppler color Doppler ultrasound B. Color Doppler ultrasound of carotid arteries in normal people.

Vd and Lp-PLA2 have higher predictive value for the prognosis of patients with carotid atherosclerotic stenosis. Vd is a crucial reference to embody the blood velocity in patients' blood vessels, and its change can directly reflect stenosis. The stenosis/occlusion leads to inflammation in vivo, which increases the expression of Lp-PLA2. This finding is consistent with our results.

In this study, we determined the prognostic value of color Doppler ultrasound parameters, D-dimer, and Lp-PLA2 levels in carotid atherosclerotic stenosis (**Figure 7**). This research still has some limitations. In this retrospective study, we have not performed a randomized controlled and prospective research, which leads to the possible bias of our results. We only followed the patients for 6 months. It is still vague whether the indicators of this study have clinical value in predicting the long-term prognosis of patients. We hope to improve our conclusions through long-term and prospective randomized controlled studies.

In summation, Vd parameters and Lp-PLA2 levels have high clinical values in carotid atherosclerotic stenosis, and are worthy of clinical application.

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Disclosure of conflict of interest

None.

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