Am J Transl Res 2022;14(11):8371-8379
www.ajtr.org /ISSN:1943-8141/AJTR0146402

Original Article

Diagnostic value of plasma D-dimer and serum lipoprotein phospholipase A2 in patients with cerebral small vessel disease and their association with severity of the disease

Yu Kong[1], Guangyao Lin[2], Mingguang Yan[3], Jingjing Wang[1], Yunyi Dai[1]

[1]Department of Cognitive and Movement Disorders, Shangqiu First People's Hospital, 292 Kaixuan South Road, Suiyang District, Shangqiu 476000, Henan, China; [2]Medical Imaging Center, Shangqiu First People's Hospital, 292 Kaixuan South Road, Suiyang District, Shangqiu 476000, Henan, China; [3]Medical Laboratory Department, Shangqiu First People's Hospital, 292 Kaixuan South Road, Suiyang District, Shangqiu 476000, Henan, China

Received September 9, 2022; Accepted November 13, 2022; Epub November 15, 2022; Published November 30, 2022

Abstract: Objective: To determine the diagnostic value of plasma D-dimer (DD) and serum lipoprotein phospholipase A2 (Lp-PLA2) in patients with cerebral small vessel disease (CSVD) and their association with severity of the disease. Methods: In this retrospective analysis, 84 patients with CSVD treated in Shangqiu First People's Hospital from February 2020 to November 2021 were included in the study group, and 75 healthy individuals were assigned into the control group. The DD and Lp-PLA2 levels in the two groups were compared, and the diagnostic value of the two in CSVD was evaluated via receiver operating characteristic (ROC) curves. Patients were assigned to a mild group or a severe group based on Fazekas scale scores. Then, the two groups were compared in terms of the DD and Lp-PLA2 levels, and the association of the two with the severity of CSVD was determined through ROC curves. With the Montreal cognitive assessment (MoCA) scale, the patients were assigned to a cognitive impairment group or a non-cognitive impairment group. Then the two groups were compared in terms of the DD and Lp-PLA2 levels, and the association of the two with the cognitive function of CSVD patients was also determined by ROC curves. Results: The research group showed higher DD and Lp-PLA2 levels than the control group; the severe group showed higher DD and Lp-PLA2 levels than the mild group; the cognitive impairment group showed higher DD and Lp-PLA2 levels than the non-cognitive impairment group (all $P < 0.001$). The areas under the curves (AUCs) of DD and Lp-PLA2 in CSVD diagnosis were 0.902 and 0.907, respectively; the AUCs of DD and Lp-PLA2 in CSVD severity determination were 0.747 and 0.704, respectively; the AUCs of DD and Lp-PLA2 in cognitive impairment diagnosis were 0.736 and 0.725, respectively. Conclusion: Plasma DD and Lp-PLA2 possess good diagnostic value in patients with CSVD, and also has certain clinical value in diagnosing patients' severity and cognitive impairment.

Keywords: Plasma D-dimer, serum lipoprotein phospholipase A2, cerebral small vessel disease, severity

Introduction

With the general aging of the population and the wide application of neuroimaging technology, more and more cerebral small vessel diseases (CSVD) have been found [1]. CSVD refers to a group of pathological changes of cerebral arterioles, venules and capillaries triggered by a number of different factors and involving various pathological processes and causes [2]. Because of the continuous progress of medical technology and the improvement of people's living standards, the life expectancy of human beings has been prolonged, which increases the prevalence of CSVD, and almost all people over 90 years old are affected [3]. Cognitive impairment is one of the primary clinical manifestations of CSVD, and CSVD-triggered cognitive impairment has become a primary cause of vascular dementia [4]. Currently, no clear prevention plan or treatment measure has been discovered to alleviate CSVD. Therefore, it is of profound significance to find biomarkers associated with the progression of CSVD and risk factors related to its onset for its early diagnosis, early intervention and alleviation [5].

D-dimer (DD), which is an end product of cross-linked fibrin, is produced under the action of coagulation factor XIIIa and degraded by plasma fibrinolysis, and it is a unique marker of secondary fibrinolysis [6]. Past research has shown rapidly rising DD levels in patients with damaged blood vessels, as well as an abnormally changed coagulation function. Especially for trauma-induced intracranial hematoma, the DD levels increase more significantly [7, 8]. Lipoprotein phospholipase A2 (Lp-PLA2) is a phospholipase secreted by macrophages, T cells and mast cells in vascular intima cells, which promotes the hydrolysis of oxidized phospholipids [9]. It can oxidize and hydrolyse oxidized phospholipids in low density lipoproteins (ox-LDL) to produce lipidic pro-inflammatory substances, resulting in the death and dysfunction of vascular endothelial cells and thus participating in cardiovascular and cerebrovascular diseases [10]. One study has confirmed that Lp-PLA2 is a biomarker of oxidative stress and inflammatory reaction, and showed that its increase can increase the risk of cardiovascular and cerebrovascular diseases [11]. However, no relevant research on the association of DD and Lp-PLA2 with CSVD patients' conditions and cognitive impairments has been reported.

This study analysed the clinical value of DD and Lp-PLA2 in patients with CSVD, with the purpose of providing reference indicators for clinicians in the therapy and diagnosis of CSVD.

Methods and data

Clinical data

A retrospective analysis was conducted with a total of 84 patients having CSVD in the study group, who were treated in Shangqiu First People's Hospital from February 2020 to November 2021, and 75 healthy individuals in the control group. This study was performed with permission from the Medical Ethics Committee of Shangqiu First People's Hospital, with ethics approval number 2020048.

Inclusion and exclusion criteria

Inclusion criteria of the research group were: Patients who were diagnosed with CSVD by MRI or brain CT and met the neuroimaging criteria for CSVD proposed in the Standards for Reporting Vascular Changes on Neuroimaging [4], patients without a history of severe stenosis of internal and external cerebral arteries, patients who received conservative treatment such as thrombolysis and antiplatelet care, and patients with detailed clinical data.

Exclusion criteria were: Patients with brain imaging changes triggered by special reasons such as multiple sclerosis, poisoning and severe sleep apnoea syndrome, patients with massive cerebral infarction, patients with a history of malignant tumour or traumatic brain injury, and patients with intracranial infection, vascular dementia, or cognitive impairment caused by other reasons (intracranial infection, Parkinson's disease).

Instruments and reagents

The Lp-PLA2 kit was provided by Jiangsu Enzyme Immunity Industry Co., Ltd., and the instrument used was an Olympus AU2700 automatic biochemical analyser from Japan. DD levels (kit batch number: ml092610) were quantified through an enzyme-linked immunosorbent assay (ELISA) with kits from Shanghai Enzyme Linked Biotechnology Co., Ltd.

Detection methods

Fasting venous blood (5 mL) was extracted from each patient' elbow on the next morning after admission, and was put in a standard anticoagulation blood vessel container with 0.2 ml sodium citrate (0.129 mmol/L). After 2 h, the blood was subjected to 10 minutes of centrifugation (3500 r/min, centrifugal radius: 16, 25°C) to collect the serum, and each sample of serum was given a uniform number. Then, the amount of Lp-PLA2 in it was quantified by the double antibody sandwich method with an automatic biochemical analyser. Afterwards, the blood samples were collected and placed in a silicified test tubes, mixed with 10^9 mmol/L sodium citrate (State Food and Drug Administration (SFDA) approval no.: H32022214) in the ratio of 1:9 for anticoagulation, and the DD levels were quantified using ELISA with a SYSMAX CA-1 500 automatic hemagglutination analyser and kit from Japan.

Table 1. Comparison of clinical data

Items	Research group (n=84)	Control group (n=75)	x^2 value	*P* value
Age			0.529	0.467
> 65 years old	54	44		
≤ 65 years old	30	31		
Sex			0.933	0.324
Male	44	45		
Female	40	30		
BMI (kg/m^2)			0.701	0.402
< 25	38	29		
≥ 25	46	46		
History of hypertension			0.182	0.669
Yes	33	27		
No	51	48		
History of diabetes mellitus			0.149	0.698
Yes	18	18		
No	66	57		
History of smoking			0.933	0.324
Yes	44	45		
No	40	30		
History of alcoholism			0.060	0.805
Yes	10	8		
No	74	67		

Note: BMI: Body Mass Index.

Outcome measures

As primary outcome measures, the DD and Lp-PLA2 levels in the two groups were compared, and the diagnostic value of the two levels in CSVD was evaluated via receiver operating characteristic (ROC) curves. Based on Fazekas scale [12], the patients were assigned to a mild group (grade 0-1) or a severe group (grade 2-3), and the two groups were compared in the levels of DD and Lp-PLA2. The association of two with CSVD severity was evaluated by ROC curves.

Secondary outcome measures: Clinical data of the two groups were compared. The Montreal cognitive assessment (MoCA) scale was adopted for evaluating cognitive impairment [13]. It has a total score of 30 points; scores < 26 points were seen as cognitive impairment and scores ≥ 26 points as normal cognition. The DD and Lp-PLA2 levels were also compared between these two groups, and the value in the cognitive function diagnosis of CSVD patients was also evaluated through ROC curves.

Statistical analysis

Each assay was repeated three times, and the measurement data were described as Mean ± SD. This study used SPSS 20.0 software (USA) for data analysis, and adopted Graphpad 8.0 d for data visualization and graphical illustration. The independent sample t-test was adopted for inter-group comparison of measurement data, and the Chi-square test was adopted for analysis of counting data. ROC was drawn to present the diagnostic curves of DD and Lp-PLA2. P < 0.05 suggested a significant difference.

Results

Comparison of clinical data

According to comparison of clinical data, the control and the research groups were similar in terms of age, sex, body mass index, and history of hypertension, diabetes mellitus smoking and drinking (P > 0.05, **Table 1**).

The level of DD Lp-PLA2 in CSVD patients

DD and Lp-PLA2 levels were notably higher in the research group than those in the control group (P < 0.001, **Figure 1**).

Value of DD and Lp-PLA2 in diagnosing CSVD

Through ROC curves, the diagnostic value of DD and Lp-PLA2 in CSVD was evaluated. According to the results, the areas under the curves (AUCs) of DD and Lp-PLA2 in diagnosing CSVD were 0.902 and 0.907, respectively (**Figure 2**; **Table 2**).

DD and Lp-PLA2 levels in CSVD patients with different severity

According to Fazekas scale, CSVD patients were assigned to a mild group (n=44) or a severe group (n=40). Then DD and Lp-PLA2 levels were compared between these two groups. Notably higher DD and Lp-PLA2 levels were found in the severe group than those in the mild group (P < 0.001, **Figure 3**).

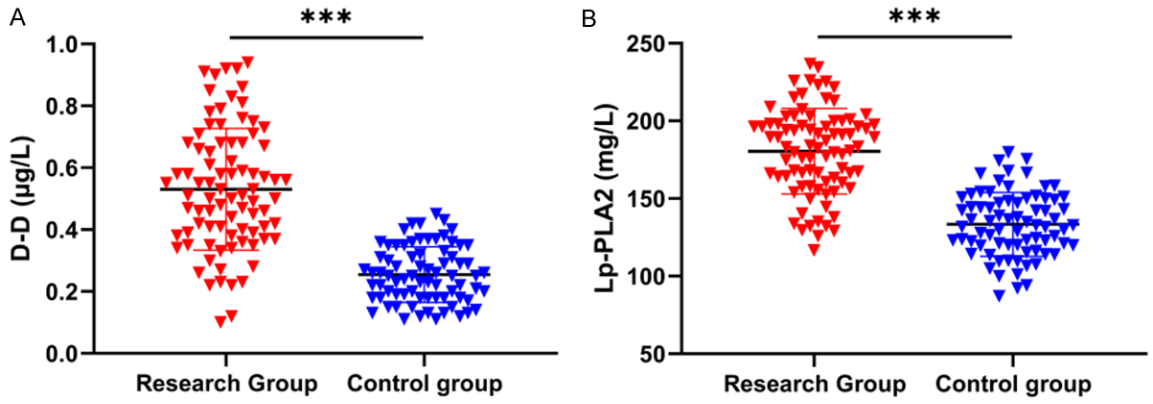

Figure 1. DD and Lp-PLA2 levels in healthy individuals and CSVD patients. A. DD level in healthy individuals and CSVD patients. B. Lp-PLA2 level in healthy individuals and CSVD patients. Notes: ***P < 0.001; DD: D-dimer; Lp-PLA2: lipoprotein phospholipase A2.

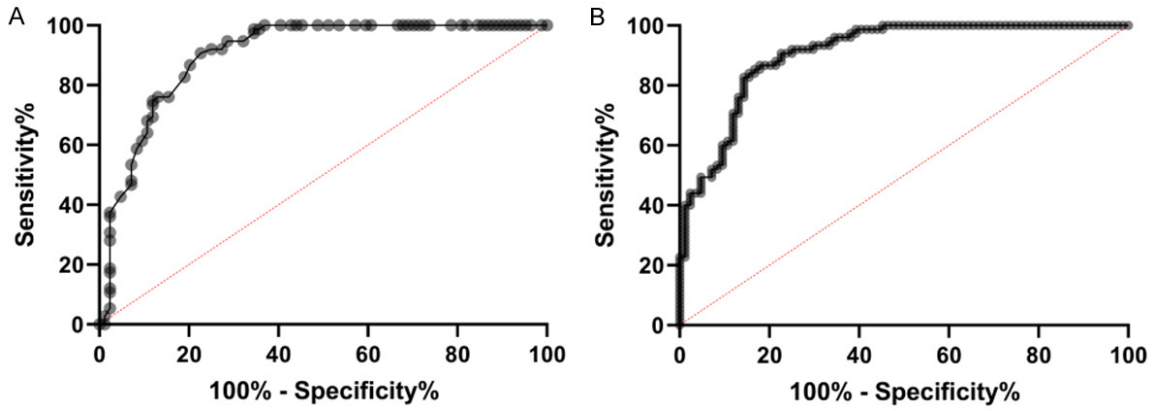

Figure 2. Diagnostic value of DD and Lp-PLA2 in CSVD. A. ROC curve of DD in CSVD diagnosis. B. ROC curve of Lp-PLA2 in CSVD diagnosis. Notes: DD: D-dimer; Lp-PLA2: lipoprotein phospholipase A2; ROC: Receiver operating characteristic.

Table 2. ROC parameters

Items	AUC	95% Confidence interval	Specificity	Sensitivity	Youden index	Cut-off value
DD	0.903	0.854-0.951	77.40%	90.70%	68.00%	0.37
Lp-PLA2	0.907	0.864-0.952	82.10%	86.70%	68.80%	154.94

Note: DD: D-dimer; Lp-PLA2: lipoprotein phospholipase A2; AUC: Area under the curve.

Diagnostic value of DD and LP-PLA 2 in CSVD severity

The association of DD and Lp PLA2 with the severity of CSVD was evaluated by ROC curve. According to the results, the AUCs of DD and Lp-PLA2 in CSVD severity determination were 0.747 and 0.704, respectively (**Figure 4**; **Table 3**).

DD and Lp-PLA2 levels in patients with or without cognitive impairment

With the MoCA scale, the patients were assigned to a cognitive impairment group (n=32) or a non-cognitive impairment group (n=52). Then DD and Lp-PLA2 levels were compared between these two groups. The results revealed notably higher DD and Lp-PLA2 levels in the

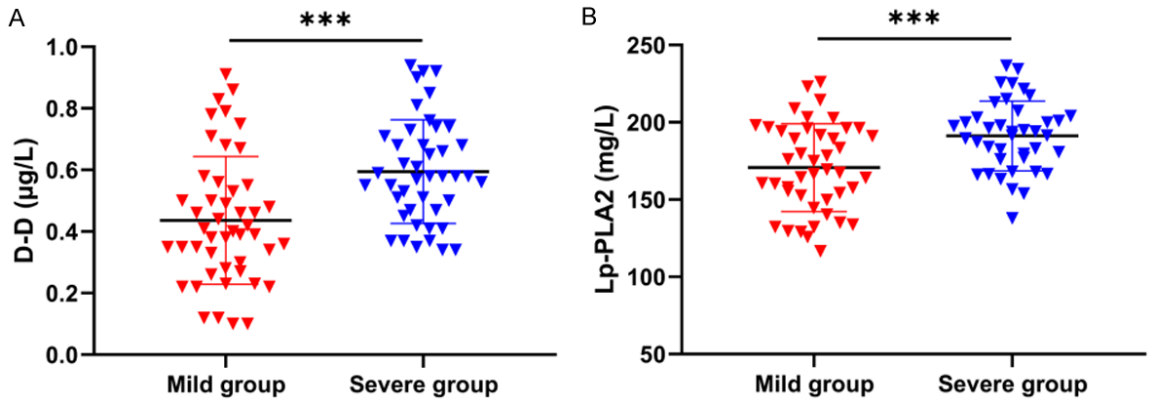

Figure 3. DD and Lp-PLA2 levels in CSVD patients with different disease severity. A. Comparison of DD between the mild group and severe group. B. Comparison of Lp-PLA2 between the mild group and severe group. Note: DD: D-dimer; Lp-PLA2: lipoprotein phospholipase A2.

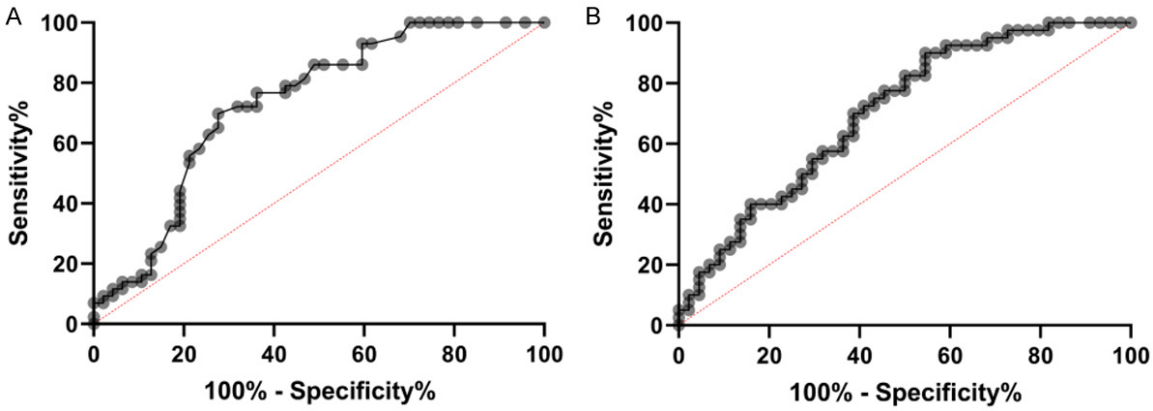

Figure 4. Diagnostic value of DD and Lp-PLA2 in CSVD severity. A. ROC curve of DD in diagnosing CSVD severity. B. ROC curve of Lp-PLA2 in diagnosing CSVD severity. Note: DD: D-dimer; Lp-PLA2: lipoprotein phospholipase A2; ROC: Receiver operating characteristic.

Table 3. ROC parameters

Items	AUC	95% Confidence interval	Specificity	Sensitivity	Youden index	Cut-off value
DD	0.747	0.639-0.854	75.00%	70.50%	45.50%	0.50
Lp-PLA2	0.704	0.593-0.815	90.00%	45.50%	35.50%	165.23

Note: DD: D-dimer; Lp-PLA2: lipoprotein phospholipase A2; AUC: Area under the curve.

cognitive impairment group than those in the non-cognitive impairment group ($P < 0.001$, **Figure 5**).

Diagnostic value of DD and Lp-PLA2 in cognitive impairment

Through ROC curves, the association of DD and Lp-PLA2 with cognitive impairment was evaluated. According to the results, the AUCs of DD and Lp-PLA2 in cognitive impairment diagnosis were 0.736 and 0.725, respectively (**Figure 6**; **Table 4**).

Discussion

With a high incidence of cardiovascular disease and CSVD in China, stroke has become the primary cause of disease-triggered death [14]. The incidence of CSVD is up to 17.2% in China, and up to 25.0% worldwide [15]. According to prior research, CSVD, with characteristic clini-

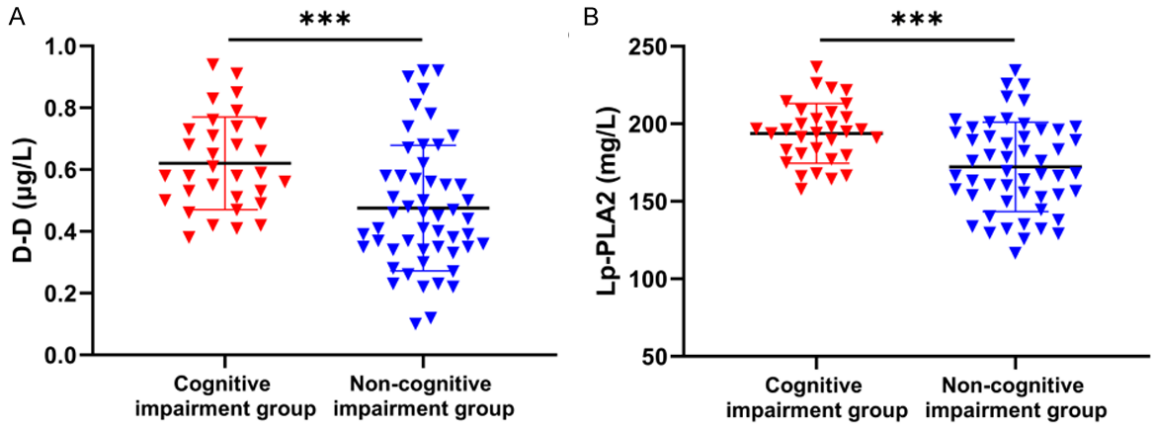

Figure 5. DD and Lp-PLA2 levels in patients with or without cognitive impairment. A. Comparison of DD between the cognitive impairment group and non-cognitive impairment group. B. Comparison of Lp-PLA2 between the cognitive impairment group and non-cognitive impairment group. Note: DD: D-dimer; Lp-PLA2: lipoprotein phospholipase A2.

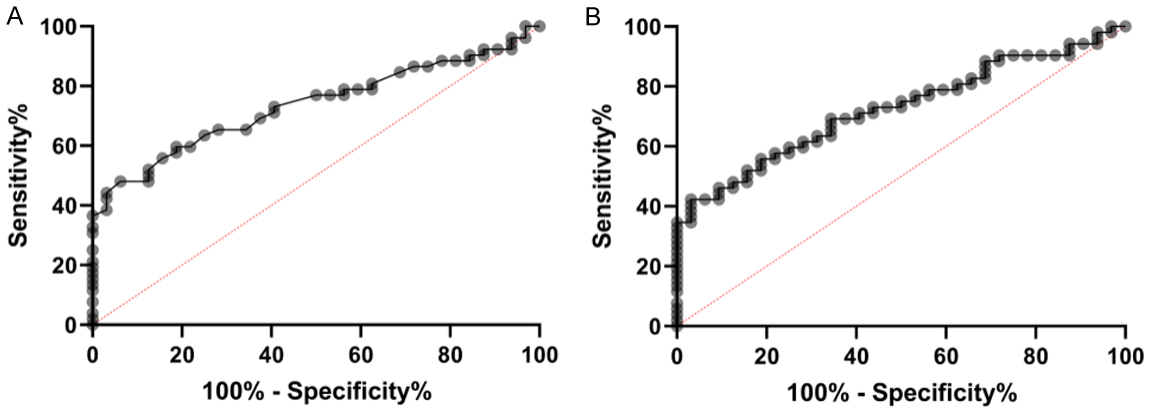

Figure 6. Value of DD and Lp-PLA2 in diagnosing cognitive impairment. A. ROC curve of DD in diagnosing cognitive impairment. B. ROC curve of Lp-PLA2 in diagnosing cognitive impairment. Note: DD: D-dimer; Lp-PLA2: lipoprotein phospholipase A2; ROC: Receiver operating characteristic.

Table 4. ROC parameters

Items	AUC	95% Confidence interval	Specificity	Sensitivity	Youden index	Cut-off value
DD	0.736	0.631-0.840	93.80%	48.10%	41.80%	0.41
Lp-PLA2	0.725	0.618-0.831	96.90%	42.30%	39.20%	164.21

Note: DD: D-dimer; Lp-PLA2: lipoprotein phospholipase A2; AUC: Area under the curve.

cal and imaging manifestations, plays a crucial role in the diagnosis of comorbid cognitive impairment [16]. CSVD causes up to 45% of dementia cases, 20% of stroke cases, 25% of cases of ischemic strokes and 20% of disability cases [17]. Cognitive impairment includes mild cognitive impairment and dementia, which brings great burden to patients and society [18]. Therefore, it is relevant to explore biomarkers strongly linked to the progress of CSVD for the early diagnosis and treatment of CSVD and the prevention and therapy of dementia.

DD, a cross-linked fibrin clot derived from fibrinolysis, mainly reflects the fibrinolysis function, which can serve as a specific molecular marker of the hypercoagulable state and hyperfibrinolysis *in vivo*. The increase of its plasma level is significant for the diagnosis of thrombotic

diseases [19, 20]. In research by Ohara et al. [21], DD was found to be a crucial biomarker of ischemic stroke and cardiovascular disease. According to research by Choi et al. [22], DD can be adopted as a useful biomarker for risk assessment and for predicting the recurrence of stroke in patients with unknown origin, especially for embolic ischemic stroke. CSVD is a primary subtype of patients with CSVD, and it is speculated that the change of DD is connected with the development of CSVD. Lp-PLA2 has been verified to be a specific index of vascular inflammation and an independent risk factor for ischemic stroke, and its hydrolysate is a powerful inflammatory substance that constantly stimulates Lp-PLA2 regeneration, resulting in a vicious circle to accelerate vascular injury [23, 24]. With a possible involvement in the development of cognitive impairment, high Lp-PLA2 can be adopted as an early serological marker for the diagnosis of non-dementia vascular cognitive impairment [25]. Therefore, this study determined the DD and Lp-PLA2 levels in patients with CSVD. In this study, CSVD patients showed notably higher DD and Lp-PLA2 levels than healthy individuals. Moreover, a ROC curve-based analysis, distinguishing healthy people from patients with CSVD using DD and Lp-PLA2, showed AUC values larger than 0.9. Prior research by Zhao et al. [26] showed greatly increased serum exosome miRNA-223-3p levels in CSVD patients, with an AUC of 0.922. Also, Janes et al. [27] determined the AUC when distinguishing sporadic small vessel disease (SVD) using asymmetric dimethyl arginine (ADMA) as 0.70. The AUCs of the two indexes in the present research were 0.903 and 0.907, respectively, which were slightly lower than the AUC in the study by Zhao et al., but the detection method and sample acquisition in the present research are more convenient and cheaper.

Besides analysing DD and Lp-PLA2 levels in healthy individuals and CSVD patients, this study also compared the magnitude of CSVD in patients with different severity according to the Fazekas scale. According to the results, the mild group showed notably lower DD and Lp-PLA2 levels than the severe group, and the AUC of DD and Lp-PLA2 in diagnosing different severities were 0.747 and 0.704, respectively, according to ROC curve analysis. Qiu et al. [28] divided patients into a low-burden group and a high-burden group based on the Fazekas scale and found the AUC of serum cortisol for diagnosing patients with different burdens to be 0.745 after analysing the expression of serum cortisol in patients with different burdens. With a value slightly lower than serum cortisol for Lp-PLA2 and of similar scale for DD, the results indicate a certain clinical value of DD and Lp-PLA2 in the diagnosis of CSVD patients with different severity.

CSVD is highly connected to neuroinflammation and cognitive impairment. CSVD-triggered cognitive impairment is an important subtype of vascular cognitive impairment, which mainly manifests in the impairment of attention, memory, information analysis and executive ability [29]. In this study, patients were grouped by MoCA scale. Patients with cognitive impairment showed greatly higher DD and Lp-PLA2 levels than those without it. Wang et al. [30] have found notably increased serum S100β levels in patients with both CSVD and cognitive impairment, and the AUC of S100β in predicting cognitive impairment was 0.845. In the present research, the AUC value of DD and Lp-PLA2 in predicting cognitive impairment was lower at 0.7. This shows that DD and Lp-PLA2 are not ideal for the diagnosis of CSVD with cognitive impairment.

This study analysed the clinical value of DD and Lp-PLA2 in CSVD patients. However, this study also has some limitations. Firstly, the changes of DD and Lp-PLA2 levels after therapy have not been collected. Secondly, the patients were not followed up in this study, and the relationship of DD and Lp-PLA2 with patients' prognosis needs further study. Finally, the analysis in a retrospective study may be biased. Therefore, we hope to carry out more prospective research in the future with increased samples and follow up results to improve the research conclusions.

To sum up, the increase of plasma DD and LP-PLA2 indicates the aggravation of CSVD patients and is expected to become a potential outcome measure of CSVD in clinical practice.

Acknowledgements

Application value of 3d-asl perfusion imaging in cerebral small vessel disease with cognitive dysfunction (LHGJ20191489); Serum MMP-9,

c-fn and S100β Clinical study on protein predicting the risk of hemorrhagic transformation after cerebral infarction (LHGJ20191490); Evaluation of neuromotor impairment and prognosis after intracerebral hemorrhage by diffusion tensor imaging and fiber bundle imaging (LHGJ20191487). Study of correlation between plasma D-dimer and lipoprotein-associated phospholipase A2 levels and the severity of white matter hyperintensity in patients with cerebral small vessel disease (No. 202203015).

Disclosure of conflict of interest

None.

Address correspondence to: Yunyi Dai, Department of Cognitive and Movement Disorders, Shangqiu First People's Hospital, 292 Kaixuan South Road, Suiyang District, Shangqiu 476000, Henan, China. E-mail: daiyunyi1983@163.com

References

[1] Litak J, Mazurek M, Kulesza B, Szmygin P, Litak J, Kamieniak P and Grochowski C. Cerebral small vessel disease. Int J Mol Sci 2020; 21: 9729.

[2] Chojdak-Lukasiewicz J, Dziadkowiak E, Zimny A and Paradowski B. Cerebral small vessel disease: a review. Adv Clin Exp Med 2021; 30: 349-356.

[3] Li Q, Yang Y, Reis C, Tao T, Li W, Li X and Zhang JH. Cerebral small vessel disease. Cell Transplant 2018; 27: 1711-1722.

[4] Zanon Zotin MC, Sveikata L, Viswanathan A and Yilmaz P. Cerebral small vessel disease and vascular cognitive impairment: from diagnosis to management. Curr Opin Neurol 2021; 34: 246-257.

[5] Ter Telgte A, van Leijsen EMC, Wiegertjes K, Klijn CJM, Tuladhar AM and de Leeuw FE. Cerebral small vessel disease: from a focal to a global perspective. Nat Rev Neurol 2018; 14: 387-398.

[6] Weitz JI, Fredenburgh JC and Eikelboom JW. A test in context: D-dimer. J Am Coll Cardiol 2017; 70: 2411-2420.

[7] Halaby R, Popma CJ, Cohen A, Chi G, Zacarkim MR, Romero G, Goldhaber SZ, Hull R, Hernandez A, Mentz R, Harrington R, Lip G, Peacock F, Welker J, Martin-Loeches I, Daaboul Y, Korjian S and Gibson CM. D-dimer elevation and adverse outcomes. J Thromb Thrombolysis 2015; 39: 55-59.

[8] Linkins LA and Takach Lapner S. Review of D-dimer testing: good, bad, and ugly. Int J Lab Hematol 2017; 39 Suppl 1: 98-103.

[9] Li X, Xu L and Xu Z. The diagnostic and prognostic performance of Lp-PLA2 in acute ischemic stroke. Med Clin (Barc) 2021; 156: 437-443.

[10] Bonnefont-Rousselot D. Lp-PLA2, a biomarker of vascular inflammation and vulnerability of atherosclerosis plaques. Ann Pharm Fr 2016; 74: 190-197.

[11] Chang JG. PLAC test for Lp-PLA2 activity to predict coronary heart disease. Am Fam Physician 2020; 101: 44-46.

[12] Cedres N, Ferreira D, Machado A, Shams S, Sacuiu S, Waern M, Wahlund LO, Zettergren A, Kern S, Skoog I and Westman E. Predicting Fazekas scores from automatic segmentations of white matter signal abnormalities. Aging (Albany NY) 2020; 12: 894-901.

[13] Ciesielska N, Sokolowski R, Mazur E, Podhorecka M, Polak-Szabela A and Kedziora-Kornatowska K. Is the Montreal Cognitive Assessment (MoCA) test better suited than the Mini-Mental State Examination (MMSE) in mild cognitive impairment (MCI) detection among people aged over 60? Meta-analysis. Psychiatr Pol 2016; 50: 1039-1052.

[14] Pasi M, Sugita L, Xiong L, Charidimou A, Boulouis G, Pongpitakmetha T, Singh S, Kourkoulis C, Schwab K, Greenberg SM, Anderson CD, Gurol ME, Rosand J, Viswanathan A and Biffi A. Association of cerebral small vessel disease and cognitive decline after intracerebral hemorrhage. Neurology 2021; 96: e182-e192.

[15] Evans LE, Taylor JL, Smith CJ, Pritchard HAT, Greenstein AS and Allan SM. Cardiovascular comorbidities, inflammation, and cerebral small vessel disease. Cardiovasc Res 2021; 117: 2575-2588.

[16] Coutureau J, Asselineau J, Perez P, Kuchcinski G, Sagnier S, Renou P, Munsch F, Lopes R, Henon H, Bordet R, Dousset V, Sibon I and Tourdias T. Cerebral small vessel disease MRI features do not improve the prediction of stroke outcome. Neurology 2021; 96: e527-e537.

[17] Liu Y, Dong YH, Lyu PY, Chen WH and Li R. Hypertension-induced cerebral small vessel disease leading to cognitive impairment. Chin Med J (Engl) 2018; 131: 615-619.

[18] Kalaria RN. The pathology and pathophysiology of vascular dementia. Neuropharmacology 2018; 134: 226-239.

[19] Bellesini M, Robert-Ebadi H, Combescure C, Dedionigi C, Le Gal G and Righini M. D-dimer to rule out venous thromboembolism during pregnancy: a systematic review and meta-analysis. J Thromb Haemost 2021; 19: 2454-2467.

[20] Zmistowski B, Chang M, Shahi A, Nicholson T, Abboud J, Lazarus M, Williams G, Parvizi J and Namdari S. Is D-dimer a reliable serum marker

for shoulder periprosthetic joint infection? Clin Orthop Relat Res 2021; 479: 1447-1454.
[21] Ohara T, Farhoudi M, Bang OY, Koga M and Demchuk AM. The emerging value of serum D-dimer measurement in the work-up and management of ischemic stroke. Int J Stroke 2020; 15: 122-131.
[22] Choi KH, Kim JH, Kim JM, Kang KW, Lee C, Kim JT, Choi SM, Park MS and Cho KH. D-dimer level as a predictor of recurrent stroke in patients with embolic stroke of undetermined source. Stroke 2021; 52: 2292-2301.
[23] Yuan L, Hou L, Zhang L, Qin Z, Zhang L and Yu C. Clinical evaluation and test of a modified Lp-PLA2 kit in diagnosing atherosclerosis. Clin Lab 2021; 67.
[24] Zhang F, Guo J, Yang F and Zhou Y. Lp-PLA2 evaluates the severity of carotid artery stenosis and predicts the occurrence of cerebrovascular events in high stroke-risk populations. J Clin Lab Anal 2021; 35: e23691.
[25] Zhang QL, Lu P and Zhang JW. Association of serum lipoprotein-associated phospholipase A2 with vascular dementia after ischemic stroke. Zhonghua Yi Xue Za Zhi 2018; 98: 1171-1175.
[26] Zhao W, Sun W, Li S, Jiao Y, Wang Z, Wu T, Liu P, Tan L and Yin C. Exosomal miRNA-223-3p as potential biomarkers in patients with cerebral small vessel disease cognitive impairment. Ann Transl Med 2021; 9: 1781.
[27] Janes F, Cifu A, Pessa ME, Domenis R, Gigli GL, Sanvilli N, Nilo A, Garbo R, Curcio F, Giacomello R, Fabris M and Valente M. ADMA as a possible marker of endothelial damage. A study in young asymptomatic patients with cerebral small vessel disease. Sci Rep 2019; 9: 14207.
[28] Qiu Q, Zhou X, Wu L, Zhang Y, Yu Z, Wang M, Huang H, Luo X and Pan D. Serum cortisol is associated with cerebral small vessel disease-related brain changes and cognitive impairment. Front Aging Neurosci 2021; 13: 809684.
[29] Zhang JF, Wiseman S, Valdes-Hernandez MC, Doubal FN, Dhillon B, Wu YC and Wardlaw JM. The application of optical coherence tomography angiography in cerebral small vessel disease, ischemic stroke, and dementia: a systematic review. Front Neurol 2020; 11: 1009.
[30] Wang F, Zou ZR, Yuan D, Gong Y, Zhang L, Chen X, Sun T and Yu HL. Correlation between serum S100beta protein levels and cognitive dysfunction in patients with cerebral small vessel disease: a case-control study. Biosci Rep 2017; 37: BSR20160446.