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Original Article

Plasma glial fibrillary acidic protein as a biomarker of blood-brain barrier integrity in patients with occult cerebral small vessel disease

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Abstract: Objective: To investigate the association between plasma glial fibrillary acidic protein (GFAP) levels and blood-brain barrier (BBB) integrity in patients with occult cerebral small vessel disease (CSVD). Methods: This retrospective study included patients with occult CSVD (CSVD group, n = 68) and age-matched individuals without CSVD (control group, n = 61). Demographic and clinical characteristics were compared between groups. Cognitive function was assessed using the Montreal Cognitive Assessment-B (MoCA-B). Plasma GFAP levels were measured, and all participants underwent sequential magnetic resonance imaging (MRI) to evaluate BBB integrity. Patients were stratified based on total MRI burden of CSVD into moderate/severe and none/mild load groups. Risk factors associated with moderate/severe CSVD load were analyzed. Results: The prevalence of hyperlipidemia was significantly higher in the CSVD group than in the control group (P = 0.020), and MoCA-B scores were significantly lower. In the CSVD group, plasma GFAP levels were negatively correlated with total cholesterol (r = -0.281, P = 0.020) and low-density lipoprotein (r = -0.282, P = 0.020), as well as with MoCA-B scores (r = -0.440, P = 0.0002). MRI analysis revealed that brain regions showing significant correlations with elevated plasma GFAP levels exhibited BBB disruption and cortical thinning. Conclusion: Elevated plasma GFAP levels are associated with cognitive impairment and BBB disruption in patients with occult CSVD. GFAP may serve as a potential biomarker for evaluating BBB integrity in this population.

Keywords: Glial fibrillary acidic protein, blood-brain barrier, cerebral small vascular disease, hyperlipidemias, case-control study

Introduction

Cerebral small vessel disease (CSVD) is a common vascular condition characterized by progressive impairment of blood flow in the brain's small vessels, including white matter arterioles, capillaries, and venules in deep brain structures [1]. CSVD is strongly associated with vascular dementia and is identified by neuroimaging findings such as lacunar infarcts, white matter lesions (WMLs), perivascular spaces, and cerebral microbleeds (CMBs) [2]. Occult CSVD refers to cases without clinical neurological symptoms but with neuroimaging findings consistent with CSVD, which are known to increase the risk of stroke, cognitive decline or dementia, disability, and mortality. Although the exact pathogenesis of CSVD, especially in asymptomatic individuals, remains unclear, growing evidence suggests that blood-brain barrier (BBB) disruption may play a critical role in its development [3-5].

The BBB is primarily composed of endothelial cells joined by tight junctions, supported by pericytes and astrocytes. While the role of endothelial cells in maintaining BBB integrity in CSVD has been relatively well studied [6-8], limited attention has been given to the contribution of astrocytes [9]. Glial fibrillary acidic protein (GFAP), an intermediate filament protein predominantly expressed in mature astrocytes, is crucial for monitoring structural and functional changes in both developing and diseased human brains [10, 11]. Elevated GFAP levels in blood are considered indicative of astrocytic

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injury and have been proposed as a potential biomarker for neurological damage [12-14]. A recent study demonstrated a significant association between serum GFAP levels and cognitive performance in patients with CSVD [15].

However, no clinical studies have specifically investigated the relationship between plasma GFAP levels and BBB integrity in patients with occult CSVD. Therefore, the present study aimed to explore this association. Understanding this link may offer insights into the underlying mechanisms of occult CSVD and support the use of GFAP as a potential biomarker for BBB disruption in this population.

Materials and methods

Participant selection

This retrospective study included patients with occult cerebral small vessel disease (CSVD group) recruited from the Fuyang Community (Anhui, China) between December 2021 and June 2022. The inclusion criteria were as follows: (1) age between 50 and 75 years; (2) absence of apparent subjective neurological symptoms; (3) normal cognitive function as assessed by the Montreal Cognitive Assessment-B (MoCA-B) score (26-30 points); (4) no history of cerebral trauma or neurosurgical procedures; (5) no long-term use of antibiotics, antiplatelet agents, or statins; (6) ability to undergo multiple sequential magnetic resonance imaging (MRI) scans; (7) fulfillment of imaging diagnostic criteria for CSVD in the absence of clinical neurological symptoms, thus meeting the definition of occult CSVD [16]; and (8) availability of complete clinical and radiographic data.

Exclusion criteria were as follows: (1) liver or renal dysfunction; history of brain tumors, cerebral trauma, central nervous system infection, thyroid dysfunction, vitamin B1/B12 deficiency, alcohol-related brain damage, syphilis, malnutrition, or other diseases potentially causing brain damage; (2) severe mental disorders or psychiatric symptoms that could affect cognitive assessment; (3) presence of macrovascular infarction, severe hemorrhagic stroke, leukodystrophy, central nervous system inflammatory demyelinating diseases, or vasculitis contributing to white matter hyperintensities (WMHs); (4) active severe infections; (5) susceptibility-weighted imaging indicating extensive cerebral microbleeds; (6) presence of metallic implants; (7) prior cerebral structural abnormalities or history of neurosurgery; and (8) incomplete clinical or radiographic data.

Age-matched controls were enrolled during the same period. Inclusion criteria for the control group were: (1) age between 50 and 75 years; and (2) absence of CSVD, age-matched to the CSVD group. Exclusion criteria included: (1) any central nervous system disease (e.g., tumors, trauma, infections, stroke); (2) multi-organ dysfunction involving the liver, kidneys, heart, or lungs; (3) psychiatric disorders or substance dependence; (4) recent severe infections or immune-inflammatory diseases; (5) metallic implants interfering with imaging; and (6) incomplete examination data. This study was approved by the Ethics Committee of Fuyang People's Hospital (Medical Ethics Review [2022]26). All subjects signed an informed consent form for participation.

Data collection

Demographic and clinical data, including age, sex, smoking history, alcohol consumption, years of education, and comorbidities (e.g., hypertension, diabetes), were collected from patients' electronic medical records.

Laboratory indicators included total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and plasma GFAP. For sample collection, 5 mL of fasting venous blood was drawn from each participant the following morning. Samples were left at room temperature for 10-20 minutes, then centrifuged at 3000 rpm for 15 minutes. The supernatant was collected for analysis. TC, HDL, and LDL were measured using an automatic biochemical analyzer, while GFAP levels were quantified using an ELISA kit (mlbio, China).

Cognitive function was assessed using the Montreal Cognitive Assessment-B (MoCA-B) scale prior to enrollment. Normal cutoff scores for MoCA-B were: > 19 for individuals with no formal education or primary education, > 22 for those with secondary education, and > 24 for university-educated individuals [17].

All participants underwent routine and dynamic contrast-enhanced MRI (DCE-MRI) of the brain

Table 1. Clinical characteristics

Characteristics	control group (n=61)	CSVD (n=68)	p
Age (years)	57 (6)	58 (9)	0.123
Education (years)	12 (3)	9 (6)	0.032
Male, n (%)	27 (44.3%)	27 (39.7%)	0.721
Hypertension, n (%)	23 (37.7%)	35 (51.5%)	0.156
Diabetes, n (%)	5 (8.2%)	14 (20.6%)	0.080
Smoking, n (%)	16 (26.2%)	22 (32.4%)	0.562
Drinking, n (%)	22 (36.1%)	27 (39.7%)	0.719
Hypercholesterolemia, n (%)	8 (13.1%)	21 (30.9%)	0.020
GFAP (pg/mL)	76.21 (37.39)	73.04 (36.35)	0.688
TC (mmol/L)	5.33 (1.24)	5.11 (1.33)	0.229
HDL (mmol/L)	1.35 (0.41)	1.25 (0.45)	0.478
LDL (mmol/L)	2.82 (0.41)	2.69 (1.21)	0.171
MoCA-B	26 (3)	25 (3)	0.010

GFAP: glial fibrillary acidic protein; TC: total cholesterol; HDL: high density lipoprotein; LDL: low density lipoprotein; MoCA-B: Montreal Cognitive Assessment-Basic; GC: control group; CSVD: cerebrovascular small vessel disease.

using a Philips Ingenia CX 3.0T scanner (Koninklijke Philips NV, Amsterdam, Netherlands). Protocol parameters included:

(1) T1-weighted imaging (T1WI): TR = 7.9 ms, TE = 3.5 ms, slice thickness = 1 mm, no interslice gap, 140 slices. (2) T2-weighted imaging (T2WI): TR = 3000 ms, TE = 90 ms, slice thickness = 5 mm, 24 slices. (3) DCE-MRI: TR = 3.5 ms, TE = 1.64 ms, slice thickness = 3 mm, 36 slices.

All imaging data were reviewed by four experienced physicians: a chief and an attending physician from the radiology department, and a chief and a deputy chief physician specializing in neurovascular diseases.

WMHs on T2-weighted FLAIR images were graded using the Fazekas scale [18]. The total CSVD imaging burden score ranged from 0 to 4, with 1 point assigned for each of the following features:

(1) Presence of ≥1 lacunar infarction. (2) Presence of ≥1 cerebral microbleed. (3) Unilateral enlarged perivascular spaces in the basal ganglia graded 2-4 (> 10 per side). (4) Fazekas grade 3 for periventricular WMHs or grade ≥2 for deep WMHs.

Patients were categorized into either the none/mild load group or the moderate/severe load group based on their total score.

T1-weighted images were analyzed using voxel-based morphometry (VBM) via the SPM8 toolkit and VBM8 toolbox in MATLAB R2012b. Images were reoriented, spatially normalized to the standard template, segmented into gray matter, white matter, and cerebrospinal fluid, and then smoothed with an 8 mm full-width at half-maximum Gaussian kernel.

Multiple regression analysis was conducted using SPM8 to assess correlations between GFAP levels and brain volume/structure. Brain regions with voxel-wise $P < 0.001$ and cluster size > 10 voxels were defined as regions of interest (ROIs). The average Ktrans values of these ROIs were obtained using Philips Intellispace Portal (v7.0.5.40155) by a professional radiologist.

Statistical analysis was performed using SPSS version 24.0 (IBM Corp., Armonk, NY, USA). Normally distributed continuous variables were presented as mean ± standard deviation (SD) and compared using independent-sample t-tests. Non-normally distributed data were presented as median and interquartile range (IQR) and analyzed using the Mann-Whitney U test. Categorical variables were expressed as frequencies (n, %) and compared using the chi-square test. VBM analysis was performed using SPM8 in MATLAB. Multiple regression was used to identify brain regions associated with GFAP levels, with a voxel-level threshold of $P < 0.001$.

Results

Comparison of general information

No significant differences were observed between the two groups regarding the prevalence of hypertension, diabetes mellitus, smoking, or alcohol consumption (all $P > 0.05$). However, the proportion of patients with hyperlipidemia was significantly higher in the CSVD group compared to the control group ($P < 0.05$). In addition, both MoCA-B scores and years of education were significantly lower in the CSVD group (both $P < 0.05$, **Table 1**).

Table 2. Multivariate logistic analysis of influence factor of CSVD

Variable	β	SE	Wald	P	HR	95% CI
Age (Continuous variable)	-0.028	0.041	0.464	0.496	0.973	0.898-1.054
Hypercholesterolemia (0 = No, 1 = Yes)	1.311	0.503	6.786	0.009	3.711	1.384-9.953
MoCA (Continuous variable)	-0.233	0.138	2.871	0.090	0.792	0.604-1.037

MoCA-B: Montreal Cognitive Assessment-Basic; SE: standard error; HR: hazard ratio; 95% CI: 95% confidence interval; CSVD: cerebrovascular small vessel disease.

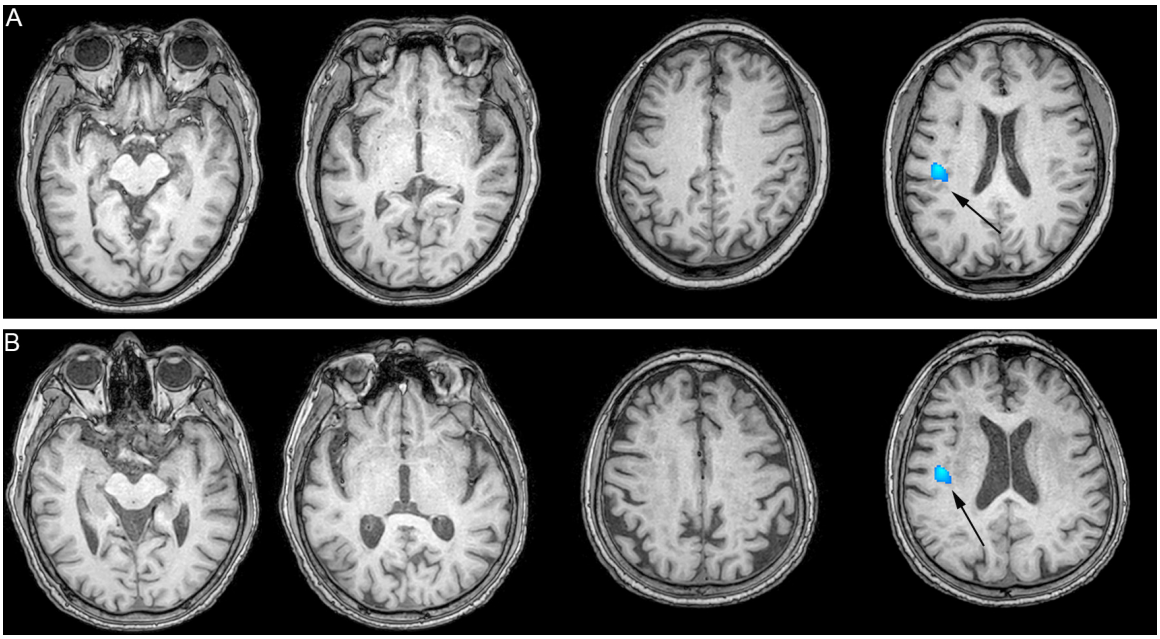

Figure 1. Typical images of patients and ROI in each group. A: Typical T1-weighted MRI brain scans from subjects in the CSVD group. B: Typical T1-weighted MRI brain scans from subjects in the control group. Arrows: observation point of the area of interest. ROI: region of interest.

Table 3. Factors associated with GFAP

	Control group		CSVD group	
	r	p	R	p
Age (years)	-0.259	0.044	0.203	0.097
Male	0.115	0.377	-0.136	0.268
Hypertension	-0.096	0.461	-0.080	0.516
Diabetes	0.007	0.959	-0.022	0.857
Smoking	-0.021	0.871	0.077	0.533
Drinking	0.004	0.976	0.114	0.354
Hypercholesterolemia	0.110	0.397	0.150	0.222
Total cholesterol (mmol/L)	-0.154	0.237	-0.281	0.020
HDL (mmol/L)	-0.025	0.851	-0.232	0.057
LDL (mmol/L)	-0.170	0.191	-0.282	0.020

GFAP: glial fibrillary acidic protein; TC: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein; control group: control group; CSVD: cerebral small vascular disease.

Logistic regression analysis incorporating age, hyperlipidemia, and MoCA-B scores identified hyperlipidemia as a significant risk factor for CSVD (**Table 2**). Representative MRI brain images from both groups are presented in **Figure 1**.

Factors associated with plasma GFAP levels

Spearman's correlation analysis showed no significant association between GFAP and other variables in the control group ($P > 0.05$). In contrast, in the CSVD group, GFAP levels were negatively correlated with TC ($r = -0.281$, $P = 0.020$) and LDL ($r = -0.282$, $P = 0.020$) (**Table 3**). Additionally, GFAP levels were inversely associated with MoCA-B scores in the CSVD group (**Figure 2**).

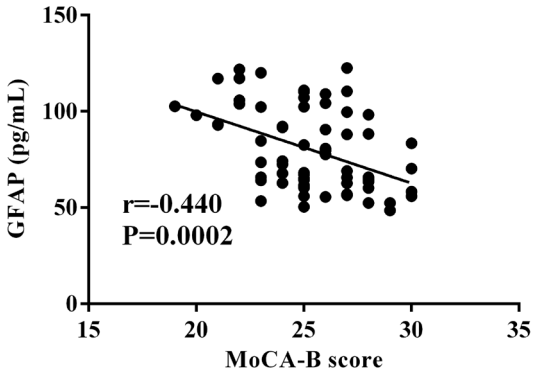

Figure 2. Correlation between GFAP and MoCA score. GFAP: glial fibrillary acidic protein; MoCA-B: Montreal Cognitive Assessment-Basic.

Analysis of the risk factor for moderate/severe load

According to the total MRI burden score for CSVD, 32 patients were classified into the moderate/severe load group and 36 into the none/light load group. The proportion of patients with older age and hypertension was significantly higher in the moderate/severe load group, suggesting that both factors may contribute to the progression of CSVD (**Table 4**).

Subsequent logistic regression analysis identified age as an independent risk factor for moderate/severe CSVD burden (**Table 5**). Furthermore, plasma GFAP levels were significantly elevated in the moderate/severe load group compared to the none/light load group (**Figure 3**).

Comparison of Ktrans values and cortical thickness in ROI

Brain regions with GFAP levels showing statistical significance were identified via VBM analysis. These regions demonstrated BBB leakage and cortical thinning in CSVD patients. The mean Ktrans values and cortical thickness of the left supramarginal gyrus differed significantly between the CSVD and control groups (both $P < 0.05$, **Table 6**).

Binary regression analysis of MoCA-B scores

Binary logistic regression analysis revealed that there was no statistically significant difference in MoCA-B scores between the CSVD and control groups ($P > 0.05$, **Table 7**).

Discussion

This study found that brain regions statistically correlated with plasma GFAP levels exhibited both BBB leakage and cortical thinning in patients with occult CSVD. These findings suggest that plasma GFAP may serve as a potential biomarker for assessing BBB integrity in this population.

We also observed that the Ktrans values in ROIs differed significantly between CSVD patients and non-CSVD individuals. As Ktrans reflects BBB permeability, this indicates increased BBB leakage in CSVD patients. These results are consistent with previous studies [19-21], which reported more extensive regional BBB disruption in individuals with CSVD compared to controls. BBB dysfunction is considered a key mechanism in CSVD pathogenesis. The extravasation of blood components may contribute to localized vascular injury and diffuse brain tissue damage, ultimately leading to cognitive decline and dementia.

In our cohort, MoCA-B scores were significantly lower in CSVD patients than in non-CSVD individuals, suggesting impaired cognitive function. However, these scores may also be influenced by differences in educational background. Nonetheless, this supports a possible link between BBB disruption and cognitive impairment in CSVD, a connection that has also been highlighted in prior studies [22-24].

Several studies have demonstrated that elevated GFAP levels are associated with various neurological conditions, including neurodegenerative diseases, traumatic brain injury, malignant brain tumors, and cerebrovascular events [25-27]. However, the role of GFAP in CSVD has not been well characterized. In the present study, we found that brain regions with significant GFAP associations also showed BBB leakage and reduced cortical thickness. Moreover, GFAP levels were negatively correlated with MoCA-B scores, suggesting that elevated GFAP may reflect both BBB impairment and cognitive dysfunction in CSVD patients.

This observation is in line with the biological role of astrocytes - key components of the neurovascular unit that are closely associated with endothelial cells, which are most affected by BBB dysfunction in CSVD [15]. Reactive astro-

Table 4. Clinical characteristics between none/light load group and moderate/severe load group

Characteristics	None/Light load group (n=36)	Moderate/Severe load group (n=32)	p
Age (years)	58 (5)	65 (10)	0.001
Education (years)	9 (6)	9 (6)	0.551
Male, n (%)	16 (44.4%)	11 (34.4%)	0.397
Hypertension, n (%)	14 (38.9%)	21 (65.6%)	0.028
Diabetes, n (%)	10 (27.8%)	4 (12.5%)	0.120
Smoking, n (%)	11 (30.6%)	11 (34.4%)	0.737
Drinking, n (%)	13 (36.1%)	14 (43.8%)	0.521
Hypercholesterolemia, n (%)	8 (22.2%)	13 (40.6%)	0.101
TC (mmol/L)	5.11 (1.20)	5.10 (1.78)	0.766
HDL (mmol/L)	1.28 (0.38)	1.25 (0.47)	0.930
LDL (mmol/L)	2.71 (0.98)	2.58 (1.40)	0.915
MoCA-B	25 (4)	26 (3)	0.906

TC: total cholesterol; HDL: high density lipoprotein; LDL: low density lipoprotein.

Table 5. Multivariate logistic analysis of influence factor of moderate/severe load

Variable	β	SE	Wald	P	HR	95% CI
Age (Continuous variable)	0.134	0.049	7.361	0.007	1.144	1.038-1.260
Hypertension (0 = No, 1 = Yes)	0.832	0.541	2.364	0.124	2.298	0.796-6.637

SE: standard error; HR: hazard ratio; 95% CI: 95% confidence interval.

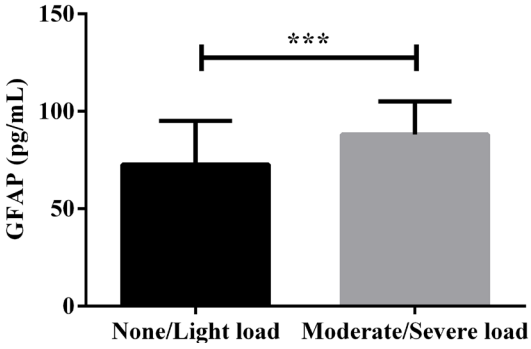

Figure 3. GFAP level between the none/light load group and moderate/severe load group. GFAP: glial fibrillary acidic protein. ***P < 0.001.

gliosis, a hallmark of astrocytic response to injury, is characterized by increased GFAP expression and morphological changes [28]. Huss et al. also reported that serum GFAP levels were correlated not only with disease severity but also with cognitive performance in CSVD patients [15]. Therefore, GFAP may serve as a valuable biomarker for early detection, risk stratification, and targeted intervention in CSVD.

In this study, ROIs associated with GFAP were primarily located in the insula and supramarginal gyrus, with cortical thinning most pronounced in the insular region. These brain regions are functionally linked to sensory processing, motor coordination, cognition, and socio-emotional regulation. The observed functional impairments are consistent with the clinical features of CSVD, further supporting the hypothesis that astrocyte-mediated BBB disruption, as indicated by abnormal GFAP levels, contributes to CSVD pathophysiology.

Notably, this study also revealed a statistically significant correlation between GFAP levels and TC and LDL levels in CSVD patients, but not in the control group. Furthermore, the prevalence of hyperlipidemia was significantly higher in CSVD patients than in non-CSVD individuals. These findings suggest that dysregulated lipid metabolism in the peripheral circulation may impact astrocyte structural stability in CSVD, potentially leading to abnormal GFAP expression. One plausible explanation is that increased BBB permeability may impair the central nervous system's ability to regulate lipid metabolism, thereby influencing early astrocytic responses.

Consistent with our findings, previous studies have reported that high-cholesterol diets can exacerbate BBB disruption, whereas lipid-low-

Table 6. Comparison of Ktrans Values and cortical thickness in ROI

	p	Mean Difference	Std. Error Difference	95% CI
Mean Ktrans of ROI	< 0.001	0.673	0.151	0.374-0.972
Cortical thickness of left supramarginal	0.030	-0.040	0.018	-0.076 - -0.004

CSVD: cerebral small vascular disease; control group: control group; ROI: region of interest.

Table 7. Binary regression analysis of MoCA scores

	B	S.E.	Wald	df	Sig.	Exp (B)	95% C.I. for EXP (B)	
							Lower	Upper
MoCA-B	0.175	0.107	2.682	1	0.101	1.191	0.966	1.468

Note: MoCA-B: Montreal Cognitive Assessment Scale-basic.

ering agents may help mitigate BBB impairment associated with hypercholesterolemia [29-31]. Moreover, lipid metabolic dysregulation, which modulates astrocyte reactivity, has been shown to be upregulated following ischemic stroke, with A2-type reactive astrocytes exhibiting neuroprotective properties. However, the phenotypic divergence between this neuroprotection and the pathological mechanisms underlying neurodegenerative disease warrants further investigation [32]. These insights imply that lipid control may play a role in improving the prognosis of CSVD.

Despite the strengths of this study, several limitations should be acknowledged. First, this was an exploratory study with a relatively small sample size, and thus the results should be interpreted cautiously. Second, the use of advanced MRI techniques involves high costs and extensive post-processing. Additionally, variability in MRI hardware and analytical pipelines poses challenges for the reproducibility of CSVD imaging markers. Finally, the causal relationship between BBB disruption, lipid metabolism abnormalities, GFAP elevation, and CSVD pathogenesis remains to be fully elucidated and warrants further investigation.

Brain regions showing significant correlations with plasma GFAP levels also demonstrated BBB leakage and cortical thinning in CSVD patients. These findings support the potential of plasma GFAP as a non-invasive biomarker for evaluating BBB integrity and neurovascular unit dysfunction in CSVD.

In conclusion, our findings suggest that plasma GFAP may serve as a promising biomarker for identifying BBB dysfunction and related neurostructural changes in this patient population, offering potential implications for early detection and targeted intervention.

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Disclosure of conflict of interest

None.

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