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Vitamin D deficiency and increased inflammatory factor intercellular cell adhesion molecule-1 indicate severe leukoaraiosis in northern China

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Abstract

Background and objective: Commonly plaguing in the frigid zone of the world, vitamin D deficiency, as indicated by low levels of 25-hydroxyvitamin D, exacerbated inflammatory responses and impaired endothelial function. Leukoaraiosis (LA) is a prevalent cause of cognitive dysfunction in the elderly and is potentially associated with inflammatory responses. This study aimed to investigate the impact of vitamin D on the severity of LA. **Methods:** Patients with LA were categorized based on 3.0 T brain MRI findings into mild (N = 43), moderate (N = 40), or severe groups (N = 29) using the Fazekas scale (scoring 1-6). A control group consisting of 41 healthy individuals was included. Serum fibrinogen C, homocysteine, plasma 25-hydroxyvitamin D, and intercellular cell adhesion molecule-1 (ICAM-1) levels were measured using ELISA. **Results:** All LA severity groups exhibited lower plasma 25-hydroxyvitamin D levels compared to the control group, with a more pronounced decrease observed as LA severity increased. Low plasma 25-hydroxyvitamin D was identified as an independent risk factor for LA (P < 0.05) according to Multiple logistic regression analysis. Additionally, a negative association was observed between 25-hydroxyvitamin D and vascular inflammatory factor ICAM-1. **Conclusions:** Disease severity positively correlated with levels of the inflammatory marker ICAM-1, worsening as plasma 25-hydroxyvitamin D concentration decreased. Low 25-hydroxyvitamin D emerged as an independent risk factor for LA, potentially exacerbating the inflammatory response. These findings suggest 25-hydroxyvitamin D supplementation as a potential therapeutic approach for LA.

Keywords

cerebral small vascular disease; degenerative disease; leukoaraiosis; white matter hyperintensities; lacunar infarction; 25-hydroxyvitamin D; ICAM-1; fibrinogen-C; inflammatory factor; fazekas scale

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1 Introduction

Leukoaraiosis (LA) is a significant form of cerebral small vascular disease (CSVD), characterized by low-density changes in the white matter of the periventricular tissue or subcortical region on brain computed tomography, and high-density signals on FLAIR (fluid-attenuated inversion recovery) and T2-weighted images on magnetic resonance imaging (MRI). Hence, it is referred to as white matter hyperintensity[1]. The prevalence of LA is approximately 5% in individuals aged 50 years, 20% in those over 60 years, and severe LA is almost always present in individuals over 80 years[2-3].

As an age-related degenerative change once considered normal, LA received little clinical attention in the past. However, recent studies have revealed its close association with cognitive dysfunction[4], dementia, stroke, and other conditions, as well as an increased risk of mortality among the elderly. Consequently, LA has garnered greater interest in both research and clinical practice[5]. In China, in particular, the incidence of LA has risen annually due to population aging, with a concerning trend toward affecting younger individuals, possibly attributed to dietary changes amid rapid social and economic development. Strategies to mitigate LA incidence include antiplatelet, antihypertensive, and anticoagulant therapies; smoking cessation; exercise, salt intake reduction; weight management; and carotid plaque removal in

severe carotid artery stenosis cases[6-8]. To promote brain health among the elderly, further insights into LA risk factors and related mechanisms are imperative for preventing and managing LA progression and potentially reversing its effects.

Previous studies have proposed that the primary mechanistic hypothesis behind LA formation and progression is chronic hypoperfusion injury to brain tissue[9-10], leading to hypoxia and decreased glucose uptake by glial cells, resulting in inadequate oxygen supply to axons[11]. Subsequently, persistent oxygen deprivation can induce inflammatory damage, local demyelination of white matter, or even axonal injury, endothelial dysfunction of small blood vessels, and compromised blood-brain barrier permeability[12]. Accepted risk factors associated with LA progression include smoking, alcohol consumption, hypertension, diabetes, age, body mass index, hyperlipidemia, and other factors [13-16].

However, traditional vascular risk factors alone cannot fully account for the occurrence and development of LA. Recent studies in the past two years have identified associations between LA elevated levels of inflammatory markers such as C-reactive protein (CRP) and matrix metalloproteinase[17]. Vascular endothelial function has been found to negatively correlate with endothelin-1 and high-sensitivity CRP (hs-CRP), while positively correlating with nitric oxide levels. Statins, known for their anti-inflammatory effects, have shown significant improvements in vascular endothelial function among LA patients[18]. Additionally, previous research has demonstrated a dependent association between LA and intercellular cell adhesion molecule-1 (ICAM-1), a member of the immunoglobulin superfamily[19]. ICAM-1, which is typically expressed at low levels in resting vascular endothelial cells, plays a significant role in maintaining blood-brain barrier integrity and facilitating the migration of white blood cells and endothelial cells. Studies on rat models with middle cerebral artery occlusion (MCAO) have indicated a significant increase in ICAM-1 levels[20]. Moreover, ICAM-1 is commonly used as an indicator to assess the inflammatory microenvironment of endothelial cells. Hence, this study selected ICAM-1 as a marker to evaluate endothelial cell damage caused by chronic low perfusion in LA.

Vitamin D is a fat-soluble steroid hormone primarily obtained through dietary intake and synthesis in the skin, with 25-hydroxyvitamin D serving as its metabolic intermediate. Beyond its classical roles in calcium and phosphorus metabolism and bone development promotion, vitamin D is recognized for its anti-inflammatory effects. It achieves this by inhibiting pro-inflammatory cytokines (including interleukin [IL]-12, IFN-γ, IL-6, IL-8, tumor necrosis factor [TNF]-α, IL-17, and IL-9) while upregulating anti-inflammatory cytokines (such as IL-4, IL-5, and IL-10). Consequently, it mitigates internal inflammatory responses and modulates the immune system's equilibrium[21]. The inverse relationship between vitamin D deficiency and heightened inflammatory markers serves as crucial biomarkers for identifying individuals at high-risk chronic diseases involving inflammation[22]. In addition, adequate vitamin D levels play a pivotal role in various biological functions, including blood glucose regulation, prevention of cardiovascular and cerebrovascular diseases, and facilitation of anti-tumor activities.

A recent large-scale prospective study revealed a negative correlation between 25-hydroxyvitamin D levels and the white matter volume of LA lesions, suggesting that low 25-hydroxyvitamin D may serve as a risk factor for LA development[23]. Nonetheless, research into the pathogenesis of LA remains limited, and it remains uncertain whether vitamin D affects LA patients by promoting inflammatory responses. The northernmost and highest latitude province in China, Heilongjiang located in middle temperate zone to cold temperate zone, characterizing by prolonged cold winters and short daylight hours. With the average monthly temperature remaining below 0 °C for approximately 6 months annually, and significant temperature fluctuations between day and night, the climate is unfavorable for prolonged outdoor activities among the elderly, and significant temperature fluctuations between day and night, the climate is unfavorable for prolonged outdoor activities among the elderly, predisposing them to vitamin D deficiency[24-25]. Hence, the present study aims to elucidate the potential pathogenesis of LA by examining vitamin D levels and inflammatory factors among patients with varying degrees of LA severity.

2 Methods

This prospective double-blind cross-sectional study received approval by the Institutional Ethics Committee of the Second Affiliated Hospital of Harbin Medical University of China (KY2016-177 and KY2019-107).

2.1 Participants

From May 2017 to October 2022, the patients with brain MRI were recruited from the Department of Geriatrics and Neurology of the Second Affiliated Hospital of Harbin Medical University, located in Heilongjiang Province. Inclusion criteria for participants were as follows: age of at least 40 years[26]; absence of a documented history of heart or brain disease; completion of a brain MRI examination; and provision of informed consent to participate in the study and provide all requested information.

Participants presenting with any of the following conditions were excluded from the study: (1) acute cerebral or myocardial infarction, hemorrhage, transient ischemic attack, or other

neurological disorders, such as epilepsy, trauma, intracranial or extracranial malignancy, schizophrenia, normal pressure hydrocephalus, depressive and anxiety disorders, Parkinson's disease, or Alzheimer's disease, and so on; (2) high signal abnormalities on MRI scans attributable to long-term radiation exposure, carbon monoxide poisoning, or a history of immune system diseases such as multiple sclerosis, vasculitis, or leukodystrophy; (3) bone metabolic disease including osteoporosis, osteomalacia, or multiple myeloma; (4) severe heart, lung, liver, kidney, thyroid dysfunction, other malignancies, or acute inflammatory disease; (5) use of glucocorticoid, vitamin D, or antibiotics in the past 3 months.

2.2 LA severity and grouping

The diagnostic criteria for LA involved the identification of diffuse high signals in the lateral ventricle or centrum semiovale white matter on T2-weighted or fluid-attenuated inversion recovery imaging in MRI[1]. The severity of LA was assessed using the Fazekas scale[26], with paraventricular and deep white matter lesions evaluated separately. Paraventricular hyperintensity was graded as follows: 0, for no lesion; 1 for cap or pencil-like thin lesion; 2 for a smooth halo of lesion; or 3 for irregular paraventricular hyperintensity extending into deep white matter. Deep white matter signal was scored as: 0 for no lesion; 1 for punctate lesion; 2 for initial lesion fusion; and 3 for large lesion fusion. These scores for paraventricular hyperintensity and deep white matter signal were combined to calculate total scores ranging from 0 to 6.

The participants were divided into four groups according to the Fazekas scale as follows: control group (score nil, indicating no LA); LA-mild (score of 1-2); LA-moderate (score of 3-4); LA-severe (score of 5-6; Fig. 1).

A double-blind design was implemented in this study. Participants were unaware of their group assignment. Additionally, neither the MRI diagnostic physicians, who were solely responsible for analyzing the MRI scans, nor the testers of plasma 25-hydroxyvitamin D and ICAM-1 levels were aware of the groupings.

2.3 Clinical parameters and biochemical measurements

In our descriptive study, clinical and demographic data were collected, including age, gender, history of smoking, history of alcohol drinking, hypertension, diabetes, coronary heart disease, and lacunar infarction. The history of smoking was defined as daily or occasional smoking for more than 5 years. Alcohol consumption was defined as at least 40 g/d for men and at least 20 g/d for women, for more than 5 years. Blood samples (2 mL) were drawn from all participants' elbow veins after overnight fasting for a minimum of 12 hours. Serum levels of the following parameters were determined using an automatic biochemistry analyzer (TBA-2000 FR, TOSHIBA) in the clinical laboratory of our hospital: albumin, creatinine, uric acid, fasting blood glucose, fibrinogen C, homocysteine, total cholesterol, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and apolipoproteins.

2.4 Plasma 25-hydroxyvitamin D and ICAM-1 measurements

Blood samples (2 mL) were drawn from the elbow veins of all participants following overnight fasting for a minimum of 12 hours. Following heparin anticoagulation, the supernatant was centrifuged at 3000×g for 30 minutes. The resulting blood supernatant was then separated and stored in a refrigerator at -80 °C for subsequent enzyme-linked immunoassay analysis (ELISA) of 25-hydroxyvitamin D and ICAM-1 concentrations. This analysis was performed in accordance with the protocol outlined in ELISA Kit of the human 25-hydroxyvitamin D and ICAM-1 (Shanghai Jianglai Biotechnology, Shanghai, China).

2.5 Statistical analysis

Statistical analyses were performed using SAS9.4 software. All tests were two-sided with a significance level set at $\alpha = 0.05$. $P < 0.05$ was considered statistically significant, while $P < 0.001$ was deemed highly significant.

For measurement data that followed a normal distribution, results were presented as mean ± standard deviation. Analysis of variance (ANOVA) was used to compare means among multiple groups, with pairwise comparisons conducted using the least significant difference t-test. Data that did not adhere to a normal distribution were described as median (interquartile range). The Kruskal-Wallis H test was used to compare multiple groups, with pairwise comparisons conducted

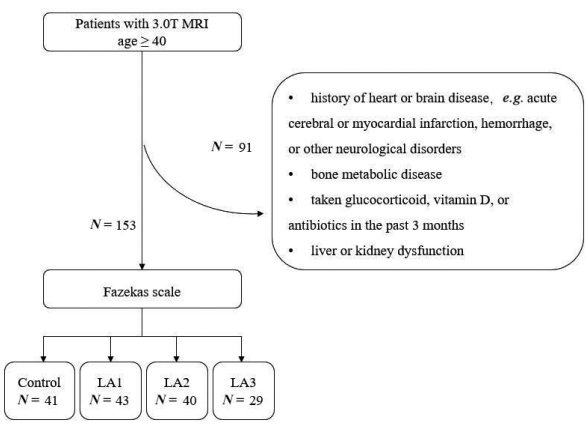

Fig. 1 Selection of participants for the control and Leukoaraiosis groups

using the Nemenyi test. Enumeration data were expressed as frequency (percentage) and compared using the chi-squared test (χ^2) or Fisher's exact test. The Nemenyi test was applied for pairwise comparisons among multiple samples. Multivariate analysis of LA disease was performed using a multiple logistic regression model with the stepwise method for independent variable screening (α = 0.05). Spearman's rho analysis was used to analyze the correlation between 25-hydroxyvitamin D and inflammatory factors (Table 1).

3 Results

It was referenced that 25-hydroxyvitamin D needs to be metabolized in the kidney and the liver; moreover, markedly abnormal renal function affects the progression of LA[19,27]. Hence, based on the inclusion and exclusion criteria, 91 individuals with abnormal liver and kidney function were excluded, leaving overall 153 individuals in the study: 41 in the control group, and 43, 40, and 29 patients, respectively, in the LA-mild, LA-moderate, and LA-severe groups.

3.1 Association of LA with general demographic data

The ages and genders of the four groups were comparable (Table 2). In the control group, 86.27% of the patients had a history of lacunar infarction, and the proportion of patients with a history of lacunar infarction increased with the severity of the disease. The rate of lacunar infarction was significantly higher in the LA-severe group compared with the control group (P < 0.001).

There were 12 drinkers in the LA-mild group (28%), whereas the number of drinkers in each of the other groups was 1, accounting for less than 5%. Fisher's exact test revealed a significant difference in drinking history among the groups (P = 0.001). The history of drinking in the LA-mild group was significantly higher than that of the control and LA-moderate groups, as indicated by the Nemenyi test.

The proportion of patients with a history of hypertension increased with the severity of LA. The history of hypertension was significantly different among the four groups (P = 0.042): the Nemenyi test showed that 69% of patients in the LA-severe group had a history of hypertension, which was significantly higher than the 37% in the control group.

Table 1 Statistical methods for different data

Data	Statistical methods
Normal distribution data	Analysis of variance (ANOVA)
Non normal distribution data	Kruskal-Wallis H test
Enumeration data	Chi-squared test (χ^2)
	Fisher's exact test
Multivariate analysis	Multiple logistic regression analysis
Correlation analysis	Spearman's rho analysis

3.2 Difference in blood parameters across LA severity levels

Blood indicator data were analyzed to compare the levels of 25-hydroxyvitamin D, apolipoproteins B, low-density lipoprotein, and albumin were compared using ANOVA (Table 3). The levels of 25-hydroxyvitamin D among the four groups were statistically significantly different (F = 8.409, P < 0.001). Pairwise comparisons indicated that 25-hydroxyvitamin D levels in the control group were significantly higher than those in the LA-mild (D = 8.56, P = 0.005), LA-moderate (D = 11.63, P < 0.001), and LA-severe (D = 15.61, P < 0.001) groups. Additionally, 25-hydroxyvitamin D levels in the LA-mild group were significantly higher than those in the LA-severe group (D = 7.05, P = 0.035), indicating an inverse relationship between 25-hydroxyvitamin D levels and LA severity.

Homocysteine, apolipoprotein A, total cholesterol, triglyceride, high-density lipoprotein, fasting blood glucose, creatinine, uric acid, fibrinogen C (FBG-C), and ICAM-1 did not follow a normally distribution, so the non-parametric Kruskal-Wallis H test was used (Table 4). FBG-C concentration increased with LA severity, showing a statistically significant difference among the groups (H = 17.196, P = 0.001). Pairwise comparisons revealed significantly higher FBG-C levels in the LA-severe group compared to the control (D = −36.32, P = 0.004) and LA-mild groups (D = −36.68, P = 0.003).

ICAM-1 concentration also showed a gradual increased with LA severity, with a statistically significant difference among the groups from mild to severe (H = 21.247, P < 0.001). Pairwise comparisons indicated a significant difference in ICAM-1 concentration between the control and LA-severe groups (D = −49.267, P < 0.001).

3.3 Multiple logistic regression for factors associated with LA disease severity

Four variables, including the history of alcohol consumption, lacunar infarction, the levels of ICAM-1 and 25-hydroxyvitamin D, were identified as independent risk factors for LA disease severity (Table 5, 6). Individuals with a history of alcohol consumption exhibited risk of LA 26.2 times higher than those without a history of alcohol consumption. Additionally, vitamin D concentration showed a negative correlation with LA disease severity. Specifically, lower levels of 25-hydroxyvitamin D were associated with a higher likelihood of LA presence.

3.4 Association between vitamin D and inflammatory factors

Spearman's rho analysis revealed a negative correlation between

Table 2 Basic medical history of the Leukoaraiosis (LA) and control groupsa

	Control (*N* = 41)	LA-mild (*N* = 43)	LA-moderate (*N* = 40)	LA-severe (*N* = 29)	χ^2/H	*P*
Gender M/F, N/N	18/23	22/21	14/26	14/15	2.408	0.492
Age, y	63.00 (59.50, 70.00)	65.00 (60.00, 68.00)	66.00 (62.00, 70.75)	71.00 (63.00, 79.00)[a]	10.50	0.015
LI	28 (68)	36 (83)	39 (98)	29 (100)[a]	20.302	< 0.001
Smoking	6 (15)	15 (35)	78 (20)	6 (21)	5.269	0.153
Drinking	1 (2)	12 (28)[a]	2 (5)[b]	3 (10)	16.048	0.001
Diabetes	4 (10)	8 (19)	10 (25)	10 (34)	6.856	0.077
Hypertension	15 (37)	20 (47)	23 (58)	20 (69)[a]	8.177	0.042
CHD	6 (15)	10 (23)	8 (20)	4 (14)	1.546	0.672

Data were presented as *N* (%), unless indicated otherwise. Age was not normally distributed among the 4 groups and was summarized using the median (interquartile 25, interquartile 75) and subjected to the Kruskal-Wallis H test. [a]Compared with control group, $P < 0.05$. [b]Compared with LA-mild, $P < 0.05$. CHD, coronary heart disease; LI, lacunar infarction.

Table 3 Blood indicators of the Leukoaraiosis (LA) and control groups

	Control (*N* = 41)	LA-mild (*N* = 43)	LA-moderate (*N* = 40)	LA-severe (*N* = 29)	*F*	*P*
Apo B, g/L	1.03 ± 0.29	0.92 ± 0.23	0.96 ± 0.25	1.02 ± 0.31	1.503	0.216
LDL, mmol/L	3.00 ± 0.85	2.65 ± 0.70	2.73 ± 0.84	2.95 ± 0.96	1.631	0.185
ALB, g/L	43.35 ± 3.83	43.72 ± 3.38	43.69 ± 3.97	41.73 ± 3.88	1.992	0.118
25(OH)D, ng/mL	33.59 ± 19.21	25.03 ± 13.63[a]	21.69 ± 9.86[a]	17.98 ±8.70[a,b]	8.409	< 0.001

Data were presented as mean±SD. [a]$P < 0.05$ compared with control group; [b]$P < 0.05$ compared with LA-mild group. Apo B, apolipoprotein B; ALB, albumin; LDL, low-density lipoprotein; 25(OH)D, 25-hydroxyvitamin D.

the levels of 25-hydroxyvitamin D and that of the inflammatory factors ICAM-1 (r = -0.21, P = 0.009; Fig. 2). This suggests that lower levels of 25-hydroxyvitamin D were associated with a more severe inflammatory response. However, no correlation was found between 25-hydroxyvitamin D and fibrinogen.

4 Discussion

LA, often overlooked due to its mild and atypical symptoms in the early stages, has seen increased detection rates in the elderly population with the advancement of imaging technology and improved health awareness. Recent studies have observed varying degrees of improvement in some patients with CSVD after intervention, particularly in those with mild LA[5,16]. Therefore, investigating the pathogenesis of LA is crucial for informing prevention and treatment strategies.

Previous studies have linked long-term hypertension to arteriolosclerosis in the brain, resulting in increased capillary permeability, local tissue ischemia, and exacerbation of white matter damage due to chronic ischemia[27]. In the present study, the history of hypertension significantly varied across different degrees of LA, showing a positive correlation with LA severity (χ^2 = 8.177, P = 0.042). The proportion of participants with hypertension increased with the severity of LA across the LA groups.

Lacunar cerebral infarction commonly coexists with LA and is prevalent in the elderly, though the age of onset has decreased in recent years. Our findings revealed an increasing trend in the proportion of lacunar infarction with LA severity, with statistically significant differences among the control, moderate, and severe LA groups. The pathogenesis and pathological process of lacunar infarction interact with LA, with the incidence of LA gradually rising in patients with lacunar infarction. Some researchers have also identified a correlation between genetic factors affecting LA and lacunar infarction[28-29].

Previous epidemiological studies have demonstrated that heavy alcohol consumption increases the risk of cerebrovascular disease, while moderate alcohol consumption have some benefits. In a study involving stroke patients with a history of drinking, heavy drinking was found to be correlated with stroke occurrence, whereas the association between mild drinking and stroke was unclear[30]. Our study indicates that alcohol consumption serves as an independent risk factor for LA disease: individuals with a history of alcohol consumption are more prone to developing LA compared to non-drinkers, with drinkers facing a risk of LA over 20 times higher than non-drinkers.

Fibrinogen, synthesized by the liver, plays crucial roles in the coagulation process and inflammatory response. It is also integral to the formation of atherosclerosis, thrombosis, and physiological hemostatic processes. Previous studies have identified plasma fibrinogen as an independent risk factor for cardiovascular and cerebrovascular diseases, with stroke incidence gradually increasing with elevated fibrinogen levels. Early defibrination intervention instroke patients can mitigate brain tissue damage and improve prognosis[31-32]. Our study

Table 4 Blood indicators of the Leukoaraiosis (LA) and control groups

	Control (*N* = 41)	LA-mild (*N* = 43)	LA-moderate (*N* = 40)	LA-severe (*N* = 29)	*H*	*P*
HcyH, μmol/L	10.48 (8.56, 12.86)	11.59 (9.52, 13.25)	10.50 (9.02, 13.11)	10.17 (8.38, 13.60)	2.480	0.479
ApoA1, g/L	1.25 (1.11, 1.37)	1.25 (1.11, 1.36)	1.28 (1.08, 1.45)	1.27 (1.10, 1.45)	0.040	0.998
TC, mmol/L	4.78 (4.21, 5.71)	4.45 (3.86, 5.16)	4.73 (3.74, 5.63)	5.11 (3.92, 5.79)	4.292	0.232
TG, mmol/L	1.35 (1.02, 1.74)	1.12 (0.86, 1.90)	1.46 (1.08, 2.24)	1.46 (1.08, 2.24)	4.820	0.185
HDL, mmol/L	1.28 (1.05, 1.63)	1.29 (1.08, 1.51)	1.34 (1.07, 1.57)	1.24 (1.08, 1.53)	0.303	0.960
FBG, mmol/L	5.37 (4.98, 5.77)	5.48 (4.89, 6.09)	5.35 (4.94, 6.67)	5.52 (4.88, 7.37)	1.701	0.637
Cr, μmol/L	72.00 (64.50, 92.00)	71.00 (65.00, 80.00)	71.50 (61.25, 85.75)	72.00 (62.00, 89.00)	0.311	0.958
UA, μmol/L	325.00 (277.80, 386.95)	307.00 (261.40, 404.90)	300.05 (236.00, 364.01)	308.80 (250.05, 385.95)	1.546	0.672
FBG- C, g/L	2.93 (2.66, 3.36)	2.86 (2.65, 3.58)	3.18 (2.98, 3.63)	3.56 (3.14, 3.91)[a,b]	17.196	0.001
ICAM-1, ng/mL	439.86 (346.10,628.29)	584.38 (432.30, 632.81)	581.26 (514.33, 669.53)	620.31 (596.04, 757.30)[a,b]	21.247	< 0.001

Data were presented as median (interquartile 25, interquartile 75). [a]*P* < 0.05 compared with control group; [b]*P* < 0.05 compared with LA-mild group. Abbreviations: ApoA1, apolipoprotein A; Cr, creatinine; FBG, fasting blood glucose; HcyH, homocysteine; HDL, high-density lipoprotein; TC, total cholesterol; TG, triglycerides; UA, uric acid.

Table 5 Variable assignment table for multiple logistic regression

	Variable Name	Variable assignment
Dependent variable	Leukoaraiosis severity	Severe = 1, Moderate = 2, Mild = 3, Not ill = 4
Independent variable	Gender	Male = 1, Female = 0
	Lacunar infarction	Yes = 1, No = 0
	Alcohol consumption	Yes = 1, No = 0
	Hypertension	Yes = 1, No = 0
	Age, y	Continuous
	25-hydroxyvitamin D	Continuous
	ICAM-1	Continuous
	FBG-C fibrinogen	Continuous

Table 6 Multiple logistic regression analysis of Leukoaraiosis

	b	SE	Wald χ^2	*P*	OR (95% CI)
Gender	0.696	0.478	2.120	0.145	2.007 (0.786, 5.124)
Lacunar infarction	1.432	0.675	4.499	0.034	4.187 (1.115 15.728)
Alcohol consumption	3.266	1.234	7.008	0.008	26.219 (2.335, 294.387)
Hypertension	0.308	0.476	0.419	0.517	1.361 (0.535, 3.459)
Age, y	0.017	0.032	0.304	0.581	1.017 (0.924, 1.045)
25-hydroxyvitamin D	–0.055	0.016	12.345	< 0.001	0.946 (1.025, 1.090)
ICAM-1	0.005	0.001	9.616	0.002	1.005 (0.992, 0.998)
FBG-C fibrinogen	0.031	0.350	0.008	0.929	1.031 (0.488, 1.925)

b, regression coefficient; CI, confidence interval; OR, odds ratio; SE, standard error.

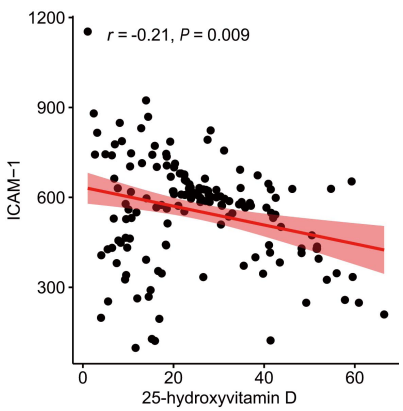

Fig. 2 Correlation between 25-hydroxyvitamin D and ICAM-1 levels

revealed higher fibrinogen levels in the severe LA group compared to the control and mild LA groups, suggesting that elevated fibrinogen levels may exacerbate CSVD progression. Fibrinogen deposition on the vessel walls and its direct adherence to endothelium, followed by red blood cell attachment post-destruction, promote thrombi or arterial plaques formation, ultimately leading to vessel lumen narrowing or blockage and subsequent ischemic brain tissue changes.

ICAM-1, a non-specific inflammatory marker, significantly rises during tissue injury or infection, participating in cell phagocytosis, complement activation, and immune function. Studies have shown elevated ICAM-1 levels individuals with CSVD compared to healthy counterparts[19]. In our study, ICAM-1 levels were notably higher in the severe LA group compared to the control group. This indicates a positive correlation between the severity of LA lesions and inflammatory factor levels. Hence, inflammatory factors likely contribute to LA pathogenesis and progression.

In addition to its well-established role in calcium and phosphorus metabolism, 25-hydroxyvitamin D's potential in preventing cardiovascular and cerebrovascular diseases prevention has garnered significant research attention. Adequate levels of 25-hydroxyvitamin D have been shown to partially repair endothelial function damage, while deficiency in 25-hydroxyvitamin D can impact inflammatory response and oxidative stress in vascular endothelium. In addition, 25-hydroxyvitamin D inhibits the activation of the reactive oxygen species (ROS) system and exerts a protective function in maintaining the integrity of the blood-brain barrier[33]. Our study found that more severe LA lesions were associated with lower plasma 25-hydroxyvitamin D levels. Vitamin D concentration emerged as an independent risk

factor for LA and exhibited a negative correlation with severity of LA, indicating that higher levels of 25-hydroxyvitamin D may mitigate the severity of LA.

The pathogenesis of CSVD remains elusive, but the inflammatory response is increasingly recognized as one of the contributing factors. Recent studies have highlighted the involvement of inflammatory mediators and lymphocytes in the progression of CSVD. As CSVD develops, recurrent small infarct lesions can compromise the blood brain barrier, allowing the release of specific antigens from the central nervous system into the bloodstream. This triggers chemotaxis, leading to the accumulation of lymphocytes at the site of injury. Blood proteins can then penetrate the blood-brain barrier, stimulating microglia to produce inflammatory mediators and chemokines, thereby fostering a chronic inflammatory microenvironment[34]. Vitamin D possesses anti-inflammatory and immunomodulatory properties that influence cardiovascular and cerebrovascular diseases[35-36]. The metabolic precursor, 25-hydroxyvitamin D, has been shown to regulate gene expression, particularly during inflammatory responses[37], which are influenced by various cells and cytokines. Vitamin D can promote the production of $CD4^+$ T cells while reducing the the release of inflammatory factors by monocytes and microglia[38]. A study involving stroke patients demonstrated that those with low serum 25-hydroxyvitamin D levels exhibited larger areas of brain injury and poorer prognosis. This suggests a protective role for 25-hydroxyvitamin D in ischemic brain injury, potentially reducing brain tissue damage by downregulating inflammatory factor expression[39]. Therefore, in view of vitamin D deficiency commonly plaguing in the frigid zone of the world, appropriate supplementation of vitamin D is deemed necessary and may alleviate vascular inflammation while potentially mitigating the severity of LA.

5 Conclusion

The inflammatory factor ICAM-1 has been extensively researched in cancer and autoimmune diseases, yet little attention has been paid to its relationship with the severity of LA. However, our study discovered a noteworthy finding: concentrations of ICAM-1 significantly increased with the severity of LA. Furthermore, vitamin D concentration exhibited a negative correlation with ICAM-1 levels, suggesting that lower vitamin D concentrations were associated with more pronounced inflammation. Based on these findings, we hypothesize that 25-hydroxyvitamin D may regulate the expression of inflammatory factors, indirectly impacting the integrity of the cerebrovascular endothelium and blood-brain barrier. This disruption could affect the normal functioning of brain tissue and contribute to the progression of LA. Therefore, supplementing with vitamin D may hold promise for reducing vascular inflammation and potentially reversing the severity of LA. Further research is warranted to elucidate the mechanisms underlying this relationship and to explore the therapeutic potential of vitamin D supplementation in managing LA.

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Author contributions

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Ethical approval

This study received approval by the Institutional Ethics Committee of the Second Affiliated Hospital of Harbin Medical University of China (KY2016-177 and KY2019-107).

Conflicts of interest

We have no conflicts of interest to this work.

Data availability statement

All data used during the study are available from the corresponding author by request.

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