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# Deep medullary vein abnormalities impact white matter hyperintensity volume through increases in interstitial free water

Haiyuan Lan[1†], Weiwen Qiu[2†], Xinjun lei[1], Zhihua Xu[3], Jie Yu[1] and Huimei Wang[4*]

## Abstract

**Background** Our intent was to explore the mediating role of interstitial free water (FW) linking deep medullary vein (DMV) score to white matter hyperintensity (WMH) volume.

**Methods** Our research team conducted a forward-looking analysis of initial clinical and imaging information gathered from 125 patients with cerebral small vessel disease. We identified six anatomic DMV regions on susceptibility weighted imaging (SWI) studies. Each region earned a score of 0–3, determined by the visual conditions of vessels, summing all six to generate a DMV score. We utilized fluid-attenuated inversion recovery (FLAIR) sequences to measure the volume of WMH. Additionally, we employed diffusion tensor imaging (DTI) to assess FW value.

**Results** DMV score significantly positively correlated with FW value and with WMH volume ($p < 0.05$), and value of FW positively correlated with WMH volume ($p < 0.05$). The indirect effect of DMV score on WMH volume was mediated by FW (β = 0.281, 95% confidence interval [CI]: 0.178–0.388), whether adjusted for age and gender (β = 0.142, 95% CI: 0.058–0.240) or for age, gender and vascular risk factors (β = 0.141, 95% CI: 0.054–0.249).

**Conclusion** DMV score correlate with WMH volume by virtue of FW increases in white matter.

**Keywords** Deep medullary vein, White matter hyperintensity, Free water, Susceptibility weighted imaging, Diffusion tensor imaging

## Introduction

White matter hyperintensity (WMH) is important imaging markers of cerebral small vessel disease, typically seen as patchy rarefaction on fluid-attenuated inversion recovery (FLAIR) sequences [1]. Studies have shown that such occurrences and their progression are associated with various neurologic disorders, particularly cognitive impairment and stroke [2, 3]. The pathogenesis of WMH is a complex process closely related to white matter damage, involving inflammatory factor release and abnormal blood-brain barrier function [4, 5]. Some study outcomes also suggest that dysfunction within the venous system may be pivotal in WMH emergence and progression [6].

†Haiyuan Lan and Weiwen Qiu contributed equally to this work.

*Correspondence:
Huimei Wang
lsleiwanhuimei@126.com
[1]Department of Radiology, Lishui Hospital of Traditional Chinese Medicine affiliated with Zhejiang Chinese Medical University, Lishui 323000, China
[2]Department of Neurology, Lishui Hospital of Traditional Chinese Medicine affiliated with Zhejiang Chinese Medical University, Lishui 323000, China
[3]Department of Radiology, Tongde Hospital of Zhejiang Province, Hangzhou 310000, China
[4]Department of Neurology, Lishui People's Hospital, Lishui 323000, China

Deep medullary vein (DMV) are primarily situated around the lateral ventricles, where they are aligned perpendicularly and appear as vertical bands of hypointense signals on susceptibility weighted imaging (SWI) [7]. These vessels serve to drain venous blood from periventricular and corona radiata regions into the deep cerebral venous system [8]. Recent data has revealed an association between diminished DMV visibility on SWI images and higher WMH burden [9], implicating DMV dysfunction as an important dynamic in the onset and evolution of WMH. However, the specific pathways entailed remain unclear. Previous research indicates that DMV narrowing due to venous collagen deposition may cause venous outflow obstruction, thus increasing interstitial fluid content [10]. The latter may lead to disruption of white matter fiber tracts and ineffective clearance of harmful metabolites, culminating in WMH. We hypothesize that DMV dysfunction exacerbates white matter damage by increasing interstitial fluid content.

Therefore, we used diffusion tensor imaging (DTI) to gauge free water (FW) value, reflecting interstitial fluid content of the brain. We also determined DMV score as DMV functional indices. Our objective was to explore the interrelations between DMV score, FW value, and WMH volume.

## Materials and methods

### Patient population

Clinical and imaging data were collected from 125 individuals with cerebral small vessel disease between March and September 2023. Inclusion criteria were as follows: (1) Be over 40 years of age; (2) magnetic resonance imaging (MRI) studies adhering to Standards for Reporting Vascular Changes on Neuroimaging guidelines; (3) at least one vascular risk factors, such as tobacco use, diabetes, high blood pressure, or abnormal blood lipid levels. The following were grounds for exclusion: (1) incomplete medical clinical data; (2) Presence of secondary demyelinating lesions (e.g., those caused by metabolic issues, toxins, or infections); (3) Other brain-related conditions such as tumors, physical injuries, bleeding within the brain, acute infarctions, etc.; (4): exhibit significant artifacts that could interfere with the accurate assessment of DMVs.

### Magnetic resonance imaging protocol

All patients underwent multimodal MRI studies, including 3D T1- (T1WI) and T2-weighted (T2WI) imaging, FLAIR sequences, SWI, and DTI, using a 1.5 Tesla scanner (MAGNETOM Aera, Syngo Platform VD13A; Siemens Healthcare, Erlangen, Germany) equipped with an eight-channel phased-array head coil. Parameters for FLAIR were as follows: repetition time=6500 ms; echo time=95 ms; flip angle=140°; slice thickness=5 mm; intersection gap=1.5 mm; field of view=23×23 $cm^2$; and matrix=256×256. For SWI, parameters were the following: repetition time=54 ms; echo time=40 ms; flip angle=15°; slice thickness=2 mm; intersection gap=0.4 mm; field of view=23×23 $cm^2$; and matrix=256×256. DTI parameters were as follows: repetition time=3600 ms; echo time=95 ms; field of view=23×23 $cm^2$; matrix=128×128; diffusion directions=30; and b values=0, 1,000, and 2,000 s/$mm^2$.

### Deep medullary vein score

During the image review process, two experienced neuroradiologists independently evaluated DMV score. Scoring of DMV was done on SWI sequences, selecting five consecutive slices at level of lateral ventricles (within basal ganglia) until the ventricles disappeared. Most of DMV were thereby included. We then divided the slices into frontal, parietal, and occipital lobes bilaterally, for a total of six anatomic regions [11] (Fig. 1). Each region was scored from 0 to 3, based on DMV signal continuity: 0, signals continuous, clear, and uniform; 1, signals still continuous but uneven; 2, weak, punctate, and discontinuous signals; or 3, no DMV signals. The DMV score (range, 0–18) was generated by adding score of all six regions. (Fig. 2).

### White matter hyperintensity volume

We measured WMH volume quantitatively on FLAIR images. These images were first converted to the Neuroimaging Informatics Technology Initiative (NIfTI) format using MRIcron software, which is available at https://www.nitrc.org/projects/mricron. The skulls had been stripped from images using the FSL BET function. After matching of 3D T1WI and FLAIR images, we obtained WMH volume using the FSL BIANCA function. All processed images were subjected to neuroradiologic review and manual correction, aided by ITK-SNAP software (http://itksnap.org).

### FW in white matter

DTI images were first preprocessed, which largely entailed denoising, artifact removal, and correcting echo planar imaging distortion. Next, we mapped extracellular FW using DIPY software (https://dipy.org) in a FW elimination two-compartmental model [12]. 3D T1WI images were further registered as b=0 (b0) images, and mean white matter FW value was ultimately calculated from each patient's white matter mask, segmented through FSL FAST using co-registered 3D T1WI images. FW value ranged from 0 to 1, corresponding with higher extracellular FW content as value increased.

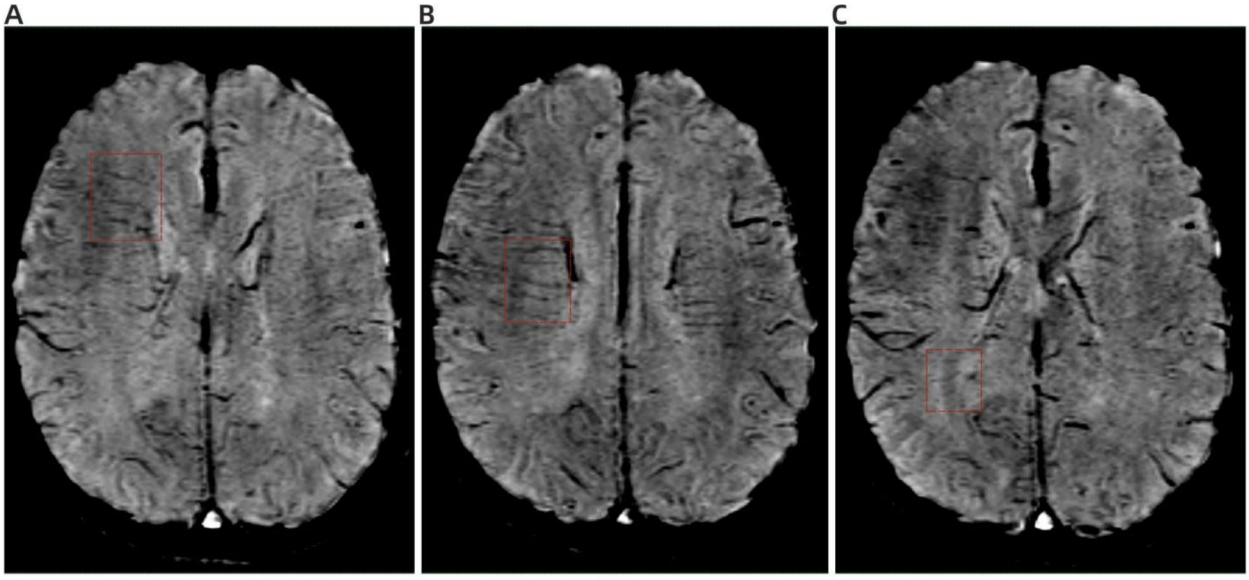


**Fig. 1** A schematic diagram of the DMVs in different brain regions. (**A**) DMVs in the frontal lobe region; (**B**) DMVs in the parietal region; (**C**) DMVs in the occipital region. DMV, deep medullary vein

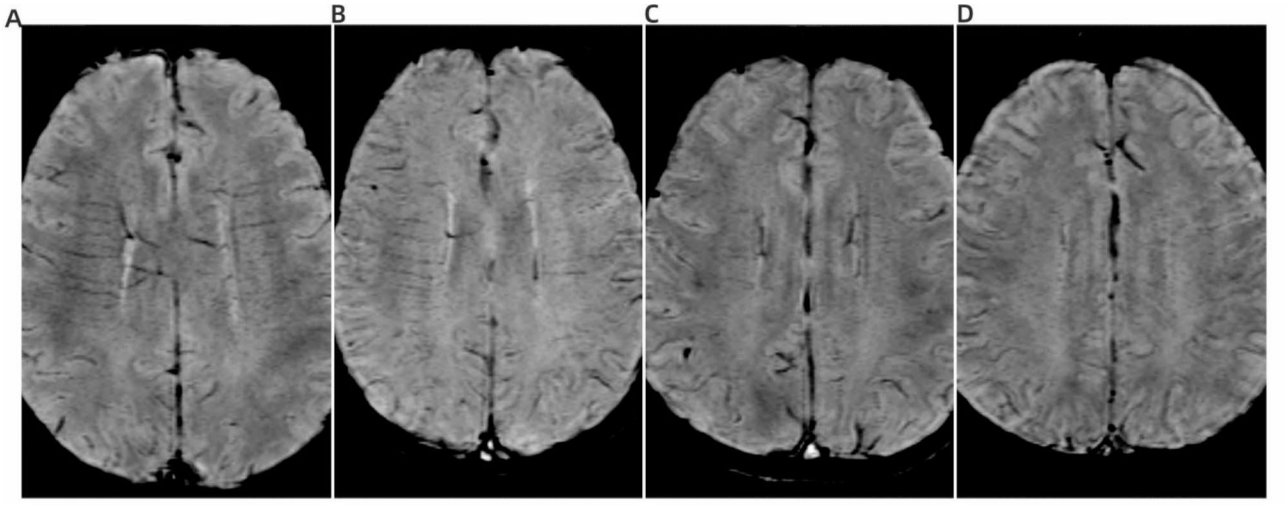


**Fig. 2** Illustration of deep medullary vein (DMV) scoring system: (**A**) signals continuous, clear, and uniform (DMV score = 0); (**B**) signals continuous but uneven (DMV score = 1); (**C**) weak, punctate, and discontinuous signals (DMV score = 2); and (**D**) no visible DMV signal (DMV score = 3)

### Data analysis

In our statistical analysis, we represented categorical variables as percentages. For continuous variables, we used mean ± standard deviation for normally distributed data, and median with interquartile ranges (IQRs) for non-parametric data. To analyze interrelations of DMV score, FW value, and WMH volume, the Spearman correlation coefficient was applied. We conducted all statistical analyses using SPSS version 26, setting significance at $p < 0.05$. The PROCESS macro [Model 4, a simple mediation effect model where an independent variable (predictor) influences a dependent variable (outcome variable) through a mediator; https://afhayes.com] was also engaged to analyze the mediating effect of FW on DMV score and WMH volume (Fig. 3). In Model 1, predictor, mediator, and outcome variables were DMV score, FW, and WMH volume, respectively. We adjusted for age and gender in Model 2, whereas Model 3 was adjusted for age, gender, hypertension, diabetes and hyperlipidemia.

## Results

Baseline clinical and imaging characteristics of the study population ($N = 125$) are shown in Table 1. There were 58 women (46.4%), and mean age was 60 ± 11 years. Median DMV score was 3 (IQR: 1–8), mean WMH volume was 12.26 ± 12.63 ml, and mean FW value was 0.24 ± 0.01.

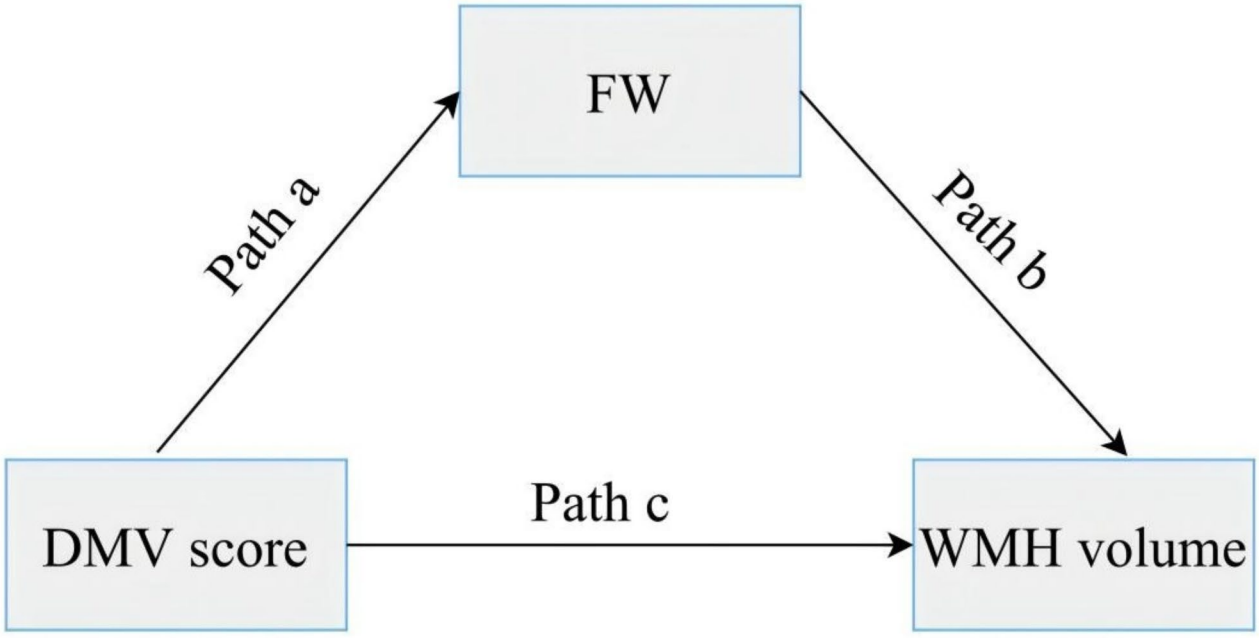


**Fig. 3** Mediation model to explore interrelations between deep medullary vein (DMV) score, free water (FW), and white matter hyperintensity (WMH) volume

**Table 1** Baseline characteristics of patient population ($N=125$)

| Variable | |
|---|---|
| Age, years | 60 ± 11 |
| Gender, female | 58 (46.4) |
| Hypertension | 68 (54.4) |
| Diabetes | 22 (17.7) |
| Hyperlipidemia | 34 (27.2) |
| Smoking | 29 (23.2) |
| DMV score, median (IQR) | 3 (1–8) |
| FW | 0.24 ± 0.01 |
| WMH volume, ml | 12.26 ± 12.63 |

Data presented as n(%) or mean ± standard deviation, unless otherwise specified

DMV, deep medullary vein; FW, free water; IQR, interquartile range; WMH, white matter hyperintensity

### Inter-reader agreement for evaluation of deep medullary vein score

DMV scoring was independently performed by two neuroradiologists blinded to clinical and imaging data. The inter-reader intraclass correlation coefficients (ICCs) for the DMV score was 0.91.

### DMV score and FW

Spearman correlation analysis indicated a positive correlation between DMV score and FW ($r=0.570$; $p<0.001$) (Fig. 4A). DMV score correlated significantly with FW in all test environments (Model 1: $\beta=0.610$; Model 2, adjusted for age and gender : $\beta=0.405$; Model 3, adjusted for age, gender and hypertension/diabetes/hyperlipidemia: $\beta=0.401$) (all $p<0.05$).

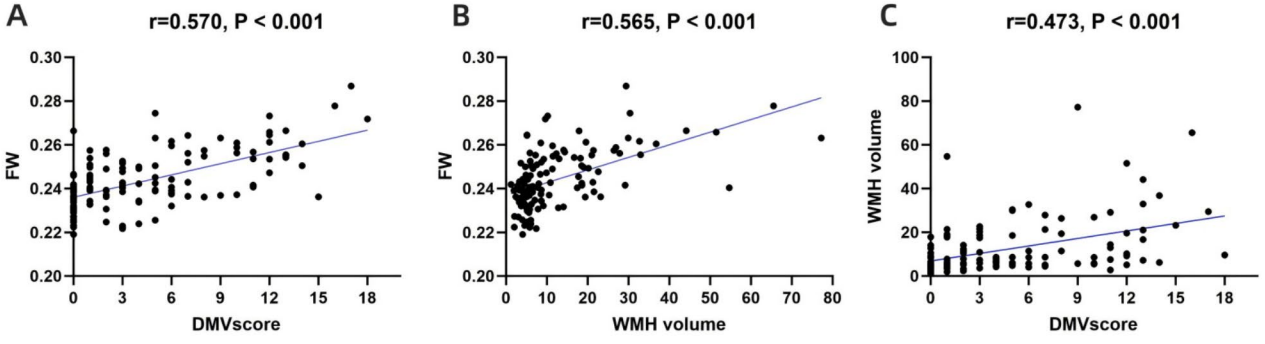


**Fig. 4** Interrelations between DMV score, FW, and WMH volume
DMV, deep medullary vein; FW, free water; WMH, white matter hyperintensity

### FW score and WMH volume

Spearman correlation analysis likewise showed a positive correlation between FW and WMH volume ($r=0.565$; $p<0.001$) (Fig. 4B). Again, DMV score regularly correlated with FW (Model 1: β=0.460; Model 2, adjusted for age and gender: β=0.351; Model 3, adjusted for age, gender and hypertension/diabetes/hyperlipidemia: β=0.351) (all $p<0.05$).

### DMV score and WMH volume

Spearman correlation analysis revealed a positive correlation between FW and WMH volume ($r=0.473$; $p<0.001$) (Fig. 4C), higher DMV score correlating with higher WMH volume.

### Mediation analysis of DMV score, FW, and WMH volume

The indirect effect of DMV score on WMH volume was clearly mediated by FW in our analyses of Model 1 (β=0.281, 95% confidence interval [CI]: 0.178–0.388); Model 2, adjusted for age and gender(β=0.142, 95% CI: 0.058–0.240); and Model 3, adjusted for age, gender, hypertension, diabetes and hyperlipidemia (β=0.141, 95% CI: 0.054-0.249) (Table 2).

## Discussion

Outcomes of the present study confirm a relation between DMV score and WMH volume that is mediated by value of FW. This mediating effect is independent of age, gender, hypertension, diabetes and hyperlipidemia, indicating a link between DMV dysfunction, increased interstitial FW content, and increased WMH volume.

SWI is an MRI imaging technology that is particularly sensitive to paramagnetic materials. The concentration of paramagnetic deoxyhemoglobin in human venous blood is high, allowing clear delineation of veins on SWI studies. Veins with smooth walls, unobstructed drainage, and high flow rates are clearly and continuously displayed by SWI. Otherwise, signaling may be discontinuous or even disappear. SWI is thus a proven mode for venous hemodynamic status assessment [13].

Diminished visibility of DMV on SWI sequences reflects luminal narrowing due to collagen deposition within venous walls [14]. As a result, there is increased vascular permeability, releasing more lytic material into the interstitium. Prolonged narrowing also leads to elevated venous pressure so that drainage of venous blood and interstitial fluid is impaired. Abnormally accumulating interstitial fluid subsequently tends to coalesce in perivascular spaces, producing interstitial edema. Furthermore, such increases in interstitial fluid hinder effective clearance of harmful metabolic substances (i.e., amyloid-β protein and plasma proteins) [15, 16]. These harmful metabolites are toxic to myelin and axons, inflicting neuronal damage but also triggering neuroinflammatory responses and thereby exacerbating interstitial fluid accumulation in the brain [17]. Interstitial edema appears as hyperintense signal on FLAIR sequences. The higher the venous pressure, the more severe interstitial edema becomes, resulting in broader areas of hyperintensity and consequently greater WMH volume.

Cerebral blood supply ordinarily is stable and non-pulsatile, maintained through a balance in cerebrospinal fluid production and cerebral venous drainage [18]. However, vascular regulation declines with age and is increasingly marked by blood flow fluctuations. Prolonged fluctuations gradually raise pressures within DMVs, reducing blood flow. The resultant vasogenic edema and increased extracellular fluid [19] subsequently promote collagen deposition in venous walls, prompting a vicious cycle of DMV luminal narrowing and venous pressure elevation.

Although prior studies of WMH volume have shown associations with age and vascular risk factors [20, 21], significance was consistently demonstrated in our mediation analyses, which adjusted for age, hypertension, diabetes and hyperlipidemia. This affirms the reliability of our data and suggests that increased interstitial fluid secondary to DMV dysfunction may precede the onset of WMH.

There are several study limitations to concede. First, this patient population was drawn from a single center only. Going forward, we intend to acquire a larger sampling for our research through multicenter recruitment. Perfusion images were also lacking and would be useful to clarify the association between WMH perfusion and DMV dysfunction. Finally, the infeasibility of long-term follow-up during this particular investigation afforded

**Table 2** Results of mediation analyses for DMV score, FW, and WMH volume

| | Path a<br>β (95% CI) | Path b<br>β (95% CI) | Path c-direct effect<br>β (95% CI) | Path ab-indirect effect<br>β (95% CI) |
|---|---|---|---|---|
| **Model 1** | 0.610 (0.468, 0.752)* | 0.460 (0.272, 0.648)* | 0.146 (-0.042, 0.334) | 0.281 (0.178, 0.388)* |
| **Model 2** | 0.405 (0.259, 0.552)* | 0.351 (0.143, 0.559)* | 0.100 (-0.088, 0.288) | 0.142 (0.058, 0.240)* |
| **Model 3** | 0.401 (0.254,0.549)* | 0.351 (0.141,0.562)* | 0.094 (-0.095,0.284) | 0.141 (0.054,0.249)* |

*$p<0.05$

Model 1: DMV score serving as predictor, FW as mediator, and WMH volume as outcome; Model 2: Model 1, adjusted for age and gender; Model 3: Model 1, adjusted for age, gender, hypertension, Diabetes and hyperlipidemia

CI, confidence interval; DMV, deep medullary vein; FW, free water; WMH, white matter hyperintensity

no real understanding of the dynamic DMV changes involved.

## Conclusions

Our analysis has revealed a significant relationship between DMV visibility and WMH volume. Importantly, this association appears to be mediated by the amount of FW present in white matter. This observation implicates venous-side pathogenic mechanisms in the WMH evolutionary process.

### Abbreviations

| | |
|---|---|
| FW | Free water |
| DMV | Deep medullary vein |
| WMH | White matter hyperintensity |
| FLAIR | Fluid attenuated inversion recovery |
| DTI | Diffusion tensor imaging |
| SWI | Susceptibility-weighted imaging |
| MRI | Magnetic resonance imaging |

### Acknowledgements

Not applicable.

### Author contributions

HL, WQ, and HW conceptualized the project and drafted the manuscript.HW was instrumental in experimental design. HL, XL and JY collected imaging and clinical data, with imaging analysis provided by HL and ZX. WQ and HW also supplied project supervision. All authors have contributed to manuscript compilation and have approved the final submission.

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### Data availability

No datasets were generated or analysed during the current study.

## Declarations

### Ethics approval and consent to participate

This study was authorized by the Lishui Hospital of Traditional Chinese Medicine, affiliated with Zhejiang Chinese Medical University. All study participants granted informed consent, and all clinical studies adhered to principles of the Declaration of Helsinki.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

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