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Impact of different white matter hyperintensities patterns on cognition: A cross-sectional and longitudinal study

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ABSTRACT

Objectives: White matter hyperintensities (WMH) are highly prevalent in older adults and considered to be a contributor to cognition impairment. However, the strategic WMH lesion distribution related to cognitive impairment is still debated. The aim of this study was to characterize the spatial patterns of WMH associated with cognitive impairment and explore its risk factors.

Methods: We retrospectively analyzed patients who underwent T2 fluid attenuated inversion recovery (FLAIR) and mini-mental state examination (MMSE) in two centers. WHM was classified into four patterns based on T2 FLAIR as follows: (1) multiple subcortical spots (multi-spots); (2) *peri*-basal ganglia (*peri*-BG); (3) anterior subcortical patches (anterior SC patches); and (4) posterior subcortical patches (posterior SC patches). We cross-sectionally and longitudinally estimated associations between different WMH patterns and all-cause dementia and cognitive decline. Multivariable logistic regression analysis was followed to identify risk factors of WMH patterns related to cognitive impairment.

Results: A total of 442 patients with WMH were enrolled, with average age of 71.6 ± 11.3 years, and MMSE score of 24.1 ± 5.4. Among them, 281 (63.6%), 66 (14.9%), 163 (36.9%) and 197 (44.6%) patients presented multi-spots, *peri*-BG, anterior SC patches and posterior SC patches, respectively. Patients with anterior SC patches were more likely to have all-cause dementia in cross-sectional study (OR 2.002; 95% CI 1.098–3.649; $p = 0.024$), and have cognitive decline in longitudinal analysis (OR 3.029; 95% CI 1.270–7.223; $p = 0.012$). Four patterns of WMH referred to different cognitive domains, and anterior SC patches had the most significant and extensive impact on cognition after Bonferroni multiple comparison correction (all $p < 0.0125$). In addition, older age (OR 1.054; 95% CI 1.027–1.082; $p < 0.001$), hypertension (OR 1.956; 95% CI 1.145–3.341; $p = 0.014$), higher percentage of neutrophils (OR 1.046; 95% CI 1.014–1.080; $p = 0.005$) and lower concentration of hemoglobin (OR 0.983; 95% CI 0.967–1.000; $p = 0.044$) were risk factors for the presence of anterior SC patches.

Conclusions: Different patterns of subcortical leukoaraiosis visually identified on MRI might have different impacts on cognitive impairment. Further studies should be undertaken to validate this simple visual classification of WMH in different population.

1. Introduction

White matter hyperintensities (WMH) of presumed vascular origin, visualized as areas of high-intensive signal on T2-weighted magnetic resonance imaging (T2WI), are a key manifestation of cerebral small vessel disease (CSVD) (Wardlaw et al., 2013), and are widely detected among older adults (de Leeuw et al., 2001). Extensive literatures have showed that WMH have detrimental effects on cognition and substantially increase risk of dementia (Prins and Scheltens, 2015). Data from several studies revealed that volume or severity of WMH was associated

Abbreviations: BG, basal ganglia; DWI, diffusion weighted imaging; FLAIR, fluid attenuated inversion recovery; GFR, glomerular filtration rate; Hcy, homocysteine; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MMSE, mini-mental state examination; SC, subcortical; WBC, white blood cell; WMH, white matter hyperintensities.

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with progressive cognitive impairment (de Groot et al., 2001; Hu et al., 2020). However, there is a clinical and radiological discrepancy between whole brain WMH and cognitive impairment (Prins and Scheltens, 2015). Actually, some individuals presenting extensive WMH still preserve normal cognitive functions.

Some studies have proposed that strategic regions of WMH have greater impact on cognitive impairment than whole brain WMH (Lampe et al., 2019; Smith et al., 2011). Traditionally, WMH can be partitioned into periventricular WMH and deep WMH based on the locations. Previous studies established that periventricular WMH were related to reduced global cognition (Burns et al., 2005; de Groot et al., 2000). By contrast, some researches demonstrated that progression of deep WMH was associated with cognitive decline in elderly (Baune et al., 2009; Silbert et al., 2008). Furthermore, the pathological mechanism of periventricular WMH and deep WMH were inconsistent across studies (Fernando et al., 2006; Shim et al., 2015). Additionally, the dichotomization methods distinguishing periventricular and deep WMH varied among studies, with a distance to lateral ventricle ranging from 3 mm to 13 mm (Griffanti et al., 2018). All these heterogeneities have led to disputes over the appropriateness of this dichotomization method.

According to the functions of different brain lobes, investigators attempted to divide WMH into different lobes. However, the results were controversial. A retrospective study found that frontal WMH were detected more in patients with Alzheimer disease than normal aging individuals (Polvikoski et al., 2010). Another study illustrated that lower memory and executive performance were mainly associated with higher deep WMH loaded in frontal areas in cognitively unimpaired participants enriched for Alzheimer disease risk factors (Brugulat-Serrat et al., 2020). While a cross-sectional study showed that parieto-temporal WMH, rather than frontal WMH deteriorated memory on healthy participants (Lampe et al., 2019).

In our clinical experience, we noticed that the distribution of WMH in different patients had some features, as some WMH lesions were scattered, some surrounded the basal ganglia, and some located near the anterior or posterior horn of the lateral ventricle. Andreas Charidimou et al. defined four WMH patterns based on these features, including multiple subcortical spots pattern (multi-spots), *peri*-basial ganglia pattern (*peri*-BG), anterior subcortical patches pattern (anterior SC patches) and posterior anterior subcortical patches pattern (posterior SC patches). In patients with intracerebral hemorrhage, they found *peri*-basial ganglia WMH was more common in the hypertensive arteriopathy group, and the prevalence of multiple subcortical spots was higher in the cerebral amyloid angiopathy group (Charidimou et al., 2016). This study inferred that these four patterns of WMH might imply different potential mechanisms of microangiopathy and tissue injury. Therefore, in the present study, we referred to this classification method and evaluated the impacts of these four WMH patterns on cognition cross-sectionally and longitudinally. Meanwhile, we sought to identify the risk factors contributing to these patterns of WMH, thereby trying to explain its underlying pathological mechanisms.

2. Materials and methods

2.1. Study subjects

We retrospectively reviewed the patients admitted to Second Affiliated Hospital of Zhejiang University and Zhejiang Hospital who presented WMH on brain magnetic resonance imaging (MRI) between January 2014 and December 2020. In the present study, we estimated the relationship between different WMH patterns and all-cause dementia cross-sectionally, and then, we investigated the association between WMH patterns and cognitive decline longitudinally. We enrolled patients who met all of the following inclusion criteria and none of the exclusion criteria into this study.

Inclusion criteria were as follows: (1) visible WMH on T2 fluid attenuated inversion recovery (FLAIR); (2) age $\geq$ 40; (3) underwent Mini-Mental State Examination (MMSE). Exclusion criteria were: (1) patients with secondary causes of white matter lesions, such as demyelinating, metabolic, immunological, toxic, infectious, and other causes; (2) patients with abnormal brain MRI findings such as head trauma, hemorrhage, infarction (except non-acute lacunas) and other space-occupying lesions; (3) patients with severe head motion during MRI scanning.

We retrieved patients' demographic, clinical, laboratory, and imaging data including age, gender, years of education, MMSE, the comorbid conditions such as history of hypertension, diabetes mellitus, hyperlipidemia, coronary heart disease and smoking, laboratory tests such as white blood cell (WBC), percentage of neutrophils (N%), hemoglobin, glomerular filtration rate (GFR), uric acid, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and homocysteine (Hcy).

2.2. Ethics statement

The protocols had been approved by the local ethics committees of these two hospitals. All clinical investigation has been conducted according to the principles expressed in the Declaration of Helsinki.

2.3. Neuropsychological assessment

The neuropsychological condition of each subject was assessed by Chinese version of the mini-mental state examination (MMSE) translated from the original version by Folstein (Zhang Z., 1989). The examination ranged from 0 to 30 with higher scores indicating better cognitive function and evaluated five cognitive domains including orientation, immediate recall, attention and calculation, long-delayed recall and language. All assessments were performed by trained physicians in accordance with the standard protocols.

All-cause dementia was diagnosed by criteria from the Diagnostic and Statistical Manual, Fourth Edition (DSM-IV) (Association, 1994), complied with the following criteria: 1) MMSE $\leq$ 24 with educational level of secondary education, or MMSE $\leq$ 20 with educational level of primary education, or MMSE $\leq$ 17 with educational level of illiteracy; 2) impairment of activity of daily living. Cognitive decline was considered as a decrease of 3 or more points in MMSE in follow-up visit (Hensel et al., 2007; Stringa et al., 2020).

2.4. MRI protocol

All subjects underwent MRI by a 3.0 T MR (MR750, GE Healthcare, United States) scanner in the Second Affiliated Hospital of Zhejiang University or 1.5 T MR (Magnetom Aera, Siemens, Germany) in Zhejiang Hospital, and the sequences included T1, T2 Fluid attenuated inversion recovery (T2 FLAIR), diffusion weighted imaging (DWI). Axial T2 FLAIR sequence was used to evaluate the WMH. The parameters of this sequence of GE MR were: repetition time = 8400 ms, echo time = 150 ms, field of view = 240 mm, matrix size = 256 × 256, inversion time = 2100 ms, slice thickness = 4.0 mm with no gap between slices; and the parameters of Siemens MR were: repetition time = 7500 ms, echo time = 115 ms, field of view = 230 mm, matrix size = 256 × 166, inversion time = 2293 ms, slice thickness = 5.0 mm.

2.5. Assessment of WMH

WMH was defined as hyperintensities without cavitation on T2 FLAIR according to the recommendations of Standards for Reporting Vascular Changes on Neuroimaging (Wardlaw et al., 2013). The Fazekas scale was used to rate for WMH severity on axial T2 FLAIR. Periventricular WMH were graded as 0 (absence), 1 (caps or pencil-thin lining), 2 (smooth haloing or thick lining), or 3 (irregular periventricular lesions extending into the deep white matter). Deep WMH were rated as 0 (absence), 1 (small punctate or nodular lesions), 2 (beginning confluent lesions), and 3 (confluent lesions) (Fazekas et al., 1987). The

WMH Fazekas score was the sum of the periventricular and deep WMH scores.

2.6. Evaluation patterns of WMH

We used RadiAnt DICOM Viewer (Version 2020.2) to evaluate patterns of WMH. Firstly, we transferred raw data to RadiAnt DICOM Viewer, and then evaluated four patterns of WMH separately on axial T2 FLAIR images. The details of the classification have been descripted in the study by Andreas Charidimou et al (Charidimou et al., 2016). Briefly, four patterns based on the location and morphology of WMH were classified as follows (Fig. 1): (1) multi-spots: this pattern appears in subcortical white matter and refers to small circles or spots of WMH (the total number of spots must be higher than 10 to meet this pattern requirement); (2) *peri*-BG: WMH following the peripheral outline of the basal ganglia; (3) anterior SC patches: large WMH volumes (generally extending more than 5 mm in the deep white matter) anterior to the frontal horn/ventricle body junction with a clear distinction from periventricular WMH; and (4) posterior SC patches: large WMH volumes (generally extending more than 5 mm in the deep white matter) posterior to the ventricular horn with a visible separation between ventricle (with or without periventricular WMH). We visually evaluated multi-spots and *peri*-BG patterns, for anterior or posterior SC patches pattern, we chose the layer of largest WMH lesion anterior or posterior to the ventricular horn, and measured whether the largest diameter of WMH lesion was more than 5 mm by RadiAnt DICOM Viewer. Two trained raters (Wang. J. and Zhou. Y.) both with seven years of neuroimaging review experience who were blinded to all other image and clinical data classified all subjects. For the inconsistent classification, two raters discussed and decided the final classification together. The inter-rater intraclass correlation coefficients (ICCs) were 0.843 for multi-spots, 0.828 for *peri*-BG, 0.903 for anterior SC patches and 0.890 for posterior SC patches. And one rater (Wang. J.) performed the assessments of 50 patients twice, with an interval of 3 months apart. The intra-rater ICCs were 0.876 for multi-spots, 0.898 for *peri*-BG, 0.901 for anterior SC patches and 0.911 for posterior SC patches.

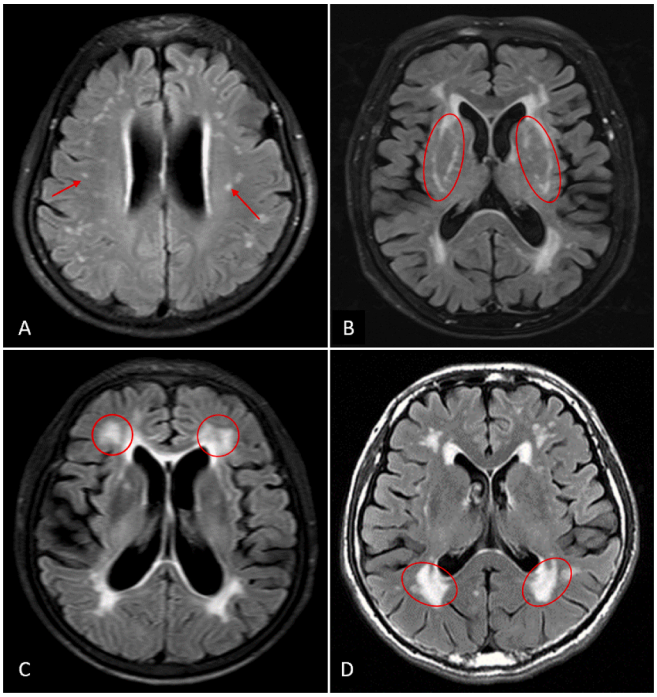

Fig. 1. Different WMH patterns on T2 FLAIR MRI: multi-spots pattern (A), *peri*-BG pattern (B), anterior SC patches pattern (C), posterior SC patches pattern (D).

2.7. Evaluation of lacunas

T2 FLAIR images were used to identify lacunas, which were defined as round or ovoid, subcortical, fluid-filled cavity (signal similar to CSF) between 3 mm and 15 mm in diameter, consistent with a previous acute small subcortical infarct or haemorrhage in the territory of one perforating arteriole (Wardlaw et al., 2013). And we evaluated lacunas by counting the number of lacunas on axial T2 FLAIR images.

2.8. Statistical analysis

The demographic and clinical characteristics of two groups were compared using 2-sample T tests, Mann-Whitney U tests, chi-squared and Fisher exact tests as appropriate. Bonferroni correction was applied if multiple comparison correction were encountered. Separate logistic regression models were performed with patterns of WMH as the predictors and dementia or cognitive decline as the dependent variable. Age, hypertension and other confounders were included as covariates. Regression models performed based on the absence of multicollinearity. Spearman's correlation analyses were performed to determine the correlation between four patterns of WMH and different cognitive domains. Multivariable logistic regression was run to look for risk factors for some patterns of WMH related to all-cause dementia. Variables that reached a p value of < 0.05 in univariate analyses were entered into multivariable logistic regression model. All analyses were performed blinded to the participant identifying information. A p value of < 0.05 was considered to be statistically significant. All statistical analysis was performed with SPSS package (IBM, Chicago, version 24.0 for Windows).

3. Results

3.1. Patient characteristics

A total of 442 WMH patients were enrolled for the final analysis, including 284 patients from Zhejiang Hospital and 158 patients from the Second Affiliated Hospital of Zhejiang University. Fig. 2 shows the flow chart. Among them, 74 were outpatients and 368 were inpatients. The reasons for admission of those patients were cognitive impairment (n = 95, 21.5%), dizziness (n = 57, 12.9%), transient ischemic attack (TIA) or non-acute lacunar (n = 72, 16.3%), headache (n = 24, 5.4%), mild anxiety or depression symptoms (n = 92, 20.8%), gait disturbances (n = 19, 4.3%), no specific symptoms but were found to have WMH on MRI (n = 83, 18.8%). The average age was 71.6 ± 11.3y, and MMSE score was 24.1 ± 5.4. Among them, 281 (63.6%), 66 (14.9%), 163 (36.9%) and 197 (44.6%) patients presented as multi-spots, *peri*-BG, anterior SC patches and posterior SC patches, respectively. Detailed demographic, clinical and imaging data were demonstrated in Table 1.

3.2. Correlation between patterns of WMH and dementia

We classified WMH patients into all-cause dementia group and non-dementia group based on the diagnostic criteria of all-cause dementia. Compared to patients in non-dementia group, patients with all-cause dementia were older ($p < 0.001$), more likely to have hypertension ($p = 0.004$) and higher Fazekas score ($p = 0.003$). A significantly higher prevalence of anterior SC patches (55.5% vs. 30.0%) and posterior SC patches (59.7% vs. 39.0%) was detected in dementia group after multiple comparison correction (Bonferroni $p < 0.0125$). And patients in dementia group had more WMH patterns than patients in non-dementia group (2.0 ± 1.3 vs. 1.4 ± 1.2, $p < 0.001$). After adjusting for age, hypertension and Fazekas score, only anterior SC patches was associated with all-cause dementia independently (OR 2.002; 95% CI 1.098–3.649; $p = 0.024$). Detailed information is provided in Table 2 and Table 3. And multivariable logistic regression model incorporating four patterns of WMH still demonstrated anterior SC patches was associated with all-cause dementia (OR 2.530; 95% CI 1.458–4.392; $p = 0.001$),

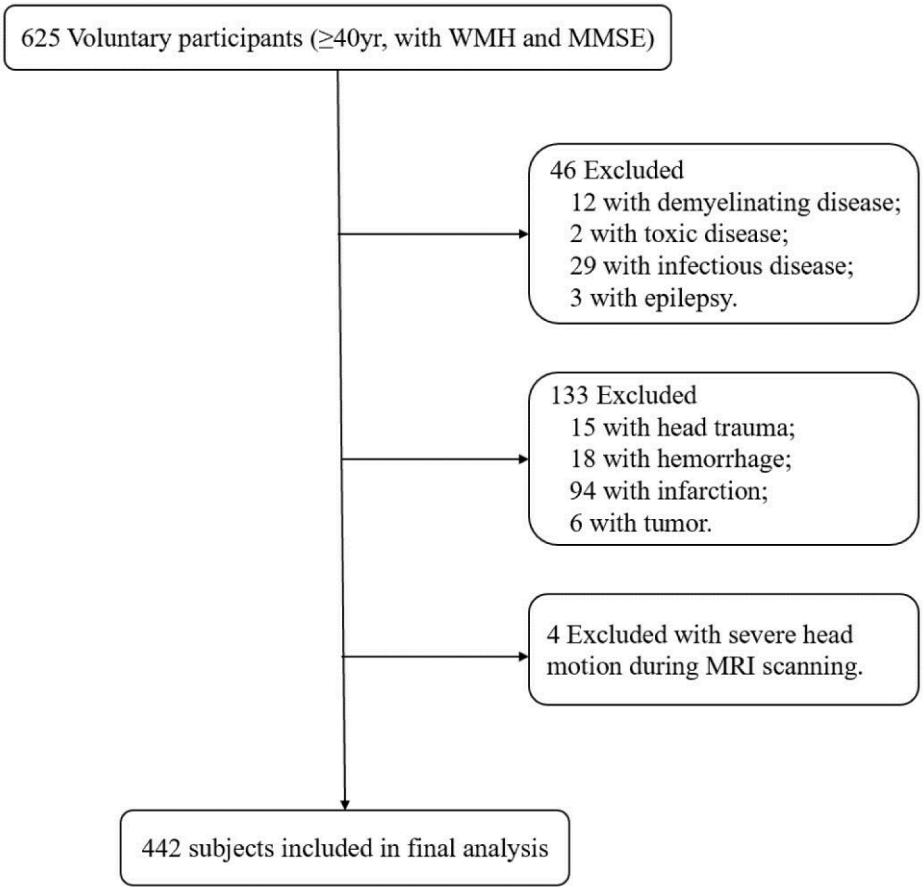

Fig. 2. Flow chart visualizing of the selection process of participants.

Table 1
Clinical and demographic data of participants.

	N = 442
Age, years, mean ± sd	71.6 ± 11.3
Male, n (%)	237 (53.6)
Years of education, median (IQR)	9 (6-12)
Hypertension, n (%)	291 (65.8)
Diabetes, n (%)	101 (22.9)
Coronary heart disease, n (%)	50 (11.3)
Hyperlipidemia, n (%)	179 (40.5)
Smoking, n (%)	112 (25.3)
MMSE, mean ± sd	24.1 ± 5.4
Neuroimaging findings	
Lacunas, n (%)	165 (37.3)
WMH Fazekas score, mean ± sd	3.79 ± 1.79
Multi-spots pattern, n (%)	281 (63.6)
Peri-BG pattern, n (%)	66 (14.9)
Anterior SC patches pattern, n (%)	163 (36.9)
Posterior SC patches pattern, n (%)	197 (44.6)
Laboratory findings (n = 356)	
WBC, 10^9/L, mean ± sd	5.6 ± 1.5
Neutrophils%, mean ± sd	60.5 ± 7.8
Hemoglobin, g/L, mean ± sd	131.2 ± 16.2
GFR, mL/min/1.73 m^2, mean ± sd	93.4 ± 27.4
Uric acid, μmol/L, mean ± sd	321.6 ± 85.7
HDL, mmol/L, mean ± sd	1.20 ± 0.34
LDL, mmol/L, mean ± sd	2.38 ± 0.86
Hcy, μmol/L, mean ± sd	15.30 ± 13.30

IQR, interquartile range; MMSE, mini-mental state examination; WMH, white matter hyperintensities; BG, basal ganglia; SC, subcortical; WBC, white blood cell; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Hcy, homocysteine.

Supplementary Table 1.

3.3. Correlation between patterns of WMH and cognitive decline

A total of 129 WMH patients rechecked MMSE at follow-up visit. The average follow-up interval was 15.5 ± 7.9 months, and the average follow-up MMSE score was 23.5 ± 5.8. Among them, 32 patients (24.8%) developed with cognitive decline (decrease of MMSE ≥ 3). As Table 2 shows, patients with cognitive decline had fewer years of education (5.5 vs. 9, $p = 0.014$) and lower baseline MMSE (22.6 ± 5.9 vs. 25.0 ± 4.6, $p = 0.019$) than patients without cognitive decline, and anterior SC patches was more common in patients with cognitive decline (62.5% vs. 32.0%, $p = 0.002$). Statistical significance of anterior SC patches between two groups was preserved after Bonferroni multiple - comparison correction ($p < 0.0125$). In addition, there was no significant difference in the number of WMH patterns between cognitive decline group and non-cognitive decline group (2.0 ± 1.3 vs. 1.7 ± 1.2, $p = 0.159$). And the mean decrease of MMSE in four WMH patterns was summarized in Fig. 3. As Table 4 shows, after adjusting for years of education, follow-up interval and baseline MMSE, anterior SC patches (OR 3.029; 95% CI 1.270–7.223; $p = 0.012$) was independently associated with cognitive decline.

3.4. Four patterns of WMH and different cognitive functions

After Bonferroni multiple comparison correction, posterior SC patches was associated with immediate recall (r = -0.137, $p = 0.004$), attention and calculation (r = -0.194, $p < 0.001$). Anterior SC patches had greatest correlation with orientation (r = -0.180, $p < 0.001$), attention and calculation (r = -0.259, $p < 0.001$) and long-delayed recall (r = -0.127, $p = 0.008$) and language (r = -0.131, $p = 0.006$), which had

Table 2
Comparison of clinical characteristics in different groups.

	All-cause dementia(n = 119)	Non-dementia(n = 323)	*p* value	Cognitive decline(n = 32)	Non-cognitive decline(n = 97)	*p* value
Age, y, mean ± sd	78.9 ± 9.0	68.9 ± 10.9	**<0.001**	70.5 ± 10.4	69.6 ± 11.0	0.675
Male, n (%)	57(47.9)	180(55.7)	0.143	20 (62.5)	49 (52.6)	0.328
Years of education, y, median (IQR)	9 (6-14)	9 (6-12)	0.717	5.5 (0-9)	9 (5-12)	**0.014**
Hypertension, n (%)	91(76.5)	200(61.9)	**0.004**	22 (68.8)	64 (66.0)	0.773
Diabetes, n (%)	30(25.2)	71(22.0)	0.473	7 (21.9)	20 (20.6)	0.880
Coronary heart disease, n (%)	12(10.1)	38(11.8)	0.621	2 (6.3)	7 (7.2)	greater than0.999
Hyperlipidemia, n (%)	56(47.1)	123(38.1)	0.088	10 (31.3)	37 (38.1)	0.482
Smoking, n (%)	28(23.5)	84(26.0)	0.595	11 (34.4)	27 (27.8)	0.482
Lacunas, n (%)	48(40.3)	117(36.2)	0.428	19 (59.4)	42 (43.3)	0.114
WMH Fazekas score, mean ± sd	4.20 ± 1.62	3.64 ± 1.83	**0.003**	4.84 ± 1.37	4.38 ± 1.63	0.151
Multi-spots, n (%)	75(63.0)	206(63.8)	0.884	21 (65.6)	65 (67.0)	0.885
Peri-BG, n (%)	24(20.2)	42(13.0)	0.061	7 (21.9)	19 (19.6)	0.780
Anterior SC patches, n (%)	66(55.5)	97(30.0)	**<0.001***	20 (62.5)	31 (32.0)	**0.002***
Posterior SC patches, n (%)	71(59.7)	126(39.0)	**<0.001***	17 (53.1)	47 (48.5)	0.647
Number of WMH patterns, mean ± sd	2.0 ± 1.3	1.4 ± 1.2	**<0.001**	2.0 ± 1.3	1.7 ± 1.2	0.159
Baseline MMSE, mean ± sd	/	/	/	22.6 ± 5.9	25.0 ± 4.6	**0.019**
Follow-up interval, month, median (IQR)	/	/	/	13.5 (11-21.5)	13 (11.5–20)	0.746

IQR, interquartile range; WMH, white matter hyperintensities; BG, basal ganglia; SC, subcortical; MMSE, mini-mental state examination. Bold indicates $p < 0.05$; * Statistically significant after Bonferroni correction ($p < 0.0125$).

Table 3
The association between different WMH patterns with all-cause dementia after adjusting for age, hypertension and Fazekas score by logistic regression model.

	R^2	OR	95%CI	*p* value
Anterior SC patches pattern	0.258			
Age		1.096	1.067–1.125	**<0.001**
Hypertension		1.390	0.816–2.370	0.226
Anterior SC patches pattern		2.002	1.098–3.649	**0.024**
WMH Fazekas score		0.971	0.814–1.159	0.748
Posterior SC patches pattern	0.245			
Age		1.099	1.070–1.128	**<0.001**
Hypertension		1.394	0.823–2.362	0.216
Posterior SC patches pattern		1.241	0.659–2.339	0.504
WMH Fazekas score		1.054	0.875–1.268	0.581
Number of WMH patterns	0.244			
Age		1.099	1.071–1.129	**<0.001**
Hypertension		1.382	0.814–2.345	0.231
Number of WMH patterns		1.059	0.799–1.403	0.689
WMH Fazekas score		1.066	0.870–1.306	0.539

SC, subcortical; BG, basal ganglia; WMH, white matter hyperintensities. Bold indicates $p < 0.05$

broader impact on cognition than other patterns. The degree of correlation between four patterns of WMH and cognitive functions is shown in Fig. 4.

3.5. Risk factors for anterior SC patches pattern of WMH

We performed regression analysis on 356 patients with laboratory tests. As Table 5 shows, univariate analysis demonstrated that age, hypertension, percentage of neutrophils, hemoglobin, GFR, LDL and Hcy were associated with anterior SC patches pattern of WMH (all $p < 0.05$). And multivariable logistic regression analysis revealed that older age (OR 1.054; 95% CI 1.027–1.082; $p < 0.001$), hypertension (OR 1.956; 95% CI 1.145–3.341; $p = 0.014$), higher percentage of neutrophils (OR 1.046; 95% CI 1.014–1.080; $p = 0.005$) and lower concentration of hemoglobin (OR 0.983; 95% CI 0.967–1.000; $p = 0.044$) were risk factors for anterior SC patches pattern of WMH, Table 6.

4. Discussion

In this study, we evaluated whether the morphological patterns of WMH on T2 FLAIR were related to cognition impairment. We found that anterior SC patches of WMH was associated with all-cause dementia on admission. Longitudinal analysis indicated a link between anterior SC patches of WMH and cognitive decline. These findings suggest that anterior SC patches of WMH can potentially be used as an imaging biomarker to predict cognition impairment. Furthermore, besides conventional risk factors of age and hypertension, higher percentage of neutrophils and lower concentration of hemoglobin were risk factors for anterior SC patches, which may bring further light into the mechanisms and preventive measures of WMH.

Compared to other three patterns of WMH, anterior SC patches pattern with anterior dominant distribution was independently associated with all-cause dementia, which is consistent with previous findings. A longitudinal study found a relationship between complex processing speed decline and anterior WMH progression (Marquine et al., 2010). In cognitively unimpaired participants, the CAIDE (Cardiovascular Risk Factors, Aging, and Incidence of Dementia) dementia risk scores were positively associated with WMH in anterior areas (Salvadó et al., 2019). Possible explanation for this finding is that anterior SC patches mainly distributed in frontal areas closing to the anterior horn of the lateral ventricle. It is reported that frontal WMH mainly affected executive function (Garnier-Crussard et al., 2020; Lampe et al., 2019). Meanwhile, the region where anterior SC patches located has extensive white matter fiber tracts and functional connections with hippocampus, temporal lobe, corpus callosum and thalamus, which are closely related to cognitive functions of the whole brain. A study based on major white matter tracts showed that WMHs located particularly within the anterior thalamic radiation and forceps minor were inversely associated with both executive functioning and visuomotor speed (Biesbroek et al., 2016). Resting-state functional MRI study revealed that functional connectivity value of interthalamic adhesion (ITA) - medial frontal gyrus (MFG) was significantly correlated with neuropsychological test results for multiple cognitive functions (Chen et al., 2021). Thus, it is conceivable that anterior SC patches of WMH places a greater burden on cognition than other patterns. However, it should be noted that some studies found that higher WMH burden in posterior region of brain was also correlated with cognitive functions, especially with visual-constructional function(Brugulat-Serrat et al., 2020; Marquine et al., 2010). Further studies need to be undertaken to identify the relationship between posterior SC patches and visual-constructional function.

In addition to the cross-sectional study of WMH patterns and

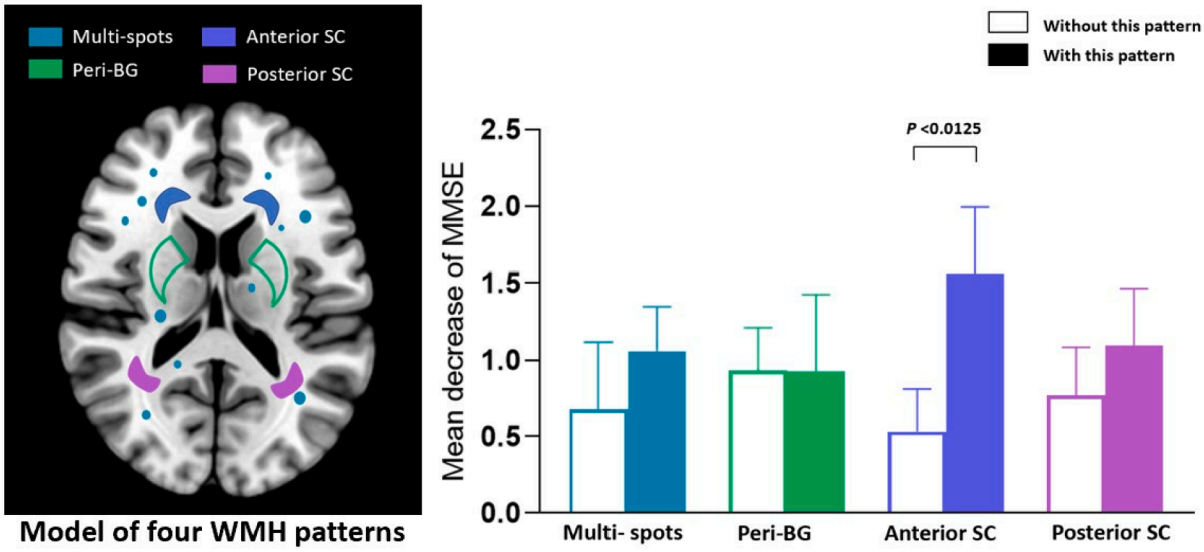

Fig. 3. Mean decrease of MMSE with and without WMH patterns.

Table 4
The association of anterior SC patches pattern and cognitive decline using logistic regression model.

	R^2	OR	95%CI	*p* value
Model 1	0.173			
Years of educaion		0.897	0.819–0.982	**0.018**
Follow-up interval		0.964	0.910–1.022	0.219
Anterior SC patches		3.248	1.377–7.659	**0.007**
Model 2	0.187			
Years of educaion		0.905	0.827–0.991	**0.032**
Follow-up interval		0.973	0.917–1.032	0.356
Baseline MMSE		0.950	0.873–1.033	0.232
Anterior SC patches		3.029	1.270–7.223	**0.012**

Model 1 adjust for year of education and follow-up interval. Model 2 adjust for year of education, follow-up interval and baseline MMSE. Bold indicates $p < 0.05$

cognitive function, our study conducted a longitudinal analysis of follow-up patients. We found anterior SC patches of WMH was correlated with cognitive decline. Previous studies demonstrated that greater WMH were associated with accelerated decline on neuropsychological tests (Puzo et al., 2019; Wang et al., 2020). Beyond the relationship between whole brain WMH and cognitive decline, Anor et al. indicated that WMH in the frontal and temporal lobes contributed most to the change of Neuropsychiatric Inventory scores (Anor et al., 2021). Our results, along with these previous studies, support the hypothesis that WMH may contribute to the cognitive decline, and the impact of anterior SC patches of WMH may be greater than other regions, which implies anterior SC patches can potentially be used as a new imaging biomarker to predict cognitive decline.

A considerable amount of literature has suggested that age and hypertension are risk factors of WMH (Abraham et al., 2016; Benedictus et al., 2013). Our results showed that neutrophil percentage and hemoglobin were risk factors of anterior SC patches besides age and hypertension. Studies on inflammation and WMH suggested inflammatory response could impair endothelium, increase microglial and astroglial activation, and finally result in blood–brain barrier (BBB) dysfunctions (Low et al., 2019; Wardlaw et al., 2019). In white matter damage model of SHR/SP rats, neutrophils appeared around endothelial cells from 1 to 3 weeks after unilateral carotid artery occlusion. Thus, we speculate that

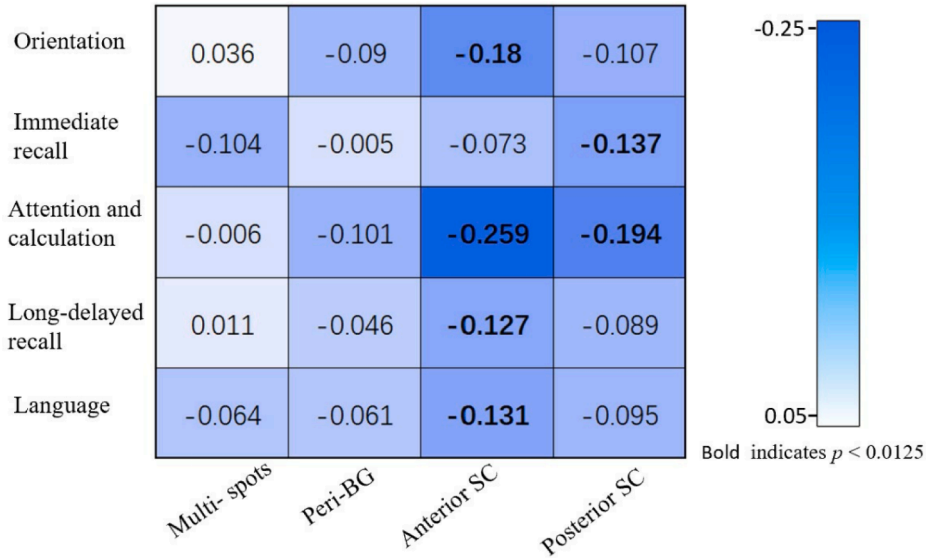

Fig. 4. The degree of correlation between four patterns of WMH and cognitive functions.

Table 5
Univariate analysis of risk factors for anterior SC patches pattern (n = 356).

Variable	Anterior SC patches pattern(n = 132)	*p* value
Age, y, mean ± sd	75.8 ± 9.4	**<0.001**
Male, n (%)	65 (49.2)	0.063
Hypertension, n (%)	104 (78.8)	**<0.001**
Diabetes, n (%)	34 (25.8)	0.657
Coronary heart disease, n (%)	19 (14.4)	0.445
Hyperlipidemia, n (%)	62 (47.0)	0.612
Smoking, n (%)	31 (23.5)	0.190
BMI, kg/m2, mean ± sd	23.12 ± 3.21	0.471
WBC, 10E9/L, mean ± sd	5.65 ± 1.41	0.752
Neutrophils%, mean ± sd	62.1 ± 7.3	**0.002**
Hemoglobin, g/L, mean ± sd	126.4 ± 17.0	**<0.001**
GFR, mL/min/1.73 m*2, mean ± sd	87.9 ± 28.1	**0.003**
Uric acid, μmol/L, mean ± sd	319.9 ± 89.9	0.779
HDL, mmol/L, mean ± sd	1.23 ± 0.35	0.233
LDL, mmol/L, mean ± sd	2.26 ± 0.86	**0.048**
Hcy, μmol/L, mean ± sd	17.3 ± 18.7	**0.033**

SC, subcortical; BMI, body mass index; WBC, white blood cell; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Hcy, homocysteine. Bold indicates $p < 0.05$

Table 6
Multivariable logistic regression analysis of risk factors for anterior SC patches pattern.

Variable	R^2	OR	CI	*p* value
Age, y	0.211	1.054	1.027–1.082	**<0.001**
Hypertension		1.956	1.145–3.341	**0.014**
Neutrophils%		1.046	1.014–1.080	**0.005**
Hemoglobin, g/L		0.983	0.967–1.000	**0.044**
GFR, mL/min/1.73 m*2		1.004	0.994–1.014	0.457
LDL, mmol/L		0.965	0.727–1.279	0.802
Hcy, μmol/L		1.015	0.990–1.040	0.249

SC, subcortical; GFR, glomerular filtration rate; LDL, low-density lipoprotein; Hcy, homocysteine. Bold indicates $p < 0.05$

neutrophils may be involved in the progress of WMH. In addition, hemoglobin was considered to be associated with the severity and progression of WMH in some studies(Inzitari et al., 2008; Todoroki et al., 2015). Moreover, hemoglobin is the dominant oxygen carrying cell, low hemoglobin may cause hypoxia, particularly cerebral hypoxia, which may further lead to white matter damage(Liu et al., 2017). This may be a potential pathophysiological mechanism between low hemoglobin and white matter damage. Future studies are needed to investigate the relevant mechanisms.

Despite robust evidence showed that vascular risk factors were related to the whole brain WMH, there are still a few studies which observed a discrepancy of risk factors in different brain regions (Habes et al., 2018; Medrano-Martorell et al., 2021). Our findings about risk factors of anterior SC patches of WMH may attribute to its frontal distribution as we have referred above. In the angioarchitecture of the frontal lobe during the late neonatal period, the density of arteries and veins in the frontal lobe is lower than other lobes (Nakamura et al., 1994). Post-mortem study suggested that the sclerotic changes of the medullary arteries were most prominent in frontal lobe(Furuta et al., 1991), resulting in the frontal white matter being particularly susceptible to haemodynamic derangement (Ihara et al., 2010). Based on our findings and pathological evidences, we speculate that anterior SC patches may be more susceptible to inflammatory response and hypoxia. Controlling blood pressure, alleviating inflammatory reaction and elevating hemoglobin may be the targets of WMH intervention.

Strengths of our study include the combination of cross-sectional and longitudinal analyses, a moderately large sample size, and verifying four WMH patterns in cognition not according to the traditional WMH regional boundaries. Our results showed that the four patterns of WMH were simple and convenience to be evaluated in clinic, only requiring T2 FLAIR sequence without post-processing. The consistency test confirmed that this visual evaluation method had high consistency and repeatability among different evaluators, which would be suitable for clinical application.

Despite the above strengths, some limitations need to be considered. First of all, our study population consists solely of patients referred to two hospitals without community-dwelling individuals, which resulting in the high ratio of dementia. Additional work is needed to validate the association of WMH patterns with cognitive impairment in community population. Secondly, there were some differences of MRI parameters between GE scanner and Siemens scanner in two centers, and we did not make the alignment between the two scanners which might introduce bias for WMH classification. Thirdly, we included patients with mild symptoms of anxiety or depression. Though their symptoms were mild and did not meet the diagnose criteria of anxiety or depression disorder, it might affect the evaluation of MMSE, which might induce bias for dementia diagnose. In addition, longitudinal analysis was conducted among only a proportion of patients in our study. The sample size was small and WMH was not reassessed during follow-up. Future studies with large sample size should consider the relationship between WMH patterns and its progress.

5. Conclusion

Our work shows that anterior SC patches of WMH is associated with all-cause dementia and cognitive decline. Higher percentage of neutrophiland and lower concentration of hemoglobin are risk factors of this pattern besides older age and hypertension. This visual evaluation method of WMH is simple and can be used as an image marker for screening patients with cognitive impairment in clinical practice. Our findings need to be further studied in different population, and pathological mechanisms warrant to be explored in future.

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CRediT authorship contribution statement

Junjun Wang: Conceptualization, Investigation, Methodology, Writing – original draft. **Ying Zhou:** Conceptualization, Investigation, Methodology, Writing – original draft. **Yaode He:** Writing – original draft, Formal analysis. **Qingqing Li:** Data curation, Investigation. **Wenhua Zhang:** Investigation, Visualization. **Zhongyu Luo:** Investigation, Data curation. **Rui Xue:** Investigation, Data curation. **Min Lou:** Conceptualization, Supervision, Methodology, Resources.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2022.102978.

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