

Original Article

Periventricular rather than deep white matter hyperintensities are associated with white matter lesion relevant vascular cognitive impairment

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Abstract: *Objective:* Cerebral white matter hyperintensities (WMHs) are frequent findings on MRI in the elderly. This study is to investigate impacts of WMHs severity and location on cognitive performance in white matter lesion relevant vascular cognitive impairment (VCI) patients. *Methods:* Fifty-nine subjects with WMHs on MRI were included within three groups: normal control (NC), VCI-no dementia (VCI-ND) and vascular dementia (VaD). WMH volumes were evaluated by Fazekas visual scale and segmental volumetric. Spearman correlation analysis, receiver operator characteristic curve (ROC) and multiple linear regression analysis were employed. *Results:* WMH volumes and Fazekas scores gradually increased from NC through VCI-ND to VaD patients. Correlations between cognitive performances and periventricular WMHs were significantly stronger than that of deep WMHs. WMH volumes were significantly correlated with Fazekas scores particularly for periventricular WMHs. ROC analysis showed a cut-off value of periventricular WMHs rather than deep WMH to distinguish VCI from NC. Linear regression analysis demonstrated that periventricular WMHs were independent predictors for cognitive impairments of VCI patients, adjusted for age, sex and education. *Conclusion:* Periventricular rather than deep WMHs are associated with white matter lesions induced vascular cognitive decline and could serve as a neuroimaging marker for vascular cognitive impairments in clinical practice.

Keywords: White matter hyperintensities (WMH), vascular cognitive impairment (VCI), periventricular, cognitive performance, correlation

Introduction

Cerebral white matter hyperintensities (WMH), detectable with Flair and T2 weighted image of MRI scan, are common radiological findings in the elderly. They are considered as markers of small vessel diseases (SVD) which result in ischemia lesions of the white matter and are well known to correlate with vascular cognitive impairment (VCI) or dementia (VaD) involving global cognitive decline, memory impairment, executive function and so on [1, 2]. However, a number of controversies about the relationship between WMHs and cognitive function

across studies still remain. For example, a few studies demonstrate that domains of cognitive impairment involve different WMH locations [3], while some other studies show the ceiling effect of visual rating scales for WMH burden assessment [4]. One research even reports that WMHs have little impact on cognitive performance [5].

Studies of WMHs in the elderly people and neurodegenerative disease are accumulated while less attention are paid to vascular cognitive decline related with WMHs. Recently, one report show that deep WMH (DWH) rather than

periventricular WMH (PWH) is increased in VaD in comparison to Alzheimer's disease (AD), therefore emphasizing the important role of DWH in VCI [6]. Inconsistently, another study finds no difference of DWH and PWH volumes between VaD and AD patients [7]. Besides, multiple studies confirm the relationship between PWH and dementia [8, 9]. Hence, it is necessary to ascertain the differential roles of WMH locations and severity on cognitive impairments in VCI patients.

Quantifying methods of WMH burden assessment usually involve visual rating scores and direct volumetric measurement. Visual scales like Fazekas scale and Scheltens score are broadly used in clinics due to convenience and time-saving. Computerized segmental volume measurement is able to directly calculate WMH load, and is shown to be more precise and subjective than visual scaling [4]. Besides, the WMH volumetric approach is confirmed to strongly correlate with visual scaling. However, visual scales seem to have ceiling effects while volumetric measurement is time-consuming and technology-dependent [4, 10].

In this study, using the above WMH assessment approaches, we sought to find out the association between WMH severity and locations and cognitive performances in VCI patients and define the cut-off value of WMH for distinguishing VCI versus normal aging.

Materials and methods

Study subjects

This was a retrospective analysis based on a total of 65 subjects with white matter hyperintensities (WMH) of MRI Flair image acquired at Affiliated Drum Tower Hospital of Nanjing University Medical School from Feb. 2013 to Sep. 2015. We identified study subjects with the following inclusion criteria: WMH on MRI T2 and Flair weighted image; eligible cognitive performance tests finished within 3 days before/after MRI scan; non-speaking dysfunction. We excluded subjects with such an exclusion criteria: primary neurological diseases associated with WMH, such as encephalitis, multiple sclerosis, poisoning and radiation encephalopathy; acute cerebrovascular diseases such as stroke, cerebral hemorrhage and transient ischemic attack (TIA); severe systemic, metabolic and endocrine diseases; other neurolo-

gical diseases associated with cognitive impairment, such as brain tumor, Parkinson's disease, trauma and epilepsy; severe depression; missing of imaging or clinical data. Finally, fifty-nine subjects were included in the analysis. According to clinical symptoms and cognitive assessment, these patients were divided into three groups: normal cognition (NC), vascular cognitive impairment-no dementia (VCI-ND) and vascular dementia (VaD).

NC group inclusion criteria: no complaints of memory and other cognitive decline; no damage of activity of daily life; clinical dementia rating (CDR) score = 0; Minimum Mental State Examination (MMSE) score \geq 27. Diagnosis of VCI-ND were following the current criteria [11, 12]. Diagnosis of probable VaD was according to NINDS-AIREN criteria with brain magnetic resonance imaging (MRI) evidence of small-vessel disease [13].

Ethics approval and consent to participate

The study was approved by the ethical committee of the Affiliated Drum Tower Hospital of Nanjing University Medical School and a waiver of informed consent was granted because of the retrospective nature of the study.

Data collection

Clinical information such as age, sex, education level and biochemical tests and MRI images were obtained from the hospital in-patient data system and image database.

Cognitive performance assessment

Cognitive performance was assessed using global cognitive or functioning scales such as Minimum Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Clinical Dementia Rating (CDR) and Activity of Daily Living (ADL). Scores of clock drawing task (CDT) from the MoCA were separately analyzed as simple indicators of subjects' executive function. Hachinski Ischemia Score was applied for vascular risk factors assessment. All subjects completed the tests within 3 days before/after MR scan.

Fazekas rating score

WMH grading of MRI images were evaluated by two neurologists separately according to the

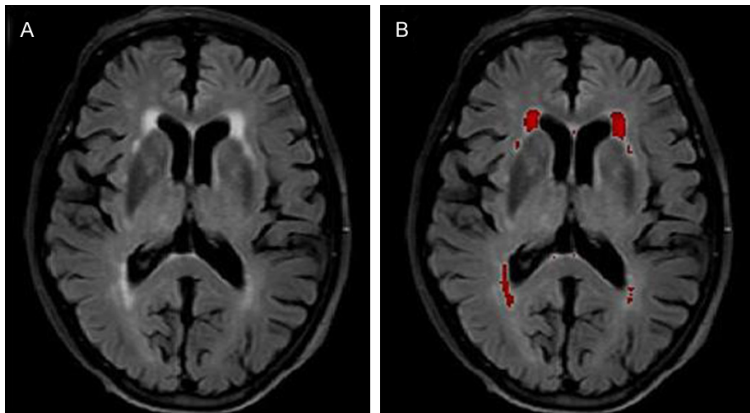


Figure 1. Semi-automatic white matter segmentation on fluid-attenuated inversion recovery. A. A coregistered FLAIR image ready for further processing. B. A probability map of the WMH under validated p value.

Fazekas rating score characterized as following: Grade 0 (no WMH), Grade 1 (punctate), Grade 2 (beginning confluent) and Grade 3 (confluent).

MR image acquisition protocol

Images were acquired on two 3.0 Tesla MR scanners (Achieva TX Imaging System and Ingenia Imaging System; Philips Medical Systems, Eindhoven, Netherlands), both using 8-channel head coil. For the Achieva TX MR scanner, a axial fluid attenuated inversion recovery (FLAIR) sequence with repetition time (TR)/echo time (TE) = 7000/120 ms, inversion time (TI) = 2200 ms, flip angle (FA) = 90, field of view (FOV) = 230 × 230 mm², acquisition matrix = 512 × 512, and slice thickness = 5 mm was performed for WMH quantification. A sagittal three dimensional T₁ weighted imaging (3DT₁WI) sequence with TR/TE = 9.7/4.6 ms, FA = 8, FOV = 256 × 256 mm², acquisition matrix = 256 × 256, slice thickness = 1 mm, voxel size = 1 × 1 × 1 mm³ was performed for the images coregistration.

A similar imaging protocol was performed on the Ingenia MR scanner. A sagittal three dimensional FLAIR sequence with TR/TE = 4500/360 ms, TI = 1600 ms, FA = 90, FOV = 288 × 288 mm², acquisition matrix = 258 × 258, slice thickness = 0.95 mm and voxel size = 1.1 × 1.1 × 0.95 mm³ was performed for WMH quantification. A sagittal 3DT₁WI sequence with TR/TE = 7.8/3.5 ms, FA = 8, FOV = 256 × 256 mm², acquisition matrix = 320 × 320, slice thickness = 0.8 mm, voxel size = 0.8 × 0.8 ×

0.8 mm³ was performed for images coregistration.

White matter hyper intensities quantification

Quantification of WMH was performed by the Wisconsin White Matter Hyperintensities Segmentation Toolbox (<http://pages.cs.wisc.edu/~vamsi/w2mhs.html>). The details of the work flow were described by the Vamsi Ithapua [14]. First, the W2MHS toolbox coregistered subjects' FLAIR images to their corresponding T₁ weighted images for tissue se-

gmentation to extract the regions of interest (ROI) of grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) partial volume estimates (PVE). Next, a voxel-level class-specific labeling algorithm was performed to calculate a probability map of the to-be-segmented FLAIR image. Each probability map was validated by a radiologist to determined a suitable p threshold for the WMH quantification (**Figure 1**). Finally, the volume of total WMH, periventricular WMH and the deep WMH were estimated and obtained by the W2MHS.

Statistical analysis

Quantitative data was presented as mean ± SD. All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 19 (SPSS IBM, New York, NY). Comparisons of subject characteristics, biochemical tests, cognitive tests and WMH volumes and Fazekas scores were conducted using analysis of variance (ANOVA) with post-hoc LSD for continuous data, while all categorical data were analyzed using Chi-squared analyses. WMH volumes underwent logarithmic transformations due to non-normal distributions and the logarithmic transformations were used in the whole analyses. Spearman correlations were used to define the association of WMH volumes or Fazekas scores with cognitive performances, and WMH volumes with Fazekas scores. Receiver operating characteristic (ROC) curve was generated to predict the cut-off of WMH volumes discriminating Normal and impaired cognitive perfor-

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Table 1. Comparisons of demographic and biochemical tests among cognitive subgroups

	NC (n = 31)	VCI-ND (n = 17)	VaD (n = 11)	p Value
Sex, M/F	20/11	10/7	7/4	0.936
Age, year	70.42±9.34	74.35±11.62	76.82±8.29	0.142
Education, year	7.29±2.51	7.18±3.11	5.00±1.73	0.040
FBG, mmol/L	5.48±1.83	4.64±0.60	5.51±1.50	0.157
Cr, umol/l	71.94±26.41	76.53±18.95	71.09±14.69	0.758
UA, umol/L	312.26±96.05	311.65±149.02	288.91±69.99	0.822
TG, mmol/L	1.33±0.74	1.41±0.70	1.33±0.52	0.937
TC, mmol/L	1.99±0.71	2.28±0.60	2.18±0.69	0.346
CRP, mg/L	3.49±1.96	4.47±1.87	5.99±3.49	0.038
DM, Y/N	8/23	4/13	3/8	1.000
HT, Y/N	18/13	11/6	5/6	0.647

FBG: Fasting Blood Glucose; Cr: Creatinine; UA: Uric Acid; TG: Triglyceride; TC: Total Cholesterol; CRP: C Reactive Protein; DM: Diabetes Mellitus; HT: Hypertension.

mances. Multiple linear regressions were performed to determine whether WMH volumes and locations were associated with cognitive performance after adjusting for age, sex and education. The level of significance was set at $p < 0.05$.

Results

Subject characteristics

Subjects demographics and biochemical tests are shown in **Table 1**. The groups differed on Education, with the mean duration in VaD group less than that in NC ($p = 0.008$) and marginally shorter than that in VCI-ND ($p = 0.073$). Conversely, the mean level of CRP in VaD group was higher than that in NC ($p < 0.05$) but VCI-ND. There were no statistical differences on sex distribution, age and other biochemical results among groups. Risk factors for VCI like diabetic mellitus and hypertension did not differ across groups either.

Differences of cognitive performance, WMH volume and Fazekas rating score across groups

Several cognitive function scales were carried out for participants. Generally, scores of MMSE, MoCA and CDT significantly gradually decreased from VaD through VCI-ND to NC ($p < 0.01$), while CDR scores occurred oppositely ($p < 0.01$). However, VFT scores did not show obvious significance among groups (**Figure 2A**).

Furthermore, relative to VCI-ND and NC, Hanchiski scores increased in VaD with ADL levels decreased, while no differences were observed on HAMD scores across groups (**Supplementary Figure 1**).

WMH volumes from periventricular and deep brain were calculated by computed volumetric. Compared to NC group, volumes of total WMH and PWH but DWH in VCI-ND showed trends of increase ($p = 0.08$, 0.055 and $p > 0.05$, respectively), while total WMH, PWH and DWH in VaD groups obviously enlarged.

Meanwhile, total WMH and PWH but DWH volumes of VaD group augmented in comparison to VCI-ND (**Figure 2B**).

Similarly, Fazekas scores of both PWH and DWH and their combination showed no significances between VCI-ND and NC, while Fazekas scores of all PWH and DWH and total WMH in VaD group were significantly higher than that in VCI-ND (**Figure 2C**).

Correlation between WMH volumes and rating scores and cognitive performance

Then, relations between WMH volumes and visual rating scores and cognitive performance were evaluated by correlation analysis. As a result, all total, PWH and DWH volumes were significantly correlated with scores of MMSE, MoCA, CDR and CDT ($r = -0.466$ to 0.479 , all $p < 0.05$). Moreover, the correlation coefficients of PWH and Total were higher than that of DWH (**Table 2**).

The situation, however, were not observed between Fazekas scores and neurocognitive scores (**Table 2**). Correlation analysis displayed that total and PWH scores were significantly related with MMSE, CDR and CDT, whereas DWH was just correlated with CDT. All Total, PWH and DWH Fazekas scores did not linked to MoCA (all $p > 0.05$; **Table 2**).

Scatter plots were used to illustrate these correlations (**Supplementary Figure 2**). In most

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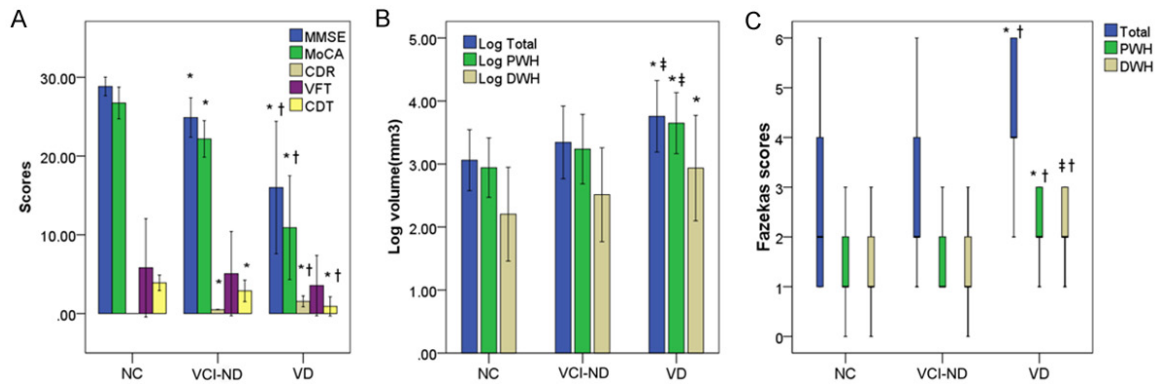


Figure 2. Comparisons of cognitive performance, WMH volumes and Fazekas scores among groups. A: Scores of five cognitive capacity tests among groups. B: Log-transformed WMH volumes computed with MRI Flair image. C: Fazekas scores of white matter lesions across groups. * vs. NC, $p < 0.01$; † vs. VCI-ND, $p < 0.01$; ‡ vs. VCI-ND, $p < 0.05$. MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; CDR, Clinical Dementia Rating; VFT, phonetic Verbal Fluency Test; CDT, Clock Drawing Task. DWH, deep white matter hyperintensities; PWH, periventricular white matter hyperintensities; total: DWH+PWH.

Table 2. Correlation between WMH volumes and rating scores and cognitive performance scores

		MMSE	MoCA	CDR	CDT
Log Total	r	-.453	-.448	.454	-.466
	p	.000	.000	.000	.000
Log PWH	r	-.454	-.451	.479	-.448
	p	.000	.000	.000	.000
Log DWH	r	-.325	-.352	.288	-.397
	p	.012	.006	.027	.002
Fazekas Total	r	-.297	-.246	.303	-.473
	p	.022	.060	.020	.000
Fazekas PWH	r	-.289	-.219	.288	-.432
	p	.027	.096	.027	.001
Fazekas DWH	r	-.244	-.232	.249	-.458
	p	.062	.077	.057	.000

Data are presented as the Spearman rho correlation coefficients and p values. WMH, White Matter Hyperintensity; PWH, Periventricular White Matter Hyperintensity; DWH, Deep White Matter Hyperintensity.

cases, quadratic regression models were seemingly better to describe the association between WMH volume and neurocognitive scores.

Association between WMH volumes and Fazekas scores

Given the significant correlation of WMH volume and Fazekas scores with cognitive levels, we tried to assess the association between these two methods by virtue of correlation

analysis. Significantly, all total, PWH and DWH volumes were positively correlated with corresponding Fazekas scores ($r = 0.556, 0.569$ and 0.234 , respectively; all $p < 0.001$; **Figure 3**). Remarkably, the correlation between PWH volume and PWH Fazekas scores was stronger than that of DWH (**Figure 3**).

Predicting value of WMH volumes for cognitive impairment

To explore the capacity of WMH volumes for predicting cognitive impairment, ROCs were computed for all the participants. The AUCs (95% CI) of total, PWH and DWH were 0.732 (0.600-0.863), 0.745 (0.617-0.873) and 0.635 (0.493-0.777) ($p = 0.002, 0.001$ and 0.076 , respectively), and the discriminative threshold for Total and PWH was 3.48 and 3.18 mm³ (log transformed), respectively (**Figure 4**). In addition, the sensitivity and specificity for Total and PWH was 57.1% and 87.1%, and 71.4% and 71.0%, respectively (**Figure 4**).

Regression analysis of cognitive performance and WMH volumes and locations

A series of multiple regression analysis were performed to evaluate the effect of WMH volumes and lesion locations on cognitive function by method of stepwise after adjusting for age, sex and education. Regression analysis showed that for MMSE, MoCA, CDR or CDT as dependent variables, only PWH volume and education were retained in the models, with

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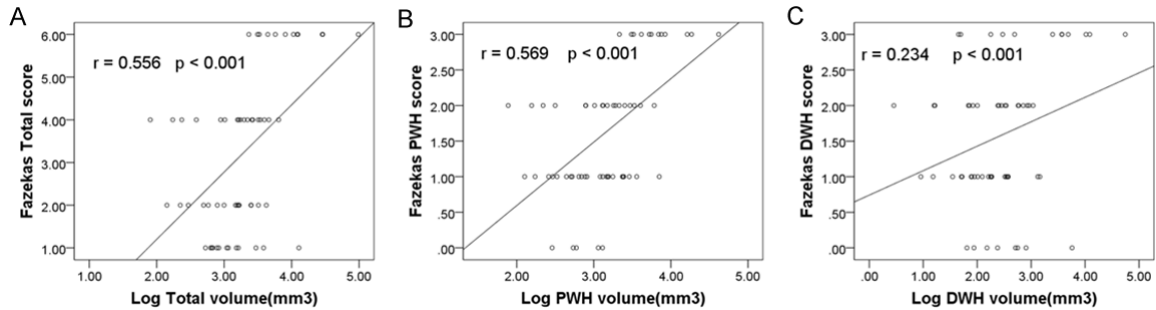


Figure 3. Correlations between WMH volumes and Fazekas rating scores by Spearman correlation analysis. DWH, deep white matter hyperintensities; PWH, periventricular white matter hyperintensities; Total, DWH+PWH.

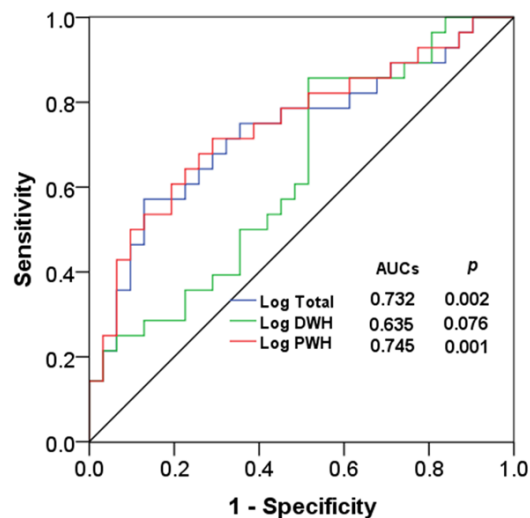


Figure 4. Receiver operating characteristic (ROC) curve predicting the cut-off of WMH volumes discriminating vascular cognitive impairment from Normal cognition.

the former negatively correlated with cognitive performance while the latter positively (Table 3).

Discussion

In the current research, we demonstrate that WMH volumetric measurement is more sensitive than visual rating scale to correlate with cognitive performance for vascular cognitive impairments, and that both PWH and total WMH volumes indicates a cut-off value of discrimination between NC and VCI. More importantly, PWH but DWH location and education are associated with neuropsychological capacity.

WMHs are frequent typical findings on MRI scans in the elderly and patients suffering from

small vessel diseases (SVD), including VCI-ND and vascular dementia. WMHs are recognized as vascular origin, due to hypoperfusion or chronic ischemia, and considered as markers of SVD together with lacuna and microbleed [15]. WMHs are presented in Alzheimer's disease as well, a neurodegenerative condition. The impact of WMHs on relationship between SVD and AD is still controversial. In general, total WMH volume was greater in VaD than in AD patients [16], and furthermore, DWH is reported to be capable of distinguishing VaD from AD [6]. These study suggests the predominant role of WMH particularly DWH in VaD pathology. However, one study shows no difference of PWH and DWH burden between VaD and AD patients [7], while our results show that PWH instead of DWH volumes is larger in VaD groups and predict cognitive performance independently. One explanation for our result were that microvascular degeneration in the periventricular white matter partially contributes to the development of white matter lesions by hindering a sufficient supply of nutrients [17] and that distinct vasculatures perfuse each WMH: non-collateralizing ventriculofugal vessels arising from subependymal arteries perfuse the periventricular WM whereas medullary arteries arising from middle cerebral arteries perfuse deep white matter, in part accounting for the vulnerability of periventricular WM to hemodynamic compromise [18].

Actually, accumulated studies find distinctive influences of PWH and DWH on cognitive function including global cognition, memory, executive function and language. Several studies show that PWHs are related with memory performance [8, 9, 19] and executive function [9, 19-21], some demonstrate that DWHs are linked to memory function [22, 23] and execu-

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Table 3. Multiple linear regression models predicting cognitive capacity associated with WMH volumes and locations after adjusting for age, sex and education

		B	Std. Error	t	p Value
MMSE	Log PWH	-5.255	1.240	-4.237	.000
	Education	.541	.258	2.097	.041
MoCA	Log PWH	-6.014	1.341	-4.484	.000
	Education	.672	.279	2.409	.019
CDR	Log PWH	.529	.132	4.019	.000
	Education	-.059	.027	-2.173	.034
CDT	Log PWH	-1.290	.315	-4.099	.000
	Education	.192	.065	2.936	.005

tive function [22], and others even do not find any associations of WMHs with these functions [5]. In our study, multiple linear regression analysis show that PWHs instead of DWHs are correlated with global and executive function after adjusting for age and sex, even though both PWHs and DWHs are related with MMSE, MoCA, CDR and CDT. This indicates that periventricular white matter lesion were more vulnerable for cognitive decline than deep white matter lesion. This is in line with that the periventricular area has a high density of long associating fibers, which connect the cortex with subcortical nuclei and other distant brain territories, whereas the subcortical area contains more short associating fibers or U fibers that link adjacent gyri [24, 25].

Previous studies find that WMH severity is correlated with cognitive impairment [26], while opposite results are also observed that no difference of WMH volumes among patients with different cognitive levels [7]. Inconsistently, our results showed just a trend of volume increase in VCI-ND versus NC, even though discrepancies of cognitive impairments were indicated between these two groups. This was supported by which ROC analysis did not get a distinctive cut-off between VCI-ND and NC in our result (Supplementary Figure 3). Nevertheless, divergences of both volumes and Fazekas scores occurred between VaD and VCI-ND/NC. These results suggest WMH burden plays a partial role and a threshold effect of WMH burden exists in small cerebral cognitive impairment.

Visual rating scales of WMH burden are still conflicting across studies, although great correlation between several visual scales and

volume measurement were observed. The AR-WMC and Scheltens scale are found to be more sensitively correlated with WMH volumes than Fazekas scale, while Fazekas scale seems most appropriate for defining different WMH groups in the LADIS Study [10]. However, inconsistent results are shown in Gao's study that Spearman correlation coefficients of volumes and Fazekas scores were slightly higher than that of ARWMC and Scheltens scale [4]. Hence, Fazekas scale was employed here and the results was in agreement with Gao's study but with relative lower correlation coefficients, likely due to different cognitive groups.

Ceiling effects have been reported to occur to WMH visual rating with respect to volume measurement [4]. We found that volumes are more sensitive to relate to cognitive performance than Fazekas scores, especially for MoCA, and that correlation coefficients between volume and visual rating are less than previously reported [4, 10]. It seems the ceiling effect did not happen in the current study, and we speculate that it is probably attributed to dementia subgroups and non-normal distribution of relative small amounts of subjects.

The results in our study should be cautiously interpreted, due to one limitation of the relative small amounts of subjects in this retrospective analysis, with normal and VCI-ND patients outnumbering VaD patients which would lead to deviation. Another shortage was related with cognitive performance without more detailed domains of cognition, such as memory, attention, language and visuospatial function, consequently failing to assess the association of WMH regions with special cognitive function.

In summary, our study demonstrate both PWHs and DWHs burden play important roles in vascular cognitive impairment, and that PWHs but DWHs are correlated with cognitive decline in relation to white matter lesions. Herein, our data indicate that PWHs are independent predictors for vascular contribution in white matter lesions and suggest clinicians that PWHs should be emphasized on evaluating vascular cognitive impairment related with white matter load.

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Disclosure of conflict of interest

None.

Abbreviations

WMH, White Matter Hyperintensities; PWH, Periventricular WMH; DWH, Deep WMH; SVD, Small Vessel Diseases; VCI, Vascular Cognitive Impairment; VCI-ND, Vascular Cognitive Impairment; VaD, Vascular Dementia; MMSE, Minimum Mental State Examination; MoCA, Montreal Cognitive Assessment; CDR, Clinical Dementia Rating; CDT, Clock Drawing Task.

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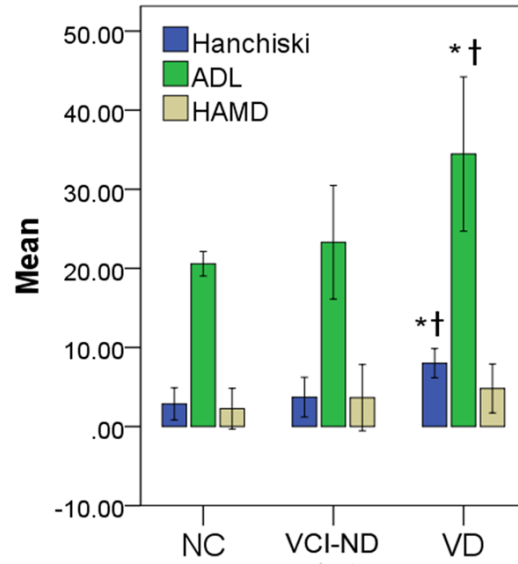
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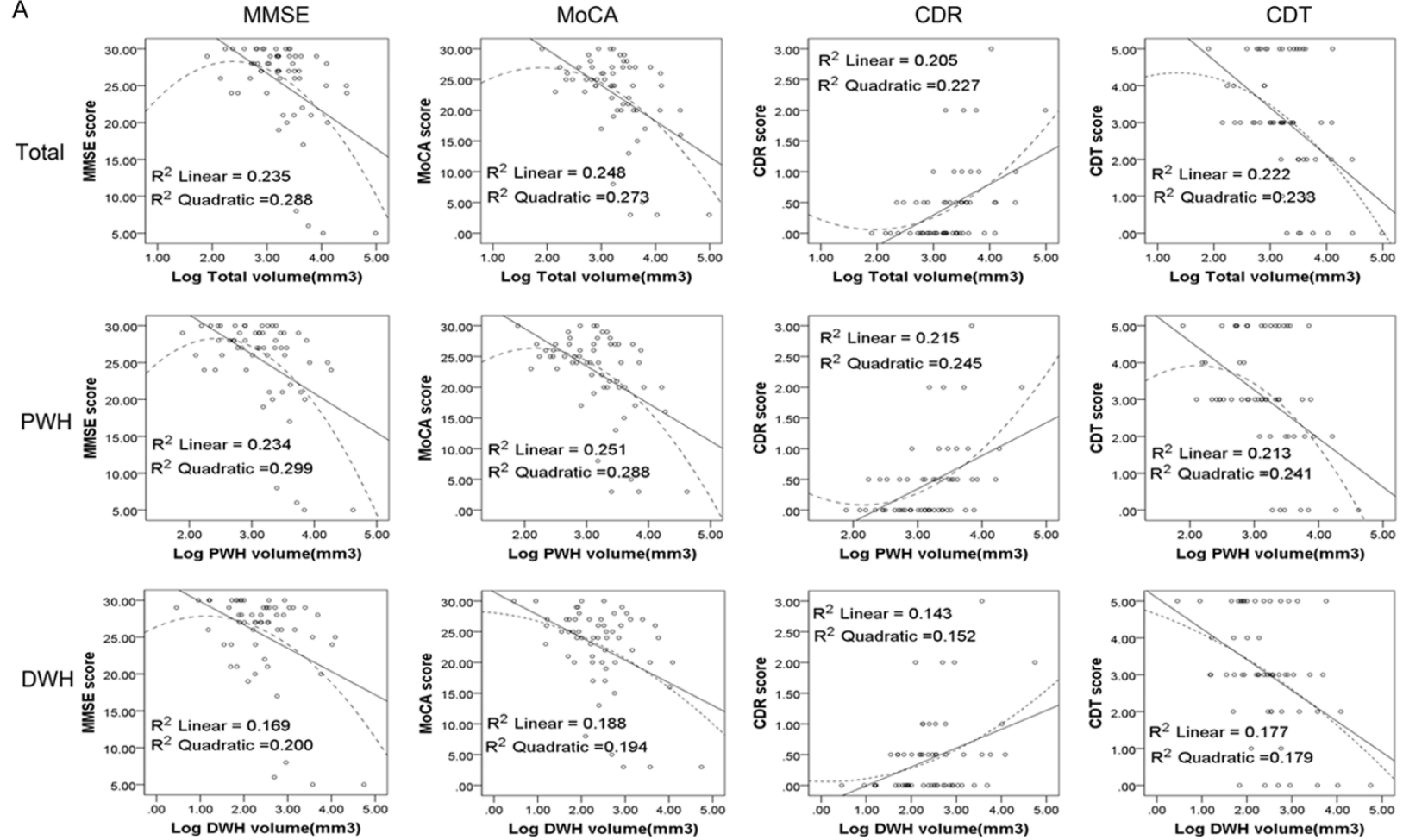
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Supplementary Figure 1. Comparison of Hanchiski, ALD and HAMD scores across groups. * vs. NC, $p < 0.01$; † vs. VCI-ND, $p < 0.01$.

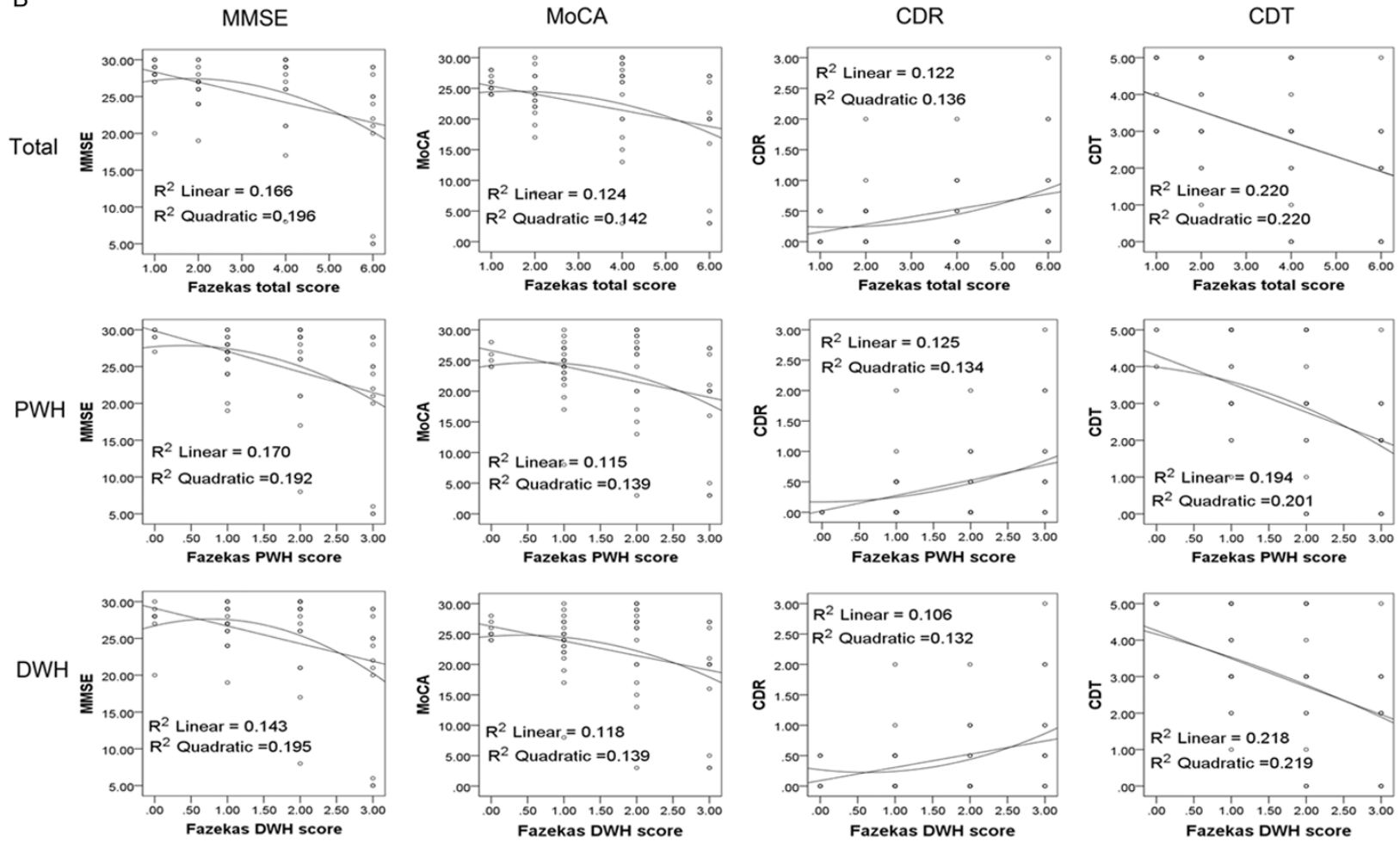
Periventricular WMHs associates with vascular cognitive impairment

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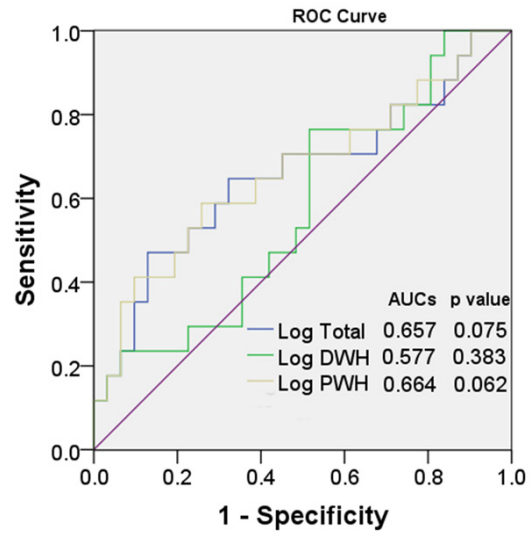
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B



Supplementary Figure 2. Correlation of WMH volumes with cognitive performance tests. Scatterplots displayed the correlations between Log transformed WMH volumes and cognitive performance tests in the whole samples. MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; CDR, Clinical Dementia Rating; CDT, Clock Drawing Task; DWH, deep white matter hyperintensities; PWH, periventricular white matter hyperintensities; Total: DWH+PWH.

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Supplementary Figure 3. Receiver operating characteristic (ROC) curve predicting the cut-off of WMH volumes discriminating mild cognitive impairment from Normal cognition.