Journal of Integrative Neuroscience

J. Integr. Neurosci. **2022**; 21(2): 051
https://doi.org/10.31083/j.jin2102051

Original Research

Presence of enlarged perivascular spaces is associated with reduced processing speed in asymptomatic, working-aged adults

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Academic Editor: Foteini Christidi
Submitted: 9 November 2021 Revised: 8 December 2021 Accepted: 24 December 2021 Published: 21 March 2022

Abstract

Background: Enlarged perivascular spaces (ePVS) and white matter hyperintensities (WMHs) are recognised neuroimaging lesions for symptomatic and/or occult cerebral small vessel disease (CSVD) that are linked with the predisposition to cardiocerebrovascular risk and neurocognitive impairment. This study aimed to determine the interrelation between the WMHs and ePVS, neurocognition, and cardiocerebrovascular risk profiles in asymptomatic working-aged adults at a single-center population-based cohort. **Methods**: Fifty-four asymptomatic subjects (mean age: 39.6 $\pm$ 11.6 years) with low-to-moderate cardiocerebrovascular risk measured by QRISK3 prediction score were recruited and underwent neurocognitive evaluation and 3T MRI brain scan. Contour plot with multiple logistic and linear regression were utilized to study the interrelation between the variables. **Results**: The presence of WMHs and ePVS was associated with hypertension, systolic blood pressure, QRISK3 score, and age, whereby asymptomatic older subjects had higher prevalence for WHMs and ePVS (mean age: WMHs [46.6 $\pm$ 12.2 years]; ePVS [43.12 $\pm$ 12.2 years]). Higher ePVS load and reduced hippocampal volume among ePVS subjects was associated with reduced processing speed (odd ratio, 1.06; 95% confidence interval: 1.00 to 1.13) and reduced working memory performance (standardized β coefficients, -0.46 [95% CI: 0.46 to 12.1], $p < 0.05$), respectively. **Conclusions**: Albeit from a single center in the suburban east coast peninsular Malaysia, this study is to first from the region to highlight the subtle impacts of occult CSVD manifestations (WMHs and ePVS) on some aspects of neurocognition in an otherwise asymptomatic, relatively young working-aged adults with low-to-moderate cardiocerebrovascular risk scores.

Keywords: White matter hyperintensities; Enlarged perivascular spaces; Cardiocerebrovascular risk; Neurocognition; Processing speed

1. Introduction

Cerebral small vessel disease (CSVD) is a pathologic process involving the small penetrating arteries and arterioles (up to 200 μm in diameter) in the brain [1], which results in magnetic resonance imaging (MRI) abnormalities, such as white matter hyperintensities (WMHs) and enlarged perivascular spaces (ePVS) [2,3]. CSVD accounts for the etiology of a quarter of acute ischemic strokes [4] and contributes to a major cause of cognitive impairment [5]. WMHs of presumed vascular origin and ePVS are very common in older individuals and regarded as typical imaging markers of CSVD [6]. WMHs and ePVS are usually occult or silent in nature (as subclinical, asymptomatic manifestations), but neurological symptoms may manifest insidiously as mild cognitive impairment and depression [1]. More alarmingly, their presence almost triples the possibility of an acute stroke, double the possibility of dementia, and may lead to premature death [7].

WMHs are commonly found in ageing brain as bright areas of small non-cavitated high signal intensities on fluid attenuated inversion recovery (FLAIR) and T2-weighted MRI sequences. In contrast, ePVS are defined as cerebrospinal fluids (CSF) filled cavities ($\geq$3 mm diameter) without hyperintensity ring seen on FLAIR, of well-defined round, tubular, or oval shape with smooth margin. WMHs and ePVS lesion can increase progressively with aging because they evolve over a few months to years [8,9]. Although the association between age with ePVS and WMHs prevalence has been consistently shown across different studies, the relationships of both CSVD manifestation with other cardiocerebrovascular risk factors, other probable pathophysiological processes (i.e., interstitial fluidophathy and glympopathy), and wider clinical spectrum are remain elusive. Since ePVS and WMHs are common even in asymptomatic individuals, risk prediction assessment would be beneficial. As part of the risk assessment, essential clinical algorithms are utilized in the prevention and management of cardiovascular disease including cerebrovascular events [10]. Thus, a tool such as QRISK has been developed to assess the cardiovascular risk including

cerebrovascular disease such as CSVD. QRISK is an online based risk prediction of cardiocerebrovascular disease [11], with better calibration and discriminative properties at predicting the 10-year risk of developing cardiocerebrovascular disease (as evidence from multiple cohort studies) compared to another instrument such as the widely used Framingham model [11,12].

It has been previously shown that executive dysfunction may correspond with diffused white matter lesion and CSVD manifestation (i.e., WMHs and ePVS) in elderly individuals [13], whilst the overall severity of subcortical lesions is known to link with the reduction in speed of information processing and executive performance in patients with subcortical ischemic vascular dementia [14]. In contrast, such global cognitive deficits are not seen in those with additional heterogenous vascular dementia (i.e., dementia with mixed or spectrum of syndrome and pathophysiology) [15]. In fact, a significant relationship between WMHs severity and processing speed in older adults (65–80 years of age) has been reported [16]. Multiple assessments tools have been developed to assess changes in cognitive performance in affected and asymptomatic individuals. To date, the Weschler Adults Intelligence Scale (WAIS) is one of the most widely used psychometric instrument and enables assessing neurocognitive function for the perceptual reasoning index (PRI), processing speed index (PSI) and working memory index (WMI). The PRI assesses the ability of the subjects to visualize, understand, hand-eye coordination and work with non-verbal information. The PSI measures the subjects' attending to visual material, visual perception and organization, visual scanning, and hand-eye coordination while the WMI assesses the ability to memorize, to hold and manipulate information in short-term memory and attention [17,18].

Furthermore, WMHs and ePVS are characterized and rated in terms of their proportion (i.e., volume, location, size, and number of lesions). Hence, various visual rating scales have been developed to assess WMHs, including the Fazekas scale [19] which provide an overall impression of the presence and proportion of the lesions in the whole brain. Apart from that, the current advancement in neuroimaging technology has enabled various specific algorithmic techniques and tools to be developed which automatically detect the presence and proportion (i.e., number, volume, and location) of WMHs and ePVS to provide more concise delineations of these lesions [20]. Therefore, this study aimed to find the interrelation between the MRI-finding of occult CSVD (i.e., WMHs and ePVS) in asymptomatic, economically active adults with their cardiocerebrovascular risk prediction score and neurocognitive performances (perceptual reasoning, working memory and processing speed).

2. Materials and methods

2.1 Subject recruitment

This study was conducted at the Hospital Universiti Sains Malaysia (HUSM), a suburban tertiary referral centre for neurological disorders in the East Coast of Malaysia with a catchment population base of over 4 million people. This study was conducted according to the guidelines of Declaration of Helsinki and ethics approval was obtained from the Human Research Ethics Committee-Universiti Sains Malaysia (USM/JEPeM/15030096).

Recruitment of subject's population was through a simple convenience random sampling (subjects who attended Family Medicine Clinic at HUSM for their general medical consults). Eligible subjects recruited were asymptomatic (i.e., no prior medical, no neurological disease symptoms, and without any past or current history of major psychiatric disorder and/or developmental disorders) individuals, working-aged 25–65 years living in the suburban east coast peninsular Malaysia. A total of 203 subjects was initially screened. Their demographic and clinical details were stratified according to cardiocerebrovascular risk calculation by QRISK version 3 (QRISK3).

The QRISK3 version 2018 (http://www.QRISK.org/index.php; University of Nottingham and EMIS, UK) is an online based cardiocerebrovascular risk calculator which was used to calculate the percentage of disease risk (for next 10-years—including myocardial infarct and/or stroke and/or transient ischemic attack) for all subjects. The projected risks were arranged according to the following criteria: 0 to 10% = no/low cardiocerebrovascular risk; 10.1 to 20% = moderate risk; and $\geq$20.1% = high risk [10]. A total of 124 subjects with 'no/low to moderate cardiocerebrovascular risk' were eligible, whilst 79 subjects with 'high risk' category was excluded. Among those invited to undergo brain MRI; 64 were excluded for numerous reasons, and 60 subjects successfully enrolled into the study procedures. From further brain MRI datasets quality assurance, 6 datasets were also excluded for a final recruited subject, N = 54. The flowchart of this study population identification is shown in Fig. 1. All subjects gave their written, informed consents.

2.2 Structural MRI brain scan

The subjects underwent a brain scanning using 32-channel head coil, 3T MRI Philip® Achieva (Philips Medical Systems, Best, The Netherlands). Three-dimensional T1-weighted images were acquired using magnetization-prepared rapid gradient-echo (MPRAGE) sequence in sagittal planes with echo time (TE)/repetition time (TR) = 3.5/7.6 ms; inversion time = 864 ms; field of view (FOV) = 250 $\times$ 250 mm^2; reconstruction matrix = 240 $\times$ 240 mm^2; voxel size = 1 $\times$ 1 $\times$ 1.2 mm^3; flip angle = 8°; 250 sagittal slices and total scan duration of about 4 minutes depending on subjects. T2-weighted images were acquired with TE/TR = 80/3000 ms; FOV = 230 $\times$ 230 mm^2; reconstruc-

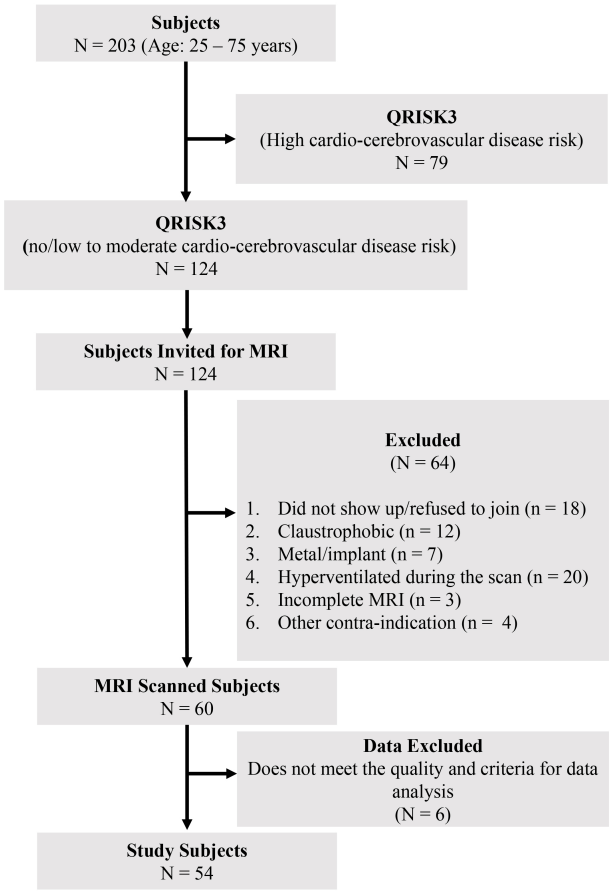

Fig. 1. Study flowchart of subjects' identification and inclusion/exclusion.

tion matrix = 512 × 512 mm^2; voxel size = 0.57 × 0.72 mm^2; slice spacing = 1.0 mm; slice thickness = 5 mm; flip angle = 90°; 24 axial slices and total scan duration of 2 minutes. Fluid attenuated inversion recovery (FLAIR) images were acquired with TE/TR = 125/11000 ms; inversion time = 2800 ms; FOV = 230 × 230 mm^2; reconstruction matrix = 512 × 512 mm^2; slice thickness = 5.0 mm; slice spacing = 1.0 mm; flip angle = 90°; 24 axial slices and total scan duration of 5 minutes. Overall, the total scanning duration for all subjects varied between 11 to 15 minutes.

2.3 Evaluation of WMHs and ePVS

Topographically, WMHs were categorized into two, i.e., periventricular, and deep WMHs. In contrast, ePVS has been recognized to be in several locations such as basal ganglia (along the proximal part of lenticulostriate arteries, e.g., globus pallidus, caudate nucleus, and putamen), centrum semiovale, midbrain (i.e., brainstem), and hippocampus. Thus, in this study WMHs and ePVS were identified and differentiated according to their signal intensities on MRI sequences, size, location, shape, and border as previously defined [21,22].

Based on the STandards for Reporting Vascular changes on nEuroimaging (STRIVE) method, WMHs featured as increase intensity or hyperintensity on T2-weighted image, and FLAIR (best identified) MRI, and hypointense (decrease intensity) on T1-weighted image. Meanwhile, ePVS had similar signal intensity with CSF, reduced FLAIR and T1-weighted signal, increased T2-weighted signal and iso-intense on diffusion-weighted imaging (DWI) and T2*-weighted gradient recalled echo (GRE) signal [2]. With their variable location, size, shape, and number, WMHs and ePVS are recognized CSVD manifestations in subcortical gray matter and mainly in white matter [23–25].

In this study, the brain MRI images were visualized using MeDINria software version 2.2 (Inria, National Institute for Research in Digital Science and Technology, France) [26] to manually detect the presence of WMHs of presumed vascular origin and ePVS from T2, T1, and FLAIR images. Their severity was evaluated using visual rating scale Fazekas scale (3-level severity score) upon FLAIR images [19,27]. Two experienced neuroradiologists who were blinded to all clinical data rated WMHs (deep and periventricular) and ePVS independently. The intra- and inter-rater agreements were assessed in random from 54 subjects with interval of longer than 1 month between the first and second readings. The kappa coefficients for the inter-rater agreements were $\kappa = 0.96$ (95% CI: 0.8 to 1) $p < 0.05$ for deep WMHs, $\kappa = 0.86$ (95% CI: 0.7 to 1.0) $p < 0.05$ for subjects that had both deep and periventricular WMHs and $\kappa = 0.88$ (95% CI: 0.8 to 1.0) $p < 0.05$ for subjects with ePVS. The kappa coefficients for the intra-rater agreements were $\kappa = 0.95$ (95% CI: 0.8 to 1) $p < 0.05$ for deep WMHs, $\kappa = 0.90$ (95% CI: 0.8 to 1) $p < 0.05$ for subjects that had both deep and periventricular WMHs and finally, $\kappa = 0.91$ (95% CI: 0.8 to 1) $p < 0.05$ for subjects with ePVS.

2.4 WMHs and ePVS lesion segmentation

The images were further processed for white matter lesion segmentation. This procedure used to automatically detect and evaluate WMHs and to study the number and volume of lesion. To do this, legion growth algorithm (LGA) as implemented in the lesion segmentation tools (LST) (http://www.statistical-modelling.de/lst.html) were used for statistical parametric mapping at $\kappa = 0.15$. LST, assessed in functional MRI Toolbox of Statistical Parametric Mapping version 12 (SPM12; http://www.fil.ion.ucl.ac.uk/spm/; Institute of Neurology, University College London, London, UK) and installed through Matrix Laboratory (MATLAB) version 2017a (The MathWorks, Natick, MA, USA). Based on MRI images, the subjects were categorized as a group of asymptomatic with normal brain finding (i.e., no WMHs) and asymptomatic with WMHs. The analysis of total WMHs number and volumes were based on a previously validated method [28].

Several subcortical and cortical structures were selected based on the presence of ePVS in subjects with CSVD neuroimaging manifestation. Subcortical segmen-

tation volumes pertaining to caudate, putamen, pallidum, hippocampus, cerebellar white matter, and brain stem were extracted from 3D MPRAGE images using FastSurfer [29], a deep learning-based neuroimaging pipeline. Unlike traditional neuroimage processing pipelines which involve time-intensive optimization processes, FastSurfer employs fully convolutional neural networks (F-CNNs) for quick and efficient whole brain segmentation, cortical surface reconstruction and implements spherical mapping using a spectral approach. Using GNU parallel [30], and on high performance computing resources at National Supercomputing Centre, NSCC, (1 Fusionopolis Way, #17-01 Connexis South, Singapore) [30], whole brain segmentation for 54 subjects was completed within 23 hours.

2.5 Neurocognitive assessment

In this assessment, the WAIS-Fourth edition,WAIS-IV (Pearson/PsychCorp, USA) was used to assess the general cognitive and memory abilities. The PRI was utilized to measure non-verbal reasoning and perceptual organization through three subtests including block design, matrix reasoning, and visual puzzle. WMI was used to measures specifically, simultaneous, and sequential processing, attention, and concentration, through two subtests including digit span and letter number sequencing. Lastly, PSI was used to measure speed of mental and grapho-motor processing, through two subtests including coding and symbol search. Scores obtained from each subtest were used for group-wise comparison and multimodal correlation.

2.6 Statistical analysis

The collected data were analyzed using Statistical Package for Social Sciences (SPSS) software version 26.0 (IBM Corp., Armonk, NY, USA). An alpha (α) was set at 0.05 with a confidence interval (CI) at 95%. Descriptive statistical analysis, such as mean, standard deviation, median and interquartile range (IQR) was applied in the data. Correlation between variables was obtained using Pearson's correlation. Mean differences between and within variables were obtained using chi square (χ^2) test and independent sample *t*-test. The analysis for the contour plot was performed using MINITAB 17 software (Minitab, LLC, Pennsylvania State University, State College, PA, USA) to determine the graphical relationship between one or more response variables and a set of quantitative experimental variables or factors [31]. Multiple logistic regression and linear regression model were used to study the association and interrelation between the variables. The analyses were adjusted for covariates.

3. Results

3.1 General characteristic of the study subjects

Table 1 shows the general characteristics of the study population, which consisted of 54 subjects (Fig. 1) with a mean age of 39.6 years $\pm$ 11.6 (standard deviation); 17 of the 54 subjects (29.8%) were male and 37 (64.9%) were female. Most of the study subjects were Malay ethnicity (88.9%) and non-smoker 48 (88.8%). Whilst 4 (7.4%) were Chinese and 2 (3.7%) were from another ethnicity.

3.2 WMHs

Table 1 describes the characteristic of study subjects with and without WMHs, whereby 18 (33%; mean age: 46.6 $\pm$ 12.2) had WMHs. Among them, the median WMHs volume was 0.00 mL (interquartile range [IQR]: 0.00–0.16 mL); in 25% of the subjects the total WMHs volume was greater than or equal to 1 mL. Median WMHs number was 0 (IQR: 0–4 mL); in more than 50% of the subjects the total WMHs number was greater than or equal to 1. Additionally, 10 (55.6%) of the subject with WMHs had a Fazekas scale of 2, whilst 8 (44.4%) had scale of 1. Spatial distribution of subjects with and without WMHs is depicted in Fig. 2. All WMHs subjects had deep WMHs (located distant from the lateral ventricles in the cerebral subcortical white matter), and 13 (72.2%) had a mixed deep and periventricular WMHs (near the lateral ventricles) and none had any exclusive periventricular WMHs.

3.3 ePVS

Table 1 also describes the characteristic of study subjects with and without ePVS. A total of 26 subjects (48%) had ePVS, whereby all of them had $>$1 number of ePVS with Fazekas scale of 2. Subject with ePVs had lower mean age (43.12 $\pm$ 12.2) compared to WMHs subjects. We found that ePVS mostly located in subcortical white matter (i.e., centrum semiovale [92.3%]), basal ganglia including caudate nucleus (CN, 7.7%), globus pallidum (GP, 19.2%), putamen (26.9%) and hippocampus (30.7%). Spatial distribution of subjects with ePVS is depicted in Fig. 2 showing the most prevalent locations for ePVS. The average volume for bilateral basal ganglia structures and hippocampus was also calculated. Their total average bilateral volume represented in median and IQR is as shown in Table 2. Subject with ePVS had lower median average volume compared to subject without ePVS, although the volumetric difference was not statistically significant.

Interestingly, 12 subjects (22%) had both WMHs and ePVS (i.e., combined lesion). Hence, among 18 subjects with WMHs, 6 subjects had WMHs alone (i.e., without ePVS). In contrast, among 26 subjects with ePVS, 14 subjects had ePVS alone (i.e., without WMHs).

3.4 Risk factors associated with the presence of WMHs and ePVS

The characteristic of subjects with and without WMHs and ePVS are listed in Table 1. The association was corrected for multivariable non-colinearity. The model fit assessment was perfomed using Hosmer-Lemeshow goodness-of-fit test, fitted for age and QRISK3 ($p > 0.05$). Therefore, we found that age had a linear association with

Table 1. Demographics and characteristics of the study subjects.

Variables	Total (N = 54)	WMHs			ePVS		
		Present (n = 18)	Absent (n = 36)	p-value	Present (n = 26)	Absent (n = 28)	p-value
Age, yrs.*	39.6 ± 11.6	46.6 ± 12.2	36.0 ± 9.60	0.00	43.12 ± 12.2	36.3 ± 10.1	0.02
Gender, n (%)				0.84			0.22
Male	17 (29.8)	6 (33.3)	11 (30.6)		10 (38.5)	7 (25)	
Female	37 (64.9)	12 (66.7)	25 (69.4)		16 (61.5)	21 (75)	
Ethnicity, n (%)				0.19			0.63
Malay	48 (88.9)	18 (100)	30 (83.3)		24 (92.4)	24 (85.7)	
Chinese	4 (7.4)	0 (0)	4 (11.1)		1 (3.8)	3 (10.7)	
Others	2 (3.7)	0 (0)	2 (5.6)		1 (3.8)	1 (3.6)	
Education level, n (%)				0.30			0.54
Low [a]	5 (9.3)	1 (5.6)	4 (11.1)		3 (11.5)	2 (7.1)	
Intermediate [b]	22 (40.7)	10 (55.6)	12 (33.3)		12 (46.2)	10 (35.7)	
High [c]	27 (50.0)	7 (38.8)	20 (55.6)		11 (42.3)	16 (57.2)	
Smoking, n (%)				0.37			0.35
Non-smoker	48 (88.8)	15 (83.3)	33 (91.7)		22 (84.6)	26 (93)	
Ex-smoker	4 (7.4)	2 (11.1)	2 (5.6)		3 (11.5)	1 (3.5)	
Light smoker	1 (1.9)	0 (0)	1 (2.7)		0 (0)	1 (3.5)	
Moderate smoker	1 (1.9)	1 (5.6)	0 (0)		1 (3.9)	0 (0)	
Heavy smoker	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	
Type 2 Diabetes, n (%)	0 (0)	0 (0)	0 (0)	-	0 (0)	0 (0)	-
Family History [d] n (%)	13 (22.8)	7 (38.8)	6 (16.6)	0.26	11 (42.3)	2 (7.1)	0.004
Atrial fibrillation, n (%)	0 (0)	0 (0)	0 (0)	-	0 (0)	0 (0)	-
Hyperlipidaemia, n (%)	0 (0)	0 (0)	0 (0)	-	0 (0)	0 (0)	-
Hypertension, n (%)	9 (15.8)	6 (33.3)	3 (8.3)	0.02	8 (30.7)	1 (3.5)	0.01
CHO to HDL ratio *	3.88 ± 0.99	3.62 ± 0.63	4.01 ± 1.12	0.20	3.97 ± 0.88	3.80 ± 1.09	0.52
SBP (mmHg) *	128.9 ± 15.4	141.3 ± 16.6	122.8 ± 10.4	0.00	134.3 ± 15.8	123.9 ± 13.5	0.01
BMI (kg/m^2) *	24.7 ± 4.4	25.8 ± 3.5	24.2 ± 4.7	0.20	26.4 ± 3.6	23.2 ± 4.6	0.00
QRISK3 Score (%) *	2.81 ± 4.6	6.07 ± 6.7	1.20 ± 1.4	0.00	4.5 ± 5.9	1.3 ± 1.7	0.01
WAIS-IV Indices *							
PRI	102.2 ± 12.9	100.8 ± 10.9	103.0 ± 13.9	0.57	101.7 ± 12.8	102.7 ± 12.3	0.78
WMI	108.0 ± 17.9	107.3 ± 13.1	108.1 ± 19.9	0.93	107.4 ± 18.5	108.5 ± 19.6	0.82
PSI	102.0 ± 13.9	98.6 ± 12.0	103.7 ± 14.6	0.21	98.7 ± 12.7	105.1 ± 14.5	0.09

Note: data values are presented as number of subjects (n), with percentage (%) in parentheses; light smoker ($\leq$10); Moderate smoker (10–19); Heavy smoker ($\geq$20); * Data are means ± standard deviations; [a] None, primary or secondary education; [b] Higher secondary or vocational; [c]University or higher professional education; [d] Angina or heart attack in a 1st degree relative <60 years of age, n (%). Subgroups according to the presence or absence of white matter hyperintensities (WMHs) and enlarged perivascular spaces (ePVS) were compared using χ^2 test and independent sample t-test (p = significant difference [2-tailed] at the <0.05 level). BMI, body mass index; CHO, Cholesterol; HDL, High Density Lipoprotein; PRI, Perceptual Reasoning Index; PSI, Processing Speed Index; SBP, Systolic Blood Pressure; WAIS-IV, Weschler Adults Intelligence Scale Version IV; WMI, Working Memory Index.

Table 2. Characteristic of structural volumetric study among study subjects with and without ePVS.

Average Volume	Median (Interquartile Range, IQR)		p-value
	ePVS Present (n = 26)	ePVS Absent (n = 28)	
Caudate Nucleus	3483.3 (3305.0–3689.7)	3564.9 (3356.7–3686.8)	0.85
Globus Pallidus	1949.7 (1902.9–1939.7)	2010.9 (1892.9–2045.3)	0.71
Putamen	4891.8 (4829.5–5334.0)	5281.0 (4920.6–5392.4)	0.66
Hippocampus	3951.3 (3866.4–4109.3)	4119.7 (3935.9–4303.6)	0.22

ePVS, enlarged perivascular spaces.

QRISK3 score (standardized β coefficients, 0.75 [95% CI: 1.44 to 2.36], $p < 0.05$), hence increased subjects age will have higher QRISK3 score (see contour plot in Fig. 3). After adjusting covariates such as gender and age, the presence of WMHs was significantly increased with age (odd ratio [OR] per standard error, 0.91; 95% CI: 0.86 to 0.97) and was more prevalent in subjects with higher QRISK3 score (OR, 0.65; 95% CI: 0.48 to 0.88). WMHs also associated with cardio-cerebrovascular risk factors such as hypertension and an increased in systolic blood pressure (SBP) (see Table 3).

The presence of ePVS is also associated with age (OR, 0.95; 95% CI: 0.89 to 0.99), QRISK3 score (OR, 0.75; 95% CI: 0.58 to 0.98), and other cardio-cerebrovascular disease risk factors (i.e., family history of cardiocerebrovascular disease, hypertension, higher SBP, and higher body mass index [BMI]). The prevalence of ePVS was found in

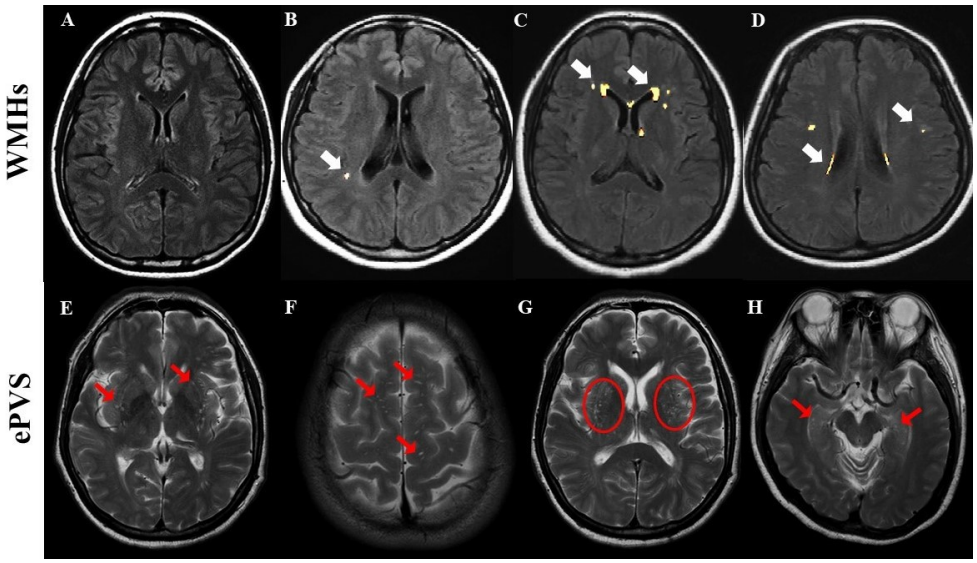

Fig. 2. Spatial distribution of white matter hyperintensities (WMHs) of presumed vascular origin and enlarged perivascular spaces (ePVS) among study subjects. Top rows represent spatial distribution of statistical probable voxels output from lesion segmentation tool (LST)-based lesion growth algorithm (LGA) (bright yellow highlighted) seen on fluid attenuated inverse recovery (FLAIR) images. (A) FLAIR image represent subject without WMHs (normal brain). (B) Represent subjects with deep WMHs (white arrows). (C,D) Represent subjects with both periventricular and deep WMHs (white arrows). Bottom rows represent the structural T2-weighted images of subjects with ePVS. (E,G) Represent subjects with multiple ePVS in basal ganglia (i.e., globus pallidus, caudate nucleus, and putamen). (F) Represent subjects with multiple ePVS in bi-hemispheric subcortical white matter such as centrum semiovale. (H) Represent subjects with multiple ePVS in bilateral hippocampus.

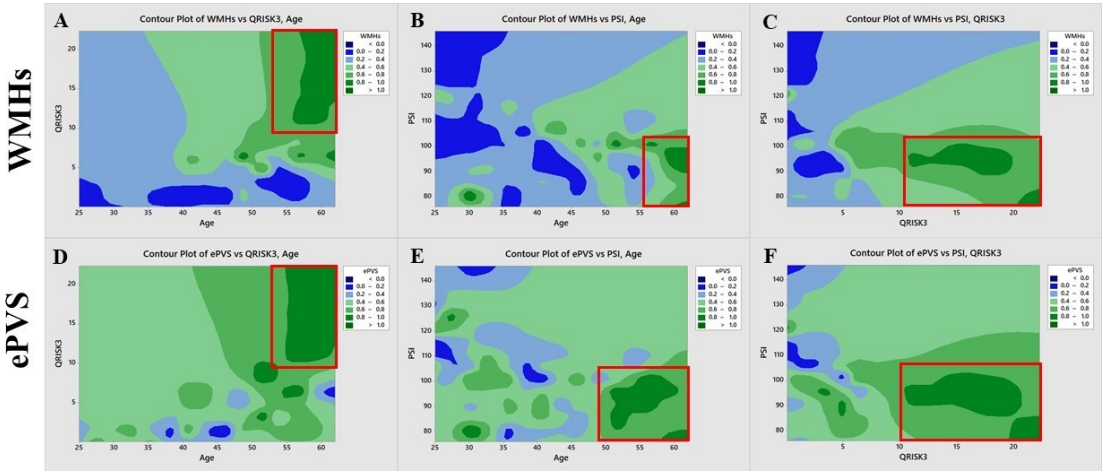

Fig. 3. Contour plots represent the graphical relationship between white matter hyperintensities (WMHs), enlarged perivascular spaces (ePVS) with QRISK3, age and processing speed index (PSI). (A,D) Relationship between (A) WMHs, (D) ePVS with QRISK3, and age. Red box (with dark green shade) indicates increased age had higher QRISK3 score (≥10%) hence increase chances of having MWHs and ePVS. (B,E) Relationship between (B) WMHs, (E) ePVS with age, and PSI. Red box (with dark green shade) indicates increased age had lower PSI (≤110) and increased chances of having WMHs (≥55 yrs) and ePVS (≥50 yrs). (C,F) Relationship between (C) WMHs, (F) ePVS with QRISK3, and PSI. Red box (with darker green shade) indicates subject with higher QRISK3 score (≥10%) may had lower PSI performance (≤110) and higher chances of having WMHs and ePVS.

much younger subjects compared to WMHs, indicating that ePVS can appear in much younger age compared to WMHs. However, WMHs was not associated with family history of cardiocerebrovascular disease and BMI. We found that, gender, ethnicity, smoking status, and education level were not associated with both WMHs and ePVS. Moreover, we found that WMHs, specifically deep MWHs, was significantly associated with average volume of globus pallidum

Table 3. Association between potential risk factors and presence of WMHs and ePVS.

Risk Factors	WMHs		ePVS	
	Present (n = 18) versus absent (n = 36)		Present (n = 26) versus absent (n = 28)	
	Multiple Logistic Regression [a]		Multiple Logistic Regression [a]	
	OR (95% CI)	p-value*	OR (95% CI)	p-value*
Age [b]	0.91 (0.86 to 0.97)	0.03	0.95 (0.89 to 0.99)	0.03
Family History [c]	2.07 (0.58 to 7.46)	0.26	9.53 (1.86 to 48.91)	0.01
Hypertension	5.50 (1.19 to 25.54)	0.03	12.0 (1.38 to 104.34)	0.02
SBP [d]	0.89 (0.83 to 0.95)	0.00	0.95 (0.91 to 0.99)	0.02
BMI	0.92 (0.80 to 1.05)	0.20	0.83 (0.72 to 0.96)	0.01
QRISK3 Score	0.65 (0.48 to 0.88)	0.00	0.75 (0.58 to 0.98)	0.03
WAIS-IV PRI	1.01 (0.94 to 1.08)	0.88	0.98 (0.92 to 1.05)	0.53
WAIS-IV WMI	0.98 (0.93 to 1.03)	0.40	0.99 (0.94 to 1.03)	0.52
WAIS-IV PSI	1.04 (0.98 to 1.11)	0.16	1.06 (1.00 to 1.13)	0.04

BMI, body mass index; CI, confidence interval; ePVS, enlarged perivascular spaces; OR, odds ratio; PRI, perceptual reasoning index; PSI, processing speed index; SBP, systolic blood pressure; WAIS, Weschler Adult Intelligence Scale version IV; WMHs, white matter hyperintensities; WMI, working memory index; [a] Adjusted for age and gender; [b] per one-year; [c] Angina or heart attack in a 1st degree relative <60 years of age; [d] per mmHg; *p = significant difference (2-tailed) at 0.05 level.

(GP) but not with CN, putamen, hippocampus (standardized β coefficients, 0.67 [95% CI: 0.001 to 0.003], $p <$ 0.05).

In addition, subjects with both WMHs and ePVS (i.e., combined lesion) had higher mean age (49.00 $\pm$ 11.80 yrs); mean SBP (146.00 $\pm$ 12.01 mmHg), BMI (26.67 $\pm$ 3.43 kg/m^2), and QRISK3 score (7.99 $\pm$ 7.33%) compared to subjects with WMHs or ePVS alone. However, the differences were not statistically significant.

3.5 Relationship between proportions of WMHs and ePVS with the risk factors and neurocognitive profiles

Based on Table 1, subjects with WMHs and ePVS had lower neurocognitive performance (corrected co-variates, i.e., age, QRISK3 profiles), although the difference was not statistically significant. However, we found that PSI had a linear relationship with age (standardized β coefficients, –0.55 [95% CI: –0.94 to –0.38], $p < 0.05$) and QRISK3 (standardized β coefficients, –0.37 [95% CI: –1.91 to –0.34], $p < 0.05$), respectively. Hence, aging, and individual with higher QRISK3 score had lower processing speed performance (see contour plot in Fig. 3). Based on Table 3, the presence of WMHs and ePVS was not associated with odds of reduction in neurocognitive performance, except that ePVS was significantly associated with reduced PSI ($p < 0.05$). Moreover, subjects with combined lesion had lower mean PRI score (99.83 $\pm$ 10.81), WMI score (106.58 $\pm$ 14.82), and PSI score (95.08 $\pm$ 12.41) compared to single lesion (i.e., either WMHs or ePVS alone), although the difference was not statisticaly significant. Additionally, the presence of combined lesion was also significantly associated with PSI (OR, 1.09; 95% CI: 1.00 to 1.18, p = 0.04 <0.05). Therefore, subjects with ePVS lesion (either combined with WMHs or not) seem likely to have lower speed of processing performance.

Additionally, in subjects with WMHs–the volume of WMHs had a linear association with age and QRISK3 score, whereby the number of WMHs was associated with QRISK3 score (Table 4). The volume and number of WMHs was not associated with cardiocerebrovascular risk factors (i.e., hypertension, SBP, family history, and BMI) and subjects' neurocognitive performances. On the other hand, subjects with ePVS showed a reduced average volume of CN, GP, putamen, and hippocampus were associated with increase age and QRISK3. Moreover, reduced average volume of hippocampus also associated with a reduced subject working memory (WMI) (standardized β coefficients, –0.46 [95% CI: 0.46 to 12.1], $p < 0.05$). Subjects with ePVS lesion in their hippocampus may have reduced working memory performance. The average volumes of putamen and hippocampus were also associated with subject BMI (see Table 4).

4. Discussion

We sought to determine the interrelations between the prevalence and proportions of WMHs and ePVS with the cardiocerebrovascular risk factors and neurocognitive profiles among asymptomatic individuals. Interestingly, out of 54 neurological asymptomatic and economically active middle-aged individuals, we found 33.3% and 48.1% with an incidental WMHs and ePVS from the MRI brain, respectively, with the severity ranging from 1 to 2, based on Fazekas scale. Moreover, ePVS was found mostly in subcortical white matter (i.e., centrum semiovale [92.3%]), basal ganglia including caudate nucleus (CN, 7.7%), globus pallidum (GP, 19.2%), and putamen (26.9%). Among subjects with ePVS, 30.7% had ePVS in hippocampus. Of note, 12 subjects had both WMHs and ePVS (combined lesion).

In this study, the presence, and the proportion of WMHs (irrespective of deep or periventricular) and ePVS

Table 4. Correlation (r) and linear regression (β) profile of study variables.

Variables	White Matter Hyperintensities (WMHs)		Enlarged Perivascular Spaces (ePVS)			
	WMHs Volume	WMHs Number	Caudate Nucleus [a]	Globus Pallidus [a]	Putamen [a]	Hippocampus [a]
Age	0.50** (−0.31*)	0.52** (−0.08)	−0.50** (−1.03*)	−0.45** (−0.59*)	−0.24 (−0.80*)	−0.16 (−0.67*)
QRISK3	0.81** (0.93*)	0.71* (0.71*)	−0.10 (0.818)	−0.16 (0.62*)	0.04 (0.56*)	0.13 (0.85*)
Hypertension	0.49** (−0.00)	0.41** (−0.05)	−0.07 (−0.21)	−0.42 (−0.09)	0.10 (−0.72)	0.12 (−0.19)
Systolic Blood Pressure	0.61** (0.21)	0.59** (0.21)	−0.16 (−0.13)	−0.11 (−0.13)	−0.05 (0.04)	0.07 (−0.09)
Family History [b]	0.16 (−0.06)	0.10 (−0.10)	0.02 (–0.03)	0.06 (0.04)	−0.11 (−0.08)	−0.16 (−0.23)
BMI	0.07 (−0.13)	0.16 (−0.04)	−0.01 (0.15)	0.67 (0.25)	0.45 (0.30*)	0.19 (0.32*)
WAIS-IV PRI	−0.18 (0.04)	−0.10 (0.07)	0.37** (0.33)	0.28* (−0.02)	−0.18 (0.09)	0.14 (−0.06)
WAIS-IV WMI	−0.21 (−0.01)	−0.10 (0.15)	0.32* (0.07)	0.28* (0.16)	0.21 (0.04)	0.30* (0.46*)
WAIS-IV PSI	−0.24 (−0.06)	−0.24 (−0.13)	0.31* (−0.20)	0.38** (0.05)	0.13 (0.12)	0.10 (−0.19)

Notes: r = Pearson correlation coefficient, β = Standard Beta Coefficients; BMI, body mass index; ePVS, enlarged perivascular spaces; PRI, perceptual reasoning index; PSI, processing speed index; WAIS, Weschler Adult Intelligence Scale version IV; WMI, working memory index; WMHs, white matter hyperintensities. **p = significant difference (2-tailed) at 0.01 level; *p = significant difference (2-tailed) at 0.05 level; [a] average volume (bilaterally); [b] Angina or heart attack in a 1st degree relative <60 years.

was significantly associated with age, whereby asymptomatic older subjects had a higher prevalence. Our findings are in line with the previous studies, whereby older individuals had higher prevalence of WMHs and ePVS [32–36]. Moreover, multiple large-scale studies had supported that the increased prevalence of WMHs with aging, for example, Study of Health in Pomerania (SHIP) cohort study (N = 2367, age: 20–90 years) that reported the presence of WMHs (deep and periventricular) are explained by an increased age [37]. Additionally, several studies had also described the prevalence of CSVD (i.e., WMHs and ePVS) in much younger individuals for example; recent studies reported that, in subjects (age 18 to 50 years) with pre-existing (yet occult) CSVD manifestations had higher chances of developing ischemic stroke and vice versa [38,39]. Moreover, Viana-Baptista and collegues also described young adults (mean age: 47.7 years) with cardio-cerebrovascular risk factors had higher prevalence of CSVD manifestation [40].

Besides, we also found the presence of WMHs and ePVS are associated with hypertension and SBP. These findings are supported by multiple studies that indicate cardio-cerebrovascular risk factors such as hypertension and elevated SBP affect small penetrating arteries of the brain leading to development of WMHs and ePVS [34,41–46].

In addition, Lai and colleagues supported that higher blood pressure was associated with presence of WMHs hence suggested that intensive blood pressure control aided in preventing the progression of WMHs [47]. Similarly, the Systolic Blood Pressure Intervention Trial (SPRINT) study suggested that intensive control (SBP <120 vs 140 mmHg) reduced the risk of cognitive decline related CSVD [48]. Finally, Salman and colleagues suggested that consecutive measurements of blood pressure may help in the management and prevention of target organ damage [49], namely, the brain.

Moreover, in this study the cardiocerebrovascular risk was cumulatively measured as QRISK3 risk prediction score or percentage. Hence it is found that QRISK3 was associated with the presence and proportion of WMHs and ePVS. Whereby individuals with WMHs and ePVS (especially subject that had combined lesion) had higher QRISK3 score, hence had more prominent cardiocerebrovascular disease risk factors such as high SBP and hypertension despite being asymptomatic at the time of MRI brain scan. Besides, we also found significant association between higher QRISK3 score with aging. Recent study by Jung and colleagues in asymptomatic older population (N = 130, aged over 50 years), revealed that periventricular and deep WMHs was associated with age and cardiocerebrovascular risk factor (i.e., hypertension) [50]. Multiple studies had supported the finding that WMHs and ePVS are associated with aging and higher cardiocerebrovascular disease risk (i.e., hypertension and high SBP) and supported the notion that both of CSVD manifestation are particularly common in the world's population including Caucasian [51], Afro-American and Afro-Caribbean [51,52], and Asian populations such as Malays and Chinese Singaporeans [53,54], Chinese populations [55], and Japanese populations [56]. Alarmingly, the prevalence of both CSVD manifestations have been reported to be higher in Asian population compared to western world [57].

The pathomechanism of WMHs and ePVS is still a subject in active research. However, it is well accepted that the pathological changes related to CSVD, and its manifestation are closely linked to the disrupted cerebral microcirculation [33] and characterized by occlusion of cerebral small vessel by age-related microvascular pathology (i.e., arteriolar tortuosity and venous collagenosis, age-related demyelination and loss of glial cells [41,58–60]. Alongside several cardiocerebrovascular risk factors such as hypertension, obesity, and type-2 diabetes which in turn lead to decreased cerebral blood flow (cBF) and blood brain barrier

(BBB) disruption in CSVD patients [61,62].

In addition, the disturbance of interstitial fluid (ISF) drainage (i.e., due to waste product accumulation alongside the cerebral perforating arteries) and disrupted CSF-ISF exchange in glymphatic system (i.e., glympopathy) has been associated with the pathomechanism of WMHs and ePVS especially in subcortical region in asymptomatic individuals [32,63–66]. Therefore, there are wealth of previous evidence to support our findings that prevalence and proportion (i.e., number and volumes) of WMHs and ePVS associated with aging and increased cardiocerebrovascular disease risk factors (as in QRIKS3 score), and WMHs and ePVS can serve as potential biomarker of aging and cardiocerebrovascular disease risk, even among younger adults as in this study. Hence, these may assist the clinicians and health practitioners in the prevention and therapeutic strategies to reduce the burden of disability and mortality from CSVD manifestations (i.e., WMHs and ePVS) in late life.

We also found that subjects with WMHs and ePVS had lower neurocognitive performance (from WAIS-IV indices) compared with individuals without WMHs and ePVS. Alarmingly, subjects with combined lesion had much lower processing speed performance. Despite no significant association between the presence and proportion of WMHs and ePVS with any of the WAIS-IV neurocognitive indices, we did find that, the presence of ePVS was associated with reduced subjects processing speed (i.e., lower WAIS-IV PSI score). Besides, reduced hippocampal volume in ePVS subjects is also associated with reduced working memory performance based on the WAIS-IV WMI scores. Additionally, we found that aging and QRISK3 was associated with reduced WAIS-IV PSI scores.

Previous studies had suggested that individuals with CSVD manifestation such as WMHs and ePVS (with higher cardiocerebrovascular disease risk) are more vulnerable in developing neurocognitive deficits (processing speed, memory, and perceptual reasoning) [67,68]. Moreover, Liu and colleagues suggested that, reduced white matter microstructural integrity due to WMHs at tract specifics and/or distal tracts were associated with reduced executive function and attention [69]. Previous cross-sectional, case control, and cohort studies using adjusted odd ratio reported that ePVS may adversely influenced the neurocognitive function [63,70–74], particularly the speed of processing [75], which are in line with our findings with reduced processing speed and working memory (i.e., ePVS-related reduced hippocampal volume). However, some studies suggested that different ePVS locations have different manifestations, and the etiology of ePVS in different locations may differ [63,76], which may also explain our results variability. More data are needed to further analyze the association between the ePVS regions and cognitive function (particularly the processing speed). Hence, further research delineating the role of the white matter tract involvement in WMHs and ePVS may be beneficial to better associate the presence and proportion of WMHs and ePVS with neurocognitive function outcome.

Furthermore, the variability of the results between neurocognitive profiles (seen in WAIS-IV indices) used in our study may be due to limited sample size and with no longer-term follow-up data. We recruited the asymptomatic individuals who were as young as 25 years old. Chen and Li in their study (N = 142) had reported that, about 67% of subjects (age: 20–59 years) with WMHs but not associated with reduced cognitive function. However, 58% of the older subjects (age: $\geq$60 years) had variance in processing speed, working memory and perceptual reasoning performance [77]. Hence, aging (independent of WMHs) may have significant role in reduced neurocognitive ability. Recent study (N = 478, age: 60–64 years) also supported that, the prevalence of WMHs is not associated with neurocognitive performance (i.e., working memory, episodic memory, and general intellect) [78]. Pertaining the association of WMHs with the degree of neurocognitive deficits, Vergoossen and colleagues had suggested that the proportion (i.e., the volume) of WMHs play an important role, whereby WMHs with 0.51 mL larger median volume is equivalent to 10 years of neurocognitive aging and was associated with processing speed and WMHs volume [79]. Their finding strengthens the notion that the effects of WMHs upon neurocognitive function are dependent of WMHs volumes and takes a considerable time prior to the overt cognitive deficits. In our study, the subjects with WMHs only had median WMHs volumes of 0.00 mL (IQR: 0.00–0.11), which may explain the lack of association between WMHs and neurocognitive function manifestation.

However, it is important to highlight the importance of aging and cardiocerebrovascular disease risk factors (independent of WMHs and ePVS) that may lead to degree of neurocognitive deficits [80]. Previous study had reported that 37% of individuals with higher cardiocerebrovascular disease risk factors had neurocognitive deficits [81], especially older individuals (age: 65–74 years) with hypertension [82]. Besides, long-term elevated SBP, especially in middle-to-old age individuals, has been reported as major risk factor for heightened neurocognitive deficits and dementia [48,80]. Therefore, a prevention strategy focusing on management of cardiocerebrovascular disease risk factor especially, hypertension and SBP may be beneficial to reduce the risk of neurocognitive decline in asymptomatic individual, with or without WMHs and ePVS.

Strength and limitation of the study

In this study, we established the interrelation of WMHs, ePVS, neurocognitive profile, aging and well-characterized cardiocerebrovascular disease risk factor (as per QRISK3 score) among a relatively young (25–62 years) sample of medically and neurologically asymptomatic adults. To the best of our knowledge, this study is the first to evaluate these multimodal interrelations in

suburban southeast Peninsular Malaysia, although further follow-up and ideally multi-site study is warranted. The current study was conducted at a single center clinical setting with limited sample size (N = 54) to explore the presence and proportion of WMHs and ePVS, hence limiting the generalizability of the study results. Moreover, as part of the study inclusion/exclusion criteria, many older adults were excluded due to their high QRISK3 scores (more than 20%) and were regarded as symptomatic individuals. Finally, WAIS-IV is labor-intensive and client-demanding to complete, which better suits the research setting and is impractical for routine daily clinical use for neurocognitive screening. Nevertheless, we consolidated the relevant WAIS-IV indices for the purposes of this research to ensure comprehensiveness of the assessment.

5. Conclusions

Albeit from a single center in the suburban east coast peninsular Malaysia, the present study is the first from the region to evaluate the presence and proportion of WMHs and ePVS in asymptomatic, economically active working-aged individuals using neuroimaging and neurocognitive profiling, stratified as low-to-moderate QRISK3 scores. The study showed interrelationship between occult CVSD manifestations (ie., WMHs and ePVS) with age, QRISK3 and neurocognitive function. Although WMHs did not influence the subjects' neurocognitive performance overall, presence of ePVS did influence subjects' processing speed and working memory (in particular, with hippocampal ePVS and reduced hippocampal volume).

Author contributions

MMG, CMNCMN and MM designed the research study. MMG and CMNCMN performed the research. MM and NSI provided help and advice on the study. MMG, CMNCMN, GC, and BPKN analyzed the data. MMG and CMNCMN wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Human Research Ethics Committee at Universiti Sains Malaysia (Protocol code: USM/JEPeM/15030096). Informed consent was obtained from all subjects involved in the study.

Acknowledgment

We thank the management of the Hospital Universiti Sains Malaysia for granting permission to the investigators to use patient medical records as well as space and assets belonging to the hospital during conduction of the research. The computational work for this article was partially performed on resources of the National Supercomputing Centre, Singapore (https://www.nscc.sg).

Funding

This research was funded by Fundamental Research Grant Scheme (FRGS), Ministry of Higher Education (Grant number 203/PPSP/61771193).

Conflict of Interest

The authors declare no conflict of interest.

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