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Association between total cerebral small vessel disease score and cognitive function in patients with vascular risk factors

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Abstract

Hypertension is the most important risk factor for cerebral small vessel disease (SVD). In this cross-sectional study, we tested the independent association of cerebral SVD burden with global cognitive function and each cognitive domain in patients with vascular risk factors. The Tokyo Women's Medical University Cerebral Vessel Disease (TWMU CVD) registry is an ongoing prospective, observational registry in which patients with any evidence of CVD in magnetic resonance imaging (MRI) and at least one vascular risk factor were consecutively enrolled. For SVD-related findings, we evaluated white matter hyperintensity, lacunar infarction, cerebral microbleeds, enlarged perivascular space, and medial temporal atrophy. We used the total SVD score as the SVD burden. They underwent the Mini-mental State Examination (MMSE) and Japanese version of the Montreal Cognitive Assessment (MoCA-J) global cognitive tests, and each cognitive domain was evaluated. After excluding patients without MRI T2* images and those with MMSE score <24, we analyzed 648 patients. The total SVD score was significantly associated with MMSE and MoCA-J scores. After adjustment for age, sex, education, risk factors, and medial temporal atrophy, the association between the total SVD score and MoCA-J score remained significant. The total SVD score was independently associated with attention. In conclusion, the total SVD score, cerebral SVD burden, was independently association with global cognitive function and attention. A strategy to reduce SVD burden will have the potential to prevent cognitive decline.

Keywords Total small vessel disease score · Cognitive function · White matter hyperintensity · Attention

Introduction

Cerebral small vessel disease (SVD) has attracted much attention because several cohort studies have shown an association between cerebral SVD and incident stroke, as well as incident dementia [1–4]. Cerebral SVD is believed to be a key factor in explaining the relationship between vascular risk factors and dementia, especially Alzheimer's disease (AD). Cross-sectional studies have shown that cerebral SVD is associated with cognitive function, especially executive function and processing speed [5]. Among risk

factors, hypertension is the most important risk factor for SVD [6].

Features of cerebral SVD seen on neuroimaging include recent small subcortical infarcts, lacunar infarction (LI), white matte hyperintensity (WMH), cerebral microbleeds (CMB), enlarged perivascular space (EPVS), and brain atrophy [7]. Previous studies have shown a significant association between cognitive function and WMH [8, 9] and CMB [10]; however, the relationship between EPVS and cognitive function is unclear [11].

Recently, the total SVD score was proposed as a simple score representing WMH, LI, CMB and EPVS [12, 13]. The total SVD scores is related to vascular risk factors [13, 14], and are associated with global cognitive function [12, 15, 16]. The total SVD score can predict the risk of recurrent stroke [17, 18], cardiovascular event [19], incident dementia [18] and cognitive decline [20].

However, several key factors such as age, education, risk factors and brain atrophy other than cerebral SVD-related findings also showed a close association with dementia [21, 22], and cerebral SVD-related findings also showed a

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Graphical Abstract

A total of 648 patients with any evidence of cerebral small vessel disease (SVD) in MRI and at least one vascular risk factor underwent Mini-mental State Examination (MMSE) and Japanese version of the Montreal Cognitive Assessment (MoCA-J) global cognitive tests. The total SVD scores count the presence of each SVD-related findings (white matter hyperintensity, Lacunar infarction, cerebral microbleeds and enlarged perivascular space), ranging from 0 to 4, as the SVD burden. Total SVD scores were significantly associated with MoCA-J scores ($r = -0.203$, $P < 0.001$). After adjustment for age, sex, education, risk factors, and medial temporal atrophy, the association between the total SVD score and global cognitive scores remained significant.

SVD related MRI findings
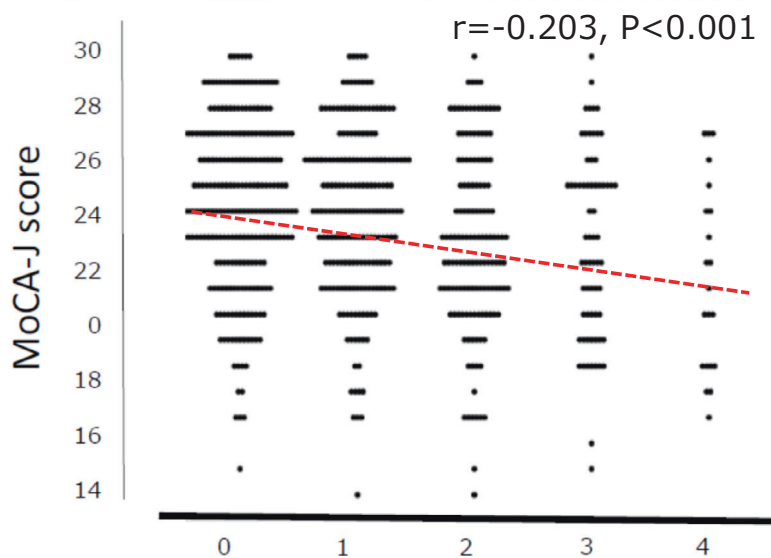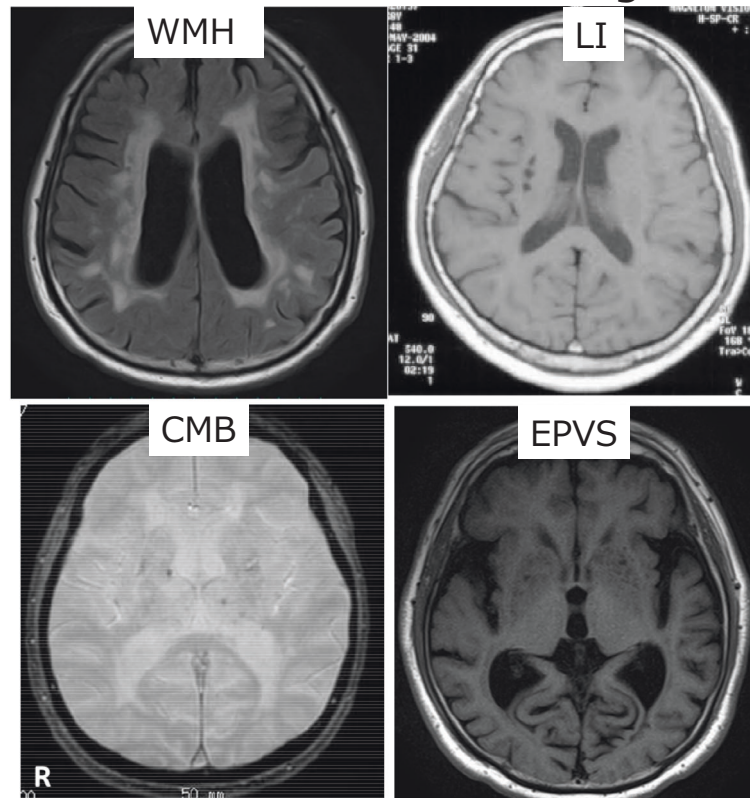
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Point of view

- Clinical relevance

   The present study showed that the total SVD score, cerebral SVD burden, was independently associated with global cognitive function and attention.
- Future direction

   Future studies need to clarify whether intensive blood pressure control inhibits development of cerebral SVD-related findings, and thus prevents cognitive decline and dementia.
- Consideration for the Asian Population

   Because SVD is the main etiology for stroke in Asian people, blood pressure management might have more advantages in reducing the risk of cognitive decline and dementia in Asian patients than in Caucasian people.

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relationship with age, vascular risk factors, and brain atrophy [23].

It still remains unclear whether SVD burden is significantly associated with global cognitive function and each cognitive subdomain independent of medial temporal atrophy (MTA), a strong biomarker predictive of incident AD [22], and other confounding factors.

Methods

Participants

Data were derived from a prospective study, the Tokyo Women's Medical University Cerebral Vessel Disease (TWMU CVD) Registry (Registration-URL: https://www.umin.ac.jp/ctr/index.htm; UMIN000026671), from October 2015 to July 2019. This study conformed to the ethical guidelines of the 1975 Declaration of Helsinki in line with the Ethical Guidelines for Epidemiological Research by the Japanese government and the Strengthening the Reporting of Observational Studies in Epidemiology guidelines. Written informed consent was obtained from all the participants. This study was approved by the institutional review board of Tokyo Women's Medical University. The research protocol and inclusion criteria of the TWMU CVD registry have been previously described in detail [24, 25]. In brief, we consecutively included outpatients aged 40 years with any vascular risk factors or a history of cerebrovascular events who underwent brain magnetic

Table 1 Baseline characteristics of patients ($N = 648$)

Characteristics	Values or frequency
Age, median (IQR), years	71 (63–77)
Sex, male, %	58.4
Education, years	16 (12–16)
Hypertension, %	68.2
Systolic blood pressure, mmHg	134 (122–147)
Diastolic blood pressure, mmHg	75 (67–84)
Diabetes mellitus, %	29.3
HbA1c, %	6.0 (5.7–6.7)
Dyslipidemia, %	51.3
LDL-C, mg/dL	105 (87–127)
HDL-C, mg/dL	60 (48–72)
Triglyceride, mg/dL	112 (78–154)
Atrial fibrillation, %	11.4
Chronic kidney disease[a], %	48.3
Creatinine, mg/dL	0.85 (0.71–1.04)
eGFR, ml/min/1.73 m^2	60.9 (51.0–71.2)
Cigarette smoking, Current smoker, n (%)	7.4
Former smoker[b], n (%)	38.6
Previous cerebrovascular disease, %	53.1
Medication, statin use, %	47.5
Anti-hypertensive drug use, %	67.5
Anti-platelet use, %	52.9
Cilostazol use, %	8.5
Anti-coagulant use, %	14.7
MRI findings	
Total WMH (0–6)	2 (2–3)
Fazekas PVH (0–3)	1 (1–1)
Fazekas DWMH (0–3)	1 (1–2)
Presence of lacuna, %	47.2
Presence of microbleeds, %	35.0
Presence of EPVS (>10), %	9.1
Medial Temporal lobe atrophy (0-6)	2 (2-4)
Presence of major cerebral artery lesion, %	12.4
Total SVD score (0-4)	1(0-2)
Score 0, %	35.8
1, %	29.6
2, %	21.1
3, %	10.2
4, %	3.2
Global cognitive function	
MMSE score	28 (26–30)
MoCA-J score	24 (21–26)
Executive function	3 (2–4)
Memory	5 (3–6)
Orientation	10 (10–10)
Language	12 (11–12)
Visuospatial	5 (4–5)
Attention	10 (8–11)

DWMH deep white matter hyperintensity, *EPVS* enlarged perivascular space, *eGFR* an estimated glomerular filtration rate, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *PVH* periventricular hyperintensity, *SVD* small vessel disease, *WMH* white matter hyperintensity

[a]Chronic kidney disease was defined as eGFR of less than 60 ml per minute per 1.73 m^2 of body-surface area

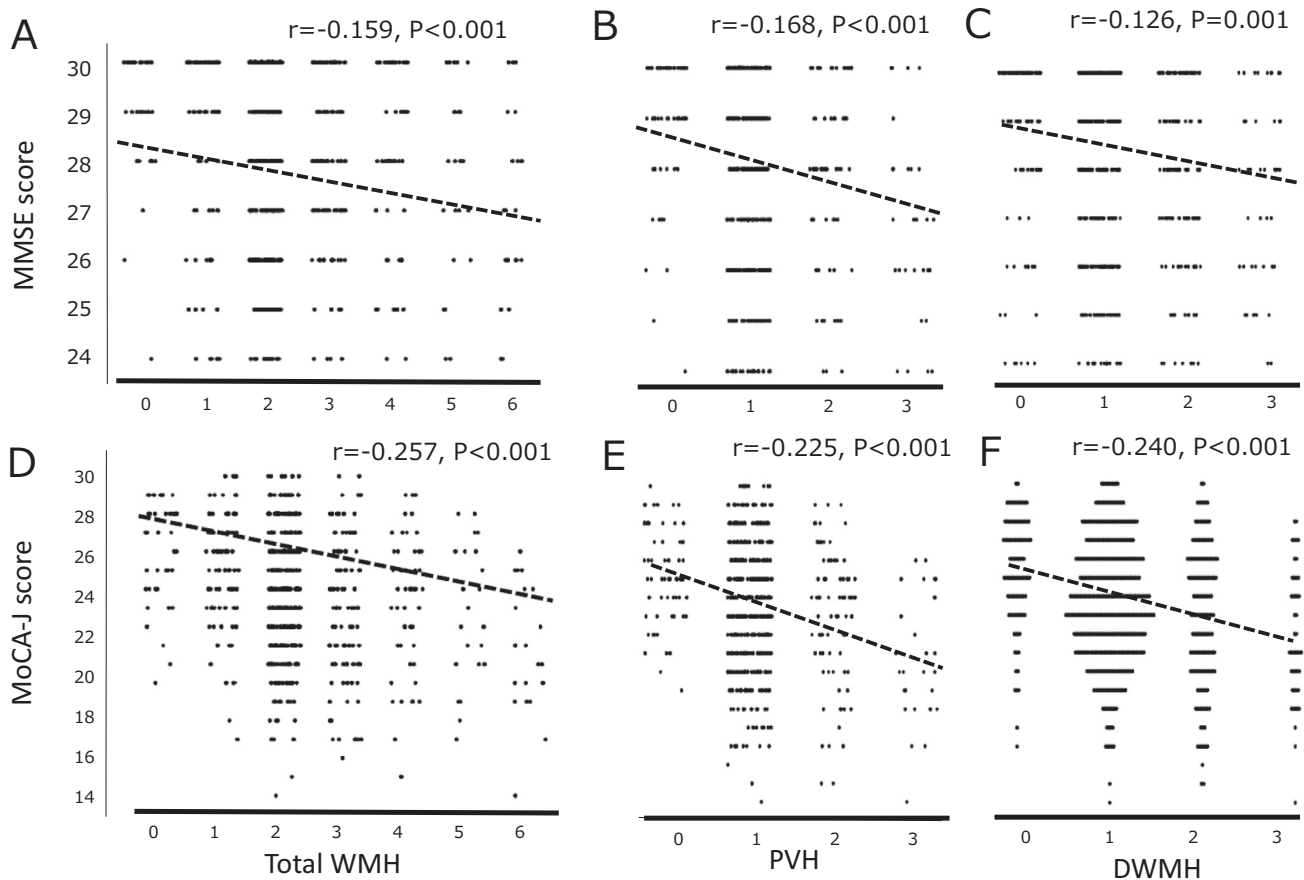[b]Former smoker was defined as quit smoking <12 months

Fig. 1 Correlation between global cognitive functions and white matter hyperintensity. Correlation between MMSE and total WMH (**A**), PVH (**B**) and DWMH (**C**). Correlation between MoCA-J and total WMH (**D**), PVH (**E**) and DWMH (**F**). MMSE Mini-Mental State Examination, MoCA-J the Japanese version of the Montreal Cognitive Assessment, WMH white matter hyperintensity, PVH periventricular hyperintensity, DWMH deep white matter hyperintensity

resonance imaging (MRI) within 1 year and had any signs of cerebral vessel disease. The exclusion criteria for the registry were any kind of aphasia, evidence of dementia (clinical dementia rating ≥1), and dependence for activities of daily living and walking. We also excluded those who suffered vascular events including stroke within one month.

Cognitive examination

Patients underwent the Mini-Mental State Examination (MMSE) and the Japanese version of Montreal Cognitive Assessment (MoCA-J) [26] within 1 year of MRI examination. Among the items in the MMSE and MoCA-J, the scores of each cognitive domain; executive function (0–4), memory (0–8), orientation (0–10), language (0–13), visuospatial function (0-5) and attention and working memory (0–11) were extracted (Supplementary Table 1).

MRI assessment

Each participant underwent a brain MRI scan within 1 year of entry into the registry. The MRI assessment included WMH consisting of periventricular hyperintensity (PVH) and deep WMH (DWMH), LI, CMB, EPVS, total SVD score [14], and MTA [27]. WMH severity was visually rated using axial fluid attenuated inversion recovery (FLAIR) images. According to the Fazekas scale (0 = none; 1 = mild; 2 = moderate; 3 = severe) [28], PVH and DWMH were evaluated from 0 to 3; additionally, the total WMH score was assigned ranging from 0 to 6 with the sum of PVH and DWMH. Lesions in the basal ganglia, internal capsule, centrum semiovale, or brainstem with hypointensity on T1-weighted imaging, hyperintensity on T2-weighted imaging, and a hyperintense rim around the cavity on FLAIR were defined as LI with sizes ranging from 3 to 15 mm. CMB were defined as punctate or small patchy lesions <10 mm in diameter with obvious low intensity on
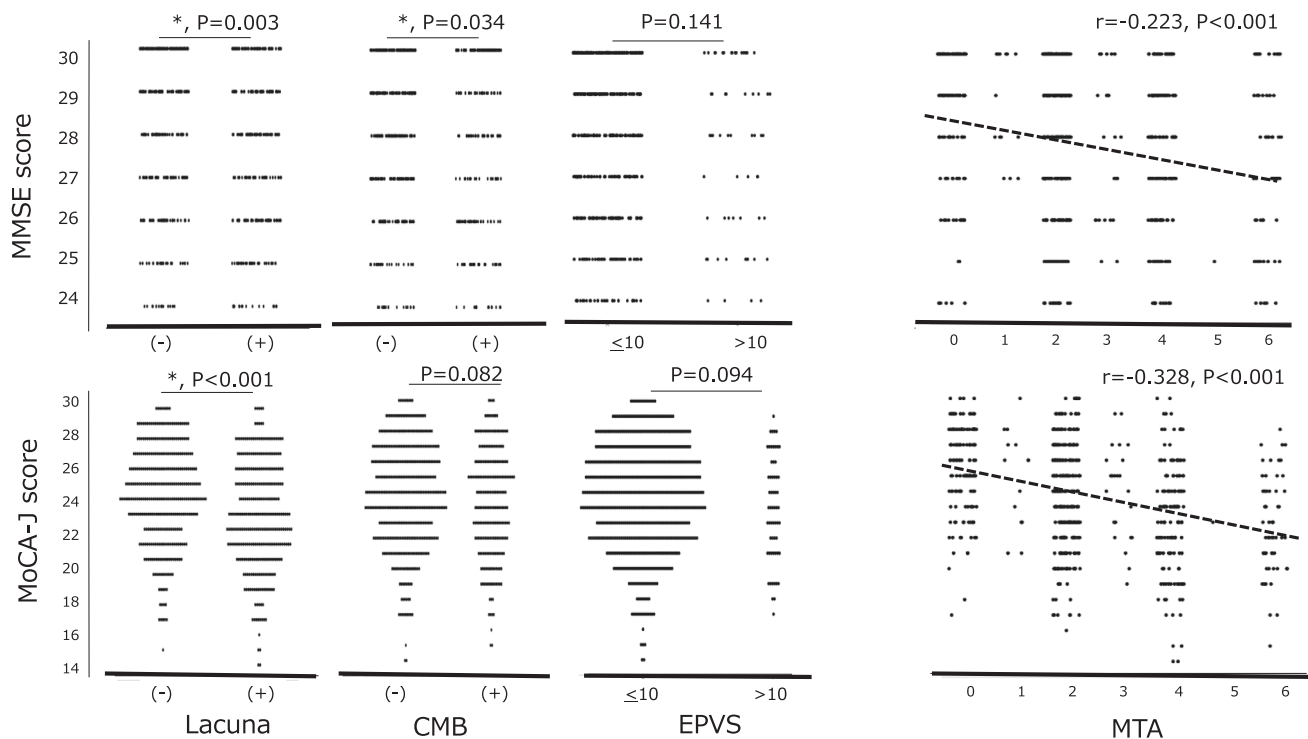
Fig. 2 Correlation between global cognitive functions and lacunar infarction, cerebral microbleeds, enlarged perivascular space or medial temporal atrophy. CMB cerebral microbleeds, EPVS enlarged perivascular space, MTA medial temporal atrophy

T2-star weighted imaging. EPVS were defined as round, oval, or linear-shaped lesions with a smooth margin and signal intensity equal to that of cerebrospinal fluid on both T1 and T2-weighted images [29]. We counted the EPVS on the slide with the highest number in the basal ganglia. MTA was rated from 0 (absent) to 4 (severe) according to the previous guideline [27].

The total SVD score was assigned from 0 to 4 by incorporating all four MRI markers including WMH, LI, CMB, and EPVS [14]. A point was awarded for WMH if PVH Fazekas 3 (extending into the deep white matter) and /or DWMH Fazekas 2-3 (confluent or early confluent) was present. For LI, one point was awarded if ≥1 asymptomatic lesions was present. For CMB, one point was awarded if ≥1 any CMB was present in the cerebellum, brainstem, the basal ganglia, white matter, or cortico-subcortical junction. For EPVS, one point was awarded if more than 10 EPVS in the slice, including the basal ganglia, were present. All grades of cerebral SVD-related findings were rated by two trained board-certified neurologists (MH and KK) who were blinded to clinical details.

Statistical analysis

All analyses were performed using JMP 13 Pro. For baseline characteristics, the mean and standard deviation (SD) were used for continuous variables, and the frequency and percentage of the total population were used for categorical variables. The median and interquartile range were presented for ordinal and non-normally distributed variables. Relationships between the MMSE, MOCA-J, or each cognitive domain and continuous variables were examined using Pearson's correlation analysis. For categorical variables, differences in MMSE and MoCA-J scores were examined using an unpaired t test. Subsequently, multiple linear regression analyses were performed to examine associations between the total SVD score and MMSE or MOCA-J scores by controlling for age, sex, education, risk factors and other MRI findings.

Results

Among the 1022 patients enrolled in the TWMU CVD registry, 64 refused to undergo cognitive examination, 234 did not undergo T2* imaging, and 76 had a MMSE score <24 (Supplementary Fig. 1). After exclusion of 374 patients, 648 patients who underwent MRI examination, including T2*, and both MMSE and MoCA-J examinations, were analyzed.

The baseline characteristics of study participants are summarized in Table 1. The median age was 71 years, 58.4% were men, and the median number of years of education was 16 years. Sixty-eight percent of the participants had hypertension, 29% had DM, and 48% had chronic kidney disease (CKD), and 53% had a history of
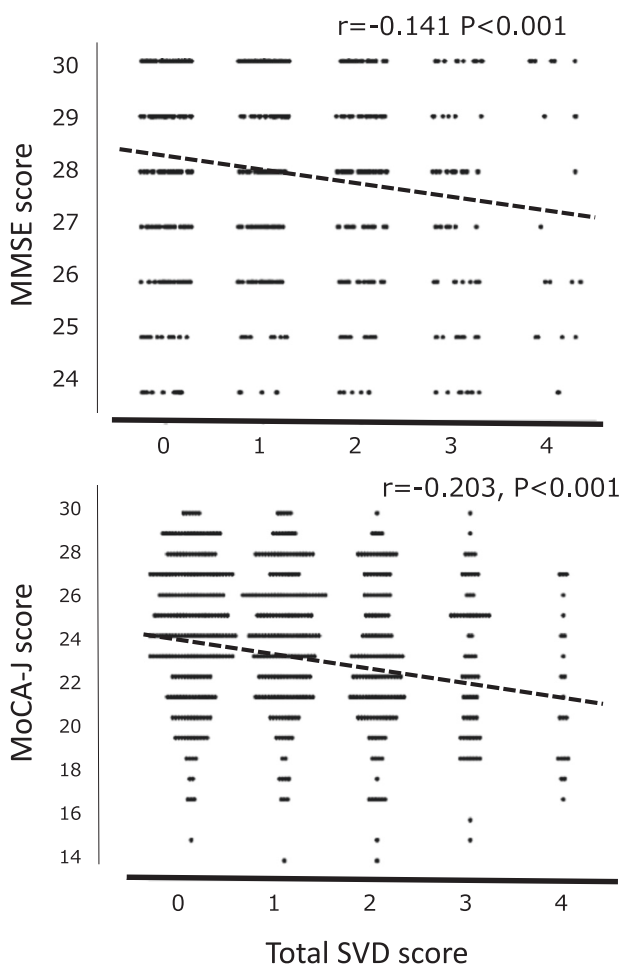
Fig. 3 Correlation between total SVD score and global cognitive functions. SVD small vessel disease

Table 2 Associations of MMSE and MOCA-J with total SVD score ($N = 648$)

	Total SVD score			
	MMSE		MoCA-J	
	r or β	P	r or β	P
Univariate	−0.141	<0.001	−0.203	<0.001
Model 1	−0.089	0.024	−0.104	0.005
Model 2	−0.079	0.055	−0.094	0.013
Model 3	−0.069	0.098	−0.083	0.029

Model 1: Adjusted for age and sex

Model 2: Adjusted for age, sex, education, a history of hypertension, diabetes mellitus and chronic kidney disease

Model 3: Adjusted for model 2 and medial temporal atrophy

SVD small vessel disease, MMSE Mini-Mental State Examination, MoCA-J Japanese version of the Montreal Cognitive Assessment

cerebrovascular disease. The median total WMH score was 2. The presence of LI, CMB and EPVS > 10 in the basal ganglia slice were 47.2%, 35.0% and 9.1%, respectively. The median total SVD scores was 1. The distribution of MMSE and MoCA-J scores is shown in Supplementary Figure 2. MMSE was 28.9 ± 1.9 (mean ± SD), and MoCA-J was 23.6 ± 3.5. In the subdomain of cognitive function, the median score for orientation and visuospatial function reached the highest point.

The association between global cognitive function and confounding factors is presented in Supplementary Table 2. Both MMSE and MoCA-J scores were correlated with age and education. MMSE scores were lower in those with hypertension than in those without it, and the MoCA-J score was lower in men, and in those with DM and CKD than in women and in those without DM and CKD, respectively.

The correlation between global cognitive function and each MRI finding is shown in Figs. 1 and 2, respectively. The total WMH, PVH and DWMH Fazekas scores were significantly related to the MMSE and MoCA-J scores (Fig. 1). However, the correlation seems stronger with

MoCA-J than with the MMSE score. Those with LI had lower MMSE and MoCA-J scores than those without LI (Supplementary Table 3). Those with CMB had lower MMSE scores than those without it, however, MoCA-J scores were similar between patients with and without CMB. Both MMSE and MoCA-J scores were similar between patients with and without EPVS > 10. Both MMSE and MoCA-J scores were significantly correlated with MTA. The correlation between the total SVD score and global cognitive function is shown in Fig. 3. There were several confounding factors related to cognitive function, as shown in Supplementary Table 2 therefore, we examined the association after controlling for these factors (Table 2). In model 1, the association between the total SVD score and global cognitive function remained significant. However, after controlling for age, sex, education and vascular risk factors (model 2), the association between the total SVD score and MMSE scores was not significant. After further controlling for MTA (model 3), the relationship between the total SVD score and MoCA-J remained significant. We analyzed the relationship between the total SVD score and each cognitive subdomain (Fig. 4). Univariate analysis revealed a significant correlation between the total SVD score and executive function, memory, language, and attention. After controlling for confounding factors, the association between the total SVD score and attention remained significant (Supplementary Table 4).

Discussion

This study clarified that the total SVD score was significantly associated with global cognitive function and its subdomains, attention, even after controlling for confounding factors and MTA.
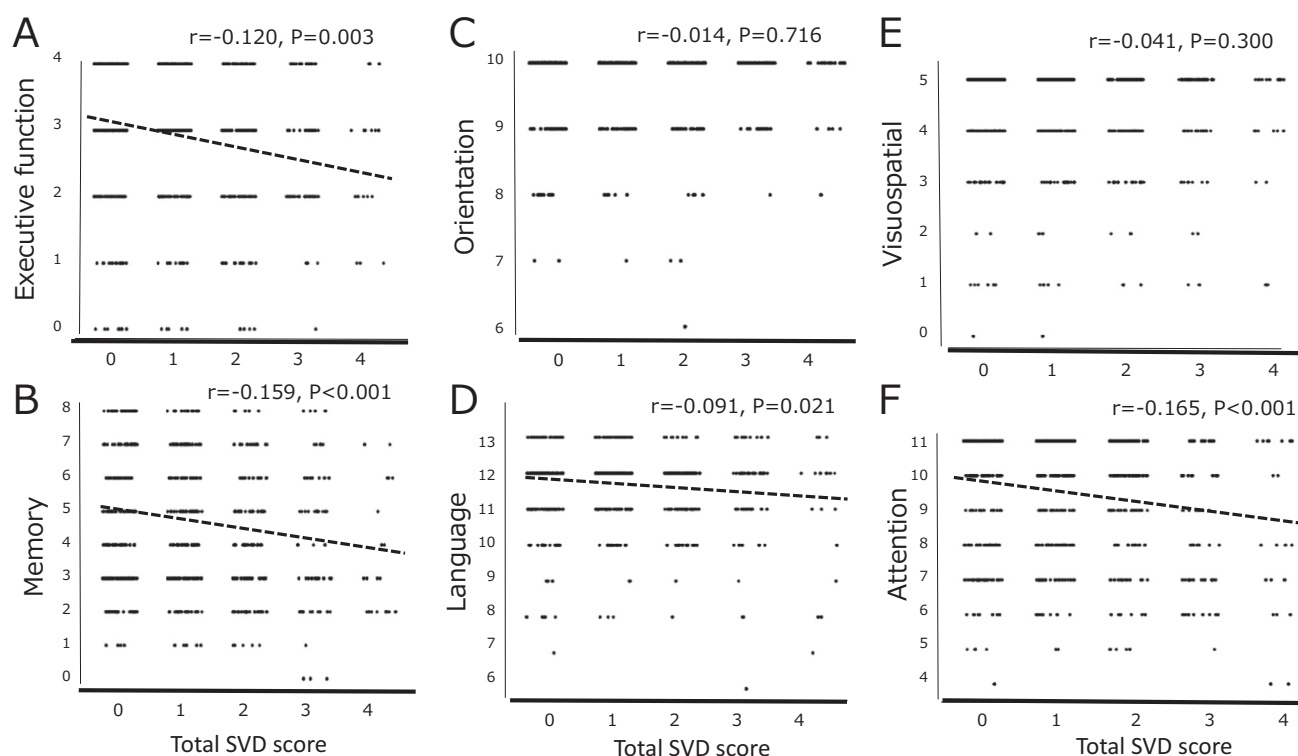
Fig. 4 Correlation between total SVD score and each cognitive domain. **A** Executive function; **B** Memory; **C** Orientation; **D** Language; **E** Visuospatial function; **F** Attention. SVD small vessel disease

Among SVD-related findings, WMH, LI and CMB were significantly associated with global cognitive function; however, the relationship between EPVS and cognitive function was not significant. These findings are consistent with previous finding [7–11]. This study is the first to show that the total SVD score was significantly associated with cognitive function independent of years of education, vascular risk factors, and MTA, strong predictor of incident AD dementia [22]. In terms of the cognitive subdomain, a significant association between attention and working memory and total SVD score was in line with previous finding [30]. Among SVD-related findings, LI and WMH were shown to be closely associated with executive function, attention and frontal assessment battery [8, 31, 32].

Previous studies have shown a close association between SVD-related findings and vascular risk factors [13, 14] and brain atrophy [23], and our study added an important aspect of the total SVD score on cognitive function. Further studies are needed to strengthen the predictive value of total SVD score for vascular events and incident dementia.

The close association between the total SVD score and cognitive function raises the question of whether therapeutic intervention for SVD-related findings reduces the risk of cognitive decline and incident dementia.

However, five categories from 0 to 4 in the total SVD score would not be suitable as a surrogate index of intervention. Evaluation of each SVD-related finding as well as the total SVD burden would be important for follow-up studies because previous studies have shown that the progression of WMH is related to cognitive decline [33, 34].

This study had several limitations. First, because of the single-center setting, the findings need to be confirmed in other centers and ethnic populations. Second, although we examined the association between each cognitive domain and total SVD score, we extracted each component from the MMSE and MoCA-J. Therefore, the power of the battery for the measurement of each component is not sufficient for a thorough investigation. This would explain why the median score in several components, such as orientation and visuospatial function, had already reached the highest score. We might have overlooked subtle changes in these cognitive domains. Third, we employed a visual rating, not a quantitative evaluation for WMH. Although the WMH grading scale is practical in routine clinical practice, it is neither an objective nor a sensitive method. A volumetric measure is needed to evaluate the longitudinal changes or effects of WMH intervention.

Perspectives in Asia

Cerebral SVD is the main etiology in Asian stroke patients. Hypertension is the most important risk factor for both symptomatic and asymptomatic SVD. Our findings showed the close association between cerebral SVD-related findings and cognitive function. Although it remains unclear whether intensive blood pressure control is effective for prevention of SVD development, our findings suggest that anti-hypertensive treatment would have potential for prevention of dementia, especially in Asian people.

Conclusions

Cerebral SVD-related findings are associated with global cognitive function and its subdomain, attention, independent of confounding factors and MTA. Preventing the development of cerebral SVD-related findings by controlling vascular risk factors, especially hypertension, could potentially prevent cognitive impairment.

Compliance with ethical standards

Conflict of interest KK reports personal fees from Daiichi Sankyo, Kyowa Kirin and Kowa. Others have nothing to disclose.

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