BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-042550
Article Type:	Original research
Date Submitted by the Author:	08-Jul-2020
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Keywords:	Delirium & cognitive disorders < PSYCHIATRY, Dementia < NEUROLOGY, Hypertension < CARDIOLOGY, Magnetic resonance imaging < RADIOLOGY & IMAGING

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Correlation between small vessel disease score and cognitive function in patients from a memory clinic study

Running title: SVD score and cognitive function in a memory clinic study

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Word count: 3453 words

ABSTRACT

Objective: Severity of cerebral small vessel disease (SVD) is assessed through neuroimaging findings, including hypertensive arteriopathy (HA)-SVD and cerebral amyloid angiopathy (CAA)-SVD. HA-SVD and CAA-SVD have been collectively estimated as total scores: the HA-SVD and CAA-SVD scores, respectively. Previous reports suggest that HA-SVD scores are associated with cognitive function; however, the relationship between CAA-SVD scores and cognitive function remains unclear. We examined the association between CAA-SVD scores and cognitive function. Furthermore, we developed a modified CAA-SVD score considering cortical microinfarcts and posterior dominant white matter hyperintensities, which are imaging findings of CAA, and examined the association between these scores and cognitive function in the same patient group.

Methods: Subjects were diagnosed with mild cognitive impairment (MCI) or mild dementia in our memory clinic between February 2017 and July 2019 and underwent clinical dementia rating scale and brain magnetic resonance imaging (MRI) assessment. A total of 42 patients (aged 75.3 ± 9.12 years) were registered prospectively. We evaluated intellectual function, memory, frontal lobe function, and constructional ability. Furthermore, the relationship between each score and cognitive function was examined.

Results: The CAA-SVD score showed significant associations with cognitive function (R^2=0.63, p=0.016), but the HA-SVD score did not (R^2=0.41, p=0.35). The modified CAA-SVD score was also significantly associated with cognitive function (R^2=0.65, p=0.008).

Conclusion: Cognitive function is associated with the CAA-SVD score, and more efficiently with the modified CAA-SVD score, in memory clinic patients. Theses scores can be a predictor of cognitive deterioration in patients with MCI and mild dementia.

Strengths and limitations of this study

1. There was an association cerebral amyloid angiopathy (CAA)-small vessel disease (SVD) score on MRI and cognitive function in memory clinic patients.

2. Modified CAA-SVD score added analysis of posterior distribution of white matter hyperintensities and cortical microinfarcts might be useful tool for the evaluation of patients with MCI or mild dementia.

3. There was no significant association between hypertensive arteriopathy HA-SVD score and cognitive function.

4. Our memory clinic's patients might have a higher burden of amyloid pathology.

Keywords: cognition, dementia, small vessel disease, hypertension, cerebral amyloid angiopathy

INTRODUCTION

Cerebral small vessel disease (SVD) is a comprehensive term that describes small vessel pathological conditions, including ischemia and haemorrhage, in the brain. Patients with SVD share common pathological, clinical and neuroimaging features.[1] Neuroradiological findings of SVD are examined using brain magnetic resonance imaging (MRI), which shows various vascular lesions, including white matter hyperintensities (WMH), lacunar infarcts, enlargement of perivascular spaces (PVS), microbleeds (MBs), cortical superficial siderosis (cSS), and cortical microinfarcts (CMIs).[1-3] SVD is the main cause of vascular dementia in older people, among which, SVD with dementia comprises nearly half of all patients with vascular dementia.[4, 5] Moreover, SVD is also present in Alzheimer's disease (AD).[6]

Although aging is one of the main causes of SVD, several other diseases such as arteriosclerosis, cerebral amyloid angiopathy (CAA), genetic predispositions and inflammation also cause SVD.[7] In particular, arteriosclerosis and CAA are the two major causes of SVD. SVD due to arteriosclerosis is particularly associated with hypertension (hypertensive arteriopathy; HA)[6]; this SVD type is also named sporadic non-amyloid microangiopathy.[8] In contrast, CAA is characterized by the progressive deposition of amyloid beta (Aβ) protein in the cerebral vessels and the major peptide isoforms of Aβ mainly consist of $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$.[7, 9] Although both HA and CAA share common MRI features, including WMH, enlargement of PVS, and MBs, the location and distribution of these radiological

findings are different. The anteroposterior distribution of WMH in CAA is posterior-dominant.[10] The enlargement of PVS in the basal ganglia (BG-PVS) is associated with hypertension, and patients with CAA show centrum semiovale PVS (CSO-PVS).[11, 12] MBs located in the basal ganglia, thalamus, or brainstem indicate HA (deep MBs) and MBs within the lobar brain compartment are associated with CAA [13]. Moreover, lacunar infarcts are associated with hypertension, whereas cSS is a representative MRI biomarkers in CAA.[14] CMIs are caused by different pathological backgrounds, including CAA, arteriosclerosis and microembolism[15]; however, neuroradiological findings obtained using 3T MRI may enable distinction between CMIs due to CAA and those due to microembolisms.[16]

Recently, two types of MRI-based assessment scores have been developed for SVD. Klarenbeek et al. enrolled patients with lacunar stroke and assessed different MRI features, including lacunar infarct, MBs, BG-PVS and WMH.[17] One point was awarded for the presence of each marker, producing a score between 0 and 4. This HA-SVD score was mainly used for the evaluation of patients with lacunar stroke and/or vascular risk factors,[18] and was associated with intellectual function.[19] Charidimou et al. developed a novel SVD score for patients with CAA (CAA-SVD score),[20] which was associated with clinical symptoms of transient focal neurological episodes.[21] However, the relationship between CAA-SVD scores and cognitive function remains unclear.

In this study, we investigated the relationship between the two types of SVD scores and cognitive function in patients who visited our memory clinic. Moreover, we added other radiological biomarkers of CAA to the CAA-SVD score and investigated its usefulness in evaluating cognitive function in patients with mild cognitive impairment (MCI) and mild dementia.

PATIENTS AND METHODS

Patients

We prospectively registered patients who consulted our hospital's memory clinic. Of the 57 enrolled patients, 42 fulfilled the inclusion criteria (Fig 1). All procedures followed the Clinical Study Guidelines of the Ethics Committee of Mie University Hospital and were approved by the internal review board (Registration number: 1596). A complete description of all procedures was provided to patients, and written informed consent was obtained directly from them or from their caregivers. Every patient was comprehensively examined by a neurologist with sufficient experience in examining patients with dementia. We collected data from patients who fulfilled the following inclusion criteria: 1) consulted with our hospital's memory clinic between February 2017 and July 2019, 2) underwent neuroimaging examinations using 3T MRI, 3) completed neuropsychological assessments, and 4) had a global Clinical Dementia Rating (CDR) score of 0.5 or 1.0. Neuropsychological tests and CDR were performed within 3 months of MRI. No neurological events occurred between these tests and MRI.

Patients were excluded if they 1) declined to or could not undergo MRI, 2) declined neuropsychological and CDR assessments, and 3) had CDR scores of 0 or ≥ 2.

A diagnosis of MCI was made if the patient met the following criteria: (1) memory complaints, (2) normal daily living activities, (3) normal general cognitive function, (4) abnormal memory for age, and (5) no history of dementia. MCI was classified into amnestic type (aMCI) or non-amnestic type (naMCI) depending on the presence or absence of memory impairment, respectively.[22] The global CDR score was 0.5. We diagnosed AD according to the National Institute on Aging–Alzheimer's Association (NIA-AA) guidelines.[23] Vascular dementia was diagnosed according to the criteria set forth by the American Heart Association/American Stroke Association.[24]

Neuropsychological assessments

The Mini-Mental State Examination (MMSE)[25] and Japanese Raven's Coloured Progressive Matrices (RCPM)[26] were used to quantify intellectual function. Memory was evaluated using the Rivermead Behavioral Memory Test (RBMT). The scores included a standard profile score (SPS) and screening score (SS).[27] Constructional ability was assessed using the Mie Constructional Apraxia Scale (MCAS).[28] Frontal lobe function was assessed using two tasks: word fluency (WF) and trail making test (TMT) -A/-B.[29] The WF test consisted of category and letter domains. In the category WF task (WF-category), participants were asked to name as many animals as possible in 1 minute. In

the letter WF task (WF-letter), participants were asked to name as many objects as possible in 1 minute, beginning with each of the following four phonemes: *ka, sa, ta,* and *te*. The average scores for these four phonemes were used for statistical analyses.

CDR was performed by two speech therapists, and results were evaluated through a discussion between two neurologists and three speech therapists based on the CDR determination rules.[30]

MRI protocol

The MRI protocol used was by Ii et al.[28] Briefly, MRI studies were performed with a 3T MRI unit (Achieva, Philips Medical System, Best, the Netherlands) using an 8- or 32-channel phased-array head coil. We used T1- and T2-weighted images and 3D-fluid attenuated inversion recovery (FLAIR) images for the evaluation of WMH, lacunar infarcts, and PVS. Susceptibility-weighted image (SWI) sequences were used for the detection of MBs and cSS. Using 3D-double inversion recovery (DIR) and 3D-FLAIR allowed for the detection of CMIs. Axial DIR imaging was performed using two different inversion pulses. The long inversion time and the short inversion time were defined as the intervals between the 180° inversion pulse and the 90° excitation pulse, respectively, which had been optimized for human brain imaging and were provided by the vendor.

Details of the 2D- and 3D-DIR protocols were as follows: field of view, 230 mm; matrix, 320 × 256 (512 × 512) after reconstruction; in-plane resolution, 0.45 mm × 0.45 mm; section thickness, 3 mm

with no intersection gap; no parallel imaging; repetition time (ms)/echo time (ms), 15,000/28; long inversion time (ms)/short inversion time (ms), 3,400/325; number of signals acquired, two; and acquisition time, 4 min 30 s for 2D, and field of view, 250 mm; matrix, 208 × 163 (256 × 256) after reconstruction; in plane resolution, 0.98 mm × 0.98 mm; section thickness, 0.65 mm with over contiguous slice; TSE factor 173; repetition time (ms)/echo time (ms), 5,500/247; long inversion time (ms)/short inversion time (ms), 2,550/450; number of signals acquired, two; and acquisition time, 5 min 13 s for 3D.

The SWI details were as follows: field of view, 230 mm; matrix, 320 × 251 (512 × 512) after reconstruction; in-plane resolution, 0.45 mm × 0.45 mm; section thickness, 0.5 mm with over contiguous slice; repetition time (ms)/echo time (ms), 22/11.5 (in-phase), 33 (shifted); number of signals acquired, one; flip angle 20°; and acquisition time, 5 min 45 s. 3D-FLAIR imaging was obtained in a sagittal direction, and then the axial and coronal images were reconstructed. The 3D-FLAIR details were as follows: field of view, 260 mm; matrix, 288 × 288 (364 × 364) after reconstruction; in-plane resolution, 0.68 × 0.67 mm); section thickness, 1 mm with 0.5 mm overlap; no parallel imaging; repetition time (ms)/echo time (ms), 6,000/400; inversion time, 2,000 ms; number of signals acquired, two; and acquisition time, 5 min 12 s.

SVD scores

The HA-SVD score was determined by Klarenbeek et al., where 1 point was awarded for each of the four markers (lacunar infarcts, MBs, BG-PVS, and WMH), with a minimum score of 0 and a maximum score of 4.[17] The CAA-SVD score was proposed by Charidimou et al. (Table 1), with 1 point awarded for each of the four markers (lobar MBs, cSS, CSO-PVS, and WMH).[20] For lobar MBs, 1 point was awarded if two to four MBs were present and 2 points for five or more MBs. The presence of cSS was awarded with 1 point if focal and 2 points if disseminated. The presence of CSO-PVSs was confirmed if there were moderate to severe (> 20) PVSs (1 point if present), with a minimum score of 0 and a maximum score of 6. Both scores were independently assessed by four raters.

Table 1. CAA-SVD score and modified CAA-SVD score

MRI marker	Cut off	Points	
CAA-SVD score			
Lobar MBs	2 to 4	1	
	≥ 5	2	
cSS	Focal	1	
	Disseminated	2	
CSO-PVSs	>20	1	
WMH	deep WMH (Fazekas 2 or 3)	1	
	periventricular WMH (Fazekas 3)	1	total /6
Modified CAA-SVD score			
posterior distribution of WMH		1	
CMI(s) due to CAA	≥1	1	total /8

Modified CAA-SVD scores

We tried to modify CAA-SVD scores by adding one point each in the presence of posteriorly dominant WMH and CMIs due to CAA (Table 1).

Tissue quantification was performed using a novel in-house software (FUsed Software for Imaging Of Nervous system: FUSION)[31] that yielded an individualized volumetric brain tissue profile. The obtained T1-weighted and FLAIR images were imported from the Digital Imaging and Communications in Medicine format files for processing. To increase the accuracy of segmentation, we used the Lesion Segmentation Tool for lesion filling.[32] Lesion filling was applied to T1-weighted images that were aligned with the lesion probability map. For pre-processing, the T1-weighted images were co-registered to the FLAIR images. Next, to separate out the white matter, segmentation was performed using the T1-weighted images and a mask covering the cerebral ventricles. The pre-processing function was based on SPM 8 (Wellcome Trust Centre for Neuroimaging, UCL). Second-level tissue segmentation was then performed to separate WMH from white matter using a semi-automated operation that extracted the pixels falling within a predetermined WMH value. The WMH volume, which appeared as hyperintense areas on FLAIR images, was quantified for each area. Brain tissue was classified into four areas based on the division of the longitudinal fissure of the cerebrum and central sulcus. WMH were automatically classified as periventricular hyperintensity or deep WMH,

and their corrected volumes were quantified in cubic centimetres.[31] The anteroposterior centre of WMH was calculated in the following way. To determine the reference point, we identified two anatomical landmarks (anterior, A and posterior, P). Point A was defined as the most anterior part on the wall of the frontal horn of the lateral ventricle. Point P was defined as the most posterior part of the dura mater covering the occipital cortex.[10] If there was a large amount of posterior WMH, 1 point was added to the CAA-SVD score.

CMIs were defined as small cortical hyperintense lesions non-adjacent to WMH. When CMIs were localized within the cortex, predominantly in the occipital lobe, were smaller than 5 mm in diameter, and had fewer than three lesions, they were defined as CMIs due to CAA.[13] When there were any CMIs due to CAA, we added 1 point to the CAA-SVD score.

Statistical analyses

The association between each SVD score (dependent variable) and cognitive function (independent variable) was analysed using linear regression analysis. Clinical and radiological characteristics are presented as numbers with percentages and means with standard deviation (SD). Statistical analyses were performed using IBM SPSS statistics software version 20 (IBM Corp., Armonk, NY, United States). Differences with $p<0.05$ were considered statistically significant.

RESULTS

Patients

In total, 57 patients were registered for this study, and 42 fulfilled the inclusion criteria (Fig 1). Clinical characteristics, neuropsychological test results, and MRI findings of the participants are shown in Table 2. Mean age was 75.3 (56–86) years, and there were 23 men (54.7%). Regarding vascular risk factors, 22 patients had hypertension (52.3%), four had diabetes mellitus (9.5%) and 11 smoked and had dyslipidaemia (26.1%). Fourteen patients had a history of lacunar stroke (33.3%) and 24 patients (57.1%) met the modified Boston criteria (ver 1.5).

The global CDR score was 0.5 for 30 patients (71.4%) and 1.0 for 12 patients (28.6%). Of the 12 patients with a global CDR score of 1.0, 10 met the criteria reflecting probable AD and two had vascular dementia. Among 30 patients with MCI, 20 had aMCI and 10 had naMCI. Regarding MRI findings, 31 patients had ≥1 MBs (73.8%), 16 had ≥2 and ≤4 lobar MBs (38.0%), and 10 had ≥5 lobar MBs (23.8%). Three patients had focal cSS (7.1%), 25 had >20 BG-PVSs (59.5%), 30 had >20 CSO-PVSs (71.4%), 26 had deep WMH (Fazekas 2 or 3) (61.9%), and 11 had periventricular WMH (Fazekas 3) (26.1%).

WMH were divided according to whether they were anterior or posterior and were analysed using FUSION. There were seven posterior superiorities (16.6%). CMIs due to CAA were detected in three patients (7.1%), and two of these patients met the modified Boston criteria for probable CAA.

Table 2. Participant characteristics

MMSE, Mini-Mental State Examination; RCPM, Raven's Colored Progressive Matrices; s, seconds; RBMT, Rivermead Behavior Memory Test ; TMT, Trail-Making Test; WF, word fluency; MCAS, Mie Constructional Ability Scale; CDR, Clinical Dementia Rating

Clinical characteristics	All participants, n= 42
Age, years, mean (SD)	75.3 (9.12)
Education, years, mean (SD)	11.9 (2.34)
Male sex (n, %)	23 (54.7)
Vascular risk factors	
hypertension (n, %)	22 (52.3)
dyslipidemia (n, %)	11 (26.1)
diabetes mellitus (n, %)	4 (9.5)
smoking (n, %)	11 (26.1)
History of any stroke (n, %)	19 (45.2)
lacunar (n, %)	14 (33.3)
Medication	
anti-hypertensive (n, %)	7 (16.6)
statin (n, %)	6 (14.2)
anti-platelet or anti-coagulation (n, %)	8 (19.0)
Meets modified Boston criteria	
probable CAA	11 (26.1)
possible CAA	13 (30.9)

Neuropsychological tests		
Global CDR	0.5 (n, %)	30 (71.4)
	1.0 (n, %)	12 (28.6)
MMSE	Score (SD)	25.2 (2.39)
RCPM	Score (SD)	24.2 (5.73)
	Time,s (SD)	440 (198)
RBMT	Standard profile score (SD)	11.5 (5.49)
	Screening score (SD)	4.5 (2.78)
TMT	A, s (SD)	257 (156)
	B, s (SD)	265 (95.6)
WF, /min	Category (SD)	10.9 (3.93)
	Letters (SD)	5 (1.72)
MCAS	Score (SD)	3.3 (1.68)
	time,s (SD)	49.6 (37.4)
MRI findings		
MBs; all	≥ 1 (n, %)	31 (73.8)
MBs; Lobar	2 to 4 (n, %)	16 (38.0)
	≥ 5 (n, %)	10 (23.8)
cSS	Focal (n, %)	3 (7.1)
	Disseminated (n, %)	0
BG-PVSs	>20 (n, %)	25 (59.5)
CSO-PVSs	>20 (n, %)	30 (71.4)
WMH	deep WMH (Fazekas 2 or 3) (n, %)	26 (61.9)
	periventricular WMH (Fazekas 3) (n, %)	11 (26.1)
posterior distributon of WMH (n, %)		7 (16.6)
CMI(s) due to CAA (n, %)		3 (7.1)

Results of each SVD score

As for each SVD score (Table 3), the HA-SVD score was 0 in 3 patients (7.1%), 1 in 7 patients (16.6%), 2 in 14 patients (33.3%), 3 in 11 patients (26.1%), and 4 in 7 patients (16.6%). The CAA-SVD score was 0 in 5 patients (11.9%), 1 in 6 patients (14.2%), 2 in 13 patients (30.9%), 3 in 12 patients (28.5%), and 4 in 6 patients (14.2%). Moreover, the modified CAA-SVD score was 0 in 1 patient (2.3%), 1 in 6 patients (14.2%), 2 in 8 patients (19%), 3 in 13 patients (30.9%), 4 in 11 patients (26.1%), 5 in 2 patients (4.7%), and 6 in 1 patient (2.3%). A significant difference was observed when the HA-SVD scores and CAA-SVD scores were analysed using Pearson's chi-square test (p=0.000).

Table 3. Cerebral small vessel disease score

Score	All participants n = 42
HA-SVD score (n, %)	
0	3 (7.1)
1	7 (16.6)
2	14 (33.3)
3	11 (26.1)
4	7 (16.6)
CAA-SVD score (n, %)	
0	5 (11.9)
1	6 (14.2)
2	13 (30.9)
3	12 (28.5)

4	6 (14.2)
5	0 (0)
6	0 (0)
Modified CAA-SVD score (n, %)	
0	1 (2.3)
1	6 (14.2)
2	8 (19.0)
3	13 (30.9)
4	11 (26.1)
5	2 (4.7)
6	1 (2.3)
7	0 (0)
8	0 (0)

Cognitive function and the three types of SVD scores

HA-SVD score

With regard to the relationship between each cognitive function and the HA-SVD score, no significant difference was found across any function (Table 4), such as MMSE (p=0.52), RCPM (p=0.47), RBMT-SPS (p=0.15), RBMT-SS (p=0.11), TMT-A (p=0.85), TMT-B (p=0.23), WF-category (p=0.10), WF-letter (p=0.17), or MCAS (p=0.23). Additionally, the linear regression models of the associations between the HA-SVD scores and cognitive function revealed that the coefficient of determination was R^2=0.409 (p=0.35), and the regression equation did not hold. The Akaike's Information Criterion (AIC) was 122.493.

Table 4. Liner regression models of associations between cognitive functions and SCD score

	unstandardized beta (SE)			*p*		
	HA-SVD score	CAA-SVD score	Modified CAA-SVD score	HA-SVD score	CAA-SVD score	Modified CAA-SVD score
MMSE	0.191	0.713	0.771	0.521	**0.006**	**0.001**
RCPM	-0.185	-0.295	-0.17	0.474	0.153	0.384
RBMT-SPS	1.057	0.732	0.622	0.159	0.209	0.267
RBMT-SS	-1.148	-1.055	-1.005	0.111	0.064	**0.048**
TMT-A	0.065	0.107	0.192	0.854	0.698	0.476
TMT-B	0.395	0.516	0.412	0.239	0.057	0.11
WF (Category)	0.426	0.414	0.448	0.104	**0.047**	**0.028**
WF (Letters)	-0.38	-0.079	-0.097	0.17	0.71	0.634
MCAS	-0.686	-0.584	-0.564	0.052	**0.036**	**0.026**

CAA-SVD score

With regard to the relationship between each cognitive function and the CAA-SVD score, a significant difference was found in 3/9 items (Table 4), including MMSE (p=0.006), WF-category (p=0.04) and MCAS (p=0.03), while there was no significant difference in 6/9 items, including RCPM (p=0.15), RBMT-SP (p=0.20), RBMT-SS (p=0.06), TMT-A (p=0.69), TMT-B (p=0.05) and WF-letter (p=0.71). The results of the linear regression models of the associations between CAA-SVD scores and cognitive function demonstrated that the coefficient of determination was R^2=0.639 (p=0.016) and the AIC was 104.269.

Modified CAA-SVD score

With regard to the relationship between each cognitive function and the modified CAA-SVD score, a significant difference was found in 4/9 items (Table 4), including MMSE (p=0.001), RBMT-SS (p=0.04), WF-category (p=0.02), and MCAS (p=0.04), while no significant difference was found in 5/9 items, including RCPM (p=0.14), RBMT-SP (p=0.33), TMT-A (p=0.19), TMT-B (p=0.21), and WF-letter (p=0.56). The results of the linear regression models of the associations between the CAA-SVD scores and cognitive function revealed that the coefficient of determination was R^2=0.645 (p=0.008) and the AIC was 103.43.

On assessing the relationship between each cognitive function and each SVD score, a significant difference was found in MMSE, WF-category, MCAS and RBMT-SS. Among these four items, the WF-category had the highest coefficient of determination for the HA-SVD score (R^2=0.0135), and the RBMT-SS had the highest coefficient of determination for the CAA-SVD (R^2=0.0142) and modified CAA-SVD scores (R^2=0.0161). In the linear regression models of the associations between each SVD score and RBMT-SS, the coefficient of determination was found to increase in the following order: HA-SVD score < CAA-SVD score < modified CAA-SVD score (Fig 2).

DISCUSSION

This study demonstrated a novel association between the CAA-SVD score and cognitive function in memory clinic patients, whereas no significant association was found between HA-SVD score and cognitive function. Additionally, there was a significant difference between the HA-SVD score and CAA-SVD score; i.e., WF-category had the highest coefficient of determination for the HA-SVD score, and the RBMT-SS had the highest coefficient of determination for the CAA-SVD and modified CAA-SVD scores. Moreover, it is plausible that the modified CAA-SVD score, in addition to the analysis of the posterior distribution of WMH and CMIs, may be a useful tool for evaluating patients with MCI or mild dementia.

Taken together, our study showed that there was a significant difference in each cognitive domain between the HA-SVD score and CAA-SVD score, and a significant association between the CAA-SVD score and cognitive function. This result indicates that the CAA-SVD score may reflect the cognitive function in patients of a memory clinic. Although a previous report showed that the HA-SVD score showed significant associations with intellectual function in patients having had a lacunar stroke and/or with hypertension,[31] our study did not show any such significant association. This may be attributed to the patients' background, such as older age and lower prevalence of vascular factors. The mean age of patients in the previous study was 63.1 years, while the mean age of patients in our study was 75.3 years. Moreover, in our study, 22 patients had hypertension (52.3%) and 14 patients had a lacunar stroke (33.3%) compared to 84.1% and 68.7%, respectively, in a previous study.

The HA-SVD score and CAA-SVD score share common components including WMH, PVS, and MBs. The HA-SVD score includes lacunar infarcts, whereas the CAA-SVD score includes cSS. Moreover, the location of PVS and MBs differs between the HA- and CAA-SVD scores. Previous reports have shown that CSO-PVS is negatively correlated with memory and that BG-PVS is negatively correlated with processing speed, executive function, and memory.[32] Additionally, the presence and number of MBs have been associated with cognitive impairment.[33] The incidence of cSS is extremely low and difficult to study in healthy individuals[34]; however, cSS is highly-specific for CAA. As described above, the CAA-SVD score was produced by adding cSS to the WMH and region-specific MBs and PVS and was more related to cognitive function than the HA-SVD score.

The modified CAA-SVD score improved the prediction accuracy of the regression equation, reduced the AIC, and slightly improved the prediction accuracy compared to the CAA-SVD score. CMIs are an important risk factor for dementia, and it has been reported that the presence of CMIs approximately doubles the risk of dementia.[34] One of the major causes of CMIs is CAA.[35] Additionally, several reports have described the relationship between WMH and cognitive function,[36] and WMH due to CAA have been reported to be posterior-dominant.[37] Therefore, it was thought that incorporation of these two markers may have affected relationship with cognitive function in an additive manner.

On observing the results for each test item, the CAA-SVD score was found to have significant associations with constructional ability and memory. This observation is in line with the diagnostic

criteria of NIA-AA, which includes constructional ability and memory as an essential cognitive domain.[38]

These results in our study may be dependent on the background of the patients in our memory clinic. In this study, 24 patients (57.1%) met the modified Boston criteria (ver 1.5), 10 of 12 patients with mild dementia had AD, and aMCI was present in 20 out of 30 MCI patients. aMCI has been reported to have a high rate of progression to AD.[39] Low prevalence of vascular risk and advanced aging in the present study may indicate that our memory clinic's patients had a higher burden of amyloid pathology. Therefore, the CAA-SVD score and modified CAA-SVD score may reflect the pathological background of AD. The CAA-SVD score may be a useful tool for memory clinic patients whereas the SVD scores may not, rather being suited for the patients with vascular risk factors. Additionally, there may be a possibility that cognitive dysfunction can be detected earlier by evaluating patients with a score that is well-tailored to them, thereby enabling appropriate subsequent patient treatment.

This study had a few limitations. First, it was based on a relatively small sample size. Second, it was unclear which SVD score would be appropriate for naMCI patients because of the large number of patients with aMCI. Finally, we were unable to carry out pathological examinations. These issues should be addressed in future studies.

Despite these limitations, our study shows that patients with MCI or mild dementia should be evaluated with the CAA-SVD score. The modified CAA-SVD score may also be applicable to these patients.

Competing Interests: The authors have no conflict of interest to declare.

Funding: No funding was received for the present study.

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Figure Legends

Figure 1. Patient enrolment process

CDR, clinical dementia rating; MRI, magnetic resonance imaging

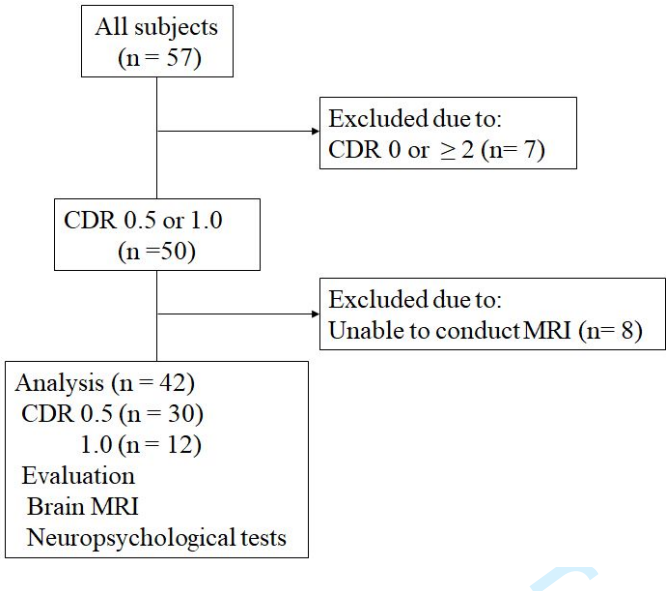


Figure 2. Linear regression models of the associations between each cerebral small vessel disease (SVD) score and the Rivermead Behavioral Memory Test-screening score (RBMT-SS)

HA, hypertensive arteriopathy; CAA, cerebral amyloid angiopathy

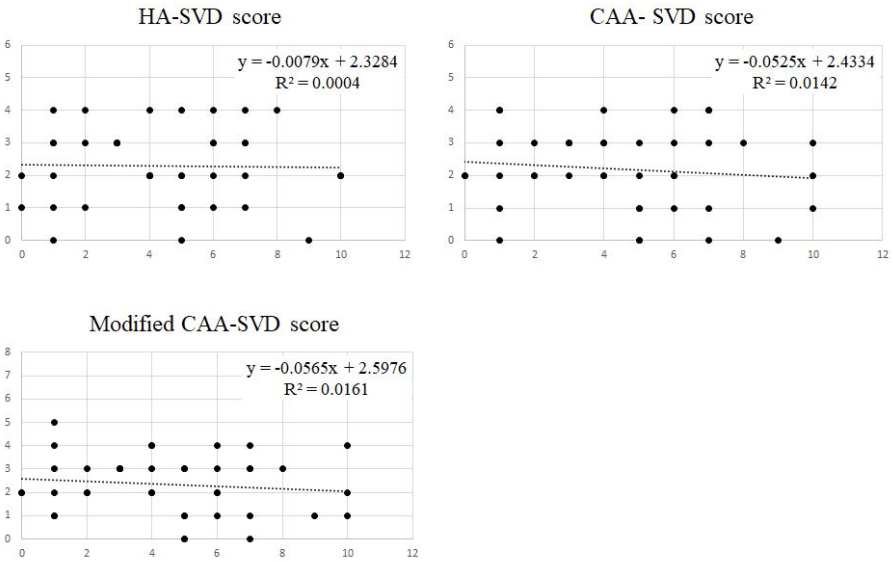


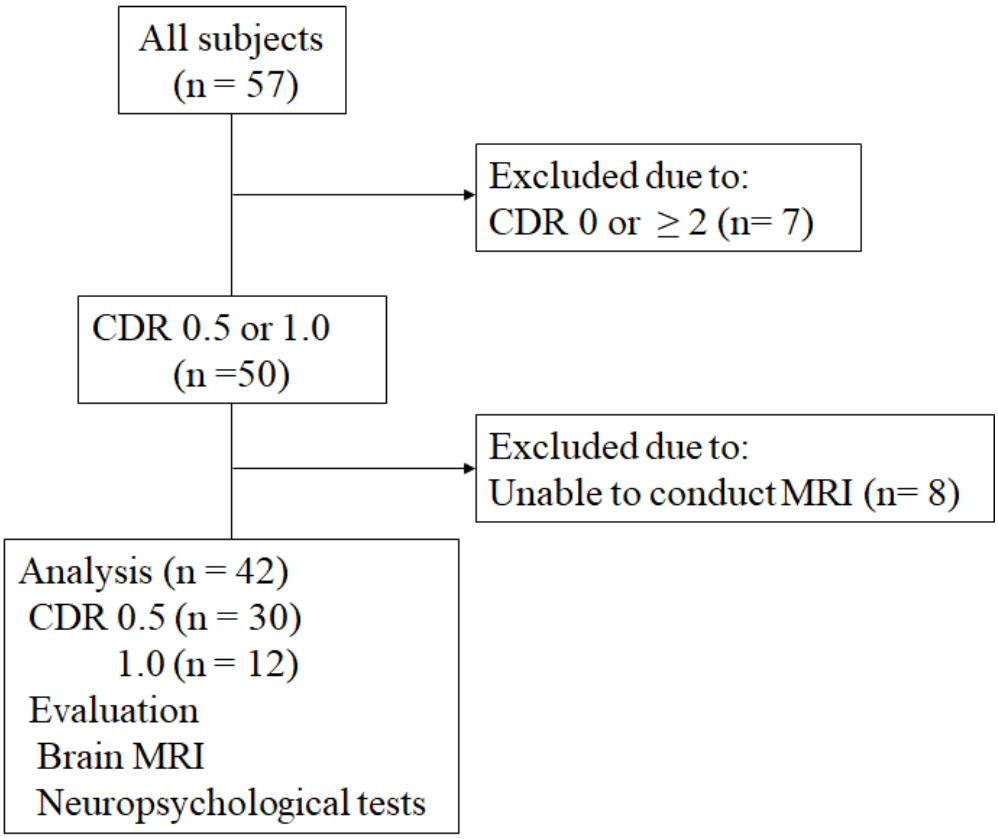
Table Legends

Table 1. Cerebral amyloid angiopathy-cerebral small vessel disease (CAA-SVD) score and modified CAA-SVD score

Table 2. Participant characteristics

Table 3. Cerebral small vessel disease score

Table 4. Liner regression models of associations between cognitive function and SVD score



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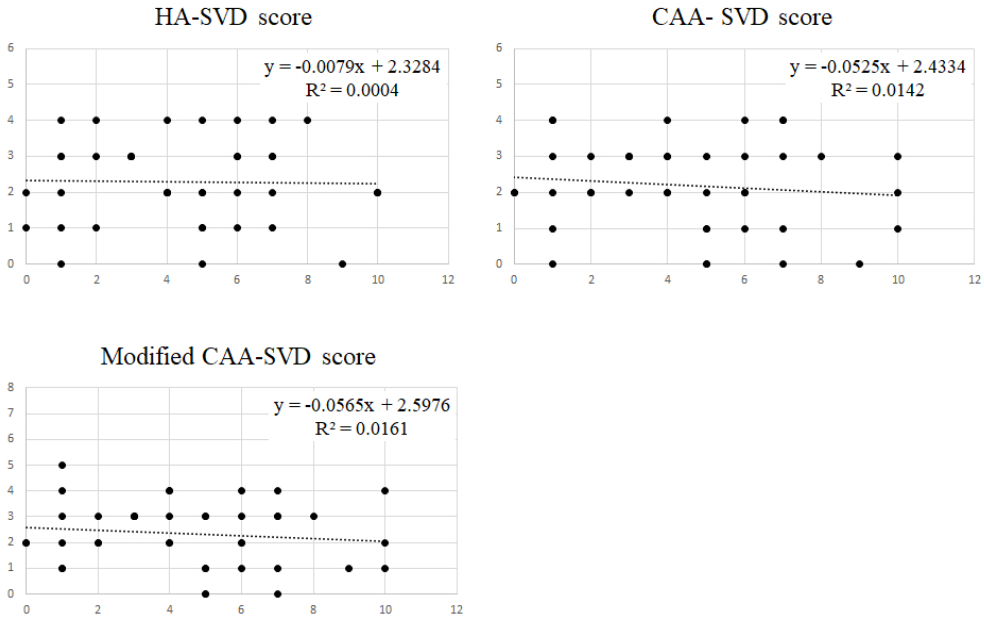

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Standards for Reporting Qualitative Research (SRQR)*

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	Page/line no(s).
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Title - Concise description of the nature and topic of the study Identifying the study as qualitative or indicating the approach (e.g., ethnography, grounded theory) or data collection methods (e.g., interview, focus group) is recommended	6-12
Abstract - Summary of key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results, and conclusions	2-3
Introduction	
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Purpose or research question - Purpose of the study and specific objectives or questions	6
Methods	
Qualitative approach and research paradigm - Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g., postpositivist, constructivist/ interpretivist) is also recommended; rationale**	6-7
Researcher characteristics and reflexivity - Researchers' characteristics that may influence the research, including personal attributes, qualifications/experience, relationship with participants, assumptions, and/or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results, and/or transferability	6-7
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Data collection instruments and technologies - Description of instruments (e.g., interview guides, questionnaires) and devices (e.g., audio recorders) used for data collection; if/how the instrument(s) changed over the course of the study	6-9
Units of study - Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results)	11
Data processing - Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymization/de-identification of excerpts	6-12
Data analysis - Process by which inferences, themes, etc., were identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale**	6-12
Techniques to enhance trustworthiness - Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale**	7-12

Results/findings

Synthesis and interpretation - Main findings (e.g., interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory	13-19
Links to empirical data - Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate analytic findings	13-19

Discussion

Integration with prior work, implications, transferability, and contribution(s) to the field - Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application/generalizability; identification of unique contribution(s) to scholarship in a discipline or field	19
Limitations - Trustworthiness and limitations of findings	22

Other

Conflicts of interest - Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed	23
Funding - Sources of funding and other support; role of funders in data collection, interpretation, and reporting	23

*The authors created the SRQR by searching the literature to identify guidelines, reporting standards, and critical appraisal criteria for qualitative research; reviewing the reference lists of retrieved sources; and contacting experts to gain feedback. The SRQR aims to improve the transparency of all aspects of qualitative research by providing clear standards for reporting qualitative research.

**The rationale should briefly discuss the justification for choosing that theory, approach, method, or technique rather than other options available, the assumptions and limitations implicit in those choices, and how those choices influence study conclusions and transferability. As appropriate, the rationale for several items might be discussed together.

Reference:

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DOI: 10.1097/ACM.0000000000000388

BMJ Open

Investigation of hypertensive arteriopathy- and cerebral amyloid angiopathy-related small vessel disease scores in patients from a memory clinic

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-042550.R1
Article Type:	Original research
Date Submitted by the Author:	10-Nov-2020
Complete List of Authors:	Matsuda, Kana; Mie University Hospital, Rehabilitation Shindo, Akihiro; Mie University Hospital, Neurology Ii, Yuichiro; Mie University Hospital, Neurology Tabei, Ken-ichi; Mie University Hospital Ueda, Yukito; Mie University Hospital Ishikawa, Hidehiro; Mie University Hospital, Neurology Matsuura, Keita; Neurology; Mie University Hospital, Yoshimaru, Kimiko Taniguchi, Akira; Mie University Hospital, Department of Neurology Kato, Natsuko; Mie University Hospital, Neurology Satoh, Masayuki; Mie University Hospital, Dementia Prevention and Therapeutics Maeda, Masayuki; Mie University Graduate School of Medicine Faculty of Medicine, Advanced Diagnostic Imaging Tomimoto , Hidekazu ; Mie University Hospital
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Radiology and imaging
Keywords:	Delirium & cognitive disorders < PSYCHIATRY, Dementia < NEUROLOGY, Hypertension < CARDIOLOGY, Magnetic resonance imaging < RADIOLOGY & IMAGING

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Investigation of hypertensive arteriopathy- and cerebral amyloid angiopathy-related small vessel disease scores in patients from a memory clinic

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Word count: 3,752 words

ABSTRACT

Objective: The severity of cerebral small vessel disease (SVD) is assessed through neuroimaging findings, including hypertensive arteriopathy (HA)-SVD and cerebral amyloid angiopathy (CAA)-SVD. HA-SVD and CAA-SVD have been collectively estimated as total scores: the HA-SVD and CAA-SVD scores, respectively. Previous reports suggest that HA-SVD scores are associated with cognitive function; however, the relationship between CAA-SVD scores and cognitive function remains unclear. Therefore, we examined the association between CAA-SVD scores and cognitive function. Furthermore, we developed a modified CAA-SVD score considering cortical microinfarcts and posterior dominant white matter hyperintensities, which are imaging findings of CAA, and examined the association between these scores and cognitive function in the same patient group.

Design: Prospective study

Setting: Single centre study from a memory clinic

Participants: Subjects were diagnosed with mild cognitive impairment (MCI) or mild dementia in our memory clinic between February 2017 and July 2019 and underwent clinical dementia rating scale and brain magnetic resonance imaging (MRI) assessment. A total of 42 patients (aged 75.3 ± 9.12 years) were registered prospectively.

Primary and secondary outcome measures: We evaluated intellectual function, memory, frontal lobe function, and constructional ability. Furthermore, the relationship between each score and cognitive function was examined.

Results: The CAA-SVD score showed significant associations with cognitive function (R^2=0.63, p=0.016), but the HA-SVD score did not (R^2=0.41, p=0.35). The modified CAA-SVD score was also significantly associated with cognitive function (R^2=0.65, p=0.008).

Conclusion: Cognitive function is associated with the CAA-SVD score, and more efficiently with the modified CAA-SVD score, in memory clinic patients. These scores can be a predictor of cognitive deterioration in patients with MCI and mild dementia.

Keywords: cognition, dementia, small vessel disease, hypertension, cerebral amyloid angiopathy

Strengths and limitations

- We examined the association between cognitive function and hypertensive arteriopathy-, and cerebral amyloid angiopathy (CAA)- small vessel disease (SVD) scores in patients from a memory clinic.
- We developed a modified CAA-SVD score considering cortical microinfarcts and posterior dominant white matter hyperintensities, which are characteristic imaging findings of CAA, and examined the association between these scores and cognitive function.
- Cognitive function was associated with the CAA-SVD score, and more efficiently with the modified CAA-SVD score.
- This study included 42 cases; therefore, the results are based on a relatively small sample size.
- - This study included relatively large number of the patients with strictly lobar microbleeds, and this might be due to selection bias from including patients from a memory clinic.

INTRODUCTION

Cerebral small vessel disease (SVD) is a comprehensive term that describes small vessel pathological conditions, including ischemia and haemorrhage, in the brain. Patients with SVD share common pathological, clinical and neuroimaging features.[1] Neuroradiological findings of SVD are examined using brain magnetic resonance imaging (MRI), which shows various vascular lesions, including white matter hyperintensities (WMH), lacunar infarcts, enlargement of perivascular spaces (PVS), microbleeds (MBs), cortical superficial siderosis (cSS), and cortical microinfarcts (CMIs).[1,2] SVD is the main cause of vascular dementia in older people, among which, SVD with dementia comprises nearly half of all patients with vascular dementia.[3] Moreover, SVD is also present in Alzheimer's disease (AD).[4]

Although aging is one of the main causes of SVD, several other diseases such as arteriosclerosis, cerebral amyloid angiopathy (CAA), genetic predispositions, and inflammation also cause SVD.[5] In particular, arteriosclerosis and CAA are the two major causes of SVD. SVD due to arteriosclerosis is particularly associated with hypertension (hypertensive arteriopathy; HA)[6]; this SVD type is also named sporadic non-amyloid microangiopathy.[7] In contrast, CAA is characterized by the progressive deposition of amyloid beta (Aβ) protein in the cerebral vessels, and the major peptide

isoforms of Aβ mainly consist of $A\beta_{1-40}$ and $A\beta_{1-42}$.[5] Although both HA and CAA share common MRI features (Fig 1), including WMH, enlargement of PVS, and MBs, the location and distribution of these radiological findings are different. The anteroposterior distribution of WMH in CAA is posterior-dominant.[8] The enlargement of PVS in the basal ganglia (BG-PVS) is associated with hypertension, and patients with CAA show centrum semiovale PVS (CSO-PVS).[9] MBs located in the basal ganglia, thalamus, or brainstem indicate HA (deep MBs) and MBs within the lobar brain compartment are associated with CAA [10]. Moreover, lacunar infarcts are associated with hypertension, whereas cSS is a representative MRI biomarker in CAA.[11] CMIs are caused by different pathological backgrounds, including CAA, arteriosclerosis and microembolism[12]; however, neuroradiological findings obtained using 3T MRI may enable distinction between CMIs related to CAA and those due to microembolisms.[13]

Recently, two types of MRI-based assessment scores have been developed for SVD. Klarenbeek et al. enrolled patients with lacunar stroke and assessed different MRI features, including lacunar infarct, MBs, BG-PVS, and WMH.[14] One point was awarded for the presence of each marker, producing a score between 0 and 4. This HA-SVD score was mainly used for the evaluation of patients with lacunar stroke and/or vascular risk factors,[15] and was associated with intellectual function.[16] Charidimou et al.

developed a novel SVD score for patients with CAA (CAA-SVD score),[17] which was associated with clinical symptoms of transient focal neurological episodes.[18] However, the relationship between CAA-SVD scores and cognitive function remains unclear.

In this study, we investigated the relationship between the two types of SVD scores and cognitive function in patients who visited our memory clinic. Moreover, we added other radiological biomarkers of CAA to the CAA-SVD score and investigated its usefulness in evaluating cognitive function in patients with mild cognitive impairment (MCI) and mild dementia.

PATIENTS AND METHODS

Patients

We prospectively registered patients who consulted our hospital's memory clinic. Of the 50 subjects, 42 fulfilled the inclusion criteria. All procedures followed the Clinical Study Guidelines of the Ethics Committee of Mie University Hospital and were approved by the internal review board (Registration number: 1596). A complete description of all procedures was provided to patients, and written informed consent was obtained directly from them or from their caregivers. All patients were comprehensively examined by a neurologist with sufficient experience in examining patients with dementia. The CDR and

MRI was performed after obtaining written informed consent. We collected data from patients who fulfilled the following inclusion criteria: 1) consulted with our hospital's memory clinic between February 2017 and July 2019, 2) underwent neuroimaging examinations using 3T MRI, 3) completed neuropsychological assessments, and 4) had a global Clinical Dementia Rating (CDR) score of 0.5 or 1.0. Neuropsychological tests and CDR were performed within 3 months of MRI. No neurological events occurred between these tests and MRI.

We diagnosed MCI according to the National Institute on Aging–Alzheimer's Association (NIA-AA) criteria for MCI patients. [19] MCI was classified into MCI due to AD or other types of MCI. The global CDR score was 0.5. We diagnosed AD according to the NIA-AA guidelines.[20] Vascular dementia was diagnosed according to the criteria set forth by the American Heart Association/American Stroke Association.[21]

Neuropsychological assessments

The Mini-Mental State Examination (MMSE)[22] and Japanese Raven's Coloured Progressive Matrices (RCPM)[23] were used to quantify intellectual function. Memory was evaluated using the Rivermead Behavioral Memory Test (RBMT). The scores included a standard profile score (SPS) and screening score (SS).[24] Constructional

ability was assessed using the Mie Constructional Apraxia Scale (MCAS).[25] Frontal lobe function was assessed using two tasks: word fluency (WF) and trail making test (TMT) -A/-B.[26] The WF test consisted of category and letter domains. In the category WF task (WF-category), participants were asked to name as many animals as possible in 1 minute. In the letter WF task (WF-letter), participants were asked to name as many objects as possible in 1 minute, beginning with each of the following four phonemes: *ka, sa, ta,* and *te*. The average scores for these four phonemes were used for statistical analyses.

CDR was performed by two speech therapists, and results were evaluated through a discussion between two neurologists and three speech therapists based on the CDR determination rules.[27]

MRI protocol

We follow the MRI protocol by Ii et al.[28] Briefly, MRI studies were performed with a 3T MRI unit (Achieva, Philips Medical System, Best, the Netherlands) using an 8- or 32-channel phased-array head coil. We used T1- and T2-weighted images and 3D-fluid attenuated inversion recovery (FLAIR) images for the evaluation of WMH, lacunar infarcts, and PVS. Susceptibility-weighted image (SWI) sequences were used for the

detection of MBs and cSS. 3D-double inversion recovery (DIR) and 3D-FLAIR was used for the detection of CMIs. Axial DIR imaging was performed using two different inversion pulses. The long inversion time and the short inversion time were defined as the intervals between the 180° inversion pulse and the 90° excitation pulse, respectively, which had been optimized for human brain imaging and were provided by the vendor.

Details of the 2D- and 3D-DIR protocols were as follows: field of view, 230 mm; matrix, 320 × 256 (512 × 512) after reconstruction; in-plane resolution, 0.45 mm × 0.45 mm; section thickness, 3 mm with no intersection gap; no parallel imaging; repetition time (ms)/echo time (ms), 15,000/28; long inversion time (ms)/short inversion time (ms), 3,400/325; number of signals acquired, two; and acquisition time, 4 min 30 s for 2D, and field of view, 250 mm; matrix, 208 × 163 (256 × 256) after reconstruction; in plane resolution, 0.98 mm × 0.98 mm; section thickness, 0.65 mm with over contiguous slice; TSE factor 173; repetition time (ms)/echo time (ms), 5,500/247; long inversion time (ms)/short inversion time (ms), 2,550/450; number of signals acquired, two; and acquisition time, 5 min 13 s for 3D.

The SWI details were as follows: field of view, 230 mm; matrix, 320 × 251 (512 × 512) after reconstruction; in-plane resolution, 0.45 mm × 0.45 mm; section thickness, 0.5 mm with over contiguous slice; repetition time (ms)/echo time (ms), 22/11.5 (in-phase), 33

(shifted); number of signals acquired, one; flip angle 20°; and acquisition time, 5 min 45 s. 3D-FLAIR imaging was obtained in a sagittal direction, and then the axial and coronal images were reconstructed. The 3D-FLAIR details were as follows: field of view, 260 mm; matrix, 288 × 288 (364 × 364) after reconstruction; in-plane resolution, 0.68 × 0.67 mm; section thickness, 1 mm with 0.5 mm overlap; no parallel imaging; repetition time (ms)/echo time (ms), 6,000/400; inversion time, 2,000 ms; number of signals acquired, two; and acquisition time, 5 min 12 s.

SVD scores

The HA-SVD score was determined by Klarenbeek et al., where 1 point was awarded for each of the four markers (lacunar infarcts, MBs, BG-PVS, and WMH), with a minimum score of 0 and a maximum score of 4.[14] The CAA-SVD score was proposed by Charidimou et al. (Table 1), with 1 point awarded for each of the four markers (lobar MBs, cSS, CSO-PVS, and WMH).[17] For lobar MBs, 1 point was awarded if two to four MBs were present and 2 points for five or more MBs. The presence of cSS was awarded with 1 point if focal and 2 points if disseminated. The presence of CSO-PVSs was confirmed if there were moderate to severe (> 20) PVSs (1 point if present), with a

minimum score of 0 and a maximum score of 6. Both scores were independently assessed by four raters.

Table 1. Cerebral amyloid angiopathy-cerebral small vessel disease (CAA-SVD) score and modified CAA-SVD score

MRI marker	Cut off	Points		
CAA-SVD score				
Lobar MBs	2 to 4	1		
	≥ 5	2		
cSS	Focal	1		
	Disseminated	2		
CSO-PVSs	>20	1		
WMH	deep WMH (Fazekas 2 or 3)	1		
	periventricular WMH (Fazekas 3)	1	total	/6
Modified CAA-SVD score				
posterior distribution of WMH		1		
CMI(s) due to CAA	≥1	1	total	/8

Modified CAA-SVD scores

We tried to modify CAA-SVD scores by adding one point each in the presence of posteriorly dominant WMH and CMIs related to CAA (Table 1).

Tissue quantification was performed using a novel in-house software (FUsed Software for Imaging Of Nervous system: FUSION)[29] that yielded an individualized volumetric brain tissue profile. The obtained T1-weighted and FLAIR images were imported from

the Digital Imaging and Communications in Medicine format files for processing. To increase the accuracy of segmentation, we used the Lesion Segmentation Tool for lesion filling.[30] Lesion filling was applied to T1-weighted images that were aligned with the lesion probability map. For pre-processing, the T1-weighted images were co-registered to the FLAIR images. Next, to separate out the white matter, segmentation was performed using the T1-weighted images and a mask covering the cerebral ventricles. The pre-processing function was based on SPM 8 (Wellcome Trust Centre for Neuroimaging, UCL). Second-level tissue segmentation was then performed to separate WMH from white matter using a semi-automated operation that extracted the pixels falling within a predetermined WMH value. The WMH volume, which appeared as hyperintense areas on FLAIR images, was quantified for each area. Brain tissue was classified into four areas based on the division of the longitudinal fissure of the cerebrum and central sulcus. WMH were automatically classified as periventricular hyperintensity or deep WMH, and their corrected volumes were quantified in cubic centimetres.[29] The anteroposterior centre of WMH was calculated in the following way. To determine the reference point, we identified two anatomical landmarks (anterior, A and posterior, P). Point A was defined as the most anterior part on the wall of the frontal horn of the lateral ventricle. Point P

was defined as the most posterior part of the dura mater covering the occipital cortex.[8] If there was a large amount of posterior WMH, 1 point was added to the CAA-SVD score.

CMIs were defined as small cortical hyperintense lesions non-adjacent to WMH. When CMIs were localized within the cortex, predominantly in the occipital lobe, were smaller than 5 mm in diameter, and had fewer than three lesions, they were defined as CMIs related to CAA.[13] When there were any CMIs related to CAA, we added 1 point to the CAA-SVD score.

Statistical analyses

The association between each SVD score (dependent variable) and cognitive function (independent variable) was analysed using linear regression analysis. Clinical and radiological characteristics are presented as numbers with percentages and means with standard deviation (SD). Statistical analyses were performed using IBM SPSS statistics software version 20 (IBM Corp., Armonk, NY, United States). Differences with $p<0.05$ were considered statistically significant.

Patient and public involvement

Patients and public were not involved in setting the research questions, outcomes measures nor the design of the study.

RESULTS

Patients

In total, 50 patients were registered for this study, and 42 fulfilled the inclusion criteria. Clinical characteristics, neuropsychological test results, and MRI findings of the participants are shown in Table 2. The mean age was 75.3±9.12 years, and there were 23 men (54.7%). Regarding vascular risk factors, 22 patients had hypertension (52.3%), four had diabetes mellitus (9.5%), and 11 smoked and had dyslipidaemia (26.1%). Fourteen patients had a history of lacunar stroke (33.3%) and 24 patients (57.1%) met the modified Boston criteria (ver 1.5).

Table 2. Participant characteristics

Clinical characteristics	All participants, n= 42
Age, years, mean (SD)	75.3 (9.12)
Education, years, mean (SD)	11.9 (2.34)
Male sex (n, %)	23 (54.7)
Vascular risk factors	
hypertension (n, %)	22 (52.3)
dyslipidemia (n, %)	11 (26.1)
diabetes mellitus (n, %)	4 (9.5)

	smoking (n, %)	11 (26.1)
History of any stroke (n, %)		19 (45.2)
	lacunar (n, %)	14 (33.3)
Medication		
	anti-hypertensive (n, %)	7 (16.6)
	statin (n, %)	6 (14.2)
	anti-platelet or anti-coagulation (n, %)	8 (19.0)
Meets modified Boston criteria		
	probable CAA	11 (26.1)
	possible CAA	13 (30.9)
Neuropsychological tests		
Global CDR	0.5 (n, %)	30 (71.4)
	1.0 (n, %)	12 (28.6)
MMSE	Score (SD)	25.2 (2.39)
RCPM	Score (SD)	24.2 (5.73)
	Time, s (SD)	440 (198)
RBMT	Standard profile score (SD)	11.5 (5.49)
	Screening score (SD)	4.5 (2.78)
TMT	A, s (SD)	257 (156)
	B, s (SD)	265 (95.6)
WF, /min	Category (SD)	10.9 (3.93)
	Letters (SD)	5 (1.72)
MCAS	Score (SD)	3.3 (1.68)
	Time, s (SD)	49.6 (37.4)
MRI findings		
MBs; all	≥ 1 (n, %)	31 (73.8)
MBs; Lobar	2 to 4 (n, %)	16 (38.0)
	≥ 5 (n, %)	10 (23.8)
cSS	Focal (n, %)	3 (7.1)
	Disseminated (n, %)	0
BG-PVSs	>20 (n, %)	25 (59.5)

CSO-PVSs	>20 (n, %)	30 (71.4)
WMH	deep WMH (Fazekas 2 or 3) (n, %)	26 (61.9)
	periventricular WMH (Fazekas 3) (n, %)	11 (26.1)
posterior distribution of WMH (n, %)		7 (16.6)
CMI(s) related to CAA (n, %)		3 (7.1)

The global CDR score was 0.5 for 30 patients (71.4%) and 1.0 for 12 patients (28.6%). Of the 12 patients with a global CDR score of 1.0, 10 met the criteria reflecting probable AD and two had vascular dementia. Among 30 patients with MCI, 20 had MCI due to AD and 10 had other types of MCI. Regarding MRI findings, 31 patients had ≥1 MBs (73.8%), 16 had ≥2 and ≤4 lobar MBs (38.0%), and 10 had ≥5 lobar MBs (23.8%). Three patients had focal cSS (7.1%), 25 had >20 BG-PVSs (59.5%), 30 had >20 CSO-PVSs (71.4%), 26 had deep WMH (Fazekas 2 or 3) (61.9%), and 11 had periventricular WMH (Fazekas 3) (26.1%).

WMH were divided according to whether they were anterior or posterior and were analysed using FUSION. There were seven posterior superiorities (16.6%). CMIs related to CAA were detected in three patients (7.1%), and two of these patients met the modified Boston criteria for probable CAA. The patients with CMI related to CAA did not have any evidence of CMI related to microembolism, such as atrial fibrillation and cerebral artery stenosis.

Results of each SVD score

As for each SVD score (Table 3), the HA-SVD score was 0 in 3 patients (7.1%), 1 in 7 patients (16.6%), 2 in 14 patients (33.3%), 3 in 11 patients (26.1%), and 4 in 7 patients (16.6%). The CAA-SVD score was 0 in 5 patients (11.9%), 1 in 6 patients (14.2%), 2 in 13 patients (30.9%), 3 in 12 patients (28.5%), and 4 in 6 patients (14.2%). Moreover, the modified CAA-SVD score was 0 in 1 patient (2.3%), 1 in 6 patients (14.2%), 2 in 8 patients (19%), 3 in 13 patients (30.9%), 4 in 11 patients (26.1%), 5 in 2 patients (4.7%), and 6 in 1 patient (2.3%). A significant difference was observed when the HA-SVD scores and CAA-SVD scores were analysed using Pearson's chi-square test (p=0.000).

Table 3. Cerebral small vessel disease score

Score	All participants n = 42
HA-SVD score (n, %)	
0	3 (7.1)
1	7 (16.6)
2	14 (33.3)
3	11 (26.1)
4	7 (16.6)
CAA-SVD score (n, %)	

0	5 (11.9)
1	6 (14.2)
2	13 (30.9)
3	12 (28.5)
4	6 (14.2)
5	0 (0)
6	0 (0)
Modified CAA-SVD score (n, %)	
0	1 (2.3)
1	6 (14.2)
2	8 (19.0)
3	13 (30.9)
4	11 (26.1)
5	2 (4.7)
6	1 (2.3)
7	0 (0)
8	0 (0)

Cognitive function and the three types of SVD scores

HA-SVD score

With regard to the relationship between each cognitive function and the HA-SVD score, no significant difference was found across any function (Table 4), such as MMSE (p=0.52), RCPM (p=0.47), RBMT-SPS (p=0.15), RBMT-SS (p=0.11), TMT-A (p=0.85), TMT-B (p=0.23), WF-category (p=0.10), WF-letter (p=0.17), or MCAS (p=0.23).

Additionally, the linear regression models of the associations between the HA-SVD scores and cognitive function revealed that the coefficient of determination was R^2=0.409 (p=0.35), and the regression equation did not hold. The Akaike's Information Criterion (AIC) was 122.493.

Table 4. Linear regression models of associations between cognitive function and SVD score

	unstandardized beta (SE)			*p*		
	HA-SVD score	CAA-SVD score	Modified CAA-SVD score	HA-SVD score	CAA-SVD score	Modified CAA-SVD score
MMSE	0.191	0.713	0.771	0.521	**0.006**	**0.001**
RCPM	-0.185	-0.295	-0.17	0.474	0.153	0.384
RBMT-SPS	1.057	0.732	0.622	0.159	0.209	0.267
RBMT-SS	-1.148	-1.055	-1.005	0.111	0.064	**0.048**
TMT-A	0.065	0.107	0.192	0.854	0.698	0.476
TMT-B	0.395	0.516	0.412	0.239	0.057	0.11
WF (Category)	0.426	0.414	0.448	0.104	**0.047**	**0.028**
WF (Letters)	-0.38	-0.079	-0.097	0.17	0.71	0.634
MCAS	-0.686	-0.584	-0.564	0.052	**0.036**	**0.026**

CAA-SVD score

With regard to the relationship between each cognitive function and the CAA-SVD score, a significant difference was found in 3/9 items (Table 4), including MMSE (p=0.006), WF-category (p=0.04), and MCAS (p=0.03), while there was no significant difference in 6/9 items, including RCPM (p=0.15), RBMT-SP (p=0.20), RBMT-SS (p=0.06), TMT-A (p=0.69), TMT-B (p=0.05), and WF-letter (p=0.71). The results of the linear regression models of the associations between CAA-SVD scores and cognitive function demonstrated that the coefficient of determination was R^2=0.639 (p=0.016) and the AIC was 104.269.

Modified CAA-SVD score

With regard to the relationship between each cognitive function and the modified CAA-SVD score, a significant difference was found in 4/9 items (Table 4), including MMSE (p=0.001), RBMT-SS (p=0.04), WF-category (p=0.02), and MCAS (p=0.04), while no significant difference was found in 5/9 items, including RCPM (p=0.14), RBMT-SP (p=0.33), TMT-A (p=0.19), TMT-B (p=0.21), and WF-letter (p=0.56). The results of the linear regression models of the associations between the CAA-SVD scores and cognitive

function revealed that the coefficient of determination was R^2=0.645 (p=0.008) and the AIC was 103.43.

On assessing the relationship between each cognitive function and each SVD score, a significant difference was found in MMSE, WF-category, MCAS, and RBMT-SS. Among these four items, the WF-category had the highest coefficient of determination for the HA-SVD score (R^2=0.0135), and the RBMT-SS had the highest coefficient of determination for the CAA-SVD (R^2=0.0142) and modified CAA-SVD scores (R^2=0.0161). In the linear regression models of the associations between each SVD score and RBMT-SS, the coefficient of determination was found to increase in the following order: HA-SVD score < CAA-SVD score < modified CAA-SVD score (Fig 2).

DISCUSSION

This study demonstrated a novel association between the CAA-SVD score and cognitive function in memory clinic patients, whereas no significant association was found between the HA-SVD score and cognitive function. Additionally, there was a significant difference between the HA-SVD score and CAA-SVD score; i.e., WF-category had the highest coefficient of determination for the HA-SVD score, and the RBMT-SS had the

highest coefficient of determination for the CAA-SVD and modified CAA-SVD scores. Moreover, it is plausible that the modified CAA-SVD score, in addition to the analysis of the posterior distribution of WMH and CMIs, may be a useful tool for evaluating patients with MCI or mild dementia.

Taken together, our study showed that there was a significant difference in each cognitive domain between the HA-SVD score and CAA-SVD score, and a significant association between the CAA-SVD score and cognitive function. This result indicates that the CAA-SVD score may reflect the cognitive function in patients of a memory clinic. Although a previous report showed that the HA-SVD score showed significant associations with intellectual function in patients having had a lacunar stroke and/or with hypertension,[16] our study did not show any such significant association. This may be attributed to the patients' background, such as older age and lower prevalence of vascular factors. The mean age of patients in the previous study was 63.1 years, while the mean age of patients in our study was 75.3 years. Moreover, in our study, 22 patients had hypertension (52.3%) and 14 patients had a lacunar stroke (33.3%) compared to 84.1% and 68.7%, respectively, in a previous study.

The HA-SVD score and CAA-SVD score share common components including WMH, PVS, and MBs. The HA-SVD score includes lacunar infarcts, whereas the CAA-SVD

score includes cSS. Moreover, the location of PVS and MBs differ between the HA- and CAA-SVD scores. Previous reports have shown that CSO-PVS is negatively correlated with memory and that BG-PVS is negatively correlated with processing speed, executive function, and memory.[16] Additionally, the presence and number of MBs have been associated with cognitive impairment.[31] The incidence of cSS is extremely low and difficult to study in healthy individuals[32]; however, cSS is highly-specific for CAA. As described above, the CAA-SVD score was produced by adding cSS to the WMH and region-specific MBs and PVS and was more related to cognitive function than the HA-SVD score.

The modified CAA-SVD score improved the prediction accuracy of the regression equation, reduced the AIC, and slightly improved the prediction accuracy compared to the CAA-SVD score. CMIs are an important risk factor for dementia, and it has been reported that the presence of CMIs approximately doubles the risk of dementia.[32] One of the major causes of CMIs is CAA.[33] Additionally, several reports have described the relationship between WMH and cognitive function,[34] and WMH due to CAA have been reported to be posterior-dominant.[35] Therefore, it was thought that incorporation of these two markers may have affected relationship with cognitive function in an additive manner.

On observing the results for each test item, the CAA-SVD score was found to have significant associations with constructional ability and memory. This observation is in line with the diagnostic criteria of NIA-AA, which includes constructional ability and memory as an essential cognitive domain.[36]

These results in our study may be dependent on the background of the patients in our memory clinic. In this study, 24 patients (57.1%) met the modified Boston criteria (ver 1.5), 10 of 12 patients with mild dementia had AD, and MCI due to AD was present in 20 out of 30 MCI patients. MCI due to AD has been reported to have a high rate of progression to AD.[37] Low prevalence of vascular risk and advanced aging in the present study may indicate that our memory clinic's patients had a higher burden of amyloid pathology. Therefore, the CAA-SVD score and modified CAA-SVD score may reflect the pathological background of AD. The CAA-SVD score may be a useful tool for memory clinic patients whereas the SVD scores may not, rather being suited for the patients with vascular risk factors. Additionally, there may be a possibility that cognitive dysfunction can be detected earlier by evaluating patients with a score that is well-tailored to them, thereby enabling appropriate subsequent patient treatment.

This study had several limitations. First, it was based on a relatively small sample size. Second, deep MBs is common in Japan [38], but the patients included in this study mostly

had strictly lobar MBs, and we believe that there was selection bias due to recruiting patients from a memory clinic. Third, we were unable to carry out pathological examinations. These issues should be addressed in future studies. Forth, currently, FUSION has its limits and cannot distinguish WML and small infarcts. At present, the radiologist visually confirmed that the total volume of lacunar infarction is limited onT1WI and therefore, the result of FUSION on FLAIR images will not be affected significantly. As for enlarged PVS, FUSION on FLAIR images is not affected by enlarged PVS significantly because it does not show hyperintensity. We aim to improve the software so that it can distinguish small infarcts and enlarged PVS in the future. Finally, there was no significant association between the HA-SVD score and cognitive function in this study, possibly due to the limited number of patients with hypertension included in this study. Therefore, as the number of cases increase, there may be a significant correlation.

Despite these limitations, our study shows that patients with MCI or mild dementia should be evaluated with the CAA-SVD score. The modified CAA-SVD score may also be applicable to these patients.

Author Contributions

KM: draft of manuscript, acquisition of data, and analysis.

AS: revision of manuscript, interpretation of data, and study supervision.
KIT and YI: revision of manuscript and interpretation of data.
YU, HI, KM, KY, AT, NK, MS, MM: acquisition of data and interpretation of data.
HT: revision of the manuscript, study concept and design, and study supervision.

Data availability statement: No additional data available

Competing Interests: The authors have no conflict of interest to declare.

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

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Figure Legends

Figure 1. Representative MRI findings of cerebral small vessel disease

The arrow shows lobar cerebral MBs on SWI sequences. MRI in a patient with CAA (A). cSS was observed in SWI sequences in CAA patients (arrows, B). Centrum semiovale enlarged perivascular spaces on T2-weighted imaging in a patient with CAA (C). WMH assessed by fluid attenuated inversion recovery imaging. WMH in CAA patients was posterior-dominant (D). Double inversion recovery imaging could clearly detect the CMIs. CMIs from patients with CAAs (E) showed that all lesions were localized within cortical structures, with a size of <5 mm [13].

MRI, magnetic resonance imaging; MBs, cerebral amyloid angiopathy; SWI, susceptibility-weighted image; CAA, cerebral amyloid angiopathy; WMH, white matter hyperintensities; CMI, cortical microinfarcts

Figure 2. Linear regression models of the associations between each cerebral small vessel disease (SVD) score and the Rivermead Behavioral Memory Test-screening score (RBMT-SS)

HA, hypertensive arteriopathy; CAA, cerebral amyloid angiopathy

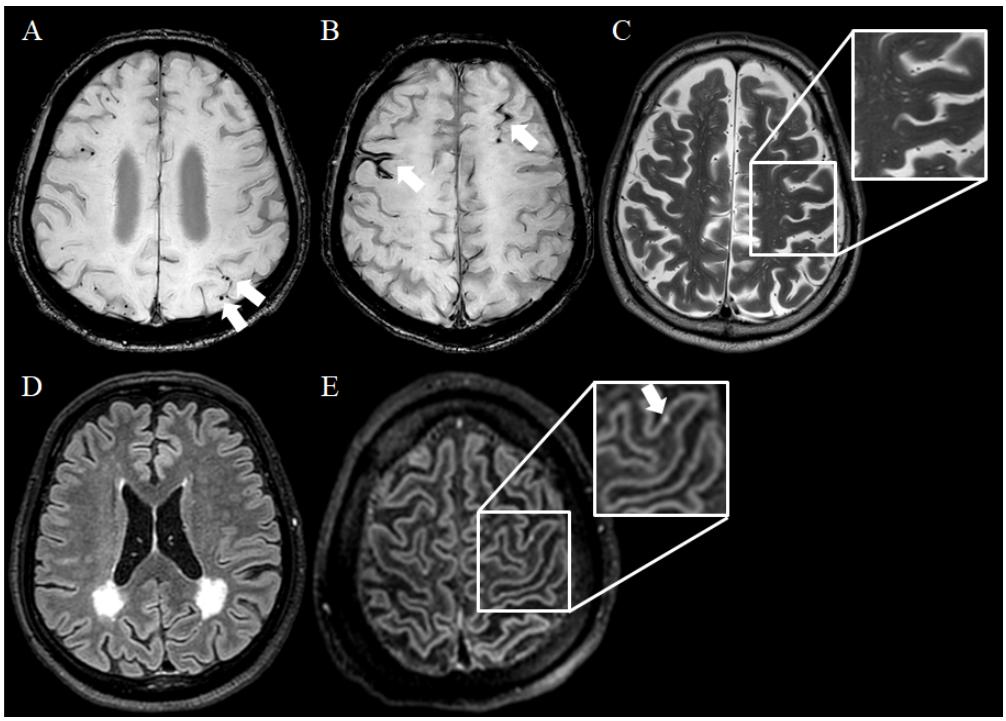
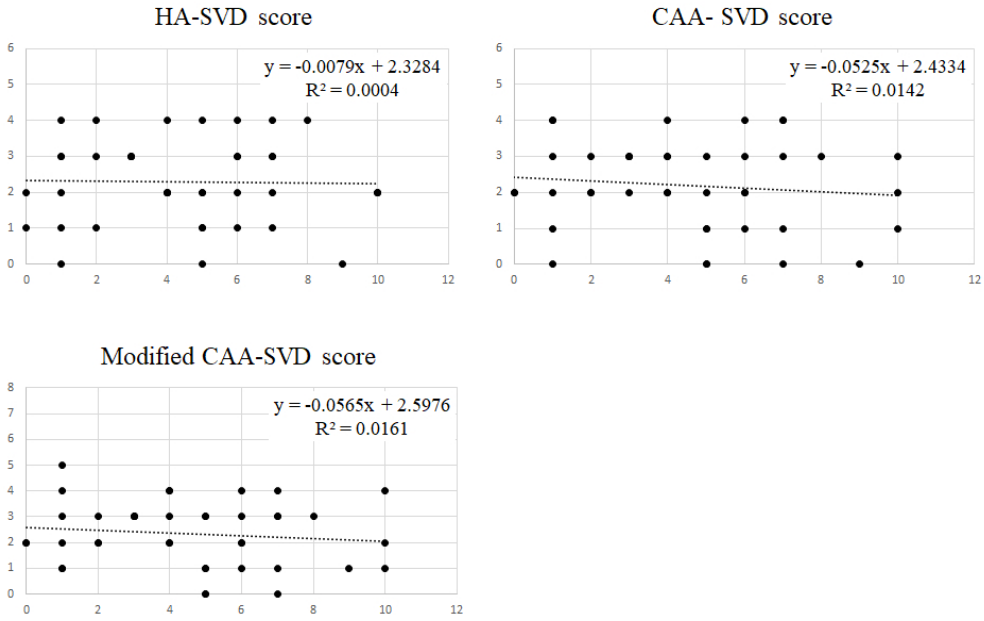


Figure 1

240x171mm (96 x 96 DPI)



165x106mm (144 x 144 DPI)

Standards for Reporting Qualitative Research (SRQR)*

http://www.equator-network.org/reporting-guidelines/srqr/

	Page/line no(s).
Title and abstract	
Title - Concise description of the nature and topic of the study Identifying the study as qualitative or indicating the approach (e.g., ethnography, grounded theory) or data collection methods (e.g., interview, focus group) is recommended	6-12
Abstract - Summary of key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results, and conclusions	2-3
Introduction	
Problem formulation - Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work; problem statement	5-6
Purpose or research question - Purpose of the study and specific objectives or questions	6
Methods	
Qualitative approach and research paradigm - Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g., postpositivist, constructivist/ interpretivist) is also recommended; rationale**	6-7
Researcher characteristics and reflexivity - Researchers' characteristics that may influence the research, including personal attributes, qualifications/experience, relationship with participants, assumptions, and/or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results, and/or transferability	6-7
Context - Setting/site and salient contextual factors; rationale**	4-6
Sampling strategy - How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g., sampling saturation); rationale**	6-7
Ethical issues pertaining to human subjects - Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues	6
Data collection methods - Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources/methods, and modification of procedures in response to evolving study findings; rationale**	6-7

Data collection instruments and technologies - Description of instruments (e.g., interview guides, questionnaires) and devices (e.g., audio recorders) used for data collection; if/how the instrument(s) changed over the course of the study	6-9
Units of study - Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results)	11
Data processing - Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymization/de-identification of excerpts	6-12
Data analysis - Process by which inferences, themes, etc., were identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale**	6-12
Techniques to enhance trustworthiness - Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale**	7-12

Results/findings

Synthesis and interpretation - Main findings (e.g., interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory	13-19
Links to empirical data - Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate analytic findings	13-19

Discussion

Integration with prior work, implications, transferability, and contribution(s) to the field - Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application/generalizability; identification of unique contribution(s) to scholarship in a discipline or field	19
Limitations - Trustworthiness and limitations of findings	22

Other

Conflicts of interest - Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed	23
Funding - Sources of funding and other support; role of funders in data collection, interpretation, and reporting	23

*The authors created the SRQR by searching the literature to identify guidelines, reporting standards, and critical appraisal criteria for qualitative research; reviewing the reference lists of retrieved sources; and contacting experts to gain feedback. The SRQR aims to improve the transparency of all aspects of qualitative research by providing clear standards for reporting qualitative research.

**The rationale should briefly discuss the justification for choosing that theory, approach, method, or technique rather than other options available, the assumptions and limitations implicit in those choices, and how those choices influence study conclusions and transferability. As appropriate, the rationale for several items might be discussed together.

Reference:

O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. **Standards for reporting qualitative research: a synthesis of recommendations.** *Academic Medicine*, Vol. 89, No. 9 / Sept 2014
DOI: 10.1097/ACM.0000000000000388

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *case-control studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	#1, #3-4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	#3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	#6-8
Objectives	3	State specific objectives, including any prespecified hypotheses	#8
Methods			
Study design	4	Present key elements of study design early in the paper	#8-12
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	#8-9
Participants	6	(a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	#8-9
		(*b*) For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	#8-12
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	#12-15
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	#8-9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	#15
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	#15
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how matching of cases and controls was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	#16
		(b) Give reasons for non-participation at each stage	#16
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	#16-18
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	#23-24
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	#26-27
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	#24-26
Generalisability	21	Discuss the generalisability (external validity) of the study results	#27
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	#27

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Investigation of hypertensive arteriopathy- and cerebral amyloid angiopathy-related small vessel disease scores in patients from a memory clinic: a prospective single-centre case series study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-042550.R2
Article Type:	Original research
Date Submitted by the Author:	22-Dec-2020
Complete List of Authors:	Matsuda, Kana; Mie University Hospital, Rehabilitation Shindo, Akihiro; Mie University Hospital, Neurology Ii, Yuichiro; Mie University Hospital, Neurology Tabei, Ken-ichi; Mie University Hospital Ueda, Yukito; Mie University Hospital Ishikawa, Hidehiro; Mie University Hospital, Neurology Matsuura, Keita; Neurology; Mie University Hospital, Yoshimaru, Kimiko Taniguchi, Akira; Mie University Hospital, Department of Neurology Kato, Natsuko; Mie University Hospital, Neurology Satoh, Masayuki; Mie University Hospital, Dementia Prevention and Therapeutics Maeda, Masayuki; Mie University Graduate School of Medicine Faculty of Medicine, Advanced Diagnostic Imaging Tomimoto , Hidekazu ; Mie University Hospital
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Radiology and imaging
Keywords:	Delirium & cognitive disorders < PSYCHIATRY, Dementia < NEUROLOGY, Hypertension < CARDIOLOGY, Magnetic resonance imaging < RADIOLOGY & IMAGING

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Investigation of hypertensive arteriopathy- and cerebral amyloid angiopathy-related small vessel disease scores in patients from a memory clinic: a prospective single-centre case series study

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Word count: 4,049words

ABSTRACT

Objective: The severity of cerebral small vessel disease (SVD) is assessed through neuroimaging findings, including hypertensive arteriopathy (HA)-SVD and cerebral amyloid angiopathy (CAA)-SVD. HA-SVD and CAA-SVD have been collectively estimated as total scores: the HA-SVD and CAA-SVD scores, respectively. Previous reports suggest that HA-SVD scores are associated with cognitive function; however, the relationship between CAA-SVD scores and cognitive function remains unclear. Therefore, we examined the association between CAA-SVD scores and cognitive function. Furthermore, we developed a modified CAA-SVD score considering cortical microinfarcts and posterior dominant white matter hyperintensities, which are imaging findings of CAA, and examined the association between these scores and cognitive function in the same patient group.

Design: Prospective study

Setting: Single centre study from a memory clinic

Participants: Subjects were diagnosed with mild cognitive impairment (MCI) or mild dementia in our memory clinic between February 2017 and July 2019 and underwent clinical dementia rating scale and brain magnetic resonance imaging (MRI) assessment. A total of 42 patients (aged 75.3 ± 9.12 years) were registered prospectively.

Primary and secondary outcome measures: We evaluated intellectual function, memory, frontal lobe function, and constructional ability. Furthermore, the relationship between each score and cognitive function was examined.

Results: The CAA-SVD score showed significant associations with cognitive function (R^2=0.63, p=0.016), but the HA-SVD score did not (R^2=0.41, p=0.35). The modified CAA-SVD score was also significantly associated with cognitive function (R^2=0.65, p=0.008).

Conclusion: Cognitive function is associated with the CAA-SVD score, and more efficiently with the modified CAA-SVD score, in memory clinic patients. These scores can be a predictor of cognitive deterioration in patients with MCI and mild dementia.

Keywords: cognition, dementia, small vessel disease, hypertension, cerebral amyloid angiopathy

Strengths and limitations

- We examined the association between cognitive function and hypertensive arteriopathy-, and cerebral amyloid angiopathy (CAA)- small vessel disease (SVD) scores in patients from a memory clinic.
- We developed a modified CAA-SVD score considering cortical microinfarcts and posterior dominant white matter hyperintensities, which are characteristic imaging findings of CAA, and examined the association between these scores and cognitive function.
- Cognitive function was associated with the CAA-SVD score, and more efficiently with the modified CAA-SVD score.
- This study included 42 cases; therefore, the results are based on a relatively small sample size.
- - This study included relatively large number of the patients with strictly lobar microbleeds, and this might be due to selection bias from including patients from a memory clinic.

INTRODUCTION

Cerebral small vessel disease (SVD) is a comprehensive term that describes small vessel pathological conditions, including ischemia and haemorrhage, in the brain. Patients with SVD share common pathological, clinical and neuroimaging features.[1] Neuroradiological findings of SVD are examined using brain magnetic resonance imaging (MRI), which shows various vascular lesions, including white matter hyperintensities (WMH), lacunar infarcts, enlargement of perivascular spaces (PVS), microbleeds (MBs), cortical superficial siderosis (cSS), and cortical microinfarcts (CMIs).[1,2] SVD is the main cause of vascular dementia in older people, among which, SVD with dementia comprises nearly half of all patients with vascular dementia.[3] Moreover, SVD is also present in Alzheimer's disease (AD).[4]

Although aging is one of the main causes of SVD, several other diseases such as arteriosclerosis, cerebral amyloid angiopathy (CAA), genetic predispositions, and inflammation also cause SVD.[5] In particular, arteriosclerosis and CAA are the two major causes of SVD. SVD due to arteriosclerosis is particularly associated with hypertension (hypertensive arteriopathy; HA)[6]; this SVD type is also named sporadic non-amyloid microangiopathy.[7] In contrast, CAA is characterized by the progressive deposition of amyloid beta (Aβ) protein in the cerebral vessels, and the major peptide

isoforms of Aβ mainly consist of $A\beta_{1-40}$ and $A\beta_{1-42}$.[5] Although both HA and CAA share common MRI features (Fig 1), including WMH, enlargement of PVS, and MBs, the location and distribution of these radiological findings are different. The anteroposterior distribution of WMH in CAA is posterior-dominant.[8] The enlargement of PVS in the basal ganglia (BG-PVS) is associated with hypertension, and patients with CAA show centrum semiovale PVS (CSO-PVS).[9] MBs located in the basal ganglia, thalamus, or brainstem indicate HA (deep MBs) and MBs within the lobar brain compartment are associated with CAA [10]. Moreover, lacunar infarcts are associated with hypertension, whereas cSS is a representative MRI biomarker in CAA.[11] CMIs are caused by different pathological backgrounds, including CAA, arteriosclerosis and microembolism[12]; however, neuroradiological findings obtained using 3T MRI may enable distinction between CMIs related to CAA and those due to microembolisms.[13]

Recently, two types of MRI-based assessment scores have been developed for SVD. Klarenbeek et al. enrolled patients with lacunar stroke and assessed different MRI features, including lacunar infarct, MBs, BG-PVS, and WMH.[14] One point was awarded for the presence of each marker, producing a score between 0 and 4. This HA-SVD score was mainly used for the evaluation of patients with lacunar stroke and/or vascular risk factors,[15] and was associated with intellectual function.[16] Charidimou et al.

developed a novel SVD score for patients with CAA (CAA-SVD score),[17] which was associated with clinical symptoms of transient focal neurological episodes.[18] However, the relationship between CAA-SVD scores and cognitive function remains unclear.

In this study, we investigated the relationship between the two types of SVD scores and cognitive function in patients who visited our memory clinic. Moreover, we added other radiological biomarkers of CAA to the CAA-SVD score and investigated its usefulness in evaluating cognitive function in patients with mild cognitive impairment (MCI) and mild dementia.

PATIENTS AND METHODS

Patients

We prospectively registered patients who consulted our hospital's memory clinic. Of the 50 subjects, 42 fulfilled the inclusion criteria. All procedures followed the Clinical Study Guidelines of the Ethics Committee of Mie University Hospital and were approved by the internal review board (Registration number: 1596). A complete description of all procedures was provided to patients, and written informed consent was obtained directly from them or from their caregivers. All patients were comprehensively examined by a neurologist with sufficient experience in examining patients with dementia. The CDR and

MRI was performed after obtaining written informed consent. We collected data from patients who fulfilled the following inclusion criteria: 1) consulted with our hospital's memory clinic between February 2017 and July 2019, 2) underwent neuroimaging examinations using 3T MRI, 3) completed neuropsychological assessments, and 4) had a global Clinical Dementia Rating (CDR) score of 0.5 or 1.0. Neuropsychological tests and CDR were performed within 3 months of MRI. No neurological events occurred between these tests and MRI.

We diagnosed MCI according to the National Institute on Aging–Alzheimer's Association (NIA-AA) criteria for MCI patients. [19] MCI was classified into MCI due to AD or other types of MCI. The global CDR score was 0.5. We diagnosed AD according to the NIA-AA guidelines.[20] Vascular dementia was diagnosed according to the criteria set forth by the American Heart Association/American Stroke Association.[21]

Neuropsychological assessments

The Mini-Mental State Examination (MMSE)[22] and Japanese Raven's Coloured Progressive Matrices (RCPM)[23] were used to quantify intellectual function. Memory was evaluated using the Rivermead Behavioral Memory Test (RBMT). The scores included a standard profile score (SPS) and screening score (SS).[24] Constructional

ability was assessed using the Mie Constructional Apraxia Scale (MCAS).[25] Frontal lobe function was assessed using two tasks: word fluency (WF) and trail making test (TMT) -A/-B.[26] The WF test consisted of category and letter domains. In the category WF task (WF-category), participants were asked to name as many animals as possible in 1 minute. In the letter WF task (WF-letter), participants were asked to name as many objects as possible in 1 minute, beginning with each of the following four phonemes: *ka, sa, ta,* and *te*. The average scores for these four phonemes were used for statistical analyses.

CDR was performed by two speech therapists, and results were evaluated through a discussion between two neurologists and three speech therapists based on the CDR determination rules.[27]

MRI protocol

We followed the MRI protocol by Ii et al.[28] Briefly, MRI studies were performed with a 3T MRI unit (Achieva, Philips Medical System, Best, the Netherlands) using an 8- or 32-channel phased-array head coil. We used T1- and T2-weighted images and 3D-fluid attenuated inversion recovery (FLAIR) images for the evaluation of WMH, lacunar infarcts, and PVS. Susceptibility-weighted image (SWI) sequences were used for the

detection of MBs and cSS. 3D-double inversion recovery (DIR) and 3D-FLAIR was used for the detection of CMIs. Axial DIR imaging was performed using two different inversion pulses. The long inversion time and the short inversion time were defined as the intervals between the 180° inversion pulse and the 90° excitation pulse, respectively, which had been optimized for human brain imaging and were provided by the vendor.

Details of the 2D- and 3D-DIR protocols were as follows: field of view, 230 mm; matrix, 320 × 256 (512 × 512) after reconstruction; in-plane resolution, 0.45 mm × 0.45 mm; section thickness, 3 mm with no intersection gap; no parallel imaging; repetition time (ms)/echo time (ms), 15,000/28; long inversion time (ms)/short inversion time (ms), 3,400/325; number of signals acquired, two; and acquisition time, 4 min 30 s for 2D, and field of view, 250 mm; matrix, 208 × 163 (256 × 256) after reconstruction; in plane resolution, 0.98 mm × 0.98 mm; section thickness, 0.65 mm with over contiguous slice; TSE factor 173; repetition time (ms)/echo time (ms), 5,500/247; long inversion time (ms)/short inversion time (ms), 2,550/450; number of signals acquired, two; and acquisition time, 5 min 13 s for 3D.

The SWI details were as follows: field of view, 230 mm; matrix, 320 × 251 (512 × 512) after reconstruction; in-plane resolution, 0.45 mm × 0.45 mm; section thickness, 0.5 mm with over contiguous slice; repetition time (ms)/echo time (ms), 22/11.5 (in-phase), 33

(shifted); number of signals acquired, one; flip angle 20°; and acquisition time, 5 min 45 s. 3D-FLAIR imaging was obtained in a sagittal direction, and then the axial and coronal images were reconstructed. The 3D-FLAIR details were as follows: field of view, 260 mm; matrix, 288 × 288 (364 × 364) after reconstruction; in-plane resolution, 0.68 × 0.67 mm; section thickness, 1 mm with 0.5 mm overlap; no parallel imaging; repetition time (ms)/echo time (ms), 6,000/400; inversion time, 2,000 ms; number of signals acquired, two; and acquisition time, 5 min 12 s.

SVD scores

The HA-SVD score was determined by Klarenbeek et al., where 1 point was awarded for each of the four markers (lacunar infarcts, MBs, BG-PVS, and WMH), with a minimum score of 0 and a maximum score of 4.[14] The CAA-SVD score was proposed by Charidimou et al. (Table 1), with 1 point awarded for each of the four markers (lobar MBs, cSS, CSO-PVS, and WMH).[17] For lobar MBs, 1 point was awarded if two to four MBs were present and 2 points for five or more MBs. The presence of cSS was awarded with 1 point if focal and 2 points if disseminated. The presence of CSO-PVSs was confirmed if there were moderate to severe (> 20) PVSs (1 point if present), with a

minimum score of 0 and a maximum score of 6. Both scores were independently assessed by four raters.

Table 1. Cerebral amyloid angiopathy-cerebral small vessel disease (CAA-SVD) score and modified CAA-SVD score

MRI marker	Cut off	Points		
CAA-SVD score				
Lobar MBs	2 to 4	1		
	≥ 5	2		
cSS	Focal	1		
	Disseminated	2		
CSO-PVSs	>20	1		
WMH	deep WMH (Fazekas 2 or 3)	1		
	periventricular WMH (Fazekas 3)	1	total	/6
Modified CAA-SVD score				
posterior distribution of WMH		1		
CMI(s) due to CAA	≥1	1	total	/8

Modified CAA-SVD scores

We tried to modify CAA-SVD scores by adding one point each in the presence of posteriorly dominant WMH and CMIs related to CAA (Table 1).

Tissue quantification was performed using a novel in-house software (FUsed Software for Imaging Of Nervous system: FUSION)[29] that yielded an individualized volumetric brain tissue profile. The obtained T1-weighted and FLAIR images were imported from

the Digital Imaging and Communications in Medicine format files for processing. To increase the accuracy of segmentation, we used the Lesion Segmentation Tool for lesion filling.[30] Lesion filling was applied to T1-weighted images that were aligned with the lesion probability map. For pre-processing, the T1-weighted images were co-registered to the FLAIR images. Next, to separate out the white matter, segmentation was performed using the T1-weighted images and a mask covering the cerebral ventricles. The pre-processing function was based on SPM 8 (Wellcome Trust Centre for Neuroimaging, UCL). Second-level tissue segmentation was then performed to separate WMH from white matter using a semi-automated operation that extracted the pixels falling within a predetermined WMH value. The WMH volume, which appeared as hyperintense areas on FLAIR images, was quantified for each area. Brain tissue was classified into four areas based on the division of the longitudinal fissure of the cerebrum and central sulcus. WMH were automatically classified as periventricular hyperintensity or deep WMH, and their corrected volumes were quantified in cubic centimetres.[29] The anteroposterior centre of WMH was calculated in the following way. To determine the reference point, we identified two anatomical landmarks (anterior, A and posterior, P). Point A was defined as the most anterior part on the wall of the frontal horn of the lateral ventricle. Point P

was defined as the most posterior part of the dura mater covering the occipital cortex.[8] If there was a large amount of posterior WMH, 1 point was added to the CAA-SVD score.

CMIs were defined as small cortical hyperintense lesions non-adjacent to WMH. When CMIs were localized within the cortex, predominantly in the occipital lobe, were smaller than 5 mm in diameter, and had fewer than three lesions, they were defined as CMIs related to CAA. (Ishikawa score) [13] When there were any CMIs related to CAA, we added 1 point to the CAA-SVD score.

Statistical analyses

The association between each SVD score (dependent variable) and cognitive function (independent variable) was analysed using linear regression analysis. Clinical and radiological characteristics are presented as numbers with percentages and means with standard deviation (SD). Statistical analyses were performed using IBM SPSS statistics software version 20 (IBM Corp., Armonk, NY, United States). Differences with $p<0.05$ were considered statistically significant.

RESULTS

Patients

In total, 50 patients were registered for this study, and 42 fulfilled the inclusion criteria. Clinical characteristics, neuropsychological test results, and MRI findings of the participants are shown in Table 2. The mean age was 75.3 ± 9.12 years, and there were 23 men (54.7%). Regarding vascular risk factors, 22 patients had hypertension (52.3%), four had diabetes mellitus (9.5%), and 11 smoked and had dyslipidaemia (26.1%). Fourteen patients had a history of lacunar stroke (33.3%) and 24 patients (57.1%) met the modified Boston criteria (ver 1.5).

Table 2. Participant characteristics

Clinical characteristics	All participants, n= 42
Age, years, mean (SD)	75.3 (9.12)
Education, years, mean (SD)	11.9 (2.34)
Male sex (n, %)	23 (54.7)
Vascular risk factors	
hypertension (n, %)	22 (52.3)
dyslipidemia (n, %)	11 (26.1)
diabetes mellitus (n, %)	4 (9.5)
smoking (n, %)	11 (26.1)
History of any stroke (n, %)	19 (45.2)
lacunar (n, %)	14 (33.3)
Medication	
anti-hypertensive (n, %)	7 (16.6)
statin (n, %)	6 (14.2)
anti-platelet or anti-coagulation (n, %)	8 (19.0)
Meets modified Boston criteria	

	probable CAA	11 (26.1)
	possible CAA	13 (30.9)
Neuropsychological tests		
Global CDR	0.5 (n, %)	30 (71.4)
	1.0 (n, %)	12 (28.6)
MMSE	Score (SD)	25.2 (2.39)
RCPM	Score (SD)	24.2 (5.73)
	Time,s (SD)	440 (198)
RBMT	Standard profile score (SD)	11.5 (5.49)
	Screening score (SD)	4.5 (2.78)
TMT	A, s (SD)	257 (156)
	B, s (SD)	265 (95.6)
WF, /min	Category (SD)	10.9 (3.93)
	Letters (SD)	5 (1.72)
MCAS	Score (SD)	3.3 (1.68)
	time,s (SD)	49.6 (37.4)
MRI findings		
MBs; all	≥ 1 (n, %)	31 (73.8)
MBs; Lobar	2 to 4 (n, %)	16 (38.0)
	≥ 5 (n, %)	10 (23.8)
cSS	Focal (n, %)	3 (7.1)
	Disseminated (n, %)	0
BG-PVSs	>20 (n, %)	25 (59.5)
CSO-PVSs	>20 (n, %)	30 (71.4)
WMH	deep WMH (Fazekas 2 or 3) (n, %)	26 (61.9)
	periventricular WMH (Fazekas 3) (n, %)	11 (26.1)
posterior distributon of WMH (n, %)		7 (16.6)
CMI(s) due to CAA (n, %)		3 (7.1)

The global CDR score was 0.5 for 30 patients (71.4%) and 1.0 for 12 patients (28.6%). Of the 12 patients with a global CDR score of 1.0, 10 met the criteria reflecting probable AD and two had vascular dementia. Among 30 patients with MCI, 20 had MCI due to AD and 10 had other types of MCI. Regarding MRI findings, 31 patients had ≥1 MBs (73.8%), 16 had ≥2 and ≤4 lobar MBs (38.0%), and 10 had ≥5 lobar MBs (23.8%). Three patients had focal cSS (7.1%), 25 had >20 BG-PVSs (59.5%), 30 had >20 CSO-PVSs (71.4%), 26 had deep WMH (Fazekas 2 or 3) (61.9%), and 11 had periventricular WMH (Fazekas 3) (26.1%).

WMH were divided according to whether they were anterior or posterior and were analysed using FUSION. There were seven posterior superiorities (16.6%). CMIs related to CAA were detected in three patients (7.1%), and two of these patients met the modified Boston criteria for probable CAA. The patients with CMIs did not have any evidence of CAA except for CMIs, such as atrial fibrillation and cerebral artery stenosis.

Results of each SVD score

As for each SVD score (Table 3), the HA-SVD score was 0 in 3 patients (7.1%), 1 in 7 patients (16.6%), 2 in 14 patients (33.3%), 3 in 11 patients (26.1%), and 4 in 7 patients (16.6%). The CAA-SVD score was 0 in 5 patients (11.9%), 1 in 6 patients (14.2%), 2 in

13 patients (30.9%), 3 in 12 patients (28.5%), and 4 in 6 patients (14.2%). Moreover, the modified CAA-SVD score was 0 in 1 patient (2.3%), 1 in 6 patients (14.2%), 2 in 8 patients (19%), 3 in 13 patients (30.9%), 4 in 11 patients (26.1%), 5 in 2 patients (4.7%), and 6 in 1 patient (2.3%). A significant difference was observed when the HA-SVD scores and CAA-SVD scores were analysed using Pearson's chi-square test (p=0.000).

Table 3. Cerebral small vessel disease score

Score	All participants n = 42
HA-SVD score (n, %)	
0	3 (7.1)
1	7 (16.6)
2	14 (33.3)
3	11 (26.1)
4	7 (16.6)
CAA-SVD score (n, %)	
0	5 (11.9)
1	6 (14.2)
2	13 (30.9)
3	12 (28.5)
4	6 (14.2)
5	0 (0)
6	0 (0)
Modified CAA-SVD score (n, %)	

0	1 (2.3)
1	6 (14.2)
2	8 (19.0)
3	13 (30.9)
4	11 (26.1)
5	2 (4.7)
6	1 (2.3)
7	0 (0)
8	0 (0)

Cognitive function and the three types of SVD scores

HA-SVD score

With regard to the relationship between each cognitive function and the HA-SVD score, no significant difference was found across any function (Table 4), such as MMSE (p=0.52), RCPM (p=0.47), RBMT-SPS (p=0.15), RBMT-SS (p=0.11), TMT-A (p=0.85), TMT-B (p=0.23), WF-category (p=0.10), WF-letter (p=0.17), or MCAS (p=0.23). Additionally, the linear regression models of the associations between the HA-SVD scores and cognitive function revealed that the coefficient of determination was R^2=0.409 (p=0.35), and the regression equation did not hold. The Akaike's Information Criterion (AIC) was 122.493.

Table 4. Linear regression models of associations between cognitive function and SVD score

	unstandardized beta (SE)			*p*		
	HA-SVD score	CAA-SVD score	Modified CAA-SVD score	HA-SVD score	CAA-SVD score	Modified CAA-SVD score
MMSE	0.191	0.713	0.771	0.521	**0.006**	**0.001**
RCPM	-0.185	-0.295	-0.17	0.474	0.153	0.384
RBMT-SPS	1.057	0.732	0.622	0.159	0.209	0.267
RBMT-SS	-1.148	-1.055	-1.005	0.111	0.064	**0.048**
TMT-A	0.065	0.107	0.192	0.854	0.698	0.476
TMT-B	0.395	0.516	0.412	0.239	0.057	0.11
WF (Category)	0.426	0.414	0.448	0.104	**0.047**	**0.028**
WF (Letters)	-0.38	-0.079	-0.097	0.17	0.71	0.634
MCAS	-0.686	-0.584	-0.564	0.052	**0.036**	**0.026**

CAA-SVD score

With regard to the relationship between each cognitive function and the CAA-SVD score, a significant difference was found in 3/9 items (Table 4), including MMSE (p=0.006), WF-category (p=0.04), and MCAS (p=0.03), while there was no significant

difference in 6/9 items, including RCPM (p=0.15), RBMT-SP (p=0.20), RBMT-SS (p=0.06), TMT-A (p=0.69), TMT-B (p=0.05), and WF-letter (p=0.71). The results of the linear regression models of the associations between CAA-SVD scores and cognitive function demonstrated that the coefficient of determination was R^2=0.639 (p=0.016) and the AIC was 104.269.

Modified CAA-SVD score

With regard to the relationship between each cognitive function and the modified CAA-SVD score, a significant difference was found in 4/9 items (Table 4), including MMSE (p=0.001), RBMT-SS (p=0.04), WF-category (p=0.02), and MCAS (p=0.04), while no significant difference was found in 5/9 items, including RCPM (p=0.14), RBMT-SP (p=0.33), TMT-A (p=0.19), TMT-B (p=0.21), and WF-letter (p=0.56). The results of the linear regression models of the associations between the CAA-SVD scores and cognitive function revealed that the coefficient of determination was R^2=0.645 (p=0.008) and the AIC was 103.43.

On assessing the relationship between each cognitive function and each SVD score, a significant difference was found in MMSE, WF-category, MCAS, and RBMT-SS.

Among these four items, the WF-category had the highest coefficient of determination for the HA-SVD score (R^2=0.0135), and the RBMT-SS had the highest coefficient of determination for the CAA-SVD (R^2=0.0142) and modified CAA-SVD scores (R^2=0.0161). In the linear regression models of the associations between each SVD score and RBMT-SS, the coefficient of determination was found to increase in the following order: HA-SVD score < CAA-SVD score < modified CAA-SVD score (Fig 2).

DISCUSSION

This study demonstrated a novel association between the CAA-SVD score and cognitive function in memory clinic patients, whereas no significant association was found between the HA-SVD score and cognitive function. Additionally, there was a significant difference between the HA-SVD score and CAA-SVD score; i.e., WF-category had the highest coefficient of determination for the HA-SVD score, and the RBMT-SS had the highest coefficient of determination for the CAA-SVD and modified CAA-SVD scores. Moreover, it is plausible that the modified CAA-SVD score, in addition to the analysis of the posterior distribution of WMH and CMIs, may be a useful tool for evaluating patients with MCI or mild dementia.

Taken together, our study showed that there was a significant difference in each cognitive domain between the HA-SVD score and CAA-SVD score, and a significant association between the CAA-SVD score and cognitive function. This result indicates that the CAA-SVD score may reflect the cognitive function in patients of a memory clinic. Although a previous report showed that the HA-SVD score showed significant associations with intellectual function in patients having had a lacunar stroke and/or with hypertension,[16] our study did not show any such significant association. This may be attributed to the patients' background, such as older age and lower prevalence of vascular factors. The mean age of patients in the previous study was 63.1 years, while the mean age of patients in our study was 75.3 years. Moreover, in our study, 22 patients had hypertension (52.3%) and 14 patients had a lacunar stroke (33.3%) compared to 84.1% and 68.7%, respectively, in a previous study.

The HA-SVD score and CAA-SVD score share common components including WMH, PVS, and MBs. The HA-SVD score includes lacunar infarcts, whereas the CAA-SVD score includes cSS. Moreover, the location of PVS and MBs differ between the HA- and CAA-SVD scores. Previous reports have shown that CSO-PVS is negatively correlated with memory and that BG-PVS is negatively correlated with processing speed, executive function, and memory.[16] Additionally, the presence and number of MBs have been

associated with cognitive impairment.[31] The incidence of cSS is extremely low and difficult to study in healthy individuals[32]; however, cSS is highly-specific for CAA. As described above, the CAA-SVD score was produced by adding cSS to the WMH and region-specific MBs and PVS and was more related to cognitive function than the HA-SVD score.

The modified CAA-SVD score improved the prediction accuracy of the regression equation, reduced the AIC, and slightly improved the prediction accuracy compared to the CAA-SVD score. CMIs are an important risk factor for dementia, and it has been reported that the presence of CMIs approximately doubles the risk of dementia.[32] One of the major causes of CMIs is CAA.[33] Additionally, several reports have described the relationship between WMH and cognitive function,[34] and WMH due to CAA have been reported to be posterior-dominant.[35] Therefore, it was thought that incorporation of these two markers may have affected relationship with cognitive function in an additive manner.

On observing the results for each test item, the CAA-SVD score was found to have significant associations with constructional ability and memory. This observation is in line with the diagnostic criteria of NIA-AA, which includes constructional ability and memory as an essential cognitive domain.[36]

These results in our study may be dependent on the background of the patients in our memory clinic. In this study, 24 patients (57.1%) met the modified Boston criteria (ver 1.5), 10 of 12 patients with mild dementia had AD, and MCI due to AD was present in 20 out of 30 MCI patients. MCI due to AD has been reported to have a high rate of progression to AD.[37] Low prevalence of vascular risk and advanced aging in the present study may indicate that our memory clinic's patients had a higher burden of amyloid pathology. Therefore, the CAA-SVD score and modified CAA-SVD score may reflect the pathological background of AD. The CAA-SVD score may be a useful tool for memory clinic patients whereas the SVD scores may not, rather being suited for the patients with vascular risk factors. Additionally, there may be a possibility that cognitive dysfunction can be detected earlier by evaluating patients with a score that is well-tailored to them, thereby enabling appropriate subsequent patient treatment.

This study had several limitations. First, it was based on a relatively small sample size. Second, deep MBs is common in Japan [38], but the patients included in this study mostly had strictly lobar MBs, and we believe that there was selection bias due to recruiting patients from a memory clinic. Third, we were unable to carry out pathological examinations. The patient who did not meet the modified Boston criteria but meet the CAA due to CMI criteria are scored as CAA related CMI. In the previous

report, 17% of the pathological patients had a CAA but a CAA score of 0, and most of the pathological changes were mild.[17] CMI is also detected by mild CAA.[39] The Ishikawa score is based on the characteristics of CAA patients, and we considered that there is no problem with this addition, but this case also requires pathological findings. These issues should be addressed in future studies. Forth, currently, FUSION has its limits and cannot distinguish small infarcts and enlarged PVS. At present, the radiologist visually confirmed whether the results of FUSION were likely to be affected, and it was determined that the results were not affected. We aim to improve the software so that it can distinguish small infarcts and enlarged PVS in the future. Fifth, we have not validated the weighting of the modified CAA-SVD score; this needs further investigation. Finally, there was no significant association between the HA-SVD score and cognitive function in this study, possible due to the limited number of patients with hypertension included in this study. Furthermore, even though there is a possibility that a larger number of cases may allow a significant correlation, further and lager studies would be required to validate this.

Despite these limitations, our study shows that patients with MCI or mild dementia should be evaluated with the CAA-SVD score. The modified CAA-SVD score may also be applicable to these patients.

Competing Interests: The authors have no conflict of interest to declare.

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

Data availability: No additional data available.

Contributorship statement:

KM: draft of manuscript, acquisition of data, and analysis.

AS: revision of manuscript, interpretation of data, and study supervision.

KIT and YI: revision of manuscript and interpretation of data.

YU, HI, KM, KY, AT, NK, MS, MM: acquisition of data and interpretation of data.

HT: revision of the manuscript, study concept and design, and study supervision.

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Figure Legends

Figure 1. Representative MRI findings of cerebral small vessel disease

The arrows show lobar cerebral MBs on SWI sequences. MRI in a patient with CAA (A). cSS was observed in SWI sequences in a patient with CAA (arrows, B). Centrum semiovale enlarged perivascular spaces on T2-weighted imaging in a patient with CAA (C). WMH assessed by fluid attenuated inversion recovery imaging. WMH in CAA patients was posterior-dominant (D). Double inversion recovery imaging shows a CMI that localized within the cortex and was 3 mm in diameter (arrow). CMIs from patients with CAAs (E) showed that all lesions were localized within cortical structures, with a size of <5 mm [13].

MRI, magnetic resonance imaging; MBs, cerebral amyloid angiopathy; SWI, susceptibility-weighted image; CAA, cerebral amyloid angiopathy; WMH, white matter hyperintensities; CMI, cortical microinfarct

Figure 2. Linear regression models of the associations between each cerebral small vessel disease (SVD) score and the Rivermead Behavioral Memory Test-screening score (RBMT-SS)

HA, hypertensive arteriopathy; CAA, cerebral amyloid angiopathy

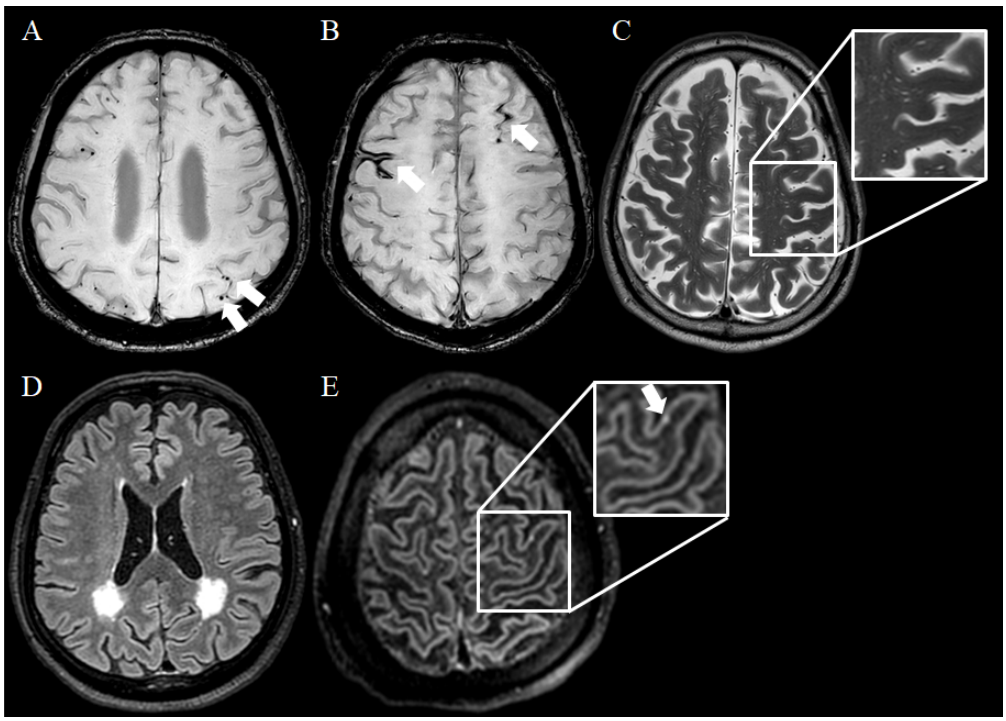
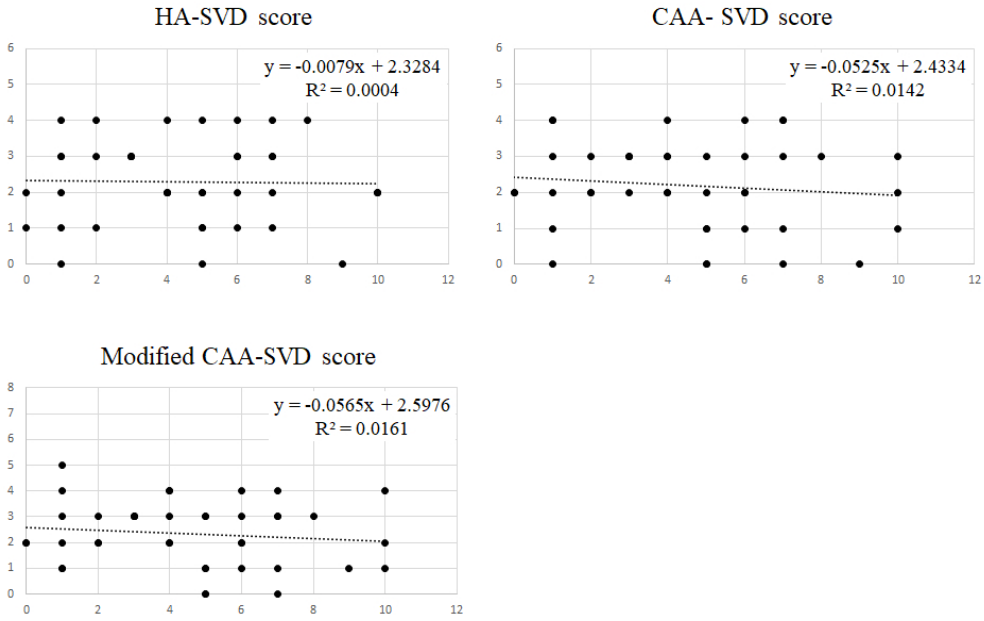


Figure 1

240x171mm (96 x 96 DPI)



165x106mm (144 x 144 DPI)

Standards for Reporting Qualitative Research (SRQR)*

http://www.equator-network.org/reporting-guidelines/srqr/

	Page/line no(s).
Title and abstract	
Title - Concise description of the nature and topic of the study Identifying the study as qualitative or indicating the approach (e.g., ethnography, grounded theory) or data collection methods (e.g., interview, focus group) is recommended	6-12
Abstract - Summary of key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results, and conclusions	2-3
Introduction	
Problem formulation - Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work; problem statement	5-6
Purpose or research question - Purpose of the study and specific objectives or questions	6
Methods	
Qualitative approach and research paradigm - Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g., postpositivist, constructivist/ interpretivist) is also recommended; rationale**	6-7
Researcher characteristics and reflexivity - Researchers' characteristics that may influence the research, including personal attributes, qualifications/experience, relationship with participants, assumptions, and/or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results, and/or transferability	6-7
Context - Setting/site and salient contextual factors; rationale**	4-6
Sampling strategy - How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g., sampling saturation); rationale**	6-7
Ethical issues pertaining to human subjects - Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues	6
Data collection methods - Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources/methods, and modification of procedures in response to evolving study findings; rationale**	6-7

Data collection instruments and technologies - Description of instruments (e.g., interview guides, questionnaires) and devices (e.g., audio recorders) used for data collection; if/how the instrument(s) changed over the course of the study	6-9
Units of study - Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results)	11
Data processing - Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymization/de-identification of excerpts	6-12
Data analysis - Process by which inferences, themes, etc., were identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale**	6-12
Techniques to enhance trustworthiness - Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale**	7-12

Results/findings

Synthesis and interpretation - Main findings (e.g., interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory	13-19
Links to empirical data - Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate analytic findings	13-19

Discussion

Integration with prior work, implications, transferability, and contribution(s) to the field - Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application/generalizability; identification of unique contribution(s) to scholarship in a discipline or field	19
Limitations - Trustworthiness and limitations of findings	22

Other

Conflicts of interest - Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed	23
Funding - Sources of funding and other support; role of funders in data collection, interpretation, and reporting	23

*The authors created the SRQR by searching the literature to identify guidelines, reporting standards, and critical appraisal criteria for qualitative research; reviewing the reference lists of retrieved sources; and contacting experts to gain feedback. The SRQR aims to improve the transparency of all aspects of qualitative research by providing clear standards for reporting qualitative research.

**The rationale should briefly discuss the justification for choosing that theory, approach, method, or technique rather than other options available, the assumptions and limitations implicit in those choices, and how those choices influence study conclusions and transferability. As appropriate, the rationale for several items might be discussed together.

Reference:

O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. **Standards for reporting qualitative research: a synthesis of recommendations.** *Academic Medicine*, Vol. 89, No. 9 / Sept 2014
DOI: 10.1097/ACM.0000000000000388

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *case-control studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	#1, #3-4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	#3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	#6-8
Objectives	3	State specific objectives, including any prespecified hypotheses	#8
Methods			
Study design	4	Present key elements of study design early in the paper	#8-12
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	#8-9
Participants	6	(a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	#8-9
		(*b*) For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	#8-12
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	#12-15
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	#8-9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	#15
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	#15
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how matching of cases and controls was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	#16
		(b) Give reasons for non-participation at each stage	#16
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	#16-18
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	#23-24
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	#26-27
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	#24-26
Generalisability	21	Discuss the generalisability (external validity) of the study results	#27
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	#27

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Investigation of hypertensive arteriopathy- and cerebral amyloid angiopathy-related small vessel disease scores in patients from a memory clinic: a prospective single-centre study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-042550.R3
Article Type:	Original research
Date Submitted by the Author:	24-Jan-2021
Complete List of Authors:	Matsuda, Kana; Mie University Hospital, Rehabilitation; Mie University Graduate School of Medicine Faculty of Medicine, Neurology Shindo, Akihiro; Mie University Graduate School of Medicine Faculty of Medicine, Neurology; Mie University Graduate School of Medicine Faculty of Medicine, Dementia Prevention and Therapeutics Ii, Yuichiro; Mie University Graduate School of Medicine Faculty of Medicine, Neurology Tabei, Ken-ichi; Mie University Graduate School of Medicine Faculty of Medicine, Dementia Prevention and Therapeutics Ueda, Yukito; Mie University Graduate School of Medicine Faculty of Medicine, Rehabilitation Ishikawa, Hidehiro; Mie University Graduate School of Medicine Faculty of Medicine, Neurology Matsuura, Keita; Mie University Graduate School of Medicine Faculty of Medicine, Neurology Yoshimaru, Kimiko; Mie University Graduate School of Medicine Faculty of Medicine, Dementia Prevention and Therapeutics Taniguchi, Akira; Mie University Graduate School of Medicine Faculty of Medicine, Neurology Kato, Natsuko; Mie University Graduate School of Medicine Faculty of Medicine, Neurology Satoh, Masayuki; Mie University Graduate School of Medicine Faculty of Medicine, Dementia Prevention and Therapeutics Maeda, Masayuki; Mie University Graduate School of Medicine Faculty of Medicine, Advanced Diagnostic Imaging Tomimoto , Hidekazu ; Mie University Graduate School of Medicine Faculty of Medicine, Neurology
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Radiology and imaging
Keywords:	Delirium & cognitive disorders < PSYCHIATRY, Dementia < NEUROLOGY, Hypertension < CARDIOLOGY, Magnetic resonance imaging < RADIOLOGY & IMAGING

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Investigation of hypertensive arteriopathy- and cerebral amyloid angiopathy-related small vessel disease scores in patients from a memory clinic: a prospective single-centre study

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Word count: 4,049words

ABSTRACT

Objective: The severity of cerebral small vessel disease (SVD) is assessed through neuroimaging findings, including hypertensive arteriopathy (HA)-SVD and cerebral amyloid angiopathy (CAA)-SVD. HA-SVD and CAA-SVD have been collectively estimated as total scores: the HA-SVD and CAA-SVD scores, respectively. Previous reports suggest that HA-SVD scores are associated with cognitive function; however, the relationship between CAA-SVD scores and cognitive function remains unclear. Therefore, we examined the association between CAA-SVD scores and cognitive function. Furthermore, we developed a modified CAA-SVD score considering cortical microinfarcts and posterior dominant white matter hyperintensities, which are imaging findings of CAA, and examined the association between these scores and cognitive function in the same patient group.

Design: Prospective study

Setting: Single centre study from a memory clinic

Participants: Subjects were diagnosed with mild cognitive impairment (MCI) or mild dementia in our memory clinic between February 2017 and July 2019 and underwent clinical dementia rating scale and brain magnetic resonance imaging (MRI) assessment. A total of 42 patients (aged 75.3 ± 9.12 years) were registered prospectively.

Primary and secondary outcome measures: We evaluated intellectual function, memory, frontal lobe function, and constructional ability. Furthermore, the relationship between each score and cognitive function was examined.

Results: The CAA-SVD score showed significant associations with cognitive function (R^2=0.63, p=0.016), but the HA-SVD score did not (R^2=0.41, p=0.35). The modified CAA-SVD score was also significantly associated with cognitive function (R^2=0.65, p=0.008).

Conclusion: Cognitive function is associated with the CAA-SVD score, and more efficiently with the modified CAA-SVD score, in memory clinic patients. Although we have not validated the weighting of the modified CAA-SVD score, these scores can be a predictor of cognitive deterioration in patients with MCI and mild dementia.

Keywords: cognition, dementia, small vessel disease, hypertension, cerebral amyloid angiopathy

Strengths and limitations

- We examined the association between cognitive function and hypertensive arteriopathy-, and cerebral amyloid angiopathy (CAA)- small vessel disease (SVD) scores in patients from a memory clinic.
- We developed a modified CAA-SVD score considering cortical microinfarcts and posterior dominant white matter hyperintensities, which are characteristic imaging findings of CAA, and examined the association between these scores and cognitive function.
- Cognitive function was associated with the CAA-SVD score, and more efficiently with the modified CAA-SVD score. However, we have not validated the weighting of the modified CAA-SVD score.
- This study included 42 cases; therefore, the results are based on a relatively small sample size.
- This study included relatively large number of the patients with strictly lobar microbleeds, and this might be due to selection bias from including patients from a memory clinic.

INTRODUCTION

Cerebral small vessel disease (SVD) is a comprehensive term that describes small vessel pathological conditions, including ischemia and haemorrhage, in the brain. Patients with SVD share common pathological, clinical and neuroimaging features.[1] Neuroradiological findings of SVD are examined using brain magnetic resonance imaging (MRI), which shows various vascular lesions, including white matter hyperintensities (WMH), lacunar infarcts, enlargement of perivascular spaces (PVS), microbleeds (MBs), cortical superficial siderosis (cSS), and cortical microinfarcts (CMIs).[1,2] SVD is the main cause of vascular dementia in older people, among which, SVD with dementia comprises nearly half of all patients with vascular dementia.[3] Moreover, SVD is also present in Alzheimer's disease (AD).[4]

Although aging is one of the main causes of SVD, several other diseases such as arteriosclerosis, cerebral amyloid angiopathy (CAA), genetic predispositions, and inflammation also cause SVD.[5] In particular, arteriosclerosis and CAA are the two major causes of SVD. SVD due to arteriosclerosis is particularly associated with hypertension (hypertensive arteriopathy; HA)[6]; this SVD type is also named sporadic non-amyloid microangiopathy.[7] In contrast, CAA is characterized by the progressive deposition of amyloid beta (Aβ) protein in the cerebral vessels, and the major peptide

isoforms of Aβ mainly consist of $A\beta_{1-40}$ and $A\beta_{1-42}$.[5] Although both HA and CAA share common MRI features (Fig 1), including WMH, enlargement of PVS, and MBs, the location and distribution of these radiological findings are different. The anteroposterior distribution of WMH in CAA is posterior-dominant.[8] The enlargement of PVS in the basal ganglia (BG-PVS) is associated with hypertension, and patients with CAA show centrum semiovale PVS (CSO-PVS).[9] MBs located in the basal ganglia, thalamus, or brainstem indicate HA (deep MBs) and MBs within the lobar brain compartment are associated with CAA [10]. Moreover, lacunar infarcts are associated with hypertension, whereas cSS is a representative MRI biomarker in CAA.[11] CMIs are caused by different pathological backgrounds, including CAA, arteriosclerosis and microembolism[12]; however, neuroradiological findings obtained using 3T MRI may enable distinction between CMIs related to CAA and those due to microembolisms.[13]

Recently, two types of MRI-based assessment scores have been developed for SVD. Klarenbeek et al. enrolled patients with lacunar stroke and assessed different MRI features, including lacunar infarct, MBs, BG-PVS, and WMH.[14] One point was awarded for the presence of each marker, producing a score between 0 and 4. This HA-SVD score was mainly used for the evaluation of patients with lacunar stroke and/or vascular risk factors,[15] and was associated with intellectual function.[16] Charidimou et al.

developed a novel SVD score for patients with CAA (CAA-SVD score),[17] which was associated with clinical symptoms of transient focal neurological episodes.[18] However, the relationship between CAA-SVD scores and cognitive function remains unclear.

In this study, we investigated the relationship between the two types of SVD scores and cognitive function in patients who visited our memory clinic. Moreover, we added other radiological biomarkers of CAA to the CAA-SVD score and investigated its usefulness in evaluating cognitive function in patients with mild cognitive impairment (MCI) and mild dementia.

PATIENTS AND METHODS

Patients

We prospectively registered patients who consulted our hospital's memory clinic. Of the 50 subjects, 42 fulfilled the inclusion criteria. All procedures followed the Clinical Study Guidelines of the Ethics Committee of Mie University Hospital and were approved by the internal review board (Registration number: 1596). A complete description of all procedures was provided to patients, and written informed consent was obtained directly from them or from their caregivers. All patients were comprehensively examined by a neurologist with sufficient experience in examining patients with dementia. The CDR and

MRI was performed after obtaining written informed consent. We collected data from patients who fulfilled the following inclusion criteria: 1) consulted with our hospital's memory clinic between February 2017 and July 2019, 2) underwent neuroimaging examinations using 3T MRI, 3) completed neuropsychological assessments, and 4) had a global Clinical Dementia Rating (CDR) score of 0.5 or 1.0. Neuropsychological tests and CDR were performed within 3 months of MRI. No neurological events occurred between these tests and MRI.

We diagnosed MCI according to the National Institute on Aging–Alzheimer's Association (NIA-AA) criteria for MCI patients. [19] MCI was classified into MCI due to AD or other types of MCI. The global CDR score was 0.5. We diagnosed AD according to the NIA-AA guidelines.[20] Vascular dementia was diagnosed according to the criteria set forth by the American Heart Association/American Stroke Association.[21]

Neuropsychological assessments

The Mini-Mental State Examination (MMSE)[22] and Japanese Raven's Coloured Progressive Matrices (RCPM)[23] were used to quantify intellectual function. Memory was evaluated using the Rivermead Behavioral Memory Test (RBMT). The scores included a standard profile score (SPS) and screening score (SS).[24] Constructional

ability was assessed using the Mie Constructional Apraxia Scale (MCAS).[25] Frontal lobe function was assessed using two tasks: word fluency (WF) and trail making test (TMT) -A/-B.[26] The WF test consisted of category and letter domains. In the category WF task (WF-category), participants were asked to name as many animals as possible in 1 minute. In the letter WF task (WF-letter), participants were asked to name as many objects as possible in 1 minute, beginning with each of the following four phonemes: *ka, sa, ta,* and *te*. The average scores for these four phonemes were used for statistical analyses.

CDR was performed by two speech therapists, and results were evaluated through a discussion between two neurologists and three speech therapists based on the CDR determination rules.[27]

MRI protocol

We followed the MRI protocol by Ii et al.[28] Briefly, MRI studies were performed with a 3T MRI unit (Achieva, Philips Medical System, Best, the Netherlands) using an 8- or 32-channel phased-array head coil. We used T1- and T2-weighted images and 3D-fluid attenuated inversion recovery (FLAIR) images for the evaluation of WMH, lacunar infarcts, and PVS. Susceptibility-weighted image (SWI) sequences were used for the

detection of MBs and cSS. 3D-double inversion recovery (DIR) and 3D-FLAIR was used for the detection of CMIs. Axial DIR imaging was performed using two different inversion pulses. The long inversion time and the short inversion time were defined as the intervals between the 180° inversion pulse and the 90° excitation pulse, respectively, which had been optimized for human brain imaging and were provided by the vendor.

Details of the 2D- and 3D-DIR protocols were as follows: field of view, 230 mm; matrix, 320 × 256 (512 × 512) after reconstruction; in-plane resolution, 0.45 mm × 0.45 mm; section thickness, 3 mm with no intersection gap; no parallel imaging; repetition time (ms)/echo time (ms), 15,000/28; long inversion time (ms)/short inversion time (ms), 3,400/325; number of signals acquired, two; and acquisition time, 4 min 30 s for 2D, and field of view, 250 mm; matrix, 208 × 163 (256 × 256) after reconstruction; in plane resolution, 0.98 mm × 0.98 mm; section thickness, 0.65 mm with over contiguous slice; TSE factor 173; repetition time (ms)/echo time (ms), 5,500/247; long inversion time (ms)/short inversion time (ms), 2,550/450; number of signals acquired, two; and acquisition time, 5 min 13 s for 3D.

The SWI details were as follows: field of view, 230 mm; matrix, 320 × 251 (512 × 512) after reconstruction; in-plane resolution, 0.45 mm × 0.45 mm; section thickness, 0.5 mm with over contiguous slice; repetition time (ms)/echo time (ms), 22/11.5 (in-phase), 33

(shifted); number of signals acquired, one; flip angle 20°; and acquisition time, 5 min 45 s. 3D-FLAIR imaging was obtained in a sagittal direction, and then the axial and coronal images were reconstructed. The 3D-FLAIR details were as follows: field of view, 260 mm; matrix, 288 × 288 (364 × 364) after reconstruction; in-plane resolution, 0.68 × 0.67 mm; section thickness, 1 mm with 0.5 mm overlap; no parallel imaging; repetition time (ms)/echo time (ms), 6,000/400; inversion time, 2,000 ms; number of signals acquired, two; and acquisition time, 5 min 12 s.

SVD scores

The HA-SVD score was determined by Klarenbeek et al., where 1 point was awarded for each of the four markers (lacunar infarcts, MBs, BG-PVS, and WMH), with a minimum score of 0 and a maximum score of 4.[14] The CAA-SVD score was proposed by Charidimou et al. (Table 1), with 1 point awarded for each of the four markers (lobar MBs, cSS, CSO-PVS, and WMH).[17] For lobar MBs, 1 point was awarded if two to four MBs were present and 2 points for five or more MBs. The presence of cSS was awarded with 1 point if focal and 2 points if disseminated. The presence of CSO-PVSs was confirmed if there were moderate to severe (> 20) PVSs (1 point if present), with a

minimum score of 0 and a maximum score of 6. Both scores were independently assessed by four raters.

Table 1. Cerebral amyloid angiopathy-cerebral small vessel disease (CAA-SVD) score and modified CAA-SVD score

MRI marker	Cut off	Points		
CAA-SVD score				
Lobar MBs	2 to 4	1		
	≥ 5	2		
cSS	Focal	1		
	Disseminated	2		
CSO-PVSs	>20	1		
WMH	deep WMH (Fazekas 2 or 3)	1		
	periventricular WMH (Fazekas 3)	1	total	/6
Modified CAA-SVD score				
posterior distribution of WMH		1		
CMI(s) due to CAA	≥1	1	total	/8

Modified CAA-SVD scores

We tried to modify CAA-SVD scores by adding one point each in the presence of posteriorly dominant WMH and CMIs related to CAA (Table 1).

Tissue quantification was performed using a novel in-house software (FUsed Software for Imaging Of Nervous system: FUSION)[29] that yielded an individualized volumetric brain tissue profile. The obtained T1-weighted and FLAIR images were imported from

the Digital Imaging and Communications in Medicine format files for processing. To increase the accuracy of segmentation, we used the Lesion Segmentation Tool for lesion filling.[30] Lesion filling was applied to T1-weighted images that were aligned with the lesion probability map. For pre-processing, the T1-weighted images were co-registered to the FLAIR images. Next, to separate out the white matter, segmentation was performed using the T1-weighted images and a mask covering the cerebral ventricles. The pre-processing function was based on SPM 8 (Wellcome Trust Centre for Neuroimaging, UCL). Second-level tissue segmentation was then performed to separate WMH from white matter using a semi-automated operation that extracted the pixels falling within a predetermined WMH value. The WMH volume, which appeared as hyperintense areas on FLAIR images, was quantified for each area. Brain tissue was classified into four areas based on the division of the longitudinal fissure of the cerebrum and central sulcus. WMH were automatically classified as periventricular hyperintensity or deep WMH, and their corrected volumes were quantified in cubic centimetres.[29] The anteroposterior centre of WMH was calculated in the following way. To determine the reference point, we identified two anatomical landmarks (anterior, A and posterior, P). Point A was defined as the most anterior part on the wall of the frontal horn of the lateral ventricle. Point P

was defined as the most posterior part of the dura mater covering the occipital cortex.[8] If there was a large amount of posterior WMH, 1 point was added to the CAA-SVD score.

CMIs were defined as small cortical hyperintense lesions non-adjacent to WMH. When CMIs were localized within the cortex, predominantly in the occipital lobe, were smaller than 5 mm in diameter, and had fewer than three lesions, they were defined as CMIs related to CAA. (Ishikawa score) [13] When there were any CMIs related to CAA, we added 1 point to the CAA-SVD score.

Statistical analyses

The association between each SVD score (dependent variable) and cognitive function (independent variable) was analysed using linear regression analysis. Clinical and radiological characteristics are presented as numbers with percentages and means with standard deviation (SD). Statistical analyses were performed using IBM SPSS statistics software version 20 (IBM Corp., Armonk, NY, United States). Differences with $p<0.05$ were considered statistically significant.

Patient and public involvement

There was no patient involvement.

RESULTS

Patients

In total, 50 patients were registered for this study, and 42 fulfilled the inclusion criteria. Clinical characteristics, neuropsychological test results, and MRI findings of the participants are shown in Table 2. The mean age was 75.3±9.12 years, and there were 23 men (54.7%). Regarding vascular risk factors, 22 patients had hypertension (52.3%), four had diabetes mellitus (9.5%), and 11 smoked and had dyslipidaemia (26.1%). Fourteen patients had a history of lacunar stroke (33.3%) and 24 patients (57.1%) met the modified Boston criteria (ver 1.5).

Table 2. Participant characteristics

Clinical characteristics	All participants, n= 42
Age, years, mean (SD)	75.3 (9.12)
Education, years, mean (SD)	11.9 (2.34)
Male sex (n, %)	23 (54.7)
Vascular risk factors	
hypertension (n, %)	22 (52.3)
dyslipidemia (n, %)	11 (26.1)
diabetes mellitus (n, %)	4 (9.5)
smoking (n, %)	11 (26.1)
History of any stroke (n, %)	19 (45.2)
lacunar (n, %)	14 (33.3)
Medication	
anti-hypertensive (n, %)	7 (16.6)

	statin (n, %)	6 (14.2)
	anti-platelet or anti-coagulation (n, %)	8 (19.0)
Meets modified Boston criteria		
	probable CAA	11 (26.1)
	possible CAA	13 (30.9)
Neuropsychological tests		
Global CDR	0.5 (n, %)	30 (71.4)
	1.0 (n, %)	12 (28.6)
MMSE	Score (SD)	25.2 (2.39)
RCPM	Score (SD)	24.2 (5.73)
	Time,s (SD)	440 (198)
RBMT	Standard profile score (SD)	11.5 (5.49)
	Screening score (SD)	4.5 (2.78)
TMT	A, s (SD)	257 (156)
	B, s (SD)	265 (95.6)
WF, /min	Category (SD)	10.9 (3.93)
	Letters (SD)	5 (1.72)
MCAS	Score (SD)	3.3 (1.68)
	time,s (SD)	49.6 (37.4)
MRI findings		
MBs; all	≥ 1 (n, %)	31 (73.8)
MBs; Lobar	2 to 4 (n, %)	16 (38.0)
	≥ 5 (n, %)	10 (23.8)
cSS	Focal (n, %)	3 (7.1)
	Disseminated (n, %)	0
BG-PVSs	>20 (n, %)	25 (59.5)
CSO-PVSs	>20 (n, %)	30 (71.4)
WMH	deep WMH (Fazekas 2 or 3) (n, %)	26 (61.9)
	periventricular WMH (Fazekas 3) (n, %)	11 (26.1)
posterior distributon of WMH (n, %)		7 (16.6)

CMI(s) due to CAA (n, %)	3 (7.1)

The global CDR score was 0.5 for 30 patients (71.4%) and 1.0 for 12 patients (28.6%). Of the 12 patients with a global CDR score of 1.0, 10 met the criteria reflecting probable AD and two had vascular dementia. Among 30 patients with MCI, 20 had MCI due to AD and 10 had other types of MCI. Regarding MRI findings, 31 patients had ≥1 MBs (73.8%), 16 had ≥2 and ≤4 lobar MBs (38.0%), and 10 had ≥5 lobar MBs (23.8%). Three patients had focal cSS (7.1%), 25 had >20 BG-PVSs (59.5%), 30 had >20 CSO-PVSs (71.4%), 26 had deep WMH (Fazekas 2 or 3) (61.9%), and 11 had periventricular WMH (Fazekas 3) (26.1%).

WMH were divided according to whether they were anterior or posterior and were analysed using FUSION. There were seven posterior superiorities (16.6%). CMIs related to CAA were detected in three patients (7.1%), and two of these patients met the modified Boston criteria for probable CAA. The patients with CMIs did not have any evidence of CAA except for CMIs, such as atrial fibrillation and cerebral artery stenosis.

Results of each SVD score

As for each SVD score (Table 3), the HA-SVD score was 0 in 3 patients (7.1%), 1 in 7 patients (16.6%), 2 in 14 patients (33.3%), 3 in 11 patients (26.1%), and 4 in 7 patients

(16.6%). The CAA-SVD score was 0 in 5 patients (11.9%), 1 in 6 patients (14.2%), 2 in 13 patients (30.9%), 3 in 12 patients (28.5%), and 4 in 6 patients (14.2%). Moreover, the modified CAA-SVD score was 0 in 1 patient (2.3%), 1 in 6 patients (14.2%), 2 in 8 patients (19%), 3 in 13 patients (30.9%), 4 in 11 patients (26.1%), 5 in 2 patients (4.7%), and 6 in 1 patient (2.3%). A significant difference was observed when the HA-SVD scores and CAA-SVD scores were analysed using Pearson's chi-square test (p=0.000).

Table 3. Cerebral small vessel disease score

Score	**All participants n = 42**
HA-SVD score (n, %)	
0	3 (7.1)
1	7 (16.6)
2	14 (33.3)
3	11 (26.1)
4	7 (16.6)
CAA-SVD score (n, %)	
0	5 (11.9)
1	6 (14.2)
2	13 (30.9)
3	12 (28.5)
4	6 (14.2)
5	0 (0)

6	0 (0)
Modified CAA-SVD score (n, %)	
0	1 (2.3)
1	6 (14.2)
2	8 (19.0)
3	13 (30.9)
4	11 (26.1)
5	2 (4.7)
6	1 (2.3)
7	0 (0)
8	0 (0)

Cognitive function and the three types of SVD scores

HA-SVD score

With regard to the relationship between each cognitive function and the HA-SVD score, no significant difference was found across any function (Table 4), such as MMSE (p=0.52), RCPM (p=0.47), RBMT-SPS (p=0.15), RBMT-SS (p=0.11), TMT-A (p=0.85), TMT-B (p=0.23), WF-category (p=0.10), WF-letter (p=0.17), or MCAS (p=0.23). Additionally, the linear regression models of the associations between the HA-SVD scores and cognitive function revealed that the coefficient of determination was R^2=0.409 (p=0.35), and the regression equation did not hold. The Akaike's Information Criterion (AIC) was 122.493.

Table 4. Linear regression models of associations between cognitive function and SVD score

	unstandardized beta (SE)			*p*		
	HA-SVD score	CAA-SVD score	Modified CAA-SVD score	HA-SVD score	CAA-SVD score	Modified CAA-SVD score
MMSE	0.191	0.713	0.771	0.521	**0.006**	**0.001**
RCPM	-0.185	-0.295	-0.17	0.474	0.153	0.384
RBMT-SPS	1.057	0.732	0.622	0.159	0.209	0.267
RBMT-SS	-1.148	-1.055	-1.005	0.111	0.064	**0.048**
TMT-A	0.065	0.107	0.192	0.854	0.698	0.476
TMT-B	0.395	0.516	0.412	0.239	0.057	0.11
WF (Category)	0.426	0.414	0.448	0.104	**0.047**	**0.028**
WF (Letters)	-0.38	-0.079	-0.097	0.17	0.71	0.634
MCAS	-0.686	-0.584	-0.564	0.052	**0.036**	**0.026**

CAA-SVD score

With regard to the relationship between each cognitive function and the CAA-SVD score, a significant difference was found in 3/9 items (Table 4), including MMSE

(p=0.006), WF-category (p=0.04), and MCAS (p=0.03), while there was no significant difference in 6/9 items, including RCPM (p=0.15), RBMT-SP (p=0.20), RBMT-SS (p=0.06), TMT-A (p=0.69), TMT-B (p=0.05), and WF-letter (p=0.71). The results of the linear regression models of the associations between CAA-SVD scores and cognitive function demonstrated that the coefficient of determination was R^2=0.639 (p=0.016) and the AIC was 104.269.

Modified CAA-SVD score

With regard to the relationship between each cognitive function and the modified CAA-SVD score, a significant difference was found in 4/9 items (Table 4), including MMSE (p=0.001), RBMT-SS (p=0.04), WF-category (p=0.02), and MCAS (p=0.04), while no significant difference was found in 5/9 items, including RCPM (p=0.14), RBMT-SP (p=0.33), TMT-A (p=0.19), TMT-B (p=0.21), and WF-letter (p=0.56). The results of the linear regression models of the associations between the CAA-SVD scores and cognitive function revealed that the coefficient of determination was R^2=0.645 (p=0.008) and the AIC was 103.43.

On assessing the relationship between each cognitive function and each SVD score, a significant difference was found in MMSE, WF-category, MCAS, and RBMT-SS. Among these four items, the WF-category had the highest coefficient of determination for the HA-SVD score (R^2=0.0135), and the RBMT-SS had the highest coefficient of determination for the CAA-SVD (R^2=0.0142) and modified CAA-SVD scores (R^2=0.0161). In the linear regression models of the associations between each SVD score and RBMT-SS, the coefficient of determination was found to increase in the following order: HA-SVD score < CAA-SVD score < modified CAA-SVD score (Fig 2).

DISCUSSION

This study demonstrated a novel association between the CAA-SVD score and cognitive function in memory clinic patients, whereas no significant association was found between the HA-SVD score and cognitive function. Additionally, there was a significant difference between the HA-SVD score and CAA-SVD score; i.e., WF-category had the highest coefficient of determination for the HA-SVD score, and the RBMT-SS had the highest coefficient of determination for the CAA-SVD and modified CAA-SVD scores. Moreover, it is plausible that the modified CAA-SVD score, in addition to the analysis of

the posterior distribution of WMH and CMIs, may be a useful tool for evaluating patients with MCI or mild dementia.

Taken together, our study showed that there was a significant difference in each cognitive domain between the HA-SVD score and CAA-SVD score, and a significant association between the CAA-SVD score and cognitive function. This result indicates that the CAA-SVD score may reflect the cognitive function in patients of a memory clinic. Although a previous report showed that the HA-SVD score showed significant associations with intellectual function in patients having had a lacunar stroke and/or with hypertension,[16] our study did not show any such significant association. This may be attributed to the patients' background, such as older age and lower prevalence of vascular factors. The mean age of patients in the previous study was 63.1 years, while the mean age of patients in our study was 75.3 years. Moreover, in our study, 22 patients had hypertension (52.3%) and 14 patients had a lacunar stroke (33.3%) compared to 84.1% and 68.7%, respectively, in a previous study.

The HA-SVD score and CAA-SVD score share common components including WMH, PVS, and MBs. The HA-SVD score includes lacunar infarcts, whereas the CAA-SVD score includes cSS. Moreover, the location of PVS and MBs differ between the HA- and CAA-SVD scores. Previous reports have shown that CSO-PVS is negatively correlated

with memory and that BG-PVS is negatively correlated with processing speed, executive function, and memory.[16] Additionally, the presence and number of MBs have been associated with cognitive impairment.[31] The incidence of cSS is extremely low and difficult to study in healthy individuals[32]; however, cSS is highly-specific for CAA. As described above, the CAA-SVD score was produced by adding cSS to the WMH and region-specific MBs and PVS and was more related to cognitive function than the HA-SVD score.

The modified CAA-SVD score improved the prediction accuracy of the regression equation, reduced the AIC, and slightly improved the prediction accuracy compared to the CAA-SVD score. CMIs are an important risk factor for dementia, and it has been reported that the presence of CMIs approximately doubles the risk of dementia.[32] One of the major causes of CMIs is CAA.[33] Additionally, several reports have described the relationship between WMH and cognitive function,[34] and WMH due to CAA have been reported to be posterior-dominant.[35] Therefore, it was thought that incorporation of these two markers may have affected relationship with cognitive function in an additive manner.

On observing the results for each test item, the CAA-SVD score was found to have significant associations with constructional ability and memory. This observation is in

line with the diagnostic criteria of NIA-AA, which includes constructional ability and memory as an essential cognitive domain.[36]

These results in our study may be dependent on the background of the patients in our memory clinic. In this study, 24 patients (57.1%) met the modified Boston criteria (ver 1.5), 10 of 12 patients with mild dementia had AD, and MCI due to AD was present in 20 out of 30 MCI patients. MCI due to AD has been reported to have a high rate of progression to AD.[37] Low prevalence of vascular risk and advanced aging in the present study may indicate that our memory clinic's patients had a higher burden of amyloid pathology. Therefore, the CAA-SVD score and modified CAA-SVD score may reflect the pathological background of AD. The CAA-SVD score may be a useful tool for memory clinic patients whereas the SVD scores may not, rather being suited for the patients with vascular risk factors. Additionally, there may be a possibility that cognitive dysfunction can be detected earlier by evaluating patients with a score that is well-tailored to them, thereby enabling appropriate subsequent patient treatment.

This study had several limitations. First, it was based on a relatively small sample size. Second, deep MBs is common in Japan [38], but the patients included in this study mostly had strictly lobar MBs, and we believe that there was selection bias due to recruiting patients from a memory clinic. Third, we were unable to carry out

pathological examinations. The patient who did not meet the modified Boston criteria but meet the CAA due to CMI criteria are scored as CAA related CMI. In the previous report, 17% of the pathological patients had a CAA but a CAA score of 0, and most of the pathological changes were mild.[17] CMI is also detected by mild CAA.[39] The Ishikawa score is based on the characteristics of CAA patients, and we considered that there is no problem with this addition, but this case also requires pathological findings. These issues should be addressed in future studies. Forth, currently, FUSION has its limits and cannot distinguish small infarcts and enlarged PVS. At present, the radiologist visually confirmed whether the results of FUSION were likely to be affected, and it was determined that the results were not affected. We aim to improve the software so that it can distinguish small infarcts and enlarged PVS in the future. Fifth, we have not validated the weighting of the modified CAA-SVD score; this needs further investigation. Finally, there was no significant association between the HA-SVD score and cognitive function in this study, possible due to the limited number of patients with hypertension included in this study. Furthermore, even though there is a possibility that a larger number of cases may allow a significant correlation, further and lager studies would be required to validate this.

Despite these limitations, our study shows that patients with MCI or mild dementia should be evaluated with the CAA-SVD score. The modified CAA-SVD score may also be applicable to these patients.

Competing Interests: The authors have no conflict of interest to declare.

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

Data availability: No additional data available.

Contributorship statement:

KM: draft of manuscript, acquisition of data, and analysis.

AS: revision of manuscript, interpretation of data, and study supervision.

KIT and YI: revision of manuscript and interpretation of data.

YU, HI, KM, KY, AT, NK, MS, MM: acquisition of data and interpretation of data.

HT: revision of the manuscript, study concept and design, and study supervision.

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Figure Legends

Figure 1. Representative MRI findings of cerebral small vessel disease

The arrows show lobar cerebral MBs on SWI sequences. MRI in a patient with CAA (A). cSS was observed in SWI sequences in a patient with CAA (arrows, B). Centrum semiovale enlarged perivascular spaces on T2-weighted imaging in a patient with CAA (C). WMH assessed by fluid attenuated inversion recovery imaging. WMH in CAA patients was posterior-dominant (D). Double inversion recovery imaging shows a CMI that localized within the cortex and was 3 mm in diameter (arrow). CMIs from patients with CAAs (E) showed that all lesions were localized within cortical structures, with a size of <5 mm [13].

MRI, magnetic resonance imaging; MBs, cerebral amyloid angiopathy; SWI, susceptibility-weighted image; CAA, cerebral amyloid angiopathy; WMH, white matter hyperintensities; CMI, cortical microinfarct

Figure 2. Linear regression models of the associations between each cerebral small vessel disease (SVD) score and the Rivermead Behavioral Memory Test-screening score (RBMT-SS)

HA, hypertensive arteriopathy; CAA, cerebral amyloid angiopathy

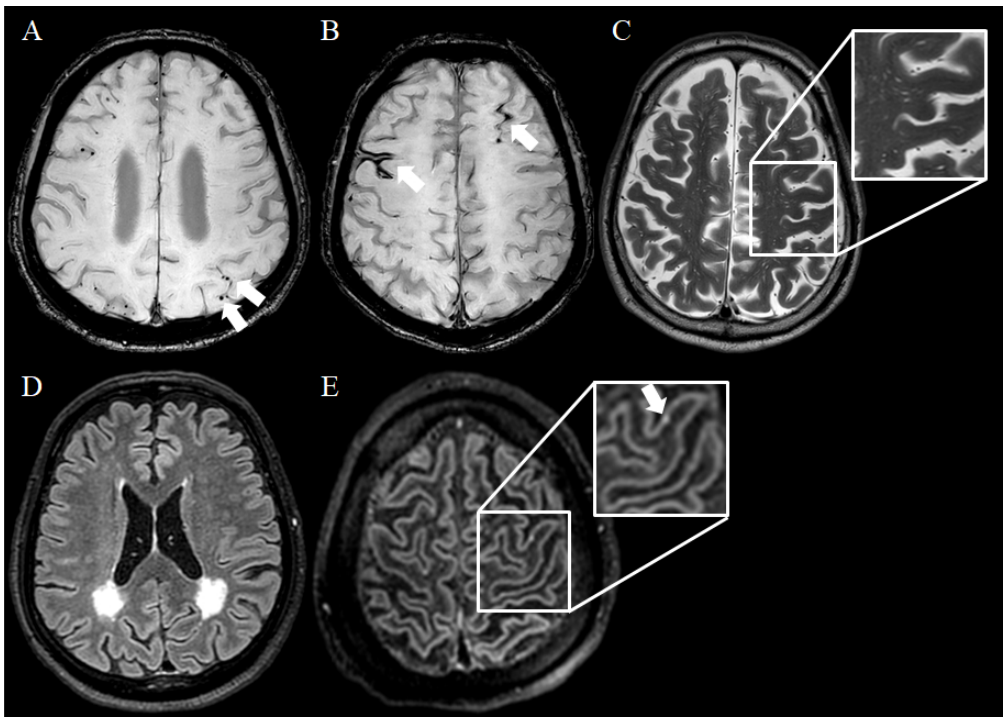
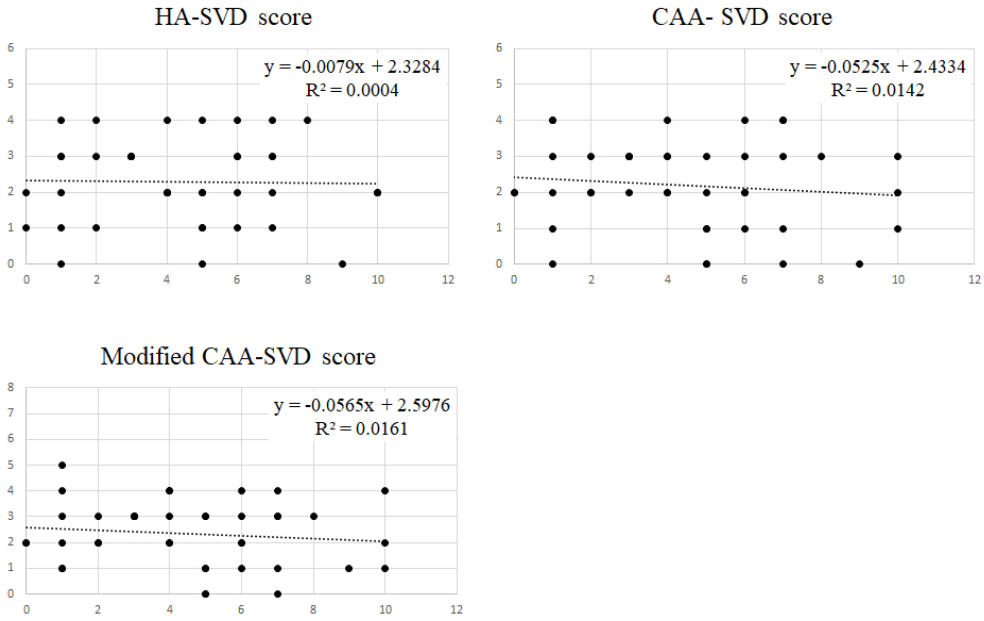


Figure 1

240x171mm (96 x 96 DPI)



165x106mm (144 x 144 DPI)

Standards for Reporting Qualitative Research (SRQR)*

http://www.equator-network.org/reporting-guidelines/srqr/

	Page/line no(s).
Title and abstract	
Title - Concise description of the nature and topic of the study Identifying the study as qualitative or indicating the approach (e.g., ethnography, grounded theory) or data collection methods (e.g., interview, focus group) is recommended	6-12
Abstract - Summary of key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results, and conclusions	2-3
Introduction	
Problem formulation - Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work; problem statement	5-6
Purpose or research question - Purpose of the study and specific objectives or questions	6
Methods	
Qualitative approach and research paradigm - Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g., postpositivist, constructivist/ interpretivist) is also recommended; rationale**	6-7
Researcher characteristics and reflexivity - Researchers' characteristics that may influence the research, including personal attributes, qualifications/experience, relationship with participants, assumptions, and/or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results, and/or transferability	6-7
Context - Setting/site and salient contextual factors; rationale**	4-6
Sampling strategy - How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g., sampling saturation); rationale**	6-7
Ethical issues pertaining to human subjects - Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues	6
Data collection methods - Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources/methods, and modification of procedures in response to evolving study findings; rationale**	6-7

Data collection instruments and technologies - Description of instruments (e.g., interview guides, questionnaires) and devices (e.g., audio recorders) used for data collection; if/how the instrument(s) changed over the course of the study	6-9
Units of study - Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results)	11
Data processing - Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymization/de-identification of excerpts	6-12
Data analysis - Process by which inferences, themes, etc., were identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale**	6-12
Techniques to enhance trustworthiness - Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale**	7-12

Results/findings

Synthesis and interpretation - Main findings (e.g., interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory	13-19
Links to empirical data - Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate analytic findings	13-19

Discussion

Integration with prior work, implications, transferability, and contribution(s) to the field - Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application/generalizability; identification of unique contribution(s) to scholarship in a discipline or field	19
Limitations - Trustworthiness and limitations of findings	22

Other

Conflicts of interest - Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed	23
Funding - Sources of funding and other support; role of funders in data collection, interpretation, and reporting	23

*The authors created the SRQR by searching the literature to identify guidelines, reporting standards, and critical appraisal criteria for qualitative research; reviewing the reference lists of retrieved sources; and contacting experts to gain feedback. The SRQR aims to improve the transparency of all aspects of qualitative research by providing clear standards for reporting qualitative research.

**The rationale should briefly discuss the justification for choosing that theory, approach, method, or technique rather than other options available, the assumptions and limitations implicit in those choices, and how those choices influence study conclusions and transferability. As appropriate, the rationale for several items might be discussed together.

Reference:

O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. **Standards for reporting qualitative research: a synthesis of recommendations.** *Academic Medicine*, Vol. 89, No. 9 / Sept 2014
DOI: 10.1097/ACM.0000000000000388

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *case-control studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	#1, #3-4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	#3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	#6-8
Objectives	3	State specific objectives, including any prespecified hypotheses	#8
Methods			
Study design	4	Present key elements of study design early in the paper	#8-12
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	#8-9
Participants	6	(a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	#8-9
		(*b*) For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	#8-12
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	#12-15
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	#8-9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	#15
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	#15
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how matching of cases and controls was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	#16
		(b) Give reasons for non-participation at each stage	#16
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	#16-18
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	#23-24
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	#26-27
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	#24-26
Generalisability	21	Discuss the generalisability (external validity) of the study results	#27
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	#27

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.