

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

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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 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-

Strengths and limitations of this study

- We examined the association between cognitive function and hypertensive arteriopathy-small vessel disease (SVD), and cerebral amyloid angiopathy (CAA)-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.

SVD score, these scores can be a predictor of cognitive deterioration in patients with MCI and mild dementia.

INTRODUCTION

Cerebral small vessel disease (SVD) is a comprehensive term that describes small vessel pathological conditions, including ischaemia and haemorrhage, in the brain. Patients with SVD share common pathological, clinical and neuroimaging features.¹ Neuroradiological findings of SVD are examined using brain MRI, which shows various vascular lesions, including white matter

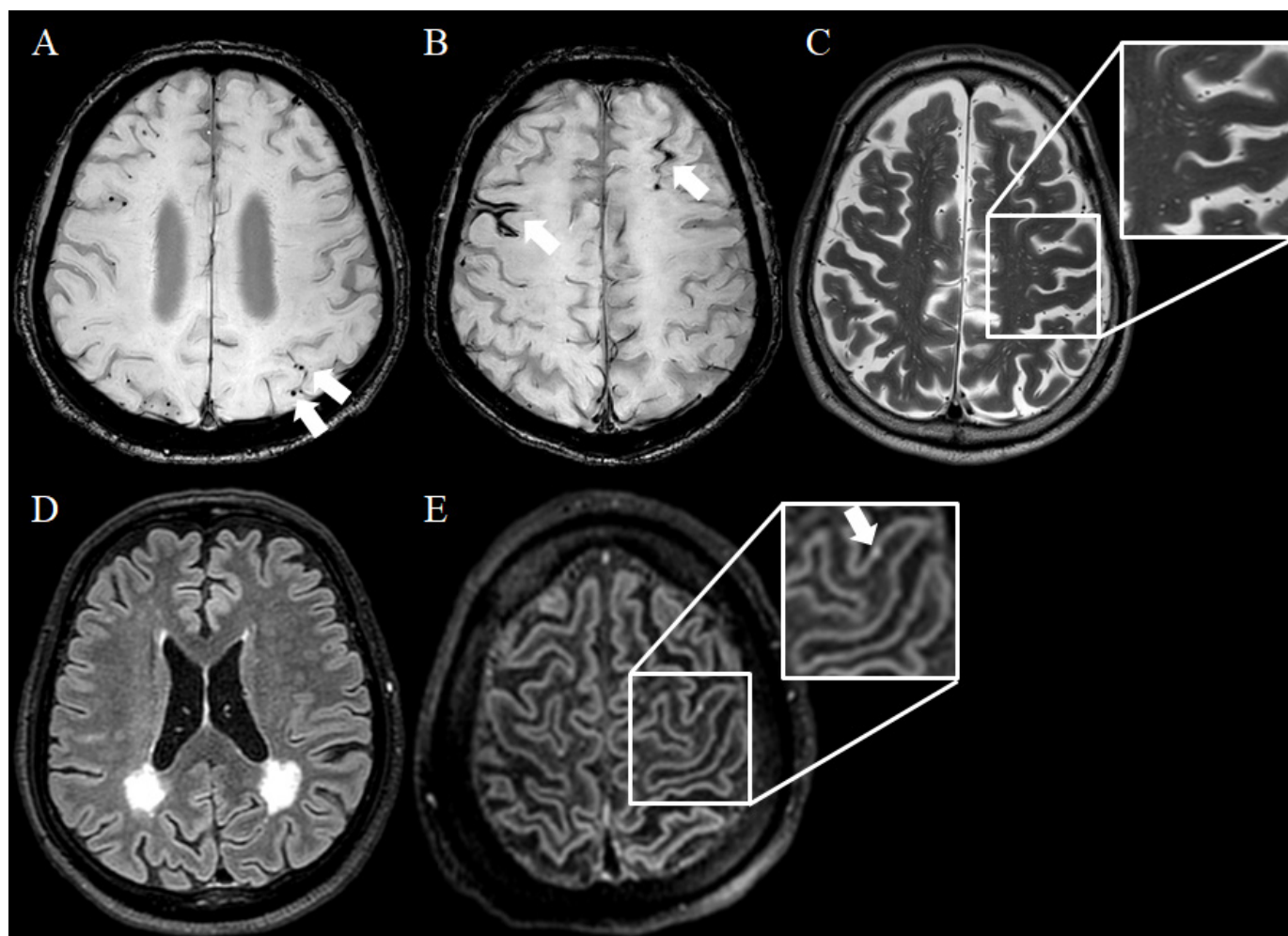


Figure 1 Representative MRI findings of cerebral small vessel disease. The arrows show lobar cerebral microbleeds on SWI sequences. MRI in a patient with CAA (A). Cortical superficial siderosis was observed in SWI sequences in a patient with CAA (arrows, B). Centrum semiovale enlarged perivascular spaces on T2-weighted imaging in a patient with CAA (C). WMH assessed by fluid attenuated inversion recovery imaging. WMH in patients with CAA was posterior-dominant (D). Double inversion recovery imaging shows a CMI that localised within the cortex and was 3 mm in diameter (arrow). CMIs from patients with CAAs (E) showed that all lesions were localised within cortical structures, with a size of <5 mm.¹³ CAA, cerebral amyloid angiopathy; CMI, cortical microinfarct; SWI, susceptibility-weighted image; WMH, white matter hyperintensities.

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 ageing 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 characterised by the progressive deposition of amyloid beta (A β) protein in the cerebral vessels, and the major peptide isoforms of A β mainly consist of A β ₁₋₄₀ and A β ₁₋₄₂.⁵ Although both HA and CAA share common

MRI features (figure 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 microembolism¹²; however, neuroradiological findings obtained using 3 Tesla (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.*¹⁴ enrolled patients with lacunar stroke and assessed different MRI features, including lacunar infarct, MBs, BG-PVS and WMH. 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.*¹⁷ developed a novel SVD score for patients with CAA (CAA-SVD score), 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. 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 Clinical Dementia Rating (CDR) and MRI were 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 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 patients with MCI.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 Behavioural 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 min. In the letter WF task (WF-letter), participants were asked to name as many objects as possible in 1 min, 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-channel or 32-channel phased-array head coil. We used T1-weighted and T2-weighted images and three-dimensional (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 were 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 optimised for human brain imaging and were provided by the vendor.

Details of the two-dimensional (2D)-DIR 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), 3400/325; 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; turbo spin echo factor (TSE) factor 173; repetition time (ms)/echo time (ms), 5500/247; long inversion time (ms)/short inversion time (ms), 2550/450; 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

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

MRI marker	Cut-off	Points	
CAA-SVD score			
Lobar microbleeds	2–4	1	
	≥5	2	
Cortical superficial siderosis	Focal	1	
	Disseminated	2	
Centrum semiovale-perivascular spaces	>20	1	
White matter hyperintensities (WMH)	Deep WMH (Fazekas 2 or 3)	1	
	Periventricular WMH (Fazekas 3)	1	Total/6
Modified CAA-SVD score			
Posterior distribution of WMH		1	
Cortical microinfarcts due to CAA	≥1	1	Total/8

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 mm×0.67 mm; section thickness, 1 mm with 0.5 mm overlap; no parallel imaging; repetition time (ms)/echo time (ms), 6000/400; inversion time, 2000 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*,¹⁴ where one 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. The CAA-SVD score was proposed by Charidimou *et al*,¹⁷ (table 1), with one point awarded for each of the four markers (lobar MBs, cSS, CSO-PVS and WMH). For lobar MBs, one point was awarded if two to four MBs were present and two points for five or more MBs. The presence of cSS was awarded with one point if focal and two points if disseminated. The presence of CSO-PVSs was confirmed if there were moderate-to-severe (>20) PVSs (one point if present), with a minimum score of 0 and a maximum score of 6. Both scores were independently assessed by four raters.

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 individualised 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, one point was added to the CAA-SVD score.

CMIs were defined as small cortical hyperintense lesions non-adjacent to WMH. When CMIs were localised within the cortex, predominantly in the occipital lobe, they 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 one 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 SD. Statistical analyses were performed using IBM SPSS statistics software V.20. 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%), 4 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 (V.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 2 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 χ^2 test ($p=0.000$).

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 ($p=0.05$). 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.

CAA-SVD score

With regard to the relationship between each cognitive function and the CAA-SVD score, a significant difference was found in three out of nine 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 six out of nine 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 four out of nine items ([table 4](#)), including MMSE ($p=0.001$), RBMT-SS ($p=0.04$), WF-category ($p=0.02$) and MCAS ($p=0.03$), while no significant difference was found in five out of nine items, including RCPM ($p=0.38$), RBMT-SPS ($p=0.33$), TMT-A ($p=0.48$), TMT-B ($p=0.11$) and WF-letter ($p=0.63$). 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 ($R^2=0.0004$), 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 ([figure 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; that is, WF-category had the highest coefficient of determination for the HA-SVD score, and the RBMT-SS had the highest

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)
	Dyslipidaemia (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	2–4 (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) due to CAA (n, %)		3 (7.1)

Continued

Table 2 Continued

Clinical characteristics

All participants, n=42

BG-PVS, PVS in the basal ganglia; CAA, cerebral amyloid angiopathy; CDR, Clinical Dementia Rating; CMI, cortical microinfarct; CSO-PVS, centrum semiovale PVS; cSS, cortical superficial siderosis; MBs, microbleeds; MCAS, Mie Constructional Apraxia Scale; MMSE, Mini-Mental State Examination; PVS, perivascular spaces; RBMT, Rivermead Behavioural Memory Test; RCPM, Raven's Coloured Progressive Matrices; TMT, trail making test; WF, word fluency; WMH, white matter hyperintensities.

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 with 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-SVD 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 individuals³²; 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 with 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.⁸ 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.³⁵

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 (V.1.5), 10 of 12 patients with mild dementia

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)

CAA, cerebral amyloid angiopathy; HA, hypertensive arteriopathy; SVD, small vessel disease.

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

	Unstandardised beta (SE)			P value		
	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

P-values less than 0.05 are shown in bold

CAA, cerebral amyloid angiopathy; HA, hypertensive arteriopathy; MCAS, Mie Constructional Apraxia Scale; MMSE, Mini-Mental State Examination; RBMT, Rivermead Behavioural Memory Test; RCPM, Raven's Coloured Progressive Matrices; SPS, standard profile score; SS, screening score; SVD, small vessel disease; TMT, trail making test; WF, word fluency.

had AD and MCI due to AD was present in 20 out of 30 patients with MCI. MCI due to AD has been reported to have a high rate of progression to AD.³⁶ Low prevalence of vascular risk and advanced ageing 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,³⁷ but the patients included in this study mostly

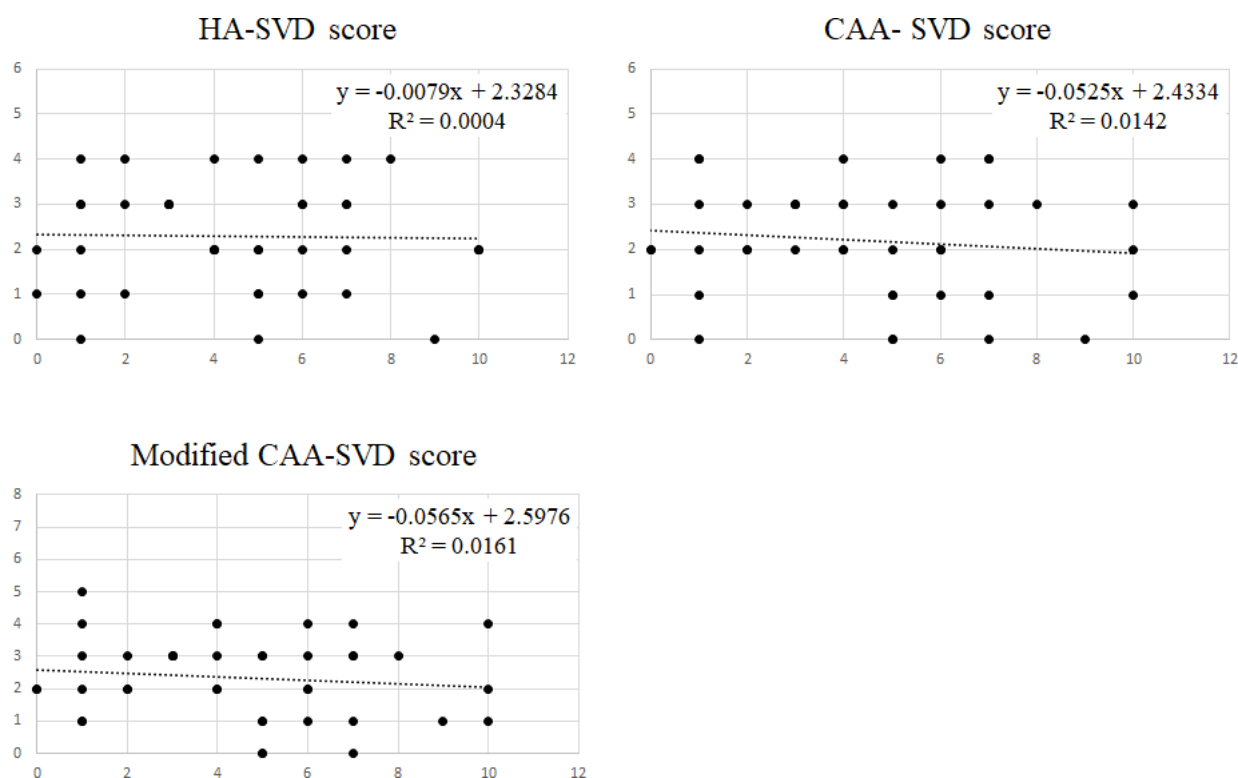


Figure 2 Linear regression models of the associations between each cerebral small vessel disease (SVD) score and the Rivermead Behavioural Memory Test-screening score. CAA, cerebral amyloid angiopathy; HA, hypertensive arteriopathy.

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.³⁸ The Ishikawa score is based on the characteristics of patients with CAA, 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. Fourth, 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, possibly 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 larger 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.

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REFERENCES

- 1 Wardlaw JM, Smith EE, Biessels GJ, *et al*. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol* 2013;12:822–38.
- 2 Wardlaw JM, Smith C, Dichgans M. Small vessel disease: mechanisms and clinical implications. *Lancet Neurol* 2019;18:684–96.
- 3 Chui H, dementia V. Vascular dementia, a new beginning: shifting focus from clinical phenotype to ischemic brain injury. *Neurol Clin* 2000;18:951–78.
- 4 Tomimoto H. Subcortical vascular dementia. *Neurosci Res* 2011;71:193–9.
- 5 Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol* 2010;9:689–701.
- 6 Charidimou A, Pantoni L, Love S. The concept of sporadic cerebral small vessel disease: a road map on key definitions and current concepts. *Int J Stroke* 2016;11:6–18.
- 7 Furuta A, Ishii N, Nishihara Y, Horie A, *et al*. Medullary arteries in aging and dementia. *Stroke* 1991;22:442–6.
- 8 Thanprasertsuk S, Martinez-Ramirez S, Pontes-Neto OM, *et al*. Posterior white matter disease distribution as a predictor of amyloid angiopathy. *Neurology* 2014;83:794–800.
- 9 Charidimou A, Jaunmuktane Z, Baron J-C, *et al*. White matter perivascular spaces: an MRI marker in pathology-proven cerebral amyloid angiopathy? *Neurology* 2014;82:57–62.
- 10 Greenberg SM, Vernooij MW, Cordonnier C, *et al*. Cerebral microbleeds: a guide to detection and interpretation. *Lancet Neurol* 2009;8:165–74.
- 11 Linn J, Halpin A, Demaerel P, *et al*. Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy. *Neurology* 2010;74:1346–50.
- 12 Kövari E, Herrmann FR, Gold G, *et al*. Association of cortical microinfarcts and cerebral small vessel pathology in the ageing brain. *Neuropathol Appl Neurobiol* 2017;43:505–13.
- 13 Ishikawa H, Li Y, Shindo A, *et al*. Cortical microinfarcts detected by 3-tesla magnetic resonance imaging. *Stroke* 2020;51:1010–3.
- 14 Klarenbeek P, van Oostenbrugge RJ, Rouhl RPW, *et al*. Ambulatory blood pressure in patients with lacunar stroke: association with total MRI burden of cerebral small vessel disease. *Stroke* 2013;44:2995–9.
- 15 Staals J, Makin SDJ, Doubal FN, *et al*. Stroke subtype, vascular risk factors, and total MRI brain small-vessel disease burden. *Neurology* 2014;83:1228–34.
- 16 Huijts M, Duits A, van Oostenbrugge RJ, *et al*. Accumulation of MRI markers of cerebral small vessel disease is associated with decreased cognitive function. A study in first-ever lacunar stroke and hypertensive patients. *Front Aging Neurosci* 2013;5:72.
- 17 Charidimou A, Martinez-Ramirez S, Reijmer YD, *et al*. Total magnetic resonance imaging burden of small vessel disease in cerebral amyloid angiopathy: an imaging-pathologic study of concept validation. *JAMA Neurol* 2016;73:994–1001.
- 18 Boulouis G, Charidimou A, Jessel MJ, *et al*. Small vessel disease burden in cerebral amyloid angiopathy without symptomatic hemorrhage. *Neurology* 2017;88:878–84.
- 19 Albert MS, DeKosky ST, Dickson D, *et al*. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7:270–9.
- 20 McKhann GM, Knopman DS, Chertkow H, *et al*. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups

- on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia* 2011;7:263–9.
- 21 Gorelick PB, Scuteri A, Black SE, *et al.* Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American heart association/american stroke association. *Stroke* 2011;42:2672–713.
 - 22 Mori E, Mitani Y, Yamadori A. Usefulness of a Japanese version of the Mini-Mental state test in neurological patients. *Jpn J Neuropsychol* 1985;1:82–90.
 - 23 Raven JC. *Coloured progressive matrices, sets a, AB, B*. London: H.K. Lewis, 1962.
 - 24 Wilson B, Cockburn J, Baddeley A, *et al.* The development and validation of a test battery for detecting and monitoring everyday memory problems. *J Clin Exp Neuropsychol* 1989;11:855–70.
 - 25 Satoh M, Mori C, Matsuda K, *et al.* Improved Necker cube drawing-based assessment battery for constructional apraxia: the Mie Constructional apraxia scale (MCAS). *Dement Geriatr Cogn Dis Extra* 2016;6:424–36.
 - 26 Abe M, Suzuki K, Okada K, *et al.* [Normative data on tests for frontal lobe functions: Trail Making Test, Verbal fluency, Wisconsin Card Sorting Test (Keio version)]. *No To Shinkei* 2004;56:567–74.
 - 27 Hughes CP, Berg L, Danziger WL, *et al.* A new clinical scale for the staging of dementia. *Br J Psychiatry* 1982;140:566–72.
 - 28 Li Y, Maeda M, Ishikawa H, *et al.* Cortical microinfarcts in patients with multiple lobar microbleeds on 3 T MRI. *J Neurol* 2019;266:1887–96.
 - 29 Tabei K-I, Kida H, Hosoya T, *et al.* Prediction of cognitive decline from white matter hyperintensity and single-photon emission computed tomography in Alzheimer's disease. *Front Neurol* 2017;8:408–18.
 - 30 Schmidt P, Gaser C, Arsic M, *et al.* An automated tool for detection of FLAIR-hyperintense white-matter lesions in multiple sclerosis. *Neuroimage* 2012;59:3774–83.
 - 31 Gregoire SM, Scheffler G, Jäger HR, *et al.* Strictly lobar microbleeds are associated with executive impairment in patients with ischemic stroke or transient ischemic attack. *Stroke* 2013;44:1267–72.
 - 32 Vernooij MW, Ikram MA, Hofman A, *et al.* Superficial siderosis in the general population. *Neurology* 2009;73:202–5.
 - 33 Kövari E, Gold G, Herrmann FR, *et al.* Cortical microinfarcts and demyelination affect cognition in cases at high risk for dementia. *Neurology* 2007;68:927–31.
 - 34 van der Flier WM, van Straaten ECW, Barkhof F, *et al.* Small vessel disease and general cognitive function in nondisabled elderly: the LADIS study. *Stroke* 2005;36:2116–20.
 - 35 McKhann GM, Knopman DS, Chertkow H, *et al.* The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7:263–9.
 - 36 Bennett DA, Schneider JA, Bienias JL, *et al.* Mild cognitive impairment is related to Alzheimer disease pathology and cerebral infarctions. *Neurology* 2005;64:834–41.
 - 37 Yakushiji Y, Wilson D, Ambler G. Distribution of cerebral microbleeds in the East and West-Individual participant meta-analysis. *Neurology* 2019;93:e1086–97.
 - 38 Arvanitakis Z, Capuano AW, Leurgans SE, *et al.* The relationship of cerebral vessel pathology to brain microinfarcts. *Brain Pathol* 2017;27:77–85.