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Original Article

Association between cerebral microbleeds and cognition in a memory clinic population

Young Min Choe [a], Hyewon Baek [b], Min Soo Byun [c,d], Dahyun Yi [e], Hyejin Ahn [f], Gijung Jung [e], Chul-Ho Sohn [g], Dong Young Lee [c,d,e,f,*]

[a] Department of Neuropsychiatry, Hallym University Dongtan Sacred Heart Hospital, 7, Keunjaebong-gil, Hwaseong 18450, Republic of Korea
[b] Department of Neuropsychiatry, Gyeonggi Provincial Hospital for the Elderly, 940, Jungbu-daero, Giheung-gu, Yongin 17089 Republic of Korea
[c] Department of Neuropsychiatry, Seoul National University Hospital, 101, Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea
[d] Department of Psychiatry, Seoul National University College of Medicine, 101, Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea
[e] Institute of Human Behavioral Medicine, Seoul National University Medical Research Center, 101, Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea
[f] Interdisciplinary program of cognitive science, Seoul National University College of Humanities, 1 Gwanak-ro, Gwanak-gu, Seoul 08826, Republic of Korea
[g] Department of Radiology, Seoul National University Hospital, 101, Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea

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ABSTRACT

Background: The cognitive consequences of cerebral microbleeds (CMBs) in memory clinic population with a diverse cognitive spectrum remain unclear.
Objectives: This study aimed to investigate how CMBs at different locations are associated with cognitive performance in a memory clinic population and whether these associations are independent of related small vessel disease (SVD) markers.
Design: A cross-sectional study.
Setting: A university hospital memory clinic. Data were collected from December 2004 to September 2014 and analyzed in June 2024.
Participants: A total of 910 participants, composed of 64 individuals with subjective cognitive decline, 399 with mild cognitive impairment (MCI), 339 with Alzheimer disease dementia (AD), 58 with vascular dementia and mixed dementia, and 50 with other types of dementia, were included.
Main Outcomes and Measures: Summary scores for global cognition, memory, language, visuospatial function, and executive function measured by the Consortium to Establish a Registry for Alzheimer's disease (CERAD) neuropsychological battery.
Results: In the overall population, the presence of deep/infratentorial CMBs was significantly associated with executive dysfunction; however, this association was attenuated after adjusting for related SVD markers. When stratified by diagnostic subgroup, strictly lobar CMBs were significantly associated with impairments in global cognition and memory in the MCI group, independent of related SVD markers. In contrast, no significant associations between CMBs and cognitive domains were observed in the AD group.
Conclusions: These findings, based on memory clinic population with a broad cognitive spectrum, suggest that CMBs, depending on their location, may have different implications for cognitive function.

1. Introduction

Cerebral microbleeds (CMBs) are radiologic findings characterized by small, round foci of low signal intensity lesions on blood-sensitive MRI sequences [1]. Histologically, they correspond to hemosiderin deposits adjacent to small vessels caused by microhemorrhage [2]. CMBs are commonly observed in patients with stroke [3,4] and have also been associated with Alzheimer disease dementia (AD) [5] and vascular dementia [6]. Evidence indicated that the pathology of CMBs differ according to their locations: CMBs in deep or infratentorial (DI) region are associated with hypertensive arteriopathy, whereas strictly lobar (SL) CMBs are linked to cerebral amyloid angiopathy (CAA) [1]. This indicates that CMBs may influence different cognitive domains through distinct mechanisms depending on their location.

* Corresponding author at: Department of Neuropsychiatry, Seoul National University Hospital, 101, Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea.
E-mail address: selfpsy@snu.ac.kr (D.Y. Lee).

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Previous studies based on community population have provided substantial evidence that CMBs are associated with poor cognitive function; however, the results for the location of CMBs, to which cognitive impairments are linked, were quite inconsistent [7–12]. Some studies suggested only DI CMBs, but not SL CMBs, were associated with cognitive impairment, [10,13] whereas another study reported the opposite [11]. Regarding specific domains of cognitive impairment, several studies reported that a higher number of CMBs were associated with poorer performance in processing speed and executive function [7, 8,12]. However, one of them demonstrated the strongest association for DI CMBs [7], while others showed a robust association for SL CMBs [8, 12]. Additionally, the population-based studies mainly included cognitively intact or only mildly impaired individuals and no or very small numbers of subjects with dementia, which could limit statistical power to reveal the actual relationship between CMBs and cognitive impairments. Several studies based on memory clinical populations have been conducted, but most of them included relatively small sample size (less than 300) and yielded inconsistent findings [14–17].

CMBs are often accompanied by other small vessel disease (SVD) markers, such as lacunar infarction and cerebral white matter lesions, suggesting a shared pathophysiologic mechanism with other SVD, which are well-known to be related to cognitive impairment in older individuals [18]. Thus, determining whether CMBs are independently related to cognitive impairment, separate from other SVD markers, is a critical issue in elucidating the underlying mechanisms linking CMBs and cognition.

Therefore, this study aimed to examine the independent relationship of CMBs with cognition in a large memory clinic population with a diverse cognitive spectrum. To achieve this goal, we first identified other measures of cerebral SVD, including white matter hyperintensities (WMHs), enlarged perivascular spaces (EPVS), and lacunes, that are related to CMBs. Subsequently, we investigated how CMBs at different locations were associated with cognitive consequences and whether these associations were independent of related SVD markers.

2. Methods

2.1. Participants

Participants who visited the Memory Clinic at the Seoul National University Hospital, Seoul, Republic of Korea, with a broad spectrum of cognitive impairment, including subjective cognitive decline (SCD), mild cognitive impairment (MCI), and dementia, between December 2004 and September 2014, were included in this study. Dementia was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) [19]. Patients with AD met the criteria established by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [20]. Vascular dementia was diagnosed based on the criteria of the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) [21]. Mixed dementia was defined as the coexistence of AD and vascular dementia. Other types of dementia group included various diagnoses, such as dementia with Lewy bodies [22], Parkinson disease dementia [22], frontotemporal dementia [23], semantic dementia [23], and progressive non-fluent aphasia [23]. All individuals with MCI met the international consensus criteria [24]: (1) cognitive decline confirmed by the patient, informant or physician; (2) objective cognitive impairment; (3) preserved basic activities of daily living; (4) relatively intact in complex instrumental functions; (5) not demented. SCD participants met the criteria for SCD established by the SCD-Initiative group [25]. The following exclusion criteria were applied to all participants: the presence of any serious medical, psychiatric, or neurological disorder that could affect mental functioning other than MCI or dementia; the presence of severe behavioral or communication problems that would make a clinical or neuroimaging examination difficult; and the absence of a reliable informant.

2.2. Clinical and neuropsychological assessment

All participants underwent a standardized clinical evaluation following the protocol of the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) clinical assessment [26]. Psychiatrists with expertise in dementia research conducted clinical evaluations, and diagnostic decisions were made through a consensus meeting involving four or more psychiatrists after a thorough review of all available data. The diagnostic algorithm followed a hierarchical structure as presented in the supplementary material.

Experienced clinical psychologists administered the Korean version of the CERAD neuropsychological battery [27,28] to all participants. The battery comprises various subsets including verbal fluency (VF), Boston naming test (BNT), Mini-Mental State Examination, word list memory (WLM), construction praxis (CP), word list recall (WLR), word list recognition (WLRc), construction recall (CR), Trail Making Test (TMT) B, and Stroop Color-Word Test (SCWT). The total score for the CERAD neuropsychological battery (TS) was calculated by summing the scores of seven tests (VF, BNT, WLM, CP, WLR, WLRc, CR) in the battery [29].

Individual cognitive tests were grouped into four cognitive domains: memory (WLM, WLR, WLRc, CR), language (BNT), visuospatial function (CP), and executive function (VF, TMT B, and SCWT). Raw scores of each individual test were transformed to z-scores using normative data [27], and the summary score for each cognitive domain was the average of the z-scores of component tests (for memory and executive function) or the z-score itself of a single component test (for language and visuospatial function). The z-score of TS was used as a measure of global cognition. Six vascular risk factors, including hypertension, diabetes, dyslipidemia, transient ischemic attack, stroke, and coronary artery disease, were systematically evaluated, and a vascular risk score (VRS) was calculated by summing the total number these risk factors [30].

2.3. MRI image acquisition and analysis

All participants underwent brain MRI scanning using either the whole-body 3.0 Tesla (T) General Electric Signa VH/I or the 3.0 T Siemens Verio machine. The following sequences were acquired from the General Electric Signa VH/i (Milwaukee, WI, USA): T1-weighted image [echo time (TE) 4.0 ms, repetition time (TR) 22.0 ms, matrix = 256 × 192, field of view (FOV) 240 mm, flip angle 40°], T2-weighted image (TE 99.7 ms, TR 4000 ms, matrix = 448 × 256, FOV 220 mm, flip angle 90°), fluid-attenuated inversion recovery (FLAIR) (TE 162.7 ms, TR 9902 ms, matrix = 320 × 192, FOV 220 mm), and axial gradient-recalled echo T2* (TE 25.0 ms, TR 400 ms, FOV 220 mm, flip angle 20°). The sequences from the Siemens Verio (Washington DC, USA) were as follows: T1-weighted image (TE 1.89 ms, TR 1500 ms, matrix = 256 × 232, FOV 250 mm, flip angle 9°), T2-weighted image (TE 101 ms, TR 3380 ms, matrix = 384 × 231, FOV 240 mm, flip angle 130°), FLAIR (TE 202 ms, TR 5000 ms, matrix = 256 × 232, FOV 250 mm), and susceptibility weighted image (TE 72 ms, TR 6700 ms, FOV 240 mm, flip angle 15°).

All images were initially reviewed by a neuroradiologist and subsequently assessed by a physician who underwent specialized training for this research. Both the neuroradiologist and physician rater were blinded to the clinical information regarding the participants. CMBs were defined as small, homogeneous, round foci of low signal intensity lesions on T2* images, measuring less than 10 mm in diameter [1]. CMBs were categorized into SL CMBs and DI CMBs. SL CMBs were identified when MB were restricted to the frontal, parietal, temporal, and occipital lobes. CMBs located in deep brain regions (basal ganglia, thalamus, internal capsule and external capsule) or infratentorial regions (brainstem and cerebellum), with or without concomitant lobar CMBs, were classified as

DI CMBs. The intra-rater reliability of CMBs was investigated in 30 randomly selected scans through scoring twice with a 4-week interval. The Cohen's kappa value was determined to be 0.830, indicating a substantial level of agreement.

Other MRI makers, including white matter hyperintensities, lacunar infarcts, and EPVS, were also assessed. On FLAIR images, periventricular white matter hyperintensities (PVWMH) and deep white matter hyperintensities (DWMH) were evaluated using the Fazekas scale [31] and grade ≥2 was regarded as severe degree. Lacunar infarcts were defined as focal lesions with a diameter of less than 15 mm, exhibiting the same signal intensities as cerebrospinal fluid and a hyperintense rim on the FLAIR images [32]. EPVS were characterized as round, ovoid, or linear structures showing high signal intensity on T2-weighted images, with a width of less than 3 mm [33]. EPVS in the basal ganglia (BG-EPVS) and EPVS in the centrum semiovale (CSO-EPVS) were assessed separately, with more than ten EPVS classified as severe.

2.4. Statistical analysis

Clinical characteristics and SVD markers among diagnostic groups were compared using analysis of variance (ANOVA) for continuous variables, and chi-square test or Fisher's exact test for categorical variables. We investigated risk factors for the presence of CMBs and assessed whether risk factors differed based on the location of CMBs using Student's *t*-test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. To identify cerebral SVD measures associated with each location of CMBs, stepwise logistic regression analyses were conducted. The models included lacunar infarcts, severe PVWMH, severe DWMH, BG-EPVS, and CSO-EPVS as independent variables; presence of any CMBs, SL CMBs, or DI CMBs as dependent variables; and age and sex as covariates. We subsequently conducted multiple linear regression analyses to investigate the association of CMB presence or location with performance in each cognitive domain by using two models. Due to the highly skewed and leptokurtic distribution of CMBs ($z_{skewness} = 8.6$; $z_{kurtosis} = 86.2$) and the low proportion of multiple CMBs ($n = 91$, 10 %), we adopted a dichotomous variable for CMBs, consistent with previous studies [11,13]. Model 1 included age, sex, education, and cognitive diagnosis (SCD, MCI, and dementia) as covariates and Model 2 included other SVD markers, which showed a significant association with the presence of CMBs in the above logistic regression analyses, as additional covariates, as well as the covariates of Model 1. Finally, we repeated the same multiple linear regression analyses in MCI and AD subgroups to examine the cognitive effect of CMBs within each diagnostic group. All analyses were conducted using IBM SPSS Statistics (version 21.0; SPSS Inc., Chicago, IL, USA), with $p < 0.05$ considered statistically significant.

2.5. Standard protocol approvals, registrations, and patient consents

The study was conducted in accordance with the principles outlined in the Declaration of Helsinki [34] and received approval from Institutional Review Board (IRB) of Seoul National University Hospital. In accordance with IRB regulations, informed consent was waived.

3. Results

3.1. Participants' characteristics

The clinical and neuroimaging characteristics of the study participants are presented in Table 1. The study included a total of 910 participants, with the mean (SD) age was 71.96 (8.44) years and 324 (35.6 %) were men. The clinical diagnostic distribution is as follows: 64 (7.0 %) with SCD, 399 (43.8 %) with MCI, 339 (37.3 %) with AD, 58 (6.4 %) with vascular dementia and mixed dementia, and 50 (5.5 %) with other types of dementia. CMBs were detected in 198 (21.8 %) participants, and of those with CMBs, 121 (13.3 %) had SL CMBs and 77 (8.5 %) had DI CMBs. The rate of the presence of CMBs significantly differed among diagnostic groups (chi-square = 22.55, $p < 0.001$) with the highest rate of SL CMBs observed in AD group, while DI CMBs were most prevalent in patients with vascular dementia and mixed dementia.

3.2. Factors associated with CMBs

The results from univariate analyses of clinical and neuroimaging risk factors that are associated with any CMBs or CMBs at a specific location are shown in Table 2. The presence of SL CMBs was associated with old age, and all SVD markers on MRI, such as severe PVWMH/DWMH, the presence of lacunar infarcts, and severe BG/CSO-EPVS. In contrast, the presence of DI CMBs was associated with old age, a history of hypertension, a history of stroke, a high VRS, and all SVD markers except CSO-EPVS. As shown in Table 3, subsequent stepwise logistic regression analyses revealed that the presence of lacunar infarcts, severe

Table 1
Characteristics of the study population according to the cognitive diagnosis.

	Total ($n = 910$)	SCD ($n = 64$)	MCI ($n = 399$)	AD ($n = 339$)	VaD+MXD ($n = 58$)	Other dementia ($n = 50$)	p
Age, years	71.96 ± 8.44	68.48 ± 6.82	71.92 ± 7.33	72.51 ± 9.23	74.83 ± 7.82	69.72 ± 11.53	<0.001[a]
Male, n (%)	324 (35.6)	19 (29.7)	129 (32.3)	114 (33.6)	36 (62.1)	26 (52.0)	<0.001[a]
Education, years	9.09 ± 5.38	10.70 ± 4.74	9.28 ± 5.26	8.82 ± 5.37	7.66 ± 6.01	9.02 ± 5.99	0.024[a]
Apolipoprotein E ε4 carrier, n (%)[b]	273 (36.1)	22 (34.4)	103 (25.8)	127 (37.5)	15 (25.9)	6 (12.0)	<0.001[a]
Vascular risk score	0.91 ± 0.89	0.73 ± 0.72	0.95 ± 0.91	0.80 ± 0.84	1.76 ± 0.82	0.68 ± 0.77	<0.001[a]
CDR SOB	3.13 ± 2.90	0.17 ± 0.41	1.37 ± 0.71	4.93 ± 2.92	6.14 ± 3.32	5.23 ± 2.50	<0.001[a]
MMSE	20.42 ± 5.89	27.30 ± 2.21	23.23 ± 3.93	16.76 ± 5.42	17.07 ± 5.67	17.88 ± 5.77	<0.001[a]
CMBs, n (%)	198 (21.8)	5 (7.8)	76 (19.0)	85 (25.1)	23 (39.7)	9 (18.0)	<0.001[a]
SL CMBs, n (%)	121 (13.3)	3 (4.7)	44 (11.0)	58 (17.1)	9 (15.5)	7 (14.0)	0.034[a]
DI CMBs, n (%)	77 (8.5)	2 (3.1)	32 (8.0)	27 (8.0)	14 (24.1)	2 (4.0)	<0.001[a]
Lacunar infarcts, n (%)	222 (24.4)	8 (12.5)	91 (22.8)	72 (21.2)	43 (74.1)	8 (16.0)	<0.001[a]
Severe PVWMH, n (%)	257 (28.2)	10 (15.6)	95 (23.8)	98 (28.9)	41 (70.7)	13 (26.0)	<0.001[a]
Severe DWMH, n (%)	163 (17.9)	10 (15.6)	60 (15.0)	63 (18.6)	22 (37.9)	8 (16.0)	0.001[a]
High degree of BG-EPVS, n (%)	183 (20.1)	9 (14.1)	77 (19.3)	64 (18.9)	23 (39.7)	10 (20.0)	0.003[a]
High degree of CSO-EPVS, n (%)	189 (20.8)	15 (23.4)	85 (21.3)	67 (19.8)	9 (15.5)	13 (26.0)	0.670

Abbreviations: SCD = subjective cognitive decline; MCI = mild cognitive impairment; AD = Alzheimer's disease dementia; VaD = vascular dementia; MXD = mixed dementia; CDR SOB = clinical dementia rating sum of boxes; MMSE = Mini-Mental Status Examination; CMB = cerebral microbleeds; SL = Strict lobar; DI = deep or infratentorial; BG-EPVS = enlarged perivascular spaces in the basal ganglia; CSO-EPVS = enlarged perivascular spaces in the centrum semiovale; PVWMH = Periventricular white matter hyperintensities; DWMH = Deep white matter hyperintensities.
Continuous variables are presented as mean ± SD and categorical variables are presented as number of subjects (%).
Compared by analysis of variance for continuous variables, and chi-square test or Fisher's exact test for categorical variables.
[a] $p<0.05$.
[b] Data were missing for 153 participants.

Table 2
Risk factors associated with presence of any CMBs or CMBs at a specific location, using univariate analyses.

	Any CMBs			SL CMBs		DI CMBs	
	absent (n = 712)	present (n = 198)	p value*	present (n = 121)	p value*	present (n = 77)	p value*
Age, years	71.04 ± 8.47	75.29 ± 7.42	<0.001	75.63 ± 7.39	<0.001	74.77 ± 7.47	<0.001
Male, n (%)	242 (34.0)	82 (41.4)	0.054	54 (44.6)	0.024	28 (36.4)	0.676
Education, years	9.02 ± 5.33	9.35 ± 5.56	0.449	9.69 ± 5.60	0.203	8.81 ± 5.50	0.737
Smoker, n (%)	127 (17.8)	39 (19.7)	0.549	28 (23.1)	0.166	11 (14.3)	0.436
Hypertension, n (%)	322 (45.2)	116 (58.6)	0.001	65 (53.7)	0.083	51 (66.2)	<0.001
Diabetes mellitus, n (%)	151 (21.2)	45 (22.7)	0.645	30 (24.8)	0.377	15 (19.5)	0.724
Dyslipidemia, n (%)	56 (7.9)	18 (9.1)	0.577	14 (11.6)	0.174	4 (5.2)	0.401
Coronary artery disease, n (%)	13 (1.8)	4 (2.0)	0.773	3 (2.5)	0.716	1 (1.3)	1.000
Stroke, n (%)	76 (10.7)	31 (15.7)	0.054	11 (9.1)	0.599	20 (26.0)	<0.001
Vascular risk score	0.87 ± 0.90	1.08 ± 0.82	0.002	1.02 ± 0.82	0.090	1.18 ± 0.82	0.004
Severe PVWMH, n (%)	160 (22.5)	97 (49.0)	<0.001	49 (40.5)	<0.001	48 (62.3)	<0.001
Severe DWMH, n (%)	93 (13.1)	70 (35.4)	<0.001	32 (26.4)	<0.001	38 (49.4)	<0.001
Lacunar infarcts, n (%)	134 (18.8)	88 (44.4)	<0.001	39 (32.2)	0.001	49 (63.6)	<0.001
Severe BG-EPVS, n (%)	110 (15.4)	73 (36.9)	<0.001	39 (32.2)	<0.001	34 (44.2)	<0.001
Severe CSO-EPVS, n (%)	137 (19.2)	52 (26.3)	0.031	38 (31.4)	0.002	14 (18.2)	0.822

Abbreviations: CMBs = cerebral microbleeds; SL = Strict lobar; DI = deep or infratentorial; PVWMH = Periventricular white matter hyperintensities; DWMH = Deep white matter hyperintensities; BG-EPVS = EPVS in the basal ganglia; CSO-EPVS = EPVS in the centrum semiovale.
Continuous variables are presented as mean ± SD and categorical variables are presented as number of subjects (%).
* By Student's *t*-test for continuous variables and chi-square test or Fisher's exact test for categorical variables.

Table 3
SVD markers associated with presence of any CMBs or CMBs at a specific location, using stepwise logistic regression.

	Lacunar infarcts OR (95 % CI)	Severe DWMH OR (95 % CI)	Severe PVWMH OR (95 % CI)	BG-EPVS OR (95 % CI)	CSO-EPVS OR (95 % CI)
Entire group					
Any CMBs	2.036 (1.394 to 2.975)	2.243 (1.495 to 3.365)		1.672 (1.124 to 2.487)	1.510 (1.014 to 2.249)
SL CMBs		1.948 (1.207 to 3.143)			2.051 (1.318 to 3.192)
DI CMBs	4.214 (2.403 to 7.390)	3.150 (1.801 to 5.510)		1.843 (1.038 to 3.271)	
MCI subgroup					
Any CMBs	2.242 (1.203 to 4.178)		2.136 (1.152 to 3.960)	1.935 (1.028 to 3.641)	
SL CMBs				2.036 (0.974 to 4.254)	
DI CMBs	10.122 (3.927 to 26.809)	3.190 (1.290 to 7.884)			
AD subgroup					
Any CMBs	1.951 (1.076 to 3.538)	2.485 (1.339 to 4.610)			
SL CMBs					
DI CMBs	2.923 (1.196 to 7.146)	4.730 (1.907 to 11.733)			

Abbreviations: SVD = small vessel disease; CMBs = cerebral microbleeds; DWMH = deep white matter hyperintensities; PVWMH = Periventricular white matter hyperintensities; BG-EPVS = enlarged perivascular spaces in the basal ganglia; CSO-EPVS = enlarged perivascular spaces in the centrum semiovale; OR = odds ratio; CI = confidence interval; SL = Strict lobar; DI = deep or infratentorial; MCI = mild cognitive impairment; AD = Alzheimer's disease dementia.
Age and sex were included as fixed covariates.

DWMH, and severe BG/CSO-EPVS were significantly associated with any CMBs. Different patterns were seen for CMBs at a specific location: Severe DWMH and severe CSO-EPVS were associated with SL CMBs, while lacunar infarcts, severe DWMH, and severe BG-EPVS were associated with DI CMBs. Notably, different patterns of association were found in MCI and AD subgroups, as detailed in Table 3.

3.3. Association between CMBs and cognitive function

As shown in Table 4, multiple linear regression analyses revealed

Table 4
Association of prevalent CMBs with cognitive function in the whole clinic population.

	Cognitive domain, β coefficient (95 % CI)				
	Global cognition	Memory	Language	Visuospatial function	Executive function
No CMB (n = 712)	Reference	Reference	Reference	Reference	Reference
Model 1					
Any CMBs (n = 198)	−0.042 (−0.337 to 0.033)	−0.015 (−0.192 to 0.105)	−0.051 (−0.356 to 0.033)	−0.014 (−0.419 to 0.264)	−0.068 (−0.300 to −0.031)*
SL CMBs (n = 121)	−0.032 (−0.365 to 0.088)	−0.015 (−0.233 to 0.131)	−0.039 (−0.386 to 0.093)	−0.011 (−0.490 to 0.347)	−0.029 (−0.249 to 0.080)
DI CMBs (n = 77)	−0.031 (−0.432 to 0.112)	−0.007 (−0.247 to 0.190)	−0.043 (−0.469 to 0.097)	−0.008 (−0.575 to 0.446)	−0.078 (−0.467 to −0.071)*
Model 2					
Any CMBs (n = 198)	−0.046 (−0.362 to 0.023)	−0.034 (−0.251 to 0.057)	−0.040 (−0.327 to 0.077)	−0.010 (−0.413 to 0.299)	−0.038 (−0.233 to 0.046)
SL CMBs (n = 121)	−0.034 (−0.375 to 0.083)	−0.023 (−0.259 to 0.108)	−0.035 (−0.370 to 0.113)	−0.006 (−0.463 to 0.382)	−0.024 (−0.235 to 0.096)
DI CMBs (n = 77)	−0.032 (−0.459 to 0.124)	−0.027 (−0.341 to 0.128)	−0.021 (−0.395 to 0.210)	−0.008 (−0.607 to 0.489)	−0.040 (−0.347 to 0.074)

Abbreviations: CI = confidence interval; CMBs = cerebral microbleeds; SL = Strict lobar; DI = deep or infratentorial.
Model 1 was adjusted for age, sex, education, and cognitive diagnosis. Model 2 was adjusted for the covariates of model 1 and additionally for SVD markers that showed significant association with each CMB.
* Significant.

that any CMBs was significantly associated with poorer scores on executive function (β coefficient = −0.068, 95 % CI = −0.300 to −0.031), but not with those of other cognitive tests, when age, sex, education, and cognitive diagnosis were controlled as covariates (Model 1). However, the association between any CMBs and executive function was no longer significant after controlling SVD markers, which were significantly related to any CMBs in the logistic regression analysis (i.e., DWMH, lacunar infarcts, BG/CSO-EPVS), as additional covariates (Model 2). DI CMBs showed the same pattern to any CMBs, being associated with executive function only in model 1 (β coefficient = −0.078, 95 % CI = −0.467 to −0.071). SL CMBs showed no significant association with any cognitive scores across all models. Further multiple linear regression analyses, adjusting for each individual SVD marker related to DI CMBs, revealed that the significant association between DI CMBs and poor scores in executive function was attenuated after adjusting for lacunar infarcts but remained unaffected when controlling for DWMH or BG-EPVS (eTable).

Finally, we repeated the same multiple linear regression analyses in the MCI and AD subgroups (Table 5). In the MCI subgroup, the presence of any CMBs was significantly associated with cognitive impairment in global cognition and executive function, although only the association with global cognition remained significant after adjusting for related SVD markers. SL CMBs were significantly associated with cognitive impairment in global cognition and memory domains, and these associations persisted even after adjusting for related SVD markers. In contrast, the presence of DI CMBs was significantly associated with poorer score in global cognition, visuospatial function and executive function; however, these associations diminished after adjusting for SVD markers. In the AD subgroup, no significant associations were observed between the presence of CMBs and cognitive performance.

4. Discussion

In a memory clinic population with a broad cognitive spectrum, we found that the presence of any CMBs, particularly DI CMBs, was significantly associated with executive dysfunction, although this association was attenuated after controlling for related SVD markers. Further subgroup analyses for MCI demonstrated that SL CMBs were associated with impairment in global cognition and memory, independently of other SVD markers, and DI CMBs were correlated with impairment in global cognition, executive function, and visuospatial function, dependent on related SVD markers. In contrast, neither DI CMBs nor SL CMBs were associated with any cognitive impairment in AD.

The observed differences in clinical risk factors and SVD markers associated with CMBs according to their locations suggest distinct underlying pathophysiological processes between SL CMBs and DI CMBs. DI CMBs were linked to stroke, hypertension, and VRS, reflecting hypertensive vasculopathy and arteriosclerosis, as indicated by previous reports [1]. Furthermore, DI CMBs showed close association with

Table 5
Association of prevalent CMBs with cognitive function in MCI and AD subgroup.

	Cognitive domain, β coefficient (95 % CI)									
	Global cognition		Memory		Language		Visuospatial function		Executive function	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
MCI (*n* = 399)										
No CMB (*n* = 323)	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Any CMBs (*n* = 76)	−0.139 (−0.568 to −0.096)*	−0.128 (−0.553 to −0.058)*	−0.093 (−0.395 to 0.015)	−0.103 (−0.424 to 0.005)	−0.089 (−0.522 to 0.031)	−0.054 (−0.438 to 0.140)	−0.094 (−0.692 to 0.019)	−0.070 (−0.623 to 0.121)	−0.147 (−0.468 to −0.092)*	−0.093 (−0.373 to 0.019)
SL CMBs (*n* = 44)	−0.115 (−0.625 to −0.031)*	−0.118 (−0.637 to −0.038)*	−0.107 (−0.525 to −0.005)*	−0.115 (−0.547 to −0.025)*	−0.066 (−0.576 to 0.130)	−0.060 (−0.555 to 0.155)	−0.030 (−0.524 to 0.290)	−0.031 (−0.529 to 0.291)	−0.086 (−0.427 to 0.042)	−0.071 (−0.393 to 0.075)
DI CMBs (*n* = 32)	−0.109 (−0.682 to −0.015)*	−0.106 (−0.710 to 0.029)	−0.038 (−0.388 to 0.181)	−0.055 (−0.463 to 0.167)	−0.075 (−0.669 to 0.109)	−0.045 (−0.596 to 0.262)	−0.133 (−1.176 to −0.149)*	−0.101 (−1.068 to 0.064)	−0.151 (−0.663 to −0.124)*	−0.105 (−0.571 to 0.023)
AD (*n* = 339)										
No CMB (*n* = 254)	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Any CMBs (*n* = 85)	−0.039 (−0.460 to 0.198)	−0.038 (−0.468 to 0.210)	−0.027 (−0.316 to 0.175)	−0.033 (−0.340 to 0.167)	−0.046 (−0.471 to 0.196)	−0.046 (−0.484 to 0.205)	0.013 (−0.608 to 0.786)	0.008 (−0.664 to 0.773)	−0.032 (−0.298 to 0.163)	−0.002 (−0.241 to 0.232)
SL CMBs (*n* = 58)	−0.053 (−0.579 to 0.181)	−0.053 (−0.579 to 0.181)	−0.022 (−0.348 to 0.220)	−0.022 (−0.348 to 0.220)	−0.042 (−0.529 to 0.246)	−0.042 (−0.529 to 0.246)	−0.041 (−1.144 to 0.503)	−0.041 (−1.144 to 0.503)	−0.026 (−0.328 to 0.205)	−0.026 (−0.328 to 0.205)
DI CMBs (*n* = 27)	0.007 (−0.506 to 0.581)	0.004 (−0.553 to 0.597)	−0.018 (−0.478 to 0.334)	−0.031 (−0.551 to 0.307)	−0.024 (−0.647 to 0.433)	−0.028 (−0.698 to 0.443)	0.091 (−0.203 to 2.114)	0.087 (−0.314 to 2.138)	−0.021 (−0.439 to 0.303)	0.016 (−0.339 to 0.443)

Abbreviations: MCI = mild cognitive impairment; AD = Alzheimer's disease dementia; CI = confidence interval; CMBs = cerebral microbleeds; SL = Strict lobar; DI = deep or infratentorial.
Model 1 was adjusted for age, sex, education. Model 2 was adjusted for the covariates of model 1 and additionally for SVD markers that showed significant association with each CMB.
* Significant.

lacunar infarcts, severe DWMH, and severe BG-EPVS, which indicated a common pathophysiological mechanism among the lesions, primarily affecting deep perforating small arteries [35]. In contrast, SL CMBs had a close association with CSO-EPVS. As previously suggested, beta-amyloid deposition in the leptomeningeal and cortical arteries or CAA may serve as a pathophysiological link explaining the association between SL CMBs and CSO-EPVS [36].

Any CMBs or DI CMBs, but not SL CMBs, were significantly associated with poor performance in executive function in our overall participants with a diverse cognitive spectrum. Among previous large community-based studies with over 1000 participants [7–10], the AGES-Reykjavik study [7], a large community-based study which included many individuals with dementia as well as those without dementia (i.e., participants with a diverse cognitive spectrum, similar to those of the current study), reported findings consistent with ours: only DI CMBs, but not SL CMBs, were associated with cognitive decline. In addition, a recent study involving clinic patients with SVD also showed that those with hypertensive arteriopathy, associated with DI CMBs, had impaired performance in attention and executive function [37].

However, the association between DI CMBs and executive dysfunction was not significant anymore after controlling for related SVD markers in overall participants and MCI subgroup. This finding indicates that DI CMBs may have just an indirect relationship with cognitive decline rather than causing direct focal damage to neurologic tracts. The apparent relationship between DI CMBs and cognition may be due to their close linkage with other SVD markers, especially lacunar infarcts and WMHs, which directly disrupt the prefrontal subcortical circuit and lead to executive dysfunction [38]. Additionally, DI CMBs, lacunar infarcts, BG-EPVS and PVWMH may represent different sequelae of the same underlying process of hypertensive arteriopathy: microvascular damage in DI CMBs, fluid extravasation in BG-EPVS, hypoperfusion in WMHs and vessel occlusion in lacunes [39].

Subgroup analyses in MCI revealed that SL CMBs were associated with dysfunction in global cognition and memory domain, even independently of other SVD markers. In line with this finding, several community-based studies, which included mostly individuals without dementia, reported that SL CMBs were associated with impaired cognition [8–10]. In addition, a large clinico-pathologic study demonstrated that CAA, closely related to SL CMBs, was associated with an increased rate of decline in global cognition, perceptual speed, and memory, independently of other brain pathologies including microinfarcts and Alzheimer's pathologies [40]. CAA was suggested to lead to cognitive impairment through multiple pathways including inflammation and oxidative stress [41]. In contrast to the results from the MCI subgroup, any association between SL CMBs and cognitive impairment was not found in the AD subgroup, as reported in the Honolulu-Asia Aging Study [42]. In the AD stage, the predominant contribution of Alzheimer's pathologies to cognitive impairment may mask the negative influence of SL CMBs on cognition, making it difficult to detect a significant correlation between SL CMBs and cognitive impairment.

The main strength of our study lies in the inclusion of a large memory clinic population with a broad cognitive spectrum, which provides sufficient power to explore the cognitive effect of CMBs. We also used a wide range of neuropsychological tests to assess each cognitive domain. In addition, unlike other previous studies, the confounding effects of the SVD markers were well controlled through a process of statistical exploration of correlation. However, our study has several limitations. First, the cross-sectional design limits the ability to explore longitudinal cognitive changes. Although it is unlikely that cognitive impairment leads to the development of CMBs, we cannot establish the causal relationship between CMBs and cognitive decline. Second, it should be noted that the majority of participants in our sample were diagnosed with AD or MCI, whereas the number of individuals with SCD or other dementia subtypes was relatively small. As such, the observed associations between cerebral microbleeds and cognitive performance may have been primarily influenced by the AD and MCI groups. Future studies with larger and more balanced samples across diagnostic categories are warranted to validate these findings and to explore potential subgroup-specific effects. Third, core AD biomarkers, such as amyloid or tau PET or CSF profiles, were not available. Although participants underwent detailed clinical and neuropsychological assessments, the lack of biomarkers may limit diagnostic specificity, particularly for distinguishing pure AD from mixed or non-AD pathologies. Last, the visual rating scales for CMBs and other SVD markers were not truly quantitative and may be subject to rater proficiency and human error. Further studies adopting quantitative technique are warranted.

In conclusion, these findings, based on a memory clinic population with a broad cognitive spectrum, suggest that CMBs, depending on their location, may have different implications for cognitive function: the presence of DI CMBs is associated with executive dysfunction, though this association is dependent on related SVD markers, while SL CMBs appear independently linked to impairments in global cognition and memory in individuals with MCI, but not in those with AD.

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Declaration of generative AI and AI-Assisted technologies in the writing process

We confirm that we have not used any AI at all except for English editing.

CRediT authorship contribution statement

Young Min Choe: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Hyewon Baek:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Min Soo Byun:** Writing – review & editing, Resources, Investigation, Formal analysis, Data curation. **Dahyun Yi:** Writing – review & editing, Resources, Investigation, Data curation. **Hyejin Ahn:** Writing – review & editing, Software, Resources, Investigation, Formal analysis, Data curation. **Gijung Jung:** Writing – review & editing, Formal analysis, Data curation. **Chul-Ho Sohn:** Writing – review & editing, Resources, Investigation. **Dong Young Lee:** Writing – review & editing, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100340.

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