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Cerebral cortical microinfarcts on MRI and their association with cognition in cerebral amyloid angiopathy

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Abstract

Background and Purpose: We aimed to explore the association between presence of cerebral cortical microinfarcts (CMIs) on MRI and other small vessel disease neuroimaging biomarkers in cerebral amyloid angiopathy (CAA) and to analyze the role of CMIs on individual cognitive domains and dementia conversion.

Methods: Participants were recruited from an ongoing longitudinal research cohort of eligible CAA patients between March 2006 and October 2016. A total of 102 cases were included in the analysis that assessed the relationship of cortical CMIs to CAA neuroimaging markers. Ninety-five subjects had neuropsychological tests conducted within 1 month of MRI scanning. Seventy-five non-demented CAA patients had cognitive evaluation data available during follow-up.

Results: Among 102 patients enrolled, 40 patients had CMIs (39%) on MRI. CMIs were uniformly distributed throughout the cortex without regional predilection ($P=0.971$). The presence of CMIs was associated with lower total brain volume (OR=0.85, 95% CI: 0.74, 0.98, $P=0.025$) and presence of cortical superficial siderosis (OR=2.66, 95% CI: 1.10, 6.39, $P=0.029$). In 95 subjects with neuropsychological tests, presence of CMIs was associated with impaired executive function ($\beta = -0.23$, 95% CI: -0.44 , -0.02 , $P=0.036$) and processing speed ($\beta = -0.24$, 95% CI: -0.45 , -0.04 , $P=0.020$). Patients with CMIs had a higher cumulative dementia incidence compared to patients without CMIs ($P=0.043$), while only baseline total brain volume (HR=0.76, 95% CI: 0.62, 0.92, $P=0.006$) independently predicted dementia conversion.

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Disclosures

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Conclusions: MRI-detected CMIs in CAA correlated with greater overall disease burden. The presence of CMIs was associated with worse cognitive performance, while only total brain atrophy independently predicted dementia conversion.

Keywords

Cerebral amyloid angiopathy; Dementia; MRI; cerebral cortical microinfarcts

Introduction

Cerebral amyloid angiopathy (CAA) is a common form of small vessel disease seen in older individuals, characterized by the deposition of the amyloid β -protein in the wall of leptomeningeal and small cortical blood vessels.¹ Hemorrhagic lesions, including lobar cerebral microbleeds, are a hallmark feature of the disease.² However, ischemic lesions are also common in CAA.³ In particular, cerebral cortical microinfarcts (CMIs) have been shown to be quite numerous on autopsy and have been postulated to play an important role in disease severity.⁴

CMIs are defined as microscopic areas of ischemic-related tissue loss. CMIs have been traditionally visualized through examination of pathologic tissue. Due to their small size, research on the association between CMIs and cognition during life has been hampered by the difficulty of detecting CMIs using conventional MRI. Recently, it has been demonstrated that cortical CMIs can be visualized *in vivo* using 7 tesla (7T) MRI.⁵ A subset of cortical CMIs can also be detected *in vivo* on standard research MRI at lower field strengths⁶. While CMIs detected on MRI likely represent only a fraction of the true CMI burden in the brain,⁷ it is unknown whether the presence of these lesions in CAA could identify a subset of patients with greater disease severity.

CMIs have been suggested to be a major component of the causal pathway between small vessel disease and cognitive dysfunction.⁸ The presence of CMIs is very common in older individuals, particularly in patients with dementia.^{9, 10} Moreover, CMIs have been associated with cognitive decline independent of Alzheimer pathology.^{10, 11} However, these previous results come from autopsy studies. It would be important to determine whether MRI-detected CMIs are associated with cognitive impairment and whether they could predict dementia conversion in CAA patients seen in the clinic.

Therefore, we aimed to 1) analyze the association between CMIs and other neuroimaging markers in CAA to understand whether the presence of CMIs could identify patients with more severe disease; 2) analyze the role of CMIs on individual cognitive domains and dementia conversion in CAA patients.

Methods

The authors declare that all supporting data are available within the article and its online supplementary files.

Study population.

Participants were recruited from an ongoing longitudinal research cohort of eligible CAA patients without prior dementia presented to Massachusetts General Hospital between March 2006 and October 2016. The Institutional Review Board approved this study and written informed consent was obtained from all participants or their surrogates prior to their enrollment.

Subjects with probable CAA diagnosis were included based on the Modified Boston Criteria.¹² The inclusive criteria include age $\geq$ 55 years old; MRI results meeting one of the two criteria: a) multiple macro/microhemorrhages restricted to lobar, cortical or corticosubcortical regions (cerebellar hemorrhages allowed) or b) a single lobar, cortical or corticosubcortical macro/microhemorrhage and focal or disseminated cortical superficial siderosis (cSS); and absence of other cause of macro/microhemorrhage or cSS. Initially, 110 patients with CAA were included. These subjects were referred either due to lobar intracerebral hemorrhage (ICH) occurrence (n=60) or non-ICH related neurological symptoms including transient focal neurological episodes or cognitive complaints (n=50). The medium time gap between ICH occurrence and enrollment is 1.48 years (25%–75% Interquartile, 0.72–2.34 years). Eight cases were excluded (1 subject with diagnosis of inflammatory CAA, 3 subjects with inadequate MRI sequences, and 4 subjects with a dementia diagnosis at baseline after an extensive clinical evaluation). Hence, a total of 102 non-demented cases were included in the analysis for the assessment of cortical CMIs and other neuroimaging markers. Seven subjects did not undergo sufficiently detailed neuropsychological testing and had to be excluded from the subsequent neuropsychological analysis. The neuropsychological tests were all conducted within 1 month from MRI scanning (n=95). Seventy-four non-demented CAA patients had cognitive evaluation data available during follow-up. Both research visits and clinical visits were systematically reviewed to determine if dementia was present at follow-up. The flowchart of patient recruitment is shown in the Supplemental Figure.

Clinical evaluations.

We collected demographics and medical history for all subjects. A brief cognitive screening test (Mini-Mental State Examination, MMSE) and a neuropsychological test battery were administered to assess cognitive function. The Trail Making Test B, Digit Span Backward and phonemic fluency were clustered to form an executive function composite score,¹³ the Trail Making Test A and WAIS-III Digit-Symbol Coding were combined to form a processing speed composite score,^{14, 15} Hopkins Verbal Learning Test-Revised immediate recall and delayed recall were used as an estimate of verbal memory,¹⁶ the Boston Naming Test and Animal Naming were used as an estimate of language function,^{17, 18} and Digit Span Forward was used as an estimate of attention. The Z-scores for each test were first calculated using the mean value and standard deviation from the corresponding published normative data with comparable adjustment including age, sex and education level.^{17, 19–21} Then we averaged the Z-scores in the same composite domain to get the domain-specific Z-scores for each individual subject. For the 74 subjects with follow-up data on cognition, the diagnoses of dementia were made according to National Institute on Aging and Alzheimer's Association workgroup criteria based on neuropsychological tests and clinical assessment.²²

Patients who developed dementia at follow-up were labeled as “converters”, while patients who were not demented at follow-up were labeled as “non-converters”.

Neuroimaging.

Among the 102 patients with MRI scans, 73 underwent 1.5T MRI (Siemens Healthcare, Magnetom Avanto) in a 12-channel head coil, and 29 3T MRI scanning (Siemens Healthcare, Magnetom Prisma-fit), in a 32-channel head coil due to the scanner upgrade around January 2015. The 1.5T MRI protocol included a 3D T1-weighted multi-echo Magnetization-Prepared Rapid gradient-Echo Sequence (MPRAGE) (slice thickness, 1mm; repetition time, 2730ms; voxel size $1 \times 1 \times 1\text{mm}^3$), a 3D fluid-attenuated inversion recovery (FLAIR) scan (slice thickness, 1mm; repetition time, 6000ms; echo time, 302ms; voxel size, $1 \times 1 \times 1\text{mm}^3$), a susceptibility-weighted imaging (SWI) scan (repetition time 48ms; echo time 40ms; voxel size $0.8 \times 0.7 \times 1.3\text{mm}^3$), and a T2*-weighted gradient-echo (GRE) scan (repetition time 763ms; echo time 24ms; voxel size $1 \times 1 \times 5\text{mm}^3$). The 3T MRI protocol included a 3D T1-weighted multi-echo scan (slice thickness, 1mm; repetition time 2510ms; voxel size $1 \times 1 \times 1\text{mm}^3$), a 3D FLAIR scan (repetition time 5000ms; echo time 356ms; voxel size, $0.9 \times 0.9 \times 0.9\text{mm}^3$), a SWI scan (repetition time 30ms; echo time 20ms; voxel size $0.9 \times 0.9 \times 1.4\text{mm}^3$), and a T2*-weighted GRE scan (repetition time 500ms; voxel size, $2 \times 2 \times 2\text{mm}^3$).

All MR images were analyzed blinded to all clinical and neuropsychological data. Cortical CMIs were graded for all subjects by one trained rater (NB) per recently proposed guidelines.^{23, 24} Consensus was reached for each subject with two additional trained raters (SJvV and LX). CMIs were assessed in a purpose-built interface incorporated in MeVisLab (version 2.17, MeVis Medical Solutions AG, Bremen, Germany). The whole cortex was first screened on T1-weighted images and possible CMIs were identified as hypointense lesions,

4 mm in diameter, restricted to the cortex, and distinct from perivascular spaces, verified in 3 dimensions. Subsequently, FLAIR images were screened to verify these locations as hyperintense or isointense compared with the surrounding tissue. Possible CMIs that appeared hypointense on GRE or SWI (e.g. hemorrhages or vessels) were discarded. Next, 3D representations were generated in MeVisLab to display the distribution of CMIs. Lesion locations were overlaid on the MNI152 standard-space brain atlas obtained by a non-linear registration.

WMH volume, total brain volume and total intracranial volume were calculated using FreeSurfer version 5.3.²⁵ The talairach transform was conducted to align the T1-weighted volume to MNI305 space to evaluate total intracranial volume. Total brain volume included the white matter and gray matter, and was calculated from the multi-echo MPRAGE images. In subjects with previous ICH, the non-hemorrhagic hemisphere was measured and the volume was doubled to calculate the total brain volume. Both WMH volume and total brain volume were expressed as percentage of total intracranial volume before any analysis to account for differences in subjects' head size.²⁶ cSS was defined as curvilinear hypointensity in the superficial layers of the cerebral cortex, distinct from the vessels, as described in a previous study.¹² The status of cSS was classified as absent or present. Lobar cerebral

microbleeds were defined as punctate foci of hypointensity <10 mm in diameter, distinct from vascular flow voids and leptomeningeal hemosiderosis.²⁷

Statistical analysis.

Clinical characteristics and neuropsychological tests of patients without and with CMIs were assessed using the independent sample t-test for continuous variables, chi square test for dichotomous variables and Mann-Whitney U test for nonparametric data as appropriate. Since WMH volume and number of lobar cerebral microbleeds had a skewed distribution, they were log transformed before included in the analysis.

Binary logistic regression models were used to explore the relationship between the presence of CMIs and other neuroimaging markers (total brain volume, WMH volume, cSS and number of lobar cerebral microbleeds) with adjustment of age, sex and previous ICH history. The association between the presence of CMIs (predictor) and cognitive performance was analyzed in linear regression models with adjustment of other small vessel disease neuroimaging markers (WMH volume, cSS and number of lobar cerebral microbleeds) and previous ICH history. Since the cognitive tests of each individual subject were all transformed into adjusted Z-scores based on normative data, age, sex and education level were not additionally included in the model.

Time to event was defined as the time from the baseline MRI scan to that of dementia diagnosis for converters, and to the last reliable follow-up time for non-converters. Last reliable follow-up time was set as the censoring time. Two subjects with a history of previous ICH had recurrence of ICH during follow-up. Another two subjects had a first ever ICH event during follow-up. Univariable Cox proportional hazard models were performed to calculate unadjusted hazard ratio for the risk of dementia conversion of each potential risk factor, including individual neuroimaging marker and clinical features. These variables with p-values less than 0.1 in the univariable analysis were included into multivariable Cox proportional hazard models. Multicollinearity was assessed using variance inflation factors (VIF) and predictors with VIF>2.5 were removed from the model.

Statistical significance level was set at 0.05 for all analyses. The SPSS 19 statistical package was used for statistical analysis (IBM Corp., Armonk, NY).

Results

Among the 102 non-demented patients with CAA, a total of 102 cortical CMIs were detected in 40 patients (39%). CMIs were uniformly distributed throughout the cortex without regional predilection (Figure 1). Eighteen patients had a single CMI and 22 patients had multiple CMIs (range 2 to 8). Among 73 patients who underwent a 1.5T MRI scan, 29 had CMIs (40%), compared to 11 of 29 patients (38%) who underwent 3T MRI scanning ($P=0.906$). There was no specific lobar predominance in the distribution CMIs ($P=0.971$) as shown in Table 1.

Binary logistic regression models were constructed to better assess the relationship between CMI and other small vessel disease neuroimaging markers in CAA. The presence of CMIs

was significantly associated with total brain volume and the presence of cSS, but not WMH volume or number of lobar cerebral microbleeds. The association did not change after the adjustment of age, sex and previous ICH history (Table 2). Adding MRI field strength in the models did not change the results.

Baseline characteristics of the 95 patients with available neuropsychological test data are summarized in Table 3. Patients with and without CMIs did not differ in demographic characteristics and medical history. There was no significant difference in global neuropsychological performance as measured by MMSE in patients with and without CMIs (the mean raw MMSE score for patients with CMIs was 28.17 ± 1.90 , and without CMIs 27.92 ± 2.04). The group with CMIs had worse performance in executive function and processing speed in comparison to the group without CMIs, while no significant difference was found in other cognitive domains of verbal memory, language and attention.

The association between the presence of CMIs and cognitive impairment (executive function and processing speed) did not change after controlling for previous history of ICH and other neuroimaging markers (total brain volume, WMH volume, presence of cSS and number of lobar cerebral microbleeds) (Table 4). These results also did not change after adding MRI field strength as an extra covariate in the models.

The patients without follow-up data on cognitive status were more likely to have had a previous ICH than those with follow-up data. However, there were no significant differences in demographic features, other past medical history, neuroimaging markers, and MMSE scores at baseline (Supplemental Table). Among the 74 patients with available follow-up dementia data, the median follow-up time was 1.65 (25%–75% QI, 1.00–3.66 years), and 15 converted to dementia (20%). Patients with CMIs had higher cumulative dementia incidence compared to those without CMIs ($P=0.043$). Age, total brain volume, WMH volume, number of lobar cerebral microbleeds and presence of CMIs were included into the multivariable model ($P<0.1$ in univariable analysis). In multivariable analyses, only total brain atrophy predicted dementia conversion ($P=0.006$) (Table 5).

Similarly, in the subgroup of subjects with 1.5T MRI scans and cognitive follow-up data ($n=57$), the presence of CMIs reached significance in the univariable model ($HR=2.97$, 95% CI: 1.04–8.42, $P=0.041$) while only total brain atrophy predicted dementia conversion in the multivariable model ($HR=0.76$, 95% CI: 0.62–0.93, $P=0.007$).

Discussion

This study showed that CMIs are a common finding on MRI in living non-demented patients with CAA. CMIs were uniformly distributed throughout the cortex. The presence of CMIs was independently associated with total brain atrophy and the presence of cSS. Moreover, the presence of CMIs was associated with cognitive deficits on executive function and processing speed. Longitudinally, patients with CMIs were more likely to develop dementia, although this association was not independent after adjusting for other CAA neuroimaging markers including total brain atrophy.

The uniform distribution of CMIs observed in this cohort differs from the distribution of lobar microbleeds in CAA, which have a well-recognized predilection for posterior lobes.²⁸ This difference may suggest different pathophysiological mechanisms between ischemic and hemorrhagic injury in CAA. However, the small sample size may have restricted our ability to detect a possible distribution discrepancy in different lobes. Moreover, it is important to note that MRI-detected CMIs reflect only a small proportion of total CMI burden.⁷ The uniform distribution of CMIs throughout the cortex has been observed in other populations.^{23, 29} However, one previous study in memory clinic patients reported that the distribution of acute CMIs (detected using diffusion-weighted imaging) varied among different lobes, with the occipital lobe having the highest, and temporal having the lowest, burden of CMIs.³⁰ The small number of acute CMIs (n=20 in total) and the measurement of acute CMIs versus chronic CMIs may account for the observed discrepancy with our results. Therefore, further studies with larger sample sizes are needed.

We found that the presence of CMIs was independently associated with total brain atrophy and cSS, which may suggest that these patients have more severe disease.^{31, 32} The association of CMIs with total brain atrophy is consistent with recent results from a memory-clinic cohort.²³ It should also be considered that *in vivo* MRI only captures the relatively larger CMIs.³³ Therefore, the presence of CMIs detected in our study likely reflects a much larger underlying total CMI burden in the whole brain.^{8, 30} It is possible that widespread CMIs may cause neural loss and brain atrophy,²⁵ although further pathological studies investigating this hypothesis are needed. By contrast, it is also possible that CMIs, brain atrophy and cSS may have a shared etiology or shared risk factors. We did not find an association between CMIs and the number of lobar microbleeds which differs from a previous study reporting the association between the presence of CMIs on pathology and the number of microbleeds on ante-mortem MRI in a CAA cohort.⁴ The wide range of lobar microbleeds in our cohort may have precluded an association between the two variables. However, both studies emphasize the simultaneous occurrence of ischemic and hemorrhagic lesions in CAA.

In terms of cognition, the presence of CMIs was associated with deficits in executive function and processing speed. Importantly, these associations remained independent after controlling for other neuroimaging markers, suggesting that CMIs exert additional independent effects on cognition beyond traditional MRI markers of small vessel disease. It is likely that the patients in our study with a few MRI-detectable lesions may have had many more additional CMIs that remained undetected.^{5, 8, 30, 33} The widespread presence of hundreds or thousands of CMIs throughout the brain could result both in direct neuronal loss and disturbances in neuronal connectivity throughout the brain, explaining our observed resulting in cognitive associations with dysfunction.^{13, 34} Previous studies in other cohorts have also reported associations between MRI-detected CMIs and deficits in global cognition, including different cognitive domains compared to our study.^{23, 35} The differences between cohort characteristics and specific cognitive tests may explain some of the observed discrepancies.

We found that the presence of CMIs predicted dementia conversion in patients with CAA, but not independently of total brain atrophy. By contrast, total brain atrophy strongly and

independently correlated with CMI presence. Given these observations, it is therefore conceivable that CMIs contribute at least in part to total brain atrophy in CAA. Larger cohorts with longitudinal follow up are required to better understand the association between CMIs and other neuroimaging markers in CAA.

This represents the first study to investigate the role of CMIs on cognitive impairment in CAA, both cross-sectionally and longitudinally. However, this study has limitations. Firstly, this cohort included patients who underwent either 1.5T or 3T MRI scans due to the scanner upgrade. This could have affected our CMI detection rates, thus leading to bias. Surprisingly, we did not find a difference in CMI occurrence between patients who underwent 1.5T compared to 3T MRI scanning, which can be explained by the similar acquisition parameters for the T1-weighted sequences between the 1.5T and 3T MRI protocol (both sequences are 3D and 1mm thickness). Moreover, adding the field strength as a covariate did not change the results. Additionally, the subgroup analysis including only subjects with 1.5T MRI scans did not change the results. Secondly, while we determined that CMI presence was associated with dementia conversion, we were unable to define the relationship of CMIs to change in specific cognitive domains longitudinally due to the lack of detailed follow-up neuropsychological testing. Larger studies focusing on cognitive status and with systematic follow-up are necessary to confirm our findings. Thirdly, we included previous history of ICH but not ICH volume in our models as a covariate in our analyses. Due to the considerable gap between ICH events and study enrollment (median time 1.48 years), CT scans related to acute ICH events were not available for ICH volume assessment in many patients. However, previous studies have consistently demonstrated that the ICH volume did not affect long-term (>6 months) cognitive deterioration in primary ICH patients.^{36, 37} Finally, all subjects were recruited from a research cohort with potential selection bias and therefore the results from our study may not directly generalize to other (clinical) populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Microinfarcts are represented by white dots.

Table 1.

Cerebral cortical microinfarcts distribution by cerebral lobe.

Lobe	Observed number of CMIs (percentage)	Lobar volume percentage	Ratio (observed/expected)	P value
Frontal	43 (42%)	45%	0.93	P=0.971
Parietal	32 (31%)	22%	1.42	
Temporal	18 (18%)	23%	0.75	
Occipital	9 (9%)	10%	0.95	

Legend of Table 1. Distribution of 102 CMIs by cerebral lobe in the non-demented patients with cerebral amyloid angiopathy (n=40).
Abbreviations: CMIs, cerebral microinfarcts.

Table 2.

Association between the presence of CMIs and other neuroimaging markers of small vessel disease (n=102).

Neuroimaging markers	Model 1		Model 2		Model 3	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
TBV/ICV	0.90 (0.81, 1.00)	0.057	0.83 (0.73, 0.96)	0.009*	0.85 (0.74, 0.98)	0.025*
WMH/ICV	1.45 (0.69, 3.02)	0.326	1.70 (0.77, 3.77)	0.189	1.82 (0.80, 4.13)	0.153
Lobar CMB	0.96 (0.54, 1.69)	0.368	0.98 (0.55, 1.74)	0.939	0.95 (0.52, 1.73)	0.857
cSS	2.83 (1.22, 6.57)	0.015*	2.88 (1.24, 6.72)	0.014*	2.66 (1.10, 6.39)	0.029*

Legend of Table 2. Model 1: without adjustment; Model 2: adjusted for age and sex; Model 3: adjusted for age, sex and history of previous intracerebral hemorrhage. Abbreviations: CMIs, cerebral microinfarcts; CMBs, cerebral microbleeds; WMH, white matter hyperintensities; cSS, cortical superficial siderosis; ICV, intracranial volume; TBV, total brain volume.

Table 3.

Comparison between CAA patients with CMIs and without CMIs on baseline demographic and clinical characteristics.

	CAA patients with CMIs (n=36)	CAA patients without CMIs (n=59)	P value
Demographics			
Age (years)	69.54±7.24	70.19±7.03	0.669
Female, n (%)	9 (25%)	16 (27.1%)	1.000
Education (years)	16.67±2.58	16.82±3.04	0.818
Previous medical history			
Hypertension, n (%)	20 (55.6%)	29 (49.2%)	0.545
Hyperlipidemia, n (%)	14 (38.9%)	27 (45.8%)	0.512
Diabetes, n (%)	4 (11.1%)	6 (10.2%)	1.000
CAD, n (%)	3 (8.3%)	6 (10.2%)	1.000
Afib, n (%)	2 (5.6%)	7 (11.9%)	0.475
Previous ICH, n (%)	26 (72.2 %)	32 (54.2%)	0.081
Neuropsychological performance (Z-scores)			
MMSE	-0.11±1.30	-0.28±1.59	0.611
Executive function	-1.62±2.4	-0.67±1.14	0.033 *
Processing speed	-1.60±2.73	-0.60±1.47	0.048 *
Verbal memory	-0.61±1.25	-0.77±0.95	0.448
Language	0.22±1.02	-0.04±0.89	0.219
Attention	-0.23±0.87	-0.16±0.93	0.730

Legend of Table 3. Variables with normal distribution are shown as mean±SD. Non-normally distributed variables are shown as median (25%, 75%). Abbreviations: CMIs, cerebral microinfarcts; CAD, cardiac artery disease; Afib, atrial fibrillation; ICH, intracerebral hemorrhage MMSE, mini-mental state examination.

* Significant.

Table 4.

Association between the presence of CMIs and cognitive performance in different domains (n=95).

Cognitive domains	Model 1		Model 2	
	β (95% CI)	<i>P</i> value	β (95% CI)	<i>P</i> value
Executive function	-0.26 (-0.46, -0.06)	0.012*	-0.23 (-0.44, -0.02)	0.036*
Processing speed	-0.23 (-0.43, -0.03)	0.022*	-0.24 (-0.45, -0.04)	0.020*
Verbal memory	0.07 (-0.13, 0.28)	0.488	0.18 (-0.03, 0.40)	0.095
Language	0.13 (-0.08, 0.34)	0.219	0.21 (-0.00, 0.42)	0.051
Attention	-0.04 (-0.20, -0.01)	0.73	0.02 (-0.22, 0.25)	0.885

Legend of Table 4. Model 1: without adjustment; Model 2: adjusted for total brain volume, white matter hyperintensities volume, number of lobar cerebral microbleeds, cortical superficial siderosis presence and history of previous intracerebral hemorrhage.

Table 5.

Cox-regression analysis of predictors for dementia conversion (n=74).

Predictors	HR	95% CI	P value
<i>Univariable Cox regression model</i>			
Age (per year)	1.09	1.00–1.08	0.051
Education (per year)	0.94	0.76–1.17	0.579
Sex (female)	0.40	0.09–1.79	0.230
HTN	1.28	0.45–3.62	0.638
HCE	0.44	0.22–1.92	0.652
DM	1.08	0.14–8.29	0.943
CAD	0.04	0.00–183.71	0.461
Afib	0.92	0.21–4.08	0.908
Previous ICH	0.81	0.29–2.33	0.700
TBV/ICV	0.73	0.62–0.86	<0.001
WMH/ICV	3.97	0.96–16.40	0.057
Lobar CMBs	2.31	0.99–5.40	0.053
cSS presence	1.64	0.59–4.59	0.344
CMI presence	2.95	1.04–8.37	0.043
<i>Multivariable Cox-regression model</i>			
Age	0.98	0.88–1.10	0.738
TBV/ICV	0.76	0.62–0.92	0.006*
WMH/ICV	4.47	0.62–32.27	0.137
Lobar CMBs	1.96	0.70–5.53	0.203
CMI presence	3.01	0.85–10.65	0.087

Legend of Table 5. Abbreviations: HR, hazard ratio; HTN, hypertension; HCE, hypercholesterolemia; DM, diabetes mellitus; CAD, cardiac artery disease; Afib, atrial fibrillation; WMH, white matter hyperintensities; CMBs, cerebral microbleeds; ICH, intracerebral hemorrhage; cSS, cortical superficial siderosis; ICV, intracranial volume; TBV, total brain volume; CMI, cerebral microinfarct. The number of lobar CMBs and WHM were log transformed before included in the model due to their skewed distribution.