ARTICLE

Cortical superficial siderosis progression in cerebral amyloid angiopathy

Prospective MRI study

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Abstract

Objective

To investigate the prevalence, predictors, and clinical relevance of cortical superficial siderosis (cSS) progression in cerebral amyloid angiopathy (CAA).

Methods

Consecutive patients with symptomatic CAA meeting Boston criteria in a prospective cohort underwent baseline and follow-up MRI within 1 year. cSS progression was evaluated on an ordinal scale and categorized into mild (score 1–2 = cSS extension within an already present cSS focus or appearance of 1 new cSS focus) and severe progression (score 3–4 = appearance of ≥2 new cSS foci). Binominal and ordinal multivariable logistic regression were used to determine cSS progression predictors. We investigated future lobar intracerebral hemorrhage (ICH) risk in survival analysis models.

Results

We included 79 patients with CAA (mean age, 69.2 years), 56 (71%) with lobar ICH at baseline. cSS progression was detected in 23 (29%) patients: 15 (19%) patients had mild and 8 (10%) severe progression. In binominal multivariable logistic regression, ICH presence (odds ratio [OR], 7.54; 95% confidence interval [CI], 1.75–53.52; $p = 0.016$) and baseline cSS (OR, 10.41; 95% CI, 2.84–52.83; $p = 0.001$) were independent predictors of cSS progression. In similar models, presence of disseminated (but not focal) cSS at baseline (OR, 5.58; 95% CI, 1.81–19.41; $p = 0.004$) was an independent predictor of cSS progression. Results were similar in ordinal multivariable logistic regression models. In multivariable Cox regression analysis, severe cSS progression was independently associated with increased future ICH risk (HR, 5.90; 95% CI, 1.30–26.68; $p = 0.021$).

Conclusions

cSS evolution on MRI is common in patients with symptomatic CAA and might be a potential biomarker for assessing disease severity and future ICH risk. External validation of these findings is warranted.

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From the Hemorrhagic Stroke Research Program, J. Philip Kistler Stroke Research Center, Department of Neurology (T.P., P.F., M.P., G.B., L.X., A.D.W., K.M.S., J.R., M.E.G., S.M.G., A.V., A.C.), and Division of Neurocritical Care and Emergency Neurology (J.R.), Massachusetts General Hospital, and MIND Informatics, Massachusetts General Hospital Biomedical Informatics Core (J.R.), Harvard Medical School, Boston; and Department of Pharmacology, Faculty of Medicine (T.P.), Chulalongkorn University, Bangkok, Thailand.

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Glossary

CAA = cerebral amyloid angiopathy; **CI** = confidence interval; **CMB** = cerebral microbleed; **cSAH** = convexal subarachnoid hemorrhage; **cSS** = cortical superficial siderosis; **FLAIR** = fluid-attenuated inversion recovery; **FOV** = field of view; **GRE** = gradient recalled echo; **HR** = hazard ratio; **ICH** = intracerebral hemorrhage; **ICV** = intracranial volume; **IQR** = interquartile range; **MGH** = Massachusetts General Hospital; **OR** = odds ratio; **SWI** = susceptibility-weighted imaging; **TE** = echo time; **TFNE** = transient focal neurologic episode; **TR** = repetition time; **WMH** = white matter hyperintensity.

Cerebral amyloid angiopathy (CAA) is a common small vessel disease of the brain characterized by progressive β-amyloid deposition in the small leptomeningeal and cortical arterioles. CAA is an important cause of spontaneous lobar intracerebral hemorrhage (ICH) in the elderly, and a key contributor in age-related cognitive decline and dementia.[1,2] CAA is associated with characteristic hemorrhagic MRI markers including multiple strictly lobar cerebral microbleeds (CMBs) and cortical superficial siderosis (cSS) on blood-sensitive sequences comprising T2*-weighted gradient recalled echo (T2* GRE) or susceptibility-weighted imaging (SWI). These lesions have become clinically useful for assessing the presence and severity of the underlying CAA pathology, and for prognosis in patients with different CAA-related syndromes.[1,3]

cSS in particular is now recognized as one of the most specific and clinically important biomarkers of CAA.[4,5] cSS is detected on blood-sensitive MRI as a characteristic curvilinear low signal lesion along the cerebral convexities or the leptomeningeal space. It is thought to represent blood-breakdown products (including hemosiderin) deposited within the supratentorial subarachnoid space and along the superficial cortical layers.[2,3] In patients presenting with advanced CAA, cSS is found in around 40%–60%[3,6] and is included in the modified Boston criteria for CAA diagnosis.[7] Recent studies have demonstrated a strong independent association between cSS and future symptomatic lobar ICH risk in patients with CAA.[8–11] In a European multicenter cohort of CAA-ICH, cSS presence and disseminated cSS in particular were independent predictors of lobar ICH recurrence (hazard ratio [HR], 2.53; 95% confidence interval [CI], 1.05–6.15; $p = 0.040$ and HR, 3.16; 95% CI, 1.35–7.43; $p = 0.008$, respectively).[9] These findings were recently replicated in other CAA-ICH cohorts,[10,11] including more advanced classification systems of cSS severity and multifocality.[12] cSS also seems to be the single most important independent risk factor of first-ever lobar ICH in patients with CAA presenting without ICH at baseline.[8] However, very little is known about cSS progression over time on serial MRIs, which might be important for both routine clinical follow-up in patients with CAA and for validating cSS as a biomarker useful for early-phase disease modification trials.[3]

In this study, we investigated the prevalence and predictors of cSS progression on follow-up MRI within 1 year in symptomatic patients with CAA from a prospective research cohort. In a secondary analysis, we also explored the association between cSS progression and risk of future symptomatic lobar ICH on clinical follow-up.

Methods

Case selection and study population

We analyzed data from an ongoing prospective longitudinal research cohort study of CAA (recruited between 2006 and 2017) at Massachusetts General Hospital (MGH), as previously described in detail.[13,14] All participants were patients ≥55 years old, who presented with CAA-related syndromes including lobar ICH, transient focal neurologic episodes, or both. Patients were diagnosed with CAA based on the classic Boston criteria.[15] Comprehensive clinical evaluation and neuroimaging acquisition data were gathered at time of enrollment and follow-up period according to the research protocol.[13,14]

A total of 152 patients with CAA from this cohort were screened for eligibility for the current study. We included the patients fulfilling the following criteria: (1) symptomatic patients with probable CAA diagnosed by classic Boston criteria who had (2) 2 available MRI scans (at baseline and at 1-year follow-up) of good quality with both blood-sensitive (SWI or T2*-GRE) and T2-weighted fluid-attenuated inversion recovery (FLAIR) sequences. We excluded patients with active CAA-related inflammation features on MRI scan.[16] Figure 1A summarizes the patient selection process in a flow chart.

Standard protocol approvals, registrations, and patient consents

This study was performed with approval of our institutional review boards at MGH and in accordance with relevant guidelines. Informed consent was obtained from patients or their surrogates.

Clinical and *APOE* data

As previously described in detail,[13,14] baseline characteristics including demographic data, full medical history, clinical presentation, and medication list were collected at presentation through in-person interview with patients or surrogates using standardized data collection forms. A standardized neuropsychiatric test battery was performed to evaluate and determine cognitive status at time of enrollment.[14] *APOE* genotype was collected in a subgroup of patients who provided blood samples and consented to genetic testing.

Follow-up clinical data were obtained by phone calls at 3 months after enrollment and every 6 months thereafter. Standardized data collection forms and comprehensive systematic chart reviews of all available information (including discharge summaries, outpatient follow-up data, clinician

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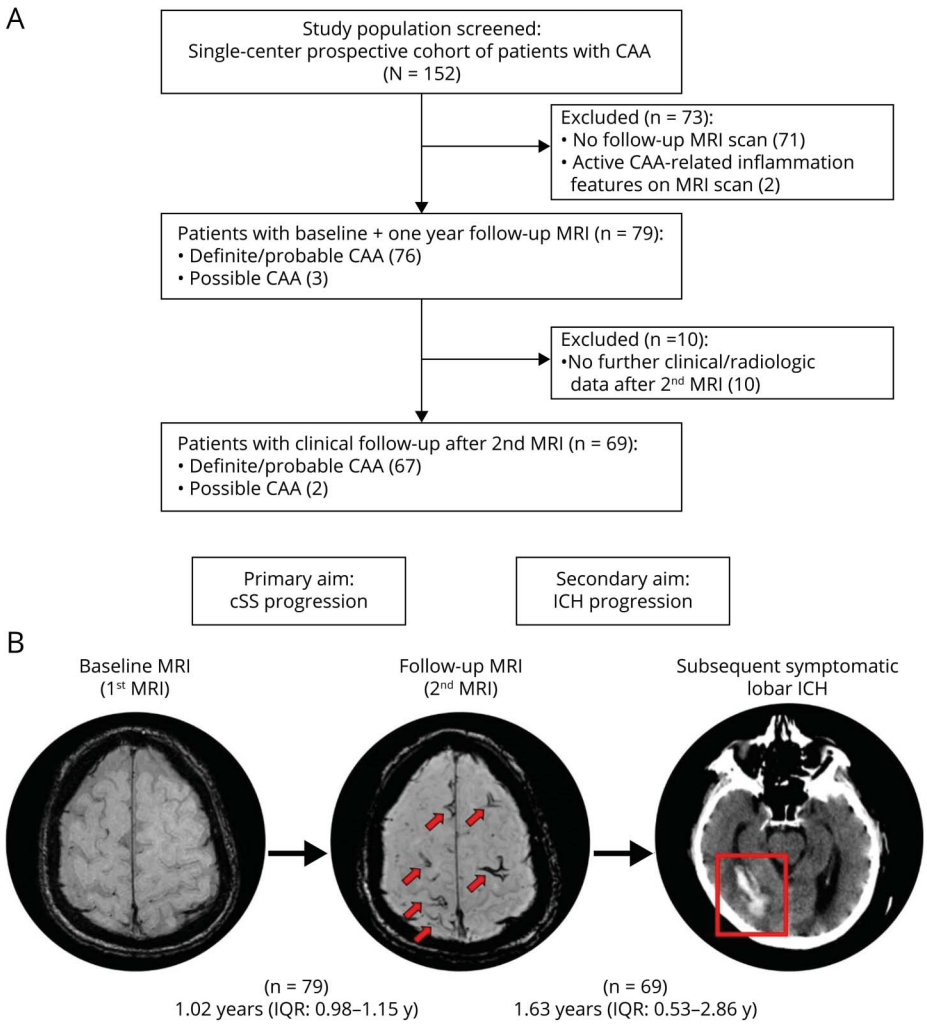
Figure 1 Schematic summary of the study methodology



(A) Flow chart of patient selection. (B) Schematic of overall study design including the primary aim (i.e., investigate cortical superficial siderosis [cSS] progression within 1 year in patients with cerebral amyloid angiopathy [CAA]) and secondary aim (i.e., evaluate the risk of future symptomatic lobar intracerebral hemorrhage [ICH]). Red arrows show newly developed multiple cSS foci on follow-up blood-sensitive MRI and the red box shows a subsequent symptomatic lobar ICH at the right occipital lobe on noncontrast CT scan, performed after the 2nd MRI. IQR = interquartile range.

letters, changes in medication list, death certificates) were supplemented as part of systematic follow-up assessment. An in-person clinical follow-up visit at a neurology clinic was performed at least once per year. Symptomatic lobar ICH, the main outcome of our study, was defined as a symptomatic stroke syndrome associated with neuroimaging evidence of a corresponding ICH in lobar brain regions. All available clinical and radiologic data were used to determine outcome events, blinded to cSS characteristics and other neuroimaging findings.

Neuroimaging data acquisition and analysis

Images were obtained using 1.5T or 3.0T MRI scanners using a standardized research protocol, as described in previous articles.[13,14] The imaging protocols for 3T MRI (Siemens Trio, Munich, Germany) were as follows: 3D FLAIR (slice thickness 1 mm, interslice gap 0 mm, in-plane resolution 1 3 1 3 1, repetition time [TR] 6,000 ms, echo time [TE] 303 ms, flip angle 120°, acquisition matrix 256 3,256, field of view [FOV] 256 3,256 mm) and SWI (slice thickness 1.2 mm, interslice gap 0 mm, in-plane resolution 0.5 3 0.5 3 0.5, TR 27 ms, TE 21 ms, flip angle 15°, acquisition matrix 448 3,299, FOV 224 3,150 mm). The neuroimaging protocols for 1.5T MRI (Signa; General Electric Medical Systems, Milwaukee, WI) included the following sequences: axial FLAIR (slice thickness 5 mm, interslice gap 1 mm, TR 10,000 ms, TE 140 ms, acquisition matrix 256 3,256) and T2* GRE (slice thickness 5 mm, interslice gap 1 mm, TR 750 ms, TE 24 ms, acquisition matrix 256 3,144). MRI scans were done at baseline (i.e., recruitment after initial clinical presentation) and at 1-year follow-up (±2 months). MRI ratings were performed in consensus by 2 trained investigators (T.P. and A.C.), in line with the STRIVE criteria[17] and blinded to all clinical, genetic, and follow-up data.

Based on recent consensus recommendations and guidelines,[3] cSS was defined as a curvilinear hypointensity lesion along the cortical surface, distinct from vessels on axial MRI blood-sensitive sequences. cSS contiguous or potentially anatomically connected with any lobar ICH were not counted into the

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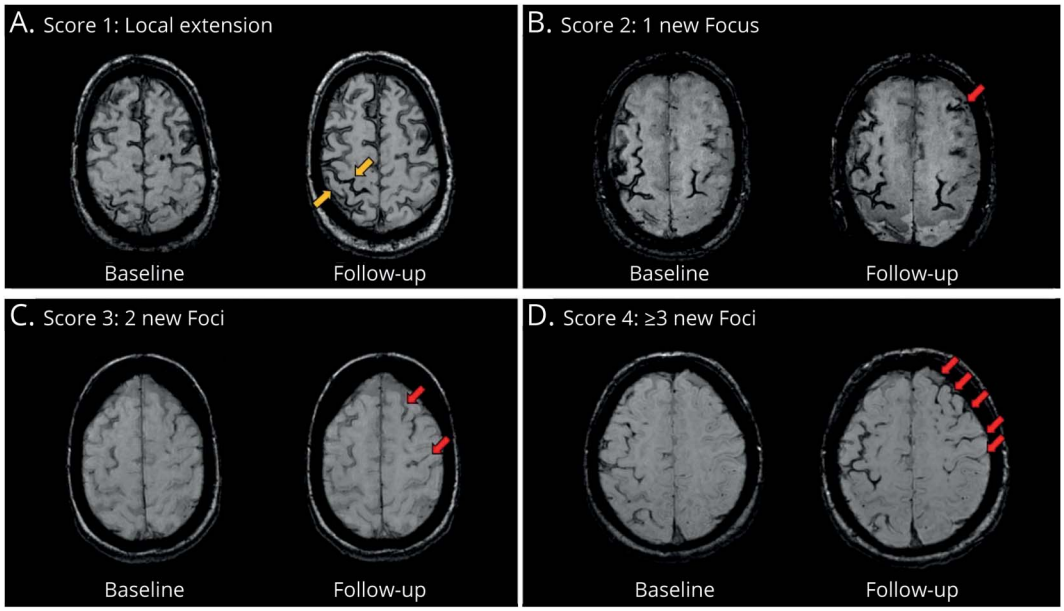
Figure 2 Cortical superficial siderosis (cSS) progression scale



Representative examples of cerebral amyloid angiopathy in patients with different cSS severity progression on follow-up susceptibility-weighted imaging. (A) Score 1: local cSS extension within an already present focus of cSS at baseline MRI in the right parietal lobe (orange arrows) in a patient with disseminated cSS at baseline. (B) Score 2: one new focus of cSS progression in the left frontal lobe. (C) Score 3: 2 new faint foci of cSS progression in the left frontal lobe next to the already present focus of cSS at baseline MRI. (D) Score 4: 5 new foci of cSS progression in the left hemisphere (cSS progression score 1–2 indicates mild cSS progression and score 3–4 indicates severe cSS progression. All new foci of cSS progression are shown in red arrows).

cSS classification. The sagittal and coronal views were also used to confirm and clarify the anatomic location of cSS in relation to lobar ICH. All areas of cSS should be separated from any lobar ICH by at least 1 unaffected sulcus at the same axial level, or by at least 2 unaffected sulci at multiple axial levels. We used FLAIR to confirm the anatomical location of the sulci and gyri, and to differentiate cSS from acute convexity subarachnoid hemorrhage, which appears as hyperintensity lesion along sulcus/sulci. The extent of cSS in both hemispheres is categorized into absent, focal (restricted 3 or less sulci), or disseminated (4 or more sulci).[6,7]

CMB presence and number were evaluated on axial SWI or T2* GRE using current consensus criteria[18,19] and the Microbleed Anatomical Rating Scale.[20] For statistical analyses, the number of lobar CMBs was categorized into 0, 1, 2–4, 5–10, and more than 10.[21] ICH was evaluated with reference to the CHARTS[22] scheme on MRI blood-sensitive and FLAIR sequences at baseline and follow-up. We rated scans for the presence and number of ICH as follows: 0, none; 1, single; 2, 2 or more ICHs.

White matter hyperintensity (WMH) volumes were measured on FLAIR sequences using a semi-automated segmentation method as previously described.[23] WMH volumes were normalized to total intracranial volume (ICV) before any analysis to account for differences in participants' head sizes. ICVs were obtained by processing scans using Freesurfer version 5.3.

Progression of neuroimaging markers on MRI

The assessment of neuroimaging markers progression was performed by consensus between 2 trained investigators using the following predefined visual rating methods. The baseline MRI at presentation and the follow-up MRI were aligned manually by navigating through the images in both series and then images were correctly aligned using the linking tool in open software 3D Slicer 4.3.[24] This simple visual comparison method was adopted so that it mirrors the MRI assessment at different time points often used in clinical practice. The details of the scales used for evaluating progression in each neuroimaging marker are described further below.

cSS progression was defined on an ordinal scale, recently designed and introduced at our center, as follows: 0, no cSS progression; 1, cSS extension within an already present focus of cSS at the baseline MRI, without a new cSS focus; 2, appearance of 1 new cSS focus; 3, appearance of 2 new cSS foci; and 4, appearance of 3 or more cSS foci. Figure 2 shows some characteristic examples for each cSS progression category. The interrater agreement between 2 trained raters using a representative sample of 25 scans was excellent ($\kappa = 0.82$). We also separately assessed the extent of cSS at baseline and follow-up MRI based on the established cSS severity scale (no, focal, and disseminated cSS).[7] Using this scheme, cSS could progress from none to focal, focal to disseminated, and none to disseminated based on the baseline and follow-up ratings. In cases that developed new ICHs during the interscan period, cSS progression was only assessed in areas not anatomically connected to the area of hematoma as described above.

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Table 1 Comparison of basic demographic and clinical characteristics of patients with cerebral amyloid angiopathy (CAA) from our cohort included in vs excluded from the current study

Characteristic	Whole CAA cohort (n = 152)	Included (n = 79)	Excluded (n = 73)	*p* Value
Age at baseline MRI, y	69.96 ± 7.86	69.41 ± 7.74	70.75 ± 7.98	0.234[a]
Male	105 (69.1)	57 (72.2)	48 (65.8)	0.395
Hypertension	79 (52.0)	48 (60.8)	32 (42.5)	0.025[b]
Hypercholesterolemia	56 (36.8)	30 (38.0)	26 (35.6)	0.764
Coronary artery disease	13 (8.6)	7 (8.9)	6 (8.2)	0.888
Atrial fibrillation	14 (9.5) (n = 148)	10 (12.7)	4 (5.8) (n = 69)	0.156
Dementia	8 (5.3)	2 (2.5)	6 (8.3)	0.290
Aspirin use	42 (27.6)	25 (31.6)	17 (23.3)	0.251
Anticoagulant use	8 (5.3)	5 (6.3)	3 (4.1)	0.542
Presence of ICH	111 (73.0)	56 (70.9)	55 (75.3)	0.537
Previous ischemic stroke	8 (5.4) (n = 149)	4 (5.2) (n = 77)	4 (5.6) (n = 72)	0.923
Transient neurologic symptoms	45 (31.9) (n = 141)	28 (38.9) (n = 72)	17 (24.6) (n = 69)	0.071
90-day mortality rate	1 (0.7)	0 (0.0)	1 (1.4)	0.298
Deceased at time of latest follow-up	52 (34.4)	16 (34.4)	36 (49.3)	0.0002[c]

Abbreviation: ICH = intracerebral hemorrhage.
Values are mean ± SD or n (%).
[a] Two-sample *t* test.
[b] *p* Value < 0.05.
[c] *p* Value < 0.001.

We visually categorized CMB progression using the following scale: 0, no new CMBs; 1, 1 or 2 new CMBs; 2, 3 to 5 new CMBs; 3, 6 to 10 new CMBs; 4, 10 or more additional CMBs. Severe CMBs progression was defined as presence of more than 5 new CMBs. ICH on follow-up MRI was also evaluated based on the CHART scheme.[22] ICH progression was assessed in relation to baseline MRI and classified into presence or absence of the new ICH or local evolution on follow-up MRI scan.

A composite variable was created to take into account potential differences between blood-sensitive MRI sequences on follow-up MRI compared with baseline MRI. We took into consideration differences in scan types (T2* GRE vs SWI or vice versa) and MRI scans field strength (i.e., 1.5T vs 3.0T). In our included cohort, 48 patients had 1.5T MRI and 31 patients had 3.0T MRI for both MRI scans. We categorized the potential differences between baseline and follow-up blood-sensitive MRI scans into 3 groups comprised of same sensitivity of the scan at follow-up (no differences between baseline/follow-up scans); lower sensitivity of the MRI scan at follow-up (i.e., SWI vs T2* GRE, respectively); and higher sensitivity at follow-up (i.e., T2* GRE vs SWI, respectively).

Statistical analysis

Categorical variables were analyzed using univariable logistic regression (odds ratio [OR]), Pearson χ^2 test, or Fisher exact tests as appropriate. Continuous variables were analyzed by the 2-sample *t* test for normal distribution, and Wilcoxon rank-sum test for non-normal distribution. Shapiro-Wilk test and visualized histogram were used to test for normal distribution of variables.

For our analysis, cSS progression score was prespecified to be analyzed into 2 models: (1) presence of any cSS progression on a binominal scale (presence or absence) and (2) severity of cSS progression on an ordinal scale: no new cSS (score 0), mild cSS progression (score 1–2 = cSS extension within an already present focus of cSS or appearance of 1 new cSS focus), and severe cSS progression (score 3–4 = appearance of 2 or more new cSS foci).

We initially investigated factors associated with cSS progression within 1 year by using univariable logistic regression analysis. Statistically significant predictors ($p < 0.05$) for cSS progression, in addition to age and MRI scan time interval (prespecified), were selected into binominal and ordinal multivariable logistic regression models.

The future risk of symptomatic lobar ICH was analyzed using Kaplan-Meier plots with significance testing by the log-rank test in univariable analysis. Survival time was calculated from

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Table 2 Comparison of demographic, clinical, and baseline imaging characteristics of patients with cerebral amyloid angiopathy (CAA) according to cortical superficial siderosis (cSS) progression during 1 year of MRI follow-up

Characteristic	Whole CAA cohort (n = 79)	With cSS progression (n = 23)	Without cSS progression (n = 56)	OR (95% CI)	*p* Value
Age at baseline MRI, y	69.2 ± 7.7	67.6 ± 8.2	69.9 ± 7.5	−1.17 (−6.36 to 1.70)[a]	0.249[a]
Male	57 (72.2)	19 (82.6)	38 (67.9)	2.25 (0.68 to 7.59)	0.187
Hypertension	48 (60.8)	11 (47.8)	37 (66.1)	0.47 (0.18 to 1.26)	0.133
Hypercholesterolemia	30 (38.0)	10 (43.5)	20 (35.7)	1.38 (0.51 to 3.72)	0.521
Aspirin use	25 (31.6)	5 (21.7)	20 (35.7)	0.50 (0.16 to 1.55)	0.228
Anticoagulant use	5 (6.3)	0 (0)	5 (8.9)	0.00 (0.00 to 0.00)	0.141
Baseline WMH volume percentage, median (IQR)	1.0195 (1.6939)	1.0182 (1.4057)	1.0527 (1.7311)	0.00; W = 646 (−0.52 to 0.45)[b]	0.987[b]
Presence of lobar CMBs at baseline	74 (93.7)	21 (91.3)	53 (94.6)	0.59 (0.09 to 3.81)	0.582
≥5 Lobar CMBs at baseline	63 (79.7)	18 (78.3)	45 (80.4)	0.88 (0.27 to 2.89)	0.834
Any CMB progression	55 (69.6)	18 (78.3)	37 (66.1)	1.85 (0.59 to 5.75)	0.288
Severe CMB progression (>5 CMBs)	31 (39.2)	12 (39.2)	19 (52.2)	2.12 (0.79 to 5.70)	0.134
Presence of cSS	46 (58.2)	20 (87.0)	26 (46.4)	7.69 (2.05 to 28.86)	<0.001[c]
Focal cSS	17 (21.5)	6 (26.1)	11 (19.6)	1.44 (0.46 to 4.52)	0.529
Disseminated cSS	29 (36.7)	14 (60.9)	15 (26.8)	4.25 (1.52 to 11.85)	0.005[d]
Presence of ICH at baseline (i.e., acute symptomatic ICH at presentation)	56 (70.9)	21 (91.3)	35 (62.5)	6.30 (1.34 to 29.62)	0.011[e]
MRI time to follow-up, y, median (IQR)	1.02 (0.13)	1.00 (0.23)	1.05 (0.15)	−0.0009; W = 561 (−0.0033 to 0.0012)	0.373[b]
Follow-up vs baseline MRI sequence differences[f]					
Same sensitivity of scan at follow-up	58 (73.4)	17 (73.9)	41 (73.2)	1.04 (0.34 to 3.12)	0.949
Less sensitive scan at follow-up	7 (8.9)	3 (13.0)	4 (7.1)	1.95 (0.40 to 9.50)	0.405
More sensitive scan at follow-up	14 (17.8)	3 (13.0)	11 (19.6)	0.61 (0.15 to 2.44)	0.488

Abbreviations: CI = confidence interval; ICH = intracerebral hemorrhage; IQR = interquartile range; OR = odds ratio; WMH = white matter hyperintensity.
Values are mean ± SD or n (%) unless otherwise indicated.
[a] Two-sample *t* test.
[b] Wilcoxon rank-sum test.
[c] *p* Value < 0.001.
[d] *p* Value < 0.01.
[e] *p* Value < 0.05.
[f] Follow-up vs baseline MRI sequence differences were considered based on blood-sensitive scan types (T2* gradient recalled echo vs susceptibility-weighted imaging) and MRI field strength (1.5T vs 3T), as defined in Methods.

date of follow-up MRI until the date of new ICH or the last known date without the outcome of interest. Univariable Cox regression analysis was used to calculate univariable HR and 95% CI. Significant predictors from univariable Cox regression analyses ($p < 0.1$) and biologically plausible predictors identified in previous studies[21,25] for recurrent CAA-related lobar ICH, including age and appearance of new lobar CMBs, were investigated in multivariable Cox regression analyses.

All statistical tests were 2-tailed and significance level was set at 0.05. R Studio program (version 1.1.383, 2009–2017 R Studio, Inc.) accompanied by add-on statistical packages was used for all analyses.[26–34] The manuscript was prepared with reference to the Strengthening the Report of Observational studies in Epidemiology (STROBE) guidelines.[35]

Data availability

All data are deposited locally and are not publicly available.

Results

A flow chart of patient selection and a schematic summary of the research design of our study are depicted in figure 1. A total of 152 patients with CAA from a research cohort were

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Table 3 Multivariable logistic regression of any cortical superficial siderosis (cSS) progression (model 1: binomial logistic regression) and cSS progression severity (i.e., per category increase) (model 2: ordinal logistic regression) during MRI follow-up

Variables	Adjusted OR (95% CI)	*p* Value
Model 1-1: Nominal scale of cSS progression (yes/no)		
Age, per year increase	0.94 (0.87–1.01)	0.122
Presence of ICH at baseline	7.54 (1.75–53.52)	0.016[a]
Presence of cSS at baseline	10.41 (2.84–52.83)	0.001[b]
Model 1-2: Nominal scale of cSS progression (yes/no)		
Age, per year increase	0.94 (0.87–1.01)	0.086
Presence of ICH at baseline	7.15 (1.64–52.50)	0.020[a]
Disseminated cSS at baseline	5.58 (1.81–19.41)	0.004[b]
Model 2-1: Ordinal scale of cSS progression (none/mild/severe)		
Age, per year increase	0.95 (0.88–1.02)	0.179
Presence of ICH at baseline	6.10 (1.48–41.91)	0.026[a]
Presence of cSS at baseline	7.95 (2.29–37.89)	0.003[b]
Model 2-2: Ordinal scale of cSS progression (none/mild/severe)		
Age, per year increase	0.94 (0.88–1.01)	0.110
Presence of ICH at baseline	5.89 (1.44–40.59)	0.029[a]
Disseminated cSS at baseline	4.67 (1.62–14.51)	0.005[b]

Abbreviations: CI = confidence interval; ICH = intracerebral hemorrhage; OR = odds ratio.
All models remain consistent and of similar effect size after further adjustment for MRI interval (months) between baseline and follow-up MRI (data not shown).
[a] *p* Value < 0.05.
[b] *p* Value < 0.01.

screened and 79 were eligible (76 definite/probable CAA and 3 possible CAA based on classic Boston criteria) and included in the current analysis. Excluded patients were similar in basic demographic and clinical characteristics compared to included patients, but were more likely to be deceased at time of follow-up (table 1). Among the included patients, 56 presented with a lobar ICH at baseline, 23 with transient focal neurologic episodes (*TFNEs*), and 5 with both ICH and TFNEs.

cSS progression: incidence and predictors

Among 79 patients with CAA (mean age 69.2 years, SD 7.7 years), the median MRI scan interval was 1.02 years (interquartile range [IQR], 0.9–1.15 years). Baseline and follow-up MRIs were mostly comparable in imaging measures (n = 72, 91.1%). Forty-eight patients were scanned under a 1.5T MRI protocol and 31 patients under a 3.0T MRI protocol for both MRI scans.

Presence of any cSS progression at MRI follow-up was observed in 23 patients (29.1%) in our cohort. In the whole cohort, 6 patients (7.6%) had cSS extension within an already present focus of cSS at baseline MRI, 9 patients (11.4%) had 1 new cSS focus, 4 patients (5.1%) had appearance of 2 new cSS foci, and 4 patients (5.1%) had 3 or more cSS foci.

Forty-six patients (58.2%) had cSS on baseline MRI: 17 focal (21.5%) and 29 disseminated (36.7%) cSS. In patients without cSS at baseline (n = 33), 3 (3.8%) developed focal cSS but none of them developed disseminated cSS during follow-up. In patients with focal cSS at baseline (n = 17), 5 patients (6.3%) showed cSS progression (but remained in the focal cSS category), and 1 patient (1.3%) showed cSS progression from focal to disseminated cSS. In patients with disseminated cSS at baseline (n = 29), 14 (17.7%) developed cSS progression.

Table 2 summarizes univariable analyses comparing patients with CAA with vs without cSS progression. cSS progression was associated with cSS presence at baseline MRI, disseminated cSS, and ICH at baseline. Age, sex, lobar CMB presence, CMB progression, and *APOE* genotype (n = 43; data not shown) were not associated with cSS progression. After comparing MRI quality between baseline and follow-up MRI as well as MRI time to follow-up for both groups, there was no significant difference in cSS

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Table 4 Comparison of demographic, clinical, and baseline imaging characteristics of patients with cerebral amyloid angiopathy (CAA) with vs without clinical follow-up data for future lobar intracerebral hemorrhage (ICH)

Characteristic	Whole CAA cohort (n = 79)	Included (n = 69)	Excluded (n = 10)	*p* Value
Age at baseline MRI, y	69.2 ± 7.7	68.7 ± 7.7	72.6 ± 7.2	0.139[a]
Male	57 (72.2)	51 (73.9)	6 (60.0)	0.362
Hypertension	48 (60.8)	41 (59.4)	7 (70.0)	0.525
Hypercholesterolemia	30 (38.0)	27 (39.1)	3 (30.0)	0.581
Aspirin use	25 (31.6)	25 (31.6)	0 (0.0)	0.022[b]
Anticoagulant use	5 (6.3)	5 (7.2)	0 (0.0)	0.382
Baseline WMH volume percentage, median (IQR)	1.0195 (1.6939)	1.0712 (1.6515)	0.7161 (1.269)	0.349
Presence of lobar CMBs at baseline	74 (93.7)	64 (92.8)	10 (100.0)	0.382
≥5 Lobar CMBs presence at baseline	63 (79.7)	57 (79.4)	6 (60.0)	0.099
Presence of CMB progression	55 (69.6)	48 (69.6)	7 (70.0)	0.978
Severe CMB progression (>5 new CMBs)	31 (39.2)	26 (37.7)	5 (50.0)	0.459
Presence of cSS	46 (58.2)	42 (60.9)	4 (40.0)	0.214
Focal cSS	17 (21.5)	15 (21.7)	2 (20.0)	0.901
Disseminated cSS	29 (36.7)	27 (39.1)	2 (20.0)	0.244
Presence of cSS progression	23 (29.1)	21 (30.4)	2 (20.0)	0.500
Severe cSS progression (yes vs no)	8 (10.1)	7 (10.1)	1 (10.0)	0.989
Presence of ICH at baseline	56 (70.9)	46 (66.7)	10 (100.0)	0.031[b]
ICH progression	11 (13.9)	9 (13.0)	2 (20.0)	0.555
MRI time to follow-up, y, median (IQR)	1.02 (0.13)	1.04 (0.17)	1.00 (0.10)	0.971[c]
Follow-up vs baseline quality of scan types[d]				
Same quality/sensitive scan at follow-up	58 (73.4)	49 (71.0)	9 (90.0)	0.207
Less quality/sensitive scan at follow-up	7 (8.9)	7 (10.1)	0 (0.0)	0.295
More quality/sensitive scan at follow-up	14 (17.8)	13 (18.8)	1 (10.0)	0.497

Abbreviations: CMB = cerebral microbleed; cSS = cortical superficial siderosis; IQR = interquartile range; WMH = white matter hyperintensity.
Values are mean ± SD or n (%) unless otherwise indicated.
[a] Two-sample *t* test.
[b] *p* Value < 0.05.
[c] Wilcoxon rank-sum test.
[d] Follow-up vs baseline MRI sequence differences were considered based on blood-sensitive scan types (T2* gradient recalled echo vs susceptibility-weighted imaging) and MRI field strength (1.5T vs 3T), as defined in Methods.

progression prevalence (table 2). In binominal multivariable logistic regression analysis, ICH presence at baseline (OR, 7.54; 95% CI, 1.75–53.52; $p = 0.016$) and cSS presence at baseline MRI (OR, 10.41; 95% CI, 2.84–52.83; $p = 0.001$) were independent predictors of cSS progression after adjustments. In similar models, disseminated cSS (but not focal cSS) at baseline MRI (OR, 5.58; 95% CI, 1.81–19.41; $p = 0.004$) was also an independent predictor of cSS progression (table 3).

In ordinal multivariable logistic regression analysis (categorizing cSS progression into the 3 severity groups), ICH presence (OR, 6.10; 95% CI, 1.48–41.91; $p = 0.026$) and cSS at baseline MRI (OR, 7.95; 95% CI, 2.29–37.89; $p = 0.003$) were independent predictors of cSS progression severity (no progression, to mild, to severe cSS progression). In similar models, disseminated cSS at baseline (OR, 4.67; 95% CI, 1.62–14.51; $p = 0.005$) was an even stronger independent predictor (table 3). All binominal and ordinal models remain consistent and of similar effect size after further adjustments for MRI scan interval.

Risk of future symptomatic lobar ICH

After excluding 10 patients without sufficient clinical follow-up data, reliable clinical follow-up information (after the 2nd MRI) were available in 69 patients with CAA (figure 1B). A

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Table 5 Univariable Cox regression analyses of cortical superficial siderosis (cSS) characteristics and other potential predictors of symptomatic lobar intracerebral hemorrhage (ICH) during clinical follow-up (i.e., after the follow-up MRI period) in patients with cerebral amyloid angiopathy

Variables	HR (95% CI)	*p* Value	Log-rank test	*p* Value
Age, per year increase	0.94 (0.88–1.01)	0.105	2.72	0.1
cSS progression (yes vs no)	1.66 (0.41–6.70)	0.477	0.52	0.5
Severe cSS progression (yes vs no)	5.45 (1.34–22.24)	0.018	7.03	0.008
Severe cSS progression vs no cSS progression	4.60 (1.13–18.68)	0.033	5.48	0.02
cSS presence at follow-up MRI	2.33 (0.48–11.22)	0.293	1.17	0.3
Severe CMBs progression (more than 5)	3.75 (0.93–15.04)	0.062	4.00	0.05
Presence of ICH at follow-up MRI	4.58 (0.57–36.68)	0.152	2.47	0.1
ICH progression at follow-up MRI	2.88 (0.59–14.07)	0.192	1.86	0.2

Abbreviations: CI = confidence interval; CMB = cerebral microbleed; HR = hazard ratio.

comparison of the 10 excluded patients vs the 69 patients with CAA finally included in the future ICH outcome analysis is summarized in table 4. Of note, excluded patients were not different in basic demographic, clinical, and MRI characteristics, including cSS prevalence and progression. All of them had lobar ICH presentation at baseline. Symptomatic lobar ICH occurred in 9 (13.0%) patients after a median of 1.63 years (IQR, 0.53–2.86 years) from the 2nd MRI. In Kaplan-Meier analysis, severe cSS progression and severe CMB progression (i.e., >5) were the only predictors of future ICH ($p < 0.05$ and $p = 0.005$, respectively, by log-rank test). In univariable Cox regression analysis (table 5), severe cSS progression was the only significant predictor of future symptomatic lobar ICH. No other demographic, clinical, or neuroimaging variables were associated with future lobar ICH in univariable analyses. Kaplan-Meier curves of the whole cohort and according to severe cSS progression are shown in figure 3.

In multivariable Cox regression analysis adjusted for age or severe CMB progression, severe cSS progression remained an independent predictor of future symptomatic lobar ICH (table 6). Severe cSS progression was also an independent predictor with similar effect size after adding previous ICH presence into models.

Discussion

cSS is commonly found in symptomatic patients with CAA and is currently emerging as one of the most specific and clinically important hemorrhagic biomarkers for CAA diagnosis, disease severity assessment, and prognosis. Our study demonstrates that cSS progresses over time in patients with CAA and it can be reliably assessed on follow-up blood-sensitive MRI sequences. Around one-third of patients with CAA in our cohort showed at least some cSS evolution at 1 year of MRI follow-up. Our findings also raise the possibility that cSS progression might have clinical applications in further stratifying future symptomatic lobar ICH risk in patients with CAA. Thus, after further validation, cSS progression, in addition to cSS presence and severity at a single time point, might serve as an additional biomarker in both clinical and research settings.

The pathophysiologic mechanisms of cSS evolution over time in CAA remain speculative. A plausible hypothesis of cSS occurrence and, by extent, cSS evolution in CAA is blood leakage (or minute bleeding events) from fragile β-amyloid-laden leptomeningeal vessels. CAA is a chronic microvascular neurodegenerative process, which, over time, disrupts vessels' integrity and architecture.[1] Hence, blood might leak from pathologic vessels into the subarachnoid space and superficial cortical layers, which can be captured on blood-sensitive MRI sequences as cSS. A higher burden of cSS on MRI might reflect increasing severity of amyloid-laden vessels in patients with CAA, potentially providing new initiation sites for future blood leakage captured as cSS evolution in subsequent MRI.[36] Indeed, a CAA cohort presenting with acute convexal subarachnoid hemorrhage (cSAH) (n = 29) recently suggested that leakage from CAA-affected leptomeningeal vessels may be an important mechanism for recurrent episodes of intrasulcal bleeding (aka cSAH), which is the acute neuroimaging manifestation of cSS.[36] Of note, acute cSAH preceding cSS progression would typically be detectable only in patients who present with stroke symptoms, generally due to location in a symptomatogenic eloquent area. Thus cSS evolution might be a potential key biomarker for assessing disease severity or a particularly hemorrhagic-prone CAA phenotype. Previous studies have shown that *APOE* ε2 allele (but not ε4) is associated with cSS as well as increased risk of future hemorrhagic events.[37–39] cSS and symptomatic ICH might share the common pathway of *APOE* ε2–related vasculopathic changes leading to CAA-laden vessel rupture and

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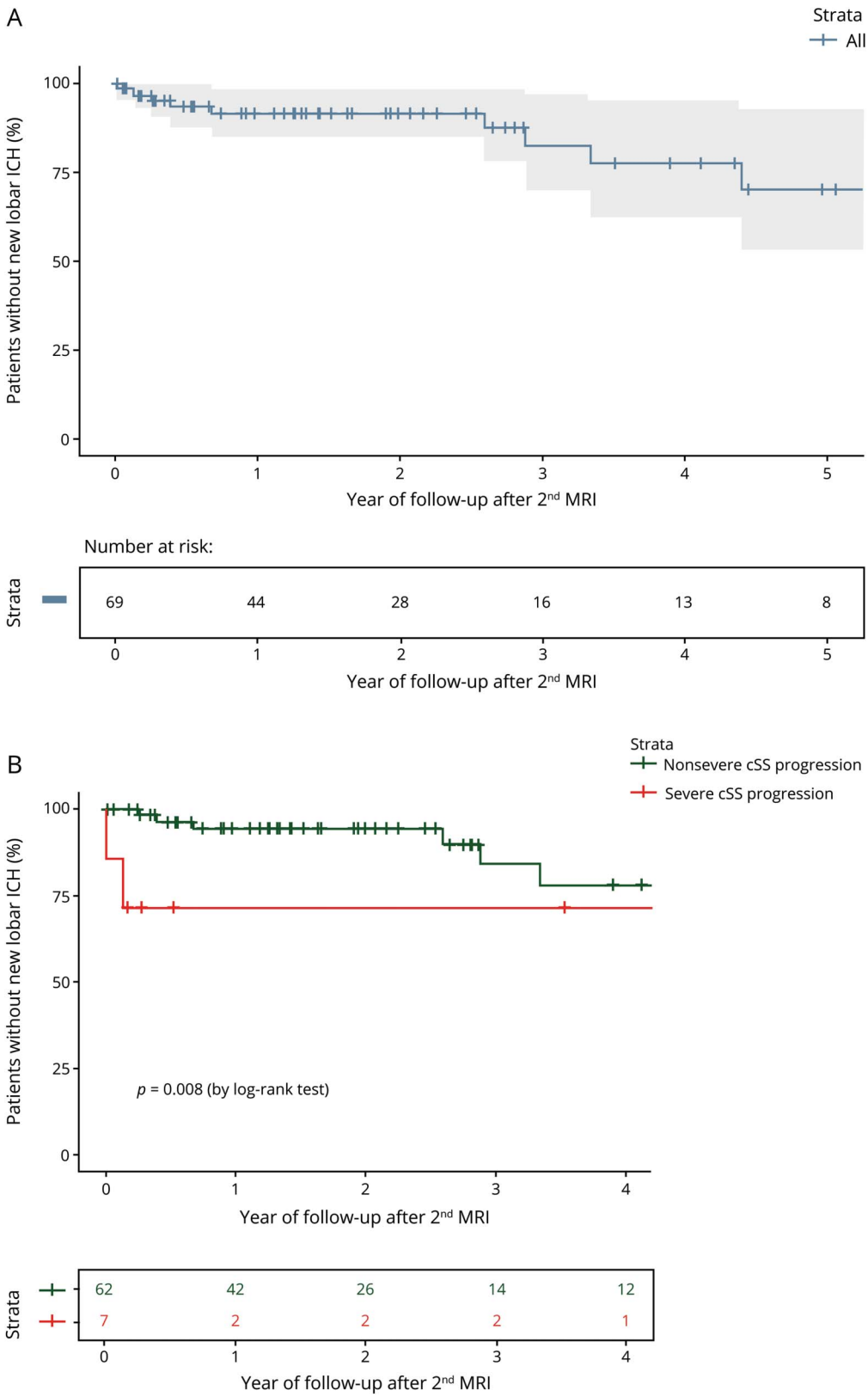
Figure 3 Kaplan-Meier curves of time to new symptomatic lobar intracerebral hemorrhage (ICH) during the clinical follow-up period



(A) Kaplan-Meier curve: time to new symptomatic lobar ICH in 69 patients with cerebral amyloid angiopathy. (B) Kaplan-Meier curve: time to new symptomatic lobar ICH according to severe cortical superficial siderosis (cSS) progression and nonsevere cSS progression.

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Table 6 Separate multivariable Cox regression analysis models of cortical superficial siderosis (cSS) progression and other potential predictors of newly developed symptomatic lobar intracerebral hemorrhage during clinical follow-up (i.e., after the follow-up MRI period) in patients with cerebral amyloid angiopathy

Variables	HR (95% CI)	*p* Value
cSS severe progression adjusted for age		
Age, per year increase	0.93 (0.87–1.00)	0.039[a]
cSS severe progression (yes vs no)	7.96 (1.78–35.59)	0.007[b]
cSS severe progression adjusted for severe CMBs progression		
cSS severe progression (yes vs no)	4.24 (1.01–17.82)	0.049[a]
Severe CMBs progression (more than 5)	3.08 (0.76–12.70)	0.120
cSS severe progression adjusted for age and severe CMBs progression		
Age, per year increase	0.93 (0.87–1.00)	0.044[a]
cSS severe progression (yes vs no)	5.90 (1.31–26.68)	0.021[a]
Severe CMBs progression (more than 5)	3.06 (0.73–12.86)	0.127

Abbreviations: CI = confidence interval; CMB = cerebral microbleed; HR = hazard ratio.
[a] *p* Value < 0.05.
[b] *p* Value < 0.01.

initiation sites for new cSS foci or future bleeding.[36,40] Due to small number of cases with *APOE* data available, our study was likely underpowered to elaborate on this interesting association between cSS progression and *APOE* alleles. Further larger studies are needed to provide direct evidence for this hypothesis. Whether future lobar ICHs directly occur in the vicinity of previously detected cSS or cSS progression areas is an interesting hypothesis, but difficult to test rigorously just by visually correlating the area of ICH with previous cSS or cSS progression. Often these patients have cSS occurring in multiple brain locations and hence a large hematoma is very likely to be close to a cSS region without a real statistical topographic correlation. Future studies will need to come up with more sophisticated approaches to test this hypothesis rigorously.

In our multivariable models, cSS, but not CMB progression, was associated with future ICH risk. While a recent meta-analysis[41] showed that lobar CMB presence increases the risk of recurrent ICH in CAA-ICH survivors, these estimates were not adjusted for other variables or confounders (including cSS). Similarly, earlier studies on the topic[21,42] that did show a correlation between CMBs and recurrent ICH risk also did not include cSS in their analysis. A more recent CAA-ICH study[9] found that cSS (but not CMBs) was independently associated with risk of new ICH in both univariable and multivariable analyses, in line with our results.

After further validation, current findings might have direct relevance for clinical practice in CAA. Preventing future lobar ICH, especially recurrent lobar ICH in CAA-ICH survivors, is at the cornerstone of patient care in the field. Adequate blood pressure control may reduce the risk of recurrent lobar ICH.[43] Whether blood pressure control could also affect cSS progression is unclear. Data on blood pressure control were not part of our cohort and their interaction with MRI markers evolution in CAA would be an interesting area for future investigation. While it remains uncertain the extent to which antithrombotic therapy could increase risk of future hemorrhage in CAA,[21,44–46] the presence of cSS seems to confer the highest risk, as has been previously suggested for the presence of multiple strictly lobar CMBs.[21] Whether antithrombotic therapy increases the risk of cSS progression needs to be examined in future cohorts.

Our study has several strengths. It is a prospective research cohort of patients with CAA that includes comprehensive clinical data and systematic clinical follow-up in standardized time frames. Patients in our cohort also underwent high-resolution research MRI, which is necessary for assessing evolution of neuroimaging biomarkers.[47–50] Moreover, our study also introduced the concept of categorizing cSS progression score into severe or nonsevere, which makes rating easier for clinical application to stratify patients at risk. However, some limitations need to be acknowledged. First, this is a single-center cohort of patients with CAA, hence, selection bias could not be excluded. All patients were enrolled in the study after surviving spontaneous lobar ICH or other acute CAA-related syndromes. Enrolled participants had good functional status (without severe cognitive impairment or dementia) and were able to undergo multiple follow-up visits according to our protocol. Of note, excluded patients (n = 73) mostly without follow-up MRI were more severely impaired and died before the occurrence of a second MRI study. Hence, our

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results can only be generalized to CAA patient populations who have similar characteristics and require external validation in unselected CAA patient populations. These patients, with similar demographic characteristics as patients with CAA without dementia presenting at a stroke unit in a previous study,[14] may be representative of symptomatic survivors without dementia with advanced CAA presenting at specialized centers. Also, the proposed cSS progression scale is simple and practical in use with high inter-rater reliability but there remains room for improvement and external validation. For example, patients with CAAs, who had disseminated cSS affecting most of the brain surface and had few remaining unaffected sulci, could potentially introduce a ceiling effect in the rating scale categories. The sample size of our study was relatively small; hence the results from our study should be considered preliminary and hypothesis-generating. Wide CIs were observed, as expected, because of the small number of outcome events, especially concerning symptomatic lobar ICH.

Despite limitations, our results indicate that cSS progression is common in symptomatic patients with CAA and can be reliably assessed on follow-up MRI scans. cSS evolution especially when severe (i.e., affecting >2 sulci) seems to be a potential MRI marker of disease severity and risk of future lobar ICH in this patient population. Overall, our findings reinforce the notion that cSS is key hemorrhagic signature for CAA.[3] Further external validation in larger cohorts or clinical trials with combined outcomes of cSS evolution and future ICH would be of interest.

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