RESEARCH ARTICLE

Mechanistic Implications of Cortical Superficial Siderosis in Patients With Mixed Location Intracerebral Hemorrhage and Cerebral Microbleeds

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Abstract

Background and Objectives

Hypertensive cerebral small vessel disease (HTN-cSVD) is the predominant microangiopathy in patients with a combination of lobar and deep cerebral microbleeds (CMBs) and intracerebral hemorrhage (mixed ICH). We tested the hypothesis that cerebral amyloid angiopathy (CAA) is also a contributing microangiopathy in patients with mixed ICH with cortical superficial siderosis (cSS), a marker strongly associated with CAA.

Methods

Brain MRIs from a prospective database of consecutive patients with nontraumatic ICH admitted to a referral center were reviewed for the presence of CMBs, cSS, and nonhemorrhagic CAA markers (lobar lacunes, centrum semiovale enlarged perivascular spaces [CSO-EPVS], and multispot white matter hyperintensity [WMH] pattern). The frequencies of CAA markers and left ventricular hypertrophy (LVH), a marker for hypertensive end-organ damage, were compared between patients with mixed ICH with cSS (mixed ICH/cSS[+]) and without cSS (mixed ICH/cSS[−]) in univariate and multivariable models.

Results

Of 1,791 patients with ICH, 40 had mixed ICH/cSS(+) and 256 had mixed ICH/cSS(−). LVH was less common in patients with mixed ICH/cSS(+) compared with those with mixed ICH/cSS(−) (34% vs 59%, $p = 0.01$). The frequencies of CAA imaging markers, namely multispot pattern (18% vs 4%, $p < 0.01$) and severe CSO-EPVS (33% vs 11%, $p < 0.01$), were higher in patients with mixed ICH/cSS(+) compared with those with mixed ICH/cSS(−). In a logistic regression model, older age (adjusted odds ratio [aOR] 1.04 per year, 95% CI 1.00–1.07, $p = 0.04$), lack of LVH (aOR 0.41, 95% CI 0.19–0.89, $p = 0.02$), multispot WMH pattern (aOR 5.25, 95% CI 1.63–16.94, $p = 0.01$), and severe CSO-EPVS (aOR 4.24, 95% CI 1.78–10.13, $p < 0.01$) were independently associated with mixed ICH/cSS(+) after further adjustment for hypertension and coronary artery disease. Among ICH survivors, the adjusted hazard ratio of ICH recurrence in patients with mixed ICH/cSS(+) was 4.65 (95% CI 1.38–11.38, $p < 0.01$) compared with that in patients with mixed ICH/cSS(−).

Discussion

The underlying microangiopathy of mixed ICH/cSS(+) likely includes both HTN-cSVD and CAA, whereas mixed ICH/cSS(−) is likely driven by HTN-cSVD. These imaging-based classifications can be important to stratify ICH risk but warrant confirmation in studies incorporating advanced imaging/pathology.

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Glossary

aHR = adjusted hazard ratio; **aOR** = adjusted odds ratio; **CAA** = cerebral amyloid angiopathy; **CMB** = cerebral microbleed; **CSO** = centrum semiovale; **cSS** = cortical superficial siderosis; **cSVD** = cerebral small vessel disease; **EPVS** = enlarged perivascular space; **HTN-cSVD** = hypertensive cSVD; **ICH** = intracerebral hemorrhage; **IQR** = interquartile range; **LVH** = left ventricular hypertrophy; **WMH** = white matter hyperintensity.

Introduction

Advances in small vessel disease research over the past decade have led to the validation of nonhemorrhagic neuroimaging markers that may be associated with either cerebral amyloid angiopathy (CAA) or hypertensive cerebral small vessel disease (HTN-cSVD), the 2 major cerebral small vessel diseases (cSVDs) in middle-aged to older adults.[1] Incorporation of these markers into the recently derived Boston criteria version 2.0 has enhanced the accuracy of diagnosing CAA using neuroimaging alone.[2] Moreover, these nonhemorrhagic imaging makers, which include basal ganglia and centrum semiovale enlarged perivascular spaces (CSO-EPVS), lobar and deep lacunes, and white matter hyperintensity (WMH) patterns, can aid in discriminating HTN-cSVD and CAA in patients with isolated lobar intracerebral hemorrhage (ICH).[3-6] However, it remains unclear whether such markers may increase the diagnostic accuracy of cSVD in situations where the underlying microangiopathy is uncertain. Determining the underlying cSVD type is critical, given that each cSVD subtype is associated with distinct recurrence rates, distinct risks of cognitive impairment, and may affect stroke prevention strategies in patients who may need antithrombotics for coexisting ischemic stroke risk.[7-10]

Patients with mixed-location ICH/cerebral microbleeds (CMBs), termed mixed ICH, present a diagnostically challenging scenario, given the presence of overlapping neuroimaging features attributed to both CAA and HTN-cSVD.[11] Such patients have a combination lobar and deep CMBs and/or ICH. While CAA is associated with lobar CMBs or a lobar ICH and HTN-cSVD is associated with deep CMBs or a deep ICH,[12,13] patients with mixed ICH share features of both cSVD subtypes. Patients with mixed ICH have a similar risk factor and MRI profile as those with HTN-cSVD, although the annual ICH recurrence rate is higher (5.1% vs 1.6%), but still less than patients with CAA (10.4%).[11] In vivo amyloid imaging using PET scans has revealed similar levels of amyloid between patients with HTN-cSVD and those with mixed ICH, both of which were lower than amyloid levels seen in patients with CAA.[14] Collectively, these findings suggest that HTN-cSVD is the predominant underlying microangiopathy of patients who present with mixed ICH.

Cortical superficial siderosis (cSS), identified as the chronic deposition of blood breakdown products over the convexities of the cerebral hemispheres, has been shown to be a strong marker for hemorrhage recurrence and is uniquely associated with CAA.[15-17] In patients with mixed ICH, which is presumed to be due to HTN-cSVD, it remains unclear whether the presence of cSS suggests significant contributions from CAA in addition to HTN-cSVD. In this study, we test the hypothesis that patients with mixed ICH and cSS are likely to have a contribution from CAA by evaluating whether such patients have a high burden of CAA-related nonhemorrhagic imaging markers compared with those without cSS.

Methods

Patient Population and Data Collection

Patients analyzed in this study were obtained from a database of consecutive patients with nontraumatic spontaneous ICH admitted to Massachusetts General Hospital from 2003 to 2019.[4] Patients with underlying vascular lesions, brain tumors, hemorrhagic conversion of an ischemic stroke, or etiologies other than cSVD disease were excluded.[3,4] All patients had a brain MRI that included a hemosiderin-sensitive MRI sequence. Medical history including vascular risk factors (hypertension, hyperlipidemia, diabetes, and coronary artery disease), tobacco usage, cardiovascular disease, and prior cerebrovascular disease was extracted from patient charts by qualified research staff. As described in detail elsewhere,[3,18] the presence of left ventricular hypertrophy (LVH) was determined by reviewing echocardiography reports (or admission electrocardiograms if no transthoracic echocardiogram was available within 1 year of the index ICH). LVH has been used in previous studies to serve as a surrogate marker for HTN-cSVD,[3,11,18,19] given its strong association with hypertensive end-organ damage.[20] LVH was defined using the following American Society of Echocardiography cutoffs for left ventricular mass indexed to body surface area: 115 g/m^2 for men and 95 g/m^2 for women.[21] The Sokolow-Lyon criteria (amplitude sum of S wave in V1 + R wave in V5 or V6 is ≥3.5 mV) were used to determine LVH on admission electrocardiograms.[22]

Longitudinal follow-up data for ICH survivors were collected as previously described.[11] Based on information obtained from the medical records, patients were followed up until their death or last relevant clinical documentation in the medical record. Information pertaining to recurrent ICH after hospital discharge from the index ICH was collected.

Neuroimaging Review

CT scans performed on admission were used to classify the hemorrhage location as either deep, lobar, primary intraventricular, or mixed location (deep ICH and lobar ICH) by board-certified neurologists (A.S.D. and R.W.R.) blinded to clinical information. Deep ICH included hemorrhages

originating from the deep gray nuclei (basal ganglia, thalamus), brainstem, or deep cerebellum.[23,24]

Brain MRIs were reviewed for the presence of hemorrhagic cSVD markers as defined by STRIVE criteria 1[1,25]: deep and lobar CMBs and focal and disseminated cSS.[13,17] During the review of hemosiderin-sensitive sequences, any chronic macrobleeds that were distinct from the admission ICH (suggestive of prior ICH) were recorded. Blinded to the hemorrhagic cSVD marker data, MRIs were then reviewed for nonhemorrhagic imaging markers such as WMH patterns (multispot WMH pattern and peribasal ganglia WMH pattern),[4] deep lacunes and lobar lacunes,[6,26,27] and basal ganglia EPVS and CSO-EPVS (graded on a 4-point scale as described elsewhere[5]). Severe EPVS were defined as a score ≥3.[5] Multispot WMH pattern, lobar lacunes, and CSO-EPVS are associated with CAA, whereas peribasal ganglia WMH pattern, deep lacunes, and basal ganglia EPVS are associated with HTN-cSVD.[4,6,28]

After cSVD markers were analyzed, hemorrhagic markers were used to determine the etiologic classification of the ICH. The diagnosis of CAA was made according to the modified Boston criteria, which incorporates the lobar location of the index ICH, chronic lobar macrobleeds (prior ICH), and the presence of strictly lobar CMBs and cSS.[15] Patients with strictly deep ICH and deep CMBs were classified as having HTN-cSVD.[3] Patients were classified as having mixed ICH if any of the following features were present: deep CMBs and lobar CMBs, deep ICH and lobar CMBs, lobar ICH and deep CMBs, deep ICH and cSS, and deep ICH and lobar ICH. The presence of cSS was allowed in all patients with mixed ICH (not just those with deep ICH). The location of the index ICH and chronic macrobleeds (prior ICHs) were incorporated into the final etiologic diagnosis. Patients with primary intraventricular hemorrhage were classified as CAA, HTN-cSVD, or mixed ICH based on the presence/distribution of CMBs and cSS.[18] Only patients diagnosed with mixed ICH were included in the final analysis. From this cohort, patients with cSS were classified as mixed ICH/cSS(+), whereas those without cSS were classified as mixed ICH/cSS(−).[14]

Statistical Analysis

For continuous variables, the mean (SD) or median values (interquartile range [IQR]) were reported based on the normality of the distribution, whereas count and percent (%) were reported for categorical variables. Differences in baseline characteristics, LVH, and neuroimaging markers among patients with mixed ICH/cSS(+) and mixed ICH/cSS(−) were assessed using either *t* test or the nonparametric Wilcoxon rank sum test for continuous variables and the Fisher exact test for categorical variables. Variables with significant differences ($p < 0.1$) between groups were entered into a multivariable regression model along with hypertension to determine associations with mixed ICH/cSS(+). To generate the final model and mitigate the possibility of overfitting, we applied backward elimination, allowing variables with a significance at $p \leq 0.1$ to remain in the model.

Among survivors of ICH, the frequency and incidence rates of recurrent ICH per 100 person-years of follow-up were determined as described elsewhere.[29] A Cox proportional hazard regression model was used to determine the association of cSS on ICH recurrence during follow-up. In brief, hazard ratios for baseline predictor variables (clinical demographics, vascular risk factors, LVH, and neuroimaging markers) and recurrent ICH were determined using univariate Cox proportional hazards tests. Significant associations ($p < 0.2$) were entered into a multivariable Cox regression model to determine adjusted hazard ratios and assess for differences in recurrent ICH risk among mixed ICH/cSS(+) and mixed ICH/cSS(−). Backward elimination was applied to remove statistically insignificant (at 10%) interaction terms. For all models, the proportional hazard assumption was tested using visual assessments of Kaplan-Meier curves. Using GraphPad Prism (version 9.5.0 for Windows; GraphPad Software, San Diego, CA), ICH recurrence probabilities of patients with mixed ICH/cSS(+) and mixed ICH/cSS(−) were plotted in a Kaplan-Meier survival plots, in which patients were censored at their first recurrence of ICH. All other statistical analyses were performed with SPSS for Windows, version 28.0 (IBM Corp., Armonk, NY). Two-tailed *p* values <0.05 were interpreted as statistically significant. Any missing data were handled using listwise deletion in models.

Standard Protocol Approvals, Registrations, and Patient Consents

Approval for this study by our hospital's institutional review board was received. Participant consent was waived for this study, given the retrospective nature of analyses and minimal patient risk.

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

A total of 1,791 patients with nontraumatic, spontaneous ICH were admitted to Massachusetts General Hospital from 2003 to 2019. Brain MRI was performed in 1,292 (72%) patients, a median of 2 (IQR 1–10) days after the occurrence of ICH. HTN-cSVD was diagnosed in 337 (26%) patients, and CAA was diagnosed in 659 (51%) patients. The remaining 296 (23%) patients were found to have mixed ICH based on the location of the ICH and the presence/distribution of hemorrhagic cSVD markers. Of the 296 patients, 40 had mixed ICH/cSS(+) and 256 had mixed ICH/cSS(−). Among patients with mixed ICH/cSS(+), 18 (45%) had ICH in lobar regions, 21 (53%) had ICH in deep regions, and 1 (3%) had primary intraventricular ICH. Among those with mixed ICH/cSS(−), 90 (35%) patients had lobar ICH, 144 (56%) had deep ICH, and 22 (9%) had primary intraventricular ICH ($p < 0.05$ for all comparisons).

Baseline differences of patients with mixed ICH/cSS(+) and mixed ICH/cSS(−) are summarized in Table 1. Patients with

Table 1 Demographics and Neuroimaging Characteristics of Patients With Mixed ICH With and Without Cortical Superficial Siderosis

	Mixed ICH/cSS(−) (n = 256)	Mixed ICH/cSS(+) (n = 40)	*p* Value
Age, y, mean ± SD	70 ± 13	77 ± 11	0.09
Female sex	105 (41)	18 (45)	0.73
Medical history			
Hypertension	232 (91)	34 (85)	0.27
Hyperlipidemia	119 (47)	23 (58)	0.23
Diabetes	66 (26)	11 (28)	0.85
Coronary artery disease	54 (21)	14 (35)	0.07
Smoking history	138 (54)	22 (55)	0.90
Ischemic stroke history	68 (27)	11 (28)	0.90
Intracerebral hemorrhage history	29 (11)	7 (18)	0.30
Dementia	29 (11)	8 (20)	0.13
Left ventricular hypertrophy	146 (59)	13 (34)	0.01
ICH location			
Deep	144 (56)	21 (53)	0.73
Lobar	90 (35)	18 (45)	0.29
Primary intraventricular	22 (9)	1 (3)	0.34
Neuroimaging markers			
Severe WMH (Fazekas ≥2)	226 (88)	34 (85)	0.60
WMH patterns			
Multispot WMH pattern	10 (4)	7 (18)	<0.01
Peribasal ganglia WMH pattern	51 (20)	6 (15)	0.53
Lacunes	141 (55)	25 (63)	0.49
Deep lacunes	121 (48)	20 (50)	0.87
Lobar lacunes	50 (20)	9 (23)	0.67
Severe EPVS	66 (26)	15 (38)	0.13
Severe basal ganglia EPVS	46 (18)	5 (13)	0.50
Severe CSO-EPVS	28 (11)	13 (33)	<0.01
Cerebral microbleeds, count	6 (3–13)	8 (2–16)	0.99
Cerebral microbleeds	240 (94)	33 (83)	0.02
Deep cerebral microbleeds, count	2 (0–4)	1 (0–3)	0.04
Deep cerebral microbleeds	186 (73)	21 (53)	0.02
Lobar cerebral microbleeds, count	2 (1–6)	3 (1–13)	0.36
Lobar cerebral microbleeds	211 (84)	32 (80)	0.66

Abbreviations: EPVS = enlarged perivascular spaces; IQR = interquartile range; WMH = white matter hyperintensity.
This table summarizes differences in baseline demographics, medical histories, and neuroimaging markers among patients with mixed-location intracerebral hemorrhage/cerebral microbleeds (mixed ICH), stratified by those who have cortical superficial siderosis (mixed ICH/cSS[+]) and those who do not (mixed ICH/cSS[–]). Data are n (%), unless specified elsewhere as mean (SD) or median (IQR).

mixed ICH/cSS(+) tended to be older than those with mixed ICH/cSS(−) (77 ± 11 years vs 70 ± 13 years, $p = 0.09$). The frequency of hypertension was similar between those with mixed ICH/cSS(+) and those with mixed ICH/cSS(−) (85% vs 91%, $p = 0.27$), although there was a trend toward an increased frequency of coronary artery disease among those with mixed ICH/cSS(+) (35% vs 21%, $p = 0.07$). Eleven patients in the study did not receive either a transthoracic echocardiogram or admission electrocardiogram. Among the patients with available data, LVH was less common in patients with mixed ICH/cSS(+) compared with those with mixed ICH/cSS(−) (34% vs 59%, $p = 0.01$).

Regarding neuroimaging markers, the frequencies of multispot pattern (18% vs 4%, $p < 0.01$) and severe CSO-EPVS (33% vs 11%, $p < 0.01$) were higher in patients with mixed ICH/cSS(+) than in those with mixed ICH/cSS(−), whereas lobar lacune frequency was similar (23% vs 20%, $p = 0.67$). The frequency of peribasal ganglia WMH pattern (15% vs 20%, $p = 0.53$) and severe basal ganglia EPVS (13% vs 18%, $p = 0.50$) was similar between patients with mixed ICH/cSS(+) and mixed ICH/cSS(−). Deep CMBs were more frequent among patients with mixed ICH/cSS(−) compared with those among patients with mixed ICH/cSS(+) (73% vs 53%, $p = 0.02$), although there was no significant difference between lobar CMBs among groups (84% vs 80%, $p = 0.66$). The frequency of CMBs overall was higher in patients with mixed ICH/cSS(−) than in those with mixed ICH/cSS(+) (94% vs 83%, $p = 0.02$). Age, hypertension, coronary artery disease, LVH, multispot WMH pattern, and severe CSO-EPVS were entered into a multivariable regression model to determine associations with mixed ICH/cSS(+). Older age (adjusted odds ratio [aOR] 1.04 per year, 95% CI 1.00–1.07, $p = 0.04$), lack of LVH (aOR 0.41, 95% CI 0.19–0.89, $p = 0.02$), presence of multispot pattern (aOR 5.25, 95% CI 1.63–16.94, $p = 0.01$), and severe CSO-EPVS (aOR 4.24, 95% CI 1.78–10.13, $p < 0.01$) were independently associated with mixed ICH/cSS(+) (Table 2).

The in-hospital case fatality rate was 14% (41 patients) among this cohort. There was no significant difference in the case fatality rate among patients with mixed ICH/cSS(+) (14%) and mixed ICH/cSS(−) (15%, $p = 0.81$). Of the 255 ICH survivors, 63 (25%) patients were lost to follow-up. There were no differences between the frequency of patients lost to follow-up between mixed ICH/cSS(+) (26%) and mixed ICH/cSS(−) (18%, $p = 0.40$). The mean follow-up of patients in the study was 4.0 ± 3.5 years. Of the 192 patients with follow-up data, ICH occurred in 15 of the 164 (9%) patients with mixed ICH/cSS(−)during follow-up, whereas it occurred in 7 of the 28 (25%) patients with mixed ICH/cSS(+) ($p = 0.02$, Table 3). Among the patients with mixed ICH/cSS(+), 6 (86%) of them experienced a recurrent ICH in lobar regions, whereas 7 (47%) patients with mixed ICH/cSS(−) experienced a recurrent lobar ICH ($p = 0.17$). The incidence of ICH per 100 person-years was 2.1% in the mixed ICH/cSS(−) cohort vs 9.1% in the mixed ICH/cSS(+) ($p < 0.01$). Of the 22 total ICH recurrences, 7 (32%) occurred in a different location (deep vs lobar)

Table 2 Associations With Mixed ICH/cSS(+)

	Univariate		Multivariable	
	OR (95% CI)	*p* Value	aOR (95% CI)	*p* Value
Age	1.05 (1.02–1.08)	<0.01	1.04 (1.00–1.07)	0.04
Hypertension	0.59 (0.22–1.54)	0.28	0.38 (0.13–1.14)	0.09
Coronary artery disease	2.01 (0.99–4.12)	0.06	2.18 (0.95–5.01)	0.07
Left ventricular hypertrophy	0.36 (0.18–0.74)	0.01	0.41 (0.19–0.89)	0.02
Multispot WMH pattern	5.22 (1.86–14.65)	<0.01	5.25 (1.63–16.94)	0.01
Severe CSO EPVS	3.92 (1.82–8.46)	<0.01	4.24 (1.78–10.13)	<0.01

Abbreviations: aOR = adjusted odds ratio; cSS = cortical superficial siderosis; OR = odds ratio; WMH = white matter hyperintensity.
This table summarizes univariate and multivariable associations between predictor variables and mixed-location intracerebral hemorrhage/cerebral microbleeds with cortical superficial siderosis [mixed ICH/cSS(+)]. Severe centrum semiovale-enlarged perivascular spaces (CSO-EPVS) were defined as a score of >2 (graded on a 4-point scale). Left ventricular hypertrophy was determined based on echocardiography reports obtained within 1 year of the hemorrhage.

than the index ICH. Six of these patients had mixed ICH/cSS(−) and 1 had mixed ICH/cSS(+).

In the univariate Cox proportional hazards analyses (Table 4), age, female sex, diabetes, prior ICH, multispot WMH pattern, deep CMBs, and mixed ICH/cSS(+) were associated with the occurrence of ICH during follow-up ($p < 0.02$ all comparisons). When these variables were entered into a multivariable model subjected to backward elimination, deep CMBs (adjusted hazard ratio [aHR] 3.68, 95% CI 1.07–12.72, $p = 0.04$) and mixed ICH/cSS(+) were significantly associated with ICH occurrence during the follow-up period (aHR 4.65, 95% CI 1.83–11.83, $p < 0.01$). The ICH recurrence probabilities among mixed ICH/cSS(−) and mixed ICH/cSS(+) patients are shown in the Figure.

Discussion

In this largest study of patients with mixed ICH, we demonstrate that both CAA and HTN-cSVD likely to contribute to the occurrence of mixed ICH when cSS is present on imaging. Among these patients, the presence of cSS, a neuroimaging marker strongly associated with CAA,[30] may aid in differentiating whether the underlying microangiopathy might include CAA in addition to HTN-cSVD. In this study, patients with mixed ICH/cSS(+) were more likely to exhibit other CAA-related nonhemorrhagic imaging markers such as severe CSO-EPVS and multispot WMH pattern, suggesting that CAA is a contributor. Based on previous data showing that mixed ICH is a more severe form of HTN-cSVD and the lack of strong evidence for CAA as a cause of deep ICH/CMBs,[11] it is unlikely that CAA is the sole underlying pathology even in patients with mixed ICH who also have cSS.

In one of the first studies of patients with mixed ICH by Pasi et al.,[11] patients with mixed ICH were more likely to have hypertension compared with those with CAA (88% vs 66%, $p < 0.01$), but of similar rates as those with HTN-cSVD (82%). In the same study, the frequency of LVH was greater among patients with mixed ICH compared with those with CAA (44% vs 21%, $p < 0.05$).[11] Our study showed a higher rate of LVH among patients with mixed ICH/cSS(−) (59%) compared with the 44% in the study conducted by Pasi et al., which included patients with and without cSS. In our study, the rate of LVH among mixed ICH/cSS(+) was lower at 34%, albeit higher than the 21% found in patients with CAA in the study conducted by Pasi et al.. In another study of mixed ICH by Tsai et al.,[14] there was a trend toward higher LVH rates among those with mixed ICH

Table 3 Incidence Rates and Hazard Ratios for ICH Recurrence

	Mixed ICH/cSS(−) survivors (n = 164)	Mixed ICH/cSS(+) survivors (n = 28)	*p* Value
Occurrence of ICH	15 (9)	7 (25)	0.02
Incidence of ICH per 100 person-years	2.05 (8.40–24.74)	9.06 (2.81–14.42)	<0.01
Crude hazard ratio	Reference	4.39 (1.75–11.03)	<0.01
Adjusted hazard ratio	Reference	4.65 (1.83–11.83)	<0.01

This table summarizes the incidence rates and hazard ratios for intracerebral hemorrhage (ICH) recurrence during a during a mean follow-up of 4.0 ± 3.5 years. The adjusted hazard ratio included the following variables in the model: female sex, deep cerebral microbleeds, and mixed ICH/cSS(+). Data are counts (n) and percentages (%) or hazard ratios with 95% CIs. Mixed ICH/cSS(−): mixed-location ICH/cerebral microbleeds without cortical superficial siderosis; mixed ICH/cSS(+): mixed-location ICH/cerebral microbleeds with cortical superficial siderosis.

Table 4 Associations With Intracerebral Hemorrhage Recurrence During Follow-up

	Univariate		Multivariable	
	HR (95% CI)	*p* Value	aHR (95% CI)	*p* Value
Age	1.03 (0.99–1.06)	0.13	—	—
Female sex	0.35 (0.14–0.85)	0.02	0.46 (0.18–1.14)	0.09
Medical history				
Hyperlipidemia	1.05 (0.45–2.48)	0.91	—	—
Diabetes	2.22 (0.93–5.32)	0.07	—	—
Coronary artery disease	1.76 (0.64–4.86)	0.27	—	—
Smoking history	0.92 (0.40–2.12)	0.84	—	—
Ischemic stroke history	1.20 (0.44–3.28)	0.72	—	—
Prior ICH	2.58 (0.95–7.02)	0.06	—	—
Left ventricular hypertrophy	0.91 (0.39–2.11)	0.83	—	—
Neuroimaging markers				
Severe WMHs (Fazekas ≥ 2)	1.54 (0.48–5.55)	0.43	—	—
Multispot WMH pattern	2.59 (0.76–8.81)	0.13	—	—
Peri-BG WMH pattern	1.15 (0.34–3.92)	0.82	—	—
Deep lacunes	0.69 (0.29–1.65)	0.41	—	—
Lobar lacunes	0.93 (0.31–2.75)	0.89	—	—
Severe BG EPVS	1.57 (0.53–4.65)	0.42	—	—
Severe CSO EPVS	1.16 (0.39–3.44)	0.79	—	—
Deep cerebral microbleeds	3.41 (1.01–11.57)	0.05	3.68 (1.07–12.72)	0.04
Lobar cerebral microbleeds	2.04 (0.48–8.79)	0.34	—	—
Mixed ICH/cSS(+)	4.39 (1.75–11.03)	<0.01	4.65 (1.83–11.83)	<0.01

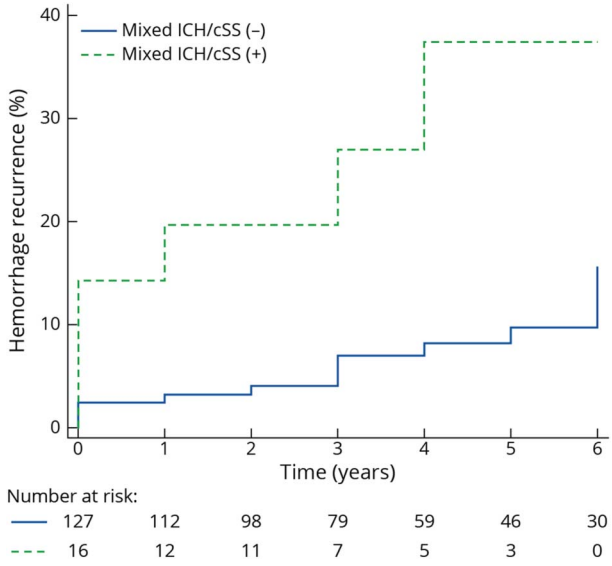
Abbreviations: aHR = adjusted hazard ratio; BG = basal ganglia; CSO = centrum semiovale; HR = hazard ratio; EPVS = enlarged perivascular spaces; ICH = intracerebral hemorrhage; mixed ICH/cSS(+) = mixed ICH with cortical superficial siderosis; WMH = white matter hyperintensity.
Univariate and multivariable Cox regression analyses showing predictors of ICH recurrence during a mean follow-up of 4.0 ± 3.5 years. Significant univariate associations ($p < 0.2$) were entered into a multivariable model subjected to backward elimination to determine associations with ICH recurrence.

compared with those with CAA (15% vs 0%, $p = 0.13$), although this was not statistically significant likely due to the small sample of patients with CAA (n = 13). In that study, the frequency of hypertension was higher among patients with mixed ICH compared with those with CAA (94% vs 54%, $p < 0.01$). Our study did not show any difference in the presence of hypertension between groups of mixed ICH with and without cSS, which is not surprising because it is common among this demographic. Moreover, it likely that HTN-cSVD is a contributor to mixed ICH/cSS(+) and mixed ICH/cSS(−). Previous work from our group has shown that LVH is a sensitive marker to distinguish HTN-cSVD from CAA.[3,18,19] Indeed, in our study, the presence of LVH was associated with mixed ICH/cSS(+) (aOR 0.41, 95% CI 0.19–0.89, $p = 0.02$).

Regarding neuroimaging markers, our study showed a higher number of deep CMBs in mixed ICH/cSS(+) compared with patients with mixed ICH/cSS(−) (73% vs 53%, $p = 0.02$), although there was a similar frequency of lobar CMBs between groups. Furthermore, deep CMBs were a found to be a predictor of ICH recurrence in follow-up, again suggesting that HTN-cSVD is an important underlying cSVD even among mixed ICH/cSS(+). Of interest, the presence of total CMBs (deep and lobar) was lower in patients with mixed ICH/cSS(+) compared with those with mixed ICH/cSS(−) (83% vs 94%, $p = 0.02$). Such results are consistent with a previous study, which demonstrates that cSS occurs in individuals with lower CMB counts and *APOE* ε2.[31]

In our study, the presence of CSO-EPVS was associated with mixed ICH/cSS(+) (aOR 4.24, 95% CI 1.78–10.13, $p < 0.01$). In addition to CSO-EPVS, multispot WMH pattern was associated with mixed ICH/cSS(+) (aOR 5.25, 95% CI 1.63–16.94, $p = 0.01$). Both these markers were recently incorporated into the revised Boston criteria version 2.0 for CAA, such that the presence of either lesion may increase the likelihood of possible

Figure ICH Recurrence Probability



The figure shows the ICH recurrence probability among patients with mixed ICH/cSS(+) and mixed ICH/cSS(−). Below the Kaplan-Meier graph, the number of patients at risk during relevant points in time are shown. Patients with mixed ICH/cSS(+) had an increased recurrence risk compared with those with mixed ICH/cSS(−) ($p < 0.01$ by log-rank test). Mixed ICH/cSS(−) = mixed-location intracerebral hemorrhage/cerebral microbleeds without cortical superficial siderosis; mixed ICH/cSS(+) = mixed-location intracerebral hemorrhage/cerebral microbleeds with cortical superficial siderosis.

or probable CAA.[2] While these criteria were not validated in patients with mixed ICH due to the low numbers of such patients in the validation study, our study suggests that the interpretation of the presence of these markers may be extended to patients with mixed ICH.

In the study by Tsai et al.,[14] in vivo amyloid imaging was used to determine the underlying microangiopathy of patients with mixed ICH. This is a method that has been validated to clarify contributions of CAA and HTN-cSVD with high sensitivity and specificity in appropriate patient groups.[32,33] Notably, patients with mixed ICH had lower amyloid burden relative to patients with CAA, but similar to that of patients with HTN-cSVD, suggesting that mixed ICH is likely driven by the latter. In this study, patients with mixed ICH were older than patients with HTN-cSVD (72 ± 13 years vs 66 ± 14 years, $p < 0.05$), but similar to patients with CAA (75 ± 9 years).[11] However, while only 9% of patients in this study had cSS, the patients who did have cSS were older than those without cSS (81 ± 10 years vs 61 ± 10 years, $p = 0.01$). Such findings were replicated in our study, which showed an association between age and mixed ICH/cSS(+) (aOR 1.04, 95% CI 1.00–1.07, $p = 0.04$). Of interest, in the study conducted by Tsai et al.[14], the amyloid burden was higher in patients with mixed ICH/cSS(+) compared with those with mixed ICH/cSS(−), suggesting that in this specific subgroup, CAA is a contributing microangiopathy.[14] There were no differences in neuroimaging markers between mixed ICH/cSS(−) and mixed ICH/cSS(+), although this may be due to the limited power to detect a difference from the very small sample size. In addition, this study did not include an analysis of WMH patterns.

A prior study suggests that recurrence risk for mixed ICH is 5.1%, which is higher than that for HTN-cSVD (1.6%), but lower than that for CAA (10.4%).[11] Of interest, our study shows that the annual recurrence rate for ICH among patients with mixed ICH/cSS(+) is significantly higher than that of patients with mixed ICH/cSS(−). The recurrence rate for mixed ICH/cSS(+) is closer to that of CAA, whereas the recurrence rate for mixed ICH/cSS(−) is closer to that of pure HTN-cSVD (patients presenting with strictly deep ICH/CMBs), again emphasizing some of the differences in the contributions of microangiopathies. Notably, nearly one-third of patients with ICH recurrence during follow-up experienced the ICH in a different location than their index ICH.

Although our work represents the largest study to date of mixed ICH, the numbers of patients with mixed ICH/cSS(+) remained low, possibly reducing the strength of our findings. Our study is also limited by the lack of pathologic correlation. While neuroimaging markers of cSVD have been validated across several studies in large populations,[1,25] we cannot account for the presence of coexisting pathologies in the same patient using neuroimaging alone. Furthermore, because we used MRI cSVD markers, we included only those patients who underwent MRI. Patients with early in-hospital mortality or transition to comfort care typically do not undergo MRI, which allows for the possibility of selection bias. However, given that only patients with mixed ICH were being studied, and no differences in in-hospital case fatality were observed between patients with mixed ICH/cSS(+) and mixed ICH/cSS(−), we believe that the effect of selection bias was minimal. It should also be noted that such bias would decrease our capacity to refute the null hypothesis and shift the results toward showing no difference (whereas we have been able to show relevant and significant differences that supported our initial hypotheses). Lastly, our study excluded a significant proportion of patients who were lost to follow-up. However, given that there were no significant differences in the proportion of patients lost to follow-up between patients with mixed ICH/cSS(−) and mixed ICH/cSS(+), this contribution to bias is likely minimal. It is important to note that fully prospective studies are needed to not miss follow-up events that could have resulted in admission to a different hospital. The recurrent ICH rates might therefore underestimate real-life events, but they were nevertheless compared with previously published data.

Our work improves the precision of noninvasive cSVD diagnosis using neuroimaging. These data support previous work, which suggests that mixed ICH is due to HTN-cSVD, while also demonstrating that in a specific subpopulation of patients, CAA might also be a contributor. Such patients may be included as candidates for therapeutic trials aimed at treating CAA.[34] Our finding that CAA is implicated in the underlying microangiopathy of patients with mixed ICH and cSS has broad implications for hemorrhagic risk in the face of

antithrombotic therapy for secondary stroke prevention. Future studies incorporating advanced neuroimaging and/or pathology are needed to verify these results.

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