Enlarged perivascular spaces and small diffusion-weighted lesions in intracerebral hemorrhage

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ABSTRACT

Objective: To examine the association between enlarged perivascular spaces (EPVS) and the prevalence and extent of small acute diffusion-weighted imaging (DWI) lesions (SA-DWIL) in patients with spontaneous supratentorial intracerebral hemorrhage (ICH).

Methods: We conducted a retrospective review of a consecutive cohort of 201 patients with spontaneous supratentorial ICH who had brain MRI with DWI within 1 month of ICH onset. We compared the clinical and imaging characteristics, including EPVS, of patients with and without SA-DWIL. We used univariate and multivariate logistic regression analyses to determine the variables associated with SA-DWIL.

Results: Small acute DWI lesions were detected in 27.9% ($n = 56$) of patients. Intraventricular and subarachnoid extension of ICH ($p \leq 0.001$), high centrum semiovale (CSO)-EPVS ($p < 0.001$), high basal ganglia-EPVS ($p = 0.007$), overall extent of white matter hyperintensity ($p = 0.018$), initial ICH volume ($p < 0.001$), and mean change in mean arterial blood pressure (δ MAP = MAP at admission – the lowest MAP before MRI scan) ($p = 0.027$) were associated with SA-DWIL on univariate analyses. On multivariate logistic regression analyses, larger ICH volume (odds ratio [OR] 1.03; 95% confidence interval [CI] 1.01–1.06; $p = 0.006$) and high CSO-EPVS (OR 12.56; 95% CI 4.40–35.85; $p < 0.001$) were independently associated with the presence of SA-DWIL.

Conclusions: In our cohort, high EPVS, in particular CSO-EPVS, and larger hematoma volume emerged as independent predictors for SA-DWIL after ICH. Our findings might provide a new explanation for the pathophysiologic mechanisms predisposing to SA-DWIL after ICH.

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GLOSSARY

ADC = apparent diffusion coefficient; **BG** = basal ganglia; **BP** = blood pressure; **CAA** = cerebral amyloid angiopathy; **CSO** = centrum semiovale; **DBP** = diastolic blood pressure; **DWI** = diffusion-weighted imaging; **DWM** = deep white matter; **EPVS** = enlarged perivascular spaces; **FLAIR** = fluid-attenuated inversion recovery; **GRE** = gradient echo; **ICH** = intracerebral hemorrhage; **IVH** = intraventricular hemorrhage; **MAP** = mean arterial blood pressure; **PVWM** = periventricular white matter; **ROI** = region of interest; **SA-DWIL** = small acute lesions on diffusion-weighted imaging; **SBP** = systolic blood pressure; **TE** = echo time; **TR** = repetition time; **WMH** = white matter hyperintensity.

Small acute lesions on diffusion-weighted imaging (SA-DWIL) are seen in 25% of intracerebral hemorrhage (ICH) patients.^{1–8} They are typically cortical or subcortical, multiple or bilateral, and may be topographically distant from the hematoma. They are often subclinical, but may be associated with worsened outcome.^{5,9}

SA-DWIL are more common in cerebral amyloid angiopathy (CAA)–related ICH than other ICH types⁶ and are associated with white matter hyperintensity (WMH) and cerebral microbleeds,^{4–7} suggesting that SA-DWIL may be attributed to an active occlusive small vessel disease. Others attribute SA-DWIL to aggressive blood pressure (BP) lowering in ICH in the setting of a diffuse arteriopathy, or ICH-triggered proinflammatory cascade.^{1,4,6,9,10} Better understanding of the pathogenesis of SA-DWIL could have important implications to improve the outcome of ICH patients.

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Virchow-Robin perivascular spaces are extensions of the subarachnoid space that accompany penetrating vessels entering the brain parenchyma, and serve as draining channels for the brain. Enlarged perivascular spaces (EPVS) can be visualized on MRI, and are commonly seen in the centrum semiovale (CSO-EPVS) in CAA-related ICH, and basal ganglia (BG-EPVS) in hypertensive ICH.^{11,12} Blood can extend to the perivascular spaces and subarachnoid space.^{13,14} Therefore, we hypothesized that EPVS are involved in the pathogenesis of ICH-associated SA-DWIL. We postulated that EPVS facilitate transport of blood toxic products to areas distant from the hemorrhage through the subarachnoid space, and that ICH patients with high EPVS would have more SA-DWIL. We examined the association between EPVS and the prevalence and extent of SA-DWIL in ICH patients in this study.

METHODS Study population and data collection. We conducted a retrospective review of a consecutive cohort of ICH patients who were admitted to the Stroke Service at Beth Israel Deaconess Medical Center from October 2007 through August 2014. Patients were included in this study if they had spontaneous supratentorial ICH and MRI with diffusion-weighted imaging (DWI) scan performed within 1 month of ICH onset. Patients who did not have MRI DWI within 1 month of ICH onset, and those with (1) secondary causes of ICH such as underlying aneurysm, vascular malformation, head trauma, venous infarction, hemorrhagic transformation of ischemic infarction, or tumor; (2) isolated intraventricular hemorrhage (IVH); or (3) infratentorial ICH were excluded.

We retrieved baseline clinical and demographic information, including age; sex; ICH onset to MRI scan time; comorbid

conditions, including history of hypertension, atrial fibrillation, diabetes mellitus, coronary artery disease, cognitive impairment, hyperlipidemia, prior ICHs, or prior ischemic stroke/TIA; medications used before ICH onset, such as antiplatelet agents, anticoagulants, and statins; systolic BP (SBP) and diastolic BP (DBP) on initial evaluation; acute emergency department or in-hospital antihypertensive treatment; and change in mean arterial BP (δ MAP = MAP at admission – the lowest MAP before MRI scan). We determined the most likely etiology for the qualifying ICH based on available clinical data and investigations and used Boston criteria for diagnosing CAA-related ICH.¹⁵

Standard protocol approvals, registrations, and patient consents. This study was approved by the Committee on Clinical Investigations at Beth Israel Deaconess Medical Center.

MRI time, acquisition, and analysis. All patients underwent MRI according to a standardized protocol as part of routine clinical assessments. The protocol included T1- and T2-weighted, fluid-attenuated inversion recovery (FLAIR), gradient-echo T2*-weighted (GRE), axial trace DWI with 2 b-values (0 and 1,000), and apparent diffusion coefficient (ADC) sequences. All studies were performed on 1.5T scanners. Sequences typically included 24–30 slices of 5-mm thickness with a matrix size of 128 × 128. The imaging parameters were as follows: T1 (repetition time [TR] 420 ms; echo time [TE] 8.8 ms); T2 (TR 4,500 ms; TE 95 ms); FLAIR (TR 9,000 ms; TE 84 ms); GRE (TR 835 ms; TE 26 ms); diffusion tensor imaging (TR 4,528 ms; TE 103 ms).

Approximately 77% of the patients had their MRI within 3 days of ICH onset; 13% within 4–7 days; and 10% between 7 and 31 days. Only 1% of patients had their MRI after 30 days.

Assessment of EPVS. EPVS were rated on axial T2-weighted MRI using a validated visual rating scale.^{16,17} EPVS were defined as ≤ 2 mm round or linear CSF isointense lesions (T2-hyperintense and T1/FLAIR hypointense with respect to brain) along the course of penetrating arteries (figure). They were distinguished from lacunes by the latter's large size (> 2 and ≤ 15 mm) and surrounding rim of FLAIR hyperintensity.^{11,18,19} Lacunar infarcts were defined as round or ovoid FLAIR lesions measuring 3–15 mm in diameter in the white matter and BG.¹⁹ EPVS were separated and rated in the BG and CSO regions using the following rating categories: 0 = no EPVS, 1 = 1 to ≤ 10 EPVS, 2 = 11 to 20 EPVS, 3 = 21 to 40 EPVS, and 4 ≥ 40

Figure Enlarged perivascular spaces and small acute diffusion-weighted lesions as seen on MRI

In a 71-year-old woman with probable cerebral amyloid angiopathy-related intracerebral hemorrhage (ICH), diffusion-weighted imaging (DWI) sequence (A) shows multiple small acute DWI lesions (white arrows) with corresponding dark area on apparent diffusion coefficient sequence (B). T2 sequence (C) shows the presence of high centrum semiovale enlarged perivascular spaces in both hemispheres and a right frontal ICH.

EPVS. EPVS were counted in both sides, ipsilateral and contralateral to the ICH, on the brain slice showing the greatest extent of EPVS. However, only the contralateral side was rated whenever the structural damage caused by ICH was severe enough to limit accurate rating of EPVS in its immediate vicinity. A sum score of EPVS was calculated as the sum of EPVS in BG and CSO regions. For the purpose of this analysis, EPVS were categorized into 0–2 vs 3–4 grades. We defined high BG-EPVS or CSO-EPVS (grades 3–4) as >20, in line with the most severe category of EPVS used in previous studies.^{20,21}

Assessment of DWI lesions. Small DWI lesions were defined as hyperintense lesions on DWI sequence, measuring less than 1 cm in diameter, with corresponding dark areas on ADC maps. Small DWI lesions in close proximity (<20 mm) to an ICH were excluded. The locations of SA-DWIL were classified as cortical or cortical-subcortical, deep (including brainstem), and cerebellum.⁶ ICH location was categorized as lobar or deep (BG and thalamus).

Assessment of hematoma volume. Hematoma volume on baseline CT scan was measured by Medical Image Processing, Analysis, and Visualization (MIPAV) software (CIT, NIH, Bethesda, MD).²² Regions of interest (ROIs) were manually drawn by tracing the perimeters of the hematoma in each slice, throughout the hemorrhagic lesion. The traced ROIs in every slice were then summed after adjusting for slice thickness to yield a hematoma volume. The volume of ICH was calculated as the sum of the ICH area on each CT slice $\times$ (slice thickness + interslice gap).⁵ Assessments of hematoma volumes were carried out collectively after completion of MRI-based assessments and locking of recorded data to avoid the confounding effects of potential unblinding.

Assessment of WMH. The presence and extent of WMH were assessed by using the Fazekas scale^{23,24} for periventricular white matter (PVWM) and deep white matter (DWM). Fazekas scale is a 4-point scale, with scores ranging from 0 to 3 on sagittal

T1-hypointense, coronal FLAIR, and axial T2 hyperintense lesions. A sum score of WMH was calculated as the sum of the PVWM and DWM scores.

Assessment of microbleeds. Microbleeds were defined as small areas (2–10 mm in diameter) of signal void with associated blooming seen on GRE image. Microbleeds were counted and classified as lobar (including cerebellum) and deep (including brainstem) by using the Microbleed Anatomical Rating Scale.^{19,25}

Two trained raters (B.W. and X.Y.) independently reviewed MRIs from 10 randomly selected scans. The inter-rater Cohen-weighted kappa was 0.97 for ICH volume, 0.78 for number of SA-DWIL, 0.8 for the class of EPVS (0–4), 0.77 for WMH score, and 0.8 for number of microbleeds. The corresponding intra-rater reliability Cohen-weighted kappa was 0.85 or above. Therefore, only one operator (B.W.) assessed the remaining scans, with occasional support from X.Y. Discussion or a third party were used to reach consensus regarding disagreements.

Statistical analysis. We divided the patients into 2 groups based on the presence vs absence of SA-DWIL. We compared the clinical and imaging characteristics, including EPVS, of patients with and without SA-DWIL using χ^2 test and Fisher exact test for categorical variables, and 2-sample *t* test or Mann-Whitney *U* test for continuous variables, as appropriate. We used univariate binary logistic regression to determine the variables associated with SA-DWIL. Variables with *p* < 0.1 on univariate analysis were entered into multivariate logistic modeling. A *p* value ≤ 0.05 was considered to be statistically significant. All statistical analyses were carried out using SPSS (version 16; IBM, Armonk, NY).

RESULTS A total of 573 ICH patients were admitted to our stroke service from October 2007 to

Table 1 Characteristics of included and excluded patients with primary ICH

Variables	Total (n = 495)	Included (n = 201)	Excluded (n = 294)	p Value
Age, y, median (SD)	70.97 (14.1)	70.46 (14.2)	71.32 (14.1)	0.508
Male sex, n (%)	280 (56.6)	120 (59.7)	160 (54.4)	0.244
Diabetes mellitus, n (%)	116 (23.4)	46 (22.9)	70 (23.8)	0.812
Hypertension, n (%)	370 (74.7)	144 (71.6)	226 (76.9)	0.189
Atrial fibrillation, n (%)	100 (20.2)	35 (17.4)	65 (22.1)	0.201
Coronary artery diseases, n (%)	87 (17.6)	37 (18.4)	50 (17.0)	0.688
Hyperlipidemia, n (%)	161 (32.5)	69 (34.3)	92 (31.3)	0.479
Cognitive impairment, n (%)	48 (9.7)	10 (5.0)	38 (12.9)	0.003
ICH history, n (%)	46 (9.3)	15 (7.5)	31 (10.5)	0.241
IS or TIA history, n (%)	68 (13.7)	27 (13.4)	41 (13.9)	0.871
Smoking history, n (%)	192 (38.8)	89 (44.3)	103 (35.0)	0.075
Antithrombotic, n (%)	269 (54.3)	112 (55.7)	157 (53.4)	0.611
Statin use, n (%)	156 (31.5)	65 (32.3)	91 (31.0)	0.744
SBP, mm Hg, median (IQR)	162 (140–186)	172 (150–192)	156 (135–178)	<0.001
DBP, mm Hg, median (IQR)	86 (75–98)	87 (77–99)	84 (74–98)	0.036
GCS score, median (IQR)	15 (10–15)	15 (13–15)	13 (7–15)	<0.001
In-hospital mortality, n (%)	99 (20.0)	15 (7.5)	84 (28.6)	<0.001

Abbreviations: DBP = diastolic blood pressure; GCS = Glasgow Coma Scale; ICH = intracerebral hemorrhage; IQR = interquartile range; IS = ischemic stroke; SBP = systolic blood pressure; TIA = transient ischemic attack.

August 2014. Sixty-nine patients had secondary causes, and 9 had isolated IVH. Therefore, 495 patients with a diagnosis of primary ICH were screened for inclusion eligibility. A total of 294 patients were excluded for the following reasons: no MRI scan ($n = 259$), poor quality of MRI images ($n = 11$), imaging data not available ($n = 4$), and infratentorial hemorrhage ($n = 20$). Therefore, the final cohort included in this analysis consisted of 201 patients. Table 1 summarizes the characteristics of included and excluded patients with primary ICH.

Tables 2 and 3 summarize the clinical and radiologic characteristics of all included patients, and the subgroups with SA-DWIL and without SA-DWIL.

Prevalence and distribution of EPVS. EPVS were detected on MRI in 99% of patients. The categories of CS-EPVS were as follows: category 0 ($n = 0$ vs 2), 1 ($n = 2$ vs 23), 2 ($n = 6$ vs 61), 3 ($n = 42$ vs 51), and 4 ($n = 6$ vs 8) in patients with SA-DWIL ($n = 56$) vs those without SA-DWIL ($n = 145$). The corresponding categories of BG-EPVS in patients

with SA-DWIL compared with those without SA-DWIL were $n = 0$ vs 1, 17 vs 72, 21 vs 50, 13 vs 15, and 5 vs 7, respectively. Overall, EPVS were rated as high CSO-EPVS in 53.2% and high BG-EPVS in 19.9% of patients; 13.4% had both high CSO-EPVS and high BG-EPVS.

Prevalence and distribution of SA-DWIL. Small DWI lesions were detected in 27.9% of patients. The DWI lesions were located in the cortex in 46.4% of patients; subcortical structures in 37.5%; deep structures in 14.3%; and cerebellum in 1.8%. The overall distribution of DWI lesions' locations did not significantly differ between patients with probable CAA-related ICH vs those with hypertensive ICH; most SA-DWIL were cortical in both groups.

The DWI lesions were more commonly seen in patients with probable CAA-related ICH (32.9%) than in patients with hypertensive ICH (32.8% vs 25.2%; $p = 0.07$). The prevalence of SA-DWIL was approximately 45% in patients with high CSO-EPVS and those with high BG-EPVS, and 63.0% in patients with

Table 2 Demographic and clinical characteristics of ICH patients with and without SA-DWIL

Characteristic	All subjects ($n = 201$)	SA-DWIL positive ($n = 56$)	SA-DWIL negative ($n = 145$)	<i>p</i> Value
Demographics				
Age, y, mean (SD)	70.46 (14.2)	69.91 (13.4)	70.67 (14.6)	0.736
Sex, male, <i>n</i> (%)	120 (59.7)	37 (66.1)	83 (57.2)	0.253
White race, <i>n</i> (%)	150 (74.6)	41 (73.2)	109 (75.2)	0.775
Medical comorbidities, <i>n</i> (%)				
Hypertension	144 (71.6)	39 (69.6)	105 (72.4)	0.696
Atrial fibrillation	35 (17.4)	10 (17.9)	25 (17.2)	0.918
DM	46 (22.9)	12 (21.4)	34 (23.4)	0.760
CAD	37 (18.4)	10 (17.9)	27 (18.6)	0.900
Hyperlipidemia	69 (34.3)	19 (33.9)	50 (34.5)	0.941
Dementia	10 (5.0)	4 (7.1)	6 (4.1)	0.470
ICH history	15 (7.5)	3 (5.4)	12 (8.3)	0.566
Ischemic stroke/TIA history	27 (13.4)	6 (10.7)	21 (14.5)	0.482
Medications, <i>n</i> (%)				
Antithrombotic	112 (55.7)	27 (48.2)	85 (58.6)	0.183
Anticoagulant	39 (19.4)	12 (21.4)	27 (18.6)	0.652
Antiplatelet	90 (44.8)	21 (37.5)	69 (47.6)	0.197
Statins	65 (32.3)	18 (32.1)	47 (32.4)	0.971
Habits, <i>n</i> (%)				
Smoker	89 (44.3)	21 (37.5)	68 (46.9)	0.229
Alcohol	77 (38.3)	21 (37.5)	56 (38.6)	0.884
Blood pressure				
Acute ED antihypertensive treatment, <i>n</i> (%)	104 (51.7)	34 (60.7)	70 (48.3)	0.114
Delta MAP, mm Hg, mean (SD)	22.7 (19.8)	28.4 (24.0)	20.5 (17.6)	0.027

Abbreviations: CAD = coronary artery disease; DM = diabetes mellitus; ED = emergency department; ICH = intracerebral hemorrhage; MAP = mean arterial blood pressure; SA-DWIL = small acute lesions on diffusion-weighted imaging.

Table 3 Imaging characteristics of ICH patients with and without DWI lesions

Characteristic	All subjects (n = 201)	SA-DWIL positive (n = 56)	SA-DWIL negative (n = 145)	p Value
Imaging data				
Time to MRI, d, median (range)	2 (0-31)	2.5 (0-31)	2 (0-31)	0.013
Hematoma location, n (%)				0.709
Lobar	136 (67.7)	39 (69.6)	97 (66.9)	
Basal ganglia	65 (32.3)	17 (30.4)	48 (33.1)	
ICH volume, median mL (range)	16.5 (0.2-145.2)	31.1 (0.7-145.2)	12.4 (0.2-98.5)	<0.001
Intraventricular extension, n (%)	73 (36.3)	31 (55.4)	42 (29.0)	<0.001
Subarachnoid extension, n (%)	111 (55.2)	41 (73.2)	70 (48.3)	0.001
MBs, n (%)	100 (49.8)	36 (64.3)	64 (44.1)	0.010
Number of MBs, median (range)	0 (0-277)	1 (0-84)	0 (0-277)	0.005
Location of MBs				0.004
Lobar MBs including cerebellum	38 (18.9)	14 (25.0)	24 (16.6)	
Deep MBs including brainstem	17 (8.5)	5 (8.9)	12 (8.3)	
Mixed	45 (22.4)	17 (30.4)	28 (19.3)	
EPVS, n (%)	199 (99.0)	56 (100.0)	143 (98.6)	0.377
High CSO-EPVS (>20)	107 (53.2)	48 (85.7)	59 (40.7)	<0.001
High BG-EPVS (>20)	40 (19.9)	18 (32.1)	22 (15.2)	0.007
WMD, n (%)	175 (87.1)	52 (92.9)	123 (84.8)	0.128
WMD score, median (range)	3 (0-6)	3 (0-6)	3 (0-6)	0.018
Nonlacunar infarct, n (%)	13 (6.5)	3 (5.4)	10 (6.9)	0.691
Old lacunar infarct, n (%)	46 (22.9)	16 (28.6)	30 (20.7)	0.233
Presumed etiology, n (%)				
Hypertensive ICH	111 (55.2)	28 (50.0)	83 (57.2)	0.355
CAA ICH	70 (34.8)	23 (41.1)	47 (32.4)	0.248
Warfarin-related or undetermined cause	20 (10.0)	5 (8.9)	15 (10.4)	0.764

Abbreviations: BG = basal ganglia; CAA = cerebral amyloid angiopathy; CSO = centrum semiovale; DWI = diffusion-weighted imaging; EPVS = enlarged perivascular spaces; ICH = intracerebral hemorrhage; MB = microbleed; SA-DWIL = small acute lesions on diffusion-weighted imaging; WMD = white matter disease.

both high BG-EPVS and CSO-EPVS. The number of SA-DWIL ranged from 1 to 42 (median 2). The total number of SA-DWIL in patients with high CSO-EPVS was greater than that in patients without high CSO-EPVS (218 vs 19; $p < 0.001$), while the total number of SA-DWIL in patients with high BG-EPVS was lower than that in patients without high BG-EPVS (55 vs 182; $p = 0.015$). The median ICH volume was greater in SA-DWIL-positive vs SA-DWIL-negative patients (31.1 vs 12.4 mL; $p < 0.001$), and the volume of ICH was associated with the number of DWI lesions ($p < 0.001$).

As tables 2 and 3 illustrate, the prevalence of intraventricular and subarachnoid extension of ICH, high CSO-EPVS, and high BG-EPVS was more common in patients with SA-DWIL. The prevalence of microbleeds and their total number were also greater in patients with SA-DWIL, and the anatomical distribution of microbleeds differed between patients with vs

without SA-DWIL ($p = 0.004$), where lobar and mixed locations were more common in the former group. In addition, the overall WMH score, initial ICH volume, and mean delta MAP were greater in patients with SA-DWIL compared to those without SA-DWIL, and the time from ICH onset to MRI scan was longer in the SA-DWIL group. These variables were entered into subsequent multivariate logistic regression models.

Table 4 lists the results of the multivariate logistic regression analyses. Larger ICH volume and high CSO-EPVS were independently associated with the presence of SA-DWIL. There was a trend for an association between high BG-EPVS and the presence of SA-DWIL ($p = 0.066$).

In additional exploratory analyses, we found no interaction between ICH subtype (hypertensive vs CAA) and the potential association between CSO-EPVS and SA-DWIL in univariate ($p = 0.079$) or

Table 4 Multivariate logistic regression analysis for presence of SA-DWIL

	Odds ratio	95% CI	p Value
Time to MRI	1.065	0.981-1.157	0.134
Delta MAP	1.019	0.998-1.040	0.080
ICH volume	1.032	1.009-1.055	0.006
Intraventricular extension	1.723	0.626-4.746	0.293
Subarachnoid extension	2.241	0.843-5.954	0.106
Microbleeds	1.674	0.658-4.258	0.280
Number of microbleeds	0.969	0.922-1.018	0.209
Location of MBs	0.709	0.409-1.227	0.219
High CSO-EPVS	12.564	4.402-35.854	<0.001
High BG-EPVS	2.774	0.934-8.241	0.066
WMD score	1.326	0.943-1.866	0.105

Abbreviations: BG = basal ganglia; CI = confidence interval; CSO = centrum semiovale; EPVS = enlarged perivascular spaces; ICH = intracerebral hemorrhage; MAP = mean arterial blood pressure; MB = microbleed; SA-DWIL = small acute lesions on diffusion-weighted imaging; WMD = white matter disease.

multivariate analyses ($p = 0.389$). We also found that high CSO-EPVS was independently associated with SA-DWIL in patients with CAA-ICH ($p = 0.027$) and non-CAA ICH ($p < 0.001$), when adjusting for the presumed etiology of ICH. We found a significant association between the number of microbleeds and white matter disease severity score ($p = 0.001$). In contrast, the association between the number of microbleeds and EPVS category was not significant ($p = 0.765$ for CS-EPVS and 0.271 for BG-EPVS).

DISCUSSION In this cross-sectional, single-center study, we found that high CSO-EPVS were significantly more prevalent in ICH patients with SA-DWIL compared to their counterparts without SA-DWIL, and patients with high CSO-EPVS had greater number of SA-DWIL. We also found a similar trend between high BG-EPVS and the presence of SA-DWIL. In addition, larger ICH volume was associated with the presence and the number of SA-DWIL. Similar to previous studies, SA-DWIL were noted in more than a quarter of our ICH patients,^{4,5,9} and were predominantly located in the cortical and subcortical regions.

The lack of a statistically significant association between high BG-EPVS and SA-DWIL is likely an artifact of our sample size. Our results might have also been confounded by the fact that a larger proportion of patients with high BG-EPVS also had high numbers of CSO-EPVS, and not vice versa.

The pathophysiology of SA-DWIL in patients with ICH is not entirely clear. Previous studies have linked SA-DWIL to underlying small vessel arteriopathy.^{2,4-6} Small DWI lesions seem to be more common in ICH related to possible CAA and are associated with small-

vessel pathogenesis, such as WMH and cerebral microbleeds. EPVS are also associated with other features of small vessel disease such as WMH and lacunes.¹⁶ They are part of the spectrum of small vessel disease and are emerging as a neuroimaging marker of small vessel disease. Our finding of an association between the presence of high EPVS, in particular CSO-EPVS, and SA-DWIL is novel. It adds to the body of literature implicating small vessel arteriopathy in the pathogenesis of SA-DWIL following ICH. It raises the intriguing hypothesis that EPVS might serve as conduits to facilitate the transport of toxic blood products to brain areas distant from the hemorrhage resulting in SA-DWIL visible on MRI. Previous reports support the notion that blood can extend into the perivascular spaces following subarachnoid and intracerebral hemorrhages.^{13,14,26,27}

Our finding that larger ICH volume is associated with SA-DWIL is in agreement with previous reports.⁴ A combination of local compression of the hematoma, cytotoxic injury, and inflammation ensues after ICH. We hypothesize that larger hematomas might result in the release of more hemoglobin degradation products and inflammatory cytokines that extend via EPVS and subarachnoid space to contribute to the pathogenesis of SA-DWIL in distant regions. This hypothesis may merit future investigations.

There are conflicting reports regarding the relationship between BP lowering and SA-DWIL in ICH. Some studies reported significant association between BP reduction and the presence of SA-DWIL in most patients with hypertensive ICH,^{1,4,8,9} whereas others did not.⁵ We observed a nonsignificant trend between δ MAP and SA-DWIL. This discrepancy may be partly due to the difference in patient population. The prevalence of hypertensive ICH in our cohort was 55.2% compared to 62%–91.5% in other studies.^{1,4,8,9} Interestingly, we found that the total number of small DWI lesions in patients with high BG-EPVS was lower than in that in patients without high BG-EPVS. This finding might seem counterintuitive, but is likely attributed to lower prevalence of hypertensive ICH in our cohort.

Our study has limitations largely attributed to its retrospective nature. There is a possibility of a selection bias towards patients with mild to moderately sized hemorrhages, as patients with more severe hemorrhages might have been too unstable to get an MRI scan. To minimize this possibility, we extended the time from ICH onset to MRI to 4 weeks. This is in line with previous studies. Furthermore, the median time to MRI was 2 days in our study. We were also unable to blind the EPVS rater to the DWI lesions. Therefore, a measurement bias towards the study hypothesis cannot be excluded. In addition, it is

important to point out that our observed association of EPVS with SA-DWIL does not necessarily imply causation. Therefore, our findings should be considered hypothesis-generating. Furthermore, we cannot exclude the possibility that the observed association between EPVS and DWI lesions in our study is merely a reflection of EPVS being a marker of an active occlusive arteriopathy contributing to both hemorrhagic and ischemic cerebrovascular disease manifestations. We only collected data on EPVS based on dichotomized categories of 0–2 vs 3–4, and not the absolute number of EPVS within each individual category. This may have limited our ability to examine the dose effect of EPVS on the risk of small DWI lesions. Finally, long-term functional outcome data were not available to allow us to assess the prognostic value of EPVS. Future prospective studies examining the relationship between EPVS and functional outcome in ICH patients are warranted.

Our data suggest that high EPVS, in particular CSO-EPVS, and larger hematoma volume are independent predictors for SA-DWIL after ICH. Our findings could provide a new explanation for the pathophysiologic mechanisms predisposing to SA-DWIL after ICH. Future prospective longitudinal studies are required to confirm our findings.

AUTHOR CONTRIBUTIONS

B.W. drafted the manuscript. X.Y. assessed the image and retrieved the data. C.L. performed the statistical analysis. M.L. critically revised the manuscript. M.H.S. takes full responsibility for the data, the analyses and interpretation, and the conduct of the research.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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