Do Imaging Markers of Cerebral Small Vessel Disease Predict Hematoma Volume and Outcome in Acute Intracerebral Hemorrhage?

Anand R. Warrier, Rohit Bhatia, Ajay Garg¹, M.V. Padma Srivastava, Deepa Dash, Manjari Tripathi, Mamt Bhushan Singh, Vishwajeet Singh², Sreenivas Vishnuhatla², Kameshwar Prasad

Departments of Neurology, ¹Neuroimaging and Interventional Neuroradiology, ²Biostatistics, All India Institute of Medical Sciences, New Delhi, India

Abstract

Background and Purpose: Cerebral small vessel disease (CSVD) markers have not been widely studied in relation to hematoma volume and growth in hypertensive intracerebral hemorrhage (ICH). The objectives to assess the relationship of white matter hyperintense lesions (WMHL), microbleeds (MBs), and cortical siderosis (CSS) with hematoma volume, hematoma expansion (HE), and 3 months outcome in patients with hypertensive ICH. Methods: All consecutive acute hypertensive supratentorial ICH presenting to the emergency were prospectively recruited. Baseline and 24 hours computed tomography (CT) to assess hematoma volume and magnetic resonance imaging (MRI) for CSVD markers were performed in all subjects. WMHL (graded using Fazekas’s scale), MBs, and CSS were assessed and compared with baseline variables and outcomes. All the images were assessed by an experienced stroke neurologist/neuroradiologist. Results: One hundred and fifty-seven patients were screened and 60 were included. Mean age was 54.08 ± 11.57 years and 47 (78%) were males. Of 60, 19 (28.1%) had HE, 31 (51.6%) had major bleed (>30 ml), and 28 (47.46%) had poor 3 month outcome (mRS 4-6). On univariate analysis, high grade WMHL was associated with greater HE [odds ratio (OR): 2.65, confidence interval (CI) 1.48–4.72, P = 0.001], greater proportion with volume >30 ml (OR: 7.16, CI: 1.09–47.13, P = 0.001) and poor outcome (OR: 2.1, CI: 0.05–3.27, P = 0.001). MBs were associated with poor outcome (P = 0.029) but not with HE/volume. CSS was related to HE (P = 0.031), a large volume bleed (P = 0.023), and poor outcome (P = 0.021). On multivariate model, only WMHL independently predicted HE (P = 0.034), greater proportion with bleed volume >30 ml (P = 0.041), and poor outcome (P = 0.042). Conclusions: WMHL in MRI serves as a predictor of hematoma expansion, a large volume bleed, and poor outcome in hypertensive ICH and may be incorporated into existing prediction models.

Keywords: Hematoma expansion, ICH, leukoaraisis, microbleeds, small vessel disease

Introduction

Major prognostic factors for poor outcomes in acute intracerebral hemorrhage (ICH) include baseline hematoma volume, hematoma growth, Glasgow coma scale (GCS), and presence of intraventricular hemorrhage (IVH)¹ of which hematoma growth is a potential therapeutic target.² Many radiological signs like Leakage sign³ and Spot sign⁴,⁵ in computed tomography/computed tomography angiography (CT/ CTA) have been known to predict hematoma growth and outcome. The role of cerebral small vessel disease (CSVD) in determining hematoma volume and growth is a subject of debate with mixed results from previous studies.⁶-⁹ white matter hyperintense lesions (WMHL) in magnetic resonance imaging (MRI)⁰ and cerebral microbleeds (MBs)¹¹,¹² and cortical siderosis (CSS)¹² are surrogate markers of CSVD. This study aimed to assess the relationship of WMHL, MBs, and CSS to hematoma volume/expansion (>33% relative increase or >6 ml absolute increase in volume) in patients with hypertensive acute supratentorial hemorrhage and to assess the relationship of these markers with the functional outcome at 3 months as measured using a modified Rankin scale (mRS) categorized as a good outcome (mRS 0-3) and poor outcome (mRS 4-6).¹³

Methods

Patient population

All hypertensive supratentorial ICH [defined as deep ICH with a history of hypertension or echocardiographic (ECG) evidence of hypertension with high blood pressure recordings and with no associated coagulopathy (PT-INR/aPTT/platelet count) or other comorbidities like kidney/liver diseases/malignancy and not on any anticoagulants] above the age of 18 years, first ever stroke of their life, presenting to the emergency department of the All

Address for correspondence: Dr. Rohit Bhatia, Department of Neurology, All India Institute of Medical Sciences, New Delhi – 110 029, India. E-mail: rohitbhatia71@yahoo.com

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India Institute of Medical Sciences (AIIMS), New Delhi, India, with a CT done in the first 12 hours were recruited prospectively [Figure 1]. Those with multiple hemorrhages, previous strokes, lobar bleeds (by Boston criteria), who had surgical intervention before a follow-up CT, poor GCS motor score (<M4 status) on admission, and whose MRI could not be done within 5 days of ictus were excluded. The time of onset of ictus is marked as the time of the event witnessed or confirmed by the patient or last found to be normal with a 30-min margin of error. The study was approved by Ethics committee of the Institute. Written informed consent was taken from either the patients or their legally authorized representatives (LAR). Since the study was exploratory, an arbitrary sample size of 60 was chosen based on feasibility. All patients were given standard medical care. CT scan was repeated 24 hours or earlier as indicated and all of them subsequently underwent MRI brain. Patients were followed up till discharge and thereafter at 3 months telephonically or in-person and mRS was assessed by an experienced neurologist (blinded). The patient selection details are outlined in Figure 1.

Image acquisition details

Computed tomography

ICH was diagnosed by CT (Siemens Somatom Definition H dual-energy 128 slices) according to a standardized institutional protocol including a slice thickness of 2 and 5 mm, the slice spacing being equal to slice thickness. Hemorrhages originating at the cortical and subcortical junction were considered lobar and excluded, bleeds involving or originating in the thalamus or basal ganglia were considered deep (included). The ICH volumes on baseline and follow-up were measured using abc/2 method[14-16] with good correlation with CT planimetry (r = 0.88 in 20 samples). Intraventricular blood was not considered for hematoma volume measurement. The final volume of hemorrhage is taken as the largest volume measured in a 24–48 hour CT image.

Magnetic resonance imaging

The MR images were obtained using GE–MR Discovery 450 W 1.5 T. Imaging included (1) T2-weighted (TR/TE of 4500/90 ms, FOV 230 * 230 mm, slice thickness 5 mm) (2) T2 fluid-attenuated inversion recovery (TR/TE of 10000/90 ms, FOV 240 * 240 mm, inversion time of 2600 milliseconds, and 5-mm section thickness), (3) Susceptibility Weighted (TR/TE 30/35 ms, slice thickness 2 mm, FOV of 250 * 250 mm, flip angle of 15°) and (4) Diffusion-weighted (TR/TE 4500/75 ms, FOV 250 * 250 mm, 3 mm slice thickness 3 mm) sequences according to the pre-set protocol for the study. The cerebral MBs are defined as punctate, hypointense foci (<10 mm in diameter) on susceptibility-weighted image (SWI), distinct from vascular flow voids and leptomeningeal hemosiderosis and were counted leaving a margin of 2 cm from the hematoma border to exclude peri ICH siderosis.[7,8] For WMHL in T2 FLAIR, MRI Fazekas scores were separately calculated for periventricular and deep lesions in the normal healthy hemisphere[4,17-19] and added up: Total score 6 [3(periventricular) +3(deep)]. Fazekas ≥3 was arbitrarily taken as a significant WMHL to account for the midline shift (may mask WMHL in the healthy hemisphere). There was no relation between the presence of midline shift and WMHL severity (P = 0.34). CSS was defined as a curvilinear signal loss on SWI following the gyrual cortical surface >3 sulcal spaces outside the bleed margin.[17,8]

Outcome measures and statistical analysis

Outcome variables assessed include presence or absence of HE (>6 ml or a 33% relative increase), a large volume bleed (at 24 hours; dichotomized at 30 ml), and poor outcome at 3 months (mRS 4-6).[13] For analysis, all baseline parameters including age, sex, history of hypertension, diabetes, dyslipidemia, smoking, presence of coronary artery disease (CAD), mean duration (hours) of CT from ictus, GCS on admission, presence of IVH, mean duration (hours) of MRI from ictus based on the previous studies[4,17-19] and outcome measures were dichotomized into those with >3 or ≤3 Fazekas score; >3 or ≤3 number of MBs and presence/absence of CSS. All associations with P < 0.1 in univariate analysis were considered for multivariate analysis. All tests of significance were 2 tailed. Stata 15 software was used for statistical purposes. The study is conducted to satisfy the STROBE guidelines for cohort studies.

Results

A total of 157 supratentorial hypertensive hemorrhages were screened and 60 patients who satisfied the inclusion criteria were included in the study. The mean age was 54.08 ± 11.57 years and 47 (78%) were males. All patients had hypertension [(45 (75%)] were known and 15 (25%) were diagnosed after the current admission. Risk factors included smoking [22 (36.7%)], alcohol use [10 (16.7%)], diabetes mellitus [6 (10%)], tobacco use [18 (30%)], dyslipidemia [12 (20%)], and CAD [12 (20%)]. The mean admission systolic blood pressure was 184 ± 21.13 mm Hg and diastolic was 105 ± 17.68 mm Hg. Only six patients were below 40 years of age (age range 29–38 years) and were hypertensive (four were known patients of hypertension and two were diagnosed in the current admission) with the presence of other vascular risk factors including smoking in four (67%), tobacco chewing in three (50%), Alcohol consumption in three (50%) and CAD in one (16.7%) patient. None had diabetes mellitus. The mean hematoma volume of the

![Figure 1: Flowchart of patient recruitment](image-url)
Table 1: Baseline Characteristics Classified According to Fazekas Score (WMH lesion) Dichotomized as Fazekas >3 and ≤3

| Baseline Characteristic | WMHLM | WMHLM | P  |
|------------------------|-------|-------|----|
|                        | ≤3 (n=40) | >3 (n=20) |    |
| Age, y, mean±SD† | 53.6±10.9 | 55.05±13.04 | 0.65 |
| Female | 8/40 (20%) | 3/20 (15%) | 0.13 |
| Past Medical History |         |         |    |
| HTN* | 28/40 (70%) | 17/20 (85%) | 0.17 |
| CAD*, n (%) | 8/40 (20%) | 4/19 (21.05%) | 0.59 |
| DM | 4/40 (10%) | 2/20 (10%) | 0.66 |
| Hyperlipidemia | 9/40 (22.5%) | 3/20 (15%) | 0.19 |
| Forgetfulness | 3/40 (7.5%) | 8/20 (40%) | 0.002 |

Table 2: Baseline Characteristics Classified According to Number of Microbleeds (MBs*)

| Baseline Characteristics | ≤3 MBs† (n=34) | >3 MBs† (n=26) | P  |
|--------------------------|----------------|----------------|----|
| Age, y, mean±SD† | 52.55±12.08 | 56.07±10.76 | 0.24 |
| Female | 6/34 (17.6%) | 7/26 (26.92%) | 0.38 |
| Past Medical History |         |         |    |
| HTN* | 26/34 (76.47%) | 19/26 (73.07%) | 0.73 |
| CAD*, n (%) | 4/34 (11.76%) | 9/26 (34.61%) | 0.058 |
| DM | 2/34 (5.88%) | 4/26 (15.38%) | 0.22 |
| Hyperlipidemia | 3/34 (8.82%) | 4/26 (15.38%) | 0.21 |
| Forgetfulness | 6/34 (17.63%) | 15/26 (57.69%) | 0.02 |

Clinical Data

- Poor GCS* (Motor≤=M4) | 8/34 (23.53%) | 13/26 (50%) | 0.033 |
- Glucose (mg/dl), mean (SD§) | 138.87±44.69 | 154.32±38.58 | 0.63 |
- Systolic BP mean±SDt | 185.03±23.93 | 182.23±17.24 | 0.88 |
- Diastolic BP, mean±SDt | 106.73±22.77 | 103.61±7.2 | 0.503 |

Radiological Data

- Smoking | 11/34 (32.35%) | 10/26 (38.46%) | 0.6 |
- Alcohol | 6/34 (17.64%) | 4/26 (15.38%) | 0.103 |
- Tobacco chewing | 4/34 (11.76%) | 2/26 (7.7%) | 0.17 |
- Prior Use of antiplatelets | 5/34 (14.7%) | 3/26 (11.54%) | 0.32 |
- Use of statin | 11/34 (32.35%) | 8/26 (30.77%) | 0.41 |

Intraventricular hemorrhage and ICH

- Hematoma expansion (HE) and CSVD markers

Hematoma expansion (HE) and CSVD markers

A total of 31.6% of the study population had HE. On univariate analysis, HE was associated with CAD (0.038), WMH Fazekas grade >3 (OR: 2.65, CI 1.48-4.72, P = 0.001; see Table 1, Figure 2a†, bleed > 30 ml (P = 0.001), intraventricular hemorrhage (IVH) (P = 0.001), a poor GCS at presentation (P = 0.002), presence of CSS [Table 3] and was associated with poor outcome at 3 months [60% vs 23.8%, P = 0.05]. The number of MBs was not associated with HE (P = 0.71). In the multivariate model, WMH grade Fazekas >3 independently predicted HE (P = 0.034) along with (P = 0.04) when adjusted for blood pressures, mean ictus to CT time (hours), baseline hematoma volume, IVH, and CSS. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for WMH for predicting HE was 63.15%, 80.49%, 60% and 82.5% respectively.

24-Hour hematoma volume and CSVD markers

In univariate analysis larger bleeds (>30 ml) at 24 hours was associated with younger age (<60 yrs) [P = 0.035], poor GCS motor score (M4/M5) (P = 0.009), greater mean ictus to CT interval (P = 0.002), high WMH grade (Mean, SD), 39.08±24.50 ml in Fazekas > 3 vs 27.66±18.48 in Fazekas ≤3, P = 0.048; OR: 7.16, CI: 1.09-47.13, P = 0.001; see table 1], IVH (P = 0.049), CSS (P = 0.02), greater probability of undergoing hematoma evacuation (P = 0.001) and poorer outcome (P = 0.001). In multivariate model adjusting for age, included and excluded patients were comparable [mean [SD] was 31.47 [21.18] vs 29.83 [19.86], P = 0.54]. For univariate analysis results of WMHL, MBs, and CSS with baseline characteristics and outcome variables see Tables 1-3.

**GCS-Glasgow coma scale, †MBs-microbleeds, ‡CSS-superficial siderosis, *SD-standard deviation; WMHL-white matter hyperintense lesion; ICH-intracerebral hemorrhage; IVH-intraventricular hemorrhage; †HTN-hypertension; ‡CAD-cerebral artery disease

| Baseline Characteristics | ≤3 MBs† (n=34) | >3 MBs† (n=26) | P  |
|--------------------------|----------------|----------------|----|
| Age, y, mean±SD† | 52.55±12.08 | 56.07±10.76 | 0.24 |
| Female | 6/34 (17.6%) | 7/26 (26.92%) | 0.38 |
| Past Medical History |         |         |    |
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Table 3: Baseline Characteristics of ICH patients with and without Cortical Superficial Siderosis

| Baseline Characteristic                  | CSS− present | CSS= Absent | P   |
|-----------------------------------------|--------------|-------------|-----|
| Age, y, mean±SD                          | 54.32±11.31  | 53.16±12.35 | 0.82|
| Female                                  | 8/40 (20%)   | 5/20 (20%)  | 0.66|
| Age, y, mean±SD                          | 54.32±11.31  | 53.6±12.35  | 0.82|
| Past Medical History                     |              |             |     |
| HTN*                                     | 29/40 (72.5%)| 16/20 (80%) | 0.53|
| CAD (%)                                  | 7/41 (17.07%)| 5/19 (26.31%)| 0.14|
| DM                                       | 4/40 (10%)   | 2/20 (10%)  | 0.71|
| Hyperlipidemia                           | 5/40 (12.5%) | 2/20 (10%)  | 0.28|
| Forgetsfulness                           | 13/40 (32.5%)| 8/20 (40%)  | 0.22|
| Clinical Data                            |              |             |     |
| Poor GCS* on admission                   | 31/40 (77.5%)| 8/20 (40%)  | 0.004|
| (Motor <=M4)                             |              |             |     |
| Glucose (mg/dl), mean±SD                 | 138.67±44.7  | 141.55, 51.24| 0.56|
| Systolic BP mean±SD mmHg                 | 182.58±21.06 | 188.9±21.15 | 0.28|
| Diastolic BP mean±SD mmHg                | 104.12±16.26 | 107.9±20.45 | 0.44|
| Smoking                                  | 12/40 (30%)  | 9/20 (45%)  | 0.25|
| Alcohol                                  | 9/40 (22.5%) | 3/20 (15%)  | 0.67|
| Tobacco chewing                          | 4/40 (10%)   | 2/20 (10%)  | 0.21|
| Prior Use of antiplatelets               | 6/40 (15%)   | 2/20 (10%)  | 0.36|
| Use of statin                            |              |             |     |
| Radiological Data                        |              |             |     |
| Midline Shift                            | 14/40 (35%)  | 14/20 (70%) | 0.01|
| Time to MRI, hrs (mean)                  | 50.67±46.45  | 62.25±46.76 | 0.37|
| ICH° volume mL                           | 27.03±18.47  | 40.35±23.82 | 0.02|
| mean±CSD                                 |              |             |     |
| Major Bleed (>30 ml)                     | 16/40 (40%)  | 13/20 (65%) | 0.068|
| Hematoma Expansion                      | 9/40 (22.5%) | 10/20 (50%) | 0.031|
| Presence of IVH*                        | 13/40 (32.5%)| 11/20 (55%) | 0.07|
| WMHL° Fazekas score>3                    | 10/40 (25%)  | 10/20 (50%) | 0.053|
| No of MBs, Mean (SD)                     | 4.25 (6.07)  | 6.6 (3.73)  | 0.2|
| Proportion with >3 MBs                   | 12/40 (30%)  | 14/20 (70%) | 0.003|
| Poor Functional Outcome                  | 15/40 (37.5%)| 14/20 (70%) | 0.018|

*GCS-Glascoma coma scale, †MBs-microbleeds, ‡CSS- superficial siderosis, §ICH-intracerebral hemorrhage, SD-standard deviation, ¶WMHL-white matter hyperintense lesion, **IVH-intraventricular hemorrhage, ‡‡HTN-hypertension, ‡registers-coronary artery disease

mean interval (hours) from ictus to CT, mean BP and CSS, high WMHL Fazekas score >3 [P = 0.041 see Figure 2b], poor GCS (P = 0.02) and IVH (P = 0.036) predicted a large volume bleed >30 ml. A β coefficient analysis to find the absolute volume increment per unit change in Fazekas score showed a β coefficient (SE) of 4.098 (1.7) ml [CI [0.68-7.51], P = 0.02] i.e., for a unit rise in Fazekas score, the hematoma volume rises by 4.1 ml. A bleed volume >30 ml was associated with a poor outcome at 3 months (P = 0.003) in this cohort.

**CSVD markers as predictor of functional outcome after hypertensive ICH**

In univariate analysis, poor outcome was associated with female sex (P = 0.08), greater ictus to CT interval (P = 0.054), WMHL. Fazekas score >3 [80% vs 32.5%, OR-2.1, CI: 0.05-3.27, P = 0.001], poor GCS (motor M4/M5) [P = 0.002], presence of larger bleed volume [72.4% with >30 ml vs 25.8% <30 ml, P = 0.0001], presence of IVH (P = 0.007), >3 MBs (61.53% vs 38.2%, P = 0.07), presence of CSS (48.27% vs 19.35%, P = 0.05). Only high-grade WMHL (P= 0.042), independently predicted poor outcome at 3 months [Figure 3] along with large volume bleed and IVH [adjusted for gender, systolic and diastolic blood pressure, mechanical ventilation requirement, CAD, and poor GCS at admission]. β coefficient analysis revealed an ordinal shift in mRS with a 1 scale rise for every 2 score rise in Fazekas score [β Coeff (SE):0.6 (0.13) [P = 0.001; CI: 0.36–0.89].

**DISCUSSION**

The major factors[4,18,20,21,22] that determine final hematoma volume are younger age, male sex, systolic and diastolic blood pressures, high blood sugars, prior warfarin or other anticoagulant use, antiplatelet use and mean hours of CT from ictus.

WMHL which is known to predict post thrombolysis hemorrhage risk,[9] also predicts hematoma volume[17,6] and probably hematoma growth in ICH [see Figure 4], evidence for which is still lacking.[6,8,23] Post mortem samples showed WMHL as areas of impaired vascular integrity[10,24-28] and may serve as possible substrates for hematoma growth in hypertensive ICH. In accordance with the avalanche model[29,30] of HE supported
by genetic data,[31] the proportion of HE is maximum early after the ictus [36% in this study at 6 hrs and 29% after 6 hrs, \( P = 0.7 \)]. The median [interquartile range (IQR)] ictus to CT time (hrs) of 5.25 (6.15) and 6.0 (7.2) in those with and without HE, respectively \( (P = 0.9) \) is comparable.

The incidence of cerebral SVD in the Indian population is 31.9 per 1000.[32] In total, 75% of them had severe WMHL. In our study, 87% (51/60) had WMHL in the healthy hemisphere of which 43% (26/60) had Fazekas >3. Poorly controlled hypertension maybe the reason for this higher WMHL.[29,35] In a retrospectively reviewed clinical and radiological data of 79 ICH by Lou et al.,[6] those with higher WMHL load had higher mean ICH volume \( (P = 0.012) \), and a trend towards HE \( (P = 0.062) \). In another retrospective study,[8] there was no association of WMHL load with either HE or hematoma volume in deep ICH. Our study showed WMHL as an independent predictor for HE and a large volume bleed, unlike the previous studies,[6,8,23,33] but in concordance with the recent results from a Chinese ICH data which showed a positive association between WMHL volume and volume of hematoma.[34] Only two studies of CSVD markers (MRI-based) exists in hypertensive bleeds, of which one showed significant association[6] of WMHL whereas others did not.[8]

Though past studies had shown that a high WMHL load is associated with poor outcome concordant with our results, a direct linear relationship with WMHL grading [for every 2 score rise in Fazekas score, mRS rises by 1 scale] was never demonstrated earlier.[6,17,23,35,36] In our study Fazekas score >3 significantly correlated with poor outcome \( [P = 0.04, \text{see Figure 3}] \) in the multivariate model. Among six patients who succumbed, four died due to non-neurological and two due to neurological worsening (one had rebleed and others had ischemic stroke during follow-up). Of 17 patients, 13 patients who underwent subsequent surgical intervention had high-grade WMHL (Fazekas grade >3) of which 8 did not show improvement in mRS until 1 year of follow-up.

A recent study[8] had shown inverse relation of MBs with the volume of lobar bleeds, but couldn’t associate MBs with deep bleeds[8] as in our cohort. Our study showed poor outcomes in those with >3 MBs in univariate analysis \( (P = 0.027) \) but not in the multivariate model and results need further confirmation with high resolution 3 T/7 T based MRI. The presence of CSS was strongly associated with HE, large volume bleed, and poor outcome in univariate, but not in multivariate models analogous to previous results.[8]

This study shows that WMHL could be a potential marker for prognostication and selection of patients for hemostatic trials in ICH similar to CTA spot sign[37] and utilizing such imaging parameters is prudent as many similar trials had failed due to poor patient selection.[1,36] The sensitivity, specificity, PPV and NPV of spot sign for HE as per the PREDICT[36] study was 51% 85% 61% and 78% respectively while that of WMHL is 63.15%, 80.49%, 60%, and 82.5%, respectively in our cohort which is comparable and when combined may yield better results in terms of predicting patients with a greater propensity for HE and hence greater hematoma volume and subsequently poorer outcome.

**Limitations**

Acute ICH could have affected scoring of WMHL but has been proven to be counterintuitive by Smith et al.[39] Fazeka’s scale being visual also has its inherent limitations. Automated methods to detect WMHL’s like the one described using convolutional methods would hold a lot of promise for lesion detection and validation even for large epidemiological studies.[40] Although we have taken all patients with hypertension and tried to exclude non-hypertensive ICH, genetic assessment for monogenic causes was not done in the very small number of younger patients. There is a possible selection bias as many ICH patients screened couldn’t be included as they didn’t meet the inclusion criteria. The study sample size is small with probable gender bias as included patients were more males (47/60). In this study, early surgical intervention might have precluded the true estimation of
WMHL grade in a few. CTA could not be done to compare the sensitivity of CSVD markers with known imaging predictors of hematoma growth like CTA-spot sign.[41]

Conclusions

CSVD in the form of cerebral WMHL in MRI may predict hematoma expansion, a large volume bleed, and consequently, poor outcomes after supratentorial hypertensive hemorrhage and may be incorporated into existing clinical prediction models[42] as a selection tool for clinical trials of hemostatic therapy in ICH. The role of other CSVD markers like MBs and CSS in determining the hematoma volume and growth remains inconclusive.

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Conflicts of interest

There are no conflicts of interest.

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