The Predictive Values of Different Small Vessel Disease Scores on Clinical Outcomes in Mild ICH Patients

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Aim: To explore the predictive values of different small vessel disease (SVD) scores on functional recoveries and the clinical cerebrovascular events in mild intracerebral hemorrhage (ICH).

Methods: In this study, we enrolled conscious and mild ICH patients without surgery and further divided them into the cerebral amyloid angiopathy (CAA)-ICH group and hypertension (HTN)-ICH group. The severity of individual SVD markers, including lacunes, cerebral microbleeds (CMBs), enlarged perivascular spaces (EPVS), white matter hyperintensity (WMH), and cortical superficial siderosis (cSS), was evaluated. The original SVD score, modified SVD score, refined SVD score, and CAA-SVD score and the total number of SVD markers were further calculated. Functional recoveries were evaluated using the modified Rankin scale. Recurrences of stroke were defined as readmission to the hospital with a definite diagnosis of stroke.

Results: A total of 163 ICH patients (60 CAA-ICH and 103 HTN-ICH) were included in the study. The CAA-SVD score (OR = 3.429; 95% confidence interval (CI) 1.518–7.748) had the best predictive effect on functional dependence in the CAA-ICH group, among which cSS severities probably played a vital role (OR = 4.665; 95% CI 1.388–15.679). The total number of SVD markers (hazard ratio (HR) = 3.765; 95% CI = 1.467–9.663) can better identify stroke recurrences in CAA-ICH. In HTN-ICH, while the total number of SVD markers (HR = 2.136; 95% CI = 1.218–3.745) also demonstrated association with recurrent stroke, this effect seems to be related with the influence of lacunes (HR = 5.064; 95% CI = 1.697–15.116).

Conclusions: The CAA-SVD score and the total number of SVD markers might identify mild CAA-ICH patients with poor prognosis. However, it would be better to focus on lacunes rather than on the overall burden of SVD to predict recurrent strokes in HTN-ICH.

Key words: Different Small Vessel Disease Scores, CAA-related ICH, HTN-related ICH, Functional recoveries, Clinical cerebrovascular events

Introduction

Cerebral small vessel disease (CSVD) is a disorder of the penetrating cerebral small vessels, such as arterioles, capillaries, and venules1). Lacunas, cerebral microbleeds (CMBs), enlarged perivascular spaces (EPVS), white matter hyperintensities (WMH), and cortical superficial siderosis (cSS) are all imaging markers of CSVD2–6). Previous studies have demonstrated the clinical significance of individual and separated CSVD markers on cognitive impairments, functional recoveries, and stroke recurrences in patients with stroke7–9). However, different CSVD markers could be simultaneously...
presented in one patient, and recent studies have attempted to convey more information by conducting different semi-quantitative assessments of the cumulative burden.

The concept of the original SVD score\(^{10,11}\) and the modified SVD score\(^{12}\), evaluated by lacunas, CMBs, EPVS, and WMHs, was first introduced in ischemic stroke patients. Moreover, it has been pointed out that the original SVD score significantly influenced the functional recoveries of ICH patients\(^{13}\). Other scholars believed that the total number of the four SVD markers previously mentioned could also predict the adverse functional outcome of ICH\(^{14}\). Besides, to accurately calculate the total SVD burden in cerebral amyloid angiopathy (CAA) patients, the cerebral amyloid angiopathy-small vessel disease (CAA-SVD) score evaluating lobar CMBs, centrum semiovale (CSO)-EPVS, WMH, and cSS was further proposed to demonstrate the underlying pathological severity of CAA\(^{15}\). Subsequently, researchers found that the CAA-SVD score could be adapted to predict the risk of ICH recurrence in patients with CAA\(^{16}\). In this study, for the first time, we put those five individual markers together and summarized the effect of different SVD scores on the prognosis of ICH patients with different etiologies. Furthermore, as deep CMBs and hypertensive ICH may be closely related\(^{17}\), we proposed the refined SVD score in the HTN-ICH group by placing more emphasis on deep CMBs, especially severe deep CMBs.

In our years of clinical practice, we have found that clinicians usually focus more on comatose ICH patients requiring surgical treatments due to the high rates of mortality and disability. However, for mild and conscious ICH patients supported with conservative medication, neurologists may be less proactive in the follow-up due to the relatively good prognosis. Thus, we enrolled mild spontaneous ICH patients without surgical treatment and further divided them into the CAA-ICH or HTN-ICH groups. We would like to explore the following questions: (1) among mild ICH patients with different etiologies, whether individualized and calculated burden of SVD markers could predict functional dependence and stroke recurrence, and (2) in different semi-quantitative methods of the SVD burden, whether there is a difference in the predictive ability of prognosis. The analysis might help neurologists identify mild ICH patients with poor outcomes and take effective preventive measures in advance.

**Methods**

**Patients**

This study retrospectively analyzed prospectively collected data from an observational study of conscious and spontaneous ICH patients without surgery. Patients were recruited from August 2012 to October 2019 in the neurology wards in seven independent general hospitals with stroke units accredited by the Chinese Stroke Association. These seven hospitals were Ruijin Hospital affiliated to Shanghai Jiao Tong University School of Medicine, Ruijin North Hospital affiliated to Shanghai Jiao Tong University School of Medicine, Pudong District Gongli Hospital, Jiaxing First Municipal Hospital, Zhongshan Hospital Qingpu Branch affiliated to Fudan University, Minhang Hospital affiliated to Fudan University, and Haiyan County People’s Hospital.

According to the modified Boston criteria, the inclusion criteria for CAA-ICH patients were as follows: 1) age ≥ 55 years; 2) multiple hemorrhages restricted to the lobar, cortical, or corticosubcortical regions (cerebellar hemorrhage allowed) or single lobar, cortical, or corticosubcortical hemorrhage and focal or disseminated superficial siderosis; and 3) the absence of other causes of hemorrhage\(^{18,19}\). The inclusion criteria for the HTN-ICH patients were as follows: 1) ≥ 1 year of hypertension history; 2) hemorrhages (ICH and CMBs) restricted to the deep regions with or without deep microbleeds but no lobar microbleeds\(^{20}\). The exclusion criteria were as follows: 1) ICH secondary to brain tumors, trauma, or hematological diseases; 2) mixed hemorrhage (ICH and CMBs) in the lobar and deep regions; 3) deep hematomas without hypertension; 4) lobar, cortical, or subcortical hematomas with age < 55 years; 5) examination with computed tomography (CT) scan over 3 days or magnetic resonance imaging (MRI) over 7 days following onset; 6) without completed or qualified clinical and imaging data; 7) lost to follow-up; and 8) pregnancy or refusal to participate in the study.

This study was approved by the ethics committee of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine. Written informed consent for data collection and clinical outcomes was obtained from the patient or a legally authorized representative.

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in all cases.

**Imaging Analysis**

All patients were examined *via* cranial CT within 3 days and MRI within 7 days following ICH onset. A GE Signa HDxT 3.0 T superconducting MRI system was utilized. All patients were first examined with axial T1WI, T2WI, and then diffusion-weighted imaging and susceptibility-weighted imaging (SWI). In this multicenter study, different hospitals used the same imaging parameters. All imaging data were randomly read and recorded by two senior radiologists under double-blind conditions. The inter-rater reliability of neuroimaging variable was tested using the kappa statistic.

Neuroimaging markers for CSVD were evaluated according to the STandards for Reporting Vascular changes on nEuroimaging (STRIVE criteria) \(^{21}\). Lacunes were defined as rounded or ovoid lesions of cerebrospinal fluid signal, that is, hyperintensities on a T2-weighted sequence with corresponding hypointensities with a hyperintense rim on fluid-attenuated inversion recovery (FLAIR), ranging from 3 to 20 mm in diameter in bilateral hemispheres \(^{22}\). CMBs were defined as round or oval foci with a low signal or signal loss on SWI, generally with diameters ranging from 2 to 5 mm and a maximum of 10 mm. CMB severity was classified as mild (\(n=1\), moderate (\(n=2–4\)), or severe (\(n \geq 5\)) \(^{23}\). EPVS were defined as \(<3 \text{ mm punctate or linear hyperintensities on a T}2\)-weighted sequence with corresponding hypointensities on a T1/FLAIR sequence. EPVS were rated in the regions of the centrum semiovale (CSO) and basal ganglia (BG). EPVS severity was classified as mild (\( \leq 10 \text{ EPVS}\)), moderate (11–20 EPVS), or severe (\( \geq 20 \text{ EPVS}\)) \(^{24}\). WMHs were identified as white matter hyperintensities on the FLAIR sequence. WMHs in the deep (DWMH) and periventricular (PVWMH) regions were graded from 0 to 3 using the semi-quantitative Fazekas scale. WMH severity was classified as mild (Fazekas score \(=1–2\)), moderate (Fazekas score \(=3–4\)), or severe (Fazekas score \(=5–6\)) \(^{25}\). cSS was defined as curvilinear signal loss on gradient-recalled echo following the cortical gyral surface, and cSS severity was classified as focal (\( \leq 3 \text{ sulci}\)) or disseminated (\( >3 \text{ sulci}\)) \(^{26}\). In this study, only one patient had acute convexity subarachnoid hemorrhage (cSAH), lacking statistical value. Thus, these data were not reflected in the paper.

The original SVD score \((0–6)\) \(^{12}\) was assessed as follows: presence of lacunes, 1 point; 1–4 CMBs, 1 point; \( \geq 5 \text{ CMBs, 2 points; } >20 \text{ BG-EPVS, 1 point; moderate WMH (total Fazekas}\geq 3–4\text{), 1 point; and severe WMH (total Fazekas}\geq 5–6\text{), 2 points. The CAA-SVD score (0–6)\) \(^{28}\) was assessed as follows: 2–4 lobar CMBs, 1 point; \( \geq 5 \text{ lobar CMBs, 2 points; } >20 \text{ CSO-EPVS, 1 point; confluent deep WMHs (Fazekas score}\geq 2 \text{ or 3) or irregular periventricular WMHs extending into the deep white matter (Fazekas score}\geq 3\text{): 1 point focal; cSS, 1 point; and disseminated cSS, 2 points. Since patients with deep CMBs were excluded from the CAA-ICH group and those with lobar CMBs were excluded from the HTN-ICH group, we proposed the refined SVD score in HTN-ICH patients by placing more emphasis on deep CMBs, especially severe deep CMBs: presence of lacunes, 1 point; 2–4 deep CMBs, 1 point; \( \geq 5 \text{ deep CMBs, 2 points; } >20 \text{ BG-EPVS, 1 point; moderate WMH (total Fazekas}\geq 3–4\text{), 1 point; and severe WMH (total Fazekas}\geq 5–6\text{), 2 points. The total number of SVD markers was assessed as follows: 1 point for each of the presence of lacunes, CMBs, EPVS, WMHs, and cSS (Fig. 1).}

**Prognoses**

Within 1 year after the onset, patients were followed up *via* telephone every 3 months by trained professional neurologists. We used two prognostic end points: functional dependence and stroke recurrence. Functional dependence was measured 3 months after the onset and was defined as modified Rankin scale (mRS) \(>2\) \(^{20}\). Recurrent stroke was defined as a sudden new neurologic deficit that suits the definition of ischemic stroke or ICH. Patients with suspected recurrent stroke received repeat neuroimaging in the form of cranial CT or MRI to support the diagnosis.

**Statistical Methods**

We consulted professional statisticians to conduct the statistical analysis. The SPSS 22.0 software (SPSS Inc., Chicago, IL, USA) and the GraphPad Prism 8.0 software (GraphPad, San Diego, CA, USA) were utilized. ICH patients were divided into the CAA-ICH group and HTN-ICH group. The baseline clinical data and imaging data of these two groups were then compared. Continuous variables were analyzed using the Kolmogorov–Smirnov normal test. The data following a normal distribution were analyzed using the Kolmogorov–Smirnov normal test. For non-normal continuous variables, a Wilcoxon test or a Mann–Whitney \(U\) test was employed. For non-normal continuous variables, data were expressed as medians (interquartile ranges), and the Mann–Whitney \(U\) test was employed. Categorical variables were expressed as frequencies or percentages and analyzed using either the \( \chi^2 \) test or a Fisher’s exact test.
Fisher’s exact test.

Univariable logistic regression was employed with functional dependence as dependent variable and different SVD scores as independent variables. Backward stepwise multiple logistic regression analysis was then conducted. Age, sex, and baseline clinical characteristics associated with functional dependence in the univariable analysis ($P < 0.1$) were further used as covariates. Univariable Cox regression was employed to analyze the relationship between stroke recurrence and different SVD scores. Backward stepwise multiple Cox regression analysis was conducted, with age, sex, and vascular risk factors fully adjusted.

**Data Availability Statement**

Patient-related data will be shared upon request by the corresponding author or any qualified investigator.

**Results**

**Study Population**

A total of 163 patients (60 with CAA-ICH and 103 with HTN-ICH) were finally included in the study (Fig. 2). Three patients died during the 1-year follow-up: two died of recurrent stroke, whereas the other one died of heart disease. Compared with HTN-ICH patients, CAA-ICH patients were more likely to be older and have larger hematoma volumes but milder clinical symptoms upon admission, as assessed by the National Institutes of Health Stroke Scale (NIHSS) score. In addition, CAA-ICH patients ($P < 0.05$ for all) were found to have more SVD markers (cSS, severe CSO-EPVS, and severe WMH) and higher CAA-SVD score. Baseline clinical characteristics and radiological outcomes are presented in Table 1.

**Univariable Analysis of Factors Associated with Functional Dependence**

In the CAA-ICH group, 11 patients (18.3%) were found to be functionally dependent 3 months after onset. Univariable analyses revealed that cSS (OR 4.322; 95% CI 1.624–11.503; $P = 0.003$) and the CAA-SVD score (OR 3.299; 95% CI 1.656–6.572; $P = 0.001$) demonstrated stronger associations with functional dependence compared with other individual and total burden of SVD markers.

In the HTN-ICH group, 19 patients (18.4%) were found to exhibit functional dependence. The modified SVD score (OR 1.764; 95% CI 1.151–2.704; $P = 0.009$) and the refined SVD score (OR 1.893; 95% CI 1.202–2.980; $P = 0.006$) both demonstrated stronger associations with functional dependence compared with other individual and total burden of SVD markers.

In the CAA-ICH group, 8 patients (13.3%) have suffered recurrent stroke within 1 year of ICH.
burden of CSVD markers (Table 5).

**Multiple Cox Regression Analysis Between Stroke Recurrence and Different SVD Scores**

The multivariate analyses revealed that the total number of SVD markers (HR = 3.765; 95% CI = 1.467–9.663; \( P = 0.006 \)) might have the best predictive value for stroke recurrence in the CAA-ICH group (Table 6). In the HTN-ICH group, while the total number of SVD markers (HR = 2.136; 95% CI = 1.218–3.745; \( P = 0.008 \)) also demonstrated association with recurrent stroke, this effect seems to be related with the influence of lacunes (HR = 5.064; 95% CI = 1.697–15.116; \( P = 0.004 \)) (Table 7).

**Discussion**

In this study, we attempted to determine whether different SVD scores have varying predictive effects on the prognosis of mild ICH patients. The results are summarized as follows: (1) The CAA-SVD score may be the best to predict poor functional outcome in CAA-ICH patients. (2) None of the SVD scores demonstrated association with functional dependence in the HTN-ICH group, which was somewhat unexpected. (3) Moreover, the total number of SVD markers was probably better than the CAA-ICH score to identify mild CAA-ICH patients with a high risk of recurrent stroke. (4) In the HTN-ICH group, while the total number of SVD markers was found to be
In this study, we found that the CAA-SVD score may be better to predict poor functional recoveries in mild CAA-ICH patients, whereas the total number of SVD markers may be more accurate to identify stroke recurrence in the same cohort. The CAA-SVD score is significant for the prediction of recurrent stroke, this effect appeared to be related with the influence of lacunes.

For the first time, we summarized the effect of different SVD scores on the prognosis of mild ICH patients without surgical treatment. Clinicians may be more concerned with the recoveries of severe ICH patients requiring surgery. Thus, our research may help neurologists identify mild ICH patients with poor prognosis and adopt effective preventive measures in advance.

In this study, we found that the CAA-SVD score may be better to predict poor functional recoveries in mild CAA-ICH patients, whereas the total number of SVD markers may be more accurate to identify stroke recurrence in the same cohort. The CAA-SVD score

### Table 1. Baseline Characteristics of the Study Population

| Baseline clinical characteristics | Total Cohort (N=163) | CAA-related ICH (n=60) | HTN-related ICH (n=103) | P value |
|-----------------------------------|----------------------|------------------------|-------------------------|---------|
| Age, means ± SD                  | 63.3 ± 13.6          | 71.0 ± 9.9             | 58.8 ± 11.8             | <0.001  |
| Sex, male (%)                    | 100 (61.3)           | 32 (53.2)              | 68 (66.0)               | 0.109   |
| Hypertension, n (%)              | 132 (80.9)           | 29 (48.3)              | 103 (100)               | <0.001  |
| Diabetes mellitus, n (%)         | 27 (16.6)            | 10 (16.7)              | 17 (16.5)               | 0.542   |
| Dyslipidemia, n (%)              | 38 (23.3)            | 15 (25.0)              | 23 (22.3)               | 0.698   |
| Atrial fibrillation, n (%)       | 6 (3.9)              | 4 (6.7)                | 2 (1.9)                 | 0.194   |
| Previous stroke, n (%)           | 23 (14.1)            | 13 (21.7)              | 10 (9.7)                | 0.034   |
| Antiplatelet use, n (%)          | 27 (16.6)            | 12 (20.0)              | 15 (14.6)               | 0.300   |
| Statin use, n (%)                | 15 (9.2)             | 7 (11.7)               | 8 (7.8)                 | 0.209   |
| Admission NIHSS, median (IQR)    | 4 (2-6)              | 2 (1-5)                | 4 (2-7)                 | 0.001   |
| Admission GCS, median (IQR)      | 15 (15-15)           | 15 (15-15)             | 15 (15-15)              | 0.319   |
| Hematoma volume, means ± SD      | 9.4 ± 10.4           | 12.4 ± 13.2            | 7.6 ± 7.9               | 0.004   |

### Imaging characteristics

| Lacunes, n (%)                  | 26 (16.0)            | 7 (11.7)                | 19 (18.4)               | 0.254   |
| CMBS, n (%)                     | 65 (39.9)            | 22 (36.2)               | 43 (41.7)               | 0.523   |
| 1                               | 28 (17.2)            | 13 (21.7)               | 15 (14.6)               | 0.246   |
| 2-4                             | 28 (17.2)            | 7 (11.7)                | 21 (20.4)               | 0.155   |
| ≥ 5                             | 9 (5.5)              | 2 (3.3)                 | 7 (6.8)                 | 0.488   |
| lobar                           | 16 (9.8)             | 16 (26.7)               | 0 (0)                   | <0.001  |
| deep                            | 39 (23.9)            | 0 (0)                   | 39 (37.9)               | <0.001  |
| >20 CSO-EPVS, n (%)             | 34 (20.8)            | 23 (38.3)               | 11 (10.7)               | <0.001  |
| >20 BG-EPVS, n (%)              | 18 (11.0)            | 5 (8.3)                 | 13 (12.6)               | 0.400   |
| WMHs, n (%)                     | 122 (74.8)           | 46 (76.7)               | 76 (73.8)               | 0.683   |
| 1-2                             | 37 (22.7)            | 8 (13.3)                | 29 (28.2)               | 0.029   |
| 3-4                             | 48 (29.4)            | 18 (30.0)               | 30 (29.1)               | 0.906   |
| 5-6                             | 37 (22.7)            | 20 (33.3)               | 17 (16.5)               | 0.013   |
| cSS, n (%)                      | 11 (6.7)             | 9 (15.0)                | 2 (1.9)                 | 0.002   |
| Disseminated cSS                | 7 (4.3)              | 6 (10.0)                | 1 (1.0)                 | 0.006   |
| Focal cSS                       | 4 (2.5)              | 3 (5.0)                 | 1 (1.0)                 | 0.109   |
| The original SVD score, median (IQR) | 1 (0-2)           | 1 (1-2)                 | 1 (0-2)                 | 0.570   |
| The modified SVD score, median (IQR) | 1 (1-3)          | 1 (1-3)                 | 1 (0-2)                 | 0.567   |
| The refined SVD score, median (IQR) | 1 (0-2)           | 1 (0-2)                 | 1 (0-2)                 | 0.822   |
| The CAA-SVD score, median (IQR) | 1 (0-1)              | 1 (0-2)                 | 0 (0-1)                 | <0.001  |
| Total number of SVD markers, median (IQR) | 1 (1-2)       | 1 (1-2)                 | 1 (1-2)                 | 0.779   |
| Recurrent stroke                | 21 (12.9)            | 8 (13.3)                | 13 (12.6)               | 0.975   |

Abbreviation: HTN=Hypertension; CAA=Cerebral amyloid angiopathy; ICH=Intracerebral Hemorrhage; NIHSS=National Institutes of Health Stroke Scale; GCS=Glasgow Coma Scale; cSS=Cortical Superficial Siderosis; CMBS=Cerebral Microbleeds; WMHs=White Matter Hyperintensities; EPVS=Enlarged Perivascular Spaces; CSO=Centrum Semiovale; BG=Basal Ganglia; SVD=Small Vessel Disease; Results are expressed as numbers (column %), means (SD) or medians (interquartile range) as appropriate.
The limited association between the calculative burden of SVD markers and worse functional outcome in HTN-ICH patients was somewhat unexpected. Prior literature demonstrated that deep CMBs were related to HTN-ICH32). Therefore, our expectation was that the refined SVD score would have a more profound effect. This result suggests that when the analysis was restricted to the mild HTN-ICH subgroup, the influence of SVD markers on functional dependence was limited. Thus, it would be better to pay more attention to age and admission NIHSS score to predict the recoveries of neurological function. Our study also suggested that lacunes and the specific imaging characteristics, rather than the overall severity of SVD burden, were responsible for the high risk of stroke recurrence in HTN-ICH patients. The pathophysiological mechanisms of lacunes were related to atherosclerosis and microenvironment of arterioles less than 100 µm. Moreover, further changes in the blood–brain barrier was proposed by the introduction of cSS, which is an emerging SVD marker. There was a hypothesis holding that cSS could reflect repeated hemorrhage in the subarachnoid space from the superficial cortical vessels. Thus, cSS may be a marker of small-vessel fragility30, 31). Previous study has indicated that cSS is a stronger risk factor for ICH recurrence in CAA patients compared with the total CAA-SVD score16). We failed to obtain a similar conclusion. However, our study indicated that the total number of SVD markers, rather than the specific disease phenotype, could better identify mild CAA-ICH patients with a high risk of stroke recurrence. This result may suggest the potential of cSS combined with other SVD markers to predict recurrent stroke in mild ICH patients. Furthermore, we innovatively found that the CAA-SVD score was also associated with functional dependence. These findings added to our understanding of the CAA neuroimaging profiles and their relationship with the clinical outcomes. More cases and longer follow-up durations would be required for further verifications.

Table 2. Univariate analysis of factors associated with functional dependence*

|                                | CAA-related ICH (n = 60) | HTN-related ICH (n = 103) |
|--------------------------------|--------------------------|---------------------------|
|                                | OR (95% CI)               | P value                   | OR (95% CI)               | P value                   |
| Baseline clinical characteristics|                          |                           |                          |                           |
| Age                            | 1.082 (1.007-1.162)       | 0.031                     | 1.031 (0.987-1.076)       | 0.176                     |
| Male                           | 0.942 (0.253-3.501)       | 0.929                     | 0.875 (0.301-2.544)       | 0.807                     |
| Hypertension                   | 0.737 (0.198-2.740)       | 0.649                     |                           |                           |
| Diabetes mellitus              | 1.111 (0.201-6.143)       | 0.904                     | 0.541 (0.113-2.596)       | 0.443                     |
| Dyslipidemia                   | 1.025 (0.365-3.648)       | 0.563                     | 1.126 (0.438-7.462)       | 0.413                     |
| Previous stroke                | 0.768 (0.144-4.089)       | 0.757                     | 1.118 (0.218-5.740)       | 0.894                     |
| Antiplatelet use               | 1.061 (0.222-5.078)       | 0.941                     | 1.023 (0.136-3.046)       | 0.867                     |
| Statin use                     | 0.702 (0.114-4.338)       | 0.703                     | 0.921 (0.256-5.471)       | 0.643                     |
| Admission NIHSS               | 1.167 (0.984-1.384)       | 0.076                     | 1.384 (1.187-1.614)       | <0.001                    |
| Admission GCS                 | 1.825 (0.303-10.979)      | 0.511                     | 0.426 (0.209-0.869)       | 0.019                     |
| Hematoma volume               | 1.052 (1.000-1.108)       | 0.051                     | 1.057 (0.998-1.120)       | 0.059                     |
| Imaging markers of CSVD        |                          |                           |                          |                           |
| Lacunes                        | 2.057 (0.330-12.809)      | 0.439                     | 1.370 (0.425-4.419)       | 0.598                     |
| CMBs                           | 1.126 (0.855-1.482)       | 0.399                     | 1.190 (0.973-1.4554)      | 0.090                     |
| EPVSs                          | 2.763 (0.712-10.725)      | 0.142                     | 1.818 (0.651-5.075)       | 0.254                     |
| WMH                            | 1.458 (1.007-2.111)       | 0.046                     | 1.215 (0.955-1.545)       | 0.113                     |
| cSS                            | 4.322 (1.624-11.503)      | 0.003                     | 2.822 (0.697-11.429)      | 0.146                     |
| The original SVD score         | 2.361 (1.033-5.398)       | 0.042                     | 1.378 (0.854-2.223)       | 0.189                     |
| The modified SVD score         | 2.249 (1.203-4.208)       | 0.011                     | 1.764 (1.151-2.704)       | 0.009                     |
| The refined SVD score          | /                         | /                         | 1.893 (1.202-2.980)       | 0.006                     |
| The CAA-SVD score              | 3.299 (1.656-6.572)       | 0.001                     | /                         |                           |
| Total number of SVD markers    | 3.728 (1.502-9.252)       | 0.005                     | 1.424 (0.800-2.538)       | 0.230                     |

Abbreviation: HTN = Hypertension; CAA = Cerebral amyloid angiopathy; ICH = Intracerebral Hemorrhage; NIHSS = National Institutes of Health Stroke Scale; GCS = Glasgow Coma Scale; cSS = Cortical Superficial Siderosis; CMBs = Cerebral Microbleeds; WMHs = White Matter Hyperintensities; EPVSs = Enlarged Perivascular Spaces; CSO = Centrum Semiovale; BG = Basal Ganglia; SVD = Small Vessel Disease.

*Functional dependence was measured 3 months after onset and defined as the modified Rankin scale (mRS) > 2
patients had recurrent hemorrhagic strokes and 13 patients had recurrent ischemic strokes, rendering further analysis difficult. In future study, we would like to include more cases to separately explore the prediction value of different SVD scores on recurrent cerebral hemorrhage and recurrent cerebral infarction.

In conclusion, the CAA-SVD score and the total number of SVD markers might help doctors identify high-risk patients with poor prognosis in the mild CAA-ICH group. It would be better for neurologists to focus on lacunes rather than the overall burden of SVD markers to identify patients who might have recurrent strokes in the mild HTN-ICH group.

Table 3. Univariate analysis of factors associated with stroke recurrences

|                          | CAA-related ICH (n = 60) |        | HTN-related ICH (n = 103) |        |
|--------------------------|--------------------------|--------|---------------------------|--------|
|                          | HR (95% CI)              | P value| HR (95% CI)               | P value|
| **Baseline clinical characteristics** |                        |        |                          |        |
| Age                      | 0.964 (0.893-1.041)      | 0.352  | 1.032 (0.985-1.081)      | 0.186  |
| Male                     | 2.073 (0.495-8.677)      | 0.318  | 1.226 (0.401-3.748)      | 0.721  |
| Hypertension             | 0.577 (0.138-2.413)      | 0.451  |                          |        |
| Diabetes mellitus        | 1.861 (0.375-9.227)      | 0.447  | 0.632 (0.174-2.298)      | 0.486  |
| Dyslipidemia             | 1.223 (0.142-7.537)      | 0.637  | 0.728 (0.331-1.601)      | 0.429  |
| Previous stroke          | 0.494 (0.061-4.016)      | 0.510  | 1.700 (0.377-7.678)      | 0.490  |
| Antiplatelet use         | 0.756 (0.222-4.078)      | 0.529  | 0.576 (0.067-5.387)      | 0.689  |
| Statin use               | 1.275 (0.653-4.338)      | 0.264  | 0.835 (0.321-3.965)      | 0.189  |
| Admission NIHSS          | 1.116 (0.960-1.297)      | 0.153  | 1.124 (0.986-1.280)      | 0.081  |
| Admission GCS            | 0.749 (0.223-2.519)      | 0.641  | 0.728 (0.331-1.601)      | 0.429  |
| Hematoma volume          | 1.033 (1.001-1.066)      | 0.045  | 1.012 (0.950-1.079)      | 0.710  |
| **Imaging markers of CVSD** |                        |        |                          |        |
| Lacunes                  | 2.120 (0.428-10.510)     | 0.357  | 6.132 (2.054-18.311)     | 0.001  |
| CMBS                     | 1.108 (0.892-1.376)      | 0.354  | 0.797 (0.258-2.455)      | 0.692  |
| EPVS                     | 0.771 (0.184-3.227)      | 0.722  | 1.957 (0.658-5.825)      | 0.228  |
| WMH                      | 1.376 (0.936-2.024)      | 0.105  | 1.251 (0.965-1.622)      | 0.091  |
| cSS                      | 1.979 (0.941-4.160)      | 0.072  | 2.176 (0.747-6.343)      | 0.154  |
| The original SVD score   | 2.449 (1.076-5.575)      | 0.033  | 1.911 (1.193-3.061)      | 0.007  |
| The modified SVD score   | 1.904 (1.051-3.448)      | 0.034  | 1.586 (1.047-2.403)      | 0.030  |
| The refined SVD score    | /                        | /      | 1.589 (1.007-2.507)      | 0.047  |
| The CAA-SVD score        | 1.894 (1.216-2.950)      | 0.005  | /                        | /      |
| Total number of SVD markers | 3.839 (1.505-9.794) | 0.005 | 2.136 (1.218-3.745) | 0.008 |

Abbreviation: HTN=Hypertension; CAA=Cerebral Amyloid Angiopathy; ICH=Intracerebral Hemorrhage; NIHSS=National Institutes of Health Stroke Scale; GCS=Glasgow Coma Scale; cSS=Cortical Superficial Siderosis; CMBS=Cerebral Microbleeds; WMHs=White Matter Hyperintensities; EPVSs=Enlarged Perivascular Spaces; CSO=Centrum Semiovale; BG=Basal Ganglia; SVD=Small Vessel Disease.

and cerebral blood flow might be the cause of recurrent stroke. Previous study has also reported that lacunes increased the risk of stroke recurrence in non-CAA-ICH patients, which is in agreement with our results. Our study has important clinical implications, which enable clinicians to better identify secondary prevention measures, especially in conscious and spontaneous ICH patients without surgical treatment, who might be easily ignored by doctors. Another strength of our work is the systematic evaluation and summary of different SVD scores by trained raters using validated scales. Our study also has some limitations. First, due to the rigidity of the inclusion criteria, the sample size in our study was small, and the findings need to be confirmed in future larger studies. Second, patients who could not be definitively diagnosed with CAA-ICH or HTN-ICH were excluded, which limited the strength of some of our results. Third, we did not assess the cognitive function during follow-up. Finally, our study was limited by the small number of some clinical outcomes, with only 8 patients who had recurrent hemorrhagic strokes and 13 patients who had recurrent ischemic strokes, rendering further analysis difficult. In future study, we would like to include more cases to separately explore the prediction value of different SVD scores on recurrent cerebral hemorrhage and recurrent cerebral infarction. The results may help clinicians to better determine the use of medications, such as anti-platelet drugs and statins.

In conclusion, the CAA-SVD score and the total number of SVD markers might help doctors identify high-risk patients with poor prognosis in the mild CAA-ICH group. It would be better for neurologists to focus on lacunes rather than the overall burden of SVD markers to identify patients who might have recurrent strokes in the mild HTN-ICH group.

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### Table 4. Multivariable adjusted models exploring associations of individual SVD markers and different SVD scores and functional dependence* in CAA-related ICH patients

|                          | OR (95% CI)       | P value |
|--------------------------|-------------------|---------|
| **Model 1: individual SVD markers** |                   |         |
| Age                      | 1.098 (0.983-1.226) | 0.097   |
| Admission NIHSS          | 1.211 (0.967-1.516) | 0.095   |
| Hematoma volume          | 0.985 (0.903-1.075) | 0.735   |
| Lacunes                  | 0.349 (0.023-5.400) | 0.451   |
| Lobar CMBs               | 2.486 (0.360-17.156) | 0.355   |
| Severe CSO-EPVS          | 4.778 (0.568-400.125) | 0.150   |
| WMH                      | 2.881 (0.234-35.407) | 0.408   |
| cSS                      | 4.665 (1.388-16.579) | 0.013   |
| **Model 2: different total SVD scores** |                   |         |
| Age                      | 1.120 (1.014-1.237) | 0.026   |
| Admission NIHSS          | 1.249 (0.979-1.594) | 0.074   |
| Hematoma volume          | 1.023 (0.935-1.120) | 0.617   |
| The original SVD score   | 0.129 (0.010-1.640) | 0.114   |
| The modified SVD score   | 3.816 (0.321-45.355) | 0.289   |
| The refined SVD score    | 0.802 (0.095-6.764) | 0.839   |
| The CAA-SVD score        | 3.429 (1.518-7.748) | 0.003   |
| Total number of SVD markers | 1.410 (0.180-11.030) | 0.744   |

Abbreviation: SVD = Small Vessel Disease; CAA = Cerebral amyloid angiopathy; NIHSS = National Institutes of Health Stroke Scale; cSS = Cortical Superficial Siderosis; CMBs = Cerebral Microbleeds; WMH = White Matter Hyperintensities; EPVS = Enlarged Perivascular Spaces; CSO = Centrum Semiovale.

*Functional dependence was measured 3 months after onset and defined as the modified Rankin scale (mRS) ≥ 2

### Table 5. Multivariable adjusted models exploring associations of individual SVD markers and different SVD scores and functional dependence* in HTN-related ICH patients

|                          | OR (95% CI)       | P value |
|--------------------------|-------------------|---------|
| **Model 1: individual SVD markers** |                   |         |
| Age                      | 1.095 (1.015-1.181) | 0.019   |
| Admission NIHSS          | 1.679 (1.316-2.142) | <0.001  |
| Admission GCS            | 0.596 (0.150-2.374) | 0.463   |
| Hematoma volume          | 0.977 (0.873-1.093) | 0.685   |
| Lacunes                  | 0.233 (0.025-1.969) | 0.177   |
| Deep CMBs                | 3.195 (0.920-11.101) | 0.068   |
| Severe BG-EPVS           | 0.634 (0.050-8.026) | 0.725   |
| WMH                      | 1.493 (0.514-4.336) | 0.461   |
| cSS                      | 3.672 (0.478-28.229) | 0.211   |
| **Model 2: different total SVD scores** |                   |         |
| Age                      | 1.066 (0.998-1.138) | 0.057   |
| Admission NIHSS          | 1.556 (1.262-1.918) | <0.001  |
| Admission GCS            | 0.941 (0.277-3.194) | 0.922   |
| Hematoma volume          | 0.950 (0.856-1.055) | 0.337   |
| The original SVD score   | 0.459 (0.102-2.058) | 0.309   |
| The modified SVD score   | 1.514 (0.913-2.512) | 0.108   |
| The refined SVD score    | 1.185 (0.184-7.624) | 0.858   |
| The CAA-SVD score        | 1.439 (0.277-7.475) | 0.665   |
| Total number of SVD markers | 0.724 (0.213-2.460) | 0.605   |

Abbreviation: SVD = Small Vessel Disease; HTN = Hypertension; NIHSS = National Institutes of Health Stroke Scale; GCS = Glasgow Coma Scale; cSS = Cortical Superficial Siderosis; CMBs = Cerebral Microbleeds; WMH = White Matter Hyperintensities; EPVS = Enlarged Perivascular Spaces; BG = Basal Ganglia.

*Functional dependence was measured 3 months after onset and defined as the modified Rankin scale (mRS) ≥ 2
Compliance with Ethical Standards

Conflicts of Interest

The authors declare no conflicts of interest.

Ethical Approval

This study was approved by the ethics committee of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine. Written informed consent to

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Table 6. Multivariable adjusted models exploring associations of individual SVD markers and different total SVD scores and stroke recurrences in CAA-related ICH patients

|                      | HR (95% CI) | P value |
|----------------------|-------------|---------|
| **Model 1: individual SVD markers** |             |         |
| Age                  | 0.948 (0.868-1.036) | 0.241   |
| Hematoma volume      | 1.022 (0.983-1.062) | 0.266   |
| Lacunes              | 2.211 (0.257-19.055) | 0.470   |
| Lobar CMBs           | 1.013 (0.177-5.804) | 0.988   |
| Severe CSO-EPVS      | 1.596 (0.348-7.328) | 0.548   |
| WMH                  | 1.376 (0.936-2.024) | 0.105   |
| cSS                  | 1.953 (0.929-4.107) | 0.078   |
| **Model 2: different total SVD scores** |             |         |
| Age                  | 0.945 (0.874-1.020) | 0.148   |
| Hematoma volume      | 1.020 (0.977-1.065) | 0.370   |
| The original SVD score | 1.107 (0.094-12.998) | 0.935   |
| The modified SVD score | 0.549 (0.049-6.218) | 0.629   |
| The refined SVD score | 3.468 (0.447-26.881) | 0.234   |
| The CAA-SVD score    | 1.304 (0.548-3.101) | 0.549   |
| Total number of SVD markers | 3.765 (1.467-9.663) | 0.006   |

Abbreviation: SVD = Small Vessel Disease; CAA = Cerebral amyloid angiopathy; cSS = Cortical Superficial Siderosis; CMBs = Cerebral Microbleeds; WMH = White Matter Hyperintensities; EPVS = Enlarged Perivascular Spaces; CSO = Centrum Semiovale.

Table 7. Multivariable adjusted models exploring associations of individual SVD markers and different total SVD scores and stroke recurrences in HTN-related ICH patients

|                      | HR (95% CI) | P value |
|----------------------|-------------|---------|
| **Model 1: individual SVD markers** |             |         |
| Age                  | 1.032 (0.985-1.081) | 0.186   |
| Admission NIHSS      | 1.108 (0.954-1.288) | 0.179   |
| Lacunes              | 5.064 (1.697-15.116) | 0.004   |
| Deep CMBs            | 0.572 (0.150-2.174) | 0.412   |
| Severe BG-EPVS       | 0.275 (0.020-3.857) | 0.338   |
| WMH                  | 1.330 (0.548-3.101) | 0.477   |
| cSS                  | 3.135 (0.799-12.309) | 0.101   |
| **Model 2: different total SVD scores** |             |         |
| Age                  | 1.035 (0.980-1.093) | 0.212   |
| Admission NIHSS      | 1.111 (0.968-1.276) | 0.135   |
| The original SVD score | 1.833 (0.702-4.784) | 0.216   |
| The modified SVD score | 0.575 (0.119-2.792) | 0.493   |
| The refined SVD score | 1.056 (0.264-4.232) | 0.939   |
| The CAA-SVD score    | 1.582 (0.614-4.074) | 0.342   |
| Total number of SVD markers | 2.136 (1.218-3.745) | 0.008   |

Abbreviation: SVD = Small Vessel Disease; HTN = Hypertension; NIHSS = National Institutes of Health Stroke Scale; cSS = Cortical Superficial Siderosis; CMBs = Cerebral Microbleeds; WMH = White Matter Hyperintensities; EPVS = Enlarged Perivascular Spaces; BG = Basal Ganglia.
collect data and clinical outcomes was obtained from the patient or a legally authorized representative in all cases.

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