

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 score¹²⁾, 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 patients¹³⁾. Other scholars believed that the total number of the four SVD markers previously mentioned could also predict the adverse functional outcome of ICH¹⁴⁾. 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 CAA¹⁵⁾. Subsequently, researchers found that the CAA-SVD score could be adapted to predict the risk of ICH recurrence in patients with CAA¹⁶⁾. 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 related¹⁷⁾, 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, Jiaying 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 \geq 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) \geq 1 year of hypertension history; 2) hemorrhages (ICH and CMBs) restricted to the deep regions with or without deep microbleeds but no lobar microbleeds²⁰⁾. 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

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 hemispheres²². 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 mm punctate or linear hyperintensities on a T2-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 (≤ 10 EPVS), moderate (11–20 EPVS), or severe (≥ 20 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)²⁴. cSS was defined as curvilinear signal loss on gradient-recalled echo following the cortical gyral surface, and cSS severity was classified as focal (≤ 3 sulci) or disseminated (>3 sulci)²⁷. 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 (0–4)¹⁰ was assessed as follows: presence of lacunes, 1 point; presence of CMBs, 1 point; >10 BG-EPVS, 1 point; and periventricular WMH (Fazekas=3) or deep WMH (Fazekas=2–3), 1 point. The modified SVD score

(0–6)¹² was assessed as follows: presence of lacunes, 1 point; 1–4 CMBs, 1 point; ≥ 5 CMBs, 2 points; >20 BG-EPVS, 1 point; moderate WMH (total Fazekas=3–4), 1 point; and severe WMH (total Fazekas=5–6), 2 points. The CAA-SVD score (0–6)²⁸ was assessed as follows: 2–4 lobar CMBs, 1 point; ≥ 5 lobar CMBs, 2 points; >20 CSO-EPVS, 1 point; confluent deep WMHs (Fazekas score=2 or 3) or irregular periventricular WMHs extending into the deep white matter (Fazekas score=3): 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; ≥ 5 deep CMBs, 2 points; >20 BG-EPVS, 1 point; moderate WMH (total Fazekas=3–4), 1 point; and severe WMH (total Fazekas=5–6), 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 ²⁹. 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 expressed as mean \pm standard deviation, and a *t* 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 χ^2 test or

Markers Scores	Lacunae	Cerebral microbleeds (CMBs)	Perivascular spaces (PVS)	White matter hyperintensities (WMH)	Cortical superficial siderosis (cSS)
The original SVD score (0-4)	Presence of lacunae, 1 point	Presence of CMBs, 1 point	> 10 BG-PVS, 1 point	PWMH (Fazekas = 3) or DWMH (Fazekas = 2-3), 1 point	/
The modified SVD score (0-6)	Presence of lacunae, 1 point	1-4 CMBs, 1 point; ≥5 CMBs, 2 points	> 20 BG-PVS, 1 point	Moderate WMH (total Fazekas = 3-4), 1 point; Severe WMH (total Fazekas = 5-6), 2 points	/
The refined SVD score (0-6)	Presence of lacunae, 1 point;	2-4 deep CMBs, 1 point; ≥5 deep CMBs, 2 points;	>20 BG-PVS, 1 point;	Moderate WMH (total Fazekas = 3-4), 1 point; Severe WMH (total Fazekas = 5-6), 2 points	/
The CAA-SVD score (0-6)	/	2-4 lobar CMBs, 1 point; ≥5 lobar CMBs, 2 points	>20 CSO-PVS, 1 point	PWMH (Fazekas = 3) or DWMH (Fazekas = 2-3), 1 point	Focal cSS, 1 point; Disseminated cSS, 2 points
The total number of SVD markers (0-5)	Presence of lacunae, 1 point	Presence of CMBs, 1 point	Presence of PVS, 1 point	Presence of WMH, 1 point	Presence of cSS, 1 point

Fig. 1. Features and categories of different small vessel disease scores

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.

Univariate 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 correlations with functional dependence in the univariable analyses (Table 2).

Univariate Analysis of Factors Associated with Stroke Recurrence

In the CAA-ICH group, eight patients (13.3%) have suffered recurrent stroke within 1 year of ICH

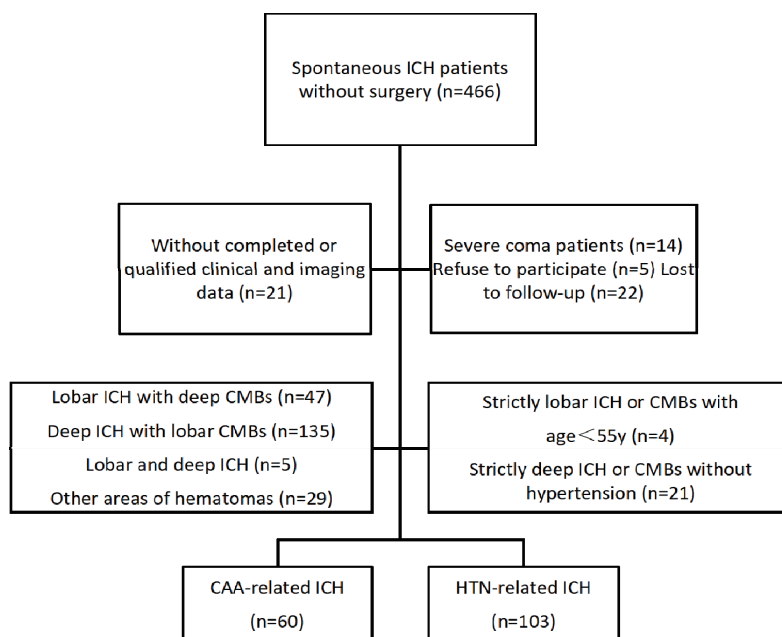


Fig. 2. Study flowchart

onset, including three cases of ischemic stroke and five cases of hemorrhagic stroke. The total number of SVD markers (OR=3.839; 95% CI=1.505–9.794; $P=0.005$) demonstrated the highest hazard ratio (HR) in univariable analyses among different SVD scores.

In the HTN-ICH group, 13 patients (12.6%) had suffered recurrent stroke, including 10 cases of ischemic stroke and three cases of hemorrhagic stroke. Univariable analyses revealed that stroke recurrence was associated with the original SVD score, modified SVD score, refined SVD score, and total number of SVD markers. However, those correlations may be significantly related to the influence of lacunes (OR=6.132; 95% CI=2.054–18.311; $P=0.001$) (Table 3).

Multiple Logistic Regression Analysis Between Functional Dependence and Different SVD Scores

After conducting univariate analyses to determine the factors associated with poor functional outcomes, age, sex, and variables with a $P < 0.10$ in Table 2 were used in the multivariate logistic regression as covariates. The multivariate analyses revealed that the CAA-SVD score (OR=3.429; 95% CI=1.518–7.748; $P=0.003$) was probably better to predict functional dependence in the CAA-ICH group (Table 4). Conversely, in the HTN-ICH group, the admission NIHSS (OR=1.556; 95% CI=1.262–1.918; $P < 0.001$) may have a stronger effect on functional dependence compared with individuals and total

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

Table 1. Baseline Characteristics of the Study Population

	Total Cohort (N=163)	CAA-related ICH (n = 60)	HTN-related ICH (n = 103)	P value
Baseline clinical characteristics				
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.

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 2. Univariate analysis of factors associated with functional dependence*

	CAA-related ICH (<i>n</i> = 60)		HTN-related ICH (<i>n</i> = 103)	
	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> 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 (0.365-6.348)	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				
Lacunae	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
EPVS	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

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 fragility^{30, 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.

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 lacunae 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 lacunae were related to atherosclerosis and microenvironment of arterioles less than 100 μ m. Moreover, further changes in the blood-brain barrier

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				
Lacunae	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 stroke³³). Previous study has also reported that lacunae increased the risk of stroke recurrence in non-CAA-ICH patients, which is in agreement with our results³⁴).

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 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. 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 lacunae 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 (1.388-15.679)	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

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 (0.606-2.916)	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.

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

collect data and clinical outcomes was obtained from the patient or a legally authorized representative in all cases.

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