Original Article

Enlarged perivascular spaces and hemorrhagic transformation after acute ischemic stroke

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Background: Enlarged perivascular spaces (EPVS) are considered to be neuroimaging markers of cerebral small vessel disease (CSVD). It remains unknown whether EPVS are associated with hemorrhagic transformation (HT) after acute ischemic stroke (AIS). We performed this retrospective cohort study to explore the associations of EPVS with clinical risk factors and other CSVD imaging features, and to investigate the relationship between EPVS and HT in patients with AIS.

Methods: AIS patients admitted within 24 hours of stroke onset between January 2016 and December 2017 were consecutively enrolled. EPVS, lacunes, and white matter hyperintensities (WMH) were rated with validated rating scales on magnetic resonance images after the stroke. HT was defined as hemorrhage determined by follow-up brain imaging during the patients' hospital stay. Logistic regression was used to determine the risk factors and associations with other CSVD markers of EPVS in the basal ganglia (BG) and centrum semiovale (CS) regions, and the impact of EPVS on HT was further explored.

Results: Among 494 included patients (mean age 66.4 years, 58.1% male), 81 (16.4%) experienced HT. In the multivariate logistic analyses, increasing age [odd ratio (OR) 1.041, 95% confidence interval (CI), 1.017–1.066], hypertension (OR 2.174, 95% CI, 1.338–3.532), lacunar stroke (OR 1.968, 95% CI, 1.169–3.314), CS-EPVS (OR 2.474, 95% CI, 1.796–3.407), and periventricular WMH (OR 2.140, 95% CI, 1.441–3.176) were significantly associated with BG-EPVS; whereas only BG-EPVS (OR 4.349, 95% CI, 2.281–8.291) were independently related to CS-EPVS. After adjustment for potential variables, neither BG-EPVS (OR 0.674, 95% CI, 0.336–1.350) nor CS-EPVS (OR 0.792, 95% CI, 0.334–1.879) was significantly associated with the occurrence of HT.

Conclusions: Our data showed that EPVS in the BG and CS regions were interrelated and had different risk factors in ischemic stroke patients. EPVS (particularly that in BG) were independently related to other CSVD markers. The presence or burden of EPVS was not significantly associated with HT after AIS.

Keywords: Enlarged perivascular spaces (EPVS); cerebral small vessel disease, hemorrhagic transformation; acute ischemic stroke (AIS)

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Introduction

Cerebral small vessel disease (CSVD) is a common age-related pathological process of the microvasculature caused by various risk factors (1). Classic neuroimaging features of CSVD include lacunes, white matter hyperintensities (WMH), and cerebral microbleeds (CMB) (1,2). Recently, enlarged perivascular spaces (EPVS) have been increasingly reported as an emerging marker of CSVD (3). Perivascular spaces (PVS), also known as Virchow–Robin spaces, are fluid-filled compartments surrounding the penetrating vessels, which facilitate interstitial fluid drainage and the removal of metabolites from the brain (4). Although normally undetectable, they may enlarge and become apparent with advancing age and increased exposure to vascular risk factors (4,5). When enlarged, PVS can be detected on T2-weighted magnetic resonance imaging (MRI) as punctate or linear hyperintensities, particularly in the basal ganglia (BG) and centrum semiovale (2,6).

Initial pathologic studies found that EPVS seldom cause damage in the brain parenchyma, and hence were regarded as normal variants with limited clinical importance (7). Recently, some studies in aging adults demonstrated that EPVS were associated with an increased risk of incident stroke, dementia, and depression (8-10). Moreover, growing evidence indicates that EPVS are more prevalent in stroke patients (11,12), and a high EPVS burden can predict poor outcomes after stroke (11,13,14). However, few studies have explored the relationship of EPVS to hemorrhagic transformation (HT) following ischemic stroke. Whether EPVS play a role in HT remains uncertain. EPVS are reported to correlate with other CSVD markers (i.e., WMH and CMB) (2,3,5), and previous studies have shown that WMH and CMB may increase the risk of HT (15-17). EPVS were also found to be associated with blood brain barrier dysfunction (1,4), which is considered to be the basic pathophysiology of HT (18). We therefore hypothesized that EPVS may be related to the occurrence of HT.

In the present study, we investigated the cross-sectional associations of EPVS with clinical factors and other CSVD markers, and further identified the relationship between EPVS and HT in patients with acute ischemic stroke (AIS).

We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/atm-21-1276).

Methods

Study population

This retrospective cohort study was derived from the Chengdu Stroke Registry, which has prospectively and consecutively recruited ischemic stroke patients admitted to Department of Neurology in West China Hospital since 2002. The details of the registry have been described previously (19). In the present study, we enrolled adult patients with ischemic stroke admitted within 24 hours after stroke onset from January 2016 to December 2017. Ischemic stroke was diagnosed according to the World Health Organization criteria (20), and confirmed by computed tomography (CT) or MRI scanning. Patients were excluded if they did not undergo MRI scans due to contraindications (e.g., claustrophobia, implanted devices incompatible with MRI) or had a severe stroke and were unable to bear MRI scanning; or if the MRI image quality was poor, making the assessment of EPVS difficult. This study was approved by the Biomedical Research Ethics Committee of West China Hospital, Sichuan University (No. 2016-339), and conformed to the provisions of the Declaration of Helsinki (as revised in 2013). Since the study was a retrospective cohort, individual consent was waived.

Data collection

Patients' baseline demographic and clinical data were retrieved as follows: age, sex, time from stroke onset to admission, medical history [hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation (AF), previous stroke or transient ischemic attack (TIA)], history of smoking and alcohol consumption, National Institutes of Health Stroke Scale (NIHSS) score, blood pressure, laboratory data, the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification, and treatments after admission (antiplatelet, anticoagulant, lipid lowering, and reperfusion therapy). The laboratory data included platelet count, neutrophil-to-lymphocyte ratio (NLR), blood glucose, creatinine, uric acid, and coagulation testing. All venous blood samples were obtained within 24 hours after admission.

Image acquisition

Brain CT was performed within 24 hours after admission, followed by regular MRI scanning within 7 days of admission or CT immediately in case of clinical worsening. CT was performed using a 64-section scanner with 7-mm slice thickness (Siemens). MRI was performed on a 3.0 T scanner with 5-mm slice thickness and matrix size was 256×256 pixels (Magnetom, Siemens, Erlangen, Germany), including the following sequences: T1-weighted, T2-weighted, and fluid-attenuated inversion recovery (FLAIR) imaging. The parameters of the above MRI sequences have been described detailly in our previous study (17).

Rating of EPVS

MRI findings were categorized and recorded in accordance with STRIVE (Standards for Reporting Vascular Changes on Neuroimaging) criteria (2). All images were assessed by two experienced neurologists (QS and YC) blinded to patients' clinical information. In case of divergence, a third neurologist (JL) was consulted and a consensus was reached.

EPVS were defined as fluid-filled spaces surrounding the penetrating vessels, with a signal intensity identical to cerebrospinal fluid (CSF) on all MRI sequences. Their appearance was linear, round or ovoid with a diameter generally smaller than 3 mm and without the surrounding FLAIR hyperintense rim (2). EPVS were counted in the BG and centrum semiovale (CS) using the following 5-point rating scale: 0= none EPVS, 1=1 to 10, 2=11 to 20, 3=21 to 40, and 4=>40 EPVS (3,6). For both regions, we chose the slice in the most affected hemisphere only. When the infarct size was too large to count the EPVS, only the contralateral hemisphere was rated. Moderate-to-severe EPVS were defined as having a score ≥2 in the BG or CS. Total EPVS burden was calculated by summing the BG and CS-EPVS scores. In this study, the inter-rater kappa values were 0.75 and 0.61 for BG and CS-EPVS, respectively.

Other CSVD markers

Lacunes were defined as round or ovoid lesions with a diameter of 3–15 mm, located in the BG, internal or external capsule, thalamus, centrum semiovale, or brainstem, showing CSF-like intensities on T2-weighted and FLAIR images, generally with a hyperintense rim on FLAIR (2). The number of lacunes was identified. WMH was rated according to the Fazekas scale, and divided into periventricular white matter hyperintensity (PWMH) and deep white matter hyperintensity (DWMH) (21). PWMH was graded as absent (score 0), cap (score 1), smooth halo (score 2), or irregular and extending into the subcortical white matter (score 3), while DWMH was rated as absent (score 0), punctate foci (score 1), early confluent (score 2), or confluent (score 3). Extensive WMH was defined as PWMH score =3 or DWMH score ≥2. The inter-rater kappa values were 0.65 for lacunes, 0.93 for PWMH, 0.90 for DWMH, respectively.

Several CSVD markers often coexist in a patient, and it seems better to quantify the total burden of CSVD to assess the cumulative effect of small vessel injury on the whole brain. Thus, in this study, we used lacunes, WMH and EPVS to calculate the "total CSVD burden" (ranging from 0 to 3) based on the validated ordinal scale (22,23): One point was awarded if lacunes ≥1, or PVWMH score =3 and/or DWMH score ≥2, or BG-EPVS score ≥2.

Outcome assessment

The main outcome measure was development of hemorrhagic transformation (HT) during patients' stay in the hospital. HT was defined as either hemorrhage within the infarcted area or parenchyma hemorrhage outside the infarct zone, which was observed on follow-up CT or MRI during hospitalization but not on the initial brain CT (24). Two trained neurologists (YW and CW) without knowledge of patient's clinical information independently assessed the presence of HT. Disagreements were solved through discussion or advice from a third neurologist (ML). HT was further classified as hemorrhagic infarction (HI) or parenchymal hematoma (PH) based on the European Cooperative Acute Stroke Study (ECASS) III criteria (25). Symptomatic HT (sHT) was defined as any intracranial hemorrhage associated with any decline in neurologic status according to National Institute of Neurological Diseases and Stroke (NINDS) criteria (26).

Statistical analysis

In this study, values were missing for platelet count in two (0.4%) patients. Data for all other variables were complete. As the level of missing data was low (<5%) and almost negligible, we decided not to impute the missing data.

Continuous data were expressed as mean with standard deviation (SD) or median with interquartile range (IQR), while categorical data were reported as numbers and

percentages. We firstly assessed the correlation between EPVS and other CSVD features (the number of lacunes and the ordinal scores of WMH) using Spearman's rank correlation. Then, the univariate and multivariate logistic analyses were performed to study the association of EPVS with clinical risk factors and CSVD markers. As EPVS scores were not normally distributed, we dichotomized EPVS into mild total EPVS (score 0-2) *vs.* moderate-to-severe total EPVS [3-8], mild BG-EPVS [0-1] *vs.* moderate-to-severe BG-EPVS [2-4], and mild CS-EPVS [0-1] *vs.* moderate-to-severe CS-EPVS [2-4], respectively. Potential variables identified from the recent literature (11,12,27) were adjusted: age, sex, hypertension, diabetes mellitus, dyslipidemia, AF, prior stroke/TIA, smoking, drinking, lacunar stroke, PWMH, DWMH, and lacunes.

For our second aim, we compared clinical and imaging characteristics of patients with HT to those without HT. Intergroup differences in categorical variables were assessed using χ^2 test or Fisher's exact test, while differences in continuous variables were compared using Student's *t*-test or Mann-Whitney U test, as appropriate. Then, multivariate logistic analyses were used to investigate the independent association between EPVS and HT, incorporating variables with P<0.1 identified in univariate analysis.

All statistical analyses were performed using SPSS 26.0 (IBM, USA), and a 2-sided P<0.05 was considered to be statistically significant.

Results

Baseline characteristics

During the study period, 627 patients within 24 hours of stroke onset were admitted to our hospital, and 133 patients were excluded for the following reasons: no MRI scans (n=108), and poor quality of MRI images (n=25). Therefore, 494 patients were finally included in this study (Figure S1). The mean age of the study population was 66.4±13.4 years (58.1% male), and the median NIHSS score was 5 (IQR, 2–11). The baseline characteristics of included patients were presented in *Table 1*. A total of 57 (11.5%) patients received reperfusion therapy after admission: 41 (8.3%) patients with thrombolytic therapy, 13 (2.6%) with endovascular therapy, and 3 (0.6%) with thrombolysis followed by endovascular therapy.

The median time from stroke onset to MRI scanning was 2.7 days (IQR, 1.8–3.7 days). EPVS were detected in 99.8% (493/494) patients, and the median EPVS scores in BG and CS were 1 (IQR, 1–2) and 2 (IQR, 2–3), respectively. Overall, 48.4% (239/494) of patients were rated as moderate-to-severe BG-EPVS, 88.1% (435/494) as moderate-to-severe CS-EPVS, and 46.6% (230/494) had both moderate-to-severe BG-EPVS and moderate-to-severe CS-EPVS.

EPVS and other CSVD markers

Compared to CS-EPVS, BG-EPVS were more closely related to other imaging markers of CSVD, with the strongest correlation for PWMH (ρ=0.515, P<0.001), followed by DWMH (ρ=0.450, P<0.001) and lacunes (ρ=0.237, P<0.001) (Table S1). There was a correlation between BG and CS-EPVS (ρ=0.243, P<0.001), but no significant correlation was found among CS-EPVS, lacunes and WMH (all P>0.05) (Table S1). The multivariate logistic analyses showed that DWMH was independently associated with total EPVS (OR 2.012, 95% CI, 1.062–3.809) (*Table 2*); age (OR 1.041, 95% CI, 1.017–1.066), hypertension (OR 2.174, 95% CI, 1.338–3.532), lacunar stroke (OR 1.968, 95% CI, 1.169–3.314), CS-EPVS (OR 2.474, 95% CI, 1.796–3.407), and PWMH (OR 2.140, 95% CI, 1.441–3.176) were significantly associated with EPVS in BG; whereas only BG-EPVS (OR 4.349, 95% CI, 2.281–8.291) were independently related to CS-EPVS (*Table 2*).

EPVS and HT

The median length of hospital stay was 11 days (IQR, 8–16 days), and there were 81 (16.4%) patients experienced HT during hospitalization (median time from onset to HT 3.5 days, IQR, 2–6 days), of whom 43 (8.7%) with HI, 38 (7.7%) with PH, and 10 (2.0%) with sHT.

The baseline clinical and imaging characteristics of patients with HT and without HT were shown in *Table 1*. Patients with HT were older, more likely to be female, had lower onset to admission time, higher proportion of AF and reperfusion therapy, higher NIHSS score, lower systolic pressure, lower proportion of alcohol consumption and antiplatelet therapy than those without HT (all P<0.05), while the application of anticoagulants was similar among the two groups (17.3% *vs.* 10.7%, P=0.09). With respect to laboratory data, compared to those without HT, patients experienced HT had lower platelet count and higher NLR level (all P<0.05) (*Table 1*).

As for CSVD markers, both the median BG-EPVS score and the proportion of moderate-to-severe BG-EPVS

Table 1 Baseline characteristics of patients with and without HT

Characteristics	Total, N=494	Without HT, N=413	With HT, N=81	P
Clinical characteristics				
Age, mean (SD)	66.4 (13.4)	65.5 (13.4)	70.9 (12.5)	0.001
Male, n (%)	287 (58.1)	252 (61.0)	35 (43.2)	0.003
Onset to admission time, h, median [IQR]	9 [4–24]	10 [4–24]	5 [4–24]	0.017
Hypertension, n (%)	308 (62.3)	258 (62.5)	50 (61.7)	0.900
Diabetes, n (%)	128 (25.9)	109 (26.4)	19 (23.5)	0.581
Dyslipidemia, n (%)	72 (14.6)	63 (15.3)	9 (11.1)	0.334
Atrial fibrillation, n (%)	127 (25.7)	79 (19.1)	48 (59.3)	<0.001
Prior stroke/TIA, n (%)	89 (18.0)	78 (18.9)	11 (13.6)	0.256
Smoking, n (%)	184 (37.2)	161 (39.0)	23 (28.4)	0.072
Alcohol consumption, n (%)	118 (23.9)	109 (26.4)	9 (11.1)	0.003
Baseline NIHSS, median [IQR]	5 [2–11]	5 [2–9]	13 [8–18]	<0.001
Systolic pressure, mmHg, mean (SD)	147.15 (23.94)	148.41 (24.32)	140.70 (20.80)	0.004
Diastolic pressure, mmHg, mean (SD)	84.55 (15.08)	84.66 (14.45)	84.04 (18.05)	0.736
TOAST classification, n (%)				<0.001
Large-artery atherosclerosis	127 (25.7)	109 (26.4)	18 (22.2)	
Lacunar stroke	146 (29.6)	144 (34.9)	2 (2.5)	
Cardio-embolism	121 (24.5)	76 (18.4)	45 (55.6)	
Undetermined etiology	90 (18.2)	75 (18.2)	15 (18.5)	
Other etiology	10 (2.0)	9 (2.2)	1 (1.2)	
Platelet count, mean (SD)[†]	170.75 (72.37)	175.01 (74.50)	148.09 (55.38)	0.002
NLR, median (IQR)	4.15 (2.52–7.03)	3.81 (2.40–6.70)	5.96 (3.44–8.60)	<0.001
Glucose, mmol/L, mean (SD)	7.15 (3.25)	8.05 (3.43)	7.88 (2.14)	0.578
Creatinine, μmol/L, mean (SD)	72.5 (35.57)	78.49 (36.75)	76.49 (28.90)	0.645
Uric acid, μmol/L, mean (SD)	345.00 (99.38)	354.40 (101.07)	358.21 (90.78)	0.753
APTT, s, mean (SD)	28.27 (4.78)	28.36 (4.97)	27.81 (3.67)	0.364
PT, s, mean (SD)	11.89 (3.07)	11.91 (3.32)	11.82 (0.93)	0.805
INR, mean (SD)	1.01 (0.27)	1.01 (0.29)	1.00 (0.08)	0.767
Fibrinogen, g/L, mean (SD)	2.88 (0.94)	2.89 (0.96)	2.83 (0.82)	0.620
Treatment after admission, n (%)				
Antiplatelet	461 (93.3)	394 (95.4)	67 (82.7)	<0.001
Anticoagulant	58 (11.7)	44 (10.7)	14 (17.3)	0.090
Lipid-lowering	468 (94.7)	395 (95.6)	73 (90.1)	0.055
Reperfusion therapy	57 (11.5)	42 (10.2)	15 (18.5)	0.032

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Total, N=494	Without HT, N=413	With HT, N=81	P
Imaging characteristics				
Infarct area >1/3MCA, n (%)	141 (28.5)	81 (19.6)	60 (74.1)	<0.001
Total EPVS, median [IQR]	4 [3–5]	4 [3–5]	4 [3–4]	0.001
BG-EPVS, median [IQR]	1 [1–2]	2 [1–2]	1 [1–2]	0.005
Moderate to severe BG-EPVS, n (%)	239 (48.4)	212 (51.3)	27 (33.3)	0.003
CS-EPVS, median [IQR]	2 [2–3]	2 [2–3]	2 [2–3]	0.019
Moderate to severe CS-EPVS, n (%)	435 (88.1)	368 (89.1)	67 (82.7)	0.105
Lacunes, n (%)	95 (19.2)	85 (20.6)	10 (12.3)	0.086
PWMH, median [IQR]	1 [0–2]	1 [0–2]	1 [0–1]	0.195
Extensive PWMH, n (%)	39 (7.9)	35 (8.5)	4 (4.9)	0.281
DWMH, median [IQR]	1 [0–1]	1 [0–1]	1 [0–1]	0.163
Extensive DWMH, n (%)	90 (18.2)	78 (18.9)	12 (14.8)	0.385
cWMH, median [IQR]	2 [0–3]	2 [1–3]	1 [0–2]	0.141
No cWMH (0), n (%)	128 (25.9)	103 (24.9)	25 (30.9)	0.287
Mild cWMH (1–2), n (%)	228 (46.2)	188 (45.5)	40 (49.4)	
Moderate cWMH (3–4), n (%)	96 (19.4)	86 (20.8)	10 (12.3)	
Severe cWMH (5–6), n (%)	42 (8.5)	36 (8.7)	6 (7.4)	
Total CSVD burden, median [IQR]	1 [0–1]	1 [0–2]	0 [0–1]	0.003
Score 0, n (%)	219 (44.3)	171 (41.4)	48 (59.3)	0.025
Score 1, n (%)	157 (31.8)	136 (32.9)	21 (25.9)	
Score 2, n (%)	83 (16.8)	75 (18.2)	8 (9.9)	
Score 3, n (%)	35 (7.1)	31 (7.5)	4 (4.9)	

[†]Platelet count was missing in 2 (0.4%) patients. HT, hemorrhagic transformation; TIA, transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of ORG 10,172 in Acute Stroke Treatment; NLR, neutrophil to lymphocyte ratio; APTT, activated partial thromboplastic time; PT, prothrombin time; INR, international normalized ratio; MCA, middle cerebral artery; BG-EPVS, basal ganglia enlarged perivascular spaces; CS-EPVS, centrum semiovale enlarged perivascular spaces; PWMH, periventricular white matter hyperintensity; DWMH, deep white matter hyperintensity; cWMH, total cerebral white matter hyperintensity; CSVD, cerebral small vessel disease; SD, standard deviation; IQR, interquartile range; reperfusion therapy refers to thrombosis and endovascular therapy.

were lower in patients with HT (all P<0.05). No significant difference was observed in moderate-to-severe CS-EPVS, lacunes, and WMH between patients with *vs.* without HT (all P>0.05) (*Table 1*). In the multivariate analyses, after adjusting for potential confounders, neither BG-EPVS nor CS-EPVS was significantly associated with HT (*Table 3*); whereas AF and infarct size >1/3 middle cerebral artery (MCA) were found to be the independent predictors of HT, which may increase HT risk by 2.5-fold and 7-fold, respectively (all P<0.05, data not shown).

In additional exploratory analysis, we investigated the relationship between "total CSVD burden" and HT. As shown in *Table 3*, after adjustment for covariates, no significant association of "total CSVD burden" with HT was found. We further explored the relationship between CSVD markers and the presence of PH, and the results showed that there were no remarkable differences in CSVD features between PH and non-PH group (Table S2).

Table 2 Univariate and multivariate associations of clinical risk factors and other CSVD markers with EPVS

Variables	Total EPVS (0–2 *vs.* 3–8)		BG–EPVS (0–1 *vs.* 2–4)		CS–EPVS (0–1 *vs.* 2–4)	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age	1.029 (1.007–1.051)	1.009 (0.982–1.037)	1.057 (1.040–1.073)	1.041 (1.017–1.066)	1.019 (0.999–1.039)	1.001 (0.974–1.028)
Male	0.916 (0.505–1.663)	1.112 (0.500–2.473)	1.074 (0.751–1.536)	1.274 (0.711–2.282)	1.022 (0.589–1.772)	1.071 (0.512–2.240)
Hypertension	2.304 (1.275–4.161)	1.704 (0.879–3.303)	3.677 (2.489–5.431)	2.174 (1.338–3.532)	1.712 (0.991–2.957)	1.145 (0.608–2.160)
Diabetes	1.120 (0.566–2.216)	0.832 (0.386–1.794)	1.743 (1.160–2.620)	0.917 (0.540–1.556)	1.272 (0.663–2.439)	1.310 (0.617–2.781)
Dyslipidemia	1.280 (0.525–3.125)	1.365 (0.539–3.456)	0.831 (0.503–1.373)	0.834 (0.448–1.553)	1.100 (0.499–2.426)	1.250 (0.523–2.988)
AF	1.107 (0.559–2.191)	0.974 (0.441–2.150)	0.667 (0.444–1.004)	0.570 (0.324–1.289)	1.128 (0.597–2.133)	1.204 (0.560–2.589)
Prior stroke/TIA	1.686 (0.695–4.088)	1.393 (0.521–3.723)	1.733 (1.087–2.763)	0.703 (0.383–1.289)	1.459 (0.666–3.193)	1.377 (0.575–3.298)
Smoking	0.731 (0.405–1.320)	0.625 (0.273–1.427)	0.999 (0.694–1.439)	1.014 (0.553–1.858)	0.848 (0.487–1.478)	0.678 (0.311–1.478)
Drinking	1.126 (0.557–2.275)	–	1.041 (0.689–1.575)	1.274 (0.680–2.386)	1.424 (0.714–2.840)	1.999 (0.854–4.677)
Lacunar stroke	1.088 (0.568–2.084)	0.830 (0.395–1.746)	2.639 (1.766–3.943)	1.968 (1.169–3.314)	0.950 (0.526–1.715)	0.662 (0.330–1.328)
BG-EPVS	–	–	–	–	3.822 (2.160–6.763)	4.349 (2.281–8.291)
CS-EPVS	–	–	2.056 (1.589–2.660)	2.474 (1.796–3.407)	–	–
PWMH	1.937 (1.311–2.862)	1.218 (0.676–2.194)	3.430 (2.654–4.434)	2.140 (1.441–3.176)	1.344 (0.980–1.844)	0.677 (0.395–1.162)
DWMH	2.385 (1.483–3.834)	2.012 (1.062–3.809)	3.140 (2.389–4.127)	1.363 (0.928–2.001)	1.565 (1.076–2.277)	1.495 (0.866–2.579)
Lacunes	1.094 (0.512–2.337)	0.497 (0.204–1.209)	2.973 (1.841–4.802)	1.377 (0.732–2.590)	0.924 (0.469–1.818)	0.536 (0.233–1.233)

The multivariate analyses adjusted for all covariates presented in the table. AF, atrial fibrillation; TIA, transient ischemic attack; CSVD, cerebral small vessel disease; BG-EPVS, basal ganglia enlarged perivascular spaces; CS-EPVS, centrum semiovale enlarged perivascular spaces; PWMH, periventricular white matter hyperintensity; DWMH, deep white matter hyperintensity; OR, odds ratio; CI, confidence interval.

Discussion

In the present study, we found that EPVS were common in patients with ischemic stroke, and EPVS in CS were more predominant than that in BG. After adjusting for potential covariates, total EPVS were independently associated with DWMH; CS-EPVS and BG-EPVS were interrelated; and BG-EPVS were significantly related to increasing age, hypertension, lacunar stroke, and PWMH. Regarding to their role in HT, the multivariate analyses showed that neither BG-EPVS nor CS-EPVS had an independent association with the occurrence of HT after ischemic stroke.

Our findings concerning the relationship of BG-EPVS with age, hypertension and WMH were consistent across different populations including lacunar stroke (28), intracerebral hemorrhage (12), and cognitive impairment (29). Besides, the stronger association between lacunar stroke and EPVS in BG than that in CS was similar to previous studies (3,30,31). However, none of any interested clinical-radiological factors (except for BG-EPVS) was identified to be independently associated with CS-EPVS. Some studies have indicated that the spatial distributions of EPVS may reflect distinct small arteriopathies such that BG-EPVS is likely caused by hypertensive arteriopathy (5,32), whereas CS-EPVS may be driven by cerebral amyloid angiopathy (4,32,33). The significant but weak correlation between BG and CS-EPVS supports such different pathophysiological mechanisms contributing to each EPVS distribution. Our results add to evidence on the association of EPVS with CSVD markers, suggesting that EPVS (particularly that in BG) are imaging manifestation of CSVD rather than incidental findings.

Several CSVD markers have been reported to associate with an increased risk of HT (15-17). However, studies

Table 3 Univariate and multivariate associations between EPVS and HT

Imaging variables	Unadjusted		Model 1		Model 2		Model 3	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Total EPVS	0.723 (0.589–0.887)	0.002	0.749 (0.581–0.965)	0.025	0.770 (0.593–1.000)	0.050	0.817 (0.617–1.081)	0.157
BG-EPVS	0.638 (0.454–0.897)	0.010	0.681 (0.448–1.037)	0.073	0.703 (0.459–1.078)	0.106	0.785 (0.499–1.235)	0.294
BG-EPVS (0–1 *vs.* 2–4)	0.474 (0.287–0.782)	0.003	0.571 (0.304–1.076)	0.083	0.595 (0.313–1.130)	0.113	0.674 (0.336–1.350)	0.265
CS-EPVS	0.690 (0.502–0.949)	0.022	0.720 (0.492–1.053)	0.090	0.752 (0.509–1.112)	0.153	0.784 (0.517–1.191)	0.254
CS-EPVS (0–1 *vs.* 2–4)	0.585 (0.304–1.125)	0.108	0.530 (0.242–1.160)	0.112	0.583 (0.262–1.300)	0.188	0.792 (0.334–1.879)	0.597
Total CSVD burden	0.669 (0.500–0.895)	0.007	0.721 (0.495–1.051)	0.089	0.725 (0.495–1.062)	0.099	0.813 (0.533–1.240)	0.337
Score 0	Reference		Reference		Reference		Reference	
Score 1	0.550 (0.314–0.863)	0.036	0.533 (0.267–1.064)	0.074	0.532 (0.264–1.072)	0.077	0.580 (0.275–1.224)	0.153
Score 2	0.380 (0.171–0.842)	0.017	0.423 (0.160–1.117)	0.082	0.398 (0.148–1.072)	0.068	0.451 (0.151–1.344)	0.153
Score 3	0.460 (0.155–1.366)	0.162	0.631 (0.164–2.435)	0.504	0.708 (0.184–2.729)	0.708	1.260 (0.287–5.524)	0.759

Model 1: adjusted for age, sex, stroke onset to admission time, AF, smoking, alcohol consumption, baseline NIHSS, systolic pressure, TOAST classification, platelet, NLR; Model 2: model 1+ treatment after admission; Model 3: model 2+ Infarct area >1/3MCA. HT, hemorrhagic transformation; BG-EPVS, basal ganglia enlarged perivascular spaces; CS-EPVS, centrum semiovale enlarged perivascular spaces; CSVD, cerebral small vessel disease; OR, odds ratio; CI, confidence interval.

focused on EPVS in the development of HT are rare. A previous study observed no significant relationship between EPVS and HT in ischemic stroke patients with AF and/or rheumatic heart disease (34), which was in line with the results of our present study. Nevertheless, another recent study, performed on 1386 patients with AF and recent TIA or ischemic stroke, found that BG-EPVS were associated with spontaneous intracranial hemorrhage occurred during follow-up (mean follow-up period 2.34 years) (35). Unlike the above study concentrated mainly on anticoagulant-related intracranial hemorrhage (median time from anticoagulation initiation to hemorrhage 272 days, IQR, 211–657 days) (35), we focused on acute hemorrhage following ischemic stroke (median time from stroke onset to hemorrhage 3.5 days, IQR, 2–6 days); in addition, variations in study population and ethnicities may be another explanation for the difference between our results and that of the above study.

CSVD features frequently occur together and focusing only on one or two individual CSVD markers while disregarding the others seems artificial. Recently, some researchers have proposed to calculate the total CSVD burden (22,23), which combines lacunes, WMH, CMB and EPVS to reflect the overall effect of small vessel injury. In this retrospective study, assessment of CMB was unavailable as susceptibility weighted imaging and gradient recalled echo sequences were not the routine MRI sequence for ischemic stroke patients in our hospital. Therefore, in our exploratory analysis, we only used lacunes, WMH and EPVS that can be available on routine MRI sequences to calculate the "total CSVD burden". Our results showed that the "total CSVD burden" was lower in patients with HT (*Table 1*). Further analysis found that the proportion of patients with infarct area >1/3 MCA decreased with the increasing of "total CSVD burden" (score 0 *vs.* 1 *vs.* 2 *vs.* 3: 37.0% *vs.* 25.5% *vs.* 19.3% *vs.* 11.4%, P=0.001). As the presence of CSVD may reflect the local chronic ischemia and hypoxia (36), we speculate that the coexistence of several CSVD markers may exert effects like those of ischemic preconditioning (37), improving the tolerance to subsequent ischemic injury and thus reducing the risk of HT. Furthermore, previous studies have found that the presence of other CSVD markers may weaken even reverse the effect of CMB on HT, making CMB exert protective rather than harmful effects (34). This finding further supports the underlying neuroprotective effect of CSVD markers. However, in the multivariate analysis incorporating clinical factors, there was no significant

relationship between "total CSVD burden" and HT, and only AF and infarct size >1/3MCA were found to be independently related to HT. In this study, as lack of CMB data, the impact of total CSVD burden on HT might be underestimated. Future prospective multicenter studies with large samples are needed to clarify the actual association between total CSVD burden and HT.

Our study has several limitations. First, this study was a retrospective analysis based on a single center stroke registry, and our data may not represent the overall Chinese population or other ethnicities. Second, potential selection bias may be introduced. Patients with MRI contraindications, with severe stroke unable to undergo MRI, and with poor image quality were excluded, which may bias the association between EPVS and HT. Third, CMB was not assessed in the present study, thus the relationship between EPVS and CMB was not explored, and the association between total CSVD burden and HT may also be underestimated. Finally, data about HT locations (lobar *vs.* deep/infratentorial) were not collected, and whether EPVS were associated with different sites of HT was unknown and required further investigation.

Conclusions

Our study found that EPVS were common in patients with ischemic stroke, and EPVS in BG and CS region were interrelated and had different risk factors. EPVS (particularly that in BG) were significantly associated with other CSVD markers. The presence or burden of EPVS was not associated with the risk of HT after ischemic stroke. More prospective multicenter studies are needed to confirm our results, and to explore the underlying mechanisms and clinical importance of EPVS.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Biomedical Research Ethics Committee of West China Hospital, Sichuan University (No. 2016-339), and conformed to the provisions of the Declaration of Helsinki (as revised in 2013). Since the study was a retrospective cohort, individual consent was waived.

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Supplementary

Table S1 Spearman's rank correlation coefficient among EPVS, lacunes, and WMH

	BG-EPVS	CS-EPVS
BG-EPVS	-	0.243*
Lacunes	0.237*	0.035
cWMH	0.526*	0.065
PWMH	0.515*	0.024
DWMH	0.450*	0.086

BG-EPVS: basal ganglia enlarged perivascular spaces; CS-EPVS: centrum semiovale enlarged perivascular spaces; cWMH: total cerebral white matter hyperintensity; PWMH: periventricular white matter hyperintensity; DWMH: deep white matter hyperintensity. *P<0.001.

Table S2 Imaging characteristics of patients with and without PH

Imaging characteristics	Without PHN=456	With PHN=38	P
Total EPVS, median (IQR)	4 (3-5)	4 (3-5)	0.407
BG-EPVS, median (IQR)	1 (1-2)	1 (1-2)	0.660
Moderate to severe BG-EPVS, n (%)	223 (48.9)	16 (42.1)	0.420
CS-EPVS, median (IQR)	2 (2-3)	2 (2-3)	0.324
Moderate to severe CS-EPVS, n (%)	401 (87.9)	34 (89.5)	0.984
Lacunes, n (%)	89 (19.5)	6 (15.8)	0.575
PWMH, median (IQR)	1 (0-2)	1 (0-1)	0.583
Extensive PWMH, n (%)	38 (8.3)	1 (2.6)	0.348
DWMH, median (IQR)	1 (0-1)	1 (0-1)	0.443
Extensive DWMH, n (%)	84 (18.4)	6 (15.8)	0.686
cWMH, median (IQR)			0.354
No cWMH, n (%)	119 (26.1)	9 (23.7)	
Mild cWMH, n (%)	206 (45.2)	22 (57.9)	
Moderate cWMH, n (%)	90 (19.7)	6 (15.8)	
Severe cWMH, n (%)	41(9.0)	1 (2.6)	
Total CSVD burden, median (IQR)	1 (0-1)	0 (0-1)	0.298
Score 0, n (%)	199 (43.6)	20 (52.6)	0.627
Score 1, n (%)	146 (32.0)	11 (28.9)	
Score 2, n (%)	79 (17.3)	4 (10.5)	
Score 3, n (%)	32 (7.0)	3 (7.9)	

PH: parenchymal hematoma; BG-EPVS: basal ganglia enlarged perivascular spaces; CS-EPVS: centrum semiovale enlarged perivascular spaces; PWMH: periventricular white matter hyperintensity; DWMH: deep white matter hyperintensity; cWMH: total cerebral white matter hyperintensity; CSVD: cerebral small vessel disease; IQR: interquartile range.

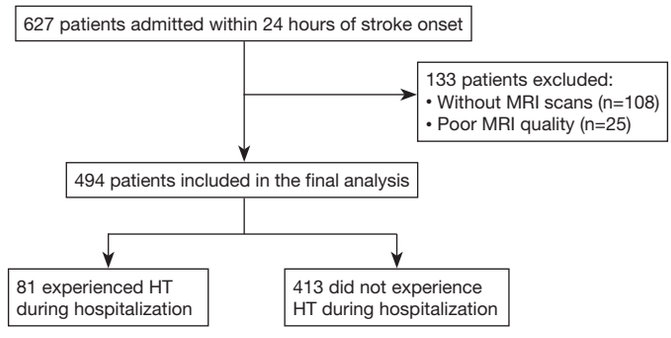

Figure S1 Flowchart of patients' enrollment.

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