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Prominent veins sign is associated with malignant cerebral edema after acute ischemic stroke

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ABSTRACT

Malignant cerebral edema (MCE) is often associated with severe physical disability and a high mortality rate. The current prediction of MCE is focused on infarct volume, and tools are relatively lacking. The prominent veins sign (PVS-SWI) is considered a marker of severely impaired tissue perfusion. This study aimed to determine whether PVS-SWI is associated with early-onset MCE. Patients with acute ischemic stroke (AIS) due to severe large arterial stenosis or occlusion (SLASO) from June 2018 to June 2020 were included. The ASPECTS score assessed the extent of PVS-SWI, and 4–10 was defined as a positive group. The primary outcome was MCE, defined as the deterioration of neurological function and midline structural excursions of >5 mm during hospitalization. The secondary outcomes included worsening of the NIHSS by ≥ 2 points, in-hospital death, and death within 1 year after stroke. Logistic regression was used to assess the correlation between PVS-SWI and outcomes. The study included 157 patients， 40 (25.5%) of whom developed MCE. PVS-SWI was more prevalent in patients who developed MCE (75.0% vs 45.3%; P = 0.001). In multivariate regression analysis, PVS-SWI was an independent predictor of MCE development in patients with larger infarct sizes (OR: 4.00， 95%CI: 1.54–10.35，p = 0.004). In patients with small infarct sizes, PVS-SWI was an independent predictor of a worsening NIHSS of ≥2(OR: 11.13， 95%CI: 2.26–54.89， p = 0.003) . However, PVS-SWI was not associated with death. The main finding of our study was that in patients with larger infarct sizes, a positive PVS-SWI increased the risk of developing MCE. In these patients, more interventions may be needed.

1. Introduction

Patients with acute ischemic stroke (AIS) caused by severe large arterial stenosis or occlusion (SLASO) often have a large cerebral infarction area and are prone to developing occupying cerebral edema within 2–3 days after the onset of symptoms, followed by midline shift, brain herniation, and increased neurological impairment, with a mortality rate of up to 80%, thus, this type of edema has been called malignant cerebral edema (MCE) [1–3]. Early MCE prediction can help in the selection and timing of interventions, such as decompressive craniectomy, to improve clinical outcomes and further reduce the burden of stroke-related disability [4]. Current

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predictions of MCE onset are mainly based on infarct volume after AIS, including EDEMA, DASH, and TURN prediction models, but the methods are relatively lacking and there is a need to find new imaging markers to improve prediction accuracy [2,5,6].

The prominent veins sign (PVS-SWI) demonstrated by magnetic susceptibility-weighted imaging (SWI) is considered to be a sign of severely impaired tissue perfusion. It is mainly characterized by a significant thickening of veins or an increased number of venous manifestations in one cerebral hemisphere compared to the contralateral hemisphere. Approximately 81% of AIS patients present with PVS-SWI [7]. PVS-SWI is related to the amount of deoxyhemoglobin in venous blood [8] and venous dilatation [9], indirectly reflecting the increased oxygen extraction fraction and hypoperfusion state. In previous studies, PVS-SWI was correlated with short-term functional outcomes, but its relationship with MCE outcome has not been systematically investigated [10].

The study primarily aimed to investigate the correlation between PVS-SWI and the onset of MCE in SLASO patients with AIS. We hypothesized that PVS-SWI could predict the occurrence of MCE early.

2. Methods

2.1. Patients

This was a retrospective case-control study with a population comprising patients attending the emergency stroke green channel at the neurology center of Beijing Tiantan Hospital, Capital Medical University, from June 1, 2018, to June 1, 2020. The study was conducted by the Declaration of Helsinki (1964) and received ethical approval from the hospital ethics committee (KY2022-125-02). Inclusion criteria were (1) AIS involving the unilateral hemisphere confirmed by diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC); (2) Severe unilateral stenosis or occlusion of the internal carotid artery or the M1 segment of middle cerebral artery; (3) cranial magnetic resonance imaging, including DWI, ADC, SWI, and three-dimensional time-of-flight magnetic resonance angiography (3D-TOF-MRA), performed within 36 h of onset. Exclusion criteria comprised (1) patients with poor quality or missing clinical and imaging information and (2) endovascular intervention after admission (endovascular intervention significantly changes hemodynamics and has a significant impact on the visualization of PVS-SWI. Previous studies have shown that PVS-SWI imaging is weaker in patients with intravascular recanalization [11]). Some of our patients were within the time window of endovascular intervention therapy, but due to their refusal to treat and potential underlying diseases, they did not receive endovascular intervention therapy.

2.2. Image acquisition

All patients underwent complete head CT after admission to exclude bleeding and evaluate thrombolysis indications (low density areas are based on head CT). MRI was performed within 36 h after the onset of AIS, and all patients with intravenous thrombolysis underwent MRI scans after thrombolysis. Scans were performed using a Discovery MR750 3.0T scanner (GE Healthcare, USA). DWI, ADC, SWI, and 3D-TOF-MRA were obtained with the following acquisition parameters. DWI (TR/TE = 2300/63.60 ms, b = 1000 s/mm^2, slice thickness = 5 mm, FOV = 240 mm, matrix = 128 × 128, and associated apparent diffusion coefficients were generated); SWI (TR/TE = 38.90/23.77 ms, flip angle = 15°, slice thickness/gap = 4/2 mm, number of slices = 60, matrix = 256 × 256, FOV = 240 mm); 3D-TOF-MRA (TR/TE = 19.00/1.80 ms,flip angle = 25°, FOV = 220 mm, matrix = 256 × 256, slice thickness = 1.2 mm). Minimum intensity projection images were reconstructed with a thickness of 5 mm, and phase, magnitude, minimum intensity

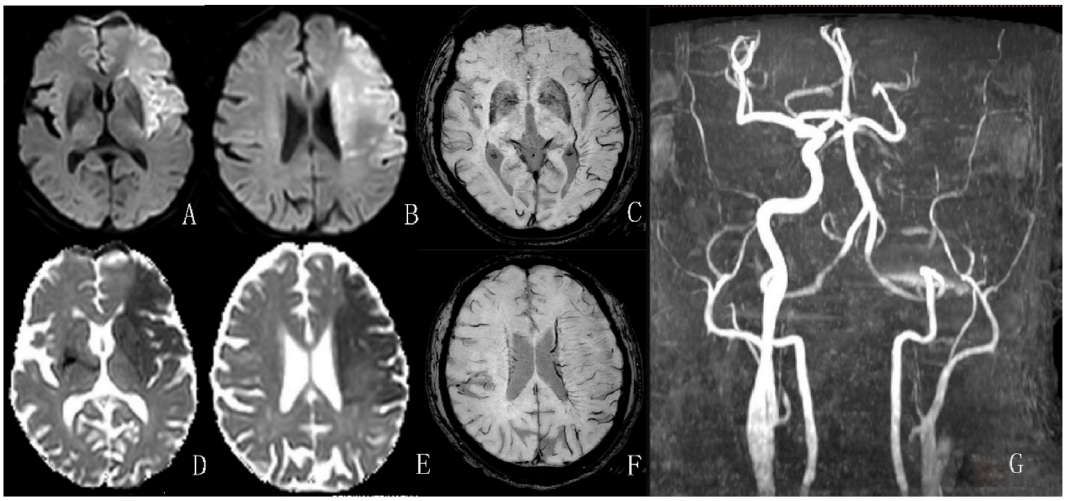

Fig. 1. A patient with prominent veins sign (PVS-SWI) on susceptibility-weighted imaging (C, F), and malignant cerebral edema. Diffusion-weighted imaging (A, B) and apparent diffusion coefficient (D, E) show a large area of infarction. Magnetic resonance angiography shows left internal carotid artery occlusion (G).

projection, and SWI (images were generated automatically).

2.3. Image analysis

The infarct extent on DWI was scored using the ASPECTS (ASPECTS-DWI) scoring system [12]. The infarct location was determined based on the ASPECTS system, and one point was subtracted for each area having a lesion, and the final total score was the requested ASPECTS-DWI score (Fig. 1-A, B, D, E).

PVS-SWI is defined as a significant thickening of veins or an increase in the number of veins visualized on SWI in the cerebral hemisphere on the side of AIS compared to the contralateral hemisphere (Fig. 1-C, F). The PVS-SWI was scored semi-quantitatively by the ASPECTS scoring system. A score of 1 was assigned for each significant vein hyposignal shadow compared to the contralateral side, and the final total score was the ASPECTS-PVS-SWI score. Based on the total score, we divided the PVS-SWI into positive and positive groups by the cut-off value at which sensitivity and specificity were at the highest level (Best cut-off value = sensitivity + specificity - 1).

We utilized 3D-TOF-MRA to assess SLASO. The warfarin-aspirin symptomatic intracranial disease (WASID) criteria were used to assess the intracranial vessels [13]. Arterial stenosis of >70% was defined as severe stenosis. Loss of blood flow signal in the arterial lumen was defined as intracranial large artery occlusion (Fig. 1-G).

2.4. Clinical outcomes

The primary outcome was MCE, defined as (1) a decrease in awareness to ≥ 1 point on item 1a of the NIH Stroke Scale (NIHSS) and an increase of ≥4 points on the NIHSS compared to baseline; (2) ≥ 5 mm horizontal shift of the septum as demonstrated by CT or MRI follow-up during the patient's hospitalization; or (3) brain swelling requiring hemicraniectomy for decompression or resulting in death [14–16]. The secondary outcomes included worsening of the NIHSS by ≥ 2 points, in-hospital death, and death within 1 year after stroke.

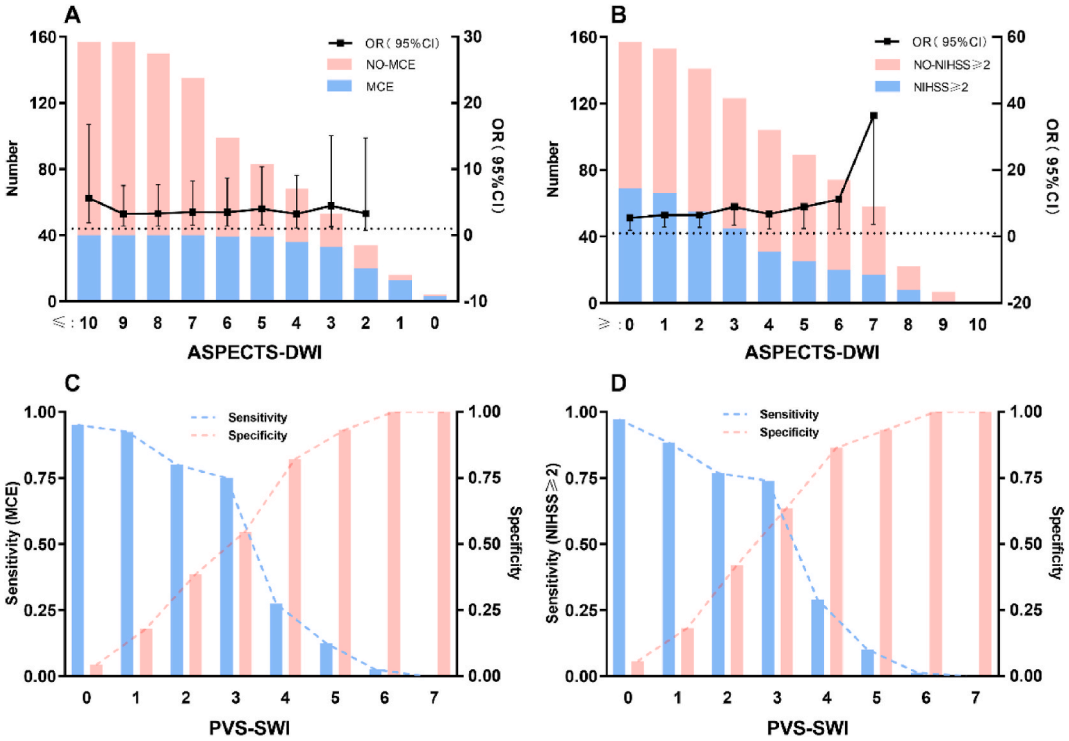

Fig. 2. FIGURE-A showed the number of patients with MCE and NO-MCE in the subgroup population for each 1-point decrease in ASPECTS-DWI, and the OR (95%CI) of PVS-SWI to MCE. FIGURE -B showed the number of patients with NIHSS≥2 and NO– NIHSS≥2 in the subgroup population for each 1-point increase in ASPECTS-DWI, and the OR (95%CI) of PVS-SWI to NIHSS≥2. FIGURE-C, D showed the division of PVS-SWI into two groups according to the best cut-off value: 0–3 for PVS-SWI negative group and 4–10 for PVS-SWI positive group. MCE: malignant cerebral edema; NIHSS: National Institutes of Health Stroke Scale; ASPECTS-DWI: scoring of infarct extent on diffusion-weighted imaging using the Alberta Stroke Program Early CT Score; PVS-SWI: prominent veins sign.

2.5. Subgroup analysis

We mainly conducted a subgroup analysis on the ASPECTS-DWI score. We divided patients into two groups: those with an ASPECTS-DWI score of <6 and those with an ASPECTS-DWI score of ≥6 because previous studies have considered the ASPECTS-DWI score of <6 as the threshold for delineation of large ischemic stroke [17]. Second, we performed subgroup analyses of admission NIHSS, smoking, and treatment modalities.

2.6. Statistical analysis

Continuous variables were expressed as means with standard deviations, ordinal variables as median values with interquartile ranges, and categorical variables as frequencies and percentages. Independent samples *t*-test or Mann-Whitney *U* test was used for continuous variables, and Fisher exact test or chi-square test was used for categorical variables. Logistic regression models were used to determine the correlation between PVS-SWI and MCE, and covariates were selected from those with P values < 0.05 in univariate analysis. The ratio (OR) and 95% confidence interval (CI) were expressed for the outcome and probability values. All statistical tests were two-sided, and P values < 0.05 were considered significant. All statistical analyses were performed using IBM SPSS Statistics 23 software and GraphPad Prism (GraphPad Software).

2.7. Quality control

Imaging features were interpreted by 2 trained neurologists, and PVS-SWI was scored before ASPECTS-DWI to avoid reading bias. When the interpretation results were inconsistent, an agreement was reached by conference.

3. Results

There were 157 patients included in the study, 111 (70.7%) of whom were male with a median age of 69.0 (59.5–78.0) years. There was a median delay of 5.7 (4.1–9.6) hours between the onset of symptoms and the MRI examination, the median NIHSS score on arrival was 12 (8–17), and the median ASPECTS-DWI score was 5 (3–7). 74 (47.1%) patients were treated with intravenous thrombolysis and 83 (52.9%) patients had positive PVS-SWI (According to the best cut-off value, PVS-SWI was divided into two groups: 0–3 as the PVS-SWI-negative group and 4–10 as the PVS-SWI-positive group, Fig. 2-C, D). 40 (25.5%) patients presented with MCE and 19 (12.1%) died while in the hospital, 13 (68.4%) of them due to MCE and 6 (31.6%) due to other causes. 41 (29.3%) patients died within 1 year of stroke onset, and 17 (10.8%) patients lost in follow-up (Table 1).

Compared with the no-MCE group, the MCE group had a higher NIHSS on arrival (16 vs. 11, $p < 0.001$), a lower ASPECTS-DWI score (2.5 vs. 6, $p < 0.001$), fewer smokers (15.0% vs. 35.0%, $p = 0.017$) and the proportion of patients positive for PVS-SWI was higher (75.0% vs. 45.3%, $p = 0.001$, Table 1). Compared with the PVS-SWI negative group, the PVS-SWI positive group had a higher incidence of MCE (36.1% vs 13.5%, $p = 0.001$) and fewer smokers (22.9% vs. 37.8%, $p = 0.041$).

Multivariate logistic regression showed that PVS-SWI was an independent risk factor for MCE (OR: 5.59, 95% CI: 1.87–16.75, $p = 0.002$; Table 2). In the subgroup analysis of ASPECTS-DWI, multifactorial logistic regression showed that PVS-SWI was associated with MCE in the ASPECTS-DWI <6 group (OR: 4.00, 95% CI: 1.54–10.35, $p = 0.004$). However, in the ASPECTS-DWI ≥6 group, PVS-SWI was not associated with MCE. Statistically, there was no significant interaction between the two groups ($p = 0.336$). Fig. 2-A showed

Table 1
Clinical characteristics of the study population and comparisons of variables between patients with and without MCE.

variables	All N = 157	No-MCE n = 117	MCE n = 40	P Value
Male, n (%)	111 (70.7)	84 (71.8)	27 (67.5)	0.606
Age(y), median (IQR)	69.0 (59.5–78.0)	69.0 (59.0–77.0)	71.0 (62.3–81.8)	0.487
Time to MRI (h), median (IQR)	5.7 (4.1–9.6)	5.9 (4.2–10.7)	5.2 (3.5–6.8)	0.118
NIHSS, median (IQR)	12 (8–17)	11 (6–16)	16 (12–19.8)	<0.001
SBP, median (IQR)	151.0 (132.0–168.5)	154.0 (132.0–170.0)	145.0 (131.8–163.0)	0.526
DBP, median (IQR)	85.0 (76.0–97.0)	86.0 (76.5–99.0)	84.0 (75.3–93.8)	0.416
Hypertension, n (%)	94 (59.9)	69 (59.0)	25 (62.5)	0.695
Diabetes, n (%)	39 (24.8)	31 (26.5)	8 (20.0)	0.412
Hyperlipidemia, n (%)	11 (7.0)	6 (5.1)	5 (12.5)	0.223
Atrial fibrillation, n (%)	37 (23.6)	25 (21.4)	12 (30.0)	0.267
CHD, n (%)	24 (15.3)	18 (15.4)	6 (15.0)	0.953
Previous stroke, n (%)	38 (24.2)	29 (24.8)	9 (22.5)	0.771
Smoking, n (%)	47 (29.9)	41 (35.0)	6 (15.0)	0.017
ASPECTS-DWI, median (IQR)	5 (3–7)	6 (4–7)	2.5 (1–3)	<0.001
PVS-SWI, n (%)	83 (52.9)	53 (45.3)	30 (75.0)	0.001
IVT, n (%)	74 (47.1)	59 (50.4)	15 (37.5)	0.157

MCE: malignant cerebral edema; MRI: magnetic resonance imaging; NIHSS: National Institutes of Health Stroke Scale; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; ASPECTS-DWI: scoring of infarct extent on diffusion-weighted imaging using the Alberta Stroke Program Early CT Score; PVS-SWI: prominent veins sign; CHD: Coronary heart disease; IVT: intravenous thrombolysis.

Table 2
Univariate and multivariate regression analysis of clinical and imaging outcome.

Outcome	N	PVS, n (%)	Univariate OR (95%Cl)	*P*-value	Multivariate OR (95%Cl)	*P*-value
MCE	40	30 (75.0)	3.62 (1.62–8.07)	0.002	5.59 (1.87–16.75)	0.002
NIHSS≥2	69	51 (73.9)	4.96 (2.49–9.90)	<0.001	7.48 (3.13–17.90)	<0.001
DEATH[1]	19	13 (68.4)	2.11 (0.76–5.86)	0.154	1.98 (0.65–6.04)	0.230
DEATH[2]	41	26 (63.4)	1.92 (0.91–4.05)	0.088	2.19 (0.94–5.09)	0.068

MCE: malignant cerebral edema; NIHSS≥2: worsening of the National Institutes of Health Stroke Scale by ≥ 2 points; PVS-SWI: prominent veins sign; DEATH[1]: in-hospital death. DEATH[2]: death within 1 year after stroke.

the number of patients with MCE and NO-MCE at decreasing ASPECTS-DWI scores and the ratio of PVS-SWI to MCE. In the subgroup analysis of treatment mode and smoking, multifactorial logistic regression analysis showed that PVS-SWI remained associated with MCE (Table 3).

Multivariate logistic regression showed that PVS-SWI was an independent risk factor for worsening of the NIHSS by ≥ 2 points (OR: 7.48, 95% CI: 3.13–17.90, $p < 0.001$; Table 2). In the subgroup analysis of admission NIHSS and ASPECTS-DWI, multifactorial logistic regression showed that PVS-SWI was associated with the worsening of the NIHSS by ≥ 2 points (Table 4). Fig. 2-B showed the number of patients with NIHSS≥2 and NO– NIHSS≥2 at increasing ASPECTS-DWI scores and the ratio of PVS-SWI to worsening of the NIHSS by ≥ 2 points. However, PVS-SWI was not associated with in-hospital death and death within 1 year after stroke (OR: 1.98, 95% CI: 0.65–6.04, $p = 0.230$; OR: 2.19, 95% CI: 0.94–5.09, $p = 0.068$) (Table 2).

4. Discussion

In this study, we investigated the impact of PVS-SWI on MCE occurrence. Our study found that PVS-SWI may increase the risk of MCE development in AIS patients with large infarct sizes. We speculate that it may be related to the following mechanisms. The level of deoxyhemoglobin in venous blood and the degree of vasodilation determines the degree of visualization of SWI veins [8,9]. The increase in deoxyhemoglobin content depends on brain tissue oxygen uptake fraction [18] and blood flow velocity [19]. The degree of venous vasodilation is associated with the dilation of small arteries and resistance vessels after stroke, compensating for decreased cerebral perfusion pressure and maintaining a relatively constant brain volume [20]. Insufficient blood perfusion to brain tissue after AIS causes dilatation, slow blood flow in the draining veins, and an increase in the deoxyhemoglobin/oxygenated hemoglobin ratio, leading to the appearance of PVS-SWI on SWI. The higher the degree of large vessel stenosis and the poorer the degree of brain tissue perfusion, the higher the rate of PVS-SWI [21]. In other words, significant PVS-SWI is related to severe hypoperfusion of the brain, larger infarct volume, and faster expansion of core infarct foci [22–24]. Previous studies have suggested that a decrease in arterial blood flow may affect venous return [25]. At the same time, significant venous vasodilatation associated with PVS-SWI leads to impaired venous return and increased venous pressure, which allows fluid extravasation into the perivascular space and ultimately leads to the development of MCE [26].

Previous studies have shown that PVS-SWI is related to poor floppy meningeal collateral circulation [27]. Interestingly, in our univariate analysis, the prevalence of smoking was significantly lower in patients with MCE than in those without MCE. At the same time, the proportion of smoking was significantly lower in PVS-SWI-positive patients than in PVS-SWI-negative patients. This may be due to long-term smoking leading to physiological and pathological collateral circulation formation [28], while better collateral

Table 3
Univariate and multivariate correlation analysis in the subgroup analysis of MCE.

Variable	N	MCE， n (%)	Univariate OR (95%Cl)	P	Multivariate OR (95%Cl)	P	Interaction p*
Admission NIHSS							
<16	103	18 (17.5)	4.13 (1.26–13.57)	0.020	4.70 (0.97–22.76)	0.055	0.685
≥16	54	22 (40.7)	3.43 (1.06–11.04)	0.039	10.60 (1.79–62.78)	0.009	
SMOKING							
Yes	47	6 (12.8)	9.64 (1.03–90.76)	0.048	34.15 (1.19–981.62)	0.039	0.341
No	110	34 (30.9)	2.64 (1.09–6.38)	0.032	4.50 (1.32–15.39)	0.016	
TREATMENT MODE							
Thrombolytic	74	15 (20.3)	4.74 (1.21–18.56)	0.025	9.04 (1.19–68.81)	0.033	0.108
Conservative	83	25 (30.1)	3.17 (1.15–8.73)	0.026	5.87 (1.23–28.01)	0.026	
ASPECTS-DWI							
≥6	73	1 (1.4)	–	0.998	–	0.998	0.336
<6	83	39 (47.0)	4.19 (1.64–10.69)	0.003	4.00 (1.54–10.35)	0.004	
<5	68	36 (52.9)	3.34 (1.22–9.18)	0.019	3.22 (1.140–9.08)	0.027	
<4	53	33 (62.3)	4.69 (1.42–15.53)	0.011	4.43 (1.30–15.07)	0.017	
<3	34	20 (58.8)	3.34 (0.80–13.94)		3.28 (0.73–14.68)	0.120	
<2	16	13 (81.2)	–	0.999	–	0.998	
<1	4	3	–	1.000	–	1.000	

MCE: malignant cerebral edema; NIHSS: National Institutes of Health Stroke Scale; ASPECTS-DWI: scoring of infarct extent on diffusion-weighted imaging using the Alberta Stroke Program Early CT Score; *Adjusted for covariates: Admission NIHSS, Smoking, ASPECTS-DWI, PVS-SWI.

Table 4
Univariate and multivariate correlation analysis in the subgroup analysis of NIHSS≥2.

Variable	N	MCE ， n (%)	Univariate OR (95%Cl)	P	Multivariate OR (95%Cl)	P	Interaction p*
Admission NIHSS							
<16	103	35 (34.0)	4.39 (1.78–10.79)	0.001	5.13 (1.78–14.78)	0.002	0.079
≥16	54	34 (63.0)	8.33 (2.35–29.58)	0.001	23.14 (3.79–141.47)	0.001	
ASPECTS-DWI							
<6	83	49 (59.0)	4.58 (1.80–11.70)	0.001	7.44 (2.39–23.17)	0.001	0.846
≥6	74	20 (27.0)	6.80 (1.99–23.20)	0.002	11.13 (2.26–54.89)	0.003	
≥7	58	17 (29.3)	10.05 (2.45–41.16)	0.001	36.38 (3.64–363.73)	0.002	
≥8	22	8 (36.4)	5.40 (0.78–37.51)	0.088	–	0.413	
≥9	7	1 (14.3)	–	0.999	–	–	
≥10	0	0 (0)	–	–	–		

NIHSS≥2: worsening of the National Institutes of Health Stroke Scale by ≥ 2 points; ASPECTS-DWI: scoring of infarct extent on diffusion-weighted imaging using the Alberta Stroke Program Early CT Score; *Adjusted for covariates: Sex, Age, Admission NIHSS, Smoking, ASPECTS-DWI, PVS-SWI, Atrial fibrillation.

circulation may reduce the occurrence of PVS-SWI and MCE [29]. However, in the multifactorial analysis, smoking was not associated with the risk reduction of MCE, although there was some tendency to do so (OR: 0.34, 95% CI: 0.10–1.21, $p = 0.095$). Based on these findings, it appears PVS-SWI may be an effective marker to evaluate the status of collateral circulation and the occurrence of MCE, which can better evaluate AIS patients with the potential risk of MCE and provide opportunities to improve the prognosis.

Previous studies have found that patients with larger infarct volumes after stroke are prone to develop MCE [30], which is consistent with our findings (OR: 0.42, 95% CI: 0.31–0.57, $p < 0.001$). Although in baseline, NIHSS scores were significantly higher in patients with MCE than in those without MCE. However, in the multifactorial analysis, NIHSS scores were not correlated with MCE (OR: 0.99, 95% CI: 0.90–1.08, $p = 0.779$). This may be due to the high correlation between NIHSS score and ASPECTS-DWI ($r = -0.532$, $P < 0.001$). However, no covariates were found among the covariates including NIHSS. In addition, previous studies have suggested that women, of younger age and not receiving intravenous thrombolytic therapy may be independent risk factors for MCE, possibly associated with hormone levels, brain volume, and population differences [30,31]. However, similar results were not obtained in our study, and this difference may be related to the larger proportion of males, older mean age, and larger infarct volume in our included population.

Regarding PVS-SWI, the latest quantitative meta-analysis included 16 cohort studies involving a total of 1605 patients, of which 11 studies concluded that the presence of PVS-SWI was related to poor prognosis in AIS, and 5 studies suggested no significant association. The meta-analysis showed that PVS-SWI was related to a poor 90-day functional prognosis and was more likely to show early neurological deterioration [10]. Unfortunately, this meta-analysis did not explore the correlation between PVS-SWI and malignant cerebral edema events, probably due to the lack of previous relevant studies. This study provided some innovative data by analyzing the correlation of PVS-SWI with MCE.

However, there were some limitations to the study. First, this was a retrospective case-control study with a potential risk of selection bias. Second, the relationship between PVS-SWI and collateral circulation was not discussed because 3D-TOF-MRA performed poorly in assessing collateral circulation, and digital subtraction angiographic assessment was not refined. Additionally, due to imaging data incompleteness, we did not assess the change in the extent of PVS-SWI before and after treatment and the increase in infarct volume on DWI, which may be the main determinant of prognosis that was not included in our analysis. Another limitation is that we did not perform a follow-up of long-term clinical outcomes to predict long-term prognostic outcomes.

5. Conclusion

A major finding of our study was that PVS-SWI was an independent predictor of MCE in AIS patients with large infarct sizes. Our study may improve clinical outcomes for patients at risk of potential MCE by assisting in the selection of patients for decompression and debridement more precisely [32].

Ethics approval

The study was conducted by the Declaration of Helsinki (1964) and received ethical approval from the hospital ethics committee (KY2022-125-02).

Informed consent

All patients have signed informed consent.

Author contribution statement

Ping Lu: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Lingyun Cui: Analyzed and interpreted the data; Wrote the paper.

Xingquan Zhao: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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