Original Article

Venous collaterals in acute ischemic stroke patients after endovascular treatments: a novel scoring system using 4D computed tomography angiography

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Background: To establish a novel cortical venous collateral score based on four-dimensional computed tomography angiography (4D CTA) and to assess the relationship between the score and clinical outcomes in patients with acute ischemic stroke (AIS) after endovascular treatments (EVTs).

Methods: This was a retrospective case-control study designed to evaluate all consecutive patients with large vessel occlusion in unilateral anterior circulation who underwent EVTs at a single institution. Two independent neuroradiologists evaluated venous collaterals using different venous collateral scores: a cortical venous collateral score based on 4D CTA (4D-VCS), the prognostic evaluation based on cortical vein score difference in stroke (PRECISE) score, and the cortical vein opacification score (COVES). Spearman correlation analysis was used to analyze the correlation of different venous collateral scoring systems with final infarct volume (FIV), modified Rankin Scale (mRS) score, and artery collateral score. Multivariate logistic regression analysis was used to identify the prognostic value of each model. The areas under the curve (AUC) of the receiver operating characteristic (ROC) curve of the 6 models were compared by the DeLong test.

Results: A total of 107 patients were enrolled in the study. The AUC of 4D-VCS was 0.92 [95% confidence interval (CI): 0.85 to 0.96; P<0.0001]. The 4D-VCS was highly correlated with FIV (r=–0.615; 95% CI: –0.737 to –0.473; P<0.001), mRS score (r=–0.706; 95% CI: –0.789 to –0.602; P<0.001), and arterial collateral score (r=0.769; 95% CI: 0.678 to 0.838; P<0.001). There were statistically significant differences between model 1 (AUC, 0.89; 95% CI: 0.81 to 0.94) and model 2 (AUC, 0.94; 95% CI: 0.88 to 0.98) (P=0.025), model 1 (AUC, 0.89; 95% CI: 0.81 to 0.94) and model 3 (AUC, 0.93; 95% CI: 0.87 to 0.97) (P=0.045), model 1 (AUC, 0.89; 95% CI: 0.81 to 0.94) and model 6 (AUC, 0.95; 95% CI: 0.89 to 0.98) (P=0.011), and model 2 (AUC, 0.94; 95% CI: 0.88 to 0.98) and model 5 (AUC, 0.89; 95% CI: 0.82 to 0.94) (P=0.032).

Conclusions: The findings of this study suggested that 4D-VCS, a novel measurement of venous enhancement based on 4D CTA, may be accurately used to identify AIS patients with high risk of poor clinical outcome after EVTs.

Keywords: Brain ischemia; collateral circulation; computed tomography; angiography; ischemic stroke

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Introduction

Vascular neuroimaging plays a decisive role in the determination of the optimal therapeutic method for patients with acute ischemic stroke (AIS). A recently published meta-analysis found that arterial cerebral collaterals were significantly associated with clinical and safety outcomes, albeit with a prognostic accuracy range of 48% to 66% (1). The effect of the venous collaterals, compared to that of the arterial collaterals, in patients with AIS has not been thoroughly elucidated (2,3). The venous system has traditionally been considered to play a secondary role in the microcirculation of ischemic brain tissues, but the venous system may actually have crucial effects on cerebral blood flow under both normal and pathological conditions. The cerebral venous system comprises about 70% of the total cerebral blood volume (CBV) and plays a pivotal role in oxygen exchange (4). Physiologically, the alternation of venous drainage can indicate a change of cerebral perfusion and the optimization of the oxygen uptake mechanism (5). Available evidence suggests that there may be a putative link between venous collaterals and long-term clinical outcome in patients with AIS who have undergone reperfusion therapy (4,6-11). The venous status may reflect the comprehensive state of blood flow compensation and tissue perfusion through the collateral branch of the microcirculation. Although previous research has emphasized the potential supplementary role of venous collaterals during the clinical decision-making process of AIS, the following problems remain: (I) the commonly used scoring methods for evaluating venous collateral circulation, such as prognostic evaluation based on cortical vein score difference in stroke score (PRECISE) (12) and cortical vein opacification score (COVES) (13), are mainly based on single-phase computed tomography angiography (sCTA), which may lose some vascular information and result in underestimation; (II) the published venous collateral studies based on four-dimensional computed tomography angiography (4D CTA) have mostly focused on the analysis of regional abnormal features of venous drainage and have not proposed a comprehensive venous collateral scoring method; and (III) most studies have targeted patients with intravenous thrombolysis. In the context of the extensive application of endovascular treatments (EVTs) for AIS, it is necessary to evaluate the correlation between venous collateral status and clinical outcome in AIS patients who have undergone EVTs.

This study aimed to establish a novel cortical venous collateral score based on 4D CTA (4D-VCS) to comprehensively assess the status of cortical venous collateral circulation in patients with AIS, and to evaluate the predictive efficacy of this method for the clinical outcome of AIS patients after EVTs. We present the following article in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-22-245/rc).

Methods

Study population

This was a retrospective case-control study. The data of all patients with AIS in the emergency department of Beijing Hospital who received EVTs from March 2016 to August 2021 were analyzed, including patients who met the criteria for intravenous thrombolysis and received recombinant tissue plasminogen activator (rtPA) treatment before EVTs (*Figure 1*).

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Institutional Review Board of Beijing Hospital approved the study, and individual consent for this retrospective analysis was waived.

The inclusion criteria were as follows: (I) age ≥18 years old; (II) patients underwent EVTs within 24 hours after symptom onset; and (III) one-stop 4D CTA-CT perfusion (CTP) examination revealed large vessel occlusion of the unilateral anterior circulation. The exclusion criteria were as follows: (I) non-contrast CT scan (NCCT) revealed intracranial hemorrhage or subarachnoid hemorrhage; (II) previous large cerebral infarction of the ipsilateral cerebral hemisphere (infarct size equal to or larger than two-thirds of the middle cerebral artery territory); (III) moderate/

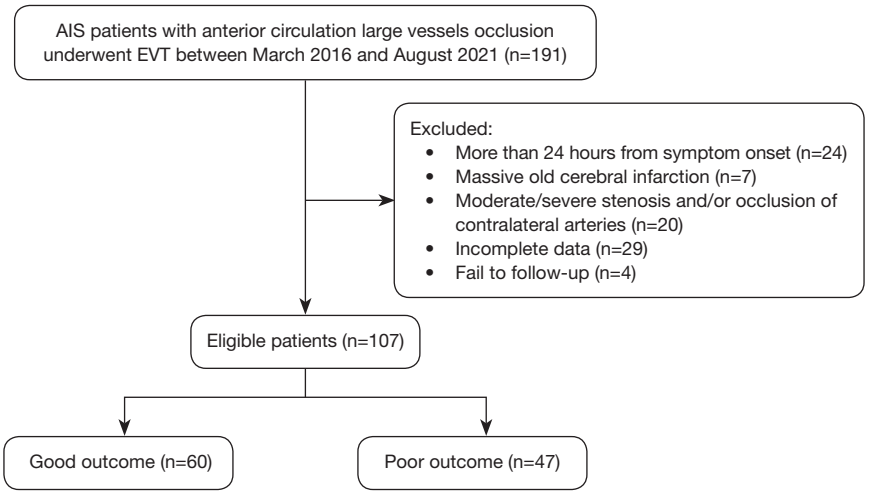

Figure 1 Flowchart of patient selection. AIS, acute ischemic stroke; EVT, endovascular treatment.

severe stenosis and/or occlusion of the contralateral arteries; and (IV) incomplete clinical, laboratory, or imaging data.

Imaging protocols

All patients underwent NCCT to exclude intracranial hemorrhage (scan parameters: 80 kV/200 mAs/detector and 0.5×80/volume scan). Then, one-stop whole-brain dynamic volume 4D CTA-CTP examinations (Aquilion ONE, Canon Medical Systems, Otawara, Japan) were performed using a 320×0.5 mm detector row CT. Non-ionic iodinated contrast medium (0.6 mL/kg; Iopamidol, Braccosine, Shanghai, China) was injected intravenously followed by 30 mL saline with a 2-channel high-pressure injector. A dynamic volume perfusion scan was performed (scan parameters: 80 kV, 100 mAs, coverage area of 160 mm, layer thickness of 0.5 mm) 7 s after contrast injection.

Venous collateral scoring methods

All CTA images were anonymized and reviewed independently at the same workstation by two experienced neuroradiologists who were blinded to the cases' clinical information and follow-up imaging information. The vascular images of each patient were evaluated for venous collaterals according to the following 3 criteria.

PRECISE (12)

The veins included for the assessment were the superficial anastomotic veins [superficial middle cerebral vein (SMCV), vein of Trolard (VOT), and vein of Labbé (VOL)] and the basal vein of Rosenthal (BVR). The veins were scored based on sCTA (the phase in which the artery had peak CT value was selected as the arterial phase from the 19 phases to generate images of sCTA for each patient). A score of 0, 1, or 2 was given for absent, partial, or full constitution, respectively. "Absent" was defined as a vascular contrast density lower than 100 HU; "Partial" was defined as a contrast density higher than 100 HU, but lower than that of the contralateral hemisphere; "Full" was defined as a contrast density comparable to the corresponding vein in the contralateral hemisphere on visual analysis.

COVES (13)

The VOL, sphenoparietal sinus, and SMCV were quantified on sCTA as follows: 0, not visible; 1, moderate opacification; and 2, full opacification.

4D-VCS

The veins included for evaluation were SMCV, sphenoparietal sinus, VOT, and VOL. These veins were chosen because they account for almost all venous drainage in the middle cerebral artery territory and show limited anatomical variability when compared to other cortical veins. Each vein was graded on a scale from 0 to 4 along the time shaft: a score of 0 indicated absent collateral vessels in the ischemic area in any phase; a score of 1 indicated partial collateral vessels were revealed until the late venous phase; a score of 2 indicated partial collateral vessels in the venous phase, and no changes until the late venous phase; a score of 3 indicated full venous vessels until the late venous phase (regardless of whether partial collateral vessels were revealed

in the venous phase or not); and a score of 4 indicated full venous vessels in the venous phase. The 4D-VCS ranged from 0 (no opacification of the 4 venous pathways) to 16 (full opacification of the 4 venous pathways). "Absent" was defined as a vascular contrast density lower than 100 HU. "Full" was defined as a contrast density comparable to that of the corresponding vein in the contralateral hemisphere on visual analysis. "Partial" was defined as a contrast density higher than 100 HU but lower than that of the contralateral hemisphere. According to the time density curve (TDC), the venous phase was defined as the peak of the venous curve and the late venous phase was defined as the phase after the peak of the venous curve (*Figures 2*,*3*).

Other imaging parameters analysis

For the arterial collateral vessels, we used the modified collateral circulation scoring system on 4D CTA with a range of 0 to 4 (14): 0 points indicated no or few collateral vessels (<50% flow of the normal side) in the ischemic area in any phase; 1 point indicated partial arterial collaterals (between 50% and 100% flow of the normal side) until the late venous phase; 2 points indicated partial arterial collaterals (between 50% and 100% flow of the normal side) before the venous phase; 3 points indicated complete arterial collaterals (≥100% flow of the normal side) in the late venous phase (regardless of whether partial collateral vessels were found before the venous phase or not); and 4 points indicated that complete collateral circulation (≥100% flow of the normal side) was found before venous phase.

The dynamic progression of the internal cerebral vein (ICV) was categorized into 3 types (11): type 1 ICV progression was defined as ipsilateral ICV showing less opacification than the asymptomatic side; type 2 was defined as ipsilateral ICV showing equal opacification to the asymptomatic side; and type 3 was defined as ipsilateral ICV showing more opacification than the asymptomatic side.

The Alberta stroke program early CT score (ASPECTS; a 10-point scale grading system) was used to evaluate early ischemic changes of the brain parenchyma on NCCT (15).

Vitrea (Vital Images, Minnetonka, MN, USA) was used to perform all the CTP analyses. The TDCs for the input artery and output vein were obtained from the internal carotid artery in the normal side and superior sagittal sinus, respectively. A 38% reduction in CBV with a 5.3-s increase of time to peak (TTP) indicated infarct core (IC), and a 5.3-s increase of TTP without CBV reduction indicated ischemic penumbra (IP). The mismatch ratio (MMR) was the IP volume divided by the IC volume (16).

Clot burden score (CBS) was scored based on maximum intensity projection, which has been described by Wei *et al.* (17).

Clinical data collection

The following information was collected: (I) the National Institutes of Health Stroke Scale (NIHSS; scale ranged from 0 to 42 points); (II) general data, including age and gender; (III) the risk factors of cerebrovascular disease; and (IV) the type of stroke, which was determined based on Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification (18).

Outcomes

Recanalization of the occluded artery was evaluated on the final digital subtraction angiography and classified according to the modified Thrombolysis In Cerebral Ischemia (mTICI) score. Successful recanalization was defined as mTICI grade ≥2b. The modified Rankin Scale (mRS) was used to evaluate the patients' clinical outcome after 3 months. The patients were regarded as having a good clinical outcome if the mRS score was <2 and a poor clinical outcome if the mRS score was ≥3 (19). Final infarct volume (FIV) was defined on NCCT or magnetic resonance imaging (MRI) after 2–7 days.

Statistical analysis

Continuous variables were described as median (interquartile range) for skewed data, and categorical data were represented as a frequency distribution. Mann-Whitney U, Pearson's chi-square, and Fisher's exact tests were used to compare the baseline information between the good and poor outcome groups. All patients were assessed twice by each observer independently. Interobserver agreement was described by the intraclass correlation coefficient (ICC). Spearman's correlation analysis was used to analyze the correlation of different venous collateral scoring systems with FIV, mRS score, and artery collateral score. Receiver operating characteristic (ROC) curves of different venous collateral scoring systems were used to analyze the sensitivity and specificity of the outcome evaluation. Multivariate logistic regression analysis of baseline clinical characteristics and collateral scores was used to identify each model's prognostic value. A total of 6 models were developed: (I) clinical information [age, NIHSS, thrombus location, atrial

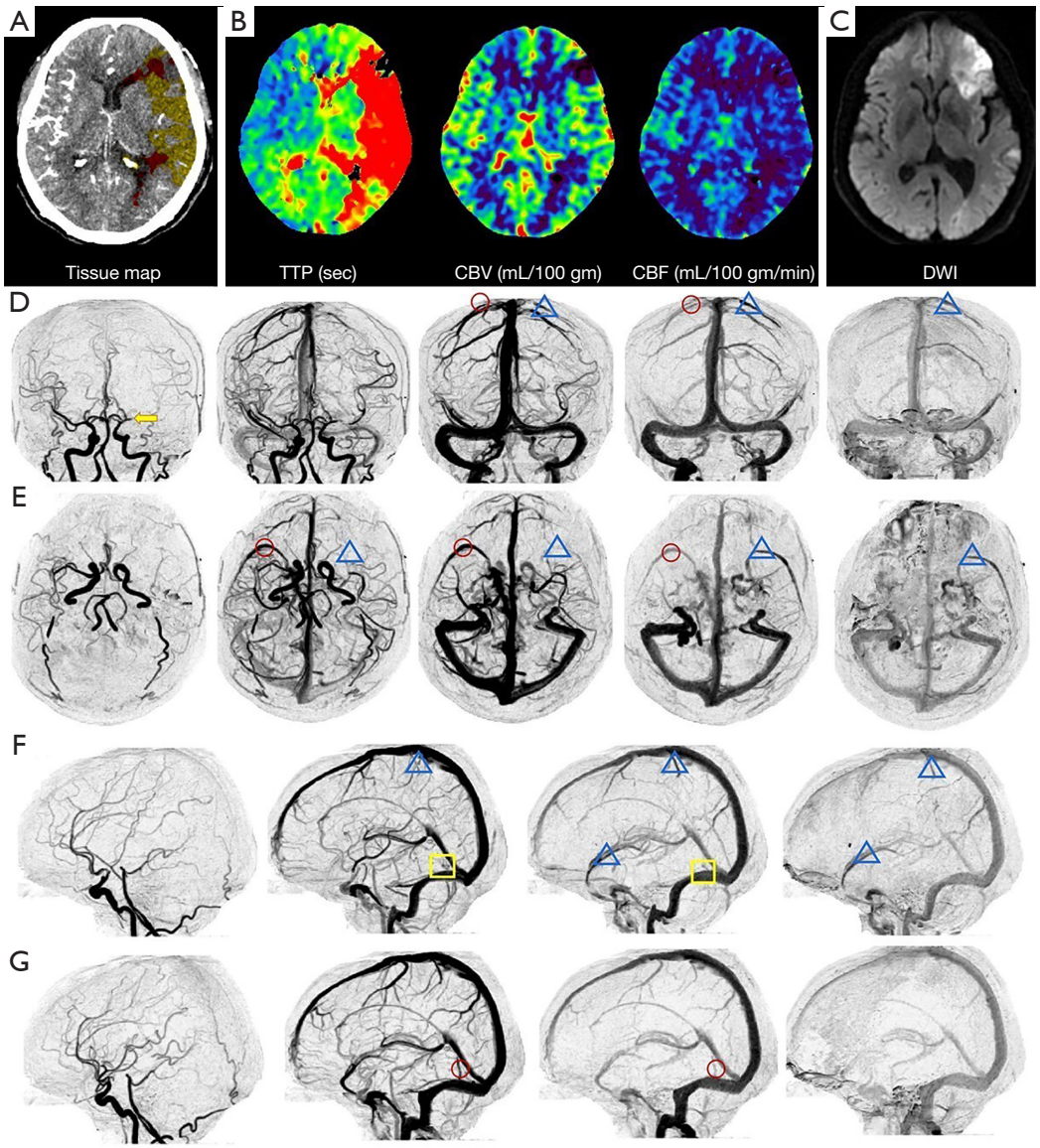

Figure 2 Good collateral case. An adult patient suddenly experienced a deviated mouth, inarticulate speech, and an inability to lift the right arm for 6 hours. This patient had an initial NIHSS score of 9 and an mRS score of 0 after 3 months. Tissue map showing an IC area (red) of 25.27 mL and an IP area (yellow) of 87.75 mL. (B) CTP (axial 5 mm average registered) showing the presence of penumbra and the region of increased TTP, as well as reduced CBF in the middle cerebral artery territory and CBV in the left frontal lobe. (C) This patient underwent EVTs and had a FIV of 31.13 mL on DWI. (D) Coronal plane: 4D CTA showing occlusion of the MCA (yellow arrow), but on delayed phase images, the branches of the left MCA were mostly developed. Thus, the patient had an artery collateral score of 3. Full VOT on the left side (blue triangle) was found in the late venous phase compared with the contralateral VOT (red circle). (E) Axial plane: full SMCV and sphenoparietal sinus on the left side (blue triangle) were found in the late venous phase compared with the contralateral side (red circle). (F) Sagittal plane (ischemic hemisphere): full SMCV and sphenoparietal sinus on the left side (blue triangle) were found in the late venous phase, but partial VOL (yellow quadrangle) was found in the venous phase. (G) Sagittal plane (non-ischemic hemisphere): full VOL was found on the right side (red circle). Thus, the total 4D-VCS score was 11. TTP, time to peak; CBV, cerebral blood volume; CBF, cerebral blood flow; DWI, diffusion weighted imaging; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; IC, ischemic core; IP, ischemic penumbra; CTP, computed tomography perfusion; EVTs, endovascular treatments; FIV, final infarct volume; 4D CTA: 4D computed tomography angiography; MCA, middle cerebral artery; VOT, vein of Trolard; SMCV, superficial middle cerebral vein; VOL, vein of Labbé; 4D-VCS, cortical venous collateral score based on 4D CTA.

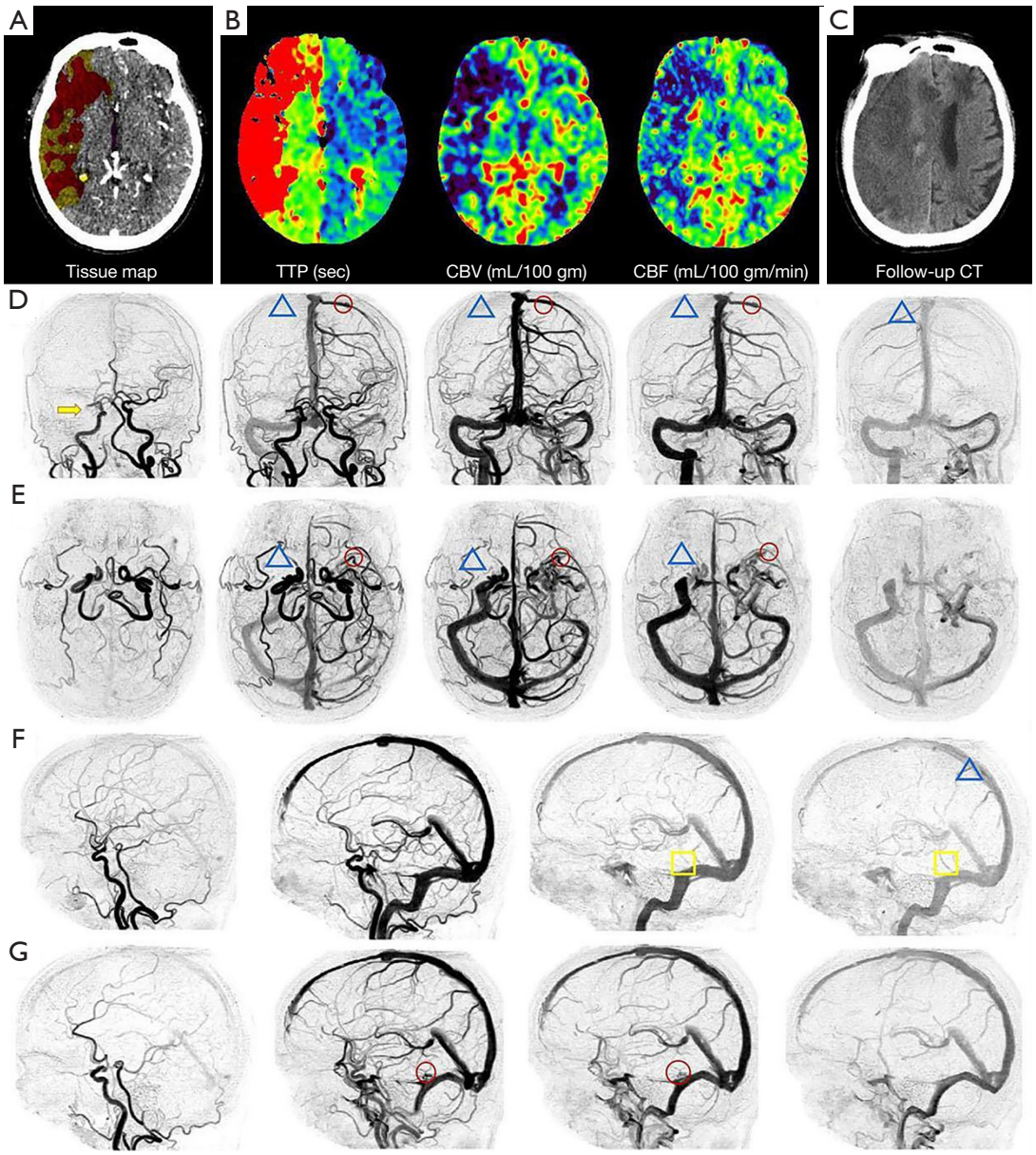

Figure 3 Poor collateral case. An adult patient suddenly fell to the ground. This patient had an initial NIHSS score of 21 and an mRS score of 5 after 3 months. Tissue map showing an IC area (red) of 127.99 mL and an IP area (yellow) of 251.38 mL. (B) CTP (axial 5 mm average registered) showing increased TTP, reduced CBF, and reduced CBV in the MCA territory. (C) The follow-up CT on day 5 showed infarct lesions with hemorrhagic transformation. (D) Coronal plane: 4D CTA showing occlusion of the right MCA (yellow arrow); on delayed phase images, the partial arterial collaterals were developed until the late venous phase. Thus, the patient had an artery collateral score of 1. Partial VOT on the right side (blue triangle) was found in the late venous phase compared with the contralateral VOT (red circle). (E) Axial plane: SMCV and sphenoparietal sinus on the right side (blue triangle) are absent compared with the contralateral side (red circle). (F) Sagittal plane (ischemic hemisphere): partial VOL (yellow quadrangle) and partial VOT (blue triangle) were found in the late venous phase. (G) Sagittal plane (non-ischemic hemisphere): full VOL was found on the left side (red circle). Thus, the total 4D-VCS score was 2. TTP, time to peak; CBV, cerebral blood volume; CBF, cerebral blood flow; CT, computed tomography; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; IC, ischemic core; IP, ischemic penumbra; CTP, computed tomography perfusion; FIV, final infarct volume; 4D CTA: 4D computed tomography angiography; MCA, middle cerebral artery; VOT, vein of Trolard; SMCV, superficial middle cerebral vein; VOL, vein of Labbé; 4D-VCS, cortical venous collateral score based on 4D CTA.

fibrillation (AF), coronary heart disease (CHD), IC volume, CBS, ICV type, and MMR]; (II) clinical information and arterial collateral score; (III) clinical information and 4D-VCS; (IV) clinical information and PRECISE; (V) clinical information and COVES; and (VI) clinical information, 4D-VCS, and arterial collateral score. Model 1 was compared with models 3, 4, 5, and 6, and model 2 was compared with models 3, 4, 5, and 6. The DeLong test was used to test differences in the area under the curve (AUC) values of the ROC curve. We calculated the adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of different variables in relation to poor outcomes. The ability of 4D-VCS to identify clinical outcome was validated internally using 1,000 bootstrap replications of the ROC. Results were considered significant for 2-tailed P<0.05. Statistical analysis was performed using the software SPSS 25.0 (SPSS, IBM Corp., Armonk, NY, USA) and MedCalc 19.6 (MedCalc Software, Mariakerke, Belgium).

Results

Study population

In total, 107 patients were consecutively enrolled in this study, including 55 males (51.4%) and 52 females (48.6%). Significant differences between the good outcome group and the poor outcome group were revealed in many variables including age, NIHSS, thrombus location, IC volume, MMR, FIV, arterial collateral score, CBS, different venous collateral scores, and ICV type (all P<0.05). Detailed information is summarized in *Table 1*.

Relationship of different venous collateral scores with FIV, mRS score, and arterial collateral score

PRECISE (r=–0.462; 95% CI: –0.603 to –0.312; P<0.001), COVES (r=–0.379; 95% CI: –0.532 to –0.215; P<0.001), and 4D-VCS score (r=–0.615; 95% CI: –0.737 to –0.473; P<0.001) showed negative correlations with FIV. PRECISE (r=–0.530; 95% CI: –0.672 to –0.382; P<0.001), COVES (r=–0.432; 95% CI: –0.600 to –0.281; P<0.001), and 4D-VCS (r=–0.706; 95% CI: –0.789 to –0.602; P<0.001) showed significant negative correlations with mRS score. PRECISE (r=0.575; 95% CI: 0.434 to 0.702; P<0.001), COVES (r=0.555; 95% CI: 0.433 to 0.683; P<0.001), and 4D-VCS (r=0.769; 95% CI: 0.678 to 0.838; P<0.001) all showed moderate negative correlations with arterial collateral score (*Table 2*).

Association of collateral circulation and clinical outcome

The results are shown in *Figure 4*: 4D-VCS had the best correlation with outcome. The AUC of 4D-VCS was 0.92 (95% CI: 0.85 to 0.96; P<0.0001). The optimal cutoff value identified by the Youden approach was 7, with a sensitivity of 0.85 and a specificity of 0.87. The AUCs were 0.80 (95% CI: 0.71 to 0.87) for PRECISE, 0.75 (95% CI: 0.66 to 0.83) for COVES, and 0.90 (95% CI: 0.83 to 0.95) for arterial collateral score.

Table 3 summarizes the results of the 6 multivariable models. In model 1, NIHSS (OR =1.14; 95% CI: 1.02 to 1.27; P<0.05) and IC volume (OR =1.04; 95% CI: 1.02 to 1.07; P<0.05) were independent predictive factors of clinical outcome. The arterial collateral score (OR =0.14; 95% CI: 0.05 to 0.37; P<0.05) and 4D-VCS (OR =0.56; 95% CI: 0.41 to 0.78; P<0.05) were independent predictive factors of prognosis in model 2 and model 3, respectively. NIHSS (OR =1.14; 95% CI: 1.01 to 1.30; P<0.05), IC volume (OR =1.03; 95% CI: 1.01 to 1.06; P<0.05), and PRECISE (OR =0.63; 95% CI: 0.45 to 0.89; P<0.05) were independent predictors of clinical outcome in model 4. NIHSS (OR =1.14; 95% CI: 1.02 to 1.29; P<0.05) and IC volume (OR =1.04; 95% CI: 1.01 to 1.07; P<0.05) were independent predictors of clinical outcome in model 5. The arterial collateral score (OR =0.22; 95% CI: 0.07 to 0.67; P<0.05) was an independent predictive factor of prognosis in model 6. The ROC curve analysis (*Figure 5*) showed the AUC of all 6 models. Compared with model 1, there was a statistically significant difference between model 1 (AUC, 0.89; 95% CI: 0.81 to 0.94) and model 2 (AUC, 0.94; 95% CI: 0.88 to 0.98) (P=0.025), between model 1 (AUC, 0.89; 95% CI: 0.81 to 0.94) and model 3 (AUC, 0.93; 95% CI: 0.87 to 0.97) (P=0.045), and also between model 1 (AUC, 0.89; 95% CI: 0.81 to 0.94) and model 6 (AUC, 0.95; 95% CI: 0.89 to 0.98) (P=0.011). Compared with model 2, there was a statistically significant difference between model 2 (AUC, 0.94; 95% CI: 0.88 to 0.98) and model 5 (AUC, 0.89; 95% CI: 0.82 to 0.94) (P=0.032).

Interobserver analysis and validation of the prognostic model

The ICC among the 2 observers was 0.89 on arterial collateral score, 0.90 on PRECISE, 0.94 on COVES, and 0.89 on 4D-VCS.

The bootstrap method was used to further validate the stability of the prognostic model, and the AUC was 0.921,

Table 1 Patient characteristics at baseline

Characteristics	All patients (n=107)	Good outcome (mRS 0–2) (n=60)	Poor outcome (mRS 3–6) (n=47)	P value
Age, years, median (IQR)	73.00 (62.00, 83.00)	68.00 (63.25, 79.50)	80.00 (68.00, 85.00)	0.003**
Women, n (%)	52 (48.60)	24 (40.0)	28 (59.6)	0.053
NIHSS, median (IQR)	13.00 (8.00, 17.00)	9.50 (6.00, 14.75)	15.00 (13.00, 21.00)	<0.001***
Stroke etiology, n (%)				0.409
Cardioembolism	58 (54.2)	30 (50.0)	28 (59.6)	
Large-artery atherosclerosis	37 (34.6)	24 (40.0)	13 (27.7)	
Other determined	1 (0.9)	0 (0)	1 (2.1)	
Cryptogenic	11 (10.3)	6 (10.0)	5 (10.6)	
Thrombus location, n (%)				0.025*
Tandem	8 (7.5)	5 (8.3)	3 (6.4)	
ICA	39 (36.4)	17 (28.3)	22 (46.8)	
Segment M1	41 (38.3)	22 (36.7)	19 (40.4)	
Segment M2	19 (17.8)	16 (26.7)	3 (6.4)	
Preoperative IVT, n (%)	21 (19.60)	12 (20.0)	9 (19.1)	1.000
mTICI, n (%)				0.056
0–2a	11 (10.3)	3 (5.0)	8 (17.0)	
2b–3	96 (89.7)	57 (95.0)	39 (83.0)	
Risk factors, n (%)				
Smoking	34 (31.8)	29 (31.9)	4 (36.4)	0.059
AF	44 (41.1)	18 (30.0)	26 (55.3)	0.010
Hypertension	73 (68.2)	41(68.3)	32 (68.1)	1.000
Diabetes mellitus	33 (30.8)	17 (28.3)	16 (34.0)	0.535
Hyperlipidemia	56 (52.3)	30 (50.0)	26 (55.3)	0.697
CHD	40 (37.4)	17 (28.3)	23 (48.9)	0.044
Previous stroke	45 (42.1)	25 (41.7)	20 (42.6)	1.000
Current anticoagulant use	13 (12.1)	7 (11.7)	6 (12.8)	1.000
Current antiplatelet use	37 (34.6)	21 (35.0)	16 (34.0)	1.000
Imaging examination				
IC volume (mL), median (IQR)	34.34 (15.20, 69.37)	21.74 (6.14, 38.51)	69.37 (41.20, 122.83)	<0.001***
IP volume (mL), median (IQR)	90.15 (51.10, 141.88)	88.51 (45.89, 131.35)	90.20 (65.29, 142.76)	0.183
MMR, median (IQR)	2.51 (1.23, 5.40)	4.40 (2.26, 7.55)	1.14 (0.71, 2.67)	<0.001***
FIV (mL), median (IQR)	43.39 (12.51, 120.75)	27.63 (7.36, 46.21)	108.15 (55.04, 247.67)	<0.001***
ASPECTS, median (IQR)	7.00 (5.00, 8.00)	7.00 (6.00, 8.00)	7.00 (3.00, 8.00)	0.134
Artery collateral scores, median (IQR)	3.00 (1.00, 3.00)	3.00 (3.00, 4.00)	1.00 (1.00, 2.00)	<0.001***

Table 1 *(continued)*

Table 1 *(continued)*

Characteristics	All patients (n=107)	Good outcome (mRS 0–2) (n=60)	Poor outcome (mRS 3–6) (n=47)	P value
CBS, median (IQR)	6.00 (1.00, 8.00)	6.00 (3.25, 9.00)	3.00 (0, 6.00)	0.002**
Total PRECISE scores, median (IQR)	3.00 (2.00, 4.00)	4.00 (2.00, 6.00)	2.00 (1.00, 3.00)	<0.001***
SMCV, median (IQR)	0 (0, 1.00)	0.50 (0, 2.00)	0 (0, 0)	<0.001***
VOL, median (IQR)	1.00 (0, 1.00)	1.00 (0, 2.00)	0 (0, 0)	<0.001***
VOT, median (IQR)	1.00 (0, 1.00)	1.00 (1.00, 2.00)	1.00 (0, 1.00)	<0.001***
BVR, median (IQR)	2.00 (0, 2.00)	2.00 (0, 2.00)	1.00 (0, 2.00)	0.008**
Total COVES scores	1.00 (0.00, 3.00)	2.00 (1.00, 4.00)	0 (0, 1.00)	<0.001***
SMCV, median (IQR)	0 (0, 1.00)	0 (0, 2.00)	0 (0, 0)	<0.001***
Sphenoid sinus, median (IQR)	0 (0, 1.00)	0 (0, 2.00)	0 (0, 0)	0.003**
VOL, median (IQR)	0 (0, 1.00)	1.00 (0, 2.00)	0 (0, 1.00)	<0.001***
Total 4D-VCS, median (IQR)	9.00 (5.00, 11.00)	10.00 (9.00, 13.00)	5.00 (3.00, 7.00)	<0.001***
SMCV, median (IQR)	2.00 (0, 3.00)	3.00 (2.00, 4.00)	0 (0, 1.00)	<0.001***
Sphenoid sinus, median (IQR)	2.00 (0, 3.00)	3.00 (1.00, 4.00)	0 (0, 1.00)	<0.001***
VOL, median (IQR)	2.00 (0, 3.00)	3.00 (1.00, 4.00)	1.00 (0, 2.00)	<0.001***
VOT, median (IQR)	3.00 (1.00, 3.00)	3.00 (3.00, 4.00)	1.00 (1.00, 3.00)	<0.001***
ICV types, n (%)				0.002**
Type 1	50 (46.7)	20 (33.3)	30 (63.8)	
Type 2	55 (51.4)	39 (65.0)	16 (34.0)	
Type 3	2 (1.9)	1 (1.7)	1 (2.1)	

*, P<0.05; **, P<0.01; ***, P<0.001. mRS, modified Rankin Scale; IQR, interquartile range; NIHSS, National Institute of Health Stroke Scale; ICA, internal carotid artery; IVT, intravenous thrombolysis; mTICI, modified thrombolysis in cerebral infarction; AF, atrial fibrillation; CHD, coronary heart disease; IC, ischemic core; IP, ischemic penumbra; MMR, mismatch ratio; FIV, final infarct volume; ASPECTS, Alberta stroke program early CT score; CBS, clot burden score; SMCV, superficial middle cerebral vein; VOL, the vein of Labbé; VOT, the vein of Trolard; BVR, basal vein of Rosenthal; ICV, internal cerebral vein asymmetry; PRECISE, prognostic evaluation based on cortical vein score difference in stroke score; COVES, cortical vein opacification score; 4D-VCS, venous collateral score based on 4D CTA.

Table 2 Correlation analysis of different venous collateral scores with final infarct volume, 90-day mRS scores, and artery collateral scores

Score	FIV		mRS scores		Artery collateral scores	
	r	95% CI	r	95% CI	r	95% CI
PRECISE	–0.462***	–0.603, –0.312	–0.530***	–0.672, –0.382	0.575***	0.434, 0.702
COVES	–0.379***	–0.532, –0.215	–0.432***	–0.600, –0.281	0.555***	0.433, 0.683
4D-VCS	–0.615***	–0.737, –0.473	–0.706***	–0.789, –0.602	0.769***	0.678, 0.838

***, P<0.001. FIV, final infarct volume; mRS, modified Rankin Scale; PRECISE, prognostic evaluation based on cortical vein score difference in stroke score; COVES, cortical vein opacification score; 4D-VCS, venous collateral score based on 4D CTA; CI, confidence interval.

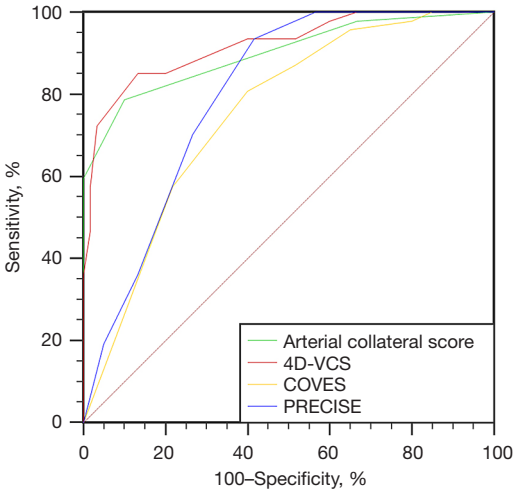

Figure 4 ROC curves of the arterial collateral score and the three different venous scoring methods. The AUCs were 0.90 (95% CI: 0.83 to 0.95) for the arterial collateral score, 0.92 (95% CI: 0.85 to 0.96) for the 4D-VCS, 0.75 (95% CI: 0.66 to 0.83) for COVES, and 0.80 (95% CI: 0.71 to 0.87) for PRECISE. ROC, receiver operating characteristic; AUCs, areas under the curve; CI, confidence interval; 4D-VCS, cortical venous collateral score based on 4D CTA; 4D CTA, 4-dimensional computed tomography angiography; COVES, cortical vein opacification score; PRECISE, prognostic evaluation based on cortical vein score difference in stroke score.

which suggested that no overfitting had occurred.

Discussion

Although the advancement of EVTs and imaging technology has remarkably increased the successful recanalization rate in patients with AIS, the rate of good outcomes (3-month mRS <2) is only 33–71%, indicating that a considerable proportion of patients with AIS still experience poor clinical outcomes (20-22). The outcome of AIS treatment may be related not only to arterial vessels but also to venous vessels. Although methods already exist to score venous collateral circulation using sCTA, this study intended to establish an improved venous collateral circulation scoring system using 4D CTA to better evaluate the venous collateral vessels. Through a retrospective analysis of the data of 107 patients with AIS who received EVTs in a single center, we found that the status of venous collaterals based on 4D CTA exhibited effective prediction of the 3-month clinical outcome. This was not inferior to the prediction effect of the arterial collaterals, which suggested that the superposition of 4D-VCS and clinical factors could improve the predictive accuracy of outcomes of AIS patients compared with other venous scoring methods.

Existing evidence has shown that the following alterations may occur in the venous vessels in the hypoperfusion area of AIS: morphological changes of the venous lumen due to contraction or passive compression, the obstruction of venules resulting from microthrombotic aggregation, and the formation of new microvascular structures. All of the abovementioned changes result in imaging findings such as poor development and delayed development of the drainage veins in the ischemic area (23,24). Parthasarathy *et al.* used the PRECISE score based on sCTA to evaluate venous status and found that cortical vein drainage, not the deep venous drainage patterns on sCTA, can predict the prognosis of patients with anterior circulation large vessel occlusion (5). Parthasarathy *et al.* later proposed a combined arterial and venous grading scale (CRISP) to assess the 4 superficial drainage veins (SMCV, VOL, VOT, and BVR) on the affected side, as well as the compensatory factors of the arterial collaterals. This scoring system predicted the clinical outcomes more accurately in patients with acute large vessel occlusion of the anterior circulation (12). Zhang *et al.* investigated the development of 3 superficial drainage veins (SMCV, VOL, and VOT) after acute stroke using 3D-CTV and 4D CTA and found that the non-opacification of SMCV was strongly related to serious insufficient cerebral perfusion and poor clinical outcomes after intravenous thrombolysis (6). Bhaskar *et al.* observed that AIS patients with larger vessel occlusion were more prone to the phenomenon of delayed cortical vein filling in the late vein stage, which was highly correlated with 24-hour poor reperfusion status after intravenous thrombolysis (7). Although emerging studies have emphasized the potential complementary role of the venous collaterals in the clinical decision-making process, they have had some limitations. Most of such studies were mainly based on sCTA, which ignores the late filling cortical veins. In addition, previous studies have mostly focused on the analysis of the clinical outcome of intravenous thrombolysis. Therefore, the present study aimed to establish an improved venous collateral scoring system based on 4D CTA to evaluate the venous collateral circulation of patients with AIS who have undergone EVTs.

The 4D-VCS with a scale of 0–16 points based on 4D CTA was established to evaluate the venous collateral vessels along the time shaft and determine the velocity of collateral

Table 3 The 6 multivariable models to predict 3-month poor outcome

Predictors	OR with 95% CI					
	Model 1 (clinical information)	Model 2 (clinical information + arterial collateral scores)	Model 3 (clinical information + 4D-VCS)	Model 4 (clinical information + PRECISE)	Model 5 (clinical information + COVES)	Model 6 (clinical information + 4D-VCS + arterial collateral scores)
Age	1.03 (0.98–1.08)	1.05 (0.99–1.13)	1.03 (0.97–1.09)	1.02 (0.97–1.08)	1.03 (0.98–1.08)	1.04 (0.98–1.12)
NIHSS	1.14* (1.02–1.27)	1.10 (0.96–1.26)	1.08 (0.94–1.24)	1.14* (1.01–1.30)	1.14* (1.02–1.29)	1.08 (0.93–1.25)
Thrombus location	0.95 (0.38–2.38)	0.70 (0.20–2.46)	1.03 (0.34–3.12)	0.98 (0.36–2.68)	0.93 (0.35–2.46)	0.83 (0.23–2.99)
AF	1.51 (0.46–4.95)	1.39 (0.29–6.75)	0.71 (0.15–3.25)	1.50 (0.42–5.32)	1.34 (0.40–4.52)	0.93 (0.16–5.28)
CHD	0.67 (0.20–2.21)	0.45 (0.10–2.14)	1.00 (0.24–4.10)	0.66 (0.18–2.42)	0.74 (0.21–2.58)	0.59 (0.12–3.01)
IC volume	1.04* (1.02–1.07)	1.03 (0.99–1.07)	1.03 (0.99–1.06)	1.03* (1.01–1.06)	1.04* (1.01–1.07)	1.03 (0.98–1.07)
MMR	1.02 (0.91–1.15)	1.04 (0.91–1.18)	1.04 (0.92–1.18)	1.01 (0.88–1.15)	1.00 (0.88–1.14)	1.04 (0.91–1.12)
CBS	1.02 (0.81–1.30)	1.18 (0.81–1.71)	1.11 (0.82–1.51)	1.02 (0.79–1.31)	1.08 (0.83–1.39)	1.17 (0.80–1.70)
ICV types	0.71 (0.24–2.12)	0.41 (0.09–1.87)	0.60 (0.14–2.65)	0.83 (0.26–2.66)	0.82 (0.26–2.55)	0.45 (0.09–2.35)
Artery collateral scores	–	0.14* (0.05–0.37)	–	–	–	0.22* (0.07–0.67)
4D-VCS	–	–	0.56* (0.41–0.78)	–	–	0.77 (0.54–1.08)
PRECISE	–	–	–	0.63* (0.45–0.89)	–	–
COVES	–	–	–	–	0.70 (0.49–1.01)	–
Model statistics						
AUC (95% CI)	0.89* (0.81–0.94)	0.94* (0.88–0.98)	0.93* (0.87–0.97)	0.91* (0.84–0.96)	0.89* (0.82–0.94)	0.95* (0.89–0.98)
Sensitivity (%)	78.72	89.36	80.85	70.21	78.72	85.11
Specificity (%)	91.67	88.33	95.00	93.33	85.00	91.67
DeLong test P value compared with model 1	–	0.025*	0.045*	0.151	0.615	0.011*
DeLong test P value compared with model 2	0.025*	–	0.618	0.113	0.032*	0.352

*P<0.05 as the threshold for statistical significance. NIHSS, National Institute of Health Stroke Scale; AF, atrial fibrillation; CHD, coronary heart disease; MMR, mismatch ratio; CBS, clot burden score; IC, ischemic core; ICV, internal cerebral vein asymmetry; PRECISE, prognostic evaluation based on cortical vein score difference in stroke score; COVES, cortical vein opacification score; 4D-VCS, venous collateral score based on 4D CTA; 4D CTA, 4-dimensional computed tomography angiography; AUC, area under the curve; CI, confidence interval; OR, odds ratio.

blood flow at the venous phase and late venous phase. This method can not only improve the accuracy of diagnosis, but can also make the diagnostic results more reliable and repeatable. The equipment used in this study was a 320-row dynamic volume CT. The whole-brain information can be collected within 60 s by 1 contrast injection, and the radiation dose of the examination is about 4–6 mSv (25).

The results of this study indicated that 4D-VCS was an independent factor affecting clinical outcome. We established different models by combining clinical factors and different venous collateral circulation scoring methods. The 4D-VCS method exhibited the best prediction value among the 3 venous collateral circulation scoring methods and was not inferior to the arterial collateral

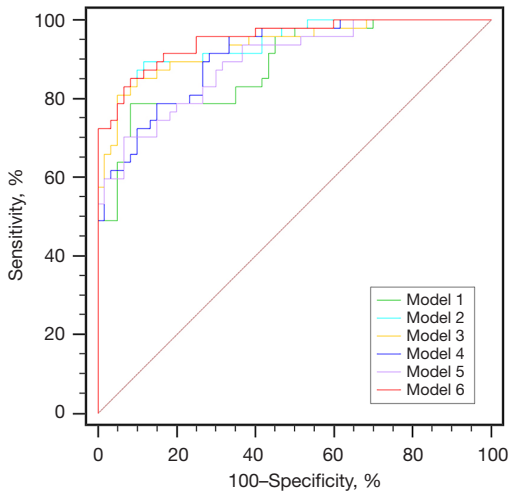

Figure 5 ROC curves of the 6 different multivariable models. Model 1 included clinical information. Model 2 included clinical information and arterial collateral score. Model 3 included clinical information and 4D-VCS. Model 4 included clinical information and PRECISE. Model 5 included clinical information and COVES. Model 6 included clinical information, 4D-VCS, and arterial collateral score. The AUCs were 0.89 (95% CI: 0.81 to 0.94) for model 1, 0.94 (95% CI: 0.88 to 0.98) for model 2, 0.93 (95% CI: 0.87 to 0.97) for model 3, 0.91 (95% CI: 0.84 to 0.96) for model 4, 0.89 (95% CI: 0.82 to 0.94) for model 5, and 0.95 (95% CI: 0.89 to 0.98) for model 6. ROC, receiver operating characteristic; 4D-VCS, cortical venous collateral score based on 4D CTA; 4D CTA, 4-dimensional computed tomography angiography; PRECISE, prognostic evaluation based on cortical vein score difference in stroke score; COVES, cortical vein opacification score; AUCs, areas under the curve; CI, confidence interval.

score in predicting clinical outcome (AUC =0.94 *vs.* AUC =0.93; P=0.618). However, in model 6, 4D-VCS was not an independent predictor. We interpret the possible reasons for this as follows: Firstly, the small sample size may have contributed to this result. Secondly, severe multicollinearity between venous the collateral circulation and the arterial collateral circulation could be one of the reasons why 4D-VCS was not statistically significant in model 6. However, the general trend can be seen in that the predictive value of model 6 was increased after adding 4D-VCS (AUC, 0.95; 95% CI: 0.89 to 0.98). Interobserver analysis and internal verification validated the high stability of 4D-VCS. The AUC of 4D-VCS used for clinical outcome prediction was 0.92. The cutoff value suggested that patients with a 4D-VCS of 7 and below were more likely to have poor outcomes 90 days after EVTs, and patients with a score higher than 7 were more likely to obtain functional independence. Therefore, our findings may provide a simple reference for predicting clinical outcomes. The venous collateral status was negatively correlated with poor outcome rate and FIV but positively correlated with the compensatory status of the arterial collateral vessels. These results suggested that the venous collateral circulation could be used as an additional imaging marker for patients with AIS. Careful observation of the venous collateral status on the affected side is critical for the prediction of clinical outcome.

This study had some limitations. Firstly, the sample size was relatively small; therefore, it is necessary to expand the sample size and conduct multicenter registration research to verify the results. Secondly, there was a certain proportion of congenital cortical vein loss in the included patients. The 4 cortical veins chosen for the 4D-VCS in this study had less anatomic variability than that of other veins, and this could reduce bias and improve the consistency of results. Thirdly, this study was a retrospective study, which may have involved selection bias.

Conclusions

Our study demonstrated that venous collateral status, in addition to arterial collateral status, is an important supplementary radiological index for predicting clinical outcomes of AIS. The 4D-VCS may be useful to evaluate the prognosis of patients with AIS after EVTs. Further large-scale and prospective studies are needed to confirm these results.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.

amegroups.com/article/view/10.21037/qims-22-245/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-22-245/coif). The authors have no conflicts of interest to declare.

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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Institutional Review Board of Beijing Hospital approved the study, and individual consent for this retrospective analysis was waived.

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