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Multiphase CTA Collateral Score to Identify Intracranial Atherosclerotic Stenosis-Related Large Vessel Occlusion

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Objective: Identification of acute ischemic stroke with large vessel occlusion (AIS-LVO) etiology is crucial for effective revascularization therapy. As collaterals are pivotal in maintaining cerebral perfusion in intracranial atherosclerotic stenosis (ICAS), we investigated whether multiphase CT angiography (mCTA) collateral score can be a diagnosis marker of ICAS-related LVO.

Methods: We reviewed clinical and imaging data from 92 patients who presented with AIS-LVO and underwent mCTA (57 ICAS-related LVO and 35 embolic LVO). Logistic regression was used to identify ICAS-related LVO. The diagnostic accuracy of the mCTA collateral score for identifying ICAS-related LVO was determined using receiver operating characteristic (ROC) analysis.

Results: Compared with patients with embolic LVO, those with ICAS-related LVO had a high median mCTA collateral score (4 vs. 3; $P < 0.0001$). The multinomial logistic regression analysis revealed a significant increase in the mCTA collateral score (OR: 3.717, 95% CI: 2.009-6.876, $P < 0.0001$) in patients with ICAS-related LVO. ROC analysis revealed that the optimal cutoff point of the mCTA collateral score to diagnosis the ICAS-related LVO was 3.5, the area under the curve (AUC) was 0.817 (95% CI: 0.736-0.899; $P < 0.0001$), sensitivity was 80.7%, and specificity was 74.3%. Further analysis revealed that patients with a 4 to 5 mCTA collateral score exhibited a significantly higher median modified Rankin Scale (mRS) at discharge compared with those with a 0 to 3 score ($P = 0.0464$).

Conclusions: The mCTA collateral score may be associated with ICAS-related LVO and could be beneficial in identifying the etiology of AIS-LVO.

Key Words: multiphase CT angiography, intracranial atherosclerotic stenosis, large vessel occlusion, acute ischemic stroke, etiology

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Intracranial atherosclerotic stenosis (ICAS) is one of the most common causes of stroke worldwide and accounts for up to half of all ischemic strokes in South and East Asia.[1] Revascularization therapy, encompassing thrombolysis and thrombectomy, has significantly improved outcomes for patients with acute ischemic stroke. However, patients with ICAS-related LVO face a significant risk of reocclusion, occurring in one-third of cases interprocedurally.[2] The most frequent cause of failed mechanical thrombectomy is underlying ICAS, a condition that often leads to larger infarct size and poorer outcomes when thrombectomy procedures are unsuccessful.[3] Due to these challenges, patients with ICAS often require specific rescue treatments, such as angioplasty, stenting, or a combination of both, to achieve successful revascularization.[4] Therefore, identifying ICAS-related LVO is crucial in selecting the appropriate management strategy. Prompt management of ICAS-related LVO should commence as soon as ICAS is suspected during the preprocedural evaluation. In such cases, pretreatment with antiplatelets may be considered as a potential therapeutic option.[5] However, although the diagnosis of ICAS-related LVO is typically made intraprocedurally, establishing an early diagnosis to identify ICAS-related LVO remains challenging.

mCTA has allowed for noninvasive, precise, and rapid evaluation of the collateral status in the whole brain.[6] Under normal conditions, cerebral collaterals remain dormant when blood flow through all major cerebral arteries is unimpeded.[7] However, in patients with ICAS, chronic hypoperfusion resulting from luminal stenosis can promote the development of collateral circulation, and the extent and capacity of this collateral circulation may change over time.[8] However, it remains unclear which collateral status specifically aids in identifying patients with ICAS-related LVO. Therefore, our objective was to identify which mCTA collateral score most accurately predicts ICAS-related LVO.

MATERIALS AND METHODS

Study Population

Clinical and imaging data from patients who presented with acute ischemic stroke (AIS) from October 2020 to December 2023 were retrospectively reviewed from a consecutively enrolled registry at the institution. The current study was reviewed and approved by the Ethics Committee

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All investigations described in this article were carried out with the approval of the responsible ethics committee and in accordance with national law and the Helsinki Declaration of 1975 (in its current revised form). Written informed consent was waived by the Institutional Review Board.

The authors declare no conflict of interest.

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of the institution, with a waiver for informed consent due to the retrospective nature of the study.

The inclusion criteria were as follows: (1) adult patients with AIS attributable to occlusion of the intracranial internal carotid artery or M1 segment of the middle cerebral artery, (2) onset to CT time $\leq$6 hours, and (3) patients who underwent mCTA before Intravenous thrombolysis (IVT) or endovascular treatment (EVT). Exclusive criteria were (1) tandem occlusion (concomitant extracranial, distal intracranial artery occlusion), (2) cerebral artery dissection, (3) bilateral anterior LVO, (4) history of head surgery, ICA or MCA angioplasty, ICA endarterectomy or endovascular treatment, (5) suffering from prestroke disability, (6) stroke of other determined cause (cerebral artery dissection and moyamoya disease) or undetermined cause, and (7) limited mCTA image quality due to inappropriate contrast injection.

Clinical Data Collection

The following clinical data were collected: age, sex, and medical history (coronary heart disease, atrial fibrillation, hypertension, diabetes, prior stroke, current smoking, and alcohol use history). The clinical variables were the baseline National Institutes of Health Stroke Scale (NIHSS) score and mRS score at discharge. Intravenous thrombolysis was performed using the approved dose of alteplase (0.9 mg/kg). In this study, the diagnoses of ICAS-related LVO and Embolic LVO were defined by the Trial of Org 10172 in Acute Stroke Treatment Classification (TOAST).[9] A patient was considered to have ICAS-related LVO if atherosclerotic stenosis or occlusion exceeded 50% at the ICA or MCA on the symptomatic side. The degree of stenosis was measured using the following formula: [1−D (stenosis)]/D (normal)].[10] In addition, patients with high- or medium-risk cardioembolic stroke sources were classified as embolic LVO.

mCTA Imaging

All patients were examined with a Toshiba 64-row volumetric CT machine. mCTA generates time-resolved cerebral angiograms of brain vasculature in three phases after contrast material injection. The first phase of CT angiography is from the arch to the vertex. The second phase allows for table repositioning to the skull base. The 3 phases were each 8 seconds apart. mCTA were reconstructed at the CT acquisition workstation. The method for scoring collateral status at single-phase CTA (sCTA) and mCTA is described in Table 1.[6] Collateral status was independently assessed by 2 experienced neurointerventionalists blinded to stroke mechanism. Disagreements were resolved by consensus readings.

Statistical Analysis

In this study, statistical analysis was conducted using IBM SPSS Statistics 18.0 (IBM Corporation, Armonk, NY). Categorical variables were described as frequency or percentage. Grade data and nonnormally distributed data are represented by the median (25% quartile, 75% quartile). Data were compared between the 2 groups utilizing the Fisher exact test, and Wilcoxon rank-sum test. Univariate and multivariate logistic regression analyses were applied for mCTA collateral score and clinical data in the ICAS-related LVO and embolic LVO. The optimal threshold of the mCTA collateral score for identifying ICAS-related LVO was determined using receiver operating characteristic (ROC) curve analysis. Statistical significance was defined when P-value of <0.05.

RESULTS

Patient Characteristics

The inclusion and exclusion criteria of patients are presented in Figure 1. Overall, 180 patients diagnosed with AIS who underwent mCTA between October 2020 and December 2023 were included in the registry. After applying the exclusion criteria, the final data set comprised 92 patients. Among the 92 patients, the median age, 73 (59.5, 83) years, median NIHSS score, 12.5 (9, 16.75), and 29 (31.5%) were women.

Compared with patients with embolic LVO, those with ICAS-related LVO had a high median mCTA collateral score

TABLE 1. Collateral Score

Score	Single-phase CTA	Multiphase CTA
5	When compared with asymptomatic contralateral hemisphere, there is increased or normal prominence and extent of pial vessels within the ischemic territory in the symptomatic hemisphere	When compared with the asymptomatic contralateral hemisphere, there is no delay and normal or increased prominence of pial vessels/normal extent within the ischemic territory in the symptomatic hemisphere
4	When compared with the asymptomatic contralateral hemisphere, there is slightly reduced prominence and extent of pial vessels within the ischemic territory in the symptomatic hemisphere	When compared with the asymptomatic contralateral hemisphere, there is a delay of one phase in filling in of peripheral vessels, but prominence and extent are the same
3	When compared with the asymptomatic contralateral hemisphere, there is moderately reduced prominence and extent of pial vessels within the ischemic territory in the symptomatic hemisphere	When compared with the asymptomatic contralateral hemisphere, there is a delay of two phases in filling in of peripheral vessels or there is a one-phase delay and a significantly reduced number of vessels in the ischemic territory
2	When compared with the asymptomatic contralateral hemisphere, there is decreased prominence and extent and regions with no vessels within the ischemic territory in the symptomatic hemisphere	When compared with the asymptomatic contralateral hemisphere, there is a delay of two phases in filling in of peripheral vessels and decreased prominence and extent or a one-phase delay, and some ischemic regions with no vessels
1	When compared with the asymptomatic contralateral hemisphere, there are just a few vessels visible in the occluded vascular territory	When compared with the asymptomatic contralateral hemisphere, there are just a few vessels visible in any phase within the occluded vascular territory
0	When compared with the asymptomatic contralateral hemisphere, there are no vessels visible within the ischemic territory	When compared with the asymptomatic contralateral hemisphere, there are no vessels visible in any phase within the ischemic vascular territory

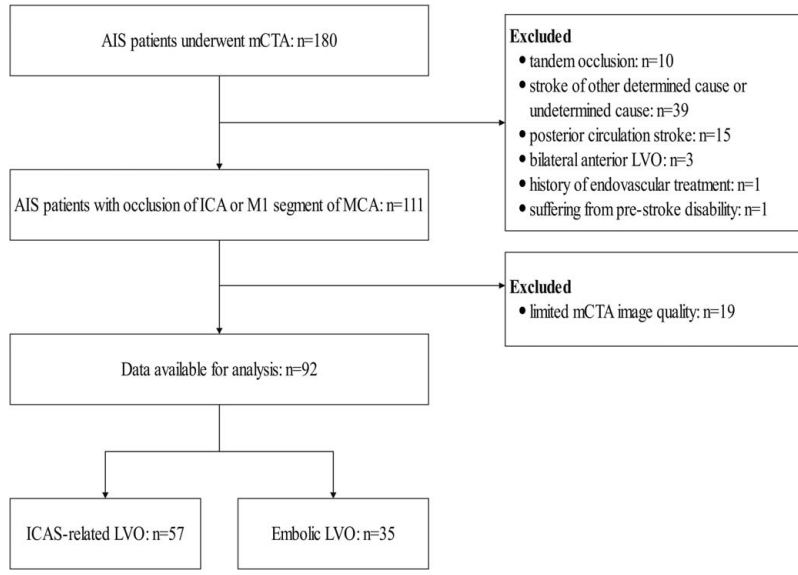

FIGURE 1. Study flowchart.

(4 vs. 3; $P < 0.0001$), lower prevalence of atrial fibrillation (7.0% vs. 48.6%; $P < 0.0001$). However, the baseline NIHSS score and mRS at discharge were not significantly different between the 2 groups. The baseline characteristics of the patients with ICAS-related LVO and those with embolic LVO are shown in Table 2. The distribution of the mCTA collateral score is shown in Figure 2.

Association of mCTA Collateral Score and ICAS-Related LVO

The univariable logistic regression analysis revealed a significant increase in mCTA collateral score (OR: 3.802, 95% CI: 2.187-6.611, $P < 0.0001$), a significant decrease in woman (OR: 0.351, 95% CI: 0.141-0.870, $P = 0.0238$), and a significant decrease in atrial fibrillation (OR 0.080, 95% CI 0.024-0.269, $P < 0.0001$) in patients with ICAS-related LVO compared with patients with embolic LVO (Fig. 3A and Table S1, Supplemental Digital Content 1, http://links.lww.com/NRL/A183). The multinomial logistic regression analysis revealed a significant increase in the mCTA collateral score (OR: 3.717, 95% CI: 2.009-6.876, $P < 0.0001$) and a significant decrease in atrial fibrillation (OR: 0.101, 95% CI: 0.025-0.409, $P < 0.0013$) in patients with ICAS-related LVO (Fig. 3B and Table S1, Supplemental Digital Content 1, http://links.lww.com/NRL/A183).

Diagnostic Ability of mCTA Collateral Score

ROC analysis revealed that the optimal cutoff point of the mCTA collateral score to diagnose the ICAS-related LVO was 3.5. The area under the curve (AUC) of the mCTA collateral score to diagnosis the ICAS-related LVO was 0.817 (95% CI: 0.736-0.899; $P < 0.0001$; Fig. 4), the sensitivity of 80.7%, and specificity of 74.3%. Similarly, cutoff point for the sCTA collateral score was identified as 1.5. The AUC of the sCTA collateral score was 0.569, with a sensitivity of 57.1% and a specificity of 59.6%. Further analysis showed that patients with 4 to 5 mCTA collateral scores had a high median mRS at discharge ($P = 0.0464$) compared with those with 0 to 3 mCTA collateral scores. The comparative analysis between patients with 0 to 3 and 4 to 5 in the mCTA collateral score is shown in Table 3.

DISCUSSION

In this study, we observed that the collateral status was associated with the etiology of AIS-LVO. Notably, the mCTA collateral score demonstrated a significant correlation with

TABLE 2. Baseline Characteristics of Patients With ICAS-Related LVO and Those With Embolic LVO

Characteristic	ICAS-Related LVO (n = 57)	Embolic LVO (n = 35)	*P*
Women	13 (22.8)	16 (45.7)	0.0365
Age, y	70 (58.5, 80.5)	78 (68, 85)	0.3333
onset-to-mCTA time	2.5 (1.25, 4)	1.5 (1, 2.5)	0.0281
Single-phase CTA collateral score	2 (1, 3)	1 (0, 3)	0.2624
mCTA collateral score	4 (4, 4.5)	3 (2, 4)	< 0.0001
Medical history			
Coronary heart disease	4 (7.0)	4 (11.4)	0.4736
Atrial fibrillation	4 (7.0)	17 (48.6)	< 0.0001
Hypertension	41 (71.9)	27 (77.1)	0.6326
Diabetes	8 (14.0)	7 (20.0)	0.5631
Prior stroke	5 (8.8)	4 (11.4)	0.7266
Current smoking	16 (28.1)	4 (11.4)	0.0721
Alcohol use history	14 (24.6)	4 (11.4)	0.1767
Occlusion site by mCTA			
Intracranial ICA	19 (33.3)	15 (42.9)	0.3817
M1	38 (66.7)	20 (57.1)	
Left hemisphere	26 (45.6)	13 (37.1)	0.5161
Treatment			
IVT	23 (40.4)	18 (51.4)	0.3881
EVT	23 (40.4)	17 (48.6)	0.5178
Clinical variables			
Baseline NIHSS score	12 (8, 16.5)	14 (10, 19)	0.6261
mRS at discharge	4 (2, 4)	4 (3, 5)	0.1120

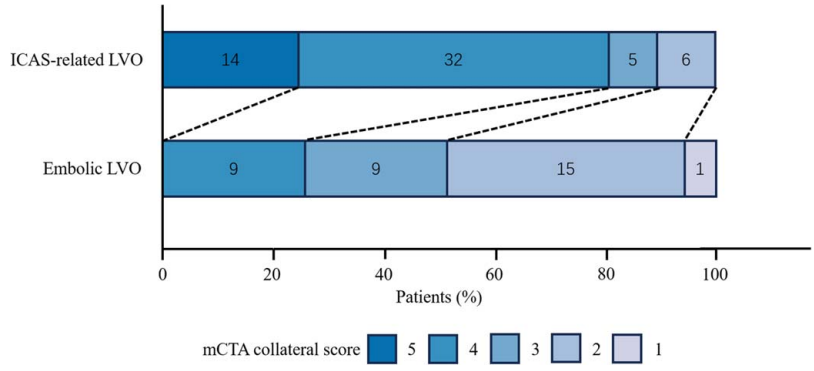

FIGURE 2. mCTA collateral score of patients with ICAS-related LVO and those with embolic LVO.

ICAS-related LVO and exhibited a robust predictive capability for identifying ICAS-related LVO. The findings suggest that the collateral score could serve as a valuable indicator in differentiating the underlying mechanisms of AIS-LVO.

As previously reported, the collateral status was associated with the etiology of AIS-LVO. In a study comparing infarct core volumes, the median infarct core volume was significantly lower in ICAS-related LVO at 14 mL compared

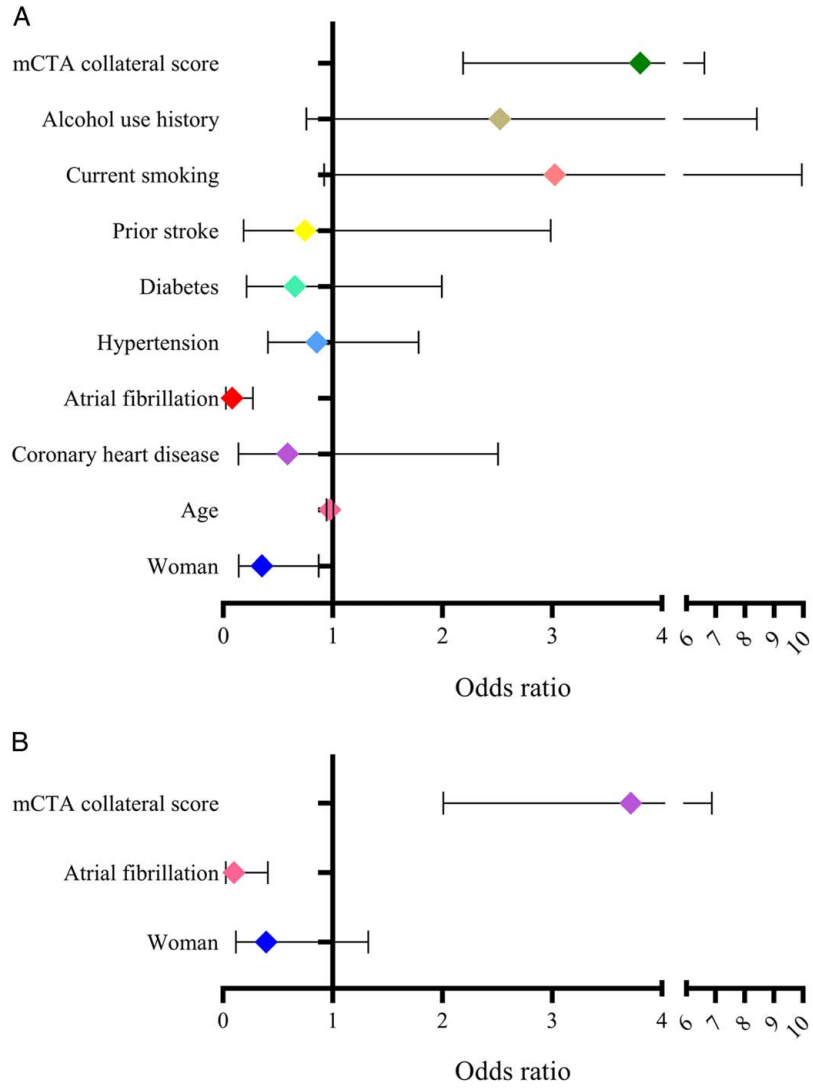

FIGURE 3. Univariable (A) and multivariable (B) logistic regression analysis of the mCTA collateral score and clinic data for prediction of ICAS-related LVO.

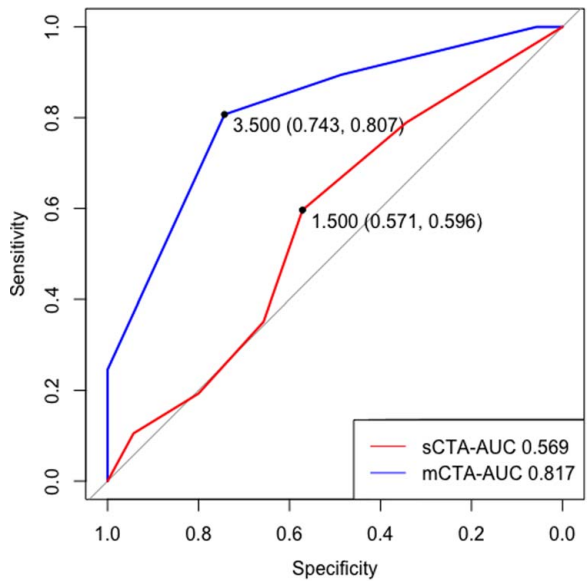

FIGURE 4. ROC analysis in the diagnosis of the ICAS-related LVO with the mCTA collateral score.

with 54 mL in embolic LVO ($P < 0.001$).[11] Recently, a study demonstrated the potential of Tmax mismatch ratios in perfusion-weighted imaging (PWI) or computed tomography perfusion (CTP) for predicting anterior ICAS-related LVO before EVT.[12] Notably, a particularly strong association was observed between a lower Tmax ratio of >10 s/>6 s and ICAS-related LVO. These findings can be attributed to the presence of pre-existing chronic hypoperfusion with good collateral flow in patients with ICAS-related LVO.[13,14]

Our study found that the mCTA collateral score demonstrated a robust predictive capability for accurately identifying ICAS-related LVO. In contrast, previous studies have utilized single-phase CTA or first-phase images of multiphase CTA to assess collateral status. However, leptomeningeal collaterals identified through these methods exhibited only a modest predictive value for ICAS-related LVO, with an AUC of 0.660, a sensitivity of 52.5%, and a specificity of 79.6%.[15] Separately, in a posthoc analysis of the DIRECTMT trial, investigators had previously constructed a predictive model using multivariate logistic regression to distinguish ICAS-related LVO from other etiologies.[16] This model incorporated various factors, including atrial fibrillation history, hypertension history, smoking personal history, occlusion located at the proximal M1 and M2 segments, hyperdense artery sign, and clot burden scores. Although our study did not perform a direct comparison, it is worth noting that the mCTA collateral score, as an independent tool, demonstrated high predictive value and may offer practical advantages due to its simplicity and convenience in clinical settings.

Furthermore, in our study, we also identified atrial fibrillation history as an independent risk factor for ICAS-related LVO, which is consistent with previous research. This finding underscores the need for a thorough history and clinical examination to be the initial step in identifying ICAS-related LVO. In addition, we must emphasize the significance of thrombus-related imaging factors to aid in differentiating ICAS-related LVO.

The study indeed has several limitations. First, the sample size was relatively small, and although efforts were made to minimize enrollment bias, it could not be completely eliminated. Future research should strive for a larger sample size across multiple centers and incorporate external validations to ensure more robust and generalizable findings. However, it is noteworthy that the age, occlusion site, and baseline NIHSS scores of the groups in this study are comparable to those reported in previous studies, indicating a certain degree of representativeness in our study population.[17–19] Second, for the sake of simplicity and clinical feasibility, we adopted a qualitative approach to assess collateral status. Although interrater reliability for multiphase CT angiography is generally excellent,[6] this qualitative assessment may still be subjective and susceptible to interrater variability. Future studies could explore more objective and quantitative methods to enhance the accuracy and consistency of collateral status assessment. Third, we did not conduct a formal evaluation of the anatomical features of the circle of Willis, such as the anterior and posterior communicating arteries, which can significantly influence the collateral circulation. This aspect remains an important consideration for future research to gain a more comprehensive understanding of the collateral status in patients with ICAS-related LVO.

TABLE 3. Comparative Analysis Between 0 to 3 and 4 to 5 mCTA Collateral Score Groups

	mCTA collateral score		
Characteristic	**0–3 (n = 37)**	**4–5 (n = 55)**	***P***
Women	15 (40.5)	14 (25.5)	0.1701
Age, y	76 (62, 85)	71 (59, 80)	0.1610
onset-to-mCTA time	1.5 (1, 4)	2 (1, 3.5)	0.6495
Medical history			
Coronary heart disease	3 (8.1)	5 (9.1)	>0.9999
Atrial fibrillation	14 (37.8)	7 (12.7)	0.0101
Hypertension	30 (81.1)	38 (69.1)	0.2331
Diabetes	7 (18.9)	8 (14.6)	0.5798
Prior stroke	5 (13.5)	4 (44.4)	0.4763
Current smoking	9 (24.3)	11 (20.0)	0.6182
Alcohol use history	7 (18.9)	11 (20.0)	>0.9999
Occlusion site by mCTA			
Intracranial ICA	18 (48.6)	16 (29.1)	0.0781
M1	19 (51.4)	39 (70.9)	
Left hemisphere	15 (40.5)	24 (43.6)	0.8315
Treatment			
IVT	17 (45.9)	18 (32.7)	0.2736
EVT	19 (51.4)	17 (30.9)	0.0543
Clinical variables			
ICAS-related LVO	9 (24.3)	46 (80.7)	<0.0001
Baseline NIHSS score	14 (10, 18.5)	10 (8, 16)	0.4586
mRS at discharge	4 (3, 5)	4 (2, 4)	0.0464

CONCLUSIONS

The mCTA collateral score may be associated with ICAS-related LVO, potentially aiding in the identification of the etiology of AIS-LVO. This study is the first to evaluate the predictive capacity of the mCTA collateral score in predicting ICAS-related LVO. Our findings emphasize the crucial role of a comprehensive collateral status assessment in these patients, which could be effectively achieved through the utilization of mCTA.

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