Absence of Collaterals is Associated with Larger Infarct Volume and Worse Outcome in Patients with Large Vessel Occlusion and Mild Symptoms

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Background: Mechanical thrombectomy is the standard of care for patients with large vessel occlusion (LVO) presenting with severe symptoms; however, little is known about the best treatment for patients with LVO and mild symptoms. The absence of good collaterals has been associated with a worse outcome in patients with LVO. In this study, we aim to assess the use of collateral score to identify patients with LVO and mild symptoms that might benefit from mechanical thrombectomy (MT). *Methods:* A retrospective review of prospectively collected data on patients presenting with mild ischemic stroke (National Institute of Health Stroke Scale [NIHSS] <6) and anterior circulation LVO between September 2015 and July 2017 was performed. Collected data included baseline demographics, NIHSS on admission, Alberta Stroke Program Early CT Score (ASPECTS), location of occlusion, collateral score using Tan scoring system, final infarct volume, and 90-day modified Rankin Scale (mRS). Patients who underwent MT were excluded from this analysis. Two multivariable models were used to assess outcomes. A gamma distributed generalized linear regression model with a log link was used to examine the impact on final infarct volume. To predict the odds of a positive 90-day outcome we estimated a logistic regression. *Results:* Forty-one patients were identified. Mean age was 67.7-years with 56.1% males. Median NIHSS on admission was 3. The most common vessels involved were the middle cerebral artery (26), internal carotid artery (14), and anterior cerebral artery (1). Twelve patients received intravenous alteplase. Median ASPECTS score was 9, median collateral score was 2.3. Median infarct volume was 10.7 mL. A good functional outcome (mRS 0-2) at 90 days was achieved in 86.4% of patients. There was a negative relationship between collateral score and final infarct volume (−.3134, $P = .046$). Multivariable regression results showed that with a one-point increase in NIHSS on admission there was a 25% increase in final infarct volume. Higher infarct volume was associated with lower odds of achieving good functional outcome (mRS 0-2) (odds ratio .96, $P = .049$ [95% confidence interval .918-.999). *Conclusions:* Most patients with anterior circulation LVO and low NIHSS achieve good long-term functional outcome, however, approximately 15% had significant disability. The absence of collaterals correlates with a larger final infarct volume and a worse long-term functional outcome. Collateral score might be a useful tool in identifying patients with LVO and low NIHSS who might benefit from MT.

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Introduction

Ischemic stroke is a leading cause of long-term disability and premature death in the United States.[1] Intravenous alteplase (tPA) had been the only acute intervention for nearly 20 years until the publication of the first successful mechanical thrombectomy (MT) trials in 2015, which offered a new successful therapy for acute strokes.[2,3] Successive studies have proven the efficacy and safety of endovascular therapy when compared to standard medical treatment for patients with severe ischemic stroke symptoms and proximal anterior circulation large vessel occlusions (LVOs) who present within 24 hours of symptom onset, making MT the standard of care for selected patients.[4-7] Most thrombectomy trials have enrolled patients with severe stroke symptoms defined as National Institute of Health Stroke Scale (NIHSS) of 6 or more; however, little is known about the best therapy for patients with anterior circulation LVOs presenting with mild stroke symptoms. Recent retrospective studies have shown that MT is safe and is associated good functional outcome in this group of patients; however, other studies have reported good functional outcome in most patients treated only with medical therapy.[8,9,10] Therefore, new strategies that aim at identifying the subgroup of patients that might benefit from MT are urgently needed.

The presence of good collateral circulation has been associated with larger perfusion-diffusion mismatches and smaller baseline diffusion-weighted stroke volumes.[11] In this study, we aim to assess the use of collateral score in predicting poorer clinical outcomes and larger final infarct volume in anterior circulation LVO patients presenting with mild symptoms (NIHSS <6).

Methods

A retrospective review of prospectively collected data on patients presenting with mild ischemic stroke (NIHSS <6) and anterior circulation LVOs between September 2015 and July 2017 was performed. The institutional review board approved the study. Collected data included baseline demographics, NIHSS on admission, Alberta Stroke Program Early CT Score (ASPECTS), location of occlusion, collateral score, final infarct volume, and 90-day modified Rankin Scale (mRS). Patients who underwent MT were excluded from this analysis to limit this cofounding factor and better characterize the natural history of these patients.

LVO was confirmed with cerebral vessel imaging (CTA or magnetic resonance angiography) and defined as an occlusion of the M1 segment of the middle cerebral artery (MCA), proximal M2 segment of the MCA, proximal anterior cerebral artery (ACA), and intracranial segment of the internal carotid artery. Collateral scores and infarct volume were measured by a board-certified neuroradiologist (GB) blinded of the clinical presentation and neurological outcomes. The Tan collateral grading system using scores of 0-3 in which 0 represents an absent collateral supply to the occluded vascular territory was utilized.[12] A score of 1 is less than 50% filling of the occluded territory compared to the contralateral hemisphere, a score of 2 is greater than 50% but not 100%, and a score of 3 is equal collateral supply between the occluded territory and the contralateral territory.[12] Final infarct volume was also quantified by a board-certified neuroradiologist using manual lesion segmentation tool in Carestream Vue, PACS version: 12.1.6.1005 (Carestream Health Inc., Rochester, NY). The region of interest was manually segmented on individual slices and the final infarct volume was obtained through automated summation of the values obtained at different slices.

Patient outcomes were assessed using 90-day mRS. We coded patients across 2 mRS categories. A good outcome was defined as mRS 0-2, and poor outcome was defined as mRS >2.

Statistical Analysis

Descriptive statistics were used for patient demographics and clinical outcomes. As appropriate, t-test was used for normally distributed interval variables, and chi-square was used for categorical variables. A spearman Rho correlation coefficient was used to evaluate the relationship between collateral score and final infarct volume. Two multivariate Generalized Linear Regression Models (GLM) were used to assess outcomes. GLM is commonly used to examine skewed outcomes in Health Services Research.[13,14] To fit the non-negative positive-skewed Final Infarct Volume, a gamma distributed GLM, with a log link was used. Logistic regression was used to predict the odds of a good 90-day outcome as a function of final infarct volume, adjusting for age and sex. Data analysis was conducted using STATA 15.1 software.

Results

Forty-nine patients were identified as having LVO with low NIHSS (<6) during the study period, 8 patients were excluded (7 patients did not have a brain magnetic resonance imaging to calculate their final infarct volume and 1 patient did not have a cerebral vessel imaging to calculate the collateral score). Forty-one patients were thus included in the final analyses.

Baseline patient characteristics are presented in Table 1. Mean age was 67.7 (SD 13.5), 92.7% of the patients were white, and 56.1% were male. Median NIHSS on admission was 3 (interquartile range [IQR] 1-4). The most common vessel involved was the MCA (63.5%) followed by the internal carotid artery (34%) and the anterior cerebral artery (2.5%). Twelve of the 41 patients received tPA (29%). Median ASPECT score was 9 (IQR 8-10) and median collateral score was 2.3 (IQR 2-3). Mean final infarct volume was 18.6 mL (SD 24.5) and median final infarct volume was 10.7 (IQR 3-19.6). Thirty-seven of the 41 patients in the final analyses had a 90-day mRS score available. Thirty-two patients (86.4%) achieved a good functional outcome (mRS of 0-2) at 90 days, 4 patients had mRS of 3 (10.8%) and 1 patient had a mRS of 4 (2.7%) at 90 days.

In univariate analysis, there was a significant negative correlation between collateral score and final infarct volume (−.3134, $P = .046$): A higher collateral score (better collaterals) was associated with a lower infarct volume (Fig 1). When adjusting for NIHSS and tPA administration, an increase in collateral score was associated with a 28% decrease in final infarct volume ($P = .022$). We also found that with a 1-point increase in NIHSS on admission there was a 25% increase in final infarct volume, which resulted in a predicted increase in final infarct volume of 3.6 mL. Larger final infarct volumes were associated with a statistically significant lower odds of achieving a good functional outcome (mRS 0-2) (odds ratio .96, $P = .049$ [95% confidence interval .918-.999), controlling for age and sex. Figure 2 illustrates a case of a proximal intracranial occlusion (left MCA) with good collaterals and small final infarct volume. Figure 3 demonstrates a case of a distal intracranial occlusion (right MCA) with poor collaterals and large final infarct volume.

Table 1. *Patient and imaging characteristics*

Variable	Total n = 41
Age, mean (SD)	67.7 (13.5)
Race n (%)	
African American	3 (7.3)
White	38 (92.7)
Sex n (%)	
Male	23 (56.1)
Female	18 (43.9)
Final infarct (mL)	
Final infarct - Median (IQR)	10.7 (3-19.6)
NIHSS	
NIHS- Median (IQR)	3 (1-4)
Location of occlusion n (%)	
MCA	26 (63.5)
ICA	14 (34)
ACA	1 (2.5)
ASPECTS score on presentation	
Aspects median (IQR)	9 (8-10)
Collateral score	
Collaterals score - Median (IQR)	2.3 (2-3)
Receipt of tPA n (%)	12 (29.3)
90 Day mRS n = 37(%)	37
0-2	32 (86.4)
3	4 (10.8)
4	1 (2.7)
5	0 (0)
6	0 (0)

Abbreviations: ACA, anterior cerebral artery; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; ICA, internal carotid artery; IQR, interquartile range; MCA, middle cerebral artery; mL, milliliter; mRS, modified Rankin Scale; N, number; SD, standard deviation; tPA, tissue plasminogen activator.

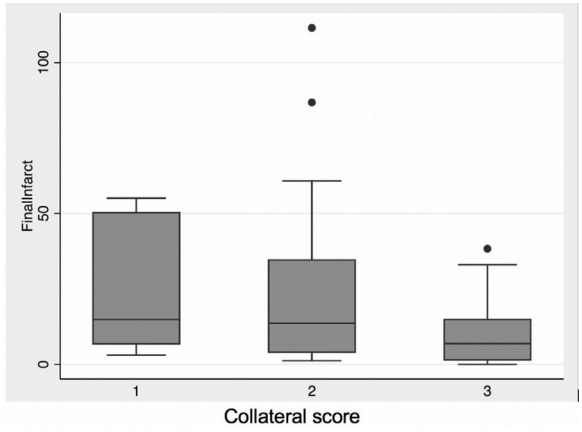

Figure 1. *Correlation between collateral score and final infarct volume.*

Discussion

This study demonstrates that in patients with anterior circulation LVOs who present with mild symptoms, there is a strong relationship between the degree of collaterals and final infarct volume as well as long-term functional outcome. Our study suggests that collateral score may be a useful tool in identifying patients with LVO and mild strokes who may benefit from early intervention with MT.

Ischemic strokes with mild presenting symptoms have been considered a "benign condition" leading to either withholding or delaying treatment. Contemporary evidence questions this approach.[4,15–17] However, a recently published study by Ali et al looking at the baseline clinical and imaging predictors of poor outcome in patients deemed to be too good to treat with intravenous thrombolysis showed that approximately one third of those patients not treated with tPA were unable to be discharged directly to home,[18] suggesting that many patients with mild presenting symptoms deteriorate over time and eventually require significant rehabilitation.

A study by Haussen et al compared best medical therapy to thrombectomy in patients presenting with mild stroke symptoms (NIHSS <6) and LVO (total of 32 patients); the study found that thrombectomy led to a shift toward lower NIHSS.[9] The most significant finding in the study by Haussen et al was that 40% of patients, who were initially treated medically, eventually deteriorated and were

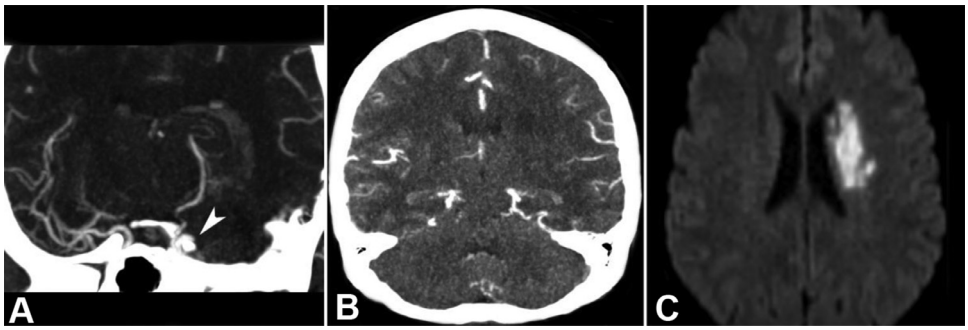

Figure 2. *A case of good collaterals and small final infarct volume. 55-year-old woman who presented with NIHSS of 5. (A) A coronal CTA demonstrates a left M1 occlusion (arrow). (B) An axial CTA demonstrates a good collateral score (Tan score = 3) with equal amount of blood vessels visualized in both hemispheres. (C) Axial MRI DWI demonstrates a small stroke with a final infarct volume of 7.9 mL. Abbreviations: CTA, computed tomography angiography; DWI, diffusion weighted imaging; MRI, magnetic resonance imaging; NIHSS, National Institute of Health Stroke Scale.*

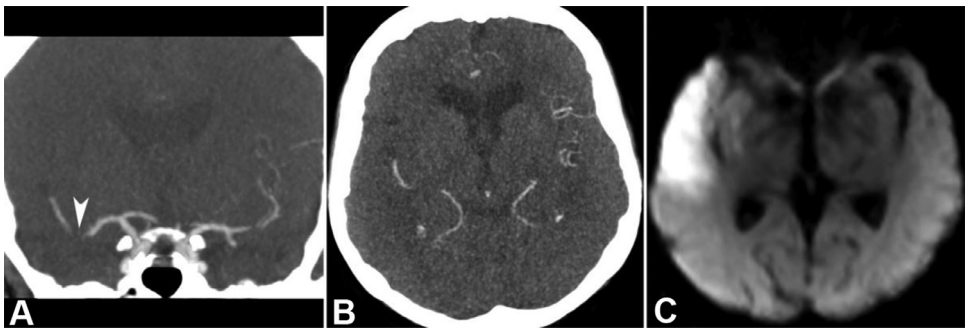

Figure 3. *A case of poor collaterals and large final infarct volume. 64-year-old woman who presented with NIHSS of 5. (A) A coronal CTA demonstrates a distal right M1 occlusion (arrow). (B) An axial CTA demonstrates a poor collateral score in the right hemisphere (Tan score = 0). (C) Axial MRI DWI demonstrates a large stroke with a final infarct volume of 34.8 mL. Abbreviations: CTA, computed tomography angiography; DWI, diffusion weighted imaging; MRI, magnetic resonance imaging; NIHSS, National Institute of Health Stroke Scale.*

subsequently taken for emergent MT. The authors also demonstrated that patients who deteriorated later (more than 3 hours after initial presentation) did not do well, suggesting that earlier intervention in these patients might be beneficial, and highlighting the importance of identifying these patients as early as possible.[9]

Collateral circulation is a known important determinant of clinical outcome after having an ischemic stroke.[2] Various scoring systems have been used to describe the collateral status in acute ischemic stroke patients with each system having their own strengths and weaknesses. The most commonly used CTA-derived collateral scoring systems used in clinical practice include the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) grading system, ASPECTS collateral scoring system, scores of Christoforidis, and the Tan scoring systems. The ASITN/SIR and Christoforidis scoring systems were initially intended for grading collaterals on digital substraction angiography (DSA), however they were later adapted for use in single-phase CTA and dynamic CTA respectively. The ASITN/SIR scoring system ranges from 0-4 on dynamic CTA where a score of 0 refers to non-existent pial collaterals and a score of 4 is complete collateral flow to the ischemic territory before the venous phase.[19] The Christoforidis scoring system on the other hand ranges from 1 to 4, where a score of 1 indicates reconstitution of flow distal to the occlusion site and a score of 5 equates little to no reconstitution distal to the occlusion.[20] The ASPECTS collateral system utilizes a score from 0 to 5 where a score of 0 indicates that there were no collateral vessels seen in the ischemic territory and a score of 5 indicates symmetric appearance of collateral vessels compared to the asymptomatic, contralateral hemisphere.[21] The Tan collateral scoring system as described above ranges from a score of 0 to 3 depending on the degree of collateral filling in the ischemic territory compared to the contralateral territory.[22] All the above collateral grading scales are limited by the fact that they are all derived from CTA imaging and carry the same CTA limitations. The ASITN/SIR, ASPECTS, and Tan collateral scoring systems correlate well with the final infarct volume.[23] The Christoforidis score has been shown to correlate poorly with final infarct volume, which is likely due to its focus on retrograde contrast filling rather than vascular enhancement.[23]

A number of studies have shown that good collateral scores on presentation are associated with increased volume of salvageable tissue and slower rate of ASPECT score deterioration.[24,25] Other studies have shown that the degree of collateral supply correlates with the presence of smaller final infarct volume in patients treated with MT.[26] Most previous studies however have focused on patients with moderate-to-severe neurological deficits on presentation and typically have evaluated only a MT group without a control group. In our study, we used the degree of collaterals to predict the final infarct volume and long-term functional outcome in patients who did not undergo MT. LVO patients with low NIHSS and poor collaterals on presentation are more likely to have larger final infarct volumes and worse functional outcomes.

The medically treated group of the ETIS REGISTRY achieved a 90-day mRS 0-2 in 74.8% of cases.[27] The authors had a broader definition of mild stroke (NIHSS <8). However, in this study approximately 18% of patients clinically deteriorated and required MT. We also encountered a similar proportion of patients (86.4%) who achieved good clinical outcome (mRS 0-2) on follow-up, while approximately 15% of patients had poor outcome. We hypothesize that using collateral score might help identifying those 15% of patients who will do poorly and may help in triaging these patients to early MT. Our findings support considering early intervention in patients with anterior circulation LVOs presenting with mild symptoms who have poor collateral scores. These patients had statistically significant increased final stroke volumes and poorer long-term functional outcomes.

Our study has some limitations. Due to its retrospective nature and the small sample size, our study should be viewed for hypothesis-generating purposes only. Currently planning is underway for 2 larger randomized trials that will try to further look into answering the question of when to pursue MT in this patient population. The study's small population also limits the ability to draw strong conclusions along with patient composition coming from a single center. Furthermore, the scoring system used in this study has its own limitations including that it is derived from CTA and not from DSA, and it only evaluates the status of MCA collaterals. Finally, although the study team reached out 3 times to capture the 90-day mRS, this outcome was missing for 3 patients. Therefore, the results of the logistic regression should be interpreted with caution.

Conclusions

The use of collateral score in patients with anterior circulation LVO who present with mild stroke symptoms may help with identifying the subgroup of patients who are at higher risk for worsening, and who may benefit from MT.

Conflicts of Interest

The authors declare no conflicts of interests.

Supplementary Material

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2019.03.032.

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