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Effect of collateral level in CT angiography on clinical prognosis in stroke patients treated with mechanical thrombectomy after six hours

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Abstract

Objectives: Collaterals have an effect on the protection of penumbra tissue. We evaluated the effect of collaterals on single-phase computed tomography angiography (CTA) in patients with AIS treated with MT after 6 hours. *Methods:* We evaluated patients with ICA or M1 segment of MCA occlusion, time of symptom-groin puncture >6 hours, having CTA before MT, modified Treatment In Cerebral Ischemia score (mTICI) 2b-3 recanalization after MT. Data of collateral levels, outcome measures, timings and other variables were collected from Turkish Interventional Neurology Database. The level of collaterals was assessed with modified Tan scale. *Results:* A total of 57 patients were included in our study. The median age was 64[56.5-75] years. The median NIHSS score at onset was 15[12-17.5] points. A total of 33 (57.9%) patients had good collaterals on CTA. Hypertension (HT) and diabetes mellitus (DM) rates were increased in the poor collaterals group. NIHSS scores decreased at the 24th hour in both good and poor collaterals groups. Twenty-two (66.7%) patients in the good collaterals group and 11 (45.8%) patients in the poor collaterals group had good clinical outcomes. However, there was not a significant difference (p=0.174, OR: 2.364; 95% CI: 0.802-6.697). Mortality rates were different in both groups, but the difference was not found to be significant (5[15.2%] versus 8[33.3%], p=0.124, OR:0.357; 95% CI: 0.1-1.278).
Conclusion: Good collaterals on single-phase CTA was not associated with improved neurological outcomes in AIS patients treated after 6 hours.

Keywords: Stroke, mechanical thrombectomy, collateral, prognosis

INTRODUCTION

Mechanical thrombectomy (MT) and intravenous thrombolytic treatment (iv-tPA) are revascularization treatments in acute ischemic stroke (AIS). In five randomized controlled trials published in 2015 (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND IA), MT was found superior to other medical treatments in AIS patients with large vessel occlusions (LVO).[1-5] In a meta-analysis evaluating these five trials, Goyal *et al*. reported that AIS patients treated with MT had better clinical outcome.[6] In American Heart Association/ American American Stroke Association (AHA/ASA) Guideline, MT was recommended to AIS patients with the internal carotid artery (ICA) or M1 segment of the middle cerebral artery (MCA) within six hours.[7] The time window was extended to 24 hours after DAWN and DEFUSE 3 trials.[8,9]

The purpose of revascularization treatments in AIS is to rescue the penumbra tissue, at risk of infarction. Collaterals have an effect on the protection of penumbra tissue. In a review, Bhaskar *et al*. showed that AIS patients with good collateral circulation had better clinical outcomes.[10] Additionally, poor collaterals were found associated with poor clinical outcomes in a metanalysis.[11] Successful recanalization is

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another factor of good clinical prognosis in AIS patients.[6] Most of the studies included patients with successful and failed racanalization after MT. Despite successful recanalization, the poor clinical prognosis can occur after MT. This indicates that other factors except successful recanalization have an effect on a good clinical prognosis. Good collateral circulation is one of these factors.[10] There are some trials about the effect of collateral circulation on the prognosis of stroke patients treated with MT within 6 hours. However, there are not many trials about the effect of collaterals in patients with AIS treated after 6 hours. Sharma *et al*. reported that presence of good collaterals was associated with beter discharge outcomes.[12] But an other analysis of DEFUSE-3 trial showed that collateral status did not have an effect on clinical prognosis.[13] These studies included patients with successful and failed recanalization. There is not any study including only AIS patients with successful recanalization after MT. In this study, we evaluated the effect of collaterals on single-phase computed tomography angiography (CTA) in patients with AIS who were treated with MT after 6 hours and achieved successful recanalization.

METHODS

Local ethics committee approved this study. We collected data from the Turkish Interventional Neurology Database (TIND). TIND is a database containing data of patients with AIS treated with endovascular techniques by interventional neurologists in Turkey. TIND is used by stroke centers. All interventional neurologists enter the data of their patients to TIND. TIND contains the data of 1,237 AIS paitents treated with endovascular techniques. We retrospectively evaluated the data of patients treated with MT between 2018 and 2020. Informed consent form was taken from all patients.

Non-contrast brain CT, single phase CTA, and diffusion-weighted (DWI) magnetic resonance (MRI) were performed on patients. Patients who were fulfilling the eligibility criteria of DAWN trial (age ≥80 years, National Institutes of Health Stroke Scale [NIHSS] score ≥10 and infarct volume <21 ml; or age <80 years, NIHSS ≥10 and infarct volume <31ml; or age<80 years, NIHSS ≥20 and infarct volume <51 ml) were included to our study.[8,9] Infarct volume was calculated by ABC/2 method.[14] The DWI image with the largest infarction was selected then the longest axis on the image (A) was measured with the ruler tool. A perpendicular line through the widest dimension (B) was measured. The third axis (C) was calculated by mulplying number of images with visible ischemic lesions by slice thickness. The formula of AxBxC/2 was applied for volume calculation. If there are multiple ischemic lesions, ABC/2 was used for each lesion. Other inclusion criteria were defined as ICA or M1 segment of MCA occlusion, time of symptom-groin puncture between 6 and 24 hours, having CTA before MT, modified Treatment In Cerebral Ischemia score (mTICI) 2b-3[15] recanalization after MT, no evidence of intracranial hemorrhage on CT or MRI and no evidence of an infarct involving more than one-third of MCA territory on CT or MRI at the onset.

Demographic and clinical data were collected, including age, sex, medical histories of patients, risk factors, symptom-groin puncture time, symptom-recanalization time and groin puncture-recanalization time, NIHSS scores at onset and 24th hour, laboratory findings, systolic blood pressures (SBP), diastolic blood pressures (DBP), modified Rankin score (mRS) at the third month and mortality data were collected. Symtom onset time was defined as the time patient was last seen at his/her neurologic baseline as expressed by patient or witness. Non-contrast brain CT was assessed with Alberta Stroke Programme Early CT (ASPECT) score.[16] Collateral levels were evaluated in monophasic CTA according to Tan and modified Tan scales. According to Tan scale, grade 0 was defined as no contrast passage in occluded MCA territory, and grade 1 was defined as contrast passage in >0% and ≤50% of occluded MCA territory, and grade 2 was defined as contrast passage in >50% and <100% of occluded MCA territory, and grade 3 was defined as contrast passage in 100% of occluded MCA territory.[17] (Figure 1) According to the modified Tan scale, collaterals ≥50% in MCA territory were defined as good collaterals.[18] Non-contrast brain CT was performed to all patients at 24th hour. Intracerebral hemorrhage (ICH) was defined according to ECASS criteria.[19] Small petechial hemorrhages in the infarction zone were defined as hemorrhagic infarction type 1, confluent petechial hemorrhages in infarction zone without mass effect was defined as hemorrhagic infarction type 2, hematoma less than 30% with mild mass effect was defined as parenchymal hematoma (PH) type1 and hematoma more than 30% with substantial mass effect was defined as PH type 2. Symptomatic intracerebral hemorrhage (SICH) was defined as any hemorrhagic transformation

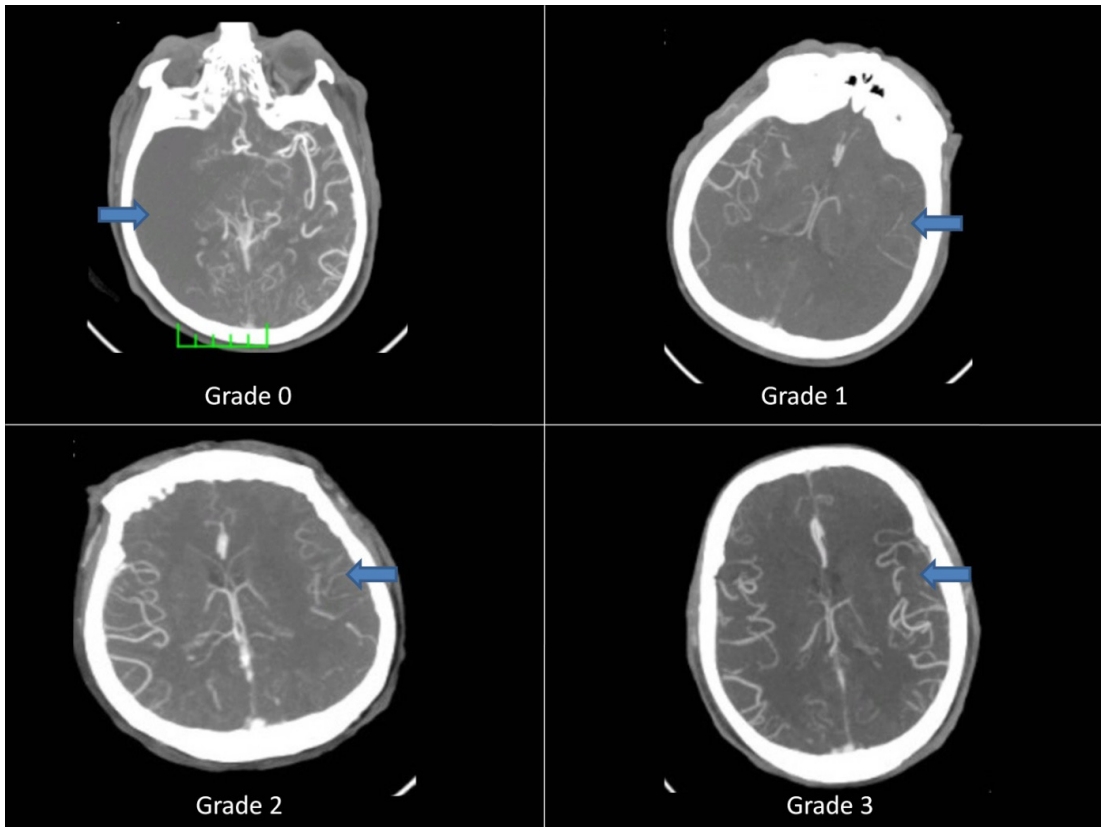

Figure 1. Tan Scale (Arrows show the occluded side)

causing an increase ≥4 points on NIHSS at the 24th hour compared with at onset. Good clinical outcome was defined as mRS≤2 on the 90th day.

Statistical analyzes were made with SPSS 15. Categorical variables were expressed as frequencies and percentages. Continuous variables were expressed as mean (SD) or median (interquartile range [IQR]) for non-normal distribution. Kolmogorov-Smirnov test was used for assessing the normality of distribution. We used Mann-Whitney U, paired T, and independent T-tests for continuous data and $\chi 2$ for binary and categorical data. Binary logistic regression analysis was performed to evaluate categorical data. All p values <0.05 were considered significant.

RESULTS

A total of 57 patients were included to our study. Twenty-seven (47.4%) patients were male (16[48.5%] patients in good collaterals group, 11 [45.8%] patients in poor collaterals group, p=1.000). Median age was 64[56.5-75] years. Median NIHSS score at onset was 15[12-17.5] points. Median NIHSS score at 24th hour was 9[3.5-15] points. A total of 19 (33.3%) patients had ICH in brain CT at 24th hour. SICH occured in 5 (8.8%) patients. ICH and SICH rates were high in poor collaterals group, but there wasn't significant difference. A total of 33 (57.9%) patients had good glinical outcome. Thirteen (22.8%) patients died.

Good collaterals were spotted in 33(57.9%) patients on CTA. We found similar good collateral rates between male and female patients(16[59.5%] versus 17[56.7%], p=1.000). Hypertension (HT) and diabetes mellitus (DM) rates were increased in the poor collaterals group. Triglyceride levels were high in the good collaterals group. Table 1 shows the demographic, clinical, and laboratory findings. NIHSS scores at onset and 24th hour were lower in the good collaterals group, but we did not find a statistically significant difference(p=0.711). As shown in Table 2, NIHSS scores improved in both good and poor collaterals groups at the 24th hour. Increased rates of ICH and SICH were found in the poor collaterals group, but we did not find a significant difference. Twenty-two (66.7%) patients in the good collaterals group and 11 (45.8%) patients in the poor collaterals group

Table 1: Demographic, clinical and angiographic datas of patients

	Total	Good Collaterals	Poor Collaterals	P
N (%)	57(100)	33(57.9)	24(42.1)	
Males (%)	27(47.4)	16(48.5)	11(45.8)	1.000
Age (IQR)	64(56.5-75)	65(58-75.5)	63.5(54.5-72.5)	0.688
Atrial Fibrillaton (%)	26(45.6)	13(39.4)	13(54.2)	0.295
HT (%)	41(71.9)	20(60.6)	21(87.5)	0.037
Obesity (%)	14(24.6)	7(21.2)	7(29.2)	0.544
Smoking (%)	16(28.1)	10(30.3)	6(25)	0.769
DM (%)	19(33.3)	7(21.2)	12(50)	0.045
CAD (%)	19(33.3)	9(27.3)	10(41.7)	0.273
Stroke (%)	4(7)	2(6.1)	2(8.3)	0.565
SBP(mmHg) (%)	160(138.5-178.5)	155(130-170)	177.5(151.3-190)	0.855
DBP(mmHg) (%)	90(80-100)	80(80-100)	97.5(85.5-100)	0.285
Glucose (mg/dl)(IQR)	125(108-176)	122(108-164)	138.5(110-177.5)	0.502
WBC (10^3/mm^3) (IQR)	9.4(7.6-12.3)	8.6(7.3-11)	10,1(7.9-13.7)	0.273
Platelet (10^3/mm^3)(IQR)	239(198.5-268)	239.5(189-264)	226(201.8-274)	0.635
HGB (g/dl)(IQR)	13.1(10.9-14.6)	12.8(11.2-14.8)	13(10.8-14.4)	0.598
RDW(IQR)	14.4(13.4-15.8)	14.4(13.4-15.5)	14.5(13.4-17)	0.900
Triglyceride (mg/dl)(IQR)	108.5(79.5-154.5)	108.5(84-142)	105(73.3-185)	0.004
LDL (mg/dl)(IQR)	119(86-135.5)	115.5(75.5-150)	119(91.8-123.8)	0.119
HDL (mg/dl)(IQR)	41.5(36.3-46)	38.5(34.3-45.3)	42.5(38.3-47.5)	0.749
Total Kolesterol (mg/dl)(IQR)	188.5(149.5-218)	184(140-214.5)	193.5(159-219)	0.410
ASPECT (IQR)	9(8-10)	9(8-10)	9(8-10)	0.666
NIHSS at onset (IQR)	15(12-17.5)	14(10-16)	15.5(14-19)	0.451
NIHSS at 24^{th} hour (IQR)	9(3.5-15)	7(2-13.5)	9.5(4.3-16.8)	0.711
Tandem Occlusion (%)	9(15.8)	4(12.1)	5(20.8)	0.470
Distal ICA Occlusion (%)	9(15.8)	6(18.2)	3(12.5)	0.720
MCA M1 Occlusion (%)	39(68.4)	23(69.7)	16(66.7)	1.000
Symptom-groin Puncture Time (min) (IQR)	420(370-579)	435(370-618)	389(367-480)	0.145
Symptom-recanalization time (min) (IQR)	465(420-609)	485(417.5-660)	438.5(420.5-517.5)	0.254
Puncture-Recanalization Time (min) (IQR)	40(30-51.5)	40(30-51)	40(28-57.8)	0.512
Thrombectomy Passes (IQR)	2(1-2,5)	2(1-2)	2(1-3)	0.274
ICH (%)	19(33.3)	9(27.3)	10(41.7)	0.273
SICH (%)	5(8.8)	1(3)	4(16.7)	0.151
Good Clinical Outcome (%)	33(57.9)	22(66.7)	11(45.8)	0.174
Mortality(%)	13(22.8)	5(15.2)	8(33.3)	0.124

CAD: Coronary artery disease, DBP: Diastolic blood pressure, DM: Diabetes mellitus, HGB: Hemoglobin, HDL: High-density lipoprotein, HT: Hypertension, ICA: Internal carotid artery, ICH: Intracerebral hemorrhage, LDL: Low-density lipoprotein, MCA: Middle cerebral artery, RDW: Red cell distribution width, SICH: Sympthomatic intracerebral hemorrhage, SBP: Systolic blood pressure, WBC: White blood cell

Table 2: NIHSS Changes of Patients with Good and Poor Collaterals

	NIHSS at onset	NIHSS at 24th hour	p
Good Collaterals	14(10-16)	7(2-13.5)	<0.001
Poor Collaterals	15.5(14-19)	9.5(4.3-16.8)	0.004

had good clinical outcomes, but there was not a significant difference (p=0.174). The mortality rate was high in poor collaterals group, but there was not a significant difference (5[15.2%] versus 8[33.3%], p=0.124). Figure 2 shows the distribution of mRS scores on the 90th day. There was not a relationship between good collaterals and good clinical outcome in subgroup analysis. Table 3 summarizes the findings of subgroup analysis.

In regression analysis, good collaterals were not found as a predictor of good clinical outcome (p=0.119, OR: 2.364; 95% CI: 0.802-6.697). We did not find a difference in the rate of mortality between good and poor collaterals groups (p=0.113, OR:0.357; 95% CI: 0.1-1.278). DM (p=0.026,OR: 3.714; 95% CI: 1.169-11.803) and HT (p=0.034, OR:4.550; 95%CI: 1.126-18.392) were found associated with poor collaterals. We did not find association between good collaterals and TG levels(p=0.370, OR: 0.994; 95% CI: 0.982-1.007). Table 4 shows the findings of multivariate logistic regression analysis.

DISCUSSION

We evaluated the effect of collaterals on the prognosis of AIS patients treated with MT after 6 hours from the onset of symptoms. We did not find the expected effect of collaterals on AIS patients with anterior LVO. Similarly, good collaterals did not have an effect on mortality in AIS patients. Improvement in NIHSS score at 24th hour was seen in both good and poor collaterals groups. HT and DM had association with poor collaterals. We did not find an association between collateral

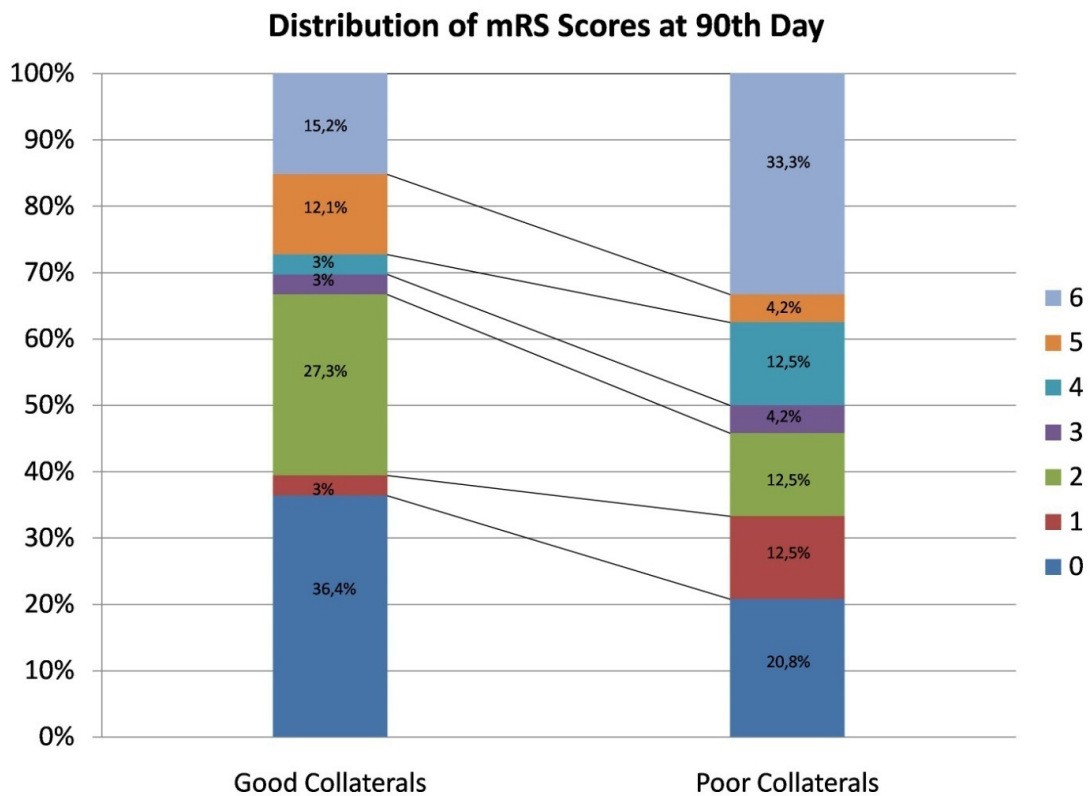

Figure 2. Distribution of mRS scores on 90th day.

Table 3: Effect of good collaterals on good clinical outcome in subgroups

Variable	p value	OR	95% CI
Age			
≤75 years	0.125	2.857	0.815-10.015
>75 years	1.000	1.5	0.156-14.420
Gender			
Males	0,675	1,714	0.323-9.109
Females	0.159	3.214	0.701-14.743
NIHSS at onset			
<17	0.147	3.150	0.747-13.286
≥17	0.603	0.389	0.032-4.796
Occlusion			
Internal Carotid Artery	0.342	3.889	0.543-27.586
Medial Cerebral Artery	0.509	1.875	0.510-6.898
Symptom-groin Puncture Time			
≤7 hours	0.143	4.000	0.876-18.256
>7 hours	1.000	1.000	0.183-5.460
Thrombeytomy Passes			
<3 Passes	0.507	1.900	0.519-6.955
≥3 Passes	0.559	4.500	0.337-60.151

The threshold for age, NIHSS and thrombectomy passes were chosen at the 75th percentile, and threshold for symptom-groin puncture time was choosen just above the median.

status and variables spotted in previous studies such as age, gender, SBP, NIHSS score at onset.[20-22] In a meta-analysis, Leng *et al*. reported that good collaterals prior to endovascular treatment were associated with increased favorable clinical outcomes, decreased risk of SICH, and 3-month mortality in early time windows.[23] Nambiar *et al*. reported that good collateral circulation was associated with a good clinical prognosis.[24] In the IMS III trial, good collaterals were found associated with good clinical outcomes and decreased mortality rates.[25] A recent meta-analysis showed that good pretreatment collaterals were associated with functional independence, decreased rates of SICH and mortality after MT in AIS pateinets with anterior circulation occlusion.[26] Xu *et al*. reported that beter collateral status was associated with increased rate of good clinical outcome and lower mortality after MT.[27] However, these studies included AIS patients in the early time window. A recent study evaluated the effect of collaterals in AIS patients treated within and

Table 4: Findings of Multivariate Regression Analysis

Good Collaterals			
	p	**OR**	**95% CI**
Good Clinical Outcome	0.119	2.364	0.802-6.967
Mortality	0.113	0.357	0.1-1.278
Triglycerid	0.370	0.994	0.982-1.007
Poor Collaterals			
	p	**OR**	**95% CI**
DM	0.026	3.714	1.169-11.803
HT	0.034	4,550	1.126-18.392

after six hours, and authors reprted that presence of good collaterals had association with better clinical outcomes.[12] The ESCAPE study included patients up to 12 hours with moderate or good collateral circulation on multiphasic CTA, and there was not a significant difference between patients treated within or after six hours.[2] In an analysis of the DEFUSE-3 trial, the authors did not find an association between collateral status and clinical outcome.[13] Our findings are compatible with this trial.

The lack of an association between good clinical outcome and good collateral circulation points out that other factors may have effect on good clinical outcome. In an exploratory analysis of DAWN trial, good clinical had association with <3 thrombectomy passes and baseline NIHSS score ≤17 points.[28] Reiff *et al*. reported that NIHSS score at admission was a determinative factor of good clinical prognosis.[29] A recent study found age, atrial fibrillation, high NIHSS score at baseline and discharge, and longer groin puncture to recanalization time as predictors of poorer functional prognosis.[30] Wirtz *et al*. reported that history of HT and NIHSS score ≤10 points at 24 hours after MT were predictors of good functional outcome at 90 days.[31] In our study, NIHSS score ≤17 points at onset (p=0.001, OR: 0.117; 95% CI: 0.031-0.436) and NIHSS score <10 points at 24 hours (p=0.000, OR:0.038; 95% CI: 0.009-0.167) had association with good clinical outcome at 90 days.

HT had association with poor collaterals. In the IMS III trial, Liebeskind *et al*. reported that history of HT was associated with poorer baseline collateral status.[32] Menon *et al*. found similar findings in another study.[20] In a trial, baseline SBP was found associated with poor collaterals.[32] Whether HT contributes to poor collaterals or is a response to poor collaterals in AIS is uncertain. It is considered that HT increases the baseline collateral vascular tonus, which triggers compensatory HT during AIS, and causes a self-perpetuating cycle of worsening collateral circulation.[22] In an animal experiment, it was observed that the leptomeningeal arteries of rats responded to increased blood pressure with vasoconstriction.[33] We found increased SBP levels in the poor collaterals group, but there was not a significant difference.

We found an association between DM and poor collaterals. There was not any data supporting this finding in the literature. Menon *et al*. found an increased rate of DM in patients with poor collaterals, but they did not find a significant difference.[20] Unlike DM, hyperglycemia was found associated with poor collaterals and poor clinical outcomes.[32] We found increased initial serum glucose levels in the poor collaterals group, but there was not a significant difference.

We found shorter symptom-recanalization time in the poor collaterals group, but we did not find a significant difference. Groin puncture-recanalization times were similar between the two groups, but symptom-groin puncture time was lower in the poor collaterals group, which is the cause of the difference. Bang *et al*. reported that patients with poor collateral circulation had a larger volume of infarction in first diffusion-weighted MRI, and good collateral circulation had association with smaller infarction core.[34] de Havenon *et al*. showed that poor collaterals were associated with significantly larger ischemic core volume and growth on the 24-hour follow-up imaging.[13] These findings suggest that infarction core volume grows more slowly in patients with good collateral circulation. Therefore, patients with good collateral circulation may have longer symptom-groin puncture and symptom-recanalization times.

Diagnostic modalities used to evaluate the collateral status are single-phase CTA, multiphasic CTA, CTP, and digital subtraction angiography (DSA). DSA is the gold standard technique for evaluating the collateral circulation.[35,36] But this technique has some disadvantages, including invasiveness, procedural risks, and higher cost.[37] Single-phase CTA allows for a rapid assessment of cerebral arterial collateral vessels with high accuracy. However it has limited sensitivity in detecting hypoplastic arterial systems and risk of underestimation of the collateral if imaging is performed before contrast reaches the leptomeningeal vessels.[38] This situation led to the development of multiphasic CTA. Multiphasic CTA is more effective than single-phase CTA in evaluating the collateral status. CTP has been used in the evaluation of collateral filling in MCA occlusions.[39] Some studies showed that collateral status is correlated with CTP.[40,41] Rapid automated multiphasic CTA and CTP processing methods for evaluating collateral circulation and mismatch profile can provide objective and quantitative collateral grading and penumbra assessment.[42] Only a few centers in our country can apply multiphasic CTA and CTP. So, single-phase CTA was used for evaluating collateral status.

Infarct volume was calculated with ABC/2 method. Previous studies reported that ABC/2 method can estimate the infarct core volume on

DWI.[13] A recent study compared the measurement of infarct volume with ABC/2 method and RAPID share, and ABC/2 method had a high accuracy for the measurement of infarct volume compared with RAPID share, especially in patients with infarct volume <70 ml.[43] This study showed that DWI infarct volume measurement with the ABC/2 method could be an alternative for evaluating the eliglibility of patients for thrombectomy with DAWN criteria.[43]

Our study has some limitations. It was designed as a retrospective study. Because of being a retrospective study, the sample size was not calculated prior. We have a small sample size. A core center did not assess the CT angiography images. Collaterals were evaluated subjectively by interventional neurologists in different centers. We used only one method for assessing collaterals. We did not have more selective techniques for assessing collateral status, such as multiphasic CT angiography. We did not assess infarction volume after MT. Some of our patients were wake-up strokes. These patients may have presented earlier from true symptom onset than 6 hours.

In conclusion, good collaterals on single-phase CTA showed a trend towards the better clinical outcome, but it was not associated with improved neurological outcomes in AIS patients treated over 6 hours. HT and DM were found associated with poor collaterals. Further prospective randomized studies are necessary for ease of understanding the role of collaterals in AIS patients with anterior LVO, who were treated in the late therapeutic window.

DISCLOSURE

Conflict of interest: None

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