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Predictive value of cerebral collaterals on CT angiography on the outcome of patients with acute anterior ischemic stroke receiving thrombolysis treatment

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Abstract

Background: Functional outcomes of patient with acute ischemic stroke are influenced by the status of the cerebral collaterals. The study aims at evaluating the influence of cerebral collaterals on clinical and radiological outcome in patients with acute anterior ischemic stroke (AAIS) treated with IV recombinant tissue plasminogen activator (IV-rtPA).

Results: Independent predictors of good functional outcomes were in the form of low NIHSS (odds ratio = 1.23, 95%CI = 1.01–2.34, $p = 0.01$), ASPECT ≥ 8 (odds ratio = 4.56, 95%CI = 3.40–7.89, $p < 0.001$), and good collateral status by Miteff grading system (odds ratio = 1.23, 95%CI = 2.22–6.79, $p < 0.001$).

Conclusion: Good collateral status is associated with milder stroke volume and good functional outcome. Also, low NIHSS, ASPECT score ≥ 8 and good collateral status by Miteff grading system were reliable independent predictors of favorable outcome in IV-rtPA treated patients with AAIS.

Keywords: Cerebral blood flow, Cerebral ischemia, Collateral circulation, Computed tomography angiography, Stroke

Introduction

Stroke ranks second as a major cause of both disability and death worldwide. The worldwide prevalence of stroke was 80.1 million in 2016 [1]. In Egypt, stroke is responsible for 6.4% of all deaths. It comes in the third place after cardiovascular and gastrointestinal diseases [2]. The emergence of reperfusion therapies for acute ischemic stroke have changed the outcome and led to significant improvements in many cases with acute brain ischemia [3, 4].

The cerebral collateral circulation represents an auxiliary chain of vascular pathways that may preserve

cerebral perfusion when the region's main primary vessel becomes occluded [5]. It consists of extracranial and intracranial sources of cerebral blood flow and can be divided into primary collaterals, the circle of Willis, secondary collaterals, the ophthalmic and leptomeningeal arteries, and tertiary collaterals, new vessels through angiogenesis [5, 6]. Recruitment of cerebral collaterals may be as a result of hypoperfusion caused by thrombotic, embolic events, or hemodynamic failure [7]. Collateral circulation has a vital impact on the outcome of acute reperfusion treatments in patients with acute ischemic stroke [8–11]. Good collaterals status associated with good functional outcome when compared to poor collateral vessels [12, 13].

This study aims at evaluating the influence of cerebral collaterals on clinical and radiological outcome in patients with acute anterior ischemic stroke (AAIS)

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treated with IV recombinant tissue plasminogen activator (IV-rtPA).

Methods

This prospective cohort study, registered trial (NCT03311386), was conducted at Assiut University stroke center, in the period between January 2018 to February 2021. The medical ethical review board of Assiut University approved the study—approval number 17200000, and we obtained informed consent from the patients and/or their relatives.

Forty patients with AAIS treated with IV-rtPA were enrolled for the study. Inclusion criteria were patients aged ≥ 18 years with AAIS eligible for IV-rtPA and had a CTA performed before receiving IV-rtPA and in the next day after treatment. Exclusion criteria were patients with renal impairments, patients unable to come for follow-up or if consent could not be obtained from the patient or relatives. Demographic data were gathered in addition to stroke risk factors such as hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, and smoking.

Stroke was classified according to the etiology into large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined etiology, and stroke of undetermined etiology based on TOAST classification [14].

National Institutes of Health Stroke Scale score was done for all patients before the IV-rtPA bolus and at 24 hours after treatment initiation [15].

Plain CT brain was performed for all patients and Alberta Stroke Program Early CT Score (ASPECTS) was obtained. According to ASPECTS, patients were categorized as having large infarcts (ASPECTS ≤ 7 points, poor ASPECTS) and small infarcts (ASPECTS 8–10 points, better ASPECTS) [16].

CTA was performed in all patients, before receiving IV-rtPA and on the next day after treatment. For assessment of intracranial collaterals we used the three following grading methodologies: Miteff collateral grading system (Fig. 1), where collateral status are classified as good, if major MCA branches are visible distal to the occlusion, moderate, if some MCA vessels are seen in the Sylvian fissure or poor, if only superficial MCA branches are reconstituted [17]. Maas system (Fig. 2) collaterals vessels are graded by comparing on the symptomatic hemisphere with the contralateral unaffected hemisphere as exuberant, greater than, less than, equal to the contralateral normal hemisphere or absent [18]. Modified Tan system (Fig. 3), grades the collaterals status as poor if the collateral supply vessels $\leq 50\%$ of the MCA territory, and good when the collateral supply vessels $> 50\%$ of the MCA territory [19].

Functional outcome was evaluated by modified Rankin Scale after 3 months from the onset. According to mRS measures patients with scores of 0–2 were defined as having good clinical outcome and those with scores 3–6 have poor clinical outcome [20–22].

Statistical analysis: Data were collected and analyzed by using SPSS (Statistical Package for the Social Science,

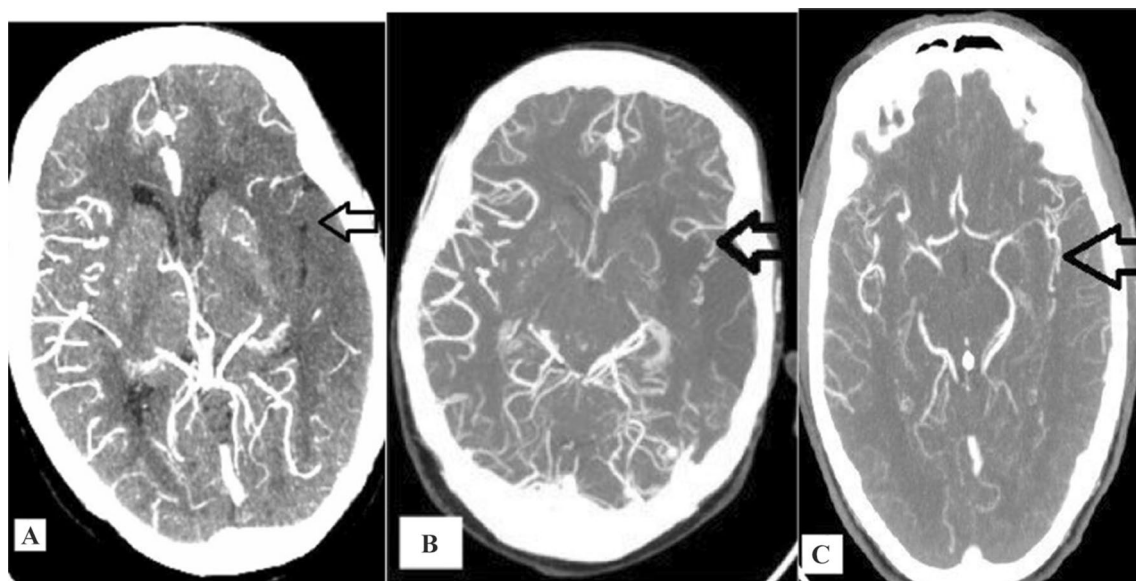


Fig. 1 Miteff system. **A** Contrast opacification is seen merely in the distal superficial branches. **B** Vessels can be seen at the Sylvian fissure. **C** Major vessels are reconstituted distal to the occlusion

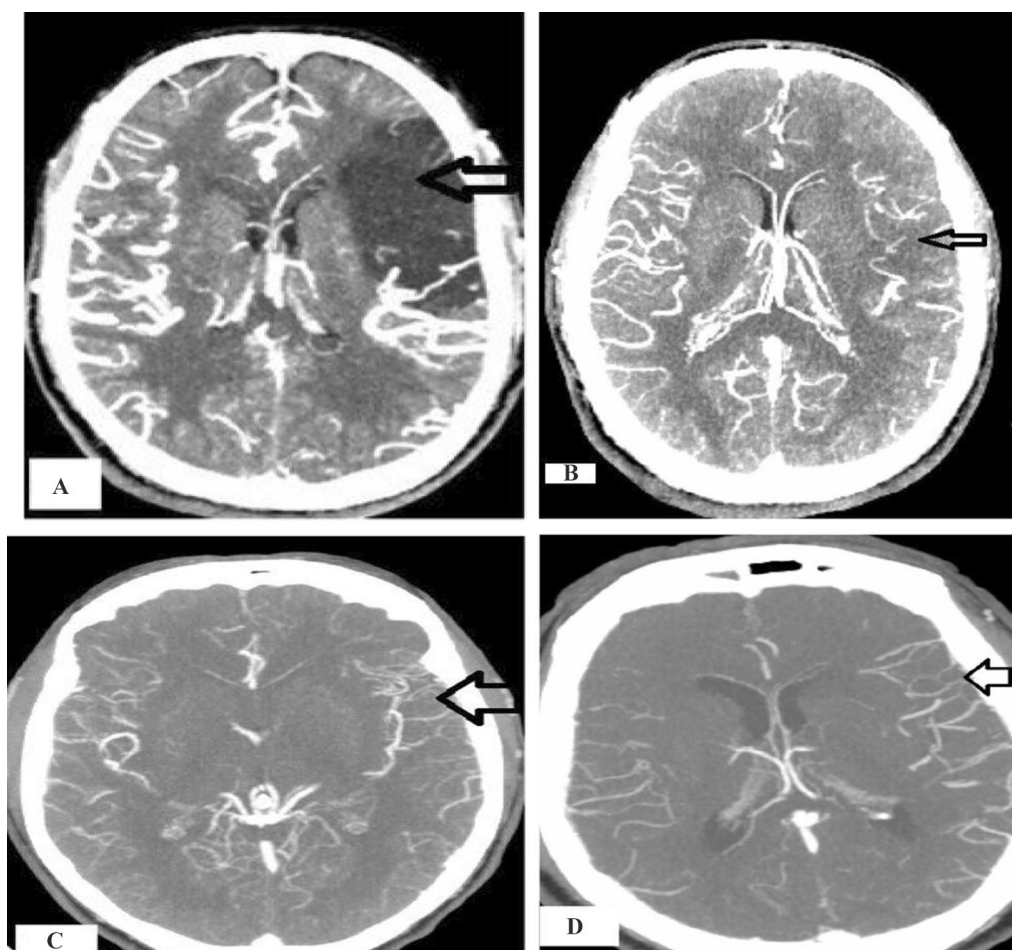


Fig. 2 Maas system. **A** No vessel opacification. **B** Opacification less than that on the contralateral side. **C** Opacification equal to that on the contralateral side is not shown. **D** More opacification than that on the contralateral side

version 20, IBM, and Armonk, New York). Quantitative data were expressed as mean \pm standard deviation (SD) and compared with Student's *t* test. Nominal data were given as number (*n*) and percentage (%). χ^2 test was implemented on such data. Predictors of functional outcome were determined by logistic regression analysis. Accuracy of ASPECTS and Miteff methods in prediction of functional outcome was determined by receiver operator characteristics (ROC) curve. Level of confidence was kept at 95% and hence, *P* value was considered significant if <0.05 .

Results

The current study included 40 patients with acute ischemic stroke. Motor disability was assessed by modified Rankin Scale at 3 months. Good and poor functional outcomes were defined by mRS scores of 0–2 and 3–6, respectively, where 26 (65%) patients had good outcome and 14 (35%) patients had poor outcome.

Mean age of enrolled patients was 58.55 ± 11.47 years. Majority (65%) of enrolled patients were men and 14 (35%) patients were women. A relatively higher proportion of patients (20, 50%) had hypertension; other factors are listed in Table 1.

The pre-rtPA mean NIHSS score was 12.20 ± 3.50 . After injection, majority (70%) of patients was improved with mean NIHSS was 6.05 ± 2.79 (Table 2).

All patients (26) with good functional outcome had ASPECT score ≥ 8 in addition to good collaterals in the pre-rtPA CTA based on Miteff method while only 22 (84.6%), and 16 (61.5%) patients of this group showed good collaterals by Tan and Maas method, respectively (Table 3).

After injection, all patients who showed poor functional outcome had poor collaterals on the second day CTA based on Miteff and Maas methods while 8 (57.1%) of patients despite having good collateral based on Tan method they had a poor functional outcome (Fig. 4).

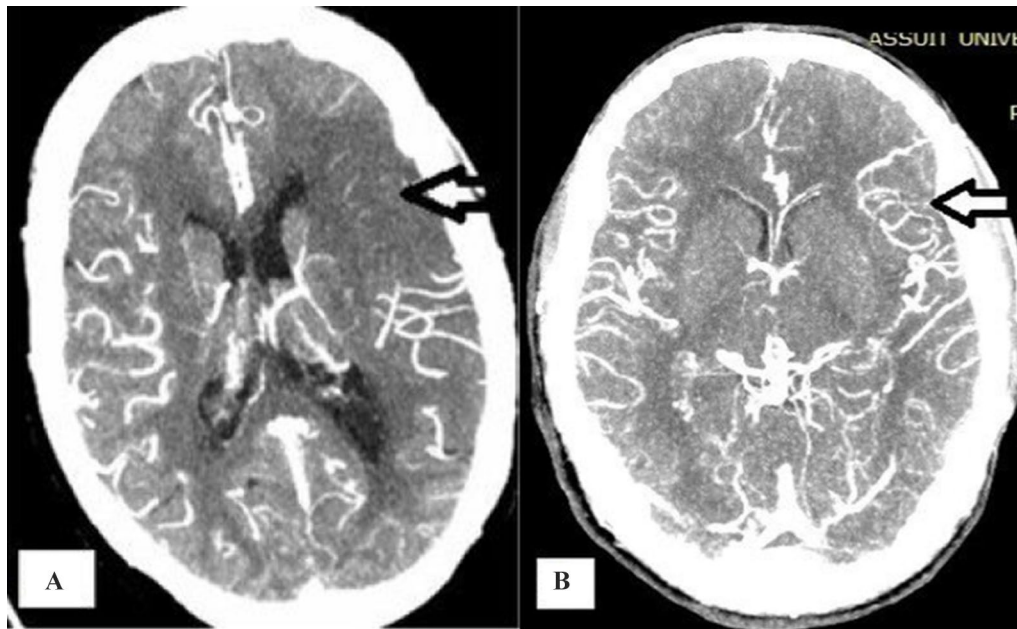


Fig. 3 Modified Tan system. **A** Less than 50% of the MCA territory. **B** More than 50% of the MCA territory

Table 1 Baseline data of studied patients based on functional outcome

	Total (n = 40)	Good outcome (n = 26)	Poor outcome (n = 14)	P value
Age (years)	58.55 ± 11.47	57.23 ± 12.25	61 ± 9.81	0.32
Age as a risk factor	22 (55%)	12 (46.2%)	10 (71.4%)	0.11
Sex				
Male	26 (65%)	18 (69.2%)	8 (57.1%)	0.33
Female	14 (35%)	8 (30.8%)	6 (42.9%)	
Hypertension	20 (50%)	14 (53.8%)	6 (42.9%)	0.37
Diabetes mellitus	10 (25%)	8 (30.8%)	2 (14.3%)	0.22
Ischemic heart disease	8 (20%)	2 (7.7%)	6 (42.9%)	0.01
Smoking	8 (20%)	6 (23.1%)	2 (14.3%)	0.41
Dyslipidemia	8 (20%)	4 (15.4%)	4 (28.6%)	0.27
Previous stroke	2 (5%)	0	2 (14.3%)	0.11

Data expressed as frequency (percentage), mean (SD). P value was significant if < 0.05. n: number

Nearly all patients with good functional outcome in the different methods had good collaterals in the follow-up CTA after injection (Table 3).

Based on the current study, it was found that predictors of good functional outcome among patients with acute ischemic stroke were low NIHSS (odds ratio = 1.23, 95%CI = 1.01–2.34, $p = 0.01$), ASPECT > 8 (odds ratio = 4.56, 95%CI = 3.40–7.89, $p < 0.001$), and Miteff (odds ratio = 1.23, 95%CI = 2.22–6.79, $p < 0.001$) (Table 4 and Fig. 5).

It was found that ASPECTS method had 100% sensitivity and 92.9% specificity for prediction of good

functional outcome with overall accuracy was 97.6% and area under curve was 0.96 while Miteff method before injection had 100% sensitivity and 71.4% specificity for prediction of good functional outcome with overall accuracy was 89.8% and area under curve was 0.85 (Table 5 and Fig. 6).

It was found that frequency of collateral failure was 8 (20%), 2 (5%) and 2 (5%) of patients based on Miteff, Tan and Maas method, respectively. Those patients had poor functional outcome (Table 6).

Table 2 National Institutes of Health Stroke Scale among studied patients

	Functional outcome			P
	Total (n = 40)	Good (n = 26)	Poor (n = 14)	
Baseline NIHSS	12.20 ± 3.50	11.69 ± 3.69	13.14 ± 3.01	0.21
Class				0.09
Moderate stroke	34 (85%)	24 (92.3%)	10 (71.4%)	
Moderate-to-severe stroke	6 (15%)	2 (7.7%)	4 (28.6%)	
Follow up NIHSS	6.05 ± 2.79	2.53 ± 1.12	12.57 ± 3.92	0.01
Class				0.01
Improved	28 (70%)	26 (100%)	2 (14.3%)	
Not improved	12 (12%)	0	12 (85.7%)	

Data expressed as mean (SD), frequency (percentage). P value was significant if < 0.05. n: number; NIHSS: National Institutes of Health Stroke Scale

Table 3 Different scores for assessment of intracranial collateral by CTA

	Functional outcome			P
	Total (n = 40)	Good (n = 26)	Poor (n = 14)	
Baseline ASPECT ≥ 8	27 (67.5%)	26 (100%)	1 (7.1%)	< 0.001
Good collateral before injection				
Miteff method	30 (75%)	26 (100%)	4 (28.6%)	< 0.001
Tan method	30 (75%)	22 (84.6%)	8 (57.1%)	0.06
Maas method	18 (45%)	16 (61.5%)	2 (14.3%)	< 0.001
Good collateral after injection				
Miteff method	26 (65%)	26 (100%)	0	< 0.001
Tan method	34 (85%)	26 (100%)	8 (57.1%)	< 0.001
Maas method	24 (60%)	24 (92.3%)	0	< 0.001

Data expressed as frequency (percentage). P value was significant if < 0.05. n: number; CTA computed tomography angiography

Discussion

In the current study, 40 patients with acute ischemic stroke were enrolled. This study aimed at evaluating the relationship between the state of the cerebral collateral blood vessels and the functional outcome of patients with acute ischemic stroke after thrombolytic therapy. Mean age of those patients was 58.55 ± 11.47 years and the majority of them were males. Also, HTN and DM were the most frequently reported risk factors (50% and 25%, respectively). These results were consistent a previously reported study by Yeo and colleagues that enrolled 209 patients with acute ischemic stroke. Mean age of patients was 64 years. Also, the most frequent risk factors were HTN (63.2%) and DM (29.2%) [23]. Besides, Eleassawi and colleagues studied 30 patients with acute stroke; 70% of them were males. Out of all patients, 56.6% had DM and 66.6% had HTN [24].

Regarding etiology of the stroke, in majority (70%) of patients, large-artery atherosclerosis was the etiology of stroke. Cardioembolic etiology was present in 6 (15%) patients. Undetermined aetiologies also, were

present in another 6 (15%) patients. In contrast, Yeo and colleagues found that the most frequent etiology was cardioembolic causes (48%) followed by large-artery atherosclerosis (26%) [25]. These discrepancies could be attributed to different population, sample size and selection bias.

Higher frequency of large-artery atherosclerosis in the current study could be explained by relatively high frequency of diabetic patients (25%). It was found that diabetic patients are susceptible to vessel insult. In patient with diabetes, the reduced elasticity of blood vessels and stenosis of the cerebral capillaries can impact adversely the establishment of collateral circulation, and aggravating clinical symptoms [26].

Functional outcome in the current study was assessed by modified Rankin Scale after 3 months from rtPA administration where 26 (65%) patients had good outcome and 14 (35%) patients had poor outcome. In line with the current study, Eleassawi and colleagues showed that 60% of patients who received rtPA had good outcome with regard to mRS after 3 months [24].

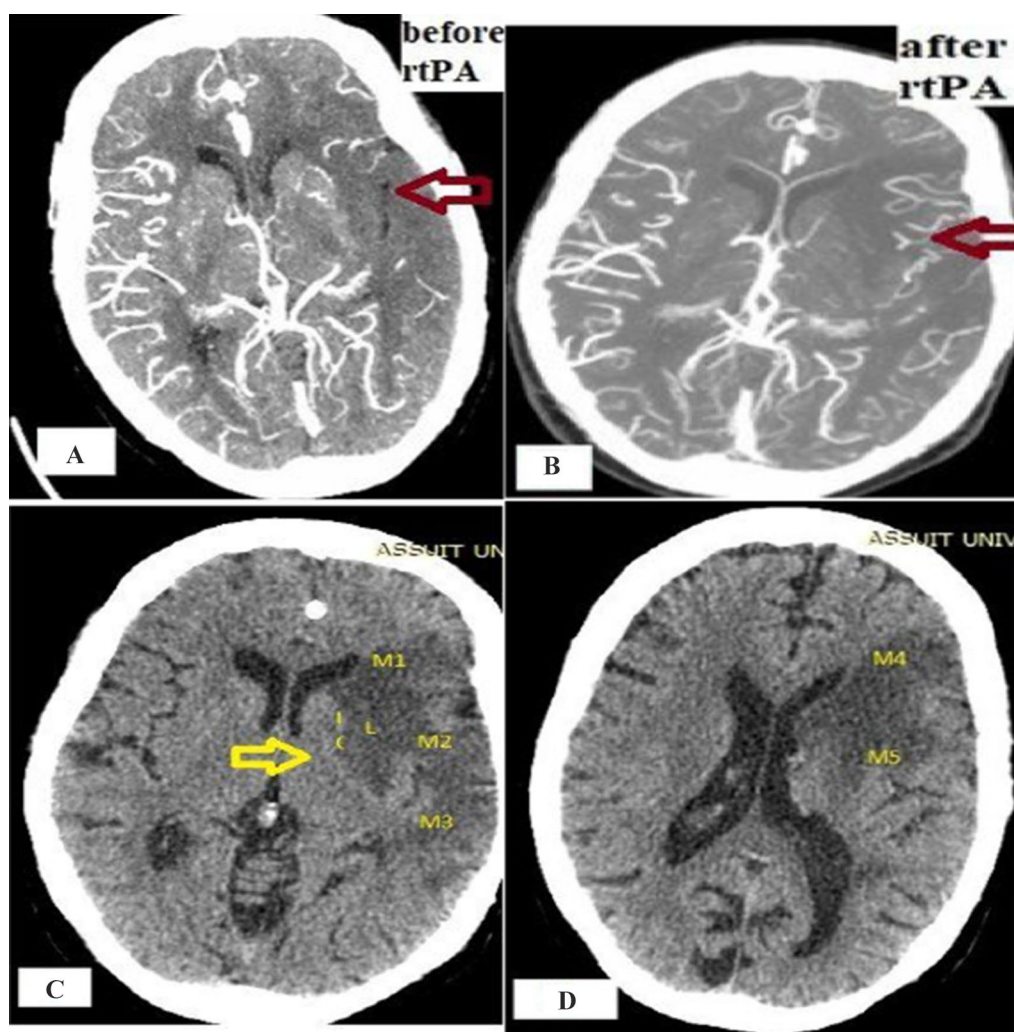


Fig. 4 Patient with mRS 6. **A** Poor collateral status before rtPA injection. **B** Poor collateral status after rtPA injection. **C, D**, Worse ASPECT score = 2

Table 4 Predictors of good functional outcome in acute ischemic stroke

	Odds ratio	95%CI	P value
Low NIHSS	1.23	1.01–2.34	0.01
ASPECT ≥ 8	4.56	3.40–7.89	<0.001
Miteff method before injection	3.30	2.22–6.79	<0.001

P value was significant if < 0.05. NIHSS National Institutes of Health Stroke Scale, CI confidence interval

Also, in agreement with the current study, a previous study by Yeo and colleagues recruited 200 patients with AIS. The authors found that good functional outcomes (mRS 0–2) at 3 months were achieved in 107 (53.5%) patients following rtPA [25]. Also, the present results

were consistent with those of Leonard and colleagues who demonstrated that early neurological improvement during the first 24 h after intravenous thrombolysis is always associated with better functional outcomes at 3 months by mRS in acute ischemic stroke patients [27].

Here, we found that both groups of patients either with poor or good functional outcome had insignificant differences with regard to baseline NIHSS (11.69 ± 3.69 versus 13.14 ± 3.01 ; $p = 0.21$). Also, we found that majority of patients had moderate stroke based on baseline NIHSS. This result was also reported by Yeo and colleagues [25].

In the current study, low NIHSS was a predictor for good functional outcome with odds ratio was 1.23. Also, Kazi and colleagues found that a lower baseline NIHSS score was independently predictive of a favorable outcome for patients with AAIS (OR 1.268, 95% CI 1.76–1.358) [28].

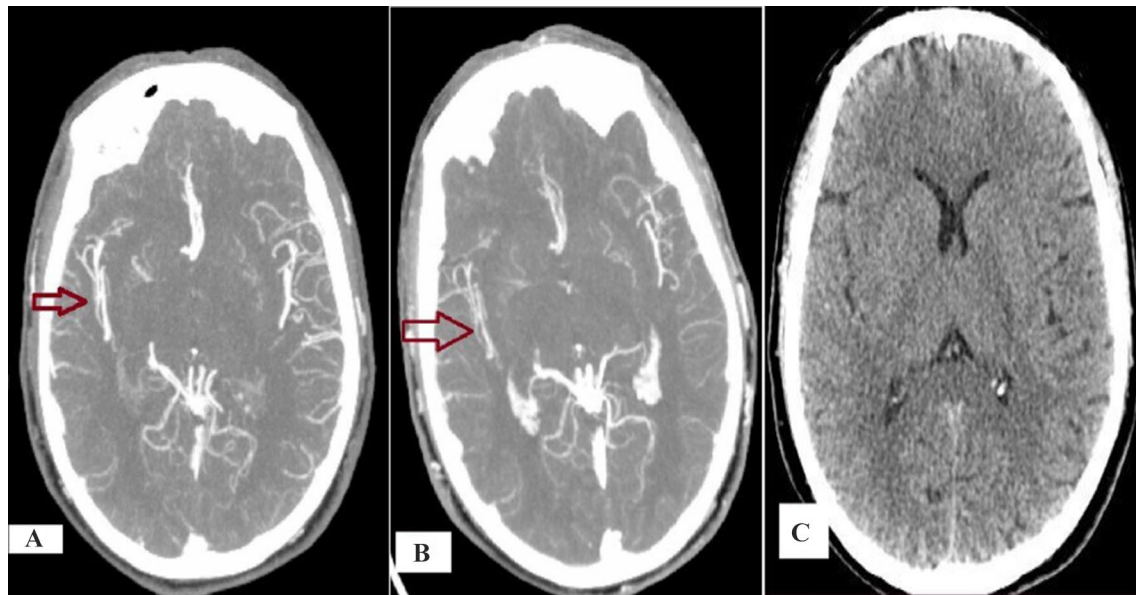


Fig. 5 Patient with pre-tPA NIHSS = 5. **A** Good collaterals before rtPA “Mittef 3”. **B** Good collaterals after rtPA. **C** Better ASPECTS “10”. mRS = 0

Table 5 ASPECT and Miteff methods in prediction of good functional outcome

	ASPECT method	Miteff method
Sensitivity	100%	100%
Specificity	92.9%	71.4%
Positive predictive value	96.3%	86.7%
Negative predictive value	100%	100%
Accuracy	97.6	89.8%
Area under curve	0.96	0.85
P value	< 0.001	< 0.001

P value was significant if < 0.05. ASPECTS Alberta Stroke Program Early CT Score

In the current study, intracranial collaterals were assessed by Miteff, Tan, and Maas method where majority of patients with good functional outcome had good collaterals either pre-rtPA or post-rtPA injection. With multivariate regression analysis, it was found that only baseline Miteff method can be used as predictors of good functional outcome with odds ratio was 3.30. Yeo and colleagues stated that Miteff methods had odds ratio 3.38 for prediction functional outcome in patients with AIS [23].

In line with the current study, it was found that only the Miteff grading system could determine good functional outcomes at 3 months. These results could be attributed to good collaterals in Sylvian fissure and the insular regions, main regions assessed by Miteff scoring system, improve perfusion which lead to better outcomes [29].

The modified Tan method is easily replicable across readers since it is a basic grading system. However, it was discovered that it was not a reliable predictor of a positive result. Similarly, the Maas system failed to predict good functional outcomes [22].

Also, in the current study, it was found that all patients with good functional outcome and only one patient with poor functional outcome had ASPECT score ≥ 8 . We found that ASPECT score ≥ 8 was a predictor for good functional outcome with odds ratio was 4.56. It was found that ASPECT method had 100% sensitivity and 92.9% specificity for prediction of good functional outcome with overall accuracy was 97.6% and area under curve was 0.96. This was consistent with Esmail and colleagues who found that patients with ASPECTS ≤ 7 were significantly associated with about fourfold increased risk of poor outcomes (OR 3.95, 95% CI 2.09–11.38, and $P < 0.01$) [30].

The current study found that failure of intracranial collaterals was able to predict poor functional outcome based on Miteff, Maas and modified Tan methods. This finding is contrary to that of Yeo and colleagues who found that collateral failure was not associated with worse outcomes, this observation was postulated to the transient during the early critical period which have disappeared in the follow-up imaging [23].

The study had limitations; obtaining 2 CTA for all patients was a challenge for the cost and the hazards of radiation dose. Also, the small sample size of our study

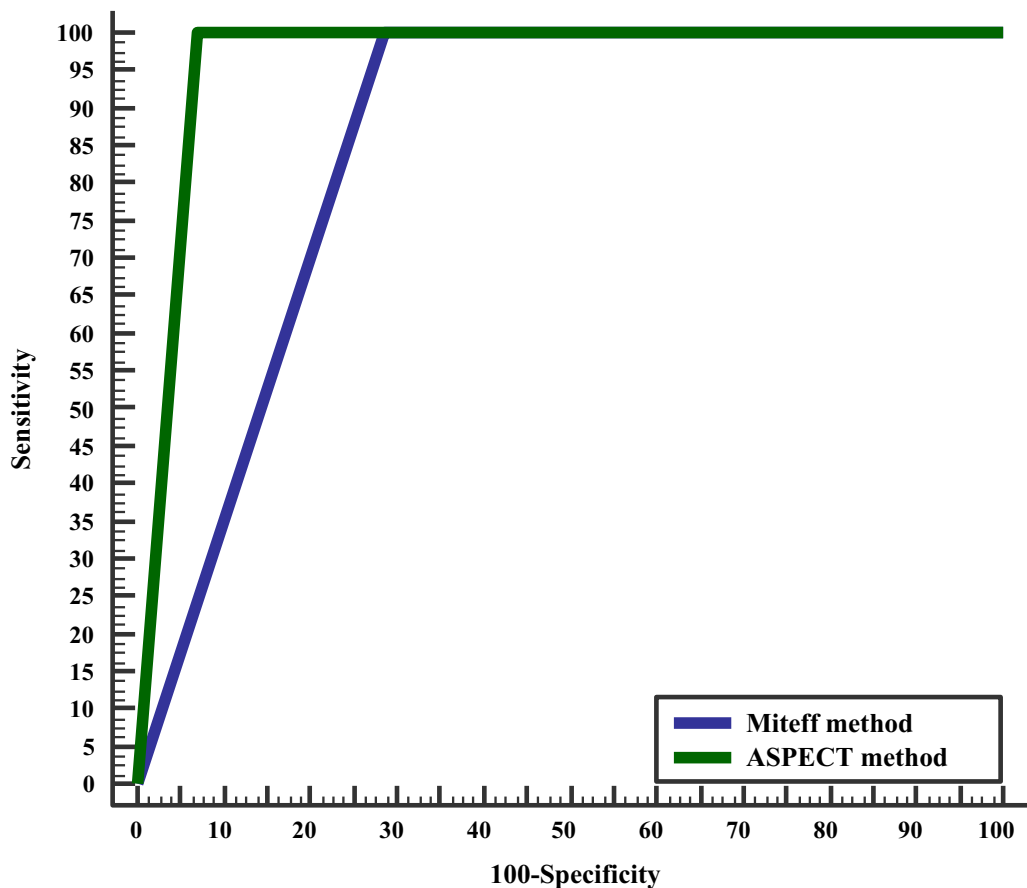


Fig. 6 ASPECT and Miteff methods in prediction of good functional outcome

Table 6 Frequency of collateral failure in the current study

	<i>N</i> = 40
Collateral failure based on	
Miteff method	8 (20%)
Tan method	2 (5%)
Maas method	2 (5%)

Data expressed as frequency (percentage)

affected the ability to show some associations which could be found with larger sample size.

Conclusion

Our study has shown that good collateral status is associated with milder stroke volume and good functional outcome. Also, it was found that low NIHSS, ASPECT score ≥ 8 and Miteff system were reliable predictors of favorable outcome in IV-rtPA treated patients with AAIS, while poor functional outcomes can be predicted

by all methodologies used for assessing the intracranial collaterals.

Abbreviations

AAIS: Acute anterior ischemic stroke; AIS: Acute ischemic stroke; ASPECTS: Alberta Stroke Program Early CT Score; CI: Confidence interval; CTA: CT angiography; MCA: Middle cerebral artery; mRS: Modified Rankin Scale; NIHSS: NIH Stroke Scale; Or: Odds ratio; rtPA: Recombinant tissue plasminogen activator.

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Author contributions

AM: recruited participants, analysis, and interpreted data, and were the contributors in writing the manuscript. ES and AH: wrote the manuscript and analysis of data. MH and AM: helped in data entry, analyze, and generate result sheets and revised data interpretation and manuscript. All authors have read and approved the manuscript.

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Availability of data and materials

All data generated or analyzed during this study are available from the corresponding author on request.

Declarations

Ethics approval and consent to participate

After a detailed explanation of the study's goal, methods, potential dangers, and side effects, each participant gave written informed consent to be included in the study. The University Hospital Institutional Review Board approved the study protocol with authorization number 17200000.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflicts of interests.

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