Neurology Asia 2022; 27(2) : 247 – 253

ASPECTS as a clinical outcome marker for MCA infarction treated with thrombolytic therapy: Non-contrast CT versus CTA source images

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Abstract

Background & Objective: Computed tomography angiography (CTA) in acute stroke has been widely used to demonstrate arterial occlusion. Alberta Stroke Program Early CT Score (ASPECTS) is used to detect early ischemic signs in non-contrast computed tomography (NCCT) in the middle cerebral artery region. We hypothesized that computed tomography angiography source image (CTA-SI) is superior to NCCT in predicting final infarct volume, 24 hour National Institutes of Health Stroke Scale (NIHSS) score and 90-day clinical outcome. *Methods:* Patients who had an acute ischemic stroke due to middle cerebral artery (MCA) occlusion and treated with tissue plasminogen activator (tPA) were retrospectively evaluated. ASPECTS was evaluated by two experienced stroke neurologists in acute NCCT, CTA-SI, and follow up imaging. The final ASPECTS was compared with the mean baseline ASPECTS of NCCT and CTA-SI. The relation of both scores with 24-hour NIHSS and clinical outcome was compared. The Modified Rankin Scale (mRS) was utilized to evaluate the 90-day outcomes. mRS score of 0-2 was considered a "good outcome". *Results:* Fifty-three patients were evaluated. We observed a significant relation among CTA-SI ASPECTS and after treatment 24hr ASPECTS (y= -3.9 + 1.4 x; 95% CI, -7.6 to -0.2) (y= -26.04 + 3.5 x; CI, -41 to -10). The median baseline 24-hr NHISS was 6 (0 - 22). We found a better correlation between CTA-SI ASPECTS and 24-hr NHISS (y= 363.06 + -37.03 x; CI, -148 to 864) than between NCCT ASPECTS and 24h NHISS (y=529.80 + -62.55 x; CI, 180 - 829). Median 90 days mRS score was 2 (0 - 6). According to Deming regression analysis, the CTA-SI ASPECTS (y= 76.10 + -7.69 x; 95% CI, -36 to 188) was more consistent with the 90 day mRS compared to NCCT ASPECTS (y=149.86 + -17.67 x; 95% CI, 23 - 267) CTA-SI was superior in predicting 24hr NIHSS and day 90 mRS compared to NCCT ASPECTS.
Conclusion: Prediction of CTA-SI ASPECTs is better than NCCT ASPECTs at 24hr NIHSS, 3-month mRS and final infarct size in acute ischemic stroke patients treated with tPA.

Keywords: Acute stroke, thrombolytic therapy, neuroimaging

INTRODUCTION

Stroke is the most common reason of long term disability in adults and the second most common reason of mortality worldwide after heart disease and cancer.[1] In acute ischemic stroke (AIS), considering that endovascular treatment can only be applied in comprehensive stroke centers, IV-tPA (intravenous tissue plasminogen activator) treatment emerges as a more available and easily applicable treatment and appropriate patient selection becomes just as important.

The primary step in the treatment of AIS is the rapid assessment of the radiological and clinical features of brain damage. Today, non-contrast computed tomography (NCCT) is the first-line preference for imaging patients with AIS.[2] Early ischemic changes seen on NCCT include loss of gray-white matter separation lateral of the insular cortex and blurring of the clarity of the internal capsule; the NCCT signs have a sensitivity of 40-60% within the first 3 hours after onset of symptoms.[3,4] The Alberta Stroke Program Early CT Score (ASPECTS) provides a simple and systematic method to quantify and describe the tissue changes in the anterior circulation of the brain due to acute ischemic stroke.[5,6] The score

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Date of Submission: 3 October 2021; Date of Acceptance: 12 January 2022

https://doi.org/10.54029/2022kmj

ranges from 10 (normal) to 0 (many areas of hypoattenuation suggestive of severe ischemia). ASPECTS can be high in patients who undergo NCCT shortly after the onset of stroke symptoms. Visible fluid change may not occur on NCCT in the early period in the brain region where ischemia has developed, and ASPECTS can be calculated as 10 points on NCCT and the patient may be mistakenly diagnosed as stroke mimic. In this regard, the clinician should be careful to avoid misdiagnosis. NCCT shows cytotoxic edema while computed tomography angiography source image (CTA-SI) detects regions of the brain with hypoattenuation, due to decrease in cerebral blood volume or because of delayed arrival of contrast medium to the ischemic brain.[7,8] Previous studies have shown that CTA-SI ASPECTS predicts the final extent of infarct better than NCCT ASPECTS.[2,9-11] We hypothesized that CTA-SI correlates better with the final infarct size, 24 hour National Institutes of Health Stroke Scale (NHISS), and clinical outcomes compared to NCCT in patients with middle cerebral artery occlusion only receiving tPA therapy. The second aim of our study is to determine other clinical factors that effects good outcome.

METHODS

In this retrospective case study, the data of AIS patients who were treated with IV-tPA within 4,5 hours of symptom onset were analyzed. This study obtained approval from the Human Research and Ethics Board and was conducted at a comprehensive stroke center (Eskisehir Osmangazi University Stroke Center, Department of Neurology). The patients were categorized as M1-middle cerebral artery (MCA), M2-MCA, and distal-MCA stroke. Patients without CTA imaging, patients with posterior system involvement, and patients who received endovascular treatment were excluded from the study.

All patients were evaluated and the NIHSS was recorded by a stroke neurologist at the emergency service. CTA and NCCT were performed in all patients. IV tPA treatment was given to patients without contraindications. Details of patient demographics, 24-hr NIHSS and 90-day Modified Rankin Scale (mRS) were noted.

Imaging and image-analysis

NCCT and CTA were obtained using a standardized acute stroke protocol on a 128 slice CT scanner (SOMATOM Perspective; Siemens) set to 130 kV, 280 mAs, and 5-mm slice diameter. Images were taken following single bolus IV injection of 50-75 mL iodinated contrast at 4.5/5 ml/s into a peripheral vein. CTA was performed after immediately NCCT without delay. Standard coverage included the area from the arch to the vertex. Follow up NCCT was obtained 24 hours after IV tPa. Images were read by two experienced stroke neurologists who were blinded to the clinical information of the patients aside from the side of involvement. ASPECTS was noted for NCCT and CTA-SI.

Statistical analysis

Deming regression analysis, which measures the specific size and direction of the deviation between the two methods, was used. It assumes unequal variances between both measurement axes. ID line at the starting point 45° as indicated by a line between the methods of "perfect" represents a compromise. The proportional deviation between the methods is indicated by the statistically significant ($P < 0.05$) deviation of the slope from 1, and the constant deviation by the statistically significant deviation of the intersection from 0. The two raters' scores for each modality (CTA, NCCT, 24-hr NHISS, and 90 day mRS parametric maps) were correlated for inter-rater agreement using Spearman's rank correlation. Agreement between paired measures was assessed with weighted kappa. There was a moderate agreement between the two raters' CT measures ($\kappa = 0.571$; 95 % CI, 0.357 to 0.785) and there was a good agreement between their CTA-SI measures ($\kappa = 0.737$; 95 % CI, 0.642 to 0.832). The SPSS statistical package (SPSS v 21.0; SPSS, Chicago, IL) and the MedCalc package (v15.2) were used for statistical analyses. A p value less than 0.05 was considered statistically significant. The descriptive statistics were expressed as ratio (percentage) for qualitative variables and the mean ± standard deviation or median (interquartile range) values for quantitative variables.

Student's t-test was used for normally distributed continuous variables and Mann-Whitney U test for continuous variables without normal distribution to determined differences between groups. Binary logistic regression analysis was used to identify risk factors thought to affect the dependent variable (mRS 0-2; good outcome).

RESULTS

Of the 273 patients in our database, we evaluated 53 patients who had an AIS due to MCA

Table 1: Demographic characteristics of patients

Variables	Values
Female, n (%)	25 (47.2)
Age, y, mean (SD)	62.5 (12.5)
Baseline NIHSS score, median (IQR)	12 (4-22)
Time to symptom IV-tPA min, mean (SD)	171 (57)
Vascular risk factors, n (%)	
Hypertension	32 (60.4)
Diabetes mellitus	13 (24.5)
Dyslipidemia	17 (32.1)
Current smoking	18 (34.0)
Atrial fibrillation	13 (24.5)
Previous stroke	5 (9.4)
90-day mRS (0-2)	34 (64.2)
NIHSS decrease (>4)	34 (64.2)

NIHSS: National Institutes of Health Stroke Scale; IV-tPA: Intravenous tissue-type plasminogen activator

occlusion, were admitted in the initial 4.5 hours of stroke onset, were treated with IV-tPA, and had no contraindications to treatment. All patients underwent NCCT and CTA-SI at admission. The mean age of the patients was 62±12 years and 52% were male. We detected MCA-M1 occlusion in 23 (43.3%) patients, MCA-M2 occlusion in 7 (13.2%) patients and MCA-distal occlusions in 23 (43.3%) patients. Demographic characteristics of patients are presented in Table 1.

While median NCCT ASPECTs score was 9 (7-10), CTA-SI ASPECTs was 8 (4-10), and final ASPECTs was 7 (2-10). There was a better correlation among CTA-SI ASPECTs and final ASPECTs (y= -3.9 + 1.4 x; 95% CI, -7.6 to -0.2) than between NCCT ASPECTs and final ASPECTs (y= -26.04 + 3.5 x; 95% CI, -41 to -10) (Figure 1).

CTA-SI predicted follow-up ASPECTs in 92.4% of patients, while NCCT predicted it in 56.6%. It was found that CTA-SI ASPECTs is superior to NCCT ASPECTs in predicting the final ASPECTs measurement.

In the analysis of factors affecting good clinical outcome (mRS:0-2), age, NHISS at admission, blood glucose level at admission, insulin level, past stroke history and initial CTA-SI ASPECTs were significant parameters Table 2. Finally, in the binary regression analyzes, just initial NIHSS

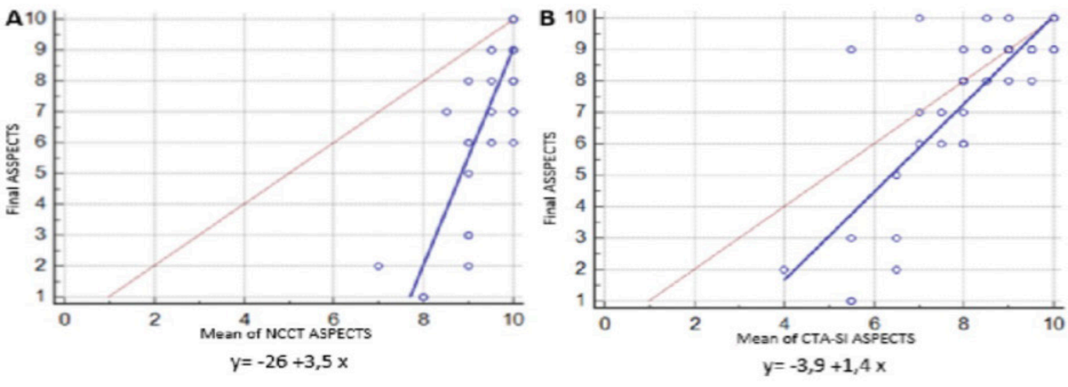

Figure 1. Comparisons between baseline ASPECTS according to NCCT and CTA-SI. It is seen that the CTA ASPECTS (B) averages predict the final ASPECT better than the NCCT ASPECTS (A) averages. When the equations are examined, it is found that the fixed value of CTA ASPECTS is closer to 0 and the parameter estimation coefficient is closer to 1.

Table 2: Univariate analysis of factors associated with good clinical outcome

Variables	mRS 0-2 n=34	mRS 3-6 n=19	p-Value
Age, y, mean (SD)	58.5 (11.4)	69.8 (11.2)	0.001
Baseline NIHSS score, mean (SD)	9.8 (4.4)	14.1 (4.3)	0.002
Time to needle, mean (SD)	161.3 (51.2)	189.4 (65.1)	0.088
Door to needle, mean(SD)	79.5 (28.9)	82.4 (38.2)	0.751
Pre-tPA systolic blood pressure, mean (SD)	81.7 (10.2)	87.6 (10.3)	0.052
Baseline glucose, mean (SD)	130.5 (36.0)	156.8 (54.5)	0.039
Insulin, mean (SD)	11.7 (9.3)	38.0 (46.2)	0.008
Vascular risk factors, n (%)			
Hypertension	16 (30.1)	14 (26.4)	0.032
Diabetes mellitus	6 (11.3)	5 (9.4)	0.475
Dyslipidemia	13 (24.5)	3 (5.6)	0.201
Active smoker	15 (28.3)	3 (5.6)	0.067
Atrial fibrillation	8 (15)	5 (14.7)	0.746
Previous stroke history	1 (1.8)	4 (7.5)	0.040
CTA-SI ASPECTs	8.88(1,12)	7.78 (1,68)	0.015
NCCT ASPECTs	9.82 (0,38)	9.31 (1,10)	0.079

NIHSS: National Institutes of Health Stroke Scale; IV-tPA: Intravenous tissue-type plasminogen activator

was found to be an independent predictor of good clinical outcome Table 3.

The median baseline 24-hr NHISS was 6 (0 - 22), we found a better correlation between CTA-SI ASPECTS and 24-hr NHISS than between NCCT ASPECTS (y= 363.06 + -37.03 x; CI, -148 to 864) and 24h NHISS (y=529.80 + -62.55 x; CI, 180 - 829).

Median 90 days mRS score was 2 (0 - 6). According to Deming regression analysis, the CTA-SI ASPECTS score (y= 76.10 + -7.69 x; 95% CI, -36 to 188) was more consistent with the 90 day mRS compared to NCCT ASPECTS (y=149.86 + -17.67 x; 95% CI, 23 - 267).

CTA-SI predicted the final infarct size better than NCCT in all localizations of the thrombus (MCA-M1, MCA-M2, and MCA-distal occlusions) Table 4.

DISCUSSION

This study shows that baseline CTA-ASPECTS is superior to baseline CT-ASPECTS to predict 24hr NIHSS, 3-month mRS and final infarct size in acute ischemic stroke patients treated with tPA. Intravenous tissue plasminogen activator (tPA), which is widely used all over the world, is the first-line treatment of acute stroke, both in bridging therapy before thrombectomy and alone.[12] Optimizing patient selection of who will benefit most from this treatment is the main goal. Previous studies have shown that a high baseline

Table 3: Factors associated with good clinical outcome - Multivariate analyses

Variables	95 % CI	B (Coefficients)	SE	OR	p
Age	0.868-1.056	-0.044	0.050	0.957	0.383
NIHSS score at admission	0.545-0.969	-0.319	0.147	0.727	**0.029**
Baseline glucose	0.993-1.084	0.037	0.023	1.038	0.103
Insulin	0.884-1.062	-0.310	0.047	0.969	0.505
Hypertension	0.006-1.972	-2.219	1.479	0.109	0.133
CTA-SI ASPECTs	0.610-3.653	0.401	0.457	1.493	0.380

CI= confidence interval; SE= standard error; OR= odds ratio; NIHSS= National Institutes of Health Stroke Scale

Table 4: **Statistics of predicting final ASPECTS according to the occlusion localizations of the methods**

	CTA-SI	NCTT
MCA-M1	y= -5.3 + 1.5 x	y= -23.3 + 3.1 x
MCA-M2	y= 4.8 + 0.4 x	y= -21.9 + 3.1 x
MCA-DISTAL	y= -0.1 + 0.9 x	y= -32.7 + 4.2 x

CTA-SI predicted the final infarct size better than NCCT in all localizations of the thrombus (MCA-M1, MCA-M2, and MCA-distal occlusions)

NIHSS score, advanced age, and poor collateral circulation are poor prognostic factors.[13,14] In recent years, ASPECTS has come to the forefront in multicenter studies on endovascular treatment; many studies have excluded patients with low ASPECTS.[15,16] With the increase in endovascular treatment methods, the number of studies in the field of IV-tPA has gradually decreased and there is insufficient data related to ASPECTS.

In this study, ASPECTS evaluated with CTA-SI was found to be superior to NCCT in predicting final infarct size and clinical outcomes in patients diagnosed with MCA infarction who were given thrombolytic therapy. This may be due to the fact that the two imaging techniques work with different mechanisms. CTA-SI may be able to detect the blood flow abnormalities before the ischemic changes are reflected on NCCT.[11] NCCT, on the other hand, can show changes in the fluid content of the brain tissue, and a significant amount of fluid shift is required for this change to be noticeable to the human eye.[17] Ischemic regions in the brain are observed as hypoattenuation in CTA-SI. The hypoattenuation is visually identified as a distinct difference between the normal and the abnormal brain.[9-11,18] (Figure 2)

CTA for the detection of intracranial stenosis or occlusion is reported to have high sensitivi-ty

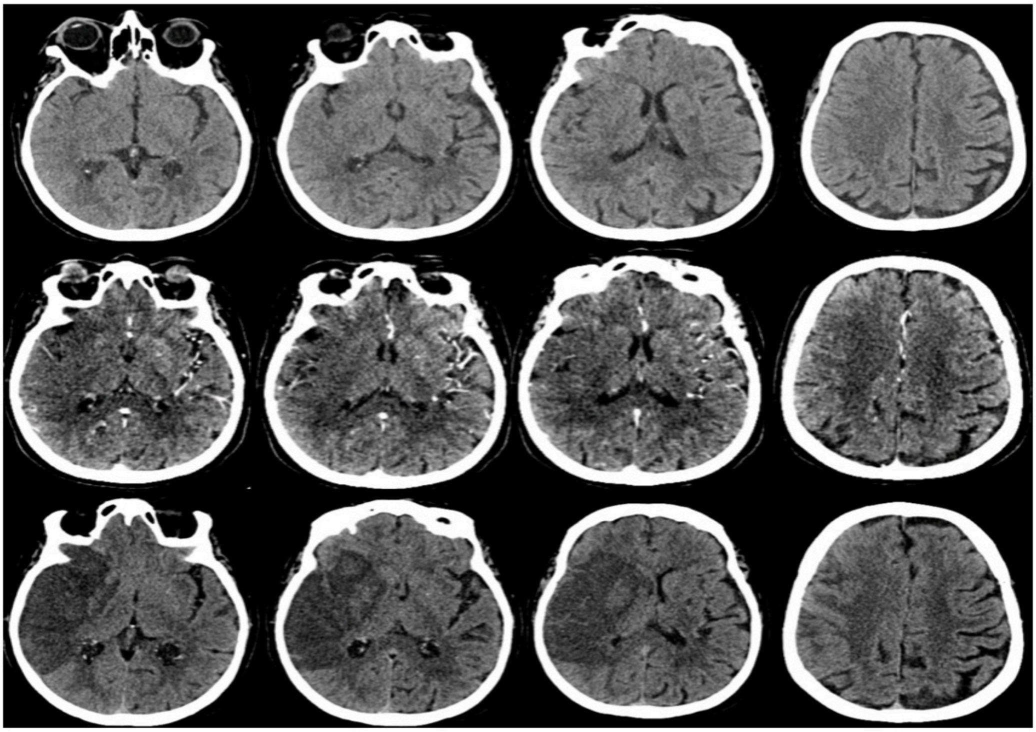

Figure 2. CT scans of a 70-year-old woman with left-sided hemiplegia, left homonymous hemianopia 2 hours after symptom onset

A. Baseline Non-contrast-CT does not show hypoattenuation

B. Baseline CTA-SI shows hypoattenuation with swelling and effacement of the MCA territory

C. Follow-up CT scans show a large area of hypoattenuation of the MCA territory.

and specificity. Previous studies indicated high sensitivity and specificity of CTA for de-tecting moderate/severe stenosis (>97%); sensitivity and specificity for occlusions were higher (closer to 100%).[19,20] In our study, when the arterial occlusion groups were evaluated, it was determined that CTA predicted all segmental MCA occlusions final infarct size better than CT (Table 4).

This study also demonstrated that CTA-SI ASPECTS correlates strongly with 24-hr NIHSS and 90-day clinical outcomes. A previous study of 261 patients with proximal occlusions showed that three-month mRS scores correlated better with baseline CTA-SI ASPECTS than NCCT ASPECTS.[11] A clinical-CT correlation with CTA-SI may reflect more sensitive detection of ischemic regions compared to NCCT ASPECTS.[11]

Many classifications developed to determine the prognosis of ischemic stroke include parameters such as age, stroke severity, and presence of risk factors.[21] In our study, young age, low NIHSS at admission, not be hypertensive, absence of previous stroke, normal glucose and insulin levels at admission were found to be associated with good prognosis, and low NIHSS at admission was found to be directly associated with good prognosis in multivariate analysis. This seems to be a predictable outcome, as high stroke severity is directly related to major vessel occlusion, weak collateral presence, and rapid progression.[22,23]

Retrospective design of this study and inclusion of only one center may limit the generalizability of the results. However we are a high volume referral center for the endovascular management of acute stroke cases, the findings are representative of the situation in the study areas. Additionally, no specific cut off value for ASPECTs associated with good outcome could be determined and patients were not grouped by age. In future multicenter studies with larger sample size, the relationship between age, ASPECTs, and outcome may be more accurately demonstrated. The study population was only on thrombolysed patients, and thus the findings cannot be generalised to non-thrombolysed patients or this who received endovascular therapy. Sample size was also small.

The results of the current study suggest that CTA-SI ASPECTs can predict final infarct size, 24hr NIHSS, and 3-month mRS better than NCCT ASPECTs in acute stroke patients treated with tPA. Acute ischemic stroke treatment algorithms based on non-contrast CT have lost their validity in groundbreaking randomized studies in endovascular treatment, while the imaging of both tissues and vessels together has been deemed a necessity; in this regard, the most widely used and easily interpreted CTA imaging has come to the forefront in managing patient selection.[15,16,24] We are of similar opinion in the selection of patients for thrombolytic therapy. According to the results of our study, which included patients who did not receive endovascular treatment and received only tPA treatment, we believe that CTA evaluation performed by an experienced clinician is effective in predicting the prognosis of the patient.

DISLOSURE

Conflict of interest: None

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