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ORIGINAL RESEARCH

Utility of the ASPECT Score for Predicting Intracranial Hemorrhage Following Intravenous Thrombolysis in Patients with Suspected MCA Infarction: Insights from the Northern Thai Stroke Registry

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Purpose: The association between the Alberta Stroke Programme Early CT Score (ASPECTS) and intracranial hemorrhage (ICH) in acute ischemic stroke (AIS) patients undergoing thrombolysis remains unclear. This study aimed to determine the relationship between ASPECTS and thrombolysis-associated outcomes, focusing on symptomatic (sICH) and asymptomatic (aICH) ICH.

Patients and methods: AIS patients with middle cerebral artery (MCA) territory treated with thrombolysis were enrolled. Patients were categorized into favorable (8–10) and unfavorable (7 or less) ASPECTS. The primary outcomes were sICH and aICH. Secondary outcomes included ICH management, modified Rankin Scale (mRS), and mortality. Multivariable logistic regression analysis evaluated the risk of unfavorable ASPECTS and its association with study outcomes.

Results: We included 622 patients (mean age 66.1 ± 13.5 years; 50.5% male); 95 (15.3%) had unfavorable ASPECTS. Patients with unfavorable ASPECTS had higher sICH but not aICH (21.1% vs 4.9%, $P < 0.001$ and 16.9% vs 17.3%, $P = 1.00$). Unfavorable ASPECTS was associated with sICH (adjusted odds ratio 5.1; 95% confidence interval 2.7–9.7, $P < 0.001$). Factors associated with lower ASPECTS included age ≥ 65 years, body weight < 60 kg, atrial fibrillation, onset-to-needle time ≥ 120 minutes, and anemia. Patients with lower ASPECTS had higher mortality and unfavorable mRS (>2) at discharge, 14 days, and 90 days (74.7% vs 50.1%, $P < 0.001$ for 90-day mRS >2).

Conclusion: ASPECTS is a simple tool to predict thrombolysis-associated sICH but not aICH. Patients with unfavorable ASPECTS are at higher risk of complications and poor functional outcomes. Alternative treatments, such as mechanical thrombectomy, might be advisable for these patients.

Keywords: ischemic stroke, intracranial hemorrhage, thrombolysis, outcome, neuroimaging, ASPECTS

Introduction

Stroke is one of the most devastating neurological conditions, and its early management using thrombolytic agents, such as recombinant tissue-type plasminogen activator (rt-PA), has the potential to reestablish blood flow and mitigate the progression of cerebral infarction.[1,2] However, rt-PA carries the risk of intracranial hemorrhage (ICH), which can be fatal. Two forms of rt-PA-associated ICH are recognized: symptomatic ICH (sICH) and asymptomatic ICH (aICH), with

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incidences of 6.9% and 16.0%, respectively.[3] Both sICH and aICH associated with thrombolysis lead to unfavorable outcomes compared to those without ICH.[3]

Growing evidence suggests that early ischemic change (EIC) from baseline computed tomography (CT) prior to rt-PA treatment can help predict outcomes and complications.[4,5] The Alberta Stroke Programme Early CT Score (ASPECTS) is a systematic quantitative scoring system that assesses the degree of middle cerebral artery (MCA) infarction by evaluating ten specific regions supplied by the MCA.[6–8] Lower ASPECTS, particularly below eight, is associated with unfavorable outcomes and higher incidence of sICH.[5,9] Nevertheless, an ongoing debate persists due to conflicting data on the potential utility of EIC for predictive purposes.[4,10] Additionally, data specifically addressing the use of ASPECTS for aICH is scarce.

Our study aims to determine the association between ASPECTS obtained from pre-rt-PA CT scans and the incidence of ICH, particularly aICH. We also investigate its correlation with the likelihood of neurosurgical interventions, the use of blood components for reversal, and functional outcomes at discharge and during the 14-day and 90-day follow-up periods.

Methods

Study Design and Population

In this single-center, retrospective study, data was retrieved from the Chiang Mai University Hospital Stroke Registry between 1995 and 2021. This registry prospectively collected information on consecutive patients diagnosed with various types of acute stroke. For this study, only cases of acute MCA infarction were included. The patients who received mechanical thrombectomy (MT) were not included in this study. The study received approval from the Institutional Review Board of the Faculty of Medicine, Chiang Mai University (Study code: MED-2566-09429). All data from this study were fully anonymized, and confidentiality was maintained before access. Since the study data were collected as part of routine clinical care, the requirement for individual patient consent was waived by the Research Ethics Committee. This study complies with the ethical principles outlined in the Declaration of Helsinki.

Data Collection and Neuroimaging

All individuals aged 18 years or older, suspected of having experienced acute MCA infarction within the past 4.5 hours, underwent a CT scan of the brain prior to the rt-PA treatment. All the CT scans were performed using a 192-slice dual-source CT system with 1 mm slice thickness without contrast media administration. Certified board neuroradiologists communicated the findings within 15 minutes of the patient's arrival. Data without reported ASPECTS was retrospectively reviewed by neuroradiologists. These results encompassed the presence of hemorrhage, abnormalities in brain tissue, and the assessment of EIC. The evaluation of EIC was conducted using the ASPECTS, ranging from zero to ten. Each point on this scale corresponds to a specific region supplied by the MCA, including the caudate (C), insular ribbon (I), internal capsule (IC), lentiform (L), and six distinct areas of brain parenchyma (M1-M6). One point was subtracted from a total of ten for each observed sign of EIC within the defined regions. The ASPECTS of a normal CT scan is 10 points, whilst a score of zero signifies the presence of extensive and diffuse ischemia within the brain region supplied by the MCA. Patients were categorized into two groups based on their ASPECTS scores: those with unfavorable ASPECTS (7 or lower) and those with favorable ASPECTS (8–10). The cut-off has been chosen in line with the previous studies regarding optimal ASPECTS for rt-PA candidates.[11]

In the absence of any contraindications, patients with acute MCA infarction would receive intravenous rt-PA at a dosage of 0.9 mg per kilogram, with a maximum allowable dose of 90 mg, administered over 60 minutes within the first hour after arriving at the emergency department. Following rt-PA treatment, patients were admitted to the Acute Stroke Unit (ASU), where their vital signs and neurological status, including the National Institutes of Health Stroke Scale (NIHSS), modified Rankin scale (mRS), and Barthel index (BI), were closely monitored. A follow-up brain CT scan was performed 24 hours after rt-PA administration to detect radiological signs of ICH. Patients underwent emergency brain imaging in cases of deteriorating neurological symptoms, defined as an NIHSS increase of four points or more, a decrease of the Glasgow Coma Scale (GCS), nausea, vomiting, sudden headache, or severe hypertension. The comprehensive ASU care team, comprising neurologists, neurosurgeons, hematologists, stroke nurses, and pharmacists, assessed and categorized patients as having aICH and sICH. Treatment decisions, including neurosurgical intervention and the use of reversal agents, were made based on consensus within the comprehensive ASU care team.

Study Outcomes

The primary outcome was the incidence of sICH and aICH corresponding to ASPECTS. Secondary outcomes included clinical parameters such as mRS, NIHSS, BI, mortality, and the use of reversal agents and neurosurgical intervention. Data was analyzed at three-time points: at discharge, 14 days, and 90 days post-stroke onset. Initial diagnosis data included demographic, medical history, laboratory results, and neuroimaging data. Bleeding events were categorized as aICH and sICH. ICH was further classified into hemorrhagic infarction (HI) and parenchymal hemorrhage (PH) according to the NINDS (National Institute of Neurological Disorders and Stroke) study.[12] Data on reversal agents, blood component transfusions, and surgical interventions were collected for rt-PA-associated bleeding. Follow-up imaging results at discharge, 14 and 90 days after rt-PA were recorded, together with functional outcomes (mRS, NIHSS, BI) and mortality, at these time points.

Statistical Analysis

Clinical data were presented in numbers and proportions for categorical data. Mean and corresponding standard deviation (SD), or median and corresponding interquartile range (IQR), were reported for continuous data as appropriate. Proportions and continuous variables were compared with the Pearson χ^2 test (or Fisher's exact test) and Student's *t*-test (or Mann–Whitney *U*-test), respectively, as appropriate. Univariable analysis using odds ratio (OR) with 95% confidence interval (CI) and multivariable logistic regression analysis, adjusted for confounders, were utilized to evaluate factors associated with unfavorable ASPECTS. The area under the receiver operating characteristic (AuROC) was calculated to demonstrate diagnostic accuracy. Statistical significance was indicated when a two-sided *P* value was less than 0.05. All statistical analyses were performed using licensed Stata statistical software version 16.1 (Stata Statistical Software: Release 16.1, Stata Corporation, College Station, TX, 2019).

Results

Baseline Characteristics and Risk of Unfavorable ASPECTS

Out of 778 eligible individuals for rt-PA treatment, 156 patients were excluded from the study due to strokes other than MCA infarction, receiving MT, stroke-mimicking conditions, and incomplete data. Among the remaining 622 patients, 95 (15.3%) had unfavorable ASPECTS, and 527 (84.7%) had favorable ASPECTS (Figure 1). The mean age of the study population was 66.1± 13.5 years, and males accounted for 50.5%.

Table 1 illustrates the demographic and clinical characteristics of the study population, categorized into two groups based on unfavorable or favorable ASPECTS. Older age (≥65 years) and low body weight (<60 kg) were significantly

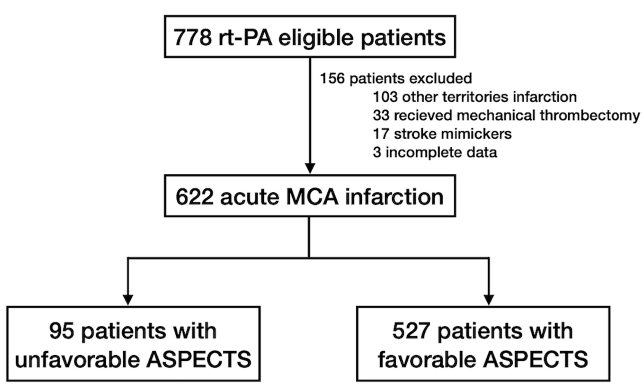

Figure 1 Flowchart of included participants. ASPECTS, Alberta Stroke Program Early Computed Tomography Score; MCA, middle cerebral artery; rt-PA, recombinant tissue-type plasminogen activator.

Table 1 Baseline Characteristics of Patients Treated with Intravenous Recombinant Tissue-Type Plasminogen Activator Classified by ASPECTS Profiles

	Total (n=622)	Unfavorable ASPECTS* (n=95)	Favorable ASPECTS* (n=527)	*P* value
Demographics – no. (%)				
Male sex	314 (50.5)	43 (45.3)	271 (51.4)	0.32
Age, year – mean ±SD	66.1 ±13.5	69.8 ±11.7	65.4 ±13.7	0.004
Age ≥65 years	347 (55.8)	66 (69.5)	281 (53.3)	0.004
Body weight, kg – median (IQR)	58.0 (50.0–66.6)	55.0 (46.0–61.5)	50.0 (58.0–67.5)	0.003
Body weight <60 kg	353 (57.0)	66 (71.0)	287 (54.6)	0.003
Comorbidities – no. (%)				
Hypertension	406 (65.3)	62 (65.3)	344 (65.3)	1.00
Diabetes	131 (21.1)	22 (23.2)	109 (20.7)	0.59
Atrial fibrillation	114 (18.3)	27 (28.4)	87 (16.5)	0.01
Dyslipidemia	186 (29.9)	26 (27.4)	160 (30.4)	0.63
Congestive heart failure	47 (7.6)	9 (9.5)	38 (7.2)	0.41
Coronary artery disease	70 (11.3)	11 (11.6)	59 (11.2)	0.86
Recurrent stroke	41 (6.6)	6 (6.3)	35 (6.6)	1.00
Smoking	80 (12.9)	16 (16.8)	64 (12.1)	0.24
Alcohol consumption	66 (10.6)	11 (11.6)	55 (10.4)	0.72
Antiplatelet	111 (17.9)	20 (21.1)	91 (17.3)	0.38
Anticoagulant	42 (6.8)	7 (7.4)	35 (6.6)	0.82
Statin used	148 (23.8)	18 (19.0)	130 (24.7)	0.24
HAS-BLED – median (IQR)	2 (1–2)	2 (1–3)	2 (1–2)	0.02
HAS-BLED ≥3	133 (21.4)	28 (29.5)	105 (19.9)	0.04
TOAST classification – no. (%)				
Large-artery atherosclerosis	329 (52.9)	51 (53.7)	278 (52.8)	0.91
Cardioembolism	222 (35.7)	41 (43.2)	181 (34.4)	0.10
Small-vessel occlusion	43 (6.9)	1 (1.1)	42 (8.0)	0.01
Other determined etiology	17 (2.7)	1 (1.1)	16 (3.0)	0.49
Undetermined etiology	11 (1.8)	1 (1.1)	10 (1.9)	1.00
Admission data – median (IQR)				
Onset to needle, minutes	158 (120–200)	174 (141–200)	155 (120–198)	0.03
Onset to image ≥120 minutes – no. (%)	478 (77.1)	83 (88.3)	395 (75.1)	0.005
Door to needle, minutes	54 (45–67)	55 (44–70)	54 (45–67)	0.84

(*Continued*)

Table 1 (Continued).

	Total (n=622)	Unfavorable ASPECTS* (n=95)	Favorable ASPECTS* (n=527)	*P* value
Door to image, minutes	34 (25–47)	35 (24–50)	34 (25–47)	0.83
Admission NIHSS	10 (6–17)	14 (10–20)	10 (6–16)	<0.001
Admission NIHSS ≥15 – no. (%)	200 (32.2)	46 (48.4)	154 (29.2)	<0.001
Admission Barthel index	25 (10–50)	10 (5–25)	25 (10–55)	<0.001
Admission Barthel index <15 – no. (%)	223 (37.6)	45 (50.6)	178 (35.3)	0.01
Admission mRS	4 (4–5)	5 (4–5)	4 (4–5)	<0.001
Admission mRS ≥2 – no. (%)	567 (93.6)	90 (98.9)	477 (92.6)	0.02
Laboratory profiles – median (IQR)				
Hemoglobin, g/dlL	12.8 (11.5–14.1)	12.2 (10.8–13.6)	12.9 (11.7–14.1)	0.005
Hemoglobin <12 g/dL – no. (%)	195 (31.5)	41 (43.2)	154 (29.3)	0.01
Platelet count – x1000 cells/mm^3	227 (183–274)	214 (174–263)	229 (184–275)	0.09
Creatinine, mg/dL	10.7 (1.6–11.4)	10.1 (1.2–11.3)	10.7 (2.3–11.4)	0.09
Albumin, g/dL	1.1 (1.0–3.3)	1.1 (1.0–3.7)	1.1 (1.0–3.2)	0.007
INR	0.2 (0.1–0.9)	0.4 (0.1–1.0)	0.2 (0.1–0.9)	0.04

Note: * Unfavorable ASPECTS defined by ASPECTS 0–7; favorable ASPECTS defined by ASPECTS 8–10.
Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; INR, international normalized ratio; IQR, inter-quartile range; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation; TOAST, trial of ORG 10172 in acute stroke treatment.

observed in the unfavorable ASPECTS group. Individuals with a HAS-BLED score of three or more were frequently observed in the unfavorable group (29.5% vs 19.9%, *P* = 0.04), corresponding with a high proportion of atrial fibrillation (AF) (28.4% vs 16.5%, *P* = 0.01). According to the TOAST classification of subtype of acute ischemic stroke (AIS), patients in the unfavorable ASPECTS had less small-vessel occlusion (SVO) (1.1% vs 8.0%, *P* = 0.01). The onset-to-needle time and proportion of participants with onset-to-image time greater than 120 minutes were higher in the unfavorable group. There was no statistical difference in other demographics or the use of statins between the two groups.

Table 2 demonstrates the results of a univariable and multivariable analysis using binary logistic regression of factors associated with unfavorable ASPECTS. The analysis was adjusted by age, onset to image, and baseline NIHSS. Elderly

Table 2 Factors Associated with Unfavorable ASPECTS*

	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)**	*P* value
Age ≥ 65 years	2.0 (1.2–3.2)	0.004	1.7 (1.0–2.8)	0.04
Body weight <60 kg	2.0 (1.3–3.3)	0.004	1.7 (1.0–2.8)	0.04
Atrial fibrillation	2.0 (1.2–3.3)	0.006	1.8 (1.1–3.0)	0.03
Onset to needle ≥ 120 minutes	2.5 (1.3–4.8)	0.006	2.8 (1.4–5.6)	0.004
Hemoglobin <12 g/dL	1.8 (1.2–2.9)	0.008	1.7 (1.1–2.7)	0.02

Notes: * Unfavorable ASPECTS defined by ASPECTS 0–7. ** Adjusted by age, onset to image, and baseline NIHSS.
Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; CI, confidence interval; NIHSS, National Institute of Health Stroke Scale; OR, odds ratio.

(age ≥65 years), low body weight (<60 kg), underlying AF, onset-to-needle time of more than 120 minutes, and anemia were all associated with an increment in unfavorable ASPECTS obtained by the initial CT scan before rt-PA treatment.

Lower ASPECTS Associated with sICH but Not aICH

The incidence of sICH, but not aICH, was higher in individuals with unfavorable ASPECTS compared to those in the favorable group (21.1% vs 4.9%, *P* <0.001) (Table 3). The association between unfavorable ASPECTS and ICH outcomes was significant only in the sICH group (adjusted OR 5.1; 95% CI 2.7–9.7, *P* <0.001), not in the aICH group. Sub-analysis of different ASPECTS demonstrated that when compared to ASPECTS 8–10 (reference), rt-PA-treated patients with ASPECTS of 6–7 and less than six were associated with an increased risk of sICH (OR 5.5; 95% CI 2.7–11.0, *P* <0.001 and 7.0; 2.0–24.3, *P* = 0.002, respectively), whilst there was no association observed between ASPECTS and aICH (Table 4). The lower ASPECTS could predict the sICH event with the AuROC of 0.68 (95% CI 0.59–0.77) (Figure 2) but not in aICH individuals (AuROC 0.53; 95% CI 0.48–0.59).

Table 3 Outcomes of Patients Treated with Intravenous Recombinant Tissue-Type Plasminogen Activator Classified by ASPECTS Profiles

	Total (n=622)	Unfavorable ASPECTS* (n=95)	Favorable ASPECTS* (n=527)	*P* value
Intracranial hemorrhage – no. (%)				
Any bleeding	153 (24.6)	36 (37.9)	117 (22.2)	0.002
Symptomatic	46 (7.4)	20 (21.1)	26 (4.9)	<0.001
Asymptomatic	107 (17.2)	16 (16.9)	91 (17.3)	1.00
Intracranial hemorrhage pattern – no. (%)				
Hemorrhagic infarction	97 (15.6)	14 (14.7)	83 (15.7)	0.88
Parenchymal hemorrhage	56 (9.0)	22 (23.2)	34 (6.5)	<0.001
Intervention profiles – no. (%)				
Craniectomy	29 (4.7)	13 (13.7)	16 (3.0)	<0.001
Cryoprecipitate	17 (2.7)	10 (10.5)	7 (1.3)	<0.001
Fresh frozen plasma	30 (4.8)	15 (15.8)	15 (2.9)	<0.001
Packed red cells	17 (2.7)	10 (10.5)	7 (1.3)	<0.001
Discharge status – median (IQR)				
Death – no. (%)	45 (7.2)	17 (17.9)	28 (5.3)	<0.001
Favorable mRS (0–2) – no. (%)	177 (28.5)	7 (7.4)	170 (32.3)	<0.001
mRS	4 (2–5)	5 (4–5)	4 (2–4)	<0.001
Barthel index	50 (10–80)	14 (0–50)	50 (15–85)	<0.001
NIHSS	4 (1–12)	9 (3–19)	4 (1–10)	<0.001
Length of stay, days	6 (4–11)	10 (5–16)	6 (4–10)	<0.001

(*Continued*)

Table 3 (Continued).

	Total (n=622)	Unfavorable ASPECTS* (n=95)	Favorable ASPECTS* (n=527)	*P* value
14-day status – median (IQR)				
Death – no. (%)	51 (8.2)	19 (20.0)	32 (6.1)	<0.001
Favorable mRS (0–2) – no. (%)	309 (49.7)	29 (30.5)	280 (53.1)	<0.001
mRS	2 (0–4)	4 (2–6)	2 (0–4)	<0.001
Barthel index	80 (30–100)	48 (0–80)	80 (50–100)	<0.001
NIHSS	2 (0–7)	5 (2–10)	2 (0–6)	<0.001
90-day status – median (IQR)				
Death – no. (%)	53 (8.5)	20 (21.1)	33 (6.3)	<0.001
Favorable mRS (0–2) – no. (%)	287 (46.1)	24 (25.3)	263 (49.9)	<0.001
mRS	2 (0–4)	4 (2–6)	2 (0–4)	<0.001
Barthel index	80 (20–100)	30 (0–80)	85 (50–100)	<0.001
NIHSS	2 (0–6)	5 (2–11)	2 (0–6)	<0.001

Note: * Unfavorable ASPECTS defined by ASPECTS 0–7; favorable ASPECTS defined by ASPECTS 8–10.
Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; IQR, interquartile range; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale.

Table 4 Risk of ICH Based on Baseline ASPECTS

ASPECTS	sICH		aICH	
	Adjusted OR (95% CI)*	*P* value	Adjusted OR (95% CI)*	*P* value
8–10	Reference	Reference	Reference	Reference
0–7	5.1 (2.7–9.7)	<0.001	1.1 (0.8–1.5)	0.51
Sub-analysis				
6–7	5.5 (2.7–11.0)	<0.001	1.4 (0.7–2.6)	0.33
<6	7.0 (2.0–24.3)	0.002	1.0 (0.2–4.7)	1.00

Note: * Adjusted with age, onset to image, and baseline NIHSS.
Abbreviations: aICH, asymptomatic intracerebral hemorrhage; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; CI, confidence interval; NIHSS, National Institute of Health Stroke Scale; OR, odds ratio; sICH, symptomatic intracerebral hemorrhage.

Lower ASPECTS Required More Neurosurgery Intervention and Blood Transfusion

Patients in the unfavorable ASPECTS group had a higher rate of neurosurgical interventions (13.7% vs 3.0%, *P* <0.001). Fresh frozen plasma and cryoprecipitate were utilized as specific treatments for intracranial bleeding occurring after administration of rt-PA and were prescribed more in the unfavorable group. Packed red cell transfusions were significantly administered in the unfavorable ASPECTS group (10.5% vs 1.3%, *P* <0.001) (Table 3).

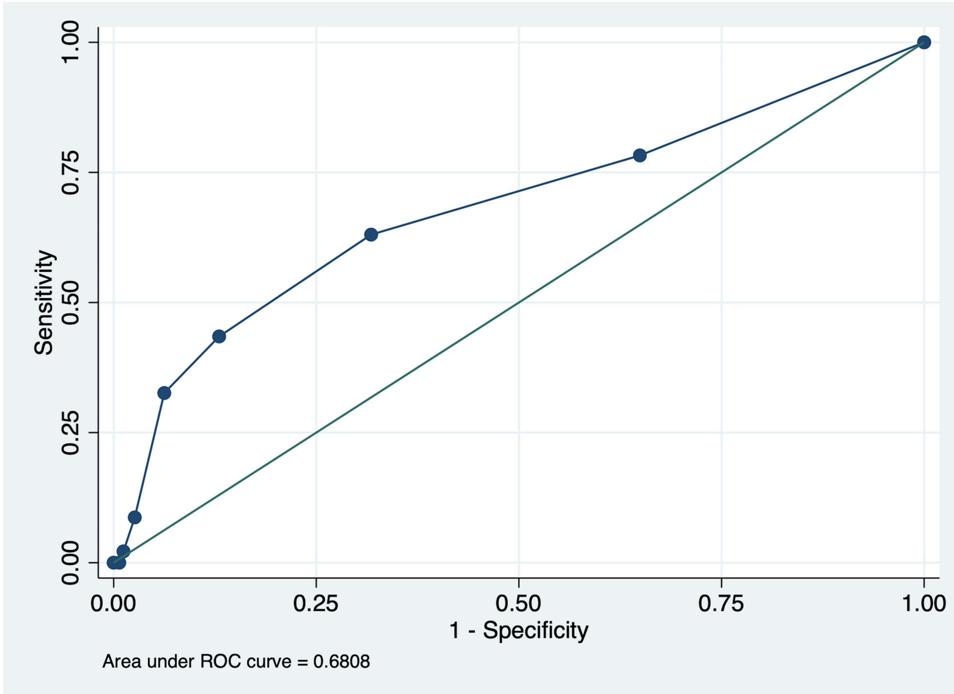

Figure 2 AuROC curve (0.68, 95% CI 0.59–0.77) of sICH with unfavorable ASPECTS. ASPECTS, Alberta Stroke Program Early Computed Tomography Score; AuROC, area under the receiver operating characteristic; CI, confident interval; sICH, symptomatic intracranial hemorrhage.

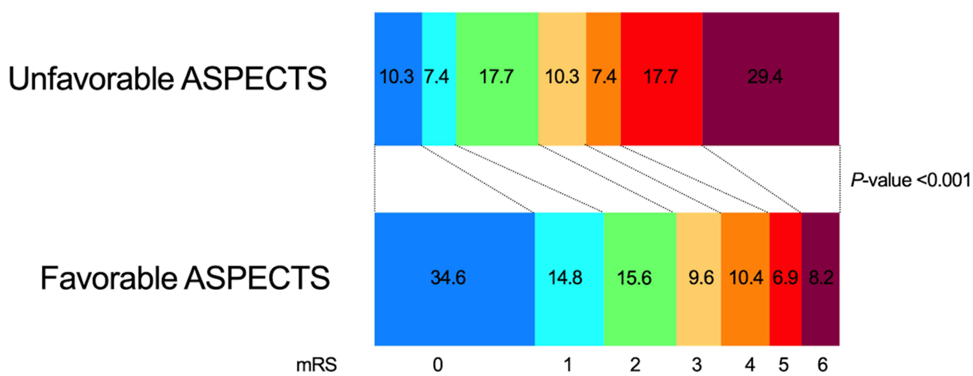

Figure 3 90-day modified Rankin Scale (mRS) in unfavorable and favorable ASPECTS groups. The figure demonstrated the mRS between unfavorable and favorable ASPECTS. The unfavorable mRS (mRS >2) was found to be higher in the unfavorable ASPECTS group (74.7% vs 50.1%, *P* <0.001). ASPECTS, Alberta Stroke Program Early Computed Tomography Score.

Association of ASPECTS and Functional Outcomes

Compared to the favorable ASPECTS group, the unfavorable ASPECTS group exhibited poorer clinical outcomes. Patients with unfavorable ASPECTS were more likely to have mRS >2 at 90 days than those with favorable ASPECTS (Table 3, Table S1, and Figure 3). A higher proportion of patients with poor functional outcomes in the short- (discharge and 14-day) and long-term (90-day), defined by NIHSS >15 and BI <25, was significantly observed in the unfavorable ASPECTS group than in the favorable ASPECTS group (Table 3 and Figure 4A-B).

ASPECTS and Correlation with Other Imaging Findings

The unfavorable ASPECTS group showed a significant correlation with large territorial infarction and hyperdense MCA sign (HMCAS) compared to the other group (22.1% vs 0.8% and 70.5% vs 39.1%, *P* <0.001, respectively). There was no statistical difference between the proportions of left hemispheric or old infarction between the groups (Table 5).

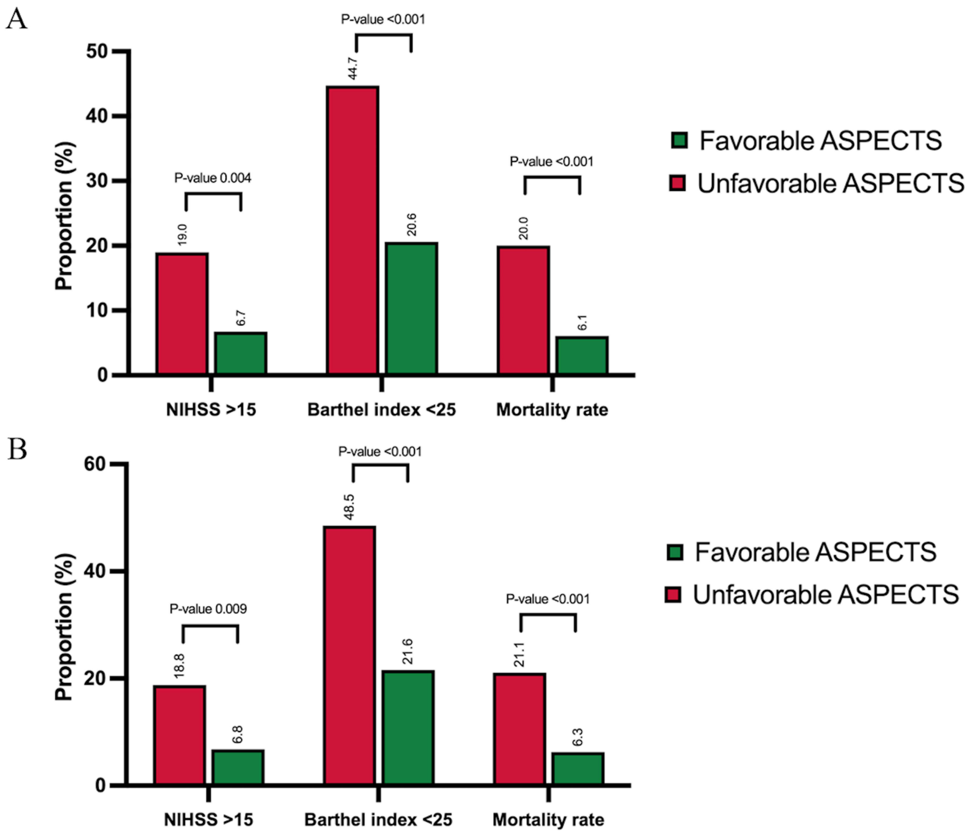

Figure 4 Unfavorable outcomes (NIHSS >15, Barthel index <25) and mortality in unfavorable and favorable ASPECTS groups. (**A**) 14-day outcomes and (**B**) 90-day outcomes. ASPECTS, Alberta Stroke Program Early Computed Tomography Score; NIHSS, National Institutes of Health Stroke Scale.

Discussion

The major findings from the present study can be summarized as follows: 1) AIS patients due to acute MCA infarction and unfavorable ASPECTS who receiving rt-PA therapy were associated with an increased risk of sICH; 2) patients with

Table 5 Association Between ASPECTS and Brain Imaging Profiles

	Total (n=622)	Unfavorable ASPECTS* (n=95)	Favorable ASPECTS* (n=527)	*P*-value
ASPECTS parameters – no. (%)				
Caudate	108 (17.4)	57 (60.0)	51 (9.7)	<0.001
Lentiform	224 (36.0)	73 (76.8)	151 (28.7)	<0.001
Insular ribbon	158 (25.4)	61 (64.2)	97 (18.4)	<0.001
Internal capsule	172 (27.7)	61 (64.2)	111 (21.1)	<0.001
M1	32 (5.1)	27 (28.4)	5 (1.0)	<0.001
M2	53 (8.5)	42 (44.2)	11 (2.1)	<0.001
M3	14 (2.3)	10 (10.5)	4 (0.8)	<0.001
M4	13 (2.1)	13 (13.7)	0 (0.0)	<0.001
M5	21 (3.4)	19 (20.0)	2 (0.4)	<0.001
M6	9 (1.5)	8 (8.4)	1 (0.2)	<0.001

(*Continued*)

Table 5 (Continued).

	Total (n=622)	Unfavorable ASPECTS* (n=95)	Favorable ASPECTS* (n=527)	*P*-value
Other neuroimaging profiles – no. (%)				
Large infarction	25 (4.0)	21 (22.1)	4 (0.8)	<0.001
Hyperdense MCA sign	273 (43.9)	67 (70.5)	206 (39.1)	<0.001
Left side infarction	297 (47.8)	48 (50.5)	249 (47.3)	0.58
Old infarction	126 (20.3)	25 (26.3)	101 (19.2)	0.13

Note:* Unfavorable ASPECTS defined by ASPECTS 0–7; favorable ASPECTS defined by ASPECTS 8–10.
Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; MCA, middle cerebral artery, M1; anterior MCA cortex; M2, MCA cortex lateral to insular ribbon; M3, posterior MCA cortex; M4, M5, and M6; anterior, lateral, posterior MCA territories immediately superior to M1, M2, and M3, rostral to basal ganglia.

lower ASPECTS received neurosurgical intervention with craniectomy and blood component as specific anticoagulant reversal as well as unfavorable short- and long-term mortality and functional outcomes more than individuals with favorable ASPECTS; and 3) elderly, low body weight, delayed onset to needle time and AF increased risk for unfavorable ASPECTS from pretreatment noncontrast CT (NCCT) brain. The association between low body weight and unfavorable ASPECTS may be attributed to factors such as reduced muscle mass, comorbidities, and poorer collateral supply, leading to more severe strokes and limited recovery.[13] Additionally, patients with AF showed more EIC on NCCT, likely due to larger embolic burdens and poorer circulation, which aligns with studies indicating increased stroke severity and faster ischemic progression in AF-related strokes.[14] Moreover, subanalysis data showed that the presence of AF in patients with low ASPECTS was associated with a higher risk of poor clinical outcomes, particularly sICH (Table S2).

The most devastating complication associated with rt-PA treatment is ICH. Data from previous studies have shown that the incidence of sICH ranges from 2.0% to 7.0%, and aICH occurs at a rate of 16.0%.[3,15,16] Both sICH and aICH are associated with unfavorable functional outcomes and high mortality rates compared to those without ICH.[3] The focus has been on assessing baseline imaging, especially NCCT scan, prior to rt-PA treatment to predict outcomes and mitigate the risk of ICH. ASPECTS, well-known for its simplicity and prompt application, was developed to ease treatment decision-making and assess the significance of EIC in treatment response.[5] The hypoattenuation observed in the NCCT scan reflects water accumulation in brain tissue and cytotoxic edema.[6] Our study found that those with unfavorable ASPECTS, defined as a score of seven or lower, had a considerable rate of sICH, compared to AIS patients with ASPECTS of 8–10 who received rt-PA therapy. A subgroup analysis further revealed that individuals with ASPECTS 6–7 and less than 6 exhibited a heightened risk of sICH. The presence of lower ASPECTS could be attributed to a longer duration from onset to needle time. A longer duration of stroke without thrombolysis reduces the chance of salvaging the penumbra, resulting in irreversible brain tissue damage, and ultimately leading to functional dependence. These findings were consistent with previous published studies.[4,10,17] The present study, however, did not observe a similar trend in the aICH outcome. These disparate results may be attributed to distinct pathophysiological mechanisms among different types of ICH. Previous studies have shown that sICH is associated with parenchymal hematoma, resulting from rt-PA-induced coagulopathy, coupled with blood vessel destruction during the ischemia-reperfusion process and blood-brain barrier disruption.[18] On the other hand, aICH is usually caused by red blood cell extravasation, which is considered a natural course of stroke and not a complication of rt-PA treatment.[19] Our results could provide evidence that patients with lower ASPECTS carry a higher risk of sICH, leading to an increased requirement for neurointervention and reversal agents. However, ASPECTS may not predict complications arising from the natural course of the disease itself.

There are still ongoing debate regarding prescribing intravenous rt-PA in acute MCA infarction with low ASPECTS patients. Data from the European Cooperative Acute Stroke Study (ECASS) I and II demonstrated that patients with extensive hypoattenuation on NCCT scan did not benefit from rt-PA; conversely, they carried a higher risk of ICH.[9,20]

However, conflicting data from the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Trial reported that patients with hypodensity in more than one-third of the brain area were not an independent risk factor for sICH and suggested not precluding the use of rt-PA.[21] This conflicting statement could arise from the sICH definition and inter-rater interpretation of EIC. The low sensitivity of using only one rater might affect the treatment decision.[5] Moreover, EIC is typically subtle, and even experienced interpreters could misdiagnose it. Utilizing a consensus from a neurologist and neuroradiologist team, combined with deep-learning artificial intelligence, might increase the sensitivity of ASPECTS interpretation.[22,23] According to our study, we suggest that acute MCA stroke patients with low ASPECTS should be cautioned against intravenous thrombolysis treatment. On the other hand, considering an alternative treatment strategy, such as MT, may shed light on these patients, given the growing evidence of its effectiveness even in cases with lower ASPECTS.[24,25] Recent systematic review and meta-analysis of four randomized controlled trials (RCTs) in patients with large-core ischemic stroke, ASPECTS 2–5, demonstrated that endovascular treatment (EVT) was significantly associated with good functional outcome (mRS 0–2) and functional independence (mRS 0–3) at 3 months, compared to best medical treatment (BMT). Whilst the rates of any ICH and sICH were more significant in the EVT group, there was no difference in 3-month mortality between the two groups.[26] The preliminary results of the MAGNA (MechAnical thrombectomy for larGe braiN infArctions), an individual-patient data meta-analysis, confirmed the benefit of MT over BMT for large core ischemic stroke, specifically for patients with ASPECTS scores of 3, 4, and 5. This effect was shown for core sizes ranging from less than 70mL to 149mL.[27] Our findings will add value to MT as an alternative to IVT in acute MCA infarctions with low ASPECTS, which is a reliable neuroimaging for large-core ischemic stroke. However, it should not be automatically withheld based solely on ASPECTS, especially in centers where EVT is available. In settings where EVT may be delayed or unavailable, rt-PA should remain a key therapeutic consideration, with the decision carefully weighing the local availability of timely treatment options.

Our observations are in line with previous studies suggesting the predictive value of ASPECTS as a simplified and appropriate neuroimaging technique to evaluate the prognosis of AIS. A study using a similar cut-off value to ours demonstrated the unfavorable outcomes in acute MCA territory infarctions with initial ASPECTS of 7 or less.[28,29] Although aICH might not be significantly associated with lower ASPECTS, our finding showed that patients with aICH received a blood transfusion or cryoprecipitate to reverse the anticoagulant effect and neurosurgical management less than another group. This emphasizes and heightens the importance of specific management in AIS patients who developed aICH following stroke reperfusion therapy because our previous study demonstrated that patients with aICH had poor clinical outcomes and were associated with the risk of mortality at 90-day, compared to non-ICH patients.[3] In addition, we found that AF was independently associated with an increased risk of unfavorable ASPECTS which corresponded with the previous studies that showed stroke attributed to cardioembolism was commonly found in HMCAS and large cerebral infarction.[30,31]

The strength of this current study lies in the inclusion of a large number of patients from a prospective stroke registry, providing findings that reflect real-world data on stroke treatment in a tertiary care center. All clinical data were recorded based on the consensus of the acute stroke care team, allowing for a comprehensive analysis of short- and long-term outcomes for patients experiencing both sICH and aICH. However, we acknowledge some limitations to our study. Firstly, we used NINDS criteria to define sICH, which might introduce minor variations compared to other studies. Secondly, limited data was focused on using ASPECTS to predict the presence of aICH, highlighting the need for further well-designed studies. Third, the study has mainly focused on IVT. A future study on the association between EIC and MT is required. Fourth, only half of our patients received vascular imaging, making it difficult to differentiate reliably between ICA and MCA occlusions, as well as between MCA subtypes, based on clinical presentation alone. Fifth, even though ASPECTS used in our cohort was based on the official report from certified board neuroradiologists, who are experienced in the field, the interrater reliability among them may remain. Further study with an interrater agreement or use of e-ASPECTS, an automated software supporting the decision for stroke signs on NCCT, is encouraged to optimize diagnostic accuracy.

Conclusions

Using ASPECTS from the NCCT scan is a simple tool that can be employed to predict the occurrence of rt-PA complications, particularly sICH, together with stroke mortality and short- and long-term functional outcomes. The ASPECTS, however, could not be applicable to predict aICH, which is mainly related to the natural course of stroke. Intravenous thrombolysis with rt-PA remains the mainstay of reperfusion therapy for patients with AIS who presented at the EVT incapable center. Selectively chosen reperfusion method could increase the chance of good functional outcomes or reduced disability and mitigate the risk of serious complications following stroke reperfusion therapy.

Data Sharing Statement

The study data are available from the corresponding author upon reasonable request and with the permission of all contributing authors.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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