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Follow-up ASPECTS improves prediction of potentially lethal malignant edema in patients with large middle cerebral artery stroke

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Contributors CJO, SKF, and SMS conceived the idea of the presented analyses and designed the overall study. RS, SC, ISYK, YZ, and AR organized and collected the patient data for analysis. RS, ISYK, CJO, SC, and AR performed manual reviews of patient notes to extract various features, such as stroke onset times, medications, procedures, and outcomes. BB developed code for automated feature extraction from radiology reports. AM and MA provided oversight and guidance on radiographic image measurements. RS, SC, BB, and CJO manually reviewed the radiographic images to measure swelling and determine radiographic outcomes. RS and YZ performed statistical analysis and interpretation. BB, AM, MA, DMG, SMS, SKF, JD, and CJO provided oversight and review of the statistical analysis. RS, SC, and CJO drafted the manuscript. BB, AM, MA, SMS, SKF, JD, and DMG helped with reviews and revisions. CJO provided overall study direction and critical review. All authors contributed to the article and approved the submitted version. CJO is the guarantor.

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Ethics approval This study involves human participants and was approved by Boston Medical Center institutional review board and MGB Human Research Committee (H-37699, 2017P002564). This was a retrospective study and our review boards classified it as exempt from consent.

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Abstract

Background—Recent studies have shown that follow-up head CT is a strong predictor of functional outcomes in patients with middle cerebral artery stroke and mechanical thrombectomy. We sought to determine whether total and/or regional follow-up Alberta Stroke Program Early CT Score ($ASPECTS_{fu}$) are associated with important clinical outcomes during hospitalization and improve the performance of clinical prediction models of potentially lethal malignant edema (PLME).

Methods—We conducted a retrospective study of patients at three medical centers in a major North American metropolitan area with baseline and follow-up head CTs after large middle cerebral artery stroke between 2006 and 2022. We used multivariable logistic regression to test the association of total and regional $ASPECTS_{fu}$ with PLME (cerebral edema related death or surgery), adjusting for total baseline ASPECTS, age, sex, admission glucose, tissue plasminogen activator, and mechanical thrombectomy. We compared existing clinical risk models with and without total or regional $ASPECTS_{fu}$ using area under the curve.

Results—In our 560 patient cohort, lower total $ASPECTS_{fu}$ was significantly associated with higher odds of PLME when adjusting for confounders (OR 1.69, 95% CI 1.49 to 2.0), and improved model discrimination compared with existing models and models using baseline ASPECTS. Deep territory involvement (OR 2.46, 95% CI 1.53 to 4.01) and anterior territory involvement (OR 3.23, 95% CI 1.88 to 5.71) were significantly associated with PLME.

Conclusions—Lower $ASPECTS_{fu}$ and certain locations on regional $ASPECTS_{fu}$, including deep and anterior areas, were significantly associated with PLME. Including $ASPECTS_{fu}$ information improved discrimination of established edema prediction models and could be used immediately to help facilitate clinical management decisions and prognostication.

INTRODUCTION

The Alberta Stroke Program Early CT Score (ASPECTS) is a semi-quantitative method to measure stroke volume.[1] It was originally designed to assess eligibility for mechanical thrombectomy (MT) within the first 6 hours from last seen well[2] and is strongly associated with clinical outcomes, including the modified Rankin Scale at 90 days.[3 4] However, initial ASPECTS on admission is not as representative of ultimate stroke volume as follow-up imaging obtained within the first 2 days of stroke onset.[5]

Previous studies have suggested that at least in patients with MT, total follow-up ASPECTS ($ASPECTS_{fu}$) obtained in the first 2 days after stroke is a predictor of clinical outcome at 3 months.[6] However, this has not been verified in a more general group of patients with large middle cerebral artery stroke without MT. Moreover, the association of $ASPECTS_{fu}$ and intermediate clinical outcomes, including potentially lethal malignant edema (PLME), defined in previous studies as the need for decompressive hemicraniectomy or death with midline shift ≥5 mm,[7] has not been rigorously studied. The ability to predict such outcomes

is important for clinical decision making and family discussions in the initial days after stroke.

AIMS and hypothesis

We hypothesized that total $ASPECTS_{fu}$ is a strong predictor and improves existing models of PLME, including the Enhanced Detection of Edema in Malignant Anterior Circulation Stroke (EDEMA) and modified EDEMA models.[6 7] We also hypothesized that evidence of injury using the ASPECTS framework in regional areas, including the middle fossa and deep structures, exert pressure vectors of mass effect toward the brainstem, predisposing patients to PLME.[8 9] Leveraging the widely used ASPECTS framework to improve PLME prediction would have immediately implementable clinical utility.

METHODS

We retrospectively collected data of adult patients with large ischemic stroke (≥1/3 of the middle cerebral artery territory visualized by trained MD reviewers) at three hospitals in a major North American metropolitan area between 2006 and 2022 with baseline and follow-up head CTs (online supplemental figure 1). We recorded baseline ASPECTS ($ASPECTS_{bl}$) (≤ 24 hours from last seen well) and $ASPECTS_{fu}$ (18–48 hours).[1] Clinical data were extracted from the electronic medical record and Research Patient Data Registry. Radiographic data were collected manually by a trained member of the research team. Additional details are included in online supplemental methods.

The primary outcome was PLME, as used previously in the literature, which is death with midline shift ≥5 mm or the need for decompressive hemicraniectomy.[7 8] The primary exposure was total $ASPECTS_{fu}$ from CT images obtained within 18–48 hours. Secondary exposures to examine whether certain anatomic areas identified using an ASPECTS framework were associated with PLME included four dichotomously defined discrete $ASPECTS_{fu}$ regions corresponding to complete involvement of the middle fossa (M2, M3, and insula), deep structures (caudate, internal capsule, and lenticular nucleus), anterior areas (M1 and M4), and posterior areas (M5 and M6) (online supplemental figure 2). Exploratory exposures to investigate further anatomic associations with PLME included the 10 individual $ASPECTS_{fu}$ regions.

We used multivariable logistic regression to predict PLME, adjusting for hypothesized confounders associated with both our primary exposure and outcome, including total $ASPECTS_{bl}$, age, sex, admission glucose, tissue plasminogen activator, and MT.[10] To further test the association of $ASPECTS_{fu}$ with PLME in patients without MT, we performed sensitivity analyses in patients with and without MT. We report odds ratios (OR) with 95% confidence intervals (CI).

We compared logistic regression models using variables in the EDEMA model (admission glucose, previous stroke, tissue plasminogen activator or MT, midline shift, and basilar cistern effacement)[6] and modified EDEMA model (original model plus National Institutes of Health Stroke Scale (NIHSS)[7] with and without (1) total $ASPECTS_{bl}$, (2) total $ASPECTS_{fu}$,

(3) follow-up middle fossa ASPECTS areas, or (4) follow-up deep ASPECTS areas) to determine the best performing model using area under the curve (AUC).

We set our significance threshold at α=0.05 for our primary hypothesis. Associations between additional outcomes and variables are hypothesis generating only. We used R V.4.2.1 for statistical analyses (R Core Team (2023) R: A language and environment for statistical computing. R Foundation for Statistical Computing). Further information is available in online supplemental methods.

RESULTS

In our cohort of 560 patients, 48% were women and median age was 69.5 years (25th–75th percentile 58–80). Median $ASPECTS_{bl}$ was 5 (3–8) and median $ASPECTS_{fu}$ was 2 (1–5). There was substantial agreement between ASPECTS raters, with an overall kappa value of 0.65. At follow-up, 63% had complete middle fossa involvement and 45% had complete deep involvement. A total of 126 patients had PLME, of whom 56 underwent decompressive hemicraniectomy; 33% died or went to a hospice (table 1).

ASPECTS individual areas ranged from insignificant correlations (eg, caudate and M6) to high correlations (ρ=0.76) for caudate and internal capsule (online supplemental figure 3). Regional correlations were all <0.4 except for the middle fossa and posterior regions, which were correlated with a coefficient of 0.64 (online supplemental figure 4). The most frequently affected regions at follow-up were the insula and M2, while the caudate appeared to only be affected when most regions were also affected, as demonstrated in the $ASPECTS_{fu}$ heat map (online supplemental figure 5).

Lower $ASPECTS_{fu}$ was associated with an increased odds of PLME when adjusting for covariates in the full cohort (OR 1.69 per point, 95% CI 1.49 to 2.0) and in the subgroups of patients with (OR 1.92, 95% CI 1.52 to 2.56) and without MT (OR 1.61, 95% CI 1.37 to 1.92) while $ASPECTS_{bl}$ was not significantly associated with outcomes in any group (table 2).

In the regional $ASPECTS_{fu}$ multivariable model, complete involvement of deep structures (OR 2.46, 95% CI 1.53 to 4.01) and anterior regions (OR 3.23, 95% CI 1.88 to 5.71) appeared to be significantly associated with PLME (table 3). In patients without MT, the regional $ASPECTS_{fu}$ multivariable model showed that deep structures (OR 2.33, 95% CI 1.31 to 4.20), anterior regions (OR 2.51, 95% CI 1.33 to 4.92), and middle fossa (OR 2.57, 95% CI 1.12 to 6.25) appeared to be significantly associated with PLME. In our exploratory multivariable models of individual $ASPECTS_{fu}$ areas, M3 and M4 appeared to have a significant association with PLME (online supplemental table 1).

Finally, when we compared the EDEMA score and modified EDEMA score with and without additional ASPECTS variables, we found that total $ASPECTS_{fu}$ had the highest AUC (0.86 in both) of any model (table 4), although the difference was marginal. Additional model fit metrics can be found in online supplemental table 2.

DISCUSSION

We found that in our multicenter study of 560 patients, lower total $ASPECTS_{fu}$ was significantly associated with PLME, even with adjusting for $ASPECTS_{bl}$. $ASPECTS_{fu}$ provides an easy to measure quantitative metric of permanent stroke injury and likelihood of edema more than baseline characteristics alone. Particularly, lower total $ASPECTS_{fu}$ was associated with higher odds of PLME both in the total cohort and in the categories of MT and no MT, highlighting its clinical significance. The finding that $ASPECTS_{fu}$ was predictive of clinical outcomes is consistent with previous work suggesting that total $ASPECTS_{fu}$ is associated with favorable 3 month outcomes after ischemic stroke that underwent MT.[6] Our work, however, also demonstrates that $ASPECTS_{fu}$ improves prediction of important hospital based clinical outcomes, including significant radiographic and clinical manifestations of cerebral edema in a broader population of patients with large ischemic stroke with or without intervention. Additionally, it is notable that compared with $ASPECTS_{bl}$ in patients both with and without MT, $ASPECTS_{fu}$ provided a benefit both to EDEMA and the modified EDEMA models. The latter includes NIHSS (also a metric of stroke severity), suggesting that $ASPECTS_{fu}$ provides important additional information not captured by the initial clinical examination or radiographic imaging.

We also observed that regional $ASPECTS_{fu}$ areas, including deep and anterior structures, were significantly associated with PLME. This is consistent with previous studies that have shown that deep structures, such as the caudate, are associated with the need for decompressive hemicraniectomy.[8] The association of PLME and anterior ASPECTS regions (M1 and M4) was an unexpected finding, and requires further verification. We found no significant association between middle fossa involvement and PLME in our total cohort. This is counter to our expectation, as we initially posited that caudal temporal involvement might exert a vector of mass effect on the midbrain, leading to worsened outcome. However, we did find a suggestive association in our cohort of patients without MT, suggesting that perhaps ASPECTS may not adequately capture the effect of the middle fossa on PLME, but that the anatomic location may still be relevant.

While singular ASPECTS area associations are strictly exploratory, we observed that M3 and M4 were associated with PLME. A systematic review and meta-analysis calculated β coefficients from pooled ORs of ASPECTS regions and showed that the M6 had the largest weight on the prediction of poor outcomes, followed by the M3.[9] We did not find that M6 was associated with intermediate hospitalization outcomes.

Limitations of this study include its retrospective nature, lack of precise infarct volume and functional outcome data, bias due to withdrawal of life sustaining therapy, inclusion criteria that patients must have a follow-up CT, correlation between two of the ASPECTS regions, and potential biases related to differences in practice over time between our three sites. However, to the best of our knowledge, this is the largest study to date testing the association of total and regional follow-up ASPECTS scores with clinically important intermediate outcomes during hospitalization.

CONCLUSION

Follow-up ASPECTS was independently associated with and improved prediction of PLME in patients with large middle cerebral artery stroke. Calculation of $ASPECTS_{fu}$ is a feasible and clinically useful addition to existing tools for prognostication and can help clinicians inform management decisions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability statement

Data are available upon reasonable request. Deidentified data are available upon request and establishment of a data use agreement. Please email the corresponding author for access.

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WHAT IS ALREADY KNOWN ON THIS TOPIC

- Follow-up Alberta Stroke Program Early CT Score (ASPECTS) obtained within the first 2 days after stroke is predictive of 3 month functional outcomes in patients treated with mechanical thrombectomy.
- However, less is known about the association between follow-up ASPECTS and important inpatient clinical outcomes, such as potentially lethal malignant edema, in large ischemic stroke with or without mechanical thrombectomy.

WHAT THIS STUDY ADDS

- This study uses the largest dataset to date of patients with large ischemic stroke to identify the association between total and regional ASPECTS obtained within 18–48 hours of last known well and potentially lethal malignant edema.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- Calculation of ASPECTS, is a feasible and clinically useful addition to existing tools for potentially lethal malignant edema prognostication and can help clinicians inform management decisions, including the need for decompressive hemicraniectomy or goals of care decisions.

Table 1

Cohort characteristics

Demographics	Total cohort (n=560)
Age (years) (median (25th, 75th))	69.5 (58, 80)
Women	269 (48)
Left sided stroke	279 (49.8)
Admission and imaging information	
NIHSS at presentation (median (25th, 75th))	18 (14, 21)
Admission glucose (mg/dL) (median (25th, 75th))	131.5 (112, 166.2)
Tissue plasminogen activator	275 (49.1)
Mechanical thrombectomy	159 (28.4)
Time to follow-up CT (hours) (median (25th, 75th))	26.9 (24.6, 30.7)
Follow-up ASPECTS (median (25th, 75th))	2 (1, 5)
Middle fossa involvement (insula, M2, M3)	351 (62.7)
Deep structure involvement (caudate, internal capsule, and lenticular nucleus)	252 (45)
Anterior region involvement (M1 and M4)	317 (56.6)
Posterior region involvement (M5 and M6)	369 (65.9)
Outcomes	
Potentially lethal malignant edema	126 (22.5)
Decompressive hemicraniectomy	56 (10)
Death with midline shift ≥5 mm	83 (14.8)
Death or hospice	185 (33)

Values are number (%), unless indicated otherwise.

ASPECTS, Alberta Stroke Program Early CT Score; NIHSS, National Institutes of Health Stroke Scale.

Table 2

Total $ASPECTS_{fu}$ multivariable models for potentially lethal malignant edema

Characteristics	OR	95% CI	P value
Total cohort (n=560)			
Follow-up ASPECTS	1.69	1.49 to 2.00	<0.001
Baseline ASPECTS	1.02	0.94 to 1.10	0.6
Patients without mechanical thrombectomy (n=401)			
Follow-up ASPECTS	1.61	1.37 to 1.92	<0.001
Baseline ASPECTS	1.01	0.92 to 1.11	0.8
Patients with mechanical thrombectomy (n=159)			
Follow-up ASPECTS	1.92	1.52 to 2.56	<0.001
Baseline ASPECTS	1.05	0.92 to 1.22	0.5

Multivariable logistic regression model of potentially lethal malignant edema and follow-up ASPECTS ($ASPECTS_{fu}$), adjusting for baseline ASPECTS ($ASPECTS_{bl}$), age, sex, admission glucose, tissue plasminogen activator, and mechanical thrombectomy in the full model, and in subgroups without mechanical thrombectomy as a covariate.

ASPECTS, Alberta Stroke Program Early CT Score.

Table 3

Regional $ASPECTS_{fu}$ multivariable models for potentially lethal malignant edema

Characteristics	OR	95% CI	P value
Total cohort (n=560)			
Deep	2.46	1.53 to 4.01	<0.001
Middle fossa (insula, M2, M3)	1.87	0.94 to 3.80	0.08
Posterior (M5, M6)	2.41	1.17 to 5.11	0.02
Anterior (M1, M4)	3.23	1.88 to 5.71	<0.001
Patients without mechanical thrombectomy (n=401)			
Deep	2.33	1.31 to 4.20	<0.01
Middle fossa (insula, M2, M3)	2.57	1.12 to 6.25	0.03
Posterior (M5, M6)	1.91	0.81 to 4.72	0.15
Anterior (M1, M4)	2.51	1.33 to 4.92	0.01
Patients with mechanical thrombectomy (n=159)			
Deep	2.92	1.18 to 7.69	0.02
Middle fossa (insula, M2, M3)	0.74	0.19 to 2.82	0.7
Posterior (M5, M6)	4.99	1.22 to 23.1	0.03
Anterior (M1, M4)	6.82	2.38 to 22.8	<0.001

Multivariable logistic regression model of regional follow-up ASPECTS ($ASPECTS_{fu}$) areas adjusting for baseline ASPECTS ($ASPECTS_{bl}$), age, sex, admission glucose, tissue plasminogen activator, and mechanical thrombectomy in the full model, and in subgroups without mechanical thrombectomy as a covariate.

ASPECTS, Alberta Stroke Program Early CT Score.

Table 4

Clinical model comparison of EDEMA and modified EDEMA with ASPECTS

Potentially lethal malignant edema (n=560)	EDEMA score	Modified EDEMA score
	AUC (95% CI)	**AUC (95% CI)**
EDEMA model	0.84 (0.80 to 0.88)	0.84 (0.80 to 0.88)
EDEMA model+$deep_{fu}$	0.85 (0.81 to 0.88)	0.84 (0.80 to 0.88)
EDEMA model+$ASPECTS_{bl}$	0.85 (0.81 to 0.88)	0.84 (0.80 to 0.89)
EDEMA model+middle $fossa_{fu}$	0.86 (0.82 to 0.90)	0.85 (0.81 to 0.89)
EDEMA model+$ASPECTS_{fu}$	0.86 (0.83 to 0.90)	0.86 (0.82 to 0.90)

EDEMA model=glucose+previous stroke+intervention+midline shift+basal cistern effacement. Modified EDEMA model=EDEMA model+National Institutes of Health Stroke Scale.

ASPECTS, Alberta Stroke Program Early CT Score; AUC, area under the curve; bl, baseline; EDEMA, Enhanced Detection of Edema in Malignant Anterior Circulation Stroke; fu, follow-up.