Supplementary Methods

These methods have been provided by the authors to give readers additional information about their methods and work.

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Data Collection

Demographic and Admission Data:
Data including last seen well, presentation time, past medical history, age, sex, admission glucose, stroke side, admission NIH Stroke Scale, and whether the patients received tissue Plasminogen Activator, mechanical thrombectomy or decompressive hemicraniectomy were extracted from the electronic medical record at one center using the Research Patient Data Registry (**RPDR**) for structured data, and radiology reports and clinical notes for unstructured data. Demographic, clinical, and outcome data were extracted at a second center from the electronic medical record at via manual chart review. A second researcher verified all data to ensure accuracy.

Radiographic Features:
Stroke size ≥ 1/3 the middle cerebral artery (**MCA**) territory was determined by visual estimate by a trained M.D. and underwent second review. Indeterminate images were reviewed for consensus by three authors

Midline shift was measured at the level of the septum pellucidum by a trained member of the team using imaging viewer software [Client Outlook, eUnity Diagnostic Viewer, version 6.10.2-489, for MacOs and PACS web viewer] by navigating to the level of the septum pellucidum at the slice of maximum midline shift. The reviewer created a line connecting the attachment of falx cerebri anteriorly and the occipital protuberance. Windows were set at W:30 L:30. The distance between the midline and the septum pellucidum both the lateral and medial boundaries was measured by adding a line perpendicular to the midline. The average distance (mm.) was calculated from the measurements of the lateral and medial boundaries and was used for the final midline shift used in analysis. A blinded assessment of >10% of the data found the mean error was 0.19 mm between the midline shift reported in the radiographic reports and our measurements.

The Alberta Stroke Program Early CT Score (**ASPECTS**) divides the brain parenchyma into 10 separate non-overlapping regions, three regions at the level just rostral to the ganglionic structures and four at the level of the thalamus.[1] ASPECTS equal to 10 implies that the brain parenchyma shows no evidence of ischemia, only at the two levels that the predetermined regions are examined. A score equal to 0 implies that all the predetermined areas have been affected by ischemia. ASPECTS scores were generated using 5mm axial slices and set to variable window widths. The window, as described by Lev et al.,[2] for optimal ischemic lesion identification is preferably set to W:30 L:30, or alternatively 40/40. As in Pexman et al.,[3] patient positioning was reviewed to determine if the eyes were at the same level in the axial view. For each area, if >10% of the area had evidence of hypodensity or sulcal effacement, that area was marked as affected by ischemia, and one point was deducted from the total score.[1] A review of 10% of scans resulted in a percent agreement between the two reviewers of 96.4% for dichotomous ASPECTS categories (10-8, 7-0), and 83.9% for high, medium, low ASPECTS (10-8, 7-4, 3-0). Cohen's Kappa was 0.647 for ASPECTS continuously.

Basal Cistern Effacement was determined (present/absent) in axial slices at the level of the orbitomeatal line after reviewing consecutive slices for evidence of partial or complete reduction of the basal cisterns space. Images were reviewed for consensus by three authors.

Outcomes:
Potentially Lethal Malignant Edema (**PLME**) is a dichotomous outcome variable and indicates death with ≥ 5mm midline shift (**MLS**) or decompressive hemicraniectomy (**DHC**) during hospital admission.

Analysis

Correlations:
We used Spearman's correlation coefficients to determine the associations between the ten individual ASPECTS areas as well as our four defined ASPECTS regions (middle fossa, deep, anterior, and posterior territories). Spearman's correlation coefficients range from -1 to 1 indicating the direction and strength of the correlation. A matrix of correlation coefficients was generated using rcorr() and corrplot() functions in R from the Hmisc and corrplot packages respectively. Results of this analysis can be seen in **Supplementary Figures 3** and **4**.

We also looked at the prevalence of each ASPECTS area for each total ASPECTS 0-10 to begin to identify patterns between ASPECT scores and area involvement. A heat map was generated in Excel Version 2301 and can be seen in **Supplementary Figure 5**.

Regression Models:
Multiple logistic regression models were used to determine the association between variables of interest and our primary outcome (PLME) using the glm() function in R. All models were adjusted for standard covariates including age, sex, admission glucose, tissue plasminogen activator, mechanical thrombectomy, and baseline ASPECTS score. These covariates were determined from the literature to be potentially associated with our outcome of interest- PLME. Odds ratios, 95% confidence intervals, and p values were generated for all variables of interest using the tbl_regression() function from the tidyverse library in R.

Model Comparison:
To determine improvement over existing models of PLME (EDEMA score, modified EDEMA score), we added the following new variables (Complete Deep Involvement, Complete Middle Fossa Involvement, Baseline ASPECTS, Follow-up ASPECTS). We compared Akaike Information Criterion (**AIC**), Bayesian Information Criterion (**BIC**), and Area Under the Curve (**AUC**).

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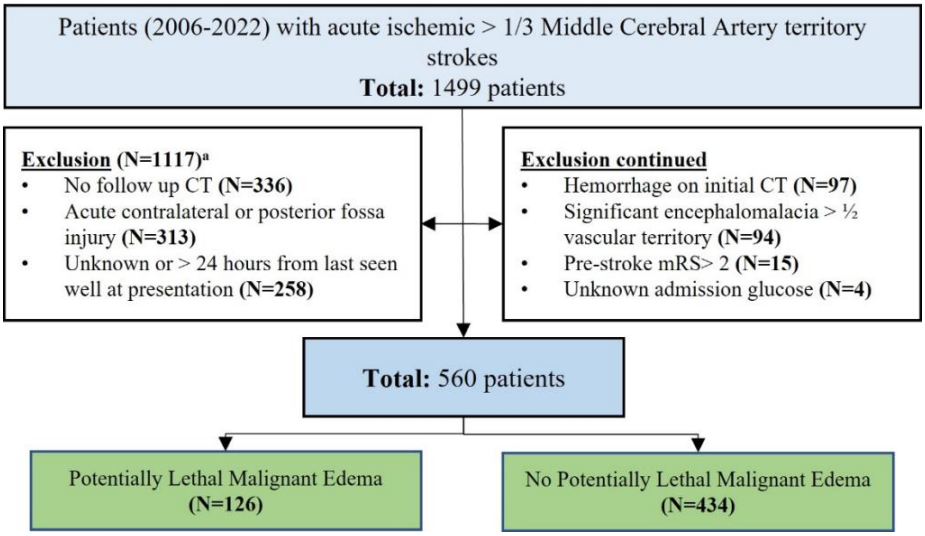
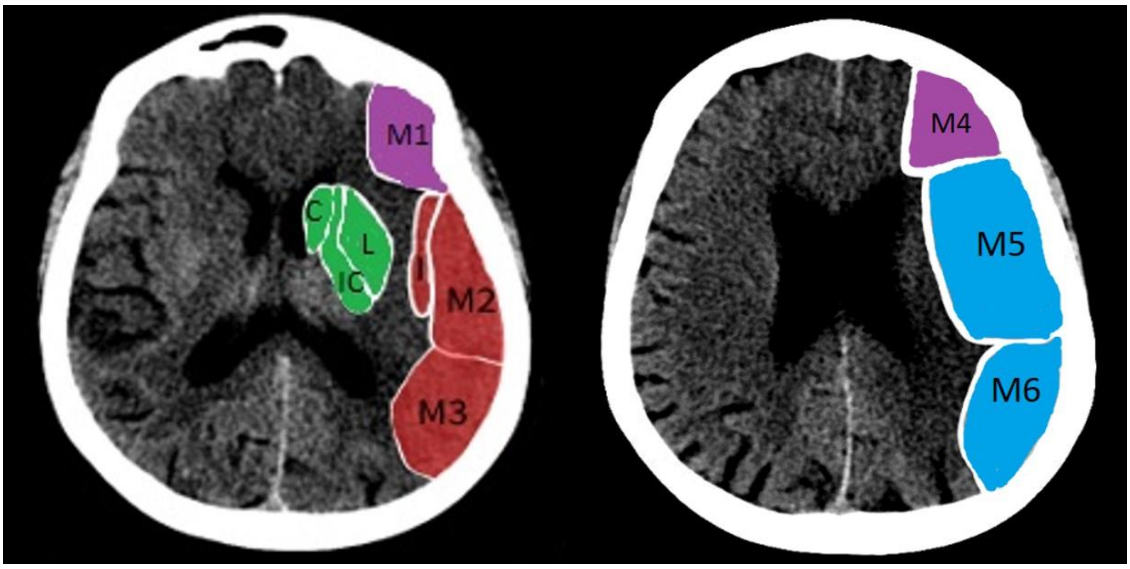
Supplementary Figures and Tables

Supplementary Figure 1: Inclusion/Exclusion Criteria



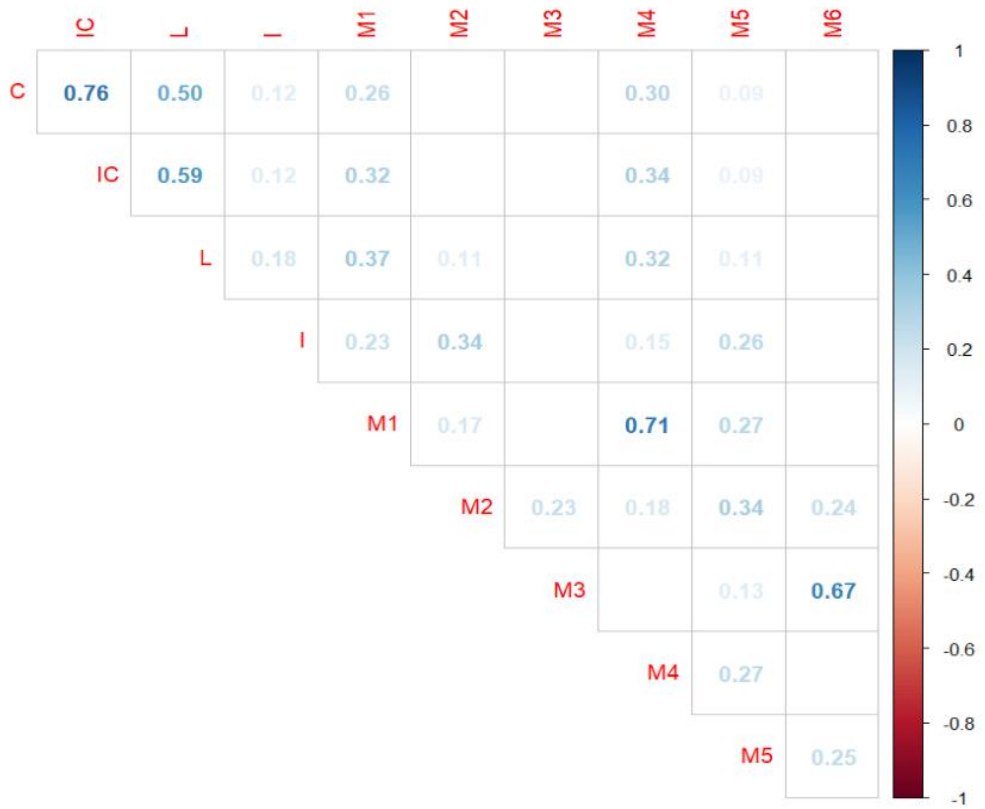
Abbr: CT=Computed Tomography; mRS=modified Rankin Scale; aPatients may have multiple exclusion criteria.

Supplementary Figure 2: ASPECTS schematic



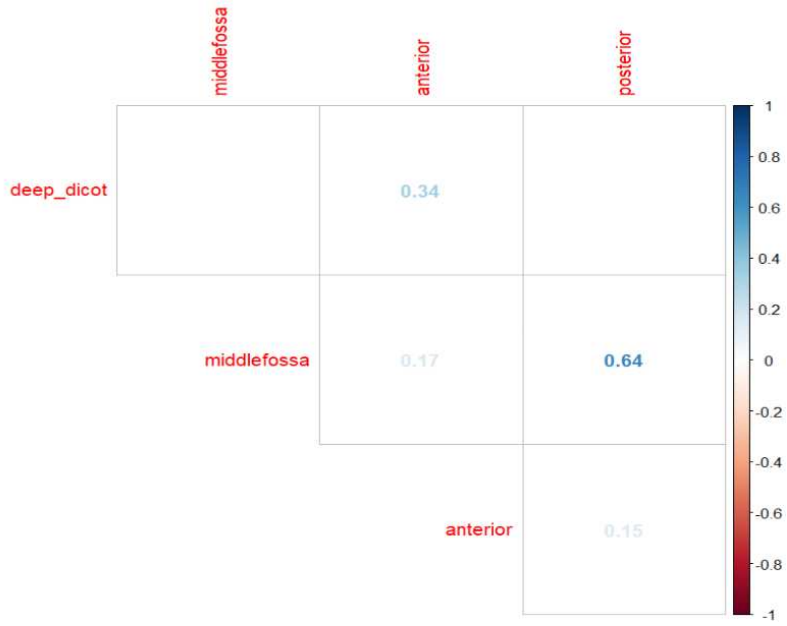
Abbr: C=caudate, IC=internal capsule, L=lentiform nucleus, I=insula, M1=anterior MCA cortex, M2=MCA cortex lateral to insular ribbon, M3=posterior MCA cortex, M4-6=MCA cortex immediately superior to M1-3. Middle fossa (red), anterior (purple), posterior (blue), and deep (green) divisions.

Supplementary Figure 3. ASPECTS$_{fu}$ Areas Correlations



Correlation matrix demonstrating correlation coefficients for the ten individual ASPECTS areas. Blank spaces indicate non-statistically significant correlations.

Supplementary Figure 4. $ASPECTS_{fu}$ Regions Correlations



Correlation matrix demonstrating correlation coefficients for the four discrete ASPECTS regions. Blank spaces indicate non-statistically significant correlations.

Supplementary Figure 5. ASPECTS$_{fu}$ Heat Map

ASPECTS	C	IC	L	I	M1	M2	M3	M4	M5	M6
10 (N=2)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
9 (N=3)	0.0	0.0	33.3	33.3	0.0	33.3	0.0	0.0	0.0	0.0
8 (N=8)	0.0	12.5	25.0	50.0	12.5	25.0	37.5	0.0	25.0	12.5
7 (N=24)	4.2	8.3	16.7	70.8	12.5	62.5	20.8	8.3	45.8	50.0
6 (N=25)	12.0	12.0	28.0	88.0	16.0	84.0	36.0	8.0	80.0	48.0
5 (N=87)	10.3	10.3	34.5	96.6	34.5	93.1	58.6	20.7	85.1	56.3
4 (N=64)	32.8	29.7	82.8	96.9	46.9	92.2	46.9	28.1	90.6	53.1
3 (N=63)	39.7	36.5	69.8	95.2	79.4	96.8	65.1	60.3	93.7	65.1
2 (N=107)	59.8	61.7	99.1	99.1	86.9	98.1	59.8	75.7	98.1	61.7
1 (N=47)	51.1	97.9	100.0	100.0	97.9	100.0	83.0	80.9	97.9	91.5
0 (N=130)	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

The heat map shows the individual percent (%) contribution of each region to the total ASPECTS$_{fu}$ of the patients included in the subset of that specific score.

Supplementary Table 1. Individual $ASPECTS_{fu}$ Multivariable Models for PLME

Characteristic	**OR***	**95% CI***	**P-value**
Caudate	1.34	0.68, 2.67	0.40
Internal Capsule	1.38	0.65, 2.99	0.40
Lentiform Nucleus	1.99	0.85, 5.02	0.13
Insula	0.51	0.12, 2.51	0.40
M1	1.49	0.61, 3.70	0.40
M2	0.88	0.19, 5.74	0.90
M3	2.45	1.17, 5.36	0.02
M4	2.82	1.35, 6.29	0.01
M5	6.56	1.18, 125	0.08
M6	1.58	0.72, 3.51	0.30

*OR = Odds Ratio, CI = Confidence Interval**.*** Multivariable logistic regression model of regional $ASPECTS_{fu}$ areas adjusting for $ASPECTS_{bl}$, age, sex, admission glucose, tissue Plasminogen Activator, and mechanical thrombectomy

Supplementary Table 2: Clinical Model Comparison of EDEMA and Modified EDEMA with ASPECTS

Potentially Lethal Malignant Edema (N=560)	**Edema Score**			**Modified Edema Score**		
Characteristic	**AIC**	**BIC**	**AUC [CI]**	**AIC**	**BIC**	**AUC [CI]**
Edema Model*	447	473	0.84 [0.80-0.88]	442	472	0.84 [0.80-0.88]
Edema Model + $Deep_{fu}$	446	477	0.85 [0.81-0.88]	442	477	0.84 [0.80-0.88]
Edema Model + $ASPECTS_{bl}$	443	473	0.85 [0.81-0.88]	439	474	0.84 [0.80-0.89]
Edema Model + Middle $Fossa_{fu}$	436	466	0.86 [0.82-0.90]	432	466	0.85 [0.81-0.89]
Edema Model + $ASPECTS_{fu}$	**427**	**457**	**0.86 [0.83-0.90]**	**426**	**460**	**0.86 [0.82-0.90]**

Abbreviations: AIC=Akaike information criterion, BIC=Bayesian information criterion, AUC=Area Under the Curve, CI=Confidence Interval

*EDEMA Model: Glucose + Prior Stroke + Intervention + Midline Shift + Basal Cistern Effacement; Modified EDEMA Model: EDEMA Model + NIHSS

References

1. Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. *The Lancet*. 2000;355(9216):1670-1674. doi:10.1016/S0140-6736(00)02237-6

2. Lev MH, Farkas J, Gemmete JJ, et al. Acute Stroke: Improved Nonenhanced CT Detection—Benefits of Soft-Copy Interpretation by Using Variable Window Width and Center Level Settings. *Radiology*. 1999;213(1):150-155. doi:10.1148/radiology.213.1.r99oc10150

3. Pexman JHW, Barber PA, Hill MD, et al. Use of the Alberta Stroke Program Early CT Score (ASPECTS) for Assessing CT Scans in Patients with Acute Stroke. Published online 2001:9.