Relationship Between Lesion Topology and Clinical Outcome in Anterior Circulation Large Vessel Occlusions

Srikant Rangaraju, MD; Christopher Streib, MD; Amin Aghaebrahim, MD; Ashutosh Jadhav, MD, PhD; Michael Frankel, MD; Tudor G. Jovin, MD

Background and Purpose—Diffusion-weighted imaging (DWI) Alberta Stroke Program Early CT Score (ASPECTS), a surrogate of infarct volume, predicts outcome in anterior large vessel occlusion strokes. We aim to determine whether topological information captured by DWI ASPECTS contributes additional prognostic value.

Methods—Adults with intracranial internal carotid artery, M1 or M2 middle carotid artery occlusions who underwent endovascular therapy were included. The primary outcome measure was poor clinical outcome (3-month modified Rankin Scale score, 3–6). Prognostic value of the 10 DWI ASPECTS regions in predicting poor outcome was determined by multivariable logistic regression, controlling for final infarct volume, age, and laterality.

Results—Two hundred and thirteen patients (mean age, 66.1±14.5 years; median National Institutes of Health Stroke Scale, 15) were included. Inter-rater reliability was good for DWI ASPECTS (deep regions, κ=0.72; cortical regions, κ=0.63). All DWI ASPECTS regions with the exception of the putamen were significant predictors (P<0.05) of poor outcome in univariate analyses. Statistical collinearity among ASPECTS regions was not observed. Using penalized multivariable logistic regression, only M4 (odds ratio, 2.82; 95% confidence interval, 1.39–5.76) and M6 (odds ratio, 2.45; 95% confidence interval, 1.15–5.3) involvement were associated with poor outcome. M6 involvement independently predicted poor outcome in right hemispheric strokes (odds ratio, 5.8; 95% confidence interval, 1.9–20.3), whereas M4 (odds ratio, 4.3; 95% confidence interval, 1.3–15.0) involvement predicted poor outcome in left hemispheric strokes adjusting for infarct volume. Topologic information modestly improved the predictive ability of a prognostic score that incorporates age, infarct volume, and hemorrhagic transformation.

Conclusions—Involvement of the right parieto-occipital (M6) and left superior frontal (M4) regions affect clinical outcome in anterior large vessel occlusions over and above the effect of infarct volume and should be considered during prognostication. (Stroke. 2015;46:1787-1792. DOI: 10.1161/STROKEAHA.115.009908.)

Key Words: anterior cerebral circulation infarction ➤ diffusion magnetic resonance ➤ outcome assessment (health care) ➤ stroke

Ischemic strokes that involve cerebral cortex result in neurocognitive deficits such as aphasia, neglect, visuospatial, and cognitive dysfunction in addition to motor disabilities that contribute to long-term disability.1–4 In patients with large vessel occlusion (LVO) stroke, 3-month modified Rankin Scale (mRS) score of 0 to 2, ie, slight disability with preserved independence, is a commonly used clinical metric and study end point to measure good outcome, whereas mRS 3 to 6 reflects poor outcome.5,6 Despite being heavily influenced by motor impairment, mRS also captures functional limitations and disabilities because of nonmotor deficits.7 Final infarct volume (FIV) is one of the most robust predictors of clinical outcomes in anterior circulation LVO (aLVO) stroke and is incorporated in the Pittsburgh Outcomes after Stroke Thrombectomy (POST) score that predicts clinical outcome with excellent discriminative power.8–10 Yet, significant deviation from predicted outcomes is not uncommon in clinical practice even with expert clinical judgment or the use of validated prognostic scores.11 It is possible that infarct topology explains some of this variability.

Previous efforts to assess the relationship between infarct topology and outcome have used computed tomography (CT) and magnetic resonance imaging (MRI)–based approaches.12,13 The Alberta Stroke Program Early CT Score (ASPECTS) captures infarct location by dividing the anterior circulation into 10 regions: 3 deep regions (caudate [C], putamen [P], and internal capsule [IC]) supplied by the lenticulostriate perforators from the M1 MCA segment, 4 cortical regions at the level of the basal ganglia (M1, M2, M3, and insula [I]), and 3 supraganglionic cortical regions (M4, M5, and M6). Hypodensity or loss of gray–white distinction on CT is scored 0, whereas the absence of hypodensity is scored 1.14 A higher

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score suggests preserved brain parenchyma and an early
CT ASPECTS ≥7 predicts better outcomes with thrombolytic
and endovascular reperfusion therapy. A study of the National
Institute for Neurological Disorders Tissue Plasminogen
Activator (NINDS tPA) trial cohort used individual regions
on pretreatment CT ASPECTS to predict long-term clinical
outcomes in patients with stroke and found that M6 region
involvement predicted poor outcomes in older patients. This
supports the hypothesis that infarct topology affects clinical
outcome; however, whether lesion location affects outcome
after controlling for infarct volume has not been evaluated.

The use of pretreatment CT to assess the impact of indi-
vidual ASPECTS regions on clinical outcome has 2 limitations:
(1) low/moderate-sensitivity for core infarct and (2) inability
to account for stroke expansion. MRI with diffusion-weighted
imaging (DWI) sequences is significantly more sensitive than
CT with a higher inter-rater reliability for the detection of early
ischemia. DWI ASPECTS on MRI performed >12 hours
from time stroke onset captures both topologic information
and the completed infarct size. This study used DWI ASPECTS
measured 12 to 72 hours post treatment in an endovascular
cohort of aLVOs to evaluate the association between lesion
topology, infarct volume, stroke latency, and clinical outcome.

Methods

Data Source and Subjects

The study cohort was derived from a prospective endovascular reg-
istry at University of Pittsburgh Medical Center and contained con-
secutively treated adult patients (aged ≥18 years) with aLVO (internal
carotid artery terminus, M1 and M2 middle carotid artery) between
January 2007 and January 2014. Patients were required to have had
a follow-up MRI scan 12 to 72 hours from treatment with a docu-
mented 3-month (+±4 weeks) mRS score. Institutional review board
approval for the maintenance of the institutional endovascular stroke
database was obtained.

Measurements

Baseline National Institutes of Health Stroke Scale scores were calcu-
lated by the treating physicians. ASPECTS on pretreatment noncon-
trast head CT scan on arrival at the stroke center was determined by the
treating neurologist before endovascular treatment. All patients under-
went CT or MR angiography before endovascular treatment, and level
of occlusion was confirmed by conventional angiography. Reperfusion
(Thrombolysis-In-Cerebral-Infarction grade) was determined by the
operating physician after the procedure. DWI ASPECTS was calcu-
lated retrospectively by 2 investigators using the DWI B-1000
sequence from a 12- to 72-hour follow-up MRI scan. Each DWI
ASPECTS region was scored 1 (preserved) or 0 (restricted diffusion
>1 mL). Punctate foci of restricted diffusion were not considered in
the ASPECTS calculation under 1 mL except when involving the deep
regions or insula. Deep DWI ASPECTS (caudate, putamen, and internal
capsule), cortical ASPECTS (M1–M6), and total DWI ASPECTS
were calculated. DWI ASPECTS information for the opposite hemi-
sphere was also collected. FIV (mL) was determined by measuring
area of restricted diffusion (DWI B-1000 hypersignal) on each slice
followed by summation over the number of slices. Three-month
mRS was measured by the treating physician at follow-up. Those who
died earlier than 3 months were assigned 3-month mRS of 6. Patients
without MRI or 3-month outcomes were excluded from the analysis.

Statistical Analysis

All DWI ASPECTS regions were evaluated in univariate analysis
and then simultaneously assessed by multivariable logistic regression
using Firth’s penalized likelihood method to predict poor outcome
(3-month mRS, 3–6). All DWI ASPECTS regions were included in
the final model regardless of statistical significance. Multicollinearity
was assessed first by creating a correlation matrix for all DWI
ASPECTS regions. Effect of collinear pairs of variables (Pearson
correlation coefficient ≥0.5) was assessed by dropping 1 variable of
each pair from the regression model and assessing for changes in the
overall model and of individual regression coefficients. Collinearity
was also evaluated by the variation inflation factors; variation infla-
tion factors ≥5.0 being considered significant. Statistical interac-
tion between laterality (right versus left hemisphere) and significant
DWI ASPECTS regions was assessed. Because interaction param-
eters reached significance, we evaluated DWI ASPECTS regions in
separate penalized regression models for right and left hemispheric
strokes adjusting for FIV. We also simultaneously assessed 20 DWI
ASPECTS variables (10 on the side of occlusion and 10 contralat-
eral) by penalized logistic regression to predict poor outcome. Four of
213 patients had contralateral hits resulting in abnormal contralateral
DWI ASPECTS (range, 8–10).

DWI ASPECTS regions of predictive value were assessed in a model
that included the POST score, which incorporates age, FIV, and parenchymal hemorrhagic transformation. Models incorporat-
ing the POST score with or without significant topological variables
were compared using −2log Likelihood and the likelihood ratio test.
Receiver operating characteristic area under the curve was used to
compare discriminatory power of the POST score for poor outcome,
with and without topological variables in the model. We also de-
termined the net reclassification improvement, integrated discrimina-
tion improvement (IDI), and relative IDI to test whether addition of
significant DWI ASPECTS regions to a model containing the POST
score improved the predictive ability of the model. All statistical
analyses were performed using IBM SPSS Statistics version 22 and
SAS software version 9.4.

Results

Patient Characteristics

Of 532 patients with aLVO treated in the study period, 250
were excluded because of lack of MRI within the 12- to
72-hour time window and 69 were excluded because of
lack of 3-month mRS data (Figure I in the online-only Data
Supplement). The 213 patients included in the analysis had
mean age of 66.1 (±14) years, median National Institutes
of Health Stroke Scale 15 (interquartile range, 11–18), median
initial CT ASPECTS 8 (interquartile range, 7–9), and mean
time from last-normal-to-treatment of 603 minutes (±58 min-
utes); 51% had right hemispheric involvement; 18.3% (n=39)
had internal carotid artery terminus; and 67.6% (n=144) had
M1 MCA occlusions. Successful reperfusion (Thrombolysis-In-
Cerebral-Infarction 2B/3) status was achieved in 66.3%
(132/199) cases (Table 1). The median FIV was 74 mL (inter-
quartile range, 16–97) and the mean POST score was 105.5
(±3.2). A total of 133 patients (53.05%) achieved poor out-
come (3-month mRS, 3–6).

Impact of Lesion Topology on 3-Month
Clinical Outcomes

Median total DWI ASPECTS was 5 (interquartile range,
2–7) for the study population, and the distribution of indi-
vidual DWI ASPECTS regions is summarized in Table 2.
Post-treatment DWI ASPECTS showed a stronger correlation (Pearson coefficient, 0.49; P<0.001) with 3-month mRS when
compared with pretreatment CT ASPECTS (Pearson coeffi-
cient, 0.22; P=0.003). Inter-rater reliability for 2 observers was

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Outcome measures after Stroke Thrombectomy; and TICI, Thrombolysis-In-Cerebral-Infarction.

<table>
<thead>
<tr>
<th>Variable (n=213)</th>
<th>Measure</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>Mean (SD)</td>
<td>66.1 (14.5)</td>
</tr>
<tr>
<td>Baseline CT ASPECTS</td>
<td>Median (IQR)</td>
<td>8 (7–9)</td>
</tr>
<tr>
<td>Baseline NIHSS score</td>
<td>Median (IQR)</td>
<td>15 (11–18)</td>
</tr>
<tr>
<td>Time-to-treatment, min</td>
<td>Mean (SEM)</td>
<td>603 (58)</td>
</tr>
<tr>
<td>Level of occlusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1 MCA occlusion n (%)</td>
<td></td>
<td>144 (67.6)</td>
</tr>
<tr>
<td>Intracranial ICAocclusion n (%)</td>
<td></td>
<td>39 (18.3)</td>
</tr>
<tr>
<td>TICI2B/3 reperfusion n (%)</td>
<td></td>
<td>123 (57.8)</td>
</tr>
<tr>
<td>Right hemisphere n (%)</td>
<td></td>
<td>109 (51)</td>
</tr>
<tr>
<td>Outcome measures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIV, mL</td>
<td>Median (IQR)</td>
<td>74 (16–97)</td>
</tr>
<tr>
<td>POST score</td>
<td>Median (IQR)</td>
<td>92.2 (74–120.1)</td>
</tr>
<tr>
<td>3-mo mRS</td>
<td>Median (IQR)</td>
<td>3 (1–6)</td>
</tr>
<tr>
<td>Poor outcome (mRS, 3–6)</td>
<td>n (%)</td>
<td>113 (53.05)</td>
</tr>
</tbody>
</table>

**Table 1. Patient Characteristics and Outcome Measures**

**Table 2. Distribution of MRI DWI ASPECTS Regions**

**Table 3. Multivariable Penalized Regression Analysis to Predict Poor Outcome (3-Month Modified Rankin Scale, 3–6)**

Good for DWI ASPECTS (deep ASPECTS regions, \( \kappa = 0.72 \); cortical ASPECTS regions, \( \kappa = 0.63 \)). In univariate analyses, all ASPECTS regions, with the exception of the putamen (\( P = 0.089 \)), were significantly associated with poor outcome (\( P < 0.05 \)). However, only M4 (odds ratio [OR], 2.82; 95% confidence interval [CI], 1.39–5.76; \( P = 0.005 \)) and M6 (OR, 2.44; 95% CI, 1.14–5.30; \( P = 0.024 \)) involvement were significantly associated with poor outcome in multivariable penalized regression analyses that included all DWI ASPECTS regions (Table 3). Highest correlation was observed between C and P (Pearson coefficient, 0.53), and I and M2 (Pearson coefficient, 0.52) DWI ASPECTS regions suggesting multicollinearity (Table I in the online-only Data Supplement). Exclusion of putamen or M2 regions from the full model to account for possible collinearity between C and P regions and between I and M2 regions did not alter the results, ie, only M4 and M6 had significant regression coefficient estimates (Table II in the online-only Data Supplement). No significant statistical collinearity was observed for any of the 10 variables (variation inflation factors, <5).

Because our goal was to estimate the topologic influence of infarction, over and above the influence of infarct volume, we controlled for FIV in the model and still found that M4 (OR, 2.27; \( P = 0.045 \)) and M6 (OR, 2.67; \( P = 0.016 \)) involvement remained significant predictors of poor outcome, whereas all other ASPECTS regions were not. Because complete MCA infarcts result in cortical ASPECTS of 0, inclusion of these patients in our analysis may have biased the estimates. In our cohort, 17.8% (38/213) of patients had involvement of all cortical regions. After excluding these patients, we still found that M4 (OR, 6.52; \( P = 0.011 \)) involvement was a significant predictor of poor outcome and M6 (OR, 2.93; \( P = 0.087 \)) involvement did not reach statistical significance.

### Hemispheric Laterality Influences the Effect of Infarct Topology on Clinical Outcome

Cortical symptoms observed in dominant and nondominant hemispheric strokes are distinct, and the association between infarct topology and clinical outcome is likely to be influenced by the side of the lesion (dominant versus nondominant). Because the majority of individuals are left hemispheric dominant, we used laterality (right versus left) as a surrogate of hemispheric dominance. In models that incorporated infarct volume, M4 and M6 DWI ASPECTS regions, we found that the interaction terms M4\times\text{laterality} (\( P = 0.038 \)) and M6\times\text{laterality} (\( P = 0.013 \)) reached statistical significance (Table III in the online-only Data Supplement), confirming the presence of effect modification. Therefore, the effect of topology on clinical outcome was assessed separately in left and right hemispheric strokes. In left...
hemispheric strokes, we found that M4 involvement was the only independent predictor of poor outcome (OR, 5.46; 95% CI, 1.47–20.34; \( P=0.012 \)), whereas all other ASPECTS regions and FIV were not. In right hemispheric strokes, only M6 involvement independently predicted poor outcome (OR, 7.47; 95% CI, 2.07–27.02; \( P=0.002 \)), whereas other ASPECTS regions and FIV were not significant predictors of poor outcome (Table 4). As an alternative approach, we used penalized regression with 10 right and 10 left DWI ASPECTS regions simultaneously in 1 model and confirmed that right M6 (OR, 6.25; 95% CI, 2.0–22.1) and left M4 (OR, 5.63; 95% CI, 1.9–18.6) regions were the only significant predictors of poor outcome (Table IV in the online-only Data Supplement).

### Topologic Information May Improve Predictive Power of the POST Score in aLVOs

We previously found that age, FIV, and parenchymal hemorrhage are among the strongest predictors of clinical outcome in aLVOs; on the basis of these observations, we developed the POST score as a reliable tool for prognostication. We used the POST score in the model to control for these variables and found that M4 involvement in left hemispheric and M6 involvement in right hemispheric strokes, in addition to the POST score, were independently associated with poor outcome (Table 5). A model incorporating the POST score along with M4 and M6 involvement status had a significantly better model fit when compared with the POST score alone (\( >2 \) log likelihood 213.32 versus 214.66, respectively; \( P<0.005 \)). Addition of M4 and M6 involvement to the POST score seemed to modestly improve the discriminative power of the prediction model when compared with the POST score alone in right (area under the curve, 0.90 versus 0.84) and left hemispheric strokes (area under the curve, 0.89 versus 0.86). Net reclassification improvement was 4.55% (\( S/110 \)) among patients with observed poor outcome and 0% (0/99) among those without poor outcome. Overall net reclassification improvement of 4.55% suggests that addition of M4 and M6 involvement improved the classification accuracy of the model (Table V in the online-only Data Supplement). IDI, a measure of separation in predicted probabilities for events (mRS, 0–2) and nonevents (mRS, 3–6) and nonevents (mRS, 0–2), was 0.038. The relative IDI, a measure of separation in predicted probabilities for events (mRS, 0–2) and nonevents (mRS, 3–6), was 0.038.

**Table 4. Infarct Laterality, Topology, and 3-Month Poor Outcomes (Modified Rankin Scale, 3–6)**

<table>
<thead>
<tr>
<th>Laterality</th>
<th>Significant Predictors</th>
<th>OR</th>
<th>95% Confidence Interval</th>
<th>( P ) Value</th>
<th>Nonsignificant Covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right (n=105)</td>
<td>M6 region</td>
<td>5.77</td>
<td>1.87–20.3</td>
<td>0.005</td>
<td>FIV, all other DWI ASPECTS regions</td>
</tr>
<tr>
<td>Left (n=103)</td>
<td>M4 region</td>
<td>4.31</td>
<td>1.34–15.03</td>
<td>0.022</td>
<td>FIV, all other DWI ASPECTS regions</td>
</tr>
</tbody>
</table>

Penalized logistic regression was used to estimate ORs that compare involvement to sparing of individual DWI ASPECTS region (\( P=0.05 \) considered nonsignificant). DWI ASPECTS indicates diffusion-weighted imaging Alberta Stroke Program Early CT Score; FIV, final infarct volume; and OR, odds ratio.

### Discussion

The ASPECTS method, originally designed for the use with noncontrast head CT scans, measures infarcted regions in the anterior circulation. ASPECTS can also be determined on DWI MRI and like CT ASPECTS, DWI ASPECTS of ≥7 is associated with smaller infarct volumes and favorable clinical outcomes. We found that post-treatment DWI ASPECTS in an endovascular aLVO cohort can reliably capture information on infarct burden and topology. The inter-rater agreement for DWI ASPECTS in our study (\( \kappa=0.7 \)) was significantly higher than previously reported for CT ASPECTS. This topological information captured by DWI ASPECTS also provided additional prognostic value in patients with aLVO. We found that involvement of specific regions, namely the left M4 (superior frontal) and the right M6 (superior parietal) regions, has independent effects on the 3-month clinical outcome. This finding is further supported by observations made by Phan et al., who assessed the use of individual pretreatment CT ASPECTS regions in an analysis of the NINDS tPA patient cohort using penalized logistic regression and found that M6 involvement was associated with poor outcomes in the elderly.

A limitation of pretreatment CT ASPECTS as a predictor of final outcome is that many patients progress to larger infarcts, especially if early recanalization of the occluded vessel is not achieved. This can be overcome using post-treatment imaging in the first 72 hours to account for infarct growth, hemorrhagic transformation without the effect of cerebral edema. In patients who have undergone endovascular therapy, rapid recanalization prevents core infarct expansion and improves long-term clinical outcomes. Partial or complete recanalization may also result in lower collinearity among ASPECTS regions, especially if ASPECTS is based on a follow-up scan at which time no further infarct expansion is anticipated. Therefore, our use of post-treatment MRI DWI ASPECTS after 12 to 72 hours may have overcome the problem of collinearity. Indeed, we did not observe multicollinearity among the 10 DWI ASPECTS regions in our analysis.

Our observations suggest that not all ASPECTS regions have equal clinical importance. Right parietal lobe involvement or left superior frontal lobe involvement seem to be independently associated with poor outcome. Furthermore, neither motor strip nor internal capsule region was found to be independently associated with clinical outcome. Because we did not capture information on hemispheric dominance in our cohort, we performed our analyses using laterality as a surrogate of hemispheric dominance. Because a large majority of individuals are expected to have left hemispheric dominance, we expect that most left hemispheric strokes in our study affected the dominant hemisphere, whereas most right hemispheric strokes affected the nondominant hemisphere. Therefore, the prognostic importance of the left M4 and right M6 regions likely reflects the importance of the dominant M4 and nondominant M6 regions, respectively.

Our findings also illustrate the impact of cortical symptoms such as aphasia or hemineglect on patient outcomes, even when the outcome measure (mRS) is heavily influenced by motor deficits that affect ambulation. This is not surprising because hemineglect has been found to impact motor functions.
independence as measured by the functional independence measure, and aphasia has been found to impact cognitive functional independence measure in patients with stroke.17 Severity of the disability and need for help or assistance distinguishes between patients with mRS of 2 (significant disability, yet independent) and 3 (moderate disability, needing some help). This explains how cortical symptoms may impact the clinical outcome when the mRS score, dichotomized as 0 to 2 (good outcome) and 3 to 6 (poor outcome) is used in stroke research involving aLVOs.5,6

Our results may also be relevant to the interpretation of pretreatment ASPECTS during patient selection for endovascular treatment. Involvement of the left M4 or right M6 regions before endovascular treatment may represent a poor prognostic factor especially if moderate core infarcts are already visible on the pretreatment scan. On the contrary, reperfusion strategies could be considered even in patients with moderately sized core infarcts or intermediate pretreatment CT ASPECTS (5–7) if the right M4 or left M6 regions are still preserved.

Robust prediction tools have been validated for the use in aLVOs but do not use information on infarct topology. One example is the POST score, which incorporates age, FIV, and the presence of parenchymal hematoma to predict clinical outcome with high accuracy (area under the curve, >0.8).10 The importance of lesion location on clinical outcome explains why a model that integrates DWI ASPECTS variables (M4 or M6) with the POST score seems to be superior to the POST score by itself. Because the patient cohort used in this analysis is a subset of the cohort used in the validation of the POST score, independent validation in other data sets is needed to further assess whether topological variables improve the predictive power of the POST score.

Our study has several limitations. First, our database did not contain information on other measures of stroke-related disability such as functional independence measure or stroke-related quality of life measures, which may have a higher sensitivity than mRS for minor disabilities.26 Although only M4 and M6 ASPECTS regions were significantly associated with clinical outcome in our analysis, other cortical and deep regions may also influence long-term clinical outcome but may not have been detected in our analysis possibly because of moderate sample size or clinical impacts that are underestimated when dichotomizing clinical outcomes as mRS of 0 to 2 and 3 to 6. We also did not measure the volumes of individual DWI ASPECTS regions and are therefore unable to address the relationship between lesion location and lesion volume for individual ASPECTS regions. Such a study using ASPECTS may be limited by the arbitrary boundaries that separate various ASPECTS regions. Instead, we used the total FIV to control for the effect of infarct size on clinical outcome. Although we did not find statistical evidence for multicollinearity in our study as measured by the variation inflation factors, this measure may have underestimated the effect of anatomy and shared vascular supply by various DWI ASPECTS regions.

The moderate correlation observed between C and P, and I and M2 regions, suggest some degree of collinearity, but these did not impact the overall results of our analysis. Voxel-based assessment of infarct location and volume may overcome the above limitations in our study and may reveal other cortical regions that are of prognostic significance.12 Next, our study is retrospective and based on a single institutional endovascular stroke cohort. A large proportion of patients (319/532) were excluded because of lack of MRI data in the 12- to 72-hour time frame (46.9%) or missing follow-up information (12.96%). Because patients who did not have follow-up MRI scans were excluded from the study, this may have introduced selection biases because of the exclusion of patients who had early fatal complications, had contraindications for MRI scans, had strokes that were large, or had no residual deficits that an MRI was not felt to be necessary. Therefore, confirmation of our results in other aLVO populations and prospective cohorts is needed before generalizing our results.

In conclusion, we have demonstrated that topological information captured by MRI DWI ASPECTS on post-treatment imaging is of prognostic value in anterior circulation LVOs. Specifically, involvement of the right parietal region (M6) or the left superior frontal (M4) regions independently increase the odds for poor outcomes, even after controlling for other robust predictors of clinical outcome including age and FIV. Our results support the hypothesis that infarct location and laterality, and not just infarct volume, impact clinical outcomes and provide additional prognostic value in aLVO patients.

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Disclosures

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References

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Relationship between Lesion Topology and Clinical Outcome In Anterior Circulation Large Vessel Occlusions

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SUPPLEMENTAL MATERIAL
Supplemental Figure I. Selection of study population. Patients treated between 2007 and 2014 at UPMC, Pittsburgh, PA with confirmed anterior LVO (M1, M2 or intracranial ICA occlusion) were included. Patients were excluded if (1) no MRI scan was performed during hospitalization, (2) no documented mRS at 3 months and (3) if MRI was not performed in the 12-72 hour time window.
Supplemental Table I. Correlation matrix of the 10 DWI ASPECTS regions

<table>
<thead>
<tr>
<th>DWI ASPECTS Region</th>
<th>C</th>
<th>P</th>
<th>IC</th>
<th>I</th>
<th>M1</th>
<th>M2</th>
<th>M3</th>
<th>M4</th>
<th>M5</th>
<th>M6</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>1</td>
<td>.53*</td>
<td>.38**</td>
<td>.03</td>
<td>.19**</td>
<td>-.05</td>
<td>-.03</td>
<td>.19**</td>
<td>.15*</td>
<td>.04</td>
</tr>
<tr>
<td>P</td>
<td>.53*</td>
<td>1</td>
<td>.42**</td>
<td>-.09</td>
<td>.11</td>
<td>-.16*</td>
<td>-.06</td>
<td>.11</td>
<td>.25**</td>
<td>.01</td>
</tr>
<tr>
<td>IC</td>
<td>.38*</td>
<td>.42**</td>
<td>1</td>
<td>.03</td>
<td>.29**</td>
<td>.15*</td>
<td>.16*</td>
<td>.19**</td>
<td>.34**</td>
<td>.20**</td>
</tr>
<tr>
<td>I</td>
<td>.03</td>
<td>-.09</td>
<td>.03</td>
<td>1</td>
<td>.38**</td>
<td>.52**</td>
<td>.36**</td>
<td>.3**</td>
<td>.17*</td>
<td>.29**</td>
</tr>
<tr>
<td>M1</td>
<td>.19**</td>
<td>.11</td>
<td>.29**</td>
<td>.38**</td>
<td>1</td>
<td>.41**</td>
<td>.22**</td>
<td>.49**</td>
<td>.26**</td>
<td>.38**</td>
</tr>
<tr>
<td>M2</td>
<td>-.05</td>
<td>-.16*</td>
<td>.15*</td>
<td>.52**</td>
<td>.41**</td>
<td>1</td>
<td>.46**</td>
<td>.25**</td>
<td>.21**</td>
<td>.27**</td>
</tr>
<tr>
<td>M3</td>
<td>-.03</td>
<td>-.06</td>
<td>.15*</td>
<td>.37**</td>
<td>.22**</td>
<td>.46**</td>
<td>1</td>
<td>.33**</td>
<td>.13</td>
<td>.49**</td>
</tr>
<tr>
<td>M4</td>
<td>.19**</td>
<td>.11</td>
<td>.19**</td>
<td>.29**</td>
<td>.48**</td>
<td>.24**</td>
<td>.33**</td>
<td>1</td>
<td>.29**</td>
<td>.39**</td>
</tr>
<tr>
<td>M5</td>
<td>.15*</td>
<td>.25**</td>
<td>.34**</td>
<td>.17*</td>
<td>.26**</td>
<td>.21**</td>
<td>.13</td>
<td>.29**</td>
<td>1</td>
<td>.19**</td>
</tr>
<tr>
<td>M6</td>
<td>.04</td>
<td>.01</td>
<td>.2**</td>
<td>.29**</td>
<td>.38**</td>
<td>.27**</td>
<td>.49**</td>
<td>.39**</td>
<td>.19**</td>
<td>1</td>
</tr>
</tbody>
</table>

*Significant at the 0.05 level. ** Significant at the 0.01 level.
Supplemental Table II. Assessment of potentially collinear terms on the multivariable regression model

<table>
<thead>
<tr>
<th>Model</th>
<th>Significant variables</th>
<th>-2LogL</th>
<th>Non-significant variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>All 10 regions included</td>
<td>M4**, M6*</td>
<td>233.62</td>
</tr>
<tr>
<td>Model 2</td>
<td>C excluded</td>
<td>M4**, M6*</td>
<td>234.78</td>
</tr>
<tr>
<td>Model 3</td>
<td>M2 excluded</td>
<td>M4**, M6*</td>
<td>236.02</td>
</tr>
</tbody>
</table>

*Significant at the 0.05 level. ** Significant at the 0.01 level. All OR estimates compare "Involvement" to "Sparing" of individual DWI ASPECTS region. Outcome variable is poor outcome (mRS 3-6 at 3 months).
**Supplemental Table III:** Relationship between DWI ASPECTS regions and 3-month clinical outcome (mRS 3-6) is affected by laterality of the infarct

<table>
<thead>
<tr>
<th>Model</th>
<th>Variables of interest</th>
<th>OR</th>
<th>95% C.I.</th>
<th>P-value</th>
<th>Other co-variates in the model</th>
</tr>
</thead>
<tbody>
<tr>
<td>No interaction model</td>
<td>M4</td>
<td>2.68</td>
<td>1.31-552</td>
<td>0.007</td>
<td>FIV*, Laterality</td>
</tr>
<tr>
<td></td>
<td>M6</td>
<td>2.58</td>
<td>1.28-5.2</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>With interaction terms</td>
<td>M4</td>
<td>6.04</td>
<td>2.2-16.6</td>
<td>&lt;0.001</td>
<td>FIV*, Laterality</td>
</tr>
<tr>
<td></td>
<td>M6</td>
<td>1.20</td>
<td>0.43-3.35</td>
<td>0.72</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M4*Laterality (Right=1)</td>
<td>0.17</td>
<td>0.04-0.39</td>
<td>0.013</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M6*Laterality (Right=1)</td>
<td>4.67</td>
<td>1.09-20.01</td>
<td>0.038</td>
<td></td>
</tr>
</tbody>
</table>

* Indicates p-value for the regression coefficient (Age, FIV) is p<0.05. All OR estimates compare "Involvement" to "Sparing" of individual DWI ASPECTS region.
Supplemental Table IV. Alternative approach to assess the importance of individual DWI ASPECTS regions in predicting clinical outcomes

<table>
<thead>
<tr>
<th>DWI Region</th>
<th>Estimate</th>
<th>95% Confidence Limits</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>R C</td>
<td>2.372</td>
<td>0.834</td>
<td>7.138</td>
</tr>
<tr>
<td>R P</td>
<td>0.807</td>
<td>0.248</td>
<td>2.459</td>
</tr>
<tr>
<td>R IC</td>
<td>1.244</td>
<td>0.439</td>
<td>3.449</td>
</tr>
<tr>
<td>R I</td>
<td>1.146</td>
<td>0.299</td>
<td>4.220</td>
</tr>
<tr>
<td>R M1</td>
<td>1.042</td>
<td>0.337</td>
<td>3.105</td>
</tr>
<tr>
<td>R M2</td>
<td>2.565</td>
<td>0.682</td>
<td>9.491</td>
</tr>
<tr>
<td>R M3</td>
<td>1.027</td>
<td>0.316</td>
<td>3.197</td>
</tr>
<tr>
<td>R M4</td>
<td>0.906</td>
<td>0.291</td>
<td>2.695</td>
</tr>
<tr>
<td>R M5</td>
<td>2.019</td>
<td>0.611</td>
<td>7.388</td>
</tr>
<tr>
<td>R M6</td>
<td>6.246</td>
<td>2.011</td>
<td>22.116</td>
</tr>
<tr>
<td>L C</td>
<td>0.965</td>
<td>0.262</td>
<td>3.462</td>
</tr>
<tr>
<td>L P</td>
<td>2.191</td>
<td>0.667</td>
<td>7.216</td>
</tr>
<tr>
<td>L IC</td>
<td>1.197</td>
<td>0.339</td>
<td>4.245</td>
</tr>
<tr>
<td>L I</td>
<td>1.683</td>
<td>0.547</td>
<td>5.217</td>
</tr>
<tr>
<td>L M1</td>
<td>1.875</td>
<td>0.585</td>
<td>6.078</td>
</tr>
<tr>
<td>L M2</td>
<td>1.838</td>
<td>0.566</td>
<td>6.014</td>
</tr>
<tr>
<td>L M3</td>
<td>0.632</td>
<td>0.198</td>
<td>1.907</td>
</tr>
<tr>
<td>L M4</td>
<td>5.632</td>
<td>1.861</td>
<td>18.553</td>
</tr>
<tr>
<td>L M5</td>
<td>2.069</td>
<td>0.683</td>
<td>6.261</td>
</tr>
<tr>
<td>L M6</td>
<td>0.985</td>
<td>0.289</td>
<td>3.235</td>
</tr>
</tbody>
</table>

Penalized logistic regression (Firth’s penalized likelihood method) was used to determine OR estimates. 20 DWI ASPECTS (10 Right [R] and 10 Left [L]) variables were determined for each individual and were entered simultaneously in the model. All OR estimates compare "Involvement" to "Sparing" of individual DWI ASPECTS regions.
Supplemental Table V. Reclassification table for models without and with M4 and M6 involvement

<table>
<thead>
<tr>
<th></th>
<th>Risk category for poor outcome (% mRS 3-6)</th>
<th>OLD MODEL</th>
<th>0-5%</th>
<th>5-20%</th>
<th>20-50%</th>
<th>&gt;50%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NEW MODEL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS 0-2 (Non-events)</td>
<td></td>
<td>0-5%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-20%</td>
<td>0</td>
<td>14</td>
<td>5</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20-50%</td>
<td>0</td>
<td>8</td>
<td>49</td>
<td>5</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;50%</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>0</td>
<td>22</td>
<td>56</td>
<td>21</td>
<td>99</td>
</tr>
<tr>
<td>mRS 3-6 (Events)</td>
<td></td>
<td>0-5%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-20%</td>
<td>0</td>
<td>1</td>
<td>20</td>
<td>12</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20-50%</td>
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<td>0</td>
<td>6</td>
<td>71</td>
<td>77</td>
</tr>
<tr>
<td></td>
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<td>0</td>
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<td>16</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
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<td>26</td>
<td>83</td>
<td>110</td>
</tr>
<tr>
<td><strong>All</strong></td>
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<td>0</td>
<td>0</td>
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<td>0</td>
</tr>
<tr>
<td></td>
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<td>5-20%</td>
<td>0</td>
<td>14</td>
<td>5</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td></td>
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<td>20-50%</td>
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<td>69</td>
<td>17</td>
<td>95</td>
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<tr>
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<td>&gt;50%</td>
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<td>0</td>
<td>8</td>
<td>87</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>0</td>
<td>23</td>
<td>82</td>
<td>104</td>
<td>209</td>
</tr>
</tbody>
</table>

Risk categories of poor outcome were classified as 0-5%, 5-20%, 20-50% and greater than 50%. The old model (POST score only) and new model (POST+M4/M6 involvement) were compared. Net reclassification Improvement (NRI) in Events was 4.55% and in Non-events was 0%. Total NRI was 4.55%.