Admission Insular Infarction >25% Is the Strongest Predictor of Large Mismatch Loss in Proximal Middle Cerebral Artery Stroke

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Background and Purpose—Previous univariate analyses have suggested that proximal middle cerebral artery infarcts with insular involvement have greater severity and are more likely to progress into surrounding penumbral tissue at risk. We hypothesized that a practical, simple scoring method to assess percent insular ribbon infarction (PIRI score) would improve prediction of penumbral loss over other common imaging biomarkers.

Methods—Of consecutive acute stroke patients from 2003 to 2008, 45 with proximal middle cerebral artery–only occlusion met inclusion criteria, including available penumbral imaging. Infarct (diffusion-weighted imaging), tissue at risk (magnetic resonance mean transit time), and final infarct volume (magnetic resonance/computed tomography) were manually segmented. Diffusion-weighted imaging images were rated according to the 5-point PIRI score (0, normal; 1, <25%; 2, 25%–49%; 3, 50%–74%; 4, ≥75% insula involvement). Percent mismatch loss was calculated as an outcome measure of infarct progression. Receiver operating characteristic curve and multivariate analyses were performed.

Results—Mean admission diffusion-weighted imaging infarct volume was 30.9 (±38.8) mL and median (interquartile range) PIRI score was 3 (0.75–4). PIRI score was significantly correlated with percent mismatch loss (P<0.0001). When percent mismatch loss was dichotomized based on its median value (30.0%), receiver operating characteristic curve area under curve was 0.89 (P=0.0001) with a 25% insula infarction optimal threshold. After adjusting for time to imaging and treatment, binary logistic regression, including dichotomized PIRI (25% threshold), age, National Institutes of Health Stroke Scale score, diffusion-weighted imaging infarct volume, and computed tomography angiography collateral score as covariates, revealed that only dichotomized insula score (P=0.03) and age (P=0.02) were independent predictors of large (68.2%) versus small (8.1%) mismatch loss. There was excellent interobserver agreement for dichotomized PIRI scoring (κ=0.91).

Conclusions—Admission insular infarction >25% is the strongest predictor of large mismatch loss in this cohort of proximal middle cerebral artery occlusive stroke. This outcome marker may help to identify treatment-eligible patients who are in greatest need of rapid reperfusion therapy. 

Key Words: imaging-predictor ■ insula ■ MCA ■ penumbra ■ stroke
intuitive appeal, as the vascular supply to the insula not only reflects the confluence of bulk flow through the superior and (less consistently) inferior MCA divisions, but is also determined by the combined effects of anatomic variants, clot location, and collateral flow.\textsuperscript{11,13,14} We hypothesized that a practical, easy-to-use scoring method, based on percent insular ribbon infarction at admission (the percent insular ribbon infarction [PIRI] score), would enhance prediction of mismatch loss in proximal MCA occlusive stroke patients compared with other currently used imaging biomarkers.

\section*{Methods}

\subsection*{Patients}

We reviewed the clinical/imaging records of consecutive patients with new onset acute stroke symptoms that underwent the standardized acute stroke imaging algorithm at our institution from April 2003 to April 2008. Our institutional review board approved this study; written informed consent was not required for this Health Insurance Portability and Accountability Act-compliant retrospective analysis of prospectively acquired routine clinical data. Forty-five patients who met the following criteria were included: (1) admission CT, CTA, magnetic resonance (MR) DWI, and perfusion imaging within 9 hours of stroke onset; (2) proximal MCA occlusion only on CTA (M1 branch); and (3) either CT or MR follow-up at >24 hours, but not at 3 to 7 days (to avoid maximal vasogenic edema); exclusion criteria were: (4) lacunar infarct (solitary DWI lesion, <15 mm); and (5) CTA occlusions at any of the following: contralateral MCA, internal carotid artery, anterior cerebral artery, and posterior cerebral artery.

\subsection*{CT/MR Acquisitions}

All imaging was obtained in the emergency department for routine clinical indications according to our standardized institutional acute stroke algorithms. Noncontrast head CT was performed helically (LightSpeed 64; GE Healthcare, Milwaukee, WI) at 120 kV, 250 mA, and 0.7 s/rotation. Filtered backprojection with standard kernel was used for image reconstruction at 5-mm-thick contiguous sections, field of view 22 cm, and matrix size 512×512. CTA immediately followed noncontrast head CT, at 120 kV, 300 mA, 0.5 to 0.7 s/rotation, with 80 to 100 mL of nonionic contrast (Omnipaque 370; Nycomed, Roskilde, Denmark) followed by 40 mL of saline, both at 4 mL/s. Noncontrast head CT was performed helically (GE Healthcare). DWI was performed using single-shot echoplanar spin-echo; high b-value images (b=1000 s/mm\textsuperscript{2}) were acquired in 6 different gradient directions, in addition to a single low b value (b=0 s/mm\textsuperscript{2}). Imaging parameters were: time repetition/time echo 5000/80 to 110 ms, field of view 22 cm, matrix 128×128 zero-filled to 256×256, and slice thickness 5 mm with 1 mm gap. Perfusion imaging was performed using dynamic susceptibility technique; serial echoplanar gradient echo images were acquired with time repetition/time echo 1500/40 ms, field of view 22 cm, matrix 128×128, and slice thickness 5 mm with a 1 mm gap. Fourteen to 16 slices were acquired every 1.5 seconds for 46 to 80 images/slice. Ten seconds after the start of image acquisition, 20 mL of gadopentetate dimeglumine 0.5 mmol/mL (Magnevist; Bayer HealthCare Pharmaceuticals) was administered at 5 mL/s using a power injector (Medrad, Warrendale, PA), followed by a 20-mL normal saline bolus.

\subsection*{Image Analysis}

Mean transit time (MTT) maps were postprocessed from the MR perfusion source data using a previously validated singular value decomposition deconvolution software platform.\textsuperscript{15} MTT images were reviewed using a rainbow color scale display that facilitated visual distinction of pixels values <7 seconds from those with values ≥7 to 10 seconds (the latter considered penumbral tissue at risk). Ischemic lesion volumes for admission infarct (DWI/apparent diffusion coefficient), tissue at risk (MR MTT), and final infarct (MR fluid attenuated inversion recovery or CT) were manually segmented using semiautomated commercially available software (Analyze 8.1; Analyze-Direct, Mayo Clinic, Rochester, MN) by an MD research scientist (S.K., 4 years of experience) and edited by a board-certified neuroradiologist (A.K. and M.H.L.). The patency of the CTA collateral circulation was scored on the CTA source images at 2 combined levels (sylvian fissure and convexity) according to a published 5-point rating scale (from absent to exuberant) by experienced board-certified neuroradiologists (A.K. and M.H.L.).\textsuperscript{11}

PIRI was independently rated on the admission DWI/apparent diffusion coefficient images according to a simple 5-point score, based on percent involvement in quartiles (0, normal; 1, <25%; 2, 25%–49%; 3, 50%–74%; 4, ≥75%), by 2 neuroradiologists, each with ≥2 years of experience (R.C.B. and L.M.), blinded to all correlative clinical and other imaging data except laterality. Assessment was based on visual estimation using 3 contiguous axial slices depicting the longest extent of the insular ribbon; disagreements were decided by consensus.

Percent mismatch loss (PML) was calculated as an outcome measure of admission DWI/apparent diffusion coefficient infarct growth into the MTT-defined tissue at risk, based on published methodolgy,\textsuperscript{11} as follows:

\[
PML = 100 \times \frac{[\text{final infarct} - \text{admit DWI}] \text{volumes}}{[\text{admit MTT} - \text{admit DWI}] \text{volumes}}
\]

\section*{Statistical Analyses}

Continuous variables are shown as means and SD, or as medians and interquartile ranges. Discrete variables are reported as counts (n) and percentages (%). The $\kappa$-statistic ($\kappa$) was used to determine interobserver agreement for PIRI grading, based on Landis and Koch guidelines.\textsuperscript{16} Spearman rank correlation and univariate linear regression were used to test the association of PIRI score with PML. PML was dichotomized at its median value, and large versus small mismatch loss were defined as the median PML values above and below this dichotomized threshold, respectively. Receiver operating characteristic (ROC) curve analysis was performed to test the accuracy of PIRI for prediction of large mismatch loss.

In addition, a multivariate approach was performed to predict PML using a linear and a binary logistic multivariate regression model. After adjusting for time to imaging and treatment assignment, the multivariate regression model of PML included PIRI scores and the 4 most relevant and well-established univariate predictors of infarct growth (age, NIHSS score, admission MTT-infarct volume, and CTA collateral score).\textsuperscript{5,4,17,18} All these variables were entered in the multivariate model and additionally tested with forward selection and backward elimination. There was no evidence of nonlinearity between PML and independent variables; in patients for whom the final infarct was larger than the tissue at risk, percent penumbra lost was recorded as 100%. Kolmogorov–Smirnov test confirmed the normality of model residuals (P=0.998). In the linear regression model, PML outcome was dichotomized at its median value, and PIRI was dichotomized at the operating point of the ROC curve. Analyses were performed using MedCalc (version 11.5.1.0; Mariakerke, Belgium), with significance defined as $P<0.05$.

\section*{Results}

\subsection*{Patients’ Characteristics}

Patients’ characteristics, both overall and stratified based on dichotomized PML at the 30% median (7.6%–65.3% interquartile range) cutoff value, are shown in Table 1.

Forty-five patients who met all inclusion/exclusion criteria were studied. Mean age was 72.4 (±17.1) years. The median admission NIHSS score was 14 (9–19). Sixty-four percent of
the strokes were right-sided. Mean time to DWI from stroke onset was 5.1 (±1.9) hours. The mean baseline admission DWI and final infarct volumes were highly variable: 30.9 (±38.8) and 87.9 (±92.3) mL, respectively.

**Accuracy of PIRI Score for Mismatch Loss**
Both Spearman rank correlation and univariate linear regression analyses revealed that PIRI score is significantly correlated with PML. ROC curve analysis revealed that PIRI score predicts large mismatch loss with odds ratio 3.2 (95% confidence interval, 1.8–5.8) for each step increase in PIRI score from 0 to 4 (>0.0001). The overall accuracy (ROC area under curve; Figure 1A) of the PIRI score to predict large mismatch loss was 0.89 (95% confidence interval, 0.79–0.98). At the optimal operating point of PIRI score (1 (<25% insula infarction), sensitivity was 91%, specificity was 74%, positive likelihood ratio was 3.5, and negative likelihood ratio was 0.12. PML stratified by PIRI score is shown in Table 2. Kruskal–Wallis test with pairwise post hoc analysis (Figure 1B) revealed that PIRI scores of 0 and 1 were significantly different from PIRI scores of 2, 3, and 4 (P=0.0003).

**Interrater Agreement**
According to the guidelines of Landis and Koch, the strength of interobserver agreement was substantial (κ=0.77; 95% confidence interval, 0.66–0.93) for the entire range of PIRI ratings and was almost perfect (κ=0.91; 95% confidence interval, 0.79–1.00) for dichotomized PIRI at the <25% insula infarction cutoff.

**Predictors of Mismatch Loss**
Univariate and multivariate regression analysis results are shown in Table 3. Univariate linear regression showed that admission PIRI score, DWI infarct volume, CTA collateral score, and NIHSS score were significant predictors of mismatch loss. In the multivariate linear regression analysis, PIRI score was the strongest independent imaging predictor of mismatch loss (P=0.03). Patient age (P=0.01) and NIHSS score (P<0.001) were significant independent clinical predictors of mismatch loss. In the binary logistic regression analysis, including dichotomized insula score (Figures 2 and 3; P=0.03) and age (P=0.02) were independent predictors of large (68.2%) versus small (8.1%) mismatch loss.

**Discussion**
We have shown that >25% admission insular infarction—determined using a simple, practical, highly reproducible visual assessment—is a stronger predictor of large mismatch loss in this cohort of proximal MCA occlusive stroke patients than NIHSS score, DWI ASPECTS, DWI infarct volume, or CTA collateral score. In our binary logistic regression analysis,
 Only age and PIRI score >1 were independent predictors of large mismatch loss.

The significant predictive value of our PIRI scoring system is in keeping with the results of earlier observational studies and univariate analyses, which suggest that proximal MCA infarcts with substantial insular involvement have greater severity and are more likely to progress into surrounding penumbral tissue at risk.\textsuperscript{11,12} One notable prior study dichotomized patients according to the presence or absence of admission infarct, also using mismatch loss as an outcome measure.\textsuperscript{11} In their univariate-only regression analysis, Ay et al\textsuperscript{11} showed that patients with insula involvement had greater mismatch loss than those without insula involvement. In another study that dichotomized patients according to major (\textgeq 2/3) versus minor (<2/3) insula involvement, Fink et al\textsuperscript{12} showed a significant difference between groups for admission NIHSS score, presence of \textgeq 1/3 MCA territory infarction, and lenticulostriate territory involvement.

Our results expand on these findings by: (1) applying this idea to a homogeneous population of MCA M1 occlusion; (2) determining the optimal percent insula infarction threshold to distinguish small versus large percent mismatch loss through ROC curve analysis; and (3) directly comparing the characteristics of our practical, simple PIRI scoring method to those of other important clinical and imaging biomarkers of stroke outcome shown in Table 1. Specifically, a highly reproducible 25\% threshold for percent insula infarction at presentation divided patients into highly distinct groups with regard to admission NIHSS score, admission and final infarct size, quality of CTA collateral circulation, and—most importantly—lesion growth. Moreover, percent insula infarction, with age, was the strongest of these potential predictors of mismatch loss in our binary logistic regression model. The addition of the insula score provides a visual marker for the potential benefit of treatment—which NIHSS score alone cannot—in patients

<table>
<thead>
<tr>
<th>PIRI Score</th>
<th>n (%)</th>
<th>Median PML (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (0% insula infarction)</td>
<td>11 (24)</td>
<td>9.8% (4.3–11.6)</td>
</tr>
<tr>
<td>1 (&lt;25% infarction)</td>
<td>8 (18)</td>
<td>5.4% (3.3–26.9)</td>
</tr>
<tr>
<td>2 (25%–49% infarction)</td>
<td>3 (7)</td>
<td>52.4% (22.6–88.1)</td>
</tr>
<tr>
<td>3 (50%–74% infarction)</td>
<td>7 (16)</td>
<td>39.0% (22.3–96.3)</td>
</tr>
<tr>
<td>4 (\textgeq 75% infarction)</td>
<td>16 (35)</td>
<td>60.7% (38.7–95.3)</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range; PIRI, percent insular ribbon infarct; and PML, percent mismatch loss.

<table>
<thead>
<tr>
<th>Admission Parameter</th>
<th>$R^2$ Univariate</th>
<th>$P$ Univariate</th>
<th>$P$ Multivariate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insula score†</td>
<td>0.39</td>
<td>&lt;0.0001</td>
<td>0.03</td>
</tr>
<tr>
<td>Age</td>
<td>0.05</td>
<td>0.15</td>
<td>0.01</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>0.52</td>
<td>&lt;0.0001</td>
<td>0.0005</td>
</tr>
<tr>
<td>DWI infarct volume/DWI ASPECTS</td>
<td>0.18/0.26</td>
<td>0.004/0.0001</td>
<td>0.69/0.86</td>
</tr>
<tr>
<td>CTA collateral score</td>
<td>0.28</td>
<td>0.0002</td>
<td>0.73</td>
</tr>
<tr>
<td>Time to DWI imaging</td>
<td>0.02</td>
<td>0.35</td>
<td>0.18</td>
</tr>
<tr>
<td>IV tPA or IA treatment</td>
<td>0.08</td>
<td>0.06</td>
<td>0.91</td>
</tr>
</tbody>
</table>

Table 3. Predictors of Mismatch Loss in Proximal MCA Occlusive Stroke Patients

ASPECTS indicates Alberta Stroke Program Early CT Score; CTA, computed tomography angiography; DWI, diffusion weighted imaging; IA, intra-arterial; IV, intravenous; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale score; PIRI, percent insular ribbon infarction; $R$, correlation coefficient; and tPA, tissue-type plasminogen activator.

*In the multivariate analyses, the $P$ values for both forward selection and backward elimination data entry were similarly highly significant only for PIRI and age.

†Insula score was ordinal PIRI for the univariate and multivariate linear regression analyses, and dichotomized PIRI at a 25\% threshold for the binary logistic model.

Figure 1. A. Receiver operating characteristic curve analysis for percent insular ribbon infarction (PIRI) prediction of large mismatch loss shows area under curve of 0.89. The operating point corresponded to a PIRI threshold score of 1 (<25\% insula infarction at admission). B. Box plot diagram of percent mismatch loss versus PIRI score.
not otherwise excluded from treatment based on time or admission infarct volume safety, that is, hemorrhagic risk, criteria. It should be noted that these findings apply to patients who present with small infarcts, as the proportion of large (>100 mL) infarcts was small in this study. However, this is the group of patients of most clinical interest because they are eligible for reperfusion therapies, as the presence of extensive infarction is an established exclusion criterion. Therefore, the insula score may help to further stratify patients with small infarcts who are likely to undergo significant infarct extension and in whom rapid treatment would be expected to yield the greatest benefit.

These results make intuitive sense when the extent of admission insular infarction is viewed as a biomarker for the combined effects of both—occlusion and pial collateral flow—on blood supply to the global MCA vascular territory. This role of insula percent infarction at presentation as an early predictor of subsequent infarct growth is supported by the unique vascular anatomy of this region. In an autopsy study of 27 patients, the superior MCA division supplied the entire insula in 51%; no insular cortex was supplied entirely by the inferior MCA division. In ≈90%, the rolandic artery arose from the same superior division branch that supplied the central insular sulcus.14,19

Insula involvement is a well-established early ischemic sign of MCA infarct, whether detected by loss of gray white matter differentiation on unenhanced CT or restricted diffusion on MR DWI.11,14,20,21 Functional studies have suggested that insular ribbon has the highest ischemic vulnerability of all the cortical and deep gray matter structures in the brain.12,22 The greater clinical severity of insular versus noninsular strokes may also, in part, be attributed to a number of familiar and recently recognized important insula functions, including speech and language, volitional swallowing, autonomic (vagal) modulation, cardiovascular regulation, vestibular system activity, and possibly immune modulation.14,16,23,24 Ischemic insular dysfunction might, directly or indirectly, be associated with stroke complications such as intracranial hemorrhage, cerebral vasoconstriction, increased blood brain barrier permeability, cardiac arrhythmia, hyperglycemia, or even hospital-acquired pneumonia.14,25–27

Figure 2. Example of a low percent insular ribbon infarction (PIRI) score without significant mismatch loss. A 34-year-old man presenting 5 hours after right hemispheric stroke onset with admission National Institutes of Health Stroke Scale score of 11. Axial images show (A) acute proximal middle cerebral artery occlusion with high collateral flow (versus contralateral) on computed tomography (CT, arrow), with a large magnetic resonance mean transit time (B) hypoperfused lesion; however, normal insula on admission apparent diffusion coefficient/diffusion-weighted imaging (C; PIRI score 0); only minimal (13%) tissue at risk infarcted on 48-hour follow-up 60 minutes (versus contralateral) on computed tomography angiography; with a large magnetic resonance mean transit time hypoperfused lesion (B); however, there is complete insula infarction on admission apparent diffusion coefficient/diffusion-weighted imaging (DWI) (C; PIRI score 4); marked (60%) progressive infarction of tissue at risk on 33-hour follow-up DWI despite treatment with intravenous tissue-type plasminogen activator at outside hospital 1 hour 40 minutes after stroke onset (D).
Our substantial interobserver agreement is supported by structural MRI studies showing high reproducibility for anatomic localization of the insula. The insula has easily and reliably recognizable features for visual inspection and rating due to its characteristic location adjacent to the frontal/temporal opercula at the brain surface and medial to the sylvian fissure, connecting the limbic system to the neocortex. Potential limitations of our study include the relatively small number of consecutive first-ever stroke patients, which was a consequence of our strict inclusion criteria; isolated proximal MCA occlusions with admission CTA, DWI, and MR perfusion; and follow-up imaging obtained within the specified time window. This limits the power of performing subgroup analyses stratified by stroke laterality, time to imaging, or treatment assignment. Despite this limitation, however, we were able to adjust for time to imaging and treatment in our multivariate analysis, mitigating the effects of these factors to suggest that insula score alone is more predictive of infarct growth than DWI ASPECTS, DWI volume, or CTA collateral score in this population with small admission infarcts. Future analyses should also adjust for reperfusion status and timing of reperfusion, which are critical determinants of infarct growth into the penumbra. Moreover, we did not have a sufficient number of patients with reliable 60- or 90-day modified Rankin Scale scores to correlate the PIRI score with clinical outcome. Because we used admission MR MTT at-risk mismatch lesion volume as an outcome marker to help quantify the degree of infarct growth, we did not additionally study the correlation of other admission MR perfusion metrics with mismatch loss in our analyses.

Conclusions

Admission insular infarction >25%, with age, is the strongest predictor of large mismatch loss in this cohort of proximal MCA occlusive stroke and can be simply and reliably determined by visual inspection. Future studies of IV-lytic and intra-arterial treated patients with known recanalization status could help to determine if this observation has added value in patient selection for novel and late time window acute stroke therapies.

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Disclosures

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