Perfusion MR Predicts Outcome in High-Risk Transient Ischemic Attack/Minor Stroke

A Derivation–Validation Study

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Background and Purpose—Transient or minor ischemic stroke is associated with an early risk of deterioration. Baseline perfusion–diffusion mismatch may predict clinical deterioration and infarct growth in this population.

Methods—High-risk transient ischemic attack and minor stroke (National Institutes of Health Stroke Scale ≤3) subjects were prospectively enrolled and imaged with MRI within 24 hours of symptom onset as part of sequential derivation and validation cohorts. Baseline diffusion-weighted imaging, perfusion-weighted imaging ($T_{\text{max}} \geq 4$ s), mismatch ($T_{\text{max}} \geq 4$ s-diffusion-weighted imaging), and follow-up fluid-attenuated inversion recovery infarct volumes were measured. Primary outcome was infarct growth on fluid-attenuated inversion recovery, and secondary outcome was symptom progression.

Results—One hundred thirty-seven and 281 subjects were included in the derivation and validation cohorts, respectively. Infarct growth occurred in 18.5% of the derivation and 5.5% of the validation cohorts. Symptom progression occurred in 9.5% of the derivation and 4.5% of the validation cohorts. In the derivation cohort, subjects with baseline mismatch were significantly more likely to show infarct growth on fluid-attenuated inversion recovery (relative risk [RR], 13.5; 95% confidence interval [CI], 4.2–38.9) and symptom progression (RR, 7.0; 95% CI, 2.0–7.3). A baseline mismatch volume of 10 mL in the derivation cohort was the optimal threshold to predict infarct growth (area under the curve, 0.89; 95% CI, 0.80–0.98). This threshold was highly predictive of infarct growth in the validation cohort ($P=0.001$). Baseline mismatch was associated with clinical deterioration in the derivation (area under the curve, 0.81; 95% CI, 0.67–0.96) and validation cohorts (area under the curve, 0.66; 95% CI, 0.46–0.85).

Conclusions—Among subjects with high-risk transient ischemic attack and minor stroke, diffusion-weighted imaging–perfusion-weighted imaging mismatch predicts infarct growth and clinical deterioration. These findings suggest that reperfusion strategies would be beneficial in this population. (Stroke. 2013;44:2486-2492.)

Key Words: cerebrovascular occlusion ■ ischemic attack, transient ■ magnetic resonance imaging ■ perfusion

Transient ischemic attack (TIA) and minor stroke portend a high risk of disabling stroke. Imaging data improve the clinical risk stratification scores for prediction of stroke after TIA. A substantial proportion of recurrent ischemic events are in fact associated with growth of the original infarct. Despite complete or near-complete resolution of symptoms, approximately one third of patients with TIA and minor stroke have evidence of persisting tissue hypoperfusion. Thus, progression is likely because of growth of the initial ischemic lesion into the regions of the brain with persisting compromised cerebral blood flow, the ischemic penumbra.

The ischemic penumbra can be functionally defined using MRI as the mismatch between hypoperfused brain tissue identified by perfusion-weighted imaging (PWI) and ischemic core identified by diffusion-weighted imaging (DWI). In large stroke, the presence of perfusion–diffusion mismatch is associated with infarct growth and poor clinical outcome, unless early reperfusion is achieved. Similarly, among patients with minor stroke and TIA, tissue hypoperfusion at baseline is associated with early radiographic deterioration (infarct growth) on follow-up MRI. The probability of infarction is dependent on the severity and duration of hypoperfusion in ischemic penumbra.

Multiple groups have shown that the distinction between TIA and minor stroke is arbitrary because they both have identical causes, near-identical prognoses, and the distinction...
can only be made retrospectively after the acute period.\textsuperscript{15,16} Furthermore, acute treatment decisions are all completed before the 24-hour mark, during which the distinction between the 2 is not possible. Thus, the distinction between TIA and minor stroke is not relevant. In this prospective study, we aimed to determine the optimal quantitative baseline mismatch parameters predictive of clinical and radiographic progression in patients with both high-risk TIA and minor stroke. We derived optimal mismatch parameters in the first study (derivation cohort) and validated this in a second prospective study (validation cohort).

**Methods**

**Patients**

Subjects with high-risk TIA (focal weakness or speech disturbance lasting \(\geq 25\) minutes) or minor ischemic stroke (with initial National Institutes of Health Stroke Scale \(\leq 5\)) were prospectively enrolled at the Foothills Medical Centre after providing informed consent. The derivation cohort included subjects who underwent perfusion MRI in the Vascular Imaging of acute Stroke for Identifying predictors of clinical Outcome and recurrent ischemic eventS (VISION) study.\textsuperscript{3} Subjects were \(\geq 18\) years of age, had a premorbid modified Rankin scale \(< 2\), had a brain computed tomographic (CT) scan, examination by a stroke neurologist within 12 hours of symptom onset, and a brain MRI, including PWI within 24 hours of onset. Subjects were excluded if they had evidence of intracranial hemorrhage or other nonvascular pathology on CT scan. The validation cohort included patients from the CT And MRI in the Triage of TIA and minor Cerebrovascular events to identify High risk patients (CATCH)\textsuperscript{3} study who underwent PWI. The inclusion criteria in CATCH were similar to those of the VISION study, with the exception that patients were included if they were assessed by a stroke neurologist and imaged within 24 hours of symptom onset. The initial imaging protocol in CATCH included a noncontrast CT and a CT angiogram of the circle of Willis and neck in all subjects. Follow-up imaging was completed at day 30 in the VISION study (derivation cohort) and at day 90 in the CATCH study (validation cohort). In both studies, patients were treated with routine clinical care, and secondary stroke prevention measures were implemented in accordance with current practice guidelines.\textsuperscript{14} Specifically, all patients were started on an antiplatelet or anticoagulant treatment depending on their clinical indication. Efforts were made to avoid hypotension in all patients in the acute period. Carotid revascularization was typically completed within 14 days of the initial event but never in the first 72 hours.

**MRI Protocol**

Subjects in both studies had MRI brain scans completed as soon as possible and within 24 hours of symptom onset. Subjects were imaged using a 3-tesla scanner (Signa VH/i; General Electric Healthcare, Waukesha, WI). Sequences included sagittal T1, axial T2, axial fluid-attenuated inversion recovery (FLAIR), and 3-dimensional time-of-flight MR angiography of the circle of Willis. Acute ischemic lesions were identified on DWI. Dynamic susceptibility contrast PWI was acquired using a gadolinium (0.1 mmol/kg) injection delivered via power injector at 5 mL/s through an 18 gauge needle in an antecubital vein, followed by 20 mL saline flush at the same rate, and echoplanar gradient-echo (T2*) images acquired every 2 s for 80 s (17 axial 5 mm+4.0 mm gap slices at each time point). Follow-up brain MRI without perfusion was performed at day 30 in the derivation cohort and at day 90 in the validation cohort.

**Image Analysis**

MR images (DWI/apparent diffusion coefficient, FLAIR, and T2) were reviewed for the presence of ischemic lesions at each time point. MR angiography source images and maximum intensity projections were assessed for the presence of intracranial stenosis/occlusion in the derivation cohort. CT angiography was used in the validation cohort to assess for the presence of relevant intracranial and extracranial occlusion/stenosis. Relevant vascular occlusion/stenosis was defined as a priori as symptomatic intra- or extracranial occlusion or stenosis \(\geq 50\%\) appropriate to the presenting symptoms.\textsuperscript{19} PWI source images were imported into custom Matlab 7.4 (The Mathworks) software (PGUI Perfusion Analysis Software, CFIN Aarhus University Hospital 2007).\textsuperscript{20,21} A whole brain mask was drawn to include all cerebral regions and vessels within scan range. An arterial input function was manually selected from the middle cerebral artery contralateral to the visible DWI lesion, and a block circular deconvolution algorithm was used to calculate voxel-wise maps of \(T_{\text{max}}\) (time to peak of the impulse response).\textsuperscript{22} Maps of \(T_{\text{max}}\) were imported into the Analyze software package (Biomedical Imaging Resource, Rochester, NY).\textsuperscript{23} Hypoperfused brain tissue was defined as those voxels with \(T_{\text{max}}\) delay \(\geq 4\) s. This threshold was chosen based on studies showing it to be a reliable estimate of the ischemic penumbra in acute stroke thrombolysis candidates.\textsuperscript{24} Furthermore, an internal validation analysis comparing all perfusion parameters (cerebral blood flow, cerebral blood volume, and \(T_{\text{max}}\)) study \(\geq 2\), 4, 6, and 8 s) in our cohort confirmed \(T_{\text{max}}\geq 4\) s threshold as the parameter with the highest predictive value, with optimal sensitivity and specificity, and was, therefore, chosen for this study.\textsuperscript{25} Perfusion–diffusion mismatch volume was defined as the difference between the \(T_{\text{max}}\geq 4\) s volume and DWI lesion volume.

**Radiographic and Clinical Outcomes**

Our primary outcome was radiographic progression. Prior volumetric studies have shown a mean inter-rater difference of 0.2 mL in volumetric acute DWI infarct measurements.\textsuperscript{26} Based on this, the primary outcome was a priori defined as either contiguous growth of the initial infarct by \(\geq 2\) mL (a value \(\geq 10\)x the baseline inter-rater measurement difference) on follow-up FLAIR imaging or the development of a new ischemic lesion within the originally hypoperfused brain tissue delineated by the baseline perfusion deficit. We attributed infarct growth \(< 2\) mL to measurement error or development of infarct edema. New infarction outside the original hypoperfused tissue was defined as radiographic recurrence. The secondary outcome of clinical progression was defined as any clinical deterioration judged by the treating stroke neurologist to be related to the initial ischemic event rather than because of a distinct second ischemic event, as previously described.\textsuperscript{27} This definition includes disabling neurological deficits not necessarily captured by the National Institutes of Health Stroke Scale.\textsuperscript{1} Disability at 90 days was defined as modified Rankin scale \(\geq 2.\textsuperscript{28}

**Statistical Analysis**

Statistical analyses were performed using SPSS version 20.0 and STATA version 12.0. The data are reported using standard descriptive statistics. We developed a logistic regression model in the derivation cohort to predict the primary outcome. Receiver operating characteristic curve analysis was used to determine the maximum sensitivity and specificity of mismatch in predicting both clinical and radiographic progression. We assessed univariable relationships among important baseline (age, sex, and time from symptom onset), clinical (hypertension, history of diabetes mellitus, congestive heart failure), and MR variables (presence of DWI and PWI lesions or vascular occlusion) and then used manual backward elimination to develop a parsimonious multivariable model. Using this model, we identified the mismatch volumes associated with the maximum sensitivity and specificity. To validate the prediction model, we used the derivation
equation to predict outcomes in the validation cohort. Predicted binary outcomes were assigned based on the probability threshold that was associated with the simultaneous maximum sensitivity and specificity in the derivation cohort. We then compared matched pairs of the predicted infarct growth to the actual infarct growth in the validation cohort using the McNemar test for matched pairs.

**Random Derivation–Validation Cohorts**

Given the differences in design between the 2 cohorts, especially the differences between the time from symptom onset to follow-up imaging (Table), we repeated the analysis on multiple random derivation–validation studies derived from the 2 initial cohorts. The data from both cohorts were combined. Using the random number generator in SPSS, 2 random cohorts were generated and referred to as random derivation and random validation cohorts. Using the same statistical model in the original study, we identified the significant mismatch with the highest sensitivity and specificity to predict clinical and radiographic outcomes and validated these results in the random validation cohorts (online-only Data Supplement).

**Results**

**Derivation Cohort**

Between April 2002 and April 2006, 161 subjects from the VISION study were enrolled and 137 were included in the derivation cohort. Twenty-four subjects were excluded because of technical inadequacy (n=14) or missing images (n=10). Baseline clinical and imaging characteristics of the subjects are summarized in the Table. Follow-up MRI was available in 86.8% (119/137) of the derivation cohort. Reasons for missing follow-up MRI included pacemaker or heart valve insertion, death, or patient refusal.

A total of 54% had DWI and 42% had PWI deficit at baseline. Fifty-six of 137 patients (41%) had neither DWI nor PWI abnormalities on the initial imaging. Radiographic progression occurred in 18% (22/119) of subjects. Radiographic recurrence occurred in 3.3% (4/119) of subjects. The median infarct growth in those with progression was 6.4 (interquartile range [IQR], 11.1) mL. Symptom onset to follow-up imaging time between subjects with infarct progression to those without was not different (31.2 [IQR, 15.2] days versus 29.1 [IQR, 7.4] days; P=0.25). Clinical progression occurred in 9.5% (13/137) of subjects. Nine of 13 (69%) patients with clinical progression also showed radiographic progression. Clinically silent radiographic progression occurred in 59% (13/22) of patients.

In the derivation cohort, 32% (44/137) of subjects had evidence of baseline perfusion–diffusion mismatch, with a median mismatch volume of 22.7 (IQR, 41.6) mL. The subjects with baseline perfusion–diffusion mismatch were more likely to develop both radiographic progression (relative risk [RR] 13.5; 95% confidence interval [CI], 4.2–38.9; 50% versus 3.8%; P<0.001) and clinical progression (RR, 7.0; 95% CI, 2.0–7.3; 22.7% versus 3.2%; P=0.001) relative to those without mismatch. Almost all radiographic progression was characterized by contiguous growth of infarct.

The optimal mismatch threshold ($T_{\text{max}} \geq 4$ s-DWI) for maximizing sensitivity and specificity in predicting infarct growth occurred at a mismatch volume of 10 mL, correctly predicting infarct expansion with 81% sensitivity and 93% specificity (area under the curve, 0.87; 95% CI, 0.76–0.98; Figure 1A). Similarly, a perfusion–diffusion mismatch of 10 mL was strongly associated with early neurological deterioration with 77% sensitivity and 83% specificity (area under the curve, 0.814; 95% CI, 0.78–0.96; Figure 1B). Radiographic progression occurred in 72.0% (18/25) of subjects with baseline mismatch 210 mL relative to 4% (4/94) of subjects without (RR, 16.9; 95% CI, 6.3–45.5). Multivariable analysis showed that this relationship was not confounded by age, sex, diabetes mellitus, or time from symptom onset. Every 10 mL of

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<th>Table. Baseline Clinical Characteristics of Patients in the Derivation and Validation Cohorts</th>
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<td><strong>Positive mismatch ($T_{\text{max}} \geq 4$ s delay-DWI/DTI)</strong></td>
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DM indicates diabetes mellitus; DTI, diffusion tensor imaging; DWI, diffusion-weighted imaging; HTN, hypertension; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; PWI, perfusion-weighted imaging; and $T_{\text{max}} \geq 4$ s delay, time to peak of the impulse response $\geq 4$ s.
mismatch was associated with 2.5 mL of infarct growth at day 30 (P<0.001, simple linear regression).

A total of 17 of 137 (12.4%) patients were disabled at 90 days. Patients with clinical deterioration (RR, 4.0; 95% CI, 1.6–9.5; 38.5% versus 9.7%; P=0.003) or radiographic progression (RR, 5.0; 95% CI, 2.0–12.4; 36.4% versus 7.2%; P<0.001) were more likely to be disabled at 90 days compared with those without. In patients who had neither DWI nor PWI deficit at baseline, the rates of radiographic progression (RR, 0; 0% versus 30%; P<0.001) and 90-day disability (RR, 0.3; 95% CI, 0.1–1.0; 5% versus 17.3%; P=0.03) were significantly lower compared with those with positive DWI or PWI imaging.

Validation Cohort

From the CATCH study, 304 subjects were enrolled between April 2008 and August 2010, and 281 were included in the validation cohort. Twenty-three subjects were excluded for technical inadequacy of PWI. Baseline clinical and imaging characteristics of the subjects are summarized in the Table. The subjects in the validation cohort had smaller DWI and PWI–DWI mismatch volumes and were imaged later relative to the validation cohort (Table). A total of 77.6% (218/281) had follow-up imaging. The reasons for missing follow-up MRI included pacemaker insertion, death, or subject refusal. Radiographic progression occurred in 5.5% (12/218) with median infarct growth of 3.7 (IQR, 3.9) mL; clinical progression occurred in 4.6% (13/281) of subjects. Radiographic recurrence occurred in 9% (20/281) of patients. There was no difference in time between symptom onset to follow-up imaging in subjects with infarct progression and those without progression (86.7 [IQR, 18.7] days versus 87.1 [IQR, 18.4] days; P=0.86). Three (30%) of 10 patients with clinical progression had radiographic progression as well. Clinically silent radiographic progression occurred in 75% (9/12) of patients.

In the validation cohort, 12.8% (36/281, 95% CI, 9.4–17) had significant mismatch (\(T_{\text{max}}\geq 4\) s-DWI\(\geq 10\) mL) on baseline imaging. Patients with a significant mismatch were much more likely to have radiographic progression (27.0% versus 2.6%; P<0.001) and clinical deterioration (19.4% versus 2.4%; P<0.001). Intracranial occlusion alone was present in 53% (19/36), intracranial occlusion or stenosis \(\geq 50\%\) in 70% (25/36), and 83% (30/36) had relevant extra or intracranial occlusion or stenosis \(\geq 50\%\). The presence of relevant intracranial occlusion/stenosis (RR, 5.2; 95% CI, 1.8–15.3; 17.1% versus 3.3%) or relevant intracranial occlusion alone (RR, 5.2; 95% CI, 1.7–15.8; 21.1% versus 4.0%) was strongly associated with radiographic progression.

We used the perfusion and diffusion volume thresholds derived from the derivation study and showed that the presence of significant mismatch at baseline had the highest predictive value for radiographic progression on follow-up imaging (odds ratio, 10.3; 95% CI, 3.5–30.2; 27.0% versus 2.6%). Using a predictive model from the derivation cohort, which adjusted for onset-to-MR time and significant mismatch at baseline, we correctly identified radiographic progression in the validation cohort (P=0.001, McNemar test). The result was unchanged if the validation population was limited to those with an onset-to-scan time ≤12 hours (n=252).

Subjects with both significant mismatch and evidence of relevant intracranial occlusion/stenosis were highly likely (29% [5/17]) to develop radiographic progression (median infarct growth, 3.5 [IQR, 7.8] mL). A total of 9 patients had a significant mismatch without an apparent occlusion/stenosis, of whom 22% (2/9) showed infarct growth on follow-up imaging (42 mL and 5.1 mL, respectively). In contrast, the presence of vascular occlusion/stenosis in the absence of mismatch did not confer a significant risk for radiographic progression in 5% (1/19) of patients.

A total of 14% (39/281) of patients were disabled at 90 days. Patients with radiographic progression (RR, 4.3; 95% CI, 1.9–9.4; 41.7% versus 9.7%; P=0.006) but not clinical deterioration (RR, 2.4; 95% CI, 0.9–5.6; 30.8% versus 13% [35/268]; P=0.089) were more likely to be disabled than those without. Radiographic progression of any definition was associated with both neurological deterioration and functional disability at 90 days in both cohorts (online-only Data Supplement).

Random Derivation–Validation Study

To ensure that the results of the study are not due to or influenced by the difference between baseline to follow-up imaging in the 2 cohorts, a random derivation–validation study was performed as described in the Methods section.
A total of 220 patients were randomly assigned to the derivation cohort and 198 patients to the validation cohort. The results of this analysis are presented in the online-only Data Supplement and are essentially the same as in the main study. Patients with a significant mismatch on baseline imaging were more likely to develop radiograph progression (RR, 9.8; 46.2% versus 4.7%; \( P<0.001 \)). Similarly, presence of a significant mismatch was predictive of early neurological deterioration in this random validation cohort (RR, 9.2; 34.3% versus 3.7%; \( P<0.001 \); online-only Data Supplement).

Discussion

We found that 10% of patients with high-risk TIA and minor stroke have evidence of infarct growth. In 2 separate cohorts, >30% of patients had evidence of tissue hypoperfusion and \( \approx \)10% had relevant vascular abnormalities on baseline imaging. Perfusion–diffusion mismatch alone or in combination with acute intracranial occlusion/stenosis is predictive of radiographic progression and clinical progression. A PWI–DWI mismatch volume of \( \geq 10 \) mL was the optimal cut point for prediction of infarct growth on follow-up imaging.

Multiple studies have emphasized that early clinical deterioration is an important cause of functional disability in patients with TIA and minor stroke.\(^{31,32}\) Although not widely clinically appreciated, early clinical deterioration is predominantly because of infarct progression rather than de novo infarct recurrence, and the risk factors for these 2 events are different.\(^{3,29}\) Among patients with large stroke, radiographic infarct growth is strongly associated with poor clinical outcome and has been used as a surrogate marker in clinical trials.\(^{10,33,34}\) Similar to these findings, in our study infarct growth was significantly associated with disability at 3 months. Infarct progression reflects the degeneration of penumbral tissue into irreversible infarction. Although the penumbra plus the core comprise the clinically symptomatic tissue at the time of presentation, regions of hypoperfusion in noneloquent regions of the brain will remain clinically undetected (case examples in Figure 2). Imaging is, therefore, a critical biomarker for the detection of those at risk for early deterioration.

Confirming prior work,\(^{8}\) a significant proportion of patients with PWI deficit did not have evidence of intracranial occlusion/stenosis on MR angiography. Although MR angiography shows limited sensitivity for detection of distal intracranial vascular occlusions and we did not undertake extracranial vascular imaging in the derivation cohort, the ratio of patients with positive PWI lesions to those with abnormal vascular imaging remained high in the validation cohort. Hypoperfusion in the absence of apparent vascular occlusion occurs in small-vessel disease,\(^{35}\) with distal branch occlusions or with persistent hypoperfusion, despite recanalization (no-reflow phenomenon).\(^{36}\) Irrespective of the vasculature, the presence of MR-defined penumbra is a poor prognostic indicator.

Approximately one third of disabling ischemic strokes are preceded by a minor ischemic event or TIA.\(^{37}\) These patients are usually treated conservatively with antiplatelet therapy. However, a substantial proportion of patients with minor stroke and TIA are dead and disabled at the time of discharge from the hospital.\(^{38}\) Despite this, acute thrombolysis in mild stroke is highly controversial with a reported risk of symptomatic intracranial hemorrhage between 2% and 4.9%.\(^{38-40}\) Our results suggest that revascularization may be appropriate in some of these patients with penumbral patterns. Future studies in this area should consider acute perfusion and vascular imaging because they may play a useful role in identifying patients who would benefit from aggressive therapy. There is currently an on-going trial assessing the efficacy of thrombolysis in patients with minor ischemic stroke and intracranial occlusion.\(^{41}\)

Our analysis is limited by restriction to subjects in whom we were able to obtain an MRI scan, making our cohorts non-sequential. A minority did not have follow-up imaging, and in both cohorts the treating physicians were not blinded to the results of the imaging findings. These measures may have reduced the rates of our primary and secondary outcomes in both cohorts. Furthermore, in patients with relevant vascular occlusion/stenosis, persistent vascular occlusion may negatively impact tissue outcome compared with those with early spontaneous recanalization. Further studies in this area should include information on early recanalization. Later follow-up imaging performed in the validation cohort (day 90) relative to the derivation cohort (day 30) may have resulted in smaller values for infarct growth because of the natural evolution of infarction resulting in infarct shrinkage related to gliosis and atrophy.\(^{42}\) All imaging measurements were performed by consensus between 3 readers; an inter-rater reliability assessment was not completed. Our study is population based because of the centralized structure of healthcare at our center, imaging was carefully analyzed in detail, and clinical evaluations were meticulous and timely. A potential limitation of the study is that the secondary outcome of clinical deterioration potentially has a subjective component to it because patients could be considered to deteriorate clinically without possibly a change in the
National Institutes of Health Stroke Scale. This definition has been used in multiple previous studies\(^1,2,17,29,30,43,44\) and is borne out by consistent results for clinical deterioration, disability at 90 days, and radiographic progression. The median time to perfusion imaging was relatively late after stroke onset, particularly in the validation population. With increasing availability of CT perfusion, earlier perfusion imaging may be feasible and could be performed either in conjunction or shortly after CT angiography is completed. Our study is novel in that it represents a large prospective derivation-validation cohort of perfusion–diffusion mismatch parameters in the high-risk TIA/minor ischemic stroke population.

In summary, high-risk TIA/minor stroke is one of the commonest causes for which the patients present to the emergency departments. Our data show that the presence of perfusion–diffusion mismatch with or without detectable vascular occlusion/significant stenosis is predictive of neurological deterioration, infarct progression, and disability in a high-risk TIA and minor stroke population. Clinical information alone is insufficient to properly triage these patients and decide on the therapeutic options, which may include thrombolytic therapies.

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**Disclosures**

None.

**References**

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SUPPLEMENTAL MATERIAL:

Random Derivation-Validation Studies

The result of the study is presented after combining the two studies and randomly dividing them into two derivation-validation cohorts as described in the methods.

Random derivation cohort:

A total of 220 patients were randomly assigned to the derivation cohort; 50.9% (112/220) were DWI positive and 30% (66/220) had PWI positivity on baseline MRI. A total of 83.2% (183/220) had follow-up imaging. Radiographic progression occurred in 8.2%, radiographic recurrence occurred in 9.3% (17/183). The median infarct growth in those with progression was 3.77 ml (IQR= 10.5). Clinical progression occurred in 3.6% (8/220) patients.

In this random derivation cohort, 24% (53/220) had evidence of perfusion-diffusion mismatch. The subjects with baseline mismatch were much more likely to develop both radiographic progression (RR= 19.3, 29% vs. 1.5%, p=0.001) and clinical progression (RR =5.2, 9.4% vs. 1.8%, P=0.02) relative to those without mismatch.

The optimal mismatch threshold (Tmax≥4s-DWI) for maximizing sensitivity and specificity in predicting infarct growth occurred at 10 ml, correctly predicting
infarct expansion with 80% sensitivity and 92% specificity (Area under the curve (AUC)= 0.87, Cl₉₅ 0.72-1.00). Similarly a perfusion-diffusion mismatch of 10ml was associated with early neurological deterioration with 62% sensitivity and 89% specificity (AUC= 0.70, Cl₉₅ 0.46-0.95). Linear regression showed that every 10 ml of mismatch on baseline imaging was associated with 2.6 ml [2.3, 2.8] of infarct growth on follow-up imaging (R=0.83, P<0.001).

Random validation cohort:

A total of 198 patients were randomly assigned to the derivation cohort; 60% (120/198) had positive DWI, 44.5% (88/198) had positive PWI on baseline imaging. Using the data derived from the derivation cohort, 17.7% (35/198) of patients in the validation cohort had evidence of significant PWI-DWI ((Tmax≥4s-DWI) ≥10ml). Follow-up imaging was available in 78% (154/198) of patients. Infarct growth on follow-up scan was seen 11.7% (18/154). Patients with a significant mismatch on baseline imaging were more likely to develop radiograph progression (RR=9.8, 46.2% vs. 4.7%, P<0.001). Similarly presence of a significant mismatch was predictive of early neurological deterioration in this random validation cohort (RR=9.3, 34.3% vs. 3.7%, P<0.001). Using a predictive model from the derivation
cohort, which adjusted for onset-to-MR time and significant mismatch at baseline, we correctly identified radiographic progression in the validation cohort \( (p=0.001, \) McNemar’s test). Repeated random assignments of Derivation-Validation cohorts, showed similar results to the above. Supplemental Table I summarizes the results of two more random derivation-validation cohorts.

*Frequency and definition of infarct progression in both cohorts*

A total of 80.4% patients in the combined derivation-validation cohorts had follow-up imaging. Table 2 shows the rates for different definitions of infarct growth. “Any infarct growth” is defined as final (FLAIR volume)-(DWI volume) \( \geq 0 \) ml.

“Radiographic progression” was a priori defined as infarct growth of 2ml or greater as growth volumes of less than 2ml may simply be due to measurement errors. A “significant infarct growth” was defined as (FLAIR volume)-(DWI volume) \( \geq 5 \) ml. In this study a total of 20.7% had “any infarct growth”, 10% had \( \geq 2 \) ml growth and 5.6% had \( \geq 5 \) ml infarct growth. All definitions of infarct growth were associated with a significant rate of neurological deterioration and functional disability at 90days (supplemental table II).
The Role of Perfusion Imaging in Predicting Outcome in the Subgroup of Patients with High risk TIA Alone

A total of 52% (219/418) of patients in the combined derivation-validation cohorts had ischemic symptoms lasting less than 24 hours. In this subgroup, 38.5% had positive DWI, 28.5% had positive PWI and 24% perfusion-diffusion mismatch at baseline. Radiographic progression and clinical deterioration occurred in 5.5% and 1% respectively.

The patients with baseline perfusion-diffusion mismatch were significantly more likely to develop radiographic progression (RR=22.2, 40% vs. 1.8%, P<0.001) relative to those without mismatch. The rate of clinical deterioration was higher in TIA patients with mismatch compared to those without, but this did not reach statistical significance (3.8% vs. 0%, P=0.058).

The optimal mismatch threshold (Tmax≥4s-DWI) for predicting infarct growth in the combined cohorts occurred at 10 ml. A 10 ml mismatch correctly predicted infarct expansion with 60% sensitivity and 89% specificity (Area under the curve (AUC)= 0.85, CI95 0.67-1.00) and clinical deterioration with 100% sensitivity and 88% specificity (AUC=0.98, CI95 0.96-1.00).
<table>
<thead>
<tr>
<th>Random Derivation</th>
<th>Second Trial (Tmax ≥ 4s-DWI) ≥ 10ml</th>
<th>Third Trial (Tmax ≥ 4s-DWI) ≥ 10ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sens</td>
<td>Spec</td>
<td>AUC</td>
</tr>
<tr>
<td>Primary Outcome</td>
<td>72%</td>
<td>89%</td>
</tr>
<tr>
<td>Secondary Outcome</td>
<td>70%</td>
<td>86%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Random Validation</th>
<th>Significant mismatch</th>
<th>Significant mismatch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
<td>RR</td>
</tr>
<tr>
<td>Primary Outcome</td>
<td>50%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Secondary Outcome</td>
<td>37%</td>
<td>1.7%</td>
</tr>
</tbody>
</table>

**Supplemental Table I:** Shows the results of two more random assignments (trials two and three) of the combined studies into random derivation-validation cohorts. The derivation cohorts show the predictive value of mismatch (Tmax ≥ 4s-DWI) in predicting the primary and secondary outcomes, and Sensitivity (Sens), Specificity (Spec) of the optimal mismatch volume (Tmax ≥ 4s-DWI ≥ 10 ml) for each outcome. The validation studies show that the optimal mismatch values derived from the derivation cohort predicted outcomes the validation cohorts independently.
<table>
<thead>
<tr>
<th>Infarct progression</th>
<th>Any infarct growth</th>
<th>Infarct Growth ≥ 2ml</th>
<th>Infarct Growth ≥ 5ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>P value</td>
</tr>
<tr>
<td>Clinical deterioration</td>
<td>24.3% (17/70)</td>
<td>% 2.2 (6/267)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Disability at 3 months (mRS ≥ 2)</td>
<td>23% (16/70)</td>
<td>9% (24/267)</td>
<td>P=0.003</td>
</tr>
</tbody>
</table>

**Supplemental Table II:** The correlation between different definitions of radiographic progression and clinical deterioration and functional disability (modified Rankin score of ≥ 2) at day 90.