Combining Acute Diffusion-Weighted Imaging and Mean Transmit Time Lesion Volumes With National Institutes of Health Stroke Scale Score Improves the Prediction of Acute Stroke Outcome

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Background and Purpose—The purpose of this study was to determine whether acute diffusion-weighted imaging (DWI) and mean transit time (MTT) lesion volumes and presenting National Institutes of Health Stroke Scale (NIHSS) can identify patients with acute ischemic stroke who will have a high probability of good and poor outcomes.

Methods—Fifty-four patients with acute ischemic stroke who had MRI within 9 hours of symptom onset and 3-month follow-up with modified Rankin scale were evaluated. Acute DWI and MTT lesion volumes and baseline NIHSS scores were calculated. Clinical outcomes were considered good if the modified Rankin Scale was 0 to 2.

Results—The 33 of 54 (61%) patients with good outcomes had significantly smaller DWI lesion volumes (P = 0.0001), smaller MTT lesion volumes (P < 0.0001), and lower NIHSS scores (P < 0.0001) compared with those with poor outcomes. Receiver operating characteristic curves for DWI, MTT, and NIHSS relative to poor outcome had areas under the curve of 0.889, 0.854, and 0.930, respectively, which were not significantly different. DWI and MTT lesion volumes predicted outcome better than mismatch volume or percentage mismatch. All patients with a DWI volume > 72 mL (13 of 54) and an NIHSS score > 20 (6 of 54) had poor outcomes. All patients with an MTT volume of < 47 mL (16 of 54) and an NIHSS score < 8 (17 of 54) had good outcomes. Combining clinical and imaging thresholds improved prognostic yield (70%) over clinical (43%) or imaging (54%) thresholds alone (P = 0.01).

Conclusions—Combining quantitative DWI and MTT with NIHSS predicts good and poor outcomes with high probability and is superior to NIHSS alone. (Stroke. 2010;41:1728-1735.)

Key Words: cerebral infarction • diffusion MRI • perforusion MRI

Reperfusion therapy is the only treatment demonstrated to improve outcomes of patients with acute ischemic stroke (AIS).1,2 The decision to treat is determined primarily by the time from symptom onset. For intravenous recombinant tissue plasminogen activator (IV tPA), the time window is 3 hours and up to 4.5 hours in some patients.3 The time window for intra-arterial therapies (IAT) is up to 8 hours. However, advanced neuroimaging techniques such as diffusion- (DWI) and perfusion-weighted (PWI) MRI may better identify treatment candidates than time considerations alone. Multiple studies have demonstrated that IV tPA can be given up to 6 hours from stroke onset with similar safety and efficacy to the 3-hour window when patients are selected based on a diffusion–perfusion mismatch.4,5

MR DWI estimates the infarct core, whereas PWI estimates the ischemic penumbra. The mismatch between these two is the potentially salvageable tissue should reperfusion occur. Despite the favorable data in support of the mismatch hypothesis, there is no conclusive evidence that the mismatch alone identifies patients who will respond to treatment. One problem may be the lack of standardization.6 Studies have used varying mismatch definitions with the most common being a perfusion abnormality 20% larger than the diffusion abnormality. Furthermore, mismatch determinations are often done by visual estimation. Controversy about the efficacy of treating patients with a diffusion–perfusion mismatch beyond 3 hours highlights the need to improve the current imaging selection criteria.7

Quantitative assessment of neuroimaging parameters may be superior for predicting treatment response. Sanak et al found that among patients with AIS treated with IV tPA or IAT, those with pretreatment DWI volume less < 70 mL had...
significantly better outcomes than patients with larger initial DWI lesion volumes. Similarly, another study of patients treated with IAT found that patients with initial DWI volumes >70 mL had poor outcomes regardless of reperfusion status.

Our purpose was to determine quantitative thresholds for MRI parameters that predict outcome with high probability in patients with anterior circulation AIS (<9 hours from symptom onset). We sought to determine: (1) if there is an initial DWI lesion volume above which all patients do poorly; (2) if there is an initial PWI lesion volume below which all patients do well; (3) if there are similar thresholds for the National Institutes of Health Stroke Scale (NIHSS); and (4) whether imaging can add prognostic information over NIHSS alone.

Methods

Patient Selection

This study was approved by the Institutional Review Board. Eligibility criteria for this study were (1) acute middle cerebral artery (MCA) and/or anterior cerebral artery stroke; (2) MR diffusion and perfusion imaging within 9 hours of symptom onset; (3) images of sufficient quality to undergo volumetric analyses; and (4) follow-up clinical evaluations for computation of modified Rankin scores (mRS).

There were a total of 180 patients that were admitted to our medical center with a diagnosis of acute anterior circulation ischemic stroke within 9 hours of symptom onset. Of this population, 18 patients were excluded on the basis of imaging evidence of chronic infarcts, and 10 patients were removed due to involvement of multiple vascular territories (eg, anterior and posterior circulation acute infarction) such that the clinical sequelae could not be ascribed to the acute anterior circulation event. Thirty-three patients were excluded because they did not undergo pretreatment MRI: 16 patients had metallic implants (eg, pacemaker, artificial heart valve), 1 patient could not hold still for the examination, and 16 patients had no identifiable reason. Eighteen patients underwent MRI but did not undergo perfusion imaging: 10 patients had minimal neurological deficits that precluded treatment (all had NIHSS score ≤2); 7 had excellent outcomes [mRS 0 to 2], and 3 did not follow-up, 1 patient could not undergo perfusion imaging due to technical problems, 1 patient could not hold still, and for 6 patients, there was no identifiable reason. Thirty patients underwent diffusion and perfusion MRI but the images were degraded by motion (n=5) or technical artifact (including incomplete lesion coverage; n=25) and could not be analyzed. Of the remaining 71 patients, 1 patient had undergone reperfusion by the time of imaging, 2 patients died during the hospital stay from unrelated causes, and 14 patients did not have follow-up mRS scores. The remaining 54 patients comprised the study cohort.

Comparing the 95 patients who were excluded from the study due to the lack of adequate imaging or adequate follow-up versus the 54 study patients, there were no significant differences in admission NIHSS scores (P=0.30), age (P=0.59), gender (P=1.00), treatment type (P=0.87), or follow-up mRS scores (P=0.75). Among the 54 study patients, 17 patients were treated with IV tPA, 4 were enrolled in Desmoteplase in Acute Ischemic Stroke (DIAS) 2,10 5 were treated with IAT alone and 28 patients were not treated.

Patient Assessment

The initial NIHSS was performed by a stroke neurologist. Clinical outcome was ascertained from each patient’s medical record using the mRS at 3 months. A mRS of 6 was used for patients who had died. An mRS of 0 to 2 was considered a good outcome. For 6 patients with good outcome at discharge who did not return for follow-up, the discharge mRS was carried forward. For 2 patients discharged to hospice, a score of 6 was used. For all other patients, the 3-month follow-up mRS was used.

Image Acquisition

MR examinations were performed on a 1.5-Tesla Signa whole-body scanner (General Electric Medical Systems, Milwaukee, Wis). DWI was performed using a single-shot echoplanar spin-echo sequence with 2 180° radiofrequency pulses to minimize eddy current warping. Five images/slice were acquired at b=0 s/mm² followed by 5 at b=1000 s/mm² in 6 directions for a total 35 images/slice. Twenty-three to 27 slices covered the entire brain. Imaging parameters were: TR/TE 5000/80 to 110 ms, field of view 22 cm, matrix 128×128 zero-filled to 256×256, section thickness 5 mm, and a 1-mm gap. PWI was performed using a dynamic susceptibility technique. Serial echoplanar gradient-echo images were acquired with TR/TE 1500/40 ms, field of view 22 cm, matrix 128×128, slice thickness 5 mm, and a 1-mm gap. Fourteen to 16 slices were acquired every 1.5 seconds for a total 46 to 80 images/slice. Ten seconds after image acquisition began, 20 mL of gadopentetate dimeglumine 0.5 mmol/mL (Magnevist; Bayer HealthCare Pharmaceuticals) was injected through a peripheral intravenous catheter at 5 mL/s using a power injector (Medrad, Warrendale, Pa) followed by a 20-mL normal saline bolus.

Image Processing

Signal intensity versus time curves for each pixel were converted to concentration versus time curves, which were integrated to yield maps of cerebral blood volume. Cerebral blood flow was calculated by singular value decomposition deconvolution.11 A global arterial input function was derived from the MCA ipsilateral to each patient’s infarct. Mean transit time (MTT) was calculated by dividing cerebral blood volume by cerebral blood flow.

Postprocessing Image Analysis

For quantitative measurement, visually detected DWI and MTT abnormalities were segmented by a research assistant using a semiautomated commercial analysis program (Analyze 7.0; AnalyzeDirect). Outlines were manually corrected by a neuroradiologist blinded to clinical information. Lesion volumes were calculated. Absolute mismatch was defined as the difference between the MTT and DWI lesion volumes. Percent mismatch was defined as the absolute mismatch divided by the MTT lesion volume.

Statistical Analysis

Cases were dichotomized into good (mRS 0 to 2) versus poor (mRS 3 to 6) outcome. The Student t test with correction for unequal variances (Welch test) was used to compare good versus poor outcome with respect to DWI lesion volume, MTT lesion volume, percentage mismatch volume, mismatch volume, and age. The Mann-Whitney U test was used for NIHSS comparison. The Fisher exact test was performed to compare categorical variables. A stepwise multiple logistic regression analysis was performed modeling the dichotomized outcome with these variables (SAS 9.1; SAS Institute, Cary, NC). Receiver operating characteristics curves were calculated for DWI, MTT and mismatch volumes, mismatch percentage, and NIHSS relative to the dichotomized outcome. The areas under the receiver operating characteristic curves were compared using the nonparametric approach of Delong et al, which is based on the theory of generalized U statistics to generate a covariance matrix.12 The univariate and receiver operating characteristic analyses were performed using MedCalc 10.0 software (Mariakerke). P<0.05 was considered significant.

Results

Baseline clinical and imaging variables, treatments, and clinical outcome data are presented in Table 1.

Clinical and Imaging Predictors of Dichotomized 3-Month Outcome

Thirty-three of 54 (61%) patients had a good clinical outcome (mRS 0 to 2). Patients with a good outcome had significantly
smaller DWI lesion volumes, smaller MTT lesion volumes, and lower NIHSS scores compared with patients with a poor outcome (Table 2). There was a trend for younger age and smaller mismatch volume in patients with good outcome. NIHSS score was the only independent predictor of outcome (P<0.0001).

The receiver operating characteristic curves for DWI lesion volume, MTT lesion volume, and NIHSS versus poor outcome yielded areas under the curve of 0.889, 0.854, and 0.930, respectively, which were not significantly different (Figure 1). In pairwise comparisons, the areas under the curve for these 3 variables were significantly higher than for mismatch percent (0.628) and mismatch volume (0.693). The probability values were 0.46 for DWI versus MTT, 0.47 for DWI versus NIHSS, 0.01 for DWI versus mismatch volume, <0.001 for DWI versus mismatch percentage, 0.24 for MTT versus NIHSS, 0.01 for MTT versus mismatch volume, 0.001 for MTT versus mismatch percentage, 0.004 for NIHSS versus mismatch volume, <0.001 for NIHSS versus mismatch percentage, and 0.33 for mismatch volume versus mismatch percentage.

A probability plot for poor outcome versus DWI lesion volume, shown in Figure 2A, demonstrates a plateau effect toward 100% in the 75- to 125-mL range. A probability plot for poor outcome versus MTT lesion volume, shown in Figure 2B, shows a plateau effect toward zero in the <50-mL range. Table 3 gives ORs for dichotomized outcome for various DWI and MTT lesion volume thresholds.

### Identifying Clinically Relevant Thresholds for DWI, MTT, and NIHSS

Scatterplots of DWI volume, MTT volume, and NIHSS score for each patient, dichotomized into good versus poor outcome, are shown in Figure 3. The minimum DWI volume above which no patient had a good outcome was 72 mL (100% specific [95% CI: 89.4% to 100%], 61.9% sensitive [95% CI: 38.4% to 81.9%] for poor outcome). All 13 patients (5 received IV tPA) with DWI volume ≥72 mL and 8 of 41 patients with DWI volume ≤72 mL had poor outcome. The maximum MTT volume under which all patients had a good outcome was 47 mL (MTT volume ≥47 mL is 100% sensitive [95% CI: 83.9% to 100%], 48.5% specific [95% CI: 30.8% to 66.5%] for poor outcome). Zero of 16 patients with MTT volume <47 mL and 21 of 38 patients with MTT volume ≥47 mL had a poor outcome.

All 17 patients with a NIHSS score <8 had a good outcome(NIHSS ≥8 is 100% sensitive [95% CI: 83.9% to 100%], 51.5% specific [95% CI: 33.5% to 69.2%] for poor outcome), whereas all 6 patients (2 received IV tPA and 1 received IAT) with an NIHSS score ≥20 had a poor outcome (100% specific [95% CI: 89.4% to 100%], 28.6% sensitive for IV tPA, 57.1% sensitive for IAT).
[95% CI: 11.3% to 52.2%] for poor outcome). Thirteen of 29 (45%) patients with NIHSS ≥8 and ≤20 had a poor outcome.

**Interaction of the Clinical and Imaging Thresholds in Predicting Outcome**

Using the previously described thresholds for DWI, MTT, and NIHSS, 23 of 54 (43%) patient outcomes were predicted by a clinical threshold (6 patients with NIHSS >20, 17 with NIHSS <8; Figure 4). Twenty-nine of 54 (54%) patient outcomes were predicted by an imaging threshold (13 patients with DWI >72 mL, 16 with MTT <47 mL). Combining clinical and imaging thresholds improved prognostic yield to 70.4% \((P=0.01)\); 38 of 54 (70.4%) patient outcomes were predicted by at least 1 clinical or imaging threshold. Of these 38, 14 (36.8%) were identified by both clinical (NIHSS) and imaging (DWI or MTT) thresholds: 9 had a good outcome (NIHSS <8, MTT volume <47 mL) and 5 had a poor outcome (NIHSS score >20, DWI volume >72 mL; Supplemental Figure I; available at http://stroke.ahajournals.org). The majority (24 of 38 patients [63.2%]) were identified by either a clinical threshold \((n=9: 1\text{ with NIHSS } >20, 8\text{ with NIHSS } <8; \text{ Supplemental Figure II})\) or an imaging threshold \((n=15: 8\text{ with DWI } >72 \text{ mL}, 7\text{ with MTT } <47 \text{ mL})\) alone.

Outcomes for the remaining 16 of 54 (29.6%) patients were not predictable using these thresholds. These patients had initial DWI volume ≤72 mL, initial MTT volume ≥47 mL, and baseline NIHSS score of 8 to 20. Of these patients, 9 of 16 (56.3%) had a good outcome: 7 were treated with intra-arterial or intravenous therapy and 2 were not. Among the 7 patients with a poor outcome, 5 were treated and 2 were not.

**Figure 2.** Probability plots for DWI lesion volume (A) and MTT lesion volume (B) versus poor outcome (mRS 3 to 6).
Discussion

We demonstrate that, in a broad cohort of patients with anterior circulation ischemic stroke imaged within 9 hours of symptom onset, quantitative thresholds applied to MRI parameters can be used to predict poor functional outcome with high specificity (initial DWI volume $>72$ mL) and high sensitivity (initial MTT volume $\leq 47$ mL). Similar thresholds exist for the baseline NIHSS (initial NIHSS $\geq 8$ is highly sensitive and initial NIHSS $>20$ is highly specific for poor outcome). Furthermore, neuroimaging provides additional prognostic information over that provided by the NIHSS alone.

These findings suggest a new approach for determining a favorable imaging profile for treatment. Most studies investigating imaging-based treatment selection have used the diffusion–perfusion mismatch. Much evidence supports this approach. Prior studies have found that selecting patients for treatment with IV tPA within the 3- to 6-hour window through the exclusion of patients with large DWI lesions ($>50\%$ of the MCA territory) and inclusion of patients with a $>20\%$ PWI/DWI mismatch improves outcomes compared with placebo and possibly to traditionally selected patients given IV tPA. Similarly, initial trials of a novel fibrinolytic agent, desmoteplase, for treatment of AIS in the 3- to 9-hour window have found that patients with a DWI lesion less than one third of the MCA territory and a DWI/PWI mismatch $>20\%$ had higher reperfusion rates and better clinical outcomes when treated with desmoteplase versus placebo. However, validation of the mismatch hypothesis awaits confirmatory studies exploring the treatment effect in the presence and absence of a mismatch. In the present study, DWI and MTT volumes performed significantly better at predicting outcome than absolute or percent mismatch.

Our finding that every patient with an acute DWI lesion volume $>72$ mL had a poor outcome agrees with recent MRI studies. Sanak et al found that 70 mL was the maximum DWI volume associated with good clinical outcome in 25 patients undergoing intravenous or intra-arterial thrombolysis. In another study of patients with anterior circulation proximal artery occlusions undergoing IAT, those with acute DWI lesion volumes $>70$ mL had poor outcomes irrespective of...
To our knowledge, no prior studies have investigated an MTT lesion volume threshold for predicting clinical outcome. Our finding that all patients with MTT lesions <47 mL had good outcome is consistent with previous studies demonstrating that proximal artery occlusions, with their much larger territories at risk, account for most of the stroke-related morbidity and mortality.18

Multiple prior studies have demonstrated that baseline NIHSS is a strong predictor of clinical outcome. In our study, NIHSS was the only independent predictor of outcome. This study expands on prior studies by establishing thresholds for outcome; all patients with an NIHSS score >20 had poor outcome, and all with an NIHSS score <8 had a good outcome regardless of treatment. The lower threshold is supported by a prior study demonstrating that patients with AIS with NIHSS ≥8 had a significantly higher rate of subsequent neurological worsening (P<5×10⁻⁶). Using baseline NIHSS alone, the most appropriate patients to treat with reperfusion therapy may be those with NIHSS scores ≥8 and ≤20, a range used in the DIAS trial.14

This study also demonstrates that treatment selection can be improved with the use of imaging. Using both clinical and imaging thresholds using NIHSS, DWI and MTT produced the highest prognostic yield. The NIHSS thresholds alone predicted outcome in 23 of 54 cases (42.6%). The DWI and MTT thresholds alone predicted outcome in 29 of 54 cases (53.7%). Using all 3 thresholds together, outcome was predicted in 38 of 54 cases (70.4%). Among these 38 cases, most outcomes (24 of 38 [63.2%]) were predicted by either a clinical or imaging threshold alone, suggesting that these parameters are highly complementary, likely because they measure different aspects of acute stroke. The NIHSS measures the functional severity of an ischemic insult, whereas the DWI and MTT reflect the cellular and hemodynamic physiology of acute ischemia respectively. Of 31 patients with indeterminate NIHSS scores (≥8 and ≤20), 15 (48.4%) satisfied 1 imaging threshold; 8 had a DWI volume >72 mL, and 7 had an MTT volume <47 mL.

There were 16 patients (29.6%) whose outcomes could not be determined using any clinical or imaging threshold. They had initial DWI lesion volume ≤72 mL, initial MTT lesion volume ≥47 mL, and baseline NIHSS score ≥8 and ≤20. These patients may represent a target population for revascularization therapy, because they may benefit from early reperfusion. Because we did not have reperfusion information, we could not assess the relationship between reperfusion and outcome.

These combined clinical and imaging thresholds provide an alternative to the clinical–diffusion mismatch model (NIHSS ≥8, DWI volume ≤25 mL).22 Although clinical–diffusion mismatch has been associated with early neurological deterioration and infarct growth, its presence is not associated with improved clinical response to IV tPA or reperfusion in recent studies.24,25 The problem may be that these studies included patients with an NIHSS >8 who would do well regardless of treatment due to an MTT volume <47 mL. It will be interesting to see whether the thresholds from this study perform better than clinical–diffusion mismatch.

Figure 4. A, Venn diagram demonstrating prediction of good outcome with a clinical threshold of NIHSS <8 and an imaging threshold of MTT <47 mL. Nine of 24 patients were identified by both thresholds, whereas 8 of 24 were identified by the NIHSS threshold and 7 of 24 were identified by the MTT threshold alone. B, Venn diagram demonstrating prediction of poor outcome with a clinical threshold of NIHSS >20 and an imaging threshold of DWI >72 mL. Five of 14 patients were identified by both thresholds, whereas 1 of 14 was identified by the NIHSS and 8 were identified by the DWI threshold alone. In A and B, there is only partial overlap of the patients predicted by NIHSS score with those predicted by the imaging criteria. This highlights the fact that NIHSS and imaging provide complementary prognostic information and that overall prediction is better when both data are used together.

whether reperfusion occurred.9 Furthermore, our 72-mL threshold for DWI lesion volume agrees with the Dose Escalation of Desmoteplase for Acute Stroke (DEDAS) trial findings.15 In that trial, patients with DWI lesions visually interpreted as more than one third of the MCA territory were excluded, but in a retrospective analysis, the largest included DWI lesion was 78.1 mL, similar to our 70-mL threshold.
Importantly, our findings need to be validated in a larger cohort. If they are confirmed to be true, there will be significant implications for both clinical practice and trial methodology. Based on these results, acute stroke trials should include patients with minimum MTT lesion volume of approximately 47 mL and exclude patients with DWI lesion volume greater than approximately 72 mL. The major hurdle to the real-time application of these imaging thresholds is the availability of reliable lesion volume quantification. Automated image analysis programs would allow for rapid and accurate measurements, but they are not widely available. Fortunately, manual calculation using the ellipsoid approximation (ABC/2 formula) yields excellent estimates of infarct volume that can be used in the clinical setting.

Limitations of this study included those inherent in a retrospective design. As a result, certain data could not be obtained such as vascular and reperfusion status, final infarct volume, and genetic and molecular markers. Also, clinical status at Day 30 was not available for this cohort. Our clinical algorithm for stroke follow-up captures patient outcomes at 3 months using the mRS score. Although this limitation may preclude comparison of our results to the DEFUSE study, which used 30-day neurological status, this is offset by the fact that the majority of thrombolytic trials, including the EchoPlanar Imaging Thrombolytic Evaluation Trial (EPITHET), use 90-day functional outcome as a clinical end point.

Additional limitations included a relatively small study cohort and variable treatments. Times from stroke onset to imaging and from imaging to follow-up clinical assessment were also variable. There was potential institutional selection bias related to using MR imaging, the decision to offer thrombolysis, and our technical approach to performing IAT. All of these factors make it difficult to establish DWI, MTT, and NIHSS thresholds with certainty. Although we recognize that a DWI lesion volume threshold of 72 mL is only applicable to our patient population (until it is validated), it adds important information to the literature because the DWI threshold for poor outcome should not be lower than 72 mL. Similarly, the MTT threshold for good outcome should not be above 47 mL. Also, segmentation of DWI and MTT abnormalities was based on visual assessment rather than thresholding. It is important to note that despite the recent support for a threshold-based approach, there are no convincing data that validate a specific perfusion threshold for clinical use in acute stroke. The majority of studies that have demonstrated a clinical benefit from penumbral imaging-based selection have used visual (nonthresholded) lesion estimation on the perfusion maps (eg, time-to-peak or MTT) either entirely or in part (eg, some centers of a multicenter study).

**Conclusion**

For AIS, thresholds applied to acute DWI and MTT lesion volumes and NIHSS can be used to determine good and poor clinical outcomes with high probability. Patients who do not meet these thresholds have variable outcomes and may represent a target population for revascularization therapy. Clinical and imaging thresholds provide complementary information and should be used together for improved treatment selection. These findings need to be validated in a larger, prospective patient cohort.

**Disclosures**

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