Brain Edema Predicts Outcome After Nonlacunar Ischemic Stroke

Thomas W.K. Battey, BS; Mahima Karki, BA; Aneesh B. Singhal, MD; Ona Wu, PhD; Saloomeh Sadaghiani, BA; Bruce C.V. Campbell, MBBS, PhD; Stephen M. Davis, MD; Geoffrey A. Donnan, MD; Kevin N. Sheth, MD; W. Taylor Kimberly, MD, PhD

Background and Purpose—In malignant infarction, brain edema leads to secondary neurological deterioration and poor outcome. We sought to determine whether swelling is associated with outcome in smaller volume strokes.

Methods—Two research cohorts of acute stroke subjects with serial brain MRI were analyzed. The categorical presence of swelling and infarct growth was assessed on diffusion-weighted imaging (DWI) by comparing baseline and follow-up scans. The increase in stroke volume (ΔDWI) was then subdivided into swelling and infarct growth volumes using region-of-interest analysis. The relationship of these imaging markers with outcome was evaluated in univariable and multivariable regression.

Results—The presence of swelling independently predicted worse outcome after adjustment for age, National Institutes of Health Stroke Scale, admission glucose, and baseline DWI volume (odds ratio, 4.55; 95% confidence interval, 1.21–18.9; P<0.02). Volumetric analysis confirmed that ΔDWI was associated with outcome (odds ratio, 4.29; 95% confidence interval, 2.00–11.5; P<0.001). After partitioning ΔDWI into swelling and infarct growth volumetrically, swelling remained an independent predictor of poor outcome (odds ratio, 1.09; 95% confidence interval, 1.03–1.17; P<0.005). Larger infarct growth was also associated with poor outcome (odds ratio, 7.05; 95% confidence interval, 1.04–143; P<0.045), although small infarct growth was not. The severity of cytotoxic injury measured on apparent diffusion coefficient maps was associated with swelling, whereas the perfusion deficit volume was associated with infarct growth.

Conclusions—Swelling and infarct growth each contribute to total stroke lesion growth in the days after stroke. Swelling is an independent predictor of poor outcome, with a brain swelling volume of ≥11 mL identified as the threshold with greatest sensitivity and specificity for predicting poor outcome. (Stroke. 2014;45:3643-3648.)

Key Words: brain edema ■ magnetic resonance imaging ■ stroke ■ swelling

Neurological deterioration is a well-described complication of a large hemispheric stroke, principally caused by the formation of cerebral edema.1-2 The disease is associated with high morbidity and mortality,3-5 with limited medical and surgical treatment options available.6-8 Edema typically peaks 3 to 5 days after stroke onset,9 although a malignant form can present within 24 hours and lead to precipitous decline.3,10

In this study, we sought to characterize the extent to which swelling or infarct growth contributed to neurological outcome in a broader range of stroke severity. Imaging markers of swelling were established in 2 cohorts with serial research MRI during the first 2 to 5 days after stroke. We also investigated the relationship of swelling to lesional tissue properties that characterize brain injury and swelling,11,12 including apparent diffusion coefficient (ADC) values representing early cytotoxic injury,13,14 and hyperintensity on T2 fluid-attenuated inversion recovery (FLAIR) imaging, a putative tissue clock for ischemia15 that may also reflect the degree of blood–brain barrier disruption.12,16 We hypothesized that brain edema is relevant to outcome in a broad stroke population, potentially making it an attractive therapeutic target.

Methods

Patient Characteristics
Brain MRI scans were retrospectively analyzed in 2 cohorts of subjects with acute stroke: the placebo arm of the Normobaric Oxygen Therapy in Acute Ischemic Stroke Trial cohort (NBO, NCT00414726) and the Echoplanar Imaging Thrombolysis Evaluation Trial cohort.
(EPITHET, NCT00238537). The NBO study enrolled patients from 2007 to 2009 who were treated with room air and acquired brain MRI within the first 9 hours of stroke symptom onset and again 4, 24, and 48 hours later. Subjects with baseline diffusion-weighted imaging (DWI) volumes of <10 mL were excluded in this study to avoid the risk of classifying volume averaging artifacts. Imaging markers were also investigated in the EPITHET cohort to perform association testing with clinical outcome. The full details of the EPITHET cohort are described elsewhere. Briefly, the EPITHET study enrolled patients from 2001 to 2007 with baseline MRI within 3 to 6 hours of stroke onset and follow-up MRI 3 to 5 days later.

For both cohorts, subjects were included in the present study if they had baseline and follow-up DWI scan available along with clinical data. Subjects without clinical data, DWI at either baseline or follow-up, or DWI of insufficient quality (attributable to excessive motion) were excluded from the study. Clinical outcome data were obtained via standard assessment 90 days after stroke using the modified Rankin Scale (mRS) score. A good outcome was defined as an mRS of 0 to 2, and a poor outcome as an mRS of 3 to 6. No subjects in either cohort had a lacunar stroke subtype or were treated with endovascular therapy. This study was approved by the Institutional Review Board, and all subjects or their legally authorized representative originally provided informed consent before participation in each study.

Imaging Analysis
Region-of-interest analysis was conducted using a semiautomated method in Analyze 11.0 (Biomedical Imaging Resource, Mayo Clinic, Rochester, MN), based on our prior methods. Briefly, the stroke lesion and normal contralateral hemisphere regions of interest were initially defined on DWI, transferred to the ADC map for removal of cerebrospinal fluid and calculation of ADC ratio (ADCr), and then applied to a coregistered FLAIR sequence when available to calculate FLAIR ratio (FLAIRr) (please see Figure I in the online-only Data Supplement). Stroke volume and intensity ratios were calculated on baseline and follow-up MRI for all subjects. Imaging analyses were performed by trained readers (T.W.K.B. and W.T.K.) blinded to clinical and outcome data and separately reviewed by another blinded reader (W.T.K.). For additional quality control, stroke volumes generated in this study were compared with prior values obtained as part of the original trial analyses. Similar to our previous experience, the intraclass correlation coefficient was 0.97.11

Stroke lesion expansion ($\Delta$DWI) was defined as the change in lesion volume between baseline and follow-up DWI. The presence or absence of swelling and infarct growth was assessed by 2 readers (T.W.K.B. and W.T.K.) blinded to clinical and outcome data. Designations were made by comparing baseline and follow-up MRI scans side-by-side simultaneously in the axial, sagittal, and coronal planes. Stroke volumes generated in this study were compared with prior values obtained as part of the original trial analyses. Similar to our prior experience, the intraclass correlation coefficient was 0.97.

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Volume Estimate and Region-of-Interest modules. New neuroanatomic areas of infarction not present on the baseline MRI were first identified on the follow-up MRI in the axial, sagittal, and coronal planes and then outlined in the Volume Edit module (see Figure I for examples). Hemorrhage was excluded, although its exclusion did not alter the final analysis. The final volumes were determined based on the relationship: $\Delta$DWI=infarct growth+sweating.

Statistical Analysis
Outcome testing with swelling and infarct growth was conducted in the EPITHET cohort, and analysis of lesional tissue properties was conducted in the NBO cohort. Descriptive statistics of baseline variables and outcomes are reported as mean±SD (for normally distributed continuous data), median with interquartile range (for non-normal or ordinal data), and proportions (for binary data). Inter-rater agreement was assessed for stroke volume using intraclass correlation coefficient and Bland–Altman analyses. The relationships between imaging and clinical covariates were assessed using Pearson or Spearman correlation testing, as appropriate. Univariate logistic regression was performed to investigate the associations of clinical and imaging variables with outcome. Multivariate logistic regression models were developed to test for independent effects. All tests were 2 sided, with the threshold of significance set at $P<0.05$. Statistical analyses were performed using JMP Pro 11.0 (SAS Institute, Cary, NC).

Results
Clinical Characteristics
The clinical characteristics of the 2 study populations are shown in Table 1. The cohorts were similar in age and...
Table 1. Clinical and Imaging Characteristics of the Patients

<table>
<thead>
<tr>
<th></th>
<th>NBO Cohort (n=19)</th>
<th>EPITHET Cohort (n=78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean±SD</td>
<td>73±13</td>
<td>72±13</td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
<td>15 (78)</td>
<td>42 (53)</td>
</tr>
<tr>
<td>Comorbidities, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4 (21)</td>
<td>19 (24)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14 (74)</td>
<td>55 (71)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>13 (63)</td>
<td>33 (42)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>10 (53)</td>
<td>33 (42)</td>
</tr>
<tr>
<td>IV tPA, n (%)†</td>
<td>0 (0)</td>
<td>36 (46)</td>
</tr>
<tr>
<td>Admission NIHSS score, median (IQR)</td>
<td>14 (7–19)</td>
<td>13 (8–17)</td>
</tr>
<tr>
<td>Time from LSW to MRI, h, mean±SD*</td>
<td>7.0±3.0</td>
<td>4.1±0.9</td>
</tr>
<tr>
<td>Admission DWI volume, mL, median (IQR) †</td>
<td>33 (14–77)</td>
<td>21 (9–51)</td>
</tr>
<tr>
<td>Admission PWI volume, mL, median (IQR)</td>
<td>140 (85–189)</td>
<td>157 (95–239)</td>
</tr>
<tr>
<td>Admission FLAIR ratio, mean±SD</td>
<td>1.21±0.12</td>
<td>...</td>
</tr>
<tr>
<td>Admission ADC ratio, mean±SD</td>
<td>0.693±0.067</td>
<td>0.685±0.075</td>
</tr>
<tr>
<td>∆DWI volume, mL, median (IQR)</td>
<td>25 (10–51)</td>
<td>14 (5–66)</td>
</tr>
<tr>
<td>Swelling, n (%)</td>
<td>13 (68)</td>
<td>53 (67)</td>
</tr>
<tr>
<td>Infarct growth, n (%)</td>
<td>7 (39)</td>
<td>34 (43)</td>
</tr>
<tr>
<td>Modified Rankin Scale score, median (IQR)</td>
<td>3 (2–6)</td>
<td>3 (1–4)</td>
</tr>
</tbody>
</table>

ADC indicates apparent diffusion coefficient; DWI, diffusion-weighted imaging; EPITHET, Echoplanar Imaging Thrombolysis Evaluation Trial; FLAIR, fluid-attenuated inversion recovery; IQR, interquartile range; IV tPA, intravenous tissue-type plasminogen activator; LSW, last seen well; NBO, Normobaric Oxygen Therapy in Acute Ischemic Stroke Trial; NIHSS, National Institutes of Health Stroke Scale; and PWI, perfusion-weighted imaging.

*P<0.001.
†P<0.05.

Swelling Predicts Outcome After Stroke

The EPITHET cohort had a baseline MRI and follow-up MRI obtained during the period of peak swelling 3 to 5 days after stroke onset. Evidence of swelling was present in 67% of subjects, with infarct growth present in 43% (Table 1). The distribution of mRS scores for subjects dichotomized into the presence or absence of swelling (univariate P<0.002) and infarct growth (univariate P<0.002) is shown in Figure 2.

Next, we performed univariate regression to identify additional predictors of poor 90-day functional outcome. Baseline National Institutes of Health Stroke Scale score, admission glucose level, swelling, and admission DWI volume were all associated with poor outcome (Table 2). After adjustment, the presence of swelling remained an independent predictor of poor 90-day outcome (P<0.002), whereas infarct growth did not (P=0.64). The inclusion of sex in the model did not alter the independent association of swelling with poor outcome.

Evaluation of incremental changes in the magnitude of infarct growth demonstrated that large infarct growth was associated with outcome in both univariate and multivariate analyses (please see Table I in the online-only Data Supplement). Importantly, swelling remained an independent predictor of poor outcome in each of the models tested.

Volumetric Lesion Analysis

The change in stroke lesion volume between baseline and follow-up scans (∆DWI) has previously been reported as a marker for lesion growth.18–20 We confirmed that ∆DWI represents a composite measure that encompasses both infarct growth into new anatomic territory and space-occupying brain edema by testing the association of the binary variables for swelling and infarct growth with ∆DWI. Both were independently associated with ∆DWI, confirming that each contributed to lesion expansion (both P<0.0001). Moreover, when ∆DWI was substituted for swelling and infarct growth in the multivariate regression model, it was independently associated with poor 90-day outcome (Table 3).

Next, we tested the relationship between the volumetric contributions of swelling and infarct growth and outcome. In
Table 3. Multivariable Modeling of the Volume of Swelling and Infarct Growth With Poor Outcome

<table>
<thead>
<tr>
<th></th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>P Value</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.07</td>
<td>1.02–1.13</td>
<td>0.01</td>
<td>1.10</td>
<td>1.03–1.18</td>
<td>0.001</td>
</tr>
<tr>
<td>Admission glucose</td>
<td>4.47</td>
<td>0.57–49.4</td>
<td>0.18</td>
<td>6.58</td>
<td>0.64–103</td>
<td>0.12</td>
</tr>
<tr>
<td>Admission NIHSS score</td>
<td>1.13</td>
<td>0.99–1.30</td>
<td>0.07</td>
<td>1.18</td>
<td>1.02–1.39</td>
<td>0.03</td>
</tr>
<tr>
<td>Admission DWI volume</td>
<td>2.41</td>
<td>0.56–11.3</td>
<td>0.24</td>
<td>1.46</td>
<td>0.26–9.33</td>
<td>0.67</td>
</tr>
<tr>
<td>ΔDWI volume</td>
<td>4.29</td>
<td>2.00–11.5</td>
<td>&lt;0.001</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Volume of swelling</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>1.09</td>
<td>1.03–1.17</td>
<td>0.003</td>
</tr>
<tr>
<td>Volume of infarct growth</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>1.08</td>
<td>0.68–1.78</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Admission glucose, DWI volume, ΔDWI volume, and infarct growth volume were log-transformed before inclusion in the regression model in the Echoplanar Imaging Thrombolysis Evaluation Trial (EPITHET) cohort. CI indicates confidence interval; DWI, diffusion-weighted imaging; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and OR, odds ratio.

univariate analysis, the volume of swelling was associated with poor outcome (Figure 3A; P<0.001), whereas infarct growth volume demonstrated a trend (P=0.11). In multivariable regression analysis, replacement of ΔDWI volume with swelling and infarct growth volumes confirmed that swelling was an independent predictor of outcome (P=0.003; Table 3). Importantly, because the baseline DWI lesion volume predicted the development of swelling (P<0.01), the inclusion (or removal) of the baseline DWI volume in the multivariable model did not alter the independent association between swelling and outcome. Receiver operating characteristic curve analysis showed that 11 mL of swelling volume had the highest sensitivity and specificity for distinguishing good versus poor outcome (Figure 3B; sensitivity, 77%; specificity, 75%; area under the curve=0.798). A similar receiver operating characteristic curve analysis for the prediction of swelling from the baseline DWI scan revealed that a volume ≥13 mL had the greatest sensitivity (81%) and specificity (67%) for identifying subjects who later developed swelling (area under the curve=0.790).

Tissue Properties Associated With Swelling

Next, we investigated whether tissue properties of the stroke lesion assessed by MRI were associated with swelling or infarct growth. First, we confirmed that admission perfusion deficit volume was associated with infarct growth (P<0.001). Next, we hypothesized that the degree of cytotoxic injury or blood–brain barrier breakdown may predict subsequent swelling.13,25 In addition to analyzing MRI scans in the EPITHET cohort, we extended our analysis to include the NBO cohort which had the added advantage of increased frequency, timing, and type of sequences available for analysis. This permitted detailed analysis of the time course of the lesional tissue characteristics (please see Figure II in the online-only Data Supplement).

We first evaluated the relative signal intensity of ADC (ADCr), which is considered a marker for cytotoxic injury.13,14 In the EPITHET cohort, a lower baseline ADCr was associated with swelling volume (r=−0.31; P=0.006). Similarly, in the NBO cohort, ADCr was associated with the presence of swelling (P=0.04). On the contrary, and in both cohorts, ADCr was not associated with outcome (P=0.32 and P=0.25 for NBO and EPITHET cohorts, respectively).

Next, we evaluated the signal intensity ratio of T2 FLAIR (FLAIRr), which is hypothesized to reflect the degree of blood–brain barrier breakdown potentially leading to extravasation of fluid into the infarct.25 FLAIR sequences were only available in the NBO cohort, and consistent with prior reports,11 FLAIRr increased progressively during the first 2 days. In addition, the baseline FLAIRr was associated with the 48-hour FLAIRr (r=0.54; P=0.03), suggesting inasubject differences that persist over time. Nevertheless, neither was FLAIRr predictive of swelling (P=0.51) nor was it associated with outcome (P=0.76).

Discussion

Brain edema is a well-recognized secondary complication of stroke; yet, the deleterious effect of swelling is only recognized in cases of malignant infarction. The main treatment option for malignant edema is surgical decompression,7,8 and existing evidence supports the conclusion that swelling is causally related to outcome, at least in large hemispheric stroke. In this study, we investigated the relationship between imaging markers of cerebral edema and clinical outcome in patients with a wider range of stroke severity. Our data provide evidence for an association between swelling and poor functional outcome in moderately sized stroke, highlighting the broader clinical relevance of brain edema in stroke populations. Although our data do not address causality of edema in this patient population, its well-defined role in malignant

Figure 3. Greater swelling is associated with poor neurological outcome. A. The volume of swelling in subjects with modified Rankin Scale (mRS) score of 3 to 6 was higher than those with a 90-day mRS score of 0 to 2 (P<0.001). B. Receiver operating characteristic curve analysis shows that swelling of 11 mL predicts poor outcome with a sensitivity of 77% and a specificity of 75%, identified by the arrow. The area under the curve was 0.798.
edema suggests that it may be causally relevant in patients with stroke across the spectrum of stroke severity.

Our analysis also demonstrated that lesional volume measures such as ΔDWI seem to represent a composite imaging measure that comprised infarct growth and edema. Although each was independently associated with ΔDWI, infarct growth had a more nuanced association with outcome. This somewhat unexpected finding might be attributable to the fact that the mRS scoring system may not discriminate differences in patients with smaller amounts of infarct growth, or that our power for detection was limited by sample size. Notably, a recent study evaluated changes in ASPECTS in an endovascular population and also found that large changes were predictive of poor outcome.26 Future work on ΔDWI may yield further insight into the relationships of infarct growth and swelling to ΔDWI and particularly whether there is a time-dependent effect of each. Validation in additional cohorts as well as prospective study will aid in more precisely defining their respective roles.

Our analysis also explored imaging determinants of swelling and found that baseline DWI volume and ADCr predicted swelling. The finding that larger strokes are associated with greater swelling is not surprising and is consistent with the malignant course that accompanies many large strokes.27 However, it is interesting that ADC signal intensity is associated with swelling, because ADC is sensitive to the early cytotoxic ischemia that develops minutes after stroke onset.13,14 Preclinical studies have demonstrated that the severity of the initial cytotoxic injury influences the volume of subsequent brain swelling in the days thereafter,28–30 a finding that is recapitulated here. Taking preclinical and clinical studies together, this raises the possibility that osmotic forces may be a primary contributor to brain swelling.31

We also explored the relationship with a marker of blood–brain barrier breakdown, FLAIRr.12,16 Our rationale for doing so was that physical leakage of fluid through degraded blood–brain barrier may contribute to brain swelling, a process sometimes termed hydrostatic edema.25 Although we cannot exclude a small association, we did not find any correlation with swelling in our study. As such, FLAIRr may serve as a risk marker for hemorrhagic transformation11,12 or to estimate the onset of hyperacute infarction,13 rather than risk of swelling.

Finally, the imaging biomarkers described here may prove useful for clinical application. First, ADCr may be used to identify patients at risk for clinically meaningful swelling. Patients with lower ADCr may warrant not only closer observation for secondary neurological decline, but also careful avoidance of factors that may exacerbate swelling, such as administration of hypertonic solutions. Second, ADCr could be used to select patients for inclusion in clinical trials targeting novel anti-edema therapies. Although prospective study would be necessary, it may also be of interest to determine whether ADCr could be used to select patients for osmotherapy treatment.

However, our data also highlight the potential challenges associated with the use of surrogate imaging markers in clinical trial design. Although strongly associated with 90-day neurological outcome, we show that ADWI is a composite marker for both swelling and infarct growth. Apportioning the total ΔDWI into swelling and infarct growth volumes may provide a more precise approach and provide greater usefulness as surrogate imaging markers. Our study has limitations. This was a retrospective analysis. However, it was performed in 2 cohorts with serial research brain MRIs and showed similar results. Nevertheless, the sample size was relatively small and included only moderate to severe infarction. It is not certain whether these data can be generalized to mild strokes with infarct volumes <10 mL or a National Institutes of Health Stroke Scale score <4. It is also possible that misclassification bias may exist in separating infarct growth and swelling, although we used conservative definitions to minimize this potential risk. The strengths of the study include the timing and frequency of brain MRI in 2 separate and well-defined study cohorts.

**Summary**

Taken together, these data demonstrate that brain edema measured on MRI is associated with poor outcome after moderate to severe stroke. Future prospective study is warranted to assess the potential causative role of edema in influencing outcome in this population.

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**Disclosures**

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**References**

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Brain edema predicts outcome after non-lacunar ischemic stroke

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Figure I. Method and quantitative time course for the stroke imaging metrics. (A) Method for generating the region of interest (ROI) corresponding to the stroke lesion and contralateral hemisphere. The lesion was first defined on diffusion weighted imaging (DWI), then transferred to the ADC maps to exclude cerebrospinal fluid (CSF) and applied to a co-registered FLAIR sequence. Stroke = red, CSF = aqua, Contralateral Hemisphere = green.
Figure II. Quantitative time course for stroke imaging metrics. The time course of (A) the change in lesional volume between baseline and each timepoint (ΔDWI), (B) FLAIR signal intensity ratio (FLAIRr), (C) the ADC signal intensity ratio (ADCr) is shown for each metric during the study period.
### Table I. Multivariable modeling of large infarct growth with poor outcome after stroke

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th></th>
<th>Model 2</th>
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<td>Adjusted OR</td>
<td>95% CI</td>
<td>P-value</td>
<td>Adjusted OR</td>
</tr>
<tr>
<td>Age</td>
<td>1.07</td>
<td>(1.02-1.14)</td>
<td>0.01</td>
<td>1.07</td>
</tr>
<tr>
<td>Admission glucose</td>
<td>4.00</td>
<td>(0.56-37.9)</td>
<td>0.17</td>
<td>4.31</td>
</tr>
<tr>
<td>Admission NIHSS</td>
<td>1.17</td>
<td>(1.01-1.38)</td>
<td>0.03</td>
<td>1.17</td>
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<tr>
<td>Admission DWI volume</td>
<td>4.42</td>
<td>(1.09-22.6)</td>
<td>0.04</td>
<td>4.25</td>
</tr>
<tr>
<td>Swelling</td>
<td>4.36</td>
<td>(1.14-18.3)</td>
<td>0.03</td>
<td>4.13</td>
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<tr>
<td>Infarct growth (ΔASPECTS ≥2)</td>
<td>1.65</td>
<td>(0.37-8.26)</td>
<td>0.51</td>
<td>-</td>
</tr>
<tr>
<td>Infarct growth (ΔASPECTS ≥3)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>7.05</td>
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