Fluid-Attenuated Inversion Recovery Hyperintensity Correlates With Matrix Metalloproteinase-9 Level and Hemorrhagic Transformation in Acute Ischemic Stroke

Ruchira Jha, MD; Thomas W. K. Battey, BA; Ly Pham, BA; Svetlana Lorenzano, MD, PhD; Karen L. Furie, MD; Kevin N. Sheth, MD; W. Taylor Kimberly, MD, PhD

Background and Purpose—Matrix metalloproteinase-9 (MMP-9) is elevated in patients with acute stroke who later develop hemorrhagic transformation (HT). It is controversial whether early fluid-attenuated inversion recovery (FLAIR) hyperintensity on brain MRI predicts hemorrhagic transformation (HT). We assessed whether FLAIR hyperintensity was associated with MMP-9 and HT.

Methods—We analyzed a prospectively collected cohort of acute stroke subjects with acute brain MRI images and MMP-9 values within the first 12 hours after stroke onset. FLAIR hyperintensity was measured using a signal intensity ratio between the stroke lesion and the corresponding normal contralateral hemisphere. MMP-9 was measured using enzyme-linked immunosorbent assay. The relationships between FLAIR ratio (FR), MMP-9, and HT were evaluated.

Results—A total of 180 subjects were available for analysis. Patients were imaged with brain MRI at 5.6±4.3 hours from last seen well time. MMP-9 blood samples were drawn within 7.7±4.0 hours from last seen well time. The time to MRI (r=0.17, P=0.027) and MMP-9 level (r=0.29, P<0.001) were each associated with FR. The association between MMP-9 and FR remained significant after multivariable adjustment (P<0.001). FR was also associated with HT and symptomatic hemorrhage (P=0.012).

Conclusions—FR correlates with both MMP-9 level and risk of hemorrhage. FLAIR changes in the acute phase of stroke may predict hemorrhagic transformation, possibly as a reflection of altered blood–brain barrier integrity.

Key Words: brain edema ■ brain ischemia ■ hemorrhage ■ magnetic resonance imaging ■ matrix metalloproteinases ■ stroke

T2 fluid-attenuated inversion recovery (FLAIR) hyperintensity has been associated with symptomatic intracerebral hemorrhage (sICH) in several studies; however, this finding has not been substantiated in some reports. The underlying basis for the increased T2 signal that comprises FLAIR hyperintensity is poorly understood, but may be secondary to vasogenic edema in the setting of blood–brain barrier (BBB) breakdown. The extent of BBB breakdown may determine the development of hemorrhagic transformation (HT).

Matrix metalloproteinase-9 (MMP-9) is a member of a family of zinc-dependent enzymes that compromises BBB integrity by degrading components of the tight junctions and extracellular matrix, and is thereby implicated in the development of cerebral edema and HT. Increased MMP-9 levels are associated with risk of HT in acute ischemic stroke in both experimental models and human subjects, both with and without thrombolysis.

Despite the potential connection to BBB dysfunction, a relationship between MMP-9 and FLAIR hyperintensity has not previously been reported. We hypothesized that FLAIR hyperintensity may serve as an imaging biomarker that reflects altered BBB integrity. The aim of this study was to assess the relationship between FLAIR hyperintensity, MMP, and HT after ischemic stroke. We also sought to develop a rapid bedside method for evaluating quantitative FLAIR ratio (FR) as a marker for assessing the risk for HT.

Methods

Patients

Subjects for this study participated in a prospective 2-center biomarker study of acute ischemic stroke as part of the Specialized Programs of Translational Research in Acute Stroke (SPOTRIAS) Network. The SPOTRIAS biomarker study enrolled consecutive patients ≥18 years between January 2007 and April 2010, who presented within 12 hours of symptom onset. The SPOTRIAS biomarker study enrolled consecutive patients ≥18 years between January 2007 and April 2010, who presented within 12 hours of symptom onset.
9 hours of symptom onset, and with symptoms consistent with ischemic stroke. For the current analysis, patients without a diffusion-weighted image (DWI) lesion or a lesion volume <5 mL, patients who did not have a T2 fluid-attenuated inversion recovery (FLAIR) sequence available for analysis or with poor technical quality, and those patients who did not have MMP levels were also excluded. Patients with stroke volume <5 mL were excluded because of the technical limitation of accurately measuring a FLAIR value in stroke lesions that did not span <1 axial slice, leading to the risk of volume averaging artifacts. Both subjects with and without intravenous thrombolysis were included because HT is a potential complication in all ischemic stroke. No subjects were treated with endovascular thrombolysis. All subjects or their healthcare proxy provided informed consent, and this study was approved by the local institutional review board.

**Imaging Analysis**

Imaging analyses were performed by trained readers blinded to all clinical and MMP data. The goal was to develop a reliable quantitative estimate of relative FLAIR hyperintensity that could be performed at the bedside. Using standard clinical imaging viewing software, 8 regions of interests (ROI) within the stroke lesion were outlined on the T2 FLAIR sequence using the following rule: 2 gray matter ROIs and 2 white matter ROIs each on 2 contiguous slices. The ROIs were mirrored to a similar location on the contralateral hemisphere, and the final FR was the average of these 8 values (Figure 1). After validating this method against a gold standard (AnalyzeDirect 11.0, seen in the online-only Data Supplement), we used it for the final analysis.

Two stroke neurologists (R.J. and W.T.K.) independently classified hemorrhagic transformation and symptomatic hemorrhage (sICH) using the European Cooperative Acute Stroke Study (ECASS) III criteria based on follow-up CT scan (n=119) or MRI (n=25) on imaging studies obtained 1.6±1.9 days after stroke onset. All cases were adjudicated by consensus. Four subjects had hemorrhage identified on MRI only, which is reported to be more sensitive than CT. Therefore, we also performed analyses with and without the subjects who had HT designated on MRI only.

**MMP Analysis**

Peripheral blood samples were collected in ethylenediaminetetraacetic acid-containing tubes, and plasma was separated from cellular material by centrifugation (1000g for 15 minutes) within 60 minutes of collection. Supernantant was aliquoted into cryo vials and frozen at −70°C (ethylenediaminetetraacetic acid plasma) until analysis. MMP-9 and MMP-2 analysis was performed using a commercially available enzyme-linked immunosorbent assay (R&D systems), according to the manufacturer instruction. The mean coefficient of variation for these assays is <5%.

**Statistical Analysis**

Descriptive statistics of baseline variables were performed and reported as mean±standard deviation (for normally distributed continuous data), median with interquartile range (IQR; for non-normal data), and proportions for binary data. Differences in continuous variables were compared using Student t test, Wilcoxon rank-sum test, or ANOVA, as appropriate. Categorical variables were compared using Fischer exact test or χ² test. Multivariate logistic regression models were developed with all variables with a univariate P value of <0.20 to determine the independent effects that were associated with FR and HT. Statistical significance was taken at a 2-sided P value of <0.05. Statistical analyses were performed with JMP Pro 10 software (SAS Institute, Cary, NC).

**Results**

The patient characteristics of the study cohort are shown in Table 1. The original cohort was designed to enroll both stroke and stroke mimics. Of 522 subjects, baseline MMP-9 values were available for 448 subjects. 50 subjects did not have an acute brain MRI performed, 68 subjects did not have an acute lesion visible on imaging, 29 did not have a T2 FLAIR sequence, and 151 subjects had a lesion volume <5 mL. The final FR cohort consisted of 180 subjects with an evaluable T2 FLAIR sequence.
and available MMP-9. There were no baseline differences in the demographics between the original cohort and that used for the final analysis, except for stroke severity (Table 1). Accordingly, the FR cohort had a higher National Institutes of Health Stroke Scale (NIHSS) score and a higher acute stroke volume (P < 0.01) compared with the original cohort, both of which were expected based on the selection criteria. The mean FR was 1.40±0.23 obtained from acute brain MRI that occurred at 5.6±4.3 hours from the last seen well time. On average, MMP-9 blood samples were collected 7.7±4.0 hours after the last seen well time. On the contrary, MMP-2, a related gelatinase that may also be upregulated in stroke,16,17 did not demonstrate an association with FR (Pearson r = −0.06, P = 0.42; Table 2).

FLAIR Ratio and MMP-9
Univariate associations with FR hyperintensity are shown in Table 2 (lefthand column). The time to MRI (Pearson r = 0.17, P = 0.027) and MMP-9 level (Pearson r = 0.29, P < 0.001; Figure I in the online-only Data Supplement) was associated with FR, but age, sex, intravenous (IV) tissue-type plasminogen activator (tPA) treatment, and DWI volume were not. We also found that MMP-9 elevation was associated with DWI volume (Pearson r = 0.15, P = 0.002) and IV tPA treatment (P = 0.012),8,10,14,15 but not with the time from stroke onset to the blood draw (P = 0.74). On the contrary, MMP-2, a related gelatinase that may also be upregulated in stroke,16,17 did not demonstrate an association with FR (Pearson r = −0.06, P = 0.42; Table 2).

Multivariate linear regression confirmed that MMP-9 was independently associated with FR hyperintensity (P < 0.001; Table 2 righthand column). Time from last seen well to MRI also remained significant (P = 0.01). The inclusion of additional

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<tr>
<th>Table 1. Characteristics of the Patients</th>
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<tr>
<th>Table 2. Univariate and Multivariate Factors Associated With FLAIR Ratio Hyperintensity</th>
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<tr>
<td><strong>Univariate Analysis of FLAIR Ratio</strong></td>
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<tr>
<td>β Coefficient*</td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td>Age</td>
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<tr>
<td>Sex (female)</td>
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<tr>
<td>IV tPA treatment (Y)</td>
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<tr>
<td>Time from last seen well to MRI, h</td>
</tr>
<tr>
<td>DWI volume</td>
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<tr>
<td>MMP-2</td>
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<tr>
<td>MMP-9</td>
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<p>| <strong>Multivariate Analysis of FLAIR Ratio</strong>                                              |</p>
<table>
<thead>
<tr>
<th>Adjusted β Coefficient*</th>
<th>95% CI</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Age</td>
<td>...</td>
<td>...</td>
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<tr>
<td>Sex (female)</td>
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<td>...</td>
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<tr>
<td>IV tPA treatment (Y)</td>
<td>...</td>
<td>...</td>
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<tr>
<td>Time from last seen well to MRI, h</td>
<td>0.010</td>
<td>(0.003 to 0.017)</td>
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<tr>
<td>DWI volume</td>
<td>...</td>
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<tr>
<td>MMP-2</td>
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<tr>
<td>MMP-9</td>
<td>0.162</td>
<td>(0.086 to 0.238)</td>
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*The β coefficient is the magnitude change in fluid-attenuated inversion recovery (FLAIR) ratio per unit or category. CI indicates confidence intervals; DWI, diffusion-weighted image; IV tPA, intravenous tissue-type plasminogen activator; and MMP, matrix metalloproteinase.
nonsignificant univariate factors in the model as potential confounders, including thrombolytic therapy, did not alter the independent association of MMP-9 with FR \((P<0.001)\).

**FLAIR Ratio and Hemorrhagic Transformation**

Previous studies have highlighted that pretreatment MMP-9 is associated with HT and symptomatic hemorrhage (sICH). Given the association of MMP-9 and FR, we hypothesized that FR may also correlate directly with HT and sICH. In our cohort, 29 patients exhibited HT (25 with hemorrhagic infarction and 4 with parenchymal hematomas). Figure 2A demonstrates that acute FR was elevated in those subjects who subsequently developed HT \((P=0.013)\). Because not all HT may be clinically relevant, we also evaluated the association of FR with symptomatic HT compared with sICH. Figure 2B demonstrates a stepwise increase in FR in patients with no hemorrhage \((1.38±0.22, n=115)\), compared with those with asymptomatic HT \((1.49±0.27, n=26)\) and those with sICH \((1.68±0.21, n=3; ANOVA, P=0.012)\).

We next evaluated previously reported predictors of HT in univariate logistic regression analysis (Table 3, lefthand column). Older age and increasing FR were associated with HT, and Admission NIHSS and IV tPA treatment demonstrated a trend toward increased risk of HT in the univariate analysis. MMP-9 level, admission blood glucose, and DWI volume did not. Additionally, a history of hypertension, diabetes mellitus, or stroke subtype were not associated with risk of HT \((P=0.36, P=0.13, P=0.41,\) respectively). Multivariate adjustment confirmed the independent effect of FR on HT \((P=0.014; Table 3, righthand column)\). In this multivariate model, IV tPA was also a significant predictor of HT \((P=0.018)\). The independent effect of FR \((P=0.014)\) remained regardless of which variables were included in the model.

Four patients were designated to have HT based solely on MRI: 2 had HI1 and the other 2 had HI2. Excluding these patients from the univariate analysis yielded similar results (see the online-only Data Supplement). Multivariate analysis of CT-defined HT demonstrated that FR again remained an independent predictor of HT \((\text{adjusted OR } 5.3, P=0.002)\) as did IV tPA treatment \((\text{adjusted OR } 5.3, P=0.008;\) see Table I in the online-only Data Supplement). Inspection of the receiver-operator characteristic curve identified the optimal FR threshold of 1.54 for the prediction of HT \((P=0.01)\). With this threshold, the sensitivity for HT was 0.48, the specificity 0.85, with a positive predictive value of 0.45 and a negative predictive value of 0.87.

### Discussion

The BBB is susceptible to dysfunction in the setting of ischemia, which is partly mediated by matrix metalloproteinases such as MMP-9. MMP-9 degrades the basal lamina and, when the disruption is severe enough, contributes to HT. The underlying physiological basis for FLAIR hyperintensity is poorly understood. Several theories have been explored including a blood oxygen level–dependent effect, temperature, and viscosity, although the anticipated influence on T2 prolongation for these factors is minor. More commonly, T2 prolongation is observed hours after stroke and is thought to be because of increasing water content in the ischemic tissue, representing vasogenic edema.

Although our analysis does not resolve the biophysical basis for FLAIR hyperintensity, nor supports a causal relationship between MMP-9 and FR, the correlation between the

### Table 3. Univariate and Multivariate Predictors of Hemorrhagic Transformation

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariate Analysis of HT</th>
<th>Multivariate Analysis of HT</th>
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<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age</td>
<td>1.03</td>
<td>1.00–1.07</td>
</tr>
<tr>
<td>Admission NIHSS</td>
<td>1.06</td>
<td>0.99–1.12</td>
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<tr>
<td>IV tPA treatment (Y)</td>
<td>2.06</td>
<td>0.80–5.34</td>
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<tr>
<td>MMP-9</td>
<td>1.48</td>
<td>0.58–3.69</td>
</tr>
<tr>
<td>Admission glucose</td>
<td>5.79</td>
<td>0.58–54.8</td>
</tr>
<tr>
<td>DWI volume</td>
<td>1.9</td>
<td>0.74–4.91</td>
</tr>
<tr>
<td>FLAIR ratio</td>
<td>7.97</td>
<td>1.56–47.4</td>
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\(\text{FlAIR}\) fluid-attenuated inversion recovery; \(\text{HIT}\), hemorrhagic transformation; \(\text{IV tPA}\), intravenous tissue-type plasminogen activator; \(\text{MMP}\), matrix metalloproteinase; \(\text{NIHSS}\), the National Institutes of Health Stroke Scale; and \(\text{OR}\), odds ratio.
Our study has 3 primary findings that cumulatively strengthen the hypothesis that FLAIR hyperintensity is associated with impairment of BBB integrity: (1) a higher FR is correlated with elevated MMP-9 levels, (2) elevated FR is correlated with HT, and (3) there is a progressive increase in FR along the spectrum of patients without HT, asymptomatic HT, and sICH. This proposed model suggests that vasogenic edema and HT represent a spectrum of BBB impairment, and that FLAIR hyperintensity is correlated (either directly or indirectly) with this phenomenon.

Some of the previously reported predictors of HT were not replicated in our cohort, including DWI volume and MMP-9 level. Differences in the cohort design and the timing of the blood sampling may account for these discrepancies. Large DWI volumes in the setting of thrombolysis are associated with increased risk of HT. Our cohort consisted of few patients with this size stroke, although all 3 patients with stroke lesions >100 mL who developed HT were also treated with IV thrombolysis. Intriguingly, MMP-9 level did not predict HT in our cohort. However, previous studies reporting this association measured pretreatment MMP-9 at early time points (0–3 hours). In contrast, our cohort contained patients with MMP-9 blood samples drawn after IV tPA treatment, which itself can influence MMP-9 level. Moreover, our cohort also included patients that did not receive thrombolysis, which could further account for the discrepant findings.

Nevertheless, our data demonstrate that FR is associated with HT, which occurs in the setting of extensive physical breakdown of the BBB, allowing erythrocytes to extravasate into the brain parenchyma. Several studies have reported a similar finding, although this has not been replicated in every study. Differences in the timing of MRI, qualitative versus quantitative measurement of FLAIR hyperintensity, or differences in the definition of hemorrhagic transformation may account for the discrepancy. For example, 38% of patients in our cohort were imaged >6 hours from last seen well time, which is in contrast to earlier imaging time points in other studies. It is also important to note that HT and sICH are uncommon, and the relatively small sample sizes in previous studies may have limited the power to detect an association. Whether or not FLAIR hyperintensity could be ultimately used to guide thrombolytic treatment is uncertain. Future prospective studies with a larger sample size would be necessary to establish a relationship definitively between FR and sICH. Nevertheless, patients with elevated FR may warrant closer observation for subsequent HT.

Given our finding that FLAIR hyperintensity reflects circulating MMP-9 level, FR may also serve as a useful imaging biomarker for future clinical trials designed to prevent HT. In this context, lower FR and MMP-9 were both observed in an exploratory analysis in the glyburide advantage in malignant edema and stroke (GAMES)-Pilot trial, a finding that is concordant with animal and human retrospective studies. Although a double-blind, placebo-controlled trial is required to validate any candidate in preventing HT, our current work highlights the potential use of imaging biomarkers for evaluating a candidate pharmaceutical agent.

The strengths of this study include a systematic collection of consecutive patients with stroke from 2 centers. FLAIR hyperintensity was measured quantitatively through a rapid bedside method, rather than qualitatively. This is also the largest cohort to our knowledge with imaging and plasma sampling obtained within an average of 2.9 hours from each other.

There are several limitations. This was a retrospective analysis and, in spite of the relatively large sample size, the number of patients with sICH was low. Our findings may not be generalizable to all patients with stroke because we excluded subjects with small infarcts <5 mL, technical reasons, and because there may be a selection bias based on the ability to tolerate an acute MRI. Moreover, the use of FR is not applicable to centers where MRIs may not be routinely obtained in the acute setting of stroke evaluations.

Finally, although we and others have found an association with FR and HT, our data do not provide sufficient specificity to propose the use of FR to exclude patients for thrombolysis who would otherwise meet current criteria for IV thrombolysis in the 0 to 4.5 hour time window. On the contrary, in those patients with an unclear time of stroke onset, FLAIR hyperintensity has been proposed as potentially representing a tissue clock. Our data offer a new dimension to the interpretation of this signal, suggesting that FLAIR hyperintensity is associated with BBB breakdown and risk for HT. Further prospective studies are warranted to evaluate this relationship and determine whether it may be used to guide treatment decisions.

Conclusions
We report a novel relationship between acute FR and MMP-9 levels. This finding in combination with the association with HT suggests that acute FR may be a bedside radiographic marker that is associated with BBB integrity. Future studies comparing FLAIR hyperintensity with other markers of BBB integrity such as HARM (hyperintense acute reperfusion marker) or evaluating the prognostic value of FR in predicting symptomatic hemorrhagic transformation are warranted.

Acknowledgments

Sources of Funding
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Disclosures
Dr Lorenzano discloses a consultant relationship with Boehringer Ingelheim. Drs Sheth and Kimberly disclose a research grant glyburide advantage in malignant edema and stroke-remedy pharmaceuticals (GAMES-RP) trial from Remedy Pharmaceuticals, Inc.

References


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The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/45/4/1040

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SUPPLEMENTAL MATERIAL

FLAIR hyperintensity correlates with MMP-9 level and hemorrhagic transformation in acute ischemic stroke

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Karen L. Furie, MD, Kevin N. Sheth, MD, and W. Taylor Kimberly, MD, PhD
Supplemental Methods

Gold standard determination of FLAIR signal intensity ratio

In order to assess the accuracy of the rapid bedside method for generating a FLAIR ratio value, we compared the bedside technique to FLAIR ratio values determined using imaging analysis software ("gold standard"). For a training set of thirty MRI scans, we used AnalyzeDirect 11.0 (AnalyzeDirect, Overland Park, KS) to outline the stroke lesion and the normal contralateral hemisphere separately on the DWI sequence, with cerebrospinal fluid spaces greater than 2mm excluded. The T2 FLAIR sequence was co-registered to the DWI and the outlines were applied to the FLAIR sequence. The signal intensity ratio was developed by normalizing the average FLAIR intensity within the stroke lesion to that of the contralateral hemisphere (FLAIR ratio, FR). The exclusion of periventricular white matter hyperintensities did not alter the final signal intensity ratio. The intraclass correlation coefficient of this method was 0.84, and Bland-Altman analysis did not reveal a systematic bias.

Supplemental References

Supplemental Figure I. Scatter plot of the association between FLAIR ratio and MMP-9 level. Because MMP-9 was skewed, the values were log transformed prior to correlation analysis.
Supplemental Table I: Univariate and Multivariate predictors of hemorrhagic transformation as determined by CT

<table>
<thead>
<tr>
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<th>Univariate analysis of HT (CT determined)</th>
<th>Multivariate analysis of HT (CT determined)</th>
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<tr>
<td></td>
<td>OR</td>
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<td>Age</td>
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<td>0.99-1.06</td>
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<td>IV tPA treatment (Y)</td>
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<td>1.1-8.0</td>
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<td>MMP-9</td>
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<td>DWI volume</td>
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<td>0.68-5.0</td>
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<tr>
<td>FLAIR ratio</td>
<td>6.23</td>
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