Immediate Changes in Stroke Lesion Volumes Post Thrombolysis Predict Clinical Outcome

Marie Luby, PhD; Steven J. Warach, MD, PhD; Zurab Nadareishvili, MD, PhD; José G. Merino, MD, MPhil

Background and Purpose—We hypothesize that reversal in diffusion-weighted imaging (DWI) volume at 24 hours predicts favorable clinical outcome only if accompanied by immediate reperfusion. Our aim was to quantify the immediate DWI and mean transit time changes at 2 and 24 hours after intravenous tissue-type plasminogen activator to evaluate the effect of reperfusion and DWI change on outcome.

Methods—Patients were selected from the Lesion Evolution in Stroke and Ischemia On Neuroimaging Project if they had an acute MRI with evaluable DWI and perfusion-weighted imaging, were treated with standard intravenous tissue-type plasminogen activator, had post-thrombolysis MRI with evaluable DWI and perfusion-weighted imaging at 2 and 24 hours and had follow-up fluid attenuated inversion recovery MRI at discharge through 90 days. A reader measured the DWI, mean transit time, and fluid attenuated inversion recovery volumes using a validated technique. A vascular neurologist scored the National Institutes of Health Stroke Scale at admit, 2, and 24 hours and the modified Rankin Scale at discharge, 5, 30, and 90 days. Favorable clinical outcome was defined as modified Rankin Scale of 0 or 1.

Results—Seventy-one patients met the study criteria with mean (±SD) age of 71.6 (±16.4) years, 58% women, median admit National Institutes of Health Stroke Scale 9 (interquartile range, 4–18), median onset to triage 45 minutes (30–65), and median first MRI to intravenous tissue-type plasminogen activator 47 minutes (39–59). In binary multiple logistic regression analysis, younger age (odds ratio, 1.165; \( P = 0.014; \) 95% confidence interval [CI], 1.031–1.316), lower admit National Institutes of Health Stroke Scale (odds ratio, 1.221; \( P = 0.012; \) 95% confidence interval, 1.045–1.427), decrease in mean transit time volume at 2 hours (odds ratio, 1.021; \( P = 0.031; \) 95% confidence interval, 1.002–1.040), and decrease in DWI volume at 24 hours (odds ratio, 1.173; \( P = 0.027; \) 95% confidence interval, 1.018–1.351) were significant predictors of favorable clinical outcome.

Conclusions—Reversal of the DWI volume at 24 hours because of immediate reperfusion in patients post thrombolysis is predictive of favorable clinical outcome.

Key Words: perfusion imaging ■ thrombolytic therapy

Several studies exploring MRI variables and their ability to predict clinical or imaging outcome post thrombolysis in patients with acute ischemic stroke have been reported.\(^1\)\(^-\)\(^6\) Some studies suggest that diffusion-weighted imaging (DWI) lesion reversal occurs with reperfusion.\(^7\)\(^-\)\(^8\) Studies investigating the change of the DWI volume after thrombolysis have demonstrated a consistent correlation with clinical outcome.\(^9\) Reperfusion and the resulting size of the DWI lesion post thrombolysis are potential markers of therapeutic efficacy and can be predictive of favorable clinical outcome.\(^11\)\(^,\)\(^12\) The EchoPlanar Imaging Thrombolytic Evaluation Trial (EPITHET),\(^13\) Diffusion and perfusion imaging Evaluation For Understanding Stroke Evolution (DEFUSE),\(^14\)\(^,\)\(^15\) and Desmoteplase in Acute Ischemic Stroke Trial (DIAS)\(^16\) studies established the feasibility and use of imaging mismatch as the penumbral target for therapy. However, the measurement of stroke lesions, the amount of acute mismatch, and their change across time are still problematic because of the dynamic evolution of stroke lesions, technical and quality limitations in the acquisition, and limited real-time processing of DWI and perfusion-weighted imaging (PWI) in the acute stroke setting. Further understanding of the immediate changes of the ischemic and perfusion lesions is necessary to evaluate the evaluation of acute mismatch and its potential as a therapeutic target and predictor of clinical outcome.

The objective of this study was to quantify the DWI and PWI changes at 2 and 24 hours after intravenous tissue-type plasminogen activator (tPA) to evaluate the effect of early reperfusion and DWI lesion decrease on clinical outcome measured as latest available modified Rankin Scale from discharge up to 90 days. Our hypothesis is that an early decrease in DWI volume at 24 hours associated with immediate reperfusion predicts favorable clinical outcome.

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Methods

Patients
This study uses data from the Lesion Evolution in Stroke and Ischemia On Neuroimaging (LESION1) project, which enrolled consecutive patients with an admission diagnosis of acute ischemic stroke or transient ischemic attack seen between August 1999 and October 31, 2009, by the National Institutes of Health Stroke Team at Suburban Hospital in Bethesda, MD, and the Medstar Washington Hospital Center in Washington DC who met the following criteria: (1) screened with MRI within 24 hours of witnessed stroke onset and had an admission National Institutes of Health Stroke Scale (NIHSS) score $\geq 3$ or (2) had a acute MRI before and received an acute intervention. The appropriate ethics and institutional review boards approved the study. For this study, patients were included from the LESION1 project if they (1) had an acute MRI with both evaluable and positive DWI and PWI, excluding lacunar strokes, (2) were treated with standard intravenous tPA, (3) had post-thrombolysis MRI with evaluable DWI and PWI at 2 or 24 hours, and (4) had fluid attenuation inversion recovery (FLAIR) at follow-up including discharge through 90 days.

Clinical Assessments
Vascular neurologists blinded to the lesion volume measurements examined all patients at every imaging time point. The primary outcome was functional status at 3 months (with last observation carried forward when the 3-month assessment was not available) using 2 cut-offs that are common in clinical trials: (1) favorable (modified Rankin Scale, 0–1) and (2) unfavorable (modified Rankin Scale 22) outcome.

Imaging Assessments
Vascular neurologists blinded to the clinical assessments and lesion volume measurements including reperfusion status examined all patients at the acute MRI for the site of vessel occlusion and recanalization status at 2 and 24 hours. The recanalization status was reported as complete, partial, or none. The available MR angiography imaging series were reviewed to determine recanalization status.

Imaging Series
The MR imaging protocol used in this study has been published. MRI was performed using 1.5T (Twinspeed, General Electric) or 3T (Achieva, Philips) clinical scanners. The DWI was a spin-echo planar series using either 40-3.5-mm-thick or 20-7-mm-thick contiguous axial oblique slices with $b=0$ and $b=1000$ s/mm$^2$, trace or isotropically weighted, repetition time/echo time (TR/TE) $=6000$ to $9000/72$ to 90 ms, acquisition matrix of $128 \times 128$ and $256 \times 256$, and 22 to 24 cm field of view. The FLAIR was a high-resolution series with TR/TE=9000/92 to 146 ms, inversion time=2200 ms, acquisition matrix of $256 \times 128$ and $256 \times 256$, using either 66-2-mm-thick or 20-7-mm-thick contiguous axial oblique slices and 24 cm field of view. The PWI was a dynamic susceptibility contrast series. The parameters for the PWI gradient-echo planar series included 20 contiguous axial oblique slices with single-dose gadolinium contrast injection of 0.1 mmol/kg of gadolinium (gadolinium–diethylenetriamine pentaacetic acid (DTPA); Magnevist; Bayer Schering Pharma) through a power injector using 25 to 40 phase measurements, TR/TE=1500 to 2200/45 ms, acquisition matrix of 64x64, 128x128, and 256x256, 7-mm-slice thickness, and 22 to 24 cm field of view. The mean transit time (MTT) maps were calculated as the first moment of the time concentration curves divided by the 0th moment with no arterial input correction or deconvolution. Only MTT maps were used for the perfusion measurements and reperfusion analysis. The DWI, FLAIR, and PWI series were acquired and colocalized over the entire brain with a superior to inferior coverage of 14 cm. The MR angiography acquired was an intracranial 3-dimensional time of flight centered in the region of the Circle of Willis using TR/TE=39/6.9 ms, flip angle=25°, matrix of $224 \times 160$, 24x18 cm field of view for an in-plane resolution of $1 \times 1$ mm, reconstructed to 92 axial images, 1.6-mm thick with a 0.8-mm overlap.

Lesion Volume Analysis
The rater reliability statistics for the planimetric method were published elsewhere. Briefly, the validated watershed-based method involved the semiautomated segmentation of the lesion areas on a slice-by-slice basis with the user placing seed points in these areas followed by user-driven editing using Cheshire (Boulder, CO). The DWI, MTT, and FLAIR volumes were automatically calculated in Cheshire using the planimetric method by multiplying the respective total lesion area by the slice thickness. DWI reversal was defined as reduction of $\geq 5$ mL of the follow-up DWI compared with the acute DWI volume. Complete reperfusion was defined as $\geq90\%$ reduction of the follow-up MTT volume.

Statistical Analysis
The following analyses were performed: (1) clinical and imaging characteristics of all 71 study patients were tabulated. Values were reported as mean (±SD), percentage, or median (interquartile range, 25–75) where appropriate. Spearman correlation coefficients were calculated with significant relationships reported. Nonparametric tests (Mann–Whitney U or $\chi^2$ test) were performed to compare the distributions or classifications of variables according to groups defined as patients with favorable versus unfavorable clinical outcome.

For multivariable analysis, significant variables, $P<0.05$, were entered in binary logistic regression to identify predictors of favorable clinical outcome. The associated sensitivity and specificity values were calculated for the significant predictors.

Linear regression was performed to investigate prediction of follow-up FLAIR volume. IBM SPSS Statistics v19.0 was used for all statistical analyses performed.

Results

Clinical and Imaging Characteristics
Seventy-one patients met the study criteria with mean (±SD) age of 71.6 (±16.4) years; 58% were women, the median admit NIHSS was 9 (interquartile range, 4–18), the median onset to triage was 45 minutes (30–65), median onset to acute MRI was 81 minutes (66–108), and median time from start of acute MRI to intravenous tPA was 47 minutes (39–59; Table). Sixty-one (86%) patients had anterior circulation and 10 (14%) had posterior circulation strokes. Patients had the following vessel occlusion sites: anterior cerebral artery 1% (1/71), basilar 1% (1/71), extracranial internal carotid artery 11% (8/71), intracranial internal carotid artery 8% (6/71), M1 25% (18/71), M2 13% (9/71), posterior cerebral artery 4% (3/71), vertebral 1% (1/71), none 32% (23/71), and not evaluable 1% (1/71). Twelve patients (17%), 10 (83%) anterior circulation, and 2 (17%) with posterior circulation stroke had immediate DWI reversal at 2 hours, and of these, 6 (8%) had sustained reversal at 24 hours. Patients at 2 and 24 hours, 13% (n=9/71) and 27% (n=19/71), respectively, had complete reperfusion. For the 9 patients with complete reperfusion at 2 hours, 7 (78%) were anterior circulation and 2 (22%) were posterior circulation strokes. For the 19 patients with complete reperfusion at 24 hours, 16 (84%) were anterior circulation and 3 (16%) were posterior circulation strokes. Patients at 2 and 24 hours, 25% (n=18/71) and 31% (n=22/71), respectively, had complete recanalization. Patients at 2 and 24 hours, 17% (n=12/71) and 15% (n=11/71), had partial recanalization, whereas 21% (15/71) and 18% (13/71) had no recanalization. Recanalization status was not applicable in cases with no vessel abnormality or not evaluable for 37% (26/71) and 35% (25/71) patients, respectively, at 2 and 24 hours. Figure 1 compares the DWI and PWI lesion volumes.
Table. All Patients vs Patients Classified With Favorable Clinical Outcome (mRS, 0 or 1) vs Unfavorable Clinical Outcome (mRS≥2)

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (n=71)</th>
<th>Favorable Clinical Outcome (n=30)</th>
<th>Unfavorable Clinical Outcome (n=41)</th>
<th>Significance, P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (±SD), y</td>
<td>71.6 (±16.4)</td>
<td>63.4 (±17)</td>
<td>77.6 (±13.2)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Sex (women), n (%)</td>
<td>41 (58%)</td>
<td>12 (40%)</td>
<td>29 (71%)</td>
<td>0.01*</td>
</tr>
<tr>
<td>Admit NIHSS [IQR, 25–75]</td>
<td>9 [4 to 18]</td>
<td>5 [2 to 11]</td>
<td>17 [7 to 24]</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Onset [IQR, min]</td>
<td>45 [30 to 65]</td>
<td>46 [35 to 65]</td>
<td>40 [25 to 65]</td>
<td>0.096</td>
</tr>
<tr>
<td>Change in mRS at 24 h [IQR], mL</td>
<td>10.5 [0.5 to 45.9]</td>
<td>1.8 [0.0 to 12.6]</td>
<td>37.9 [8.3 to 65.2]</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Acute DWI volume [IQR], mL</td>
<td>8.4 [2.1 to 51.5]</td>
<td>4.3 [1.1 to 17.0]</td>
<td>18.1 [3.2 to 63.1]</td>
<td>0.021*</td>
</tr>
<tr>
<td>Acute MTT volume [IQR], mL</td>
<td>128.6 [27.2 to 206.9]</td>
<td>63.0 [0.3 to 156.3]</td>
<td>152.0 [55.1 to 236.7]</td>
<td>0.013*</td>
</tr>
<tr>
<td>Acute mismatch volume [IQR], mL</td>
<td>93.4 [6.1 to 180.6]</td>
<td>40.4 [0.0 to 146.6]</td>
<td>129.5 [11.7 to 210.1]</td>
<td>0.077</td>
</tr>
<tr>
<td>Change in NIHSS at 2 h [IQR]</td>
<td>−2 [−3 to 0]</td>
<td>−2 [−6 to 0]</td>
<td>−1 [−2 to 0]</td>
<td>0.213</td>
</tr>
<tr>
<td>Change in DWI volume at 2 h [IQR], mL</td>
<td>−26.4 [−58.9 to 4.4]</td>
<td>−27.4 [−93.4 to 0]</td>
<td>−2.7 [−46.6 to 27.8]</td>
<td>0.028*</td>
</tr>
<tr>
<td>Change in MTT volume at 2 h [IQR], mL</td>
<td>−2.7 [−10.1 to 5.1]</td>
<td>−2.7 [−10.1 to 5.1]</td>
<td>−2.7 [−10.1 to 5.1]</td>
<td>0.014*</td>
</tr>
<tr>
<td>Complete (≥90%) reperfusion at 2 h (%)</td>
<td>19 (27%)</td>
<td>12 (40%)</td>
<td>17 (41%)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Complete recanalization at 2 h (%)</td>
<td>9 (13%)</td>
<td>7 (13%)</td>
<td>11 (27%)</td>
<td>0.74</td>
</tr>
<tr>
<td>Change in NIHSS at 24 h [IQR]</td>
<td>−2 [−6 to 0]</td>
<td>−2 [−8 to −1]</td>
<td>−1 [−4 to 0]</td>
<td>0.027*</td>
</tr>
<tr>
<td>Change in DWI volume at 24 h [IQR], mL</td>
<td>5.1 [0.0 to 31.2]</td>
<td>0.5 [−1.7 to 9.1]</td>
<td>19.0 [1.1 to 73.1]</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Change in MTT volume at 24 h [IQR], mL</td>
<td>−43.8 [−133.4 to −5.4]</td>
<td>−68.7 [152.9 to −27.2]</td>
<td>−41.4 [−115.7 to 2.0]</td>
<td>0.108</td>
</tr>
<tr>
<td>Complete (≥90%) reperfusion at 24 h (%)</td>
<td>19 (27%)</td>
<td>12 (40%)</td>
<td>7 (17%)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Complete recanalization at 24 h (%)</td>
<td>22 (31%)</td>
<td>9 (30%)</td>
<td>13 (32%)</td>
<td>0.879</td>
</tr>
<tr>
<td>Follow-up mRS [IQR]</td>
<td>2 [0 to 5]</td>
<td>0 [0 to 1]</td>
<td>4 [3 to 6]</td>
<td>...</td>
</tr>
<tr>
<td>Follow-up FLAIR volume at 5 to 90 days [IQR, mL]</td>
<td>0.01 [−2.9 to 15.5]</td>
<td>−0.7 [−8.3 to 4.3]</td>
<td>9.7 [−3.6 to 36.0]</td>
<td>0.011*</td>
</tr>
<tr>
<td>Change in follow-up FLAIR volume [IQR, mL]</td>
<td>−0.7 [−8.3 to 4.3]</td>
<td>9.7 [−3.6 to 36.0]</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

DWI indicates diffusion-weighted imaging; FLAIR, fluid attenuated inversion recovery; IQR, interquartile range; IV tPA, intravenous tissue-type plasminogen activator; mRS, modified Rankin Scale; MTT, mean transit time; and NIHSS, National Institutes of Health Stroke Scale.

*Significance is 0.05.

Discussions

The major finding of this study is that, in addition to age and acute NIHSS score, early reperfusion at 2 hours and a sustained decrease in DWI lesion volume at 24 hours are independent predictors of favorable clinical outcome after thrombolysis. This is the first study to our knowledge that the specific relationship between immediate reperfusion at 2 hours and the sustained DWI lesion volume decrease at 24 hours for prediction of favorable clinical outcome has been identified. Prior studies have shown separately that DWI reversal and reperfusion and findings have significant clinical implications across all time points for all patients versus the classification of patients with favorable clinical outcome (n=30) versus the patients with unfavorable clinical outcome (n=41).

The univariate comparison of variables according to favorable versus unfavorable clinical outcome is reported in the Table. Younger, male, lower admit NIHSS, smaller acute DWI and MTT volumes, decrease in DWI and MTT volumes at 2 and 24 hours, and decrease in FLAIR volume from 5 to 90 days were significantly associated with favorable clinical outcome. In binary multiple logistic regression analysis, younger age (per year decrease; OR, 1.102; P=0.005; 95% CI, 1.03–1.18), admit NIHSS (per point decrease; OR, 1.136; P=0.02; 95% CI, 1.02–1.264), and decrease in DWI volume at 24 hours (OR, 1.221; P=0.014; 95% confidence interval [CI], 1.031–1.316), lower admit NIHSS (per point decrease; OR, 1.126; P=0.008; 95% CI, 1.032–1.23) were significant predictors of favorable clinical outcome. Interestingly, combination of younger age (per year decrease; OR, 1.111; P=0.001; 95% CI, 1.04–1.182) with decrease in DWI volume at 24 hours (OR, 1.128; P=0.004; 95% CI, 1.04–1.224) yielded the best prediction of favorable clinical outcome (sensitivity of 81%, specificity of 88%) compared with the model with age and admit NIHSS (sensitivity of 68%, specificity of 72%).

Among the 43 patients with acute DWI ≥5 mL, those with a decrease in DWI volume at 2 hours ≥5 mL were more likely than those with no decrease to have a favorable outcome with modified Rankin Scale 0 to 1 (60% versus 18%; P=0.014). Among the 53 patients with an acute MTT ≥5 mL, 42 (79%) had a decrease in MTT lesion volume ≥7 mL and 11 (21%) had an increase or no change (P<0.001) at 24 hours. A higher proportion of patients with reperfusion at 24 hours had a favorable outcome (45% versus 0%; P=0.002; Figure 2). Using linear regression, 24-hour DWI volume was highly correlated with follow-up FLAIR volume (P<0.01; R²=0.675).
indicating the importance of acute multimodal MRI in evaluation of efficacy of thrombolytic therapy. The percentage of thrombolytic-treated patients, ≈40%, with complete reperfusion is also consistent with prior studies. The study has several strengths. The imaging acquisition and analysis are comprehensive because it includes prethrombolysis DWI and PWI, both 2 and 24 hours post thrombolysis and chronic FLAIR imaging. Comparable studies have included imaging protocols at prethrombolysis and 2 or 24 hours, but not both immediate post-thrombolysis time points and with limited or no PWI data. Furthermore, the relationship of the chronic FLAIR imaging for infarct growth relative to reperfusion and the 24-hour DWI volume is demonstrated. However, the additional imaging data and the range of lesion volumes in this study provide further insight into the specific acute mismatch volume and subsequent imaging changes characteristic of patients with favorable clinical outcome post thrombolysis. In all study patients, immediate reperfusion at 2 hours and subsequent decrease in DWI volume at 24 hours in patients post thrombolysis is the imaging changes most predictive of favorable clinical outcome. For example, in patients with a substantial acute DWI lesion, defined by >5 mL, the decrease of DWI volume at 2 hours post thrombolysis is a significant predictor favorable clinical outcome. In patients with any reperfusion, the decrease of NIHSS and MTT volume at 24 hours post thrombolysis are significant predictors of favorable clinical outcome.

The study also has some limitations. Although acute primary vessel involvement and recanalization status were assessed on MR angiography across the time points, the analysis was limited. The recanalization categorization was simply scored as complete, partial, or none and specifics on proximal versus distal site of occlusion, Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification, and collateral circulation data were not captured. In this study, reperfusion but not recanalization was a significant predictor of favorable outcome. One possible explanation for this finding was the relatively low number of patients with complete recanalization. Furthermore, the validated measurement technique of lesion volumes in this study is time consuming and is not applicable to real-time treatment decision making in the acute stroke clinical setting. An untreated patient group for comparison purposes was not included in this study because of the limited imaging data at follow-up for these patients. Therefore, the immediate lesion volume changes and their impact on clinical outcome seen in this intravenous tPA–treated patient population are not translatable to an untreated patient population. However, the acute mismatch volumes are applicable to an untreated patient population. Although not statistically significant, the patients with a favorable outcome had a much smaller median acute mismatch volume compared with those with an unfavorable outcome (Table). The differences in acute DWI and MTT volumes between the favorable and unfavorable outcome patients support the concept of an imaging profile of patient that will most likely benefit from thrombolysis, patients with smaller DWI lesion volumes, and significant MTT lesion volumes that do not exceed a certain threshold. Furthermore, the clinical use of the immediate follow-up DWI and PWI in patients treated with thrombolysis is demonstrated to gauge the attenuation of the acute DWI lesion growth and the coincident reperfusion. The advantage of paired DWI and PWI at follow-up is evident (Figure 2) as patients with similar acute imaging profiles may have different follow-up imaging changes and resulting clinical outcome.

Figure 1. Median diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI) lesion volumes from baseline, 2- to 24-hour time points, fluid attenuated inversion recovery lesion volume from chronic time points for patients with favorable clinical outcome (blue lines) vs unfavorable clinical outcome (red lines). Median mismatch lesion volumes at baseline are included (blue dot vs red dot).

Figure 2. Patient (top row), 47-year-old male, with admit National Institutes of Health Stroke Scale (NIHSS) 4, partial reperfusion (71% reduction) with complete recanalization at 2 hours, and complete reperfusion and recanalization at 24 hours with 50% reduction in diffusion-weighted imaging (DWI) volume by 24 hours and outcome modified Rankin Scale (mRS)=1. Patient (bottom row), 74-year-old female, with admit NIHSS 26, partial reperfusion (24% reduction) with no recanalization at 2 hours, and no change in mean transit time (MTT) volume with no recanalization at 24 hours with significant growth in DWI volume by 24 hours with outcome mRS=6.
outcomes. Finally, the application of acute and immediate follow-up DWI and PWI in testing new thrombolytics is another advantage because of the smaller number of patients needed to compare the new thrombolytic and its effects on DWI lesion growth and immediate reperfusion with responses of standard intravenous tPA in this study and others.8–10 A future study is in progress to measure the immediate changes in lesion volumes in an untreated population and to compare the clinical and imaging variables using the same favorable and unfavorable clinical outcome definitions.

In conclusion the immediate changes in lesion volume, specifically immediate reperfusion and corresponding DWI reversal, are predictive of favorable clinical outcome. The role of recanalization needs further investigation. This study supports the usage of multimodal MRI pre and post thrombolysis for understanding the relationship between immediate lesion change and its impact on long-term clinical outcome. It provides a cohort of data on standard intravenous tPA–treated patients that may be used for comparison in future imaging-based stroke clinical trials.

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None.

**References**
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