Perihematomal Edema Is Greater in the Presence of a Spot Sign but Does Not Predict Intracerebral Hematoma Expansion

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for the PREDICT/Sunnybrook ICH CTA Study Group

Background and Purpose—Perihematomal edema volume may be related to intracerebral hemorrhage (ICH) volume at baseline and, consequently, with hematoma expansion. However, the relationship between perihematomal edema and hematoma expansion has not been well established. We aimed to investigate the relationship among baseline perihematomal edema, the computed tomographic angiography spot sign, hematoma expansion, and clinical outcome in patients with acute ICH.

Methods—Predicting Hematoma Growth and Outcome in Intracerebral Hemorrhage Using Contrast Bolus CT (PREDICT) was a prospective observational cohort study of ICH patients presenting within 6 hours from onset. Patients underwent computed tomography and computed tomographic angiography scans at baseline and 24-hour computed tomography scan. A post hoc analysis of absolute perihematomal edema and relative perihematomal edema (absolute perihematomal edema divided by ICH) volumes was performed on baseline computed tomography scans (n=353). Primary outcome was significant hematoma expansion (>6 mL or >33%). Secondary outcomes were early neurological deterioration, 90-day mortality, and poor outcome.

Results—Absolute perihematomal edema volume was higher in spot sign patients (24.5 [11.5–41.8] versus 12.6 [6.9–22] mL; P<0.001), but it was strongly correlated with ICH volume (r=0.905; P<0.001). Patients who experienced significant hematoma expansion had absolute perihematomal edema volume (18.4 [10–34.6] versus 11.8 [6.5–22] mL; P<0.001) but similar relative perihematomal edema volume (1.09 [0.89–1.37] versus 1.12 [0.88–1.54]; P=0.400). Absolute perihematomal edema volume and poorer outcomes were higher by tertiles of ICH volume, and perihematomal edema volume did not independently predict significant hematoma expansion.

Conclusions—Perihematomal edema volume is greater at baseline in the presence of a spot sign. However, it is strongly correlated with ICH volume and does not independently predict hematoma expansion. (Stroke. 2016;47:350-355.)

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Key Words: computed tomographic angiography ■ edema ■ hematoma expansion ■ intracerebral hemorrhage ■ outcome ■ spot sign

Intracerebral hemorrhage (ICH) initiates a secondary injury cascade inducing perihematomal edema development within 3 hours from symptom onset.1 Perihematomal edema increases over time by ≈100% of absolute volume within the first 24 hours.2 However, the relationship among perihematomal edema, ICH volume, and hematoma expansion has not been well established.

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Some studies have suggested that baseline ICH volume could be related to perihematomal edema volume during the first hours.³,⁴ Conversely, another study did not find any relationship between perihematomal edema volume and ICH volume or hematoma expansion.² Moreover, because of the different timing of hematoma and edema enlargement, the potential relationship between perihematomal edema and ICH volumes at baseline may vary depending on the time from symptom onset to baseline computed tomography (CT) scan. Both initial ICH volume and hematoma expansion have been shown to be determinants of poor outcome.⁸,⁹ yet the influence of baseline perihematomal edema on clinical outcome remains controversial.¹⁰–¹⁴

The main objective of the present study was to determine the relationship among baseline perihematomal edema, the computed tomographic angiography (CTA) spot sign, and hematoma expansion in patients with acute ICH. We hypothesized that a small amount of perihematomal edema relative to ICH may suggest either a early time point from ICH onset or actively bleeding ICH and, therefore, have a high likelihood of both CTA spot sign positivity and hematoma expansion. Secondarily, we aimed to determine the potential link between perihematomal edema and ICH by onset to baseline CT time and to evaluate associations between perihematomal edema and clinical outcome.

Subjects and Methods

Study Population

The methodology of the Predicting Hematoma Growth and Outcome in Intracerebral Hemorrhage Using Contrast Bolus CT (PREDICT) study has been previously published.¹¹ In brief, PREDICT was a multicenter, prospective, observational cohort study of consecutive adult patients with spontaneous ICH of <100 mL presenting within 6 hours from symptom onset. All patients from the entire PREDICT study cohort were eligible for the present study.¹⁶

The PREDICT study protocol was approved by the research ethics board of the University of Calgary, Calgary, Alberta, Canada. The requirement for additional local ethics approval differed among participating countries, and additional consent was obtained if required by the local ethics board. All patients gave written informed consent according to the requirements established by each site ethics board. When a patient was incapacitated by the stroke and unable to give consent, the next of kin or legal guardian gave surrogate consent.

Procedures

Relevant demographic and clinical characteristics were recorded. The National Institutes of Health Stroke Scale (NIHSS) score on admission and at 24 hours was collected, as well as modified Rankin scale (mRS) score at 90 days. Noncontrast CT scan at baseline and at 24 hours and CTA immediately after baseline CT scan were performed. The details of image acquisition and processing have been described before.¹⁵

Baseline and 24-hour ICH volumes were determined by a stroke neurologist (Dr Demchuk) masked to CTA scans. The perihematomal hypodensity surrounding ICH was interpreted to represent perihematomal edema. Total lesion (ICH plus perihematomal edema) volumes were measured by a trained research nurse (T. Stewart) masked to CTA and follow-up CT scans using semiautomated Hounsfield-unit, threshold-based, computerized planimetry software.¹³ Absolute perihematomal edema volume was calculated as the difference between total lesion volume and ICH volume. When perihematomal edema was undetectable, perihematomal edema volume value of zero was assigned. Relative perihematomal edema volume was defined as absolute perihematomal edema volume divided by ICH volume. The CTA source image data were independently interpreted for the presence of the spot sign by a neuroradiologist (R.I. Aviv) masked to follow-up CT scans. The spot sign was defined according to previously established criteria.¹⁶

Outcomes

Primary outcome was significant hematoma expansion at 24 hours defined as the composite of an ICH absolute growth >6 mL or relative enlargement of >33% from baseline CT.¹⁴ Secondary outcomes were early neurological deterioration, poor outcome, and mortality at 90 days. Early neurological deterioration was defined as an increase ≥4 points in the NIHSS score or death at 24 hours and poor outcome as an mRS score >2 at 90 days. Patients with an mRS score >2 at baseline were excluded from poor outcome analysis.

Statistical Analysis

Statistical analysis was performed using SPSS version 17.0 software. The categorical variables are presented as absolute values (percentages) and the continuous variables as means±standard deviation or medians (interquartile intervals). Statistical significance for intergroup differences was assessed by Pearson χ² for categorical variables and by Student’s t or Mann–Whitney U test for continuous variables. Correlations between continuous variables were assessed by Spearman’s correlation coefficient. The relationship between ICH and perihematomal edema volumes was further investigated through adjusted partial correlation analysis. For descriptive purposes, baseline ICH volume was divided into tertiles. Multivariable logistic regression analysis was performed to determine whether perihematomal edema could be considered as independent predictor of significant hematoma expansion (>6 mL or >33%). Because a lower hematoma expansion threshold might be more suitable for smaller hematomas, a post hoc sensitivity analysis was also performed at an absolute ICH growth of 4 mL threshold. The logistic regression results are presented as odds ratio (OR) and 95% confidence interval (CI). A 2-sided P value of <0.05 was considered significant for all tests.

Results

From 386 patients in the entire PREDICT study cohort, 353 were included; 33 subjects were excluded for the following reasons: 23 underwent baseline CT scan beyond 6 hours from symptom onset and 10 did not have available baseline CT or CTA images.

CTA Spot Sign, ICH Volume, and Perihematomal Edema Volume

Mean age was 67.8±15.2 years, 58.6% of patients were male, and median NIHSS score on admission was 14 (7–18). Nearly all patients (98%) had measurable perihematomal edema on the baseline CT scan. Median total lesion volume was 28.7 (15.6–61.6) mL, ICH volume 14.4 (6.7–28.8) mL, absolute perihematomal edema volume 15.0 (8.0–29.1) mL, and relative perihematomal edema volume 1.1 (0.9–1.5) at baseline. There were no differences of absolute perihematomal edema volume at baseline between males and females (14.5 [8.3–24.8] versus 18.6 [7.8–35.5] mL; P=0.103).

The CTA spot sign was present in 108 (30.6%) patients. Patients with spot sign had higher median absolute perihematomal edema but lower relative perihematomal edema volume than patients without a spot sign (Table 1). Absolute perihematomal edema volume was strongly correlated with ICH.
stroke volume at baseline ($\rho=0.905$; $P<0.001$; Figure 1). The correlation between absolute perihematomal edema volume and ICH volume remained strong adjusting for age, sex, hypertension, diabetes mellitus, and spot sign (partial correlation coefficient=0.877; $P<0.001$).

Median time from symptom onset to baseline CT scan (onset–CT time) was 135 (88–204) minutes. Neither absolute ($\rho=-0.081$; $P=0.131$) nor relative ($\rho=0.092$; $P=0.087$) perihematomal edema volume was correlated with onset–CT time. Similarly, absolute ($\rho=-0.076$; $P=0.156$) and relative ($\rho=0.079$; $P=0.158$) perihematomal edema volumes were not correlated with onset–CT time at hourly intervals (Table 2).

### Perihematomal Edema Volume, Hematoma Expansion, and Clinical Outcomes

Outcome analyses were limited to 322 patients after the exclusion of 14 patients treated with off-label rFVIIa and 17 who underwent a neurosurgical procedure (hematoma evacuation or ventriculostomy). From 322 patients, 305 had a 24-hour CT scan, 273 had 24-hour clinical data, and 309 were successfully followed up at 90 days, 21 of whom were excluded from poor outcome analysis because they had an nRS score $\geq 2$ at baseline.

Significant hematoma expansion (>6 mL or $>33\%$) occurred in 98 (32.1%) patients. Patients who experienced significant hematoma expansion had higher absolute perihematomal edema volume (18.4 [10.0–34.6] mL; $P<0.001$) but similar relative perihematomal edema volume (1.1 [0.9–1.4] versus 1.1 [0.9–1.5]; $P=0.400$) at baseline than patients who did not experience hematoma expansion. However, absolute perihematomal edema volume and frequency of significant hematoma expansion were higher by tertiles of ICH volume in both spot sign–positive and spot sign–negative patients (Figure 2). Further, multivariable analysis showed that absolute perihematomal edema volume was not independently related to hematoma expansion (OR 1.0, 95% CI 0.98–1.02) after the adjustment for sex (OR 1.2, 95% CI 0.69–2.02), anticoagulant use (OR 3.9, 95% CI 1.68–9.11), baseline NIHSS score (OR 1.1, 95% CI 1.02–1.13), onset–CT time (OR 1.0, 95% CI 0.99–1.00), and ICH location (OR 2.0, 95% CI 0.98–4.01). Similarly, absolute perihematomal edema volume was not independently related to $>4$ mL hematoma expansion in a repeated adjusted multivariable analysis (OR 1.0, 95% CI 0.99–1.02).

Overall, 50 (18.3%) patients suffered early neurological deterioration, 188 (65.3%) had a poor outcome (nRS score 3–6), and 81 (26.2%) had died at 90 days. Absolute perihematomal edema volume was higher at baseline in those patients who experienced early neurological deterioration (25.7 [13.1–42.1] mL; $P<0.001$), in those who had a poor outcome (18.1 [10.3–33.2] versus 9.5 [5.4–17] mL; $P<0.001$), and in those who had died at 90 days (24.9 [15.5–48.3] versus 12.1 [6.7–22.1] mL; $P<0.001$). However, the frequency of poorer clinical outcomes was higher by tertiles of ICH volume and absolute perihematomal edema volume in both spot sign–positive and spot sign–negative patients (Figure 2).

### Table 1. Relationship Between Baseline Lesion Volumes and the Presence of the CTA Spot Sign

<table>
<thead>
<tr>
<th>CTA Spot Sign</th>
<th>Yes (n=108)</th>
<th>No (n=245)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total lesion, mL</td>
<td>46.5 (25.5–88.6)</td>
<td>24.3 (11.9–45.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICH, mL</td>
<td>21.6 (12.6–41.7)</td>
<td>10.8 (4.7–22.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Absolute perihematomal edema, mL</td>
<td>24.5 (11.5–41.8)</td>
<td>12.6 (6.9–22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Relative perihematomal edema</td>
<td>1.0 (0.8–1.3)</td>
<td>1.2 (0.9–1.5)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Data are expressed as median (interquartile interval). CTA indicates computed tomographic angiography; and ICH, intracerebral hemorrhage.

*P values for Mann–Whitney U test.

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**Figure 1.** Scatterplot showing the relationship between absolute perihematomal edema volume and intracerebral hemorrhage (ICH) volume at baseline. For every 10 mL increase in ICH volume, perihematomal edema volume increased by 9.5 mL.
This study provides further insight into the relationship among baseline perihematomal edema volume, the CTA spot sign, hematoma expansion, and clinical outcome in patients with acute ICH. Absolute perihematomal edema volume was greater in the presence of a CTA spot sign but was strongly correlated with ICH volume. Although higher perihematomal edema volume was found in patients who experienced significant hematoma expansion, absolute perihematomal edema volume and poorer outcomes were higher proportionally by tertiles of ICH volume. Perihematomal edema did not independently predict significant hematoma expansion.

Perihematomal edema develops immediately after an ICH and is present in most patients with ICH. 1,19 In this study in which patients were scanned within 6 hours from symptom onset, perihematomal edema was present in nearly all patients and represented about half of total lesion volume. Although absolute perihematomal edema volume was higher than observed in another study of ICH patients scanned within the first 3 hours,2 the baseline ICH volume was also higher in our study. Previous small case series focused on the relationship between perihematomal edema and ICH volumes have shown divergent results,2–7 but overall, they suggest that perihematomal edema volume could be related to ICH volume at baseline in patients scanned during the first hours from symptom onset.3–7 Our results support a relationship between perihematomal edema and ICH volumes because both were strongly positively correlated at baseline.

### Table 2. ICH, Absolute Perihematomal Edema, and Relative Perihematomal Edema Volumes and Correlation Between Absolute Perihematomal Edema and ICH Volumes at Baseline in Each Hourly Onset–CT Time Interval

<table>
<thead>
<tr>
<th>Onset–CT Time Intervals</th>
<th>n (%)</th>
<th>ICH Volume, mL</th>
<th>Absolute Perihematomal Edema Volume, mL</th>
<th>Relative Perihematomal Edema Volume</th>
<th>Absolute Perihematomal Edema and ICH Volumes Correlation</th>
<th>Spearman’s ρ</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–60 min</td>
<td>28 (7.9)</td>
<td>11.3 (5.8–17.8)</td>
<td>10.1 (7.6–18.2)</td>
<td>1.0 (0.8–1.3)</td>
<td>0.942 &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>61–120 min</td>
<td>126 (35.7)</td>
<td>17.9 (8.5–35.1)</td>
<td>17.7 (9.2–34.5)</td>
<td>1.0 (0.8–1.4)</td>
<td>0.921 &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>121–180 min</td>
<td>88 (24.9)</td>
<td>14.3 (7.7–27.8)</td>
<td>16 (8.9–29.7)</td>
<td>1.2 (1.0–1.5)</td>
<td>0.863 &lt;0.001</td>
<td></td>
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<tr>
<td>181–240 min</td>
<td>49 (13.9)</td>
<td>12.6 (4.4–26.9)</td>
<td>14.8 (8.4–25)</td>
<td>1.2 (0.9–1.7)</td>
<td>0.867 &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>241–300 min</td>
<td>34 (9.6)</td>
<td>10.3 (5.3–37.1)</td>
<td>11.8 (5.9–36.1)</td>
<td>1.1 (0.9–1.6)</td>
<td>0.930 &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>301–360 min</td>
<td>28 (7.9)</td>
<td>12 (3.7–18.9)</td>
<td>11.7 (5.6–20.4)</td>
<td>1.0 (0.8–1.3)</td>
<td>0.947 &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>353 (100)</td>
<td>14.4 (6.7–28.8)</td>
<td>15.0 (8.0–29.1)</td>
<td>1.1 (0.9–1.5)</td>
<td>0.905 &lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Volumes data are expressed as median (interquartile interval). CT indicates computed tomography; and ICH, intracerebral hemorrhage.

*P values for Spearman’s correlation coefficient.

### Figure 2. Baseline absolute perihematomal edema volume, significant hematoma expansion, and clinical outcomes stratified by tertiles of intracerebral hemorrhage (ICH) volume in spot sign–negative (A) and spot sign–positive (B) patients.
Hematoma expansion occurs mainly during the first 6 hours and is unusual after 24 hours from symptom onset. Similarly to ICH, perihematomatal edema increases over time by 75% of relative volume during the first 24 hours in patients scanned within the first 3 hours from symptom onset. Although baseline ICH volume has been shown to be associated with hematoma expansion, the relationship between baseline perihematomatal edema volume and hematoma expansion has not been well established. The CTA spot sign is a powerful predictor of hematoma expansion and represents a surrogate of active bleeding. We hypothesized that lower relative perihematomatal edema volume at baseline may suggest a early time point from onset or actively bleeding ICH and, therefore, present a high likelihood of both CTA spot sign positivity and hematoma expansion at 24 hours. However, relative perihematomatal edema volume at baseline was not significantly correlated with onset–CT time within the first 6 hours in our study. Therefore, baseline relative perihematomata volume is not a surrogate marker of the time from symptom onset. Further, lower relative perihematomatal edema volume at baseline was associated with a higher CTA spot sign positivity, neither relative nor absolute perihematomatal edema volumes independently predicted hematoma expansion at 24 hours.

Theoretically, perihematomatal edema may lead to additional mass effect and contribute to further neuronal injury and poor outcome. Although perihematomatal edema growth has been consistently associated with poorer clinical outcomes, conflicting results showing no effect, positive and negative effect on the relationship between perihematomatal edema volume at baseline and clinical outcomes have been reported. Our results show that baseline perihematomatal edema volume is a surrogate for ICH volume with no prognostic significance by itself.

The strengths of this multicenter study include its large sample size, the early assessment of patients after symptom onset, the evaluation of CTA spot sign positivity as a surrogate of active bleeding, and the volumetric quantitative assessment of perihematomatal edema and ICH. The study has, however, some limitations. We assumed perihematomatal hypodensity surrounding ICH as perihematomatal edema; yet, other processes may coexist to produce perihematomatal edema volume at baseline and clinical outcomes have been reported. Our results show that baseline perihematomatal edema volume is a surrogate for ICH volume with no prognostic significance by itself.

Conclusions

In patients with acute spontaneous ICH, it is not possible to estimate the time from symptom onset based on relative perihematomatal edema volume. Absolute perihematomatal edema volume at baseline is greater in the presence of a CTA spot sign but is a surrogate for baseline ICH volume with no prognostic significance by itself.

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