Original Contribution

Predicting Intracerebral Hemorrhage Growth With the Spot Sign
The Effect of Onset-to-Scan Time

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Background and Purpose—Hematoma expansion after acute intracerebral hemorrhage is common and is associated with early deterioration and poor clinical outcome. The computed tomographic angiography (CTA) spot sign is a promising predictor of expansion; however, frequency and predictive values are variable across studies, possibly because of differences in onset-to-CTA time. We performed a patient-level meta-analysis to define the relationship between onset-to-CTA time and frequency and predictive ability of the spot sign.

Methods—We completed a systematic review for studies of CTA spot sign and hematoma expansion. We subsequently pooled patient-level data on the frequency and predictive values for significant hematoma expansion according to 5 predefined categorized onset-to-CTA times. We calculated spot-sign frequency both as raw and frequency-adjusted rates.

Results—Among 2051 studies identified, 12 met our inclusion criteria. Baseline hematoma volume, spot-sign status, and time-to-CTA were available for 1176 patients, and 1039 patients had follow-up computed tomographies for hematoma expansion analysis. The overall spot sign frequency was 26%, decreasing from 39% within 2 hours of onset to 13% beyond 8 hours (P<0.001). There was a significant decrease in hematoma expansion in spot-positive patients as onset-to-CTA time increased (P=0.004), with positive predictive values decreasing from 53% to 33%.

Conclusions—The frequency of the CTA spot sign is inversely related to intracerebral hemorrhage onset-to-CTA time. Furthermore, the positive predictive value of the spot sign for significant hematoma expansion decreases as time-to-CTA increases. Our results offer more precise risk stratification for patients with acute intracerebral hemorrhage and will help refine clinical prediction rules for intracerebral hemorrhage expansion. (Stroke. 2016;47:00-00. DOI: 10.1161/STROKEAHA.115.012012.)

Key Words: cerebral hemorrhage ■ CT angiography ■ hematoma expansion ■ intracerebral hemorrhage ■ spot sign

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Intracerebral hemorrhage (ICH) causes the majority of stroke morbidity and mortality. Although ICH volume and location are strong predictors of outcome, neither are modifiable at the time of diagnosis. However, hematoma expansion occurs in ≤40% of patients, worsens outcome, can potentially be prevented, and is therefore a therapeutic target of ongoing clinical trials (NCT00810888, NCT01359202, NCT01702636, and ISRCTN93732214).

Attempts to mitigate hematoma expansion failed to demonstrate improved outcomes in large randomized controlled trials. This is partially attributed to the challenge of accurately identifying patients most likely to benefit from interventions targeting hematoma expansion. To date, only one trial demonstrated a shift toward reduced disability with blood pressure lowering, which was achieved with a marginal reduction in hematoma expansion. We can potentially increase the absolute effect of such therapies by using biomarkers to identify patients at highest risk of this expansion. Contrast extravasation after computed tomographic angiography (CTA), termed the spot sign, is a promising radiological marker that predicts hematoma expansion.

The spot sign is appealing to clinicians and researchers because CTA is a rapid and noninvasive imaging modality used in acute stroke. However, the predictive performance of the spot sign is highly variable across studies, with positive predictive values (PPV) ranging from 0.22 to 1.00. Although preliminary data suggests that onset-CTA time may explain some of this variability, the relationship remains unclear. We, therefore, performed a systematic review and patient-level meta-analysis to assess the frequency and predictive performance of the spot sign in relation to onset-to-CTA times in patients presenting with acute ICH.

Table 1. Systematic Review Results and Patient-Level Data Available for Meta-Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Year</th>
<th>Enrollment Window</th>
<th>Spot Frequency</th>
<th>PPV</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demchuk et al17</td>
<td>Multicenter§</td>
<td>2012</td>
<td>&lt;6 h</td>
<td>29%</td>
<td>61%</td>
<td>386</td>
</tr>
<tr>
<td>Wada et al18</td>
<td>Japan</td>
<td>2007</td>
<td>&lt;3 h</td>
<td>33%</td>
<td>77%</td>
<td>126</td>
</tr>
<tr>
<td>Goldstein et al19</td>
<td>USA</td>
<td>2007</td>
<td>None</td>
<td>56%</td>
<td>24%</td>
<td>414</td>
</tr>
<tr>
<td>Li et al16</td>
<td>China</td>
<td>2011</td>
<td>&lt;6 h</td>
<td>22%</td>
<td>79%</td>
<td>139</td>
</tr>
<tr>
<td>Murali et al17</td>
<td>Japan</td>
<td>1999</td>
<td>&lt;12 h</td>
<td>21%</td>
<td>60%</td>
<td>24</td>
</tr>
<tr>
<td>Kim et al20</td>
<td>USA</td>
<td>2008</td>
<td>None</td>
<td>18%</td>
<td>NR</td>
<td>56</td>
</tr>
<tr>
<td>Sorimachi et al21</td>
<td>Japan</td>
<td>2013</td>
<td>&lt;24 h</td>
<td>21%</td>
<td>NR</td>
<td>141</td>
</tr>
<tr>
<td>Rizos et al22</td>
<td>Germany</td>
<td>2013</td>
<td>&lt;6 h</td>
<td>27%</td>
<td>59%</td>
<td>57</td>
</tr>
<tr>
<td>Becker et al23</td>
<td>USA</td>
<td>1999</td>
<td>None</td>
<td>46%</td>
<td>NR</td>
<td>NA</td>
</tr>
<tr>
<td>Park et al24</td>
<td>Korea</td>
<td>2010</td>
<td>&lt;24 h</td>
<td>17%</td>
<td>NR</td>
<td>NA</td>
</tr>
<tr>
<td>Wang et al25</td>
<td>China</td>
<td>2011</td>
<td>&lt;3 h</td>
<td>24%</td>
<td>83%</td>
<td>NA</td>
</tr>
<tr>
<td>Hallevi et al26</td>
<td>USA</td>
<td>2010</td>
<td>&lt;4 h</td>
<td>41%</td>
<td>100%</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA indicates patient-level data not available; NR, not reported in primary publication; and PPV, positive predictive value.

*Enrollment window refers to inclusion time windows of published studies.
†Spot prevalence as reported in the initial publications.
‡As some studies continued enrollment after publication, number of patients refers to the final number available for pooled analysis.
§Participating centers were in Canada, Spain, Germany, USA, Poland, and India.
Table 2. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Included Patients (n=1039)</th>
<th>Excluded Patients (n=304)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y (mean, SD)*</td>
<td>66 (15)</td>
<td>73 (12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex (% n/N)††</td>
<td>59% (618/1039)</td>
<td>52% (154/295)</td>
<td>0.028</td>
</tr>
<tr>
<td><strong>Medical History</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic (% n/N)‡‡</td>
<td>18% (68/372)</td>
<td>24% (6/25)</td>
<td>0.435</td>
</tr>
<tr>
<td>Hyperlipidemia (% n/N)‡</td>
<td>23% (86/372)</td>
<td>32% (8/25)</td>
<td>0.333</td>
</tr>
<tr>
<td>HTN (% n/N)§§</td>
<td>74% (745/1009)</td>
<td>76% (223/292)</td>
<td>0.403</td>
</tr>
<tr>
<td>Baseline systolic BP (median, IQR)¶¶</td>
<td>174 (45)</td>
<td>177.5 (45.8)</td>
<td>0.208</td>
</tr>
<tr>
<td>Baseline diastolic BP (median, IQR)¶¶</td>
<td>92 (29)</td>
<td>90 (24)</td>
<td>0.074</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticoagulant use (% n)#</td>
<td>10% (97/961)</td>
<td>13% (39/295)</td>
<td>0.134</td>
</tr>
<tr>
<td>Antiplatelet use (% n)**</td>
<td>33% (289/879)</td>
<td>41% (122/294)</td>
<td>0.009</td>
</tr>
<tr>
<td>Statin use (% n)††</td>
<td>25% (91/360)</td>
<td>27% (69/256)</td>
<td>0.642</td>
</tr>
<tr>
<td><strong>Baseline laboratories</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INR (median, IQR)††</td>
<td>1.02 (0.13)</td>
<td>1.00 (0.13)</td>
<td>0.956</td>
</tr>
<tr>
<td>INR &gt;1.7 (% n)‡‡</td>
<td>8% (86)</td>
<td>12% (35)</td>
<td>0.088</td>
</tr>
<tr>
<td>Hg (median, IQR)§§</td>
<td>140 (23)</td>
<td>137 (23)</td>
<td>0.033</td>
</tr>
<tr>
<td>Platelets (median, IQR)¶¶</td>
<td>224 (90)</td>
<td>230 (91)</td>
<td>0.144</td>
</tr>
<tr>
<td>Glucose (median, IQR)¶¶</td>
<td>7.1 (2.8)</td>
<td>8.0 (3.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine (median, IQR)¶¶</td>
<td>77.8 (27.5)</td>
<td>76.9 (30.9)</td>
<td>0.957</td>
</tr>
<tr>
<td>Onset to CTA time (min) (median, IQR)***</td>
<td>199 (253)</td>
<td>180 (251)</td>
<td>0.235</td>
</tr>
<tr>
<td>Spot positive (% n)</td>
<td>24% (252)</td>
<td>29% (85)</td>
<td>0.094</td>
</tr>
<tr>
<td>Hematoma volume, mL (median, IQR)¶¶</td>
<td>15.5 (208.1)</td>
<td>45.1 (235.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CTA indicates computed tomographic angiography; Hg, hemoglobin; HTN, hypertension; INR, international normalized ratio; and IQR, interquartile range.

*Missing 1 value.
†Missing 9 values.
‡Missing 946 values.
§Missing 42 values.
¶Missing 169 values.
∥Missing 193 values.
#Missing 87 values.
**Missing 170 values.
††Missing 727 values.
‡‡Missing 195 values.
§§Missing 521 values.
¶¶Missing 217 values.
∥∥Missing 799 values.
***Missing 190 values.
	†††Missing 44 values. Of the 304 excluded patients, 44 were excluded because of missing baseline CT, 3 for missing spot sign data, 120 because of missing time data precluding assignment to a time strata, and 137 because of missing follow-up CT.

times (means weighted by total N). Similarly, we reported absolute hematoma growth and proportion of patients with significant hematoma growth from all patients with baseline CTA, baseline NCCT, and follow-up NCCT. We defined significant hematoma expansion as an increase of 6 mL or 33% in parenchymal hematoma volume between baseline and follow-up NCCT23,24,31 and calculated sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios, and the area under the curve (AUC) for the spot sign as a predictor of significant hematoma expansion. We modeled the probability of ICH growth over time, stratified by the spot sign. We used a logistic regression model with time and spot-sign status as covariates and estimated the predicted probabilities of ICH growth in each stratum. We used SPSS v20 (IBM, Armonk, NY) and STATA (College Station, TX) for all analyses.

Results

We identified 2051 potential studies in our search of which 11 met our inclusion criteria (Table 1). A 12th study was identified by bibliography review. Of these, we were able to obtain patient-level data on 8 studies, and to minimize risk of reporting bias, we obtained the full data set from the authors (N=1343). Spot sign status was identified by the local investigators in all studies and was considered to be present if high-density contrast material or foci of enhancement was seen within the hematoma without connection to outside vessels.24,27,34 All studies included first-pass CTAs except one, which included both first and second pass CTA.23 Hematoma volume was measured in the 8 studies with available data by either computer-assisted planimetry (3 studies17,19,23 or the ABC/2 method (5 studies).24,16,22,24,32

Of the 1343 patients, 44 did not have a baseline computed tomography scan, 3 did not have spot sign assessment, and 120 could not be classified into time strata because of incomplete time of onset or last seen well information. We were able to obtain baseline hematoma volumes, spot sign status, and time-to-CTA for 1176 patients, which formed the spot-sign frequency cohort, and had follow-up hematoma volumes for 1039 patients for the hematoma expansion cohort. Patients excluded because of incomplete data were older (mean age 75 versus 67 years), more likely to be female, found to use antiplatelets, found to have lower hemoglobin and higher baseline glucose, and found to have larger hematoma volumes (Table 2). The median time to follow-up NCCT was 22.8 hours (interquartile range 8.7) for spot-negative patients and 22.9 hours (interquartile range 8.8) for spot-positive patients.

There was significant heterogeneity of spot-sign frequency between studies ($I^2=20.67, P=0.004$), and this was because of heterogeneity in the 0- to 2-hour strata ($I^2=15.51, P=0.016$)

Figure 1. Frequency of spot sign by time strata (frequency-weighted %); $P=283.5, P<0.001$. The cohort was N=1176, consisting of all patients with baseline computed tomographic angiography (CTA) spot status.
and the 2- to 4-hour strata ($I^2 = 16.5$, $P = 0.011$). There was no heterogeneity by study observed at the later time strata. The frequency of the spot sign was 26% for the group as a whole and showed a significant relationship with onset-to-CTA time strata ($P < 0.001$), decreasing from 39% within 2 hours of onset to 13% after 8 hours (Figure 1).

There was no heterogeneity in hematoma expansion between studies ($F = 0.45$; $P = 0.87$) or time strata ($F = 0.75$; $P = 0.56$). In all time intervals, the median volume of hematoma expansion was greater for spot-positive as compared with spot-negative patients, but there was no demonstrable decrease in median hematoma expansion by time strata in spot-positive patients (overall model $F = 1.28$; $P = 0.14$; Table I in the online-only Data Supplement). However, there was a decreasing relationship between spot positivity and significant hematoma expansion ($\geq 6 \text{ mL or } \geq 33\%)$ as onset-to-CTA time strata increased (Figure 2; Table II in the online-only Data Supplement). Furthermore, sensitivity and PPV of the spot sign to predict significant hematoma expansion was greatest in the earlier time strata, whereas the specificity and negative predictive value of spot sign increased with time (Table 3).

**Discussion**

We performed a large patient-level meta-analysis and found significant variation in the frequency and predictive value of the CTA spot sign based on onset to CTA time. Frequency of spot sign decreased to a third of its value between the earliest (0–2 hours) and latest (>8 hours) onset to scan times. The sensitivity and PPV of the spot sign to predict hematoma expansion was similarly highest in early time strata. Although the CTA spot sign is a promising radiological biomarker for prognostication and patient selection for emerging ICH therapies, the onset-to-imaging time should be considered when attempting to identify patients at highest risk for hematoma expansion.

Our study provides important data to optimize patient selection in ongoing clinical trials and offers frequency and performance data to inform future trial design. However, we also highlight the limitations of the spot sign: the best sensitivity to detect hematoma expansion was achieved in the first 2 hours from symptom onset and was only 60%. This modest predictive performance precludes the use of the spot sign in isolation and argues for its inclusion into expansion prediction scores. By explaining the variability by time in spot sign performance, our study allows for the refinement of emerging ICH expansion scores and the future development of clinical prediction rules. Furthermore, we highlight that even in the best-case scenario where patients present hyperacutely, 40% of those destined for hematoma expansion will not be identified by the spot sign, which supports the need for prediction rules that do not solely rely on CTA. Conversely, our data suggests that in later time points, the spot sign has a high

| Table 3. Predictive Values for Spot Sign to Predict Hematoma Expansion ($\geq 6 \text{ mL or } \geq 33\%)$ by Time Strata |
|-----------------|------------|-----------------|----------|-------|-------|-------|---------------|
| n               | Sensitivity | Specificity     | PPV      | NPV   | +LR   | −LR   | AUC (95% CI)  |
| Overall         | 1039       | 0.51            | 0.85     | 0.53  | 0.84  | 3.31  | 0.58          | 0.68 (0.66–0.69) |
| 0–2 h           | 266        | 0.60            | 0.76     | 0.61  | 0.76  | 2.56  | 0.52          | 0.68 (0.63–0.74) |
| 2–4 h           | 307        | 0.55            | 0.84     | 0.57  | 0.82  | 3.37  | 0.54          | 0.69 (0.64–0.75) |
| 4–6 h           | 170        | 0.44            | 0.91     | 0.56  | 0.87  | 5.01  | 0.61          | 0.68 (0.59–0.76) |
| 6–8 h           | 82         | 0.56            | 0.92     | 0.64  | 0.90  | 7.41  | 0.47          | 0.74 (0.61–0.87) |
| >8 h            | 214        | 0.30            | 0.90     | 0.33  | 0.89  | 3.06  | 0.78          | 0.60 (0.52–0.69) |

AUC indicates area under the curve; CI, confidence interval; LR, likelihood ratio; NPV, negative predictive value; and PPV, positive predictive value.
specificity and negative predictive value, which may reassure treating clinicians and clinical trialists that spot-negative patients presenting after 6 hours likely have stable hematomas. 

Our findings are consistent with the presumed underlying pathology of the spot sign as the source of ICH and help unify existing theories around its pathophysiology. A recent dynamic CTA study revealed that early spot signs behave in a manner consistent with active extravasation. But as time goes on, endogenous hemostatic mechanisms ultimately stop the bleeding. In the classical ICH pathology series, Dr Fisher discussed bleeding globes consisting of concentric fibrin rings attached to the walls of parenchymal hematomas. These 100- to 200-μm globes were thought to be thrombosed sites of vascular rupture and, because they fall within the spatial resolution of CTA, are likely a pathological equivalent to the spot sign. But these autopsy samples would have been acquired many hours after ICH onset, by which time the formation of stable fibrin globes around a ruptured vessel would have reduced the chance of ongoing bleeding; if imaged, these would likely be spot-positive yet unlikely to expand. The onset to CTA time relationship in our study fits with the hypothesis that the radiological spot sign initially represents a site of vessel rupture. Indeed, a recent pathological report demonstrated a focal vessel disruption in a spot-positive patient undergoing hematoma evacuation. We hypothesize that over time the vessel disruption thrombososes forms concentric fibrin rings and ultimately achieves hemostasis. Nevertheless, this explanation for late spot sign is speculative; it is entirely possible that late spot signs may also represent active extravasation, albeit at a lower rate.

The major strength of this study is the availability of patient-level data from different studies. However, there are several important limitations. Among other missing data, we did not have access to clinical outcome data from all studies and restricted our analysis to radiological outcomes only. We were also unable to access patient-level radiological data from 4 studies identified in our review representing 563 patients, which may have introduced a bias. But we note that the PPV was reported in one of these studies, and it was found consistent with our current findings. There have also been additional spot sign publications since our initial search strategy. This was unavoidable because of the prolonged timelines required to acquire regulatory approvals necessary for access to patient-level data, particularly across national jurisdictions. A second limitation to our study is the different techniques used to measure hematoma volumes. Although this can contribute to variability in absolute volumes, it is less likely to affect the dichotomous hematoma expansion cut-offs (6 mL or ≥33%). The third limitation is the relatively low number of spot-positive patients in later time windows. Although this may increase variability in point estimates at later time points, the finding of low spot-sign prevalence design is in line with previous studies and is nevertheless useful for future studies. A fourth limitation is the different CTA techniques used throughout the different studies included in this analysis, and we cannot exclude the possibility that in some cases, there may have been delays between NCCT and CTA which may contribute to heterogeneity. Finally, we found that patients with incomplete data had markers of poor outcome, as advanced age and increased glucose and hematoma volumes; it is possible that our estimates of hematoma expansion may be conservative because of their exclusion.

Conclusions

We demonstrate that spot-sign frequencies decreased as onset to scan times increase. Although the spot sign remains predictive of hematoma expansion in delayed presentations, PPV and sensitivity decrease and negative predictive value and specificity increase as time-to-CTA increases. Furthermore, the overall performance of the spot sign is modest, suggesting the need for additional clinical and radiological factors to predict hematoma expansion. Our results open a path for more precise risk stratification for patients with acute ICH and inform ongoing and emerging clinical trials.

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Disclosures

Dr Dowlatshahi has a patent pending for computerized automatic detection of contrast extravasation. Dr Goldstein reports grants and personal fees from CSL Behring, both outside the submitted work. Dr Hill sat on boards for the Heart & Stroke Foundation of Alberta/NWT/NU, Institute for Circulatory and Respiratory Health of CIHR, Canadian Federation of Neurological Sciences, provided consultancies for Vernalis Group Ltd and Merck Ltd, has grants from Hoffman-La Roche Canada Ltd, Coviden, holds stocks in Calgary Scientific inc, and has received speaker honoraria from Servier Canada, BMS Canada; all are unrelated to the current work. Dr Rizos has received consulting and speaking honoraria from BMS Pfizer, Bayer Healthcare, and Boehringer Ingleheim, unrelated to the current work. Dr Rosand reports portions of the patient-level data were funded by the US National Institutes of Health. Dr Sharma has received consulting and speaker’s honoraria from Boehringer Ingelheim, Bayer, BMS Pfizer, provided consultation for Daiichi Sankyo, unrelated to the current work. All other authors have nothing to disclose.

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Predicting Intracerebral Hemorrhage Growth With the Spot Sign: The Effect of Onset-to-Scan Time
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**Supplemental Table I:** Absolute hematoma expansion by time strata, mL (Median [IQR])

<table>
<thead>
<tr>
<th>Time</th>
<th>Spot positive</th>
<th>Spot negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2h</td>
<td>6.6 [22.2]</td>
<td>0.4 [3.2]</td>
</tr>
<tr>
<td>2-4h</td>
<td>4.9 [20.3]</td>
<td>0.3 [3.2]</td>
</tr>
<tr>
<td>4-6h</td>
<td>5.6 [15]</td>
<td>0.2 [2.4]</td>
</tr>
<tr>
<td>6-8h</td>
<td>14.0 [36.2]</td>
<td>0.0 [1.3]</td>
</tr>
<tr>
<td>&gt;8h</td>
<td>0.0 [6.1]</td>
<td>0.0 [2.8]</td>
</tr>
</tbody>
</table>

Frequency-weighted values are shown, p=0.14.
**Supplemental Table II**: Spot status of patients with hematoma expansion ≥6mL or ≥33% (n=220) by time strata (% (n)).

<table>
<thead>
<tr>
<th>Time Strata</th>
<th>Spot Positive</th>
<th>Spot Negative</th>
<th>Spot Positive*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Un-weighted (n=128)</td>
<td>Un-weighted (n=92)</td>
<td>Frequency-weighted</td>
</tr>
<tr>
<td>0-2h (n=87)</td>
<td>63.2% (55)</td>
<td>36.8% (32)</td>
<td>60.1%</td>
</tr>
<tr>
<td>2-4h (n=72)</td>
<td>59.7% (43)</td>
<td>40.3% (29)</td>
<td>58.1%</td>
</tr>
<tr>
<td>4-6h (n=26)</td>
<td>50.0% (13)</td>
<td>50.0% (13)</td>
<td>52.9%</td>
</tr>
<tr>
<td>6-8h (n=14)</td>
<td>64.3% (9)</td>
<td>35.7% (5)</td>
<td>60.5%</td>
</tr>
<tr>
<td>&gt;8h (n=21)</td>
<td>38.1% (8)</td>
<td>61.9% (13)</td>
<td>37.2%</td>
</tr>
</tbody>
</table>

*p=0.004
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