Do Intracerebral Hemorrhage Nonexpanders Actually Expand Into the Ventricular Space?

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Background and Purpose**—**The computed tomographic angiography spot sign as a predictor of hematoma expansion is limited by its modest sensitivity and positive predictive value. It is possible that hematoma expansion in spot-positive patients is missed because of decompression of intracerebral hemorrhage (ICH) into the ventricular space. We hypothesized that revising hematoma expansion definitions to include intraventricular hemorrhage (IVH) expansion will improve the predictive performance of the spot sign. Our objectives were to determine the proportion of ICH nonexpanders who actually have IVH expansion, determine the proportion of false-positive spot signs that have IVH expansion, and compare the known predictive performance of the spot sign to a revised definition incorporating IVH expansion.

Methods**—**We analyzed patients from the multicenter PREDICT ICH spot sign study. We defined hematoma expansion as ≥6 mL or ≥33% ICH expansion or >2 mL IVH expansion and compared spot sign performance using this revised definition with the conventional 6 mL/33% definition using receiver operating curve analysis.

Results**—**Of 311 patients, 213 did not meet the 6-mL/33% expansion definition (nonexpanders). Only 13 of 213 (6.1%) nonexpanders had ≥2 mL IVH expansion. Of the false-positive spot signs, 4 of 40 (10%) had >2 mL ventricular expansion. The area under the curve for spot sign to predict significant ICH expansion was 0.65 (95% confidence interval, 0.58–0.72), which was no different than when IVH expansion was added to the definition (area under the curve, 0.66; 95% confidence interval, 0.58–0.71).

Conclusions**—**Although IVH expansion does indeed occur in a minority of ICH nonexpanders, its inclusion into a revised hematoma expansion definition does not alter the predictive performance of the spot sign. **(*Stroke*. 2018;49:201-203. DOI: 10.1161/STROKEAHA.117.018716.)**

Key Words: area under curve ■ cerebral hemorrhage ■ hematoma ■ humans ■ ROC curve

Early hematoma expansion occurs in approximately one third of patients with intracerebral hemorrhage (ICH) and is strongly associated with poor clinical outcome.[1,2] The computed tomographic (CT) angiography spot sign is a promising imaging predictor of hematoma expansion[3–5]; however, its usefulness is limited by its modest sensitivity and positive predictive value.[6] Spot sign studies typically restrict the definition of significant hematoma expansion to the parenchymal component of ICH and have not consistently evaluated intraventricular hemorrhage (IVH) expansion. Decompression of ICH into the ventricular space can lead to underestimation of hematoma expansion and overestimation of false-positive spot signs.

We hypothesized that a proportion of patients with ICH that fail to meet the definition for significant hematoma expansion

Received May 10, 2017; final revision received September 28, 2017; accepted October 5, 2017.

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Guest Editor for this article was Giuseppe Lanzino, MD.

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(nonexpanders) in fact expand into the ventricular space. Furthermore, revising hematoma expansion definitions to include IVH expansion may improve the predictive performance of the spot sign. Our objectives were to (1) determine the proportion of patients with ICH identified as nonexpanders by a conventional parenchymal hematoma expansion definition, who actually have IVH expansion, (2) similarly determine the proportion of false-positive spot signs that actually have IVH expansion, and (3) compare the predictive performance of the spot sign using the conventional parenchymal expansion definition with that of a revised definition incorporating IVH expansion.

Methods

We analyzed patients from the multicenter PREDICT ICH spot sign study, which has been described in detail.[3] Briefly, PREDICT was a prospective multicenter observational study of patients presenting with spontaneous ICH under 6 hours, with baseline CT, CT angiogram, and follow-up imaging at 24 hours. Exclusion criteria were ICH >100 mL, known renal impairment precluding CT angiogram, premorbid mRS >3, or terminal illness. For the current study, we excluded any patients who had missing baseline or follow-up CT, missing CT angiogram, and patients who received hemostatic therapy or underwent surgical hematoma evacuation. The PREDICT protocol was approved by local institutional research ethics boards with a waiver for deferred consent. Data, analytic methods, and study materials are only available to enrolling investigators.

Based on precedent, we defined significant hematoma expansion as ≥6 mL or ≥33% parenchymal expansion.[3,7] We proposed a revised definition for hematoma expansion incorporating IVH expansion as ≥6 mL or ≥33% parenchymal expansion or >2 mL ventricular expansion. We chose the >2-mL IVH threshold because it was previously shown to independently predict poor outcome and mortality in acute ICH.[8] We used receiver operating curve analysis and C statistics to assess the performance of this revised definition and compared it with the C statistic of the conventional 6-mL/33% parenchymal definition using the Hanley and McNeil test. Hematoma volumes were assessed in the PREDICT study using computerized planimetry.[9]

Results

A total of 311 patients with baseline CT, CT angiogram, 24-hour CT, and meeting study criteria were available for analysis (Table 1); 39 patients did not have IVH on the baseline scan but developed IVH on 24-hour CT. Of the 311 patients, 213 (68.5%) did not meet the conventional significant hematoma expansion definition of 6 mL/33%. Of these nonexpanders, 13 of 213 (6.1%) had >2 mL expansion into the ventricular space. Four of the 13 were spot positive (Figure). Spot sign was seen in 86 of 311 (27.7%) patients, but 40 of 86 (46.5%) patients did not meet the 6-mL/33% criteria for hematoma expansion (false positives). Of these false positives, only 4 of 40 (10%) had 2-mL expansion into the ventricular space. The area under the curve for spot sign to predict 6-mL/33% ICH expansion was 0.65 (95% confidence interval, 0.58–0.72), which was no different when >2-mL IVH expansion was added to the definition (area under the curve, 0.66; 95% confidence interval, 0.58–0.72; z=0.0627; P=0.95 for comparison); positive predictive value increased marginally from 53.5% to 58.1% (Table 2).

Table 1. Baseline Characteristics

n	311
Age (median, IQR)	70 (21)
Male sex	185 (59.5%)
Onset to CT (median, IQR, min)	137 (125)
Baseline to follow-up CT (median, h)	23.9 (4.1)
Baseline ICH volume (median, IQR, mL)	12.1 (20)
Baseline IVH volume (median, IQR, mL)	0 (2.2)
6 mL or 33% hematoma expansion, n (%)	98 (31.5%)
6 mL or 33% hematoma expansion or >2 mL ventricular expansion, n (%)	111 (35.7%)
Spot sign positive, n (%)	86 (27.7%)

CT indicates computed tomography; ICH, intracerebral hemorrhage; IQR, interquartile range; and IVH, intraventricular hemorrhage.

Discussion

We report that a small proportion of patients with ICH classified as nonexpanders and false-positive spot signs actually expand into the ventricular space. Studies of early hematoma expansion typically limit volume measurements to the parenchymal component of ICH. Conventional definitions of hematoma expansion have relied on absolute and relative growth thresholds, which although clinically significant,[7] may underestimate the ICH expansion when there is extension into the intraventricular compartment. Although we report that this occurs in only a minority of patients (6.1% or 13 of 213 patients classified as nonexpanders using parenchymal definitions), classifying these patients as expanders may be helpful when designing treatment

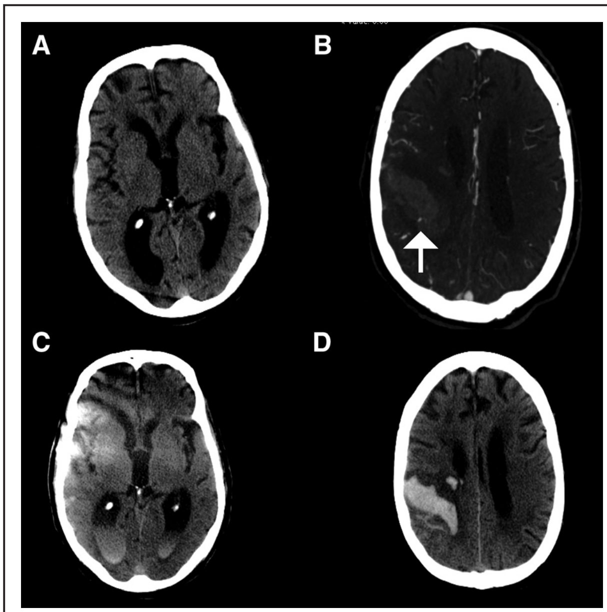

Figure. Baseline computed tomography (**A**) and computed tomographic angiography (**B**) reveal a parenchymal hematoma with spot sign (arrow). Follow-up imaging at 24 hours reveals a new intraventricular hemorrhage of 13 mL (**C**) and a smaller parenchymal hematoma (**D**). Using conventional parenchymal expansion definitions, this patient would be classified as a nonexpander, in spite of a net total intracerebral hemorrhage volume increase of 7 mL.

Table 2. Spot Sign Predictive Performance to Detect the 2 Definitions of Significant Hematoma Expansion

	6 mL or 33% Parenchymal Expansion	6 mL or 33% Parenchymal or >2 mL IVH Expansion
Sensitivity	46.9%	45%
Specificity	81.2%	82%
Positive predictive value	53.5%	58.1%
Negative predictive value	76.9%	72.9%
AUC (95% CI)	0.652 (0.581–0.723)	0.655 (0.585–0.725)

AUC indicates area under the curve; CI, confidence interval; and IVH, intraventricular hemorrhage.

trials aiming to mitigate early hematoma expansion. It may also be helpful to understand situations where a treatment has an apparent clinical benefit, without appearing to reduce parenchymal hematoma expansion (eg, Interact-2[10]).

When we incorporated ventricular expansion into the definition of significant ICH expansion, 10% of spot signs initially classified as false positive were reclassified as true positive, thereby marginally increasing its positive predictive value. However, the spot sign sensitivity remained poor, and there was no improvement in its overall predictive performance. Although the spot sign was initially a highly promising predictive marker for hematoma expansion,[4,5] subsequent studies revealed considerable variability in predictive performance, in part, because of image acquisition phase,[11] tube current,[12] and onset-to-imaging time.[6] Our study suggests that accounting for ventricular expansion is insufficient to improve spot sign performance and supports the need for other predictive features on neuroimaging, such as heterogeneity and morphology.[13]

Our study has important limitations. There is no clear consensus on the best definition for ventricular expansion in ICH. Nevertheless, we based our threshold for ventricular expansion on prior studies showing a relationship to clinical outcome. In addition, the boundaries between parenchyma and ventricle can be difficult to demarcate when anatomic landmarks are disrupted by large hematomas, requiring subjective interpretation by the image readers. Furthermore, although the original PREDICT study was prospective in design, this analysis was retrospective and potentially susceptible to confounding. Finally, our sample size is relatively small and warrants replication in a larger cohort.

Summary

We report that refining the definition of significant ICH expansion to account for ventricular expansion had minimal effect on the predictive performance of the spot sign. This reinforces the need to develop better predictive models for ICH expansion, perhaps by combining spot sign with clinical features and noncontrast CT markers.

Disclosures

Dr Demchuk received consulting fees from Portola. Dr Kase provided consultancy to Boehringer-Ingleheim. The other authors report no conflicts.

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Stroke
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Stroke. 2018;49:201-203; originally published online November 22, 2017;
doi: 10.1161/STROKEAHA.117.018716
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628