Black Hole Sign

Novel Imaging Marker That Predicts Hematoma Growth in Patients With Intracerebral Hemorrhage

Qi Li, MD, PhD; Gang Zhang, MD; Xin Xiong, MD; Xing-Chen Wang, MD; Wen-Song Yang, MD; Ke-Wei Li, MD; Xiao Wei, MA; Peng Xie, MD

Background and Purpose—Early hematoma growth is a devastating neurological complication after intracerebral hemorrhage. We aim to report and evaluate the usefulness of computed tomography (CT) black hole sign in predicting hematoma growth in patients with intracerebral hemorrhage.

Methods—Patients with intracerebral hemorrhage were screened for the presence of CT black hole sign on admission head CT performed within 6 hours after onset of symptoms. The black hole sign was defined as hypoattenuating area encapsulated within the hyperattenuating hematoma with a clearly defined border. The sensitivity, specificity, and positive and negative predictive values of CT black hole sign in predicting hematoma expansion were calculated. Logistic regression analyses were used to assess the presence of the black hole sign and early hematoma growth.

Results—A total of 206 patients were enrolled. Black hole sign was found in 30 (14.6%) of 206 patients on the baseline CT scan. The black hole sign was more common in patients with hematoma growth (31.9%) than those without hematoma growth (5.8%; \( P < 0.001 \)). The sensitivity, specificity, positive predictive value, and negative predictive value of black hole sign in predicting early hematoma growth were 31.9%, 94.1%, 73.3%, and 73.2%, respectively. The time-to-admission CT scan, baseline hematoma volume, and the presence of black hole sign on admission CT independently predict hematoma growth in multivariate model.

Conclusions—The CT black hole sign could be used as a simple and easy-to-use predictor for early hematoma growth in patients with intracerebral hemorrhage. (Stroke. 2016;47:1777-1781. DOI: 10.1161/STROKEAHA.116.013186.)

Key Words: cerebral hemorrhage ▪ hematoma ▪ logistic models ▪ sensitivity and specificity ▪ tomography, x-ray computed

Intracerebral hemorrhage (ICH) constitutes 10% to 30% of first-ever strokes and is associated with high morbidity and mortality.1 The reported 30-day mortality of ICH ranges from 30% to 50% and nearly half of the patients died within 2 days after the onset of symptoms.2,3 The initial hematoma volume, level of consciousness, and intraventricular extension of bleeding are well-established predictors of functional outcome in patients with ICH.4–7 Early hematoma expansion is reported in 19% to 38% of patients with ICH and is associated with poor functional outcome.8–11 Identification of useful imaging predictor for hematoma expansion is crucial for therapeutic intervention.

The computed tomography angiography (CTA) spot sign is a well-established imaging marker that independently predicts hematoma expansion in patients with ICH.12,13 A recent large-scale multicenter observational study suggests that the sensitivity and specificity of CTA spot sign in predicting hematoma expansion were 51% and 85%, respectively.14 However, early CTA examination requires contrast administration and was contraindicated in patients with severe renal function impairment. In addition, CTA spot sign requires immediate admission of CTA examination within the first several hours after onset of symptoms, which was not applicable in many institutions. Therefore, scrutinizing nonenhanced CT scan for possible imaging predictors of hematoma expansion is urgently demanded for patients with ICH. We have identified a new CT-based sign called the black hole sign that may be used as a novel imaging predictor...
predictor for early hematoma growth. The aim of our study was to investigate the role of CT black hole sign in predicting hematoma growth.

**Materials and Methods**

**Patients**
We have prospectively included patients aged >18 years who presented with spontaneous ICH to a tertiary academic hospital between July 2011 and August 2015. Patients were eligible for the study if the initial CT scan was performed within 6 hours after the ictus and follow-up CT scan was obtained within 30 hours after the initial CT scan. Patients were excluded from the study if they had secondary ICH caused by arteriovenous malformation, cerebral aneurysm, traumatic brain injury, brain tumor stroke, or hemorrhagic infarction. Patients were also excluded from the study if they had surgical intervention before the follow-up CT scan. The demographic data, history of all diseases (diabetes mellitus, hypertension, coronary heart disease, cigarette smoking, alcohol consumption, and medication use) were recorded. The admission blood pressure, Glasgow Coma Scale score, and time-to-admission and follow-up CT scan were also documented. This study was approved by the Ethics Committee of Chongqing Medical University. All study protocol and procedure were conducted in accordance with the declaration of Helsinki.

**Definition of Black Hole Sign and Hematoma Expansion**
The CT black hole sign was defined as (1) relatively hypoattenuated area (black hole) encapsulated within the hyperattenuating hematoma. (2) The black hole could be round, oval, or rod-like but was not connected with the adjacent brain tissue. (3) The relatively hypoattenuated area should have an identifiable border. (4) The hematoma should have at least a 28 Hounsfield unit (HU) difference between the 2 density regions. The black hole sign and its mimics are illustrated in Figures 1 and 2. Early hematoma expansion was defined as an increase of hematoma volume >33% or absolute hematoma growth >12.5 mL from initial CT scan.

All CT examinations were performed using a multidetector CT-scanner with axial 5-mm section thickness. The CT images were acquired and stored in digital format for future use. Two readers, who were blinded to the clinical information of patients and the results of the follow-up CT scan, independently evaluated the baseline CT images. During CT densitometry, 2 regions of interest (ROI) were drawn on the CT images. Readers were allowed to zoom in the image to more accurately draw the ROIs. The ROI of the black hole should be carefully drawn to cover most part of the black hole but not to include the adjacent hyperattenuating hematoma. In a heterogeneous hematoma, the readers should try to place the ROI on the most hyperattenuating part, rather than a heterogenous part of the hematoma (Figure 3). The 2 ROIs should be placed on the same CT section where the black hole sign was present. In interpretation of the black hole sign, readers have to follow a 4-step evaluation approach (Figure I in the online-only Data Supplement). Black hole sign was considered negative in patients with vaguely defined border even if the HU difference was ≥28 between the 2 density regions. The readers have to assess the presence or absence of the CT black hole sign and the intraventricular extension of the bleeding location of hematoma. The location of the hematoma was assessed and categorized as basal ganglia, thalamus, lobe, brain stem, and cerebellum. The hematoma volume was measured by using the abc/2 formula.

**Statistical Analysis**
All statistical analyses were performed by using a SPSS software (version 21). Continuous variables were presented using means or medians; categorical variables were presented as percentages. The degree of interobserver agreement for judgment of the presence of CT black hole sign was determined by using κ values with κ of 1 indicates total agreement. The κ values of 0.21 to 0.4, 0.41 to 0.6, 0.61 to 0.8, and 0.81 to 1 indicate low, moderate, substantial, and excellent agreement between the readers. The clinical and imaging variables were compared between patients with black hole sign and those without the sign by using Fisher exact test, and Student t test as appropriate. Two-tailed P<0.05 was considered significant. Multivariate logistic regression analysis was performed to investigate whether black hole sign was an independent predictor of hematoma expansion in patients with ICH.

**Results**
A total of 206 patients (135 men and 71 women) with spontaneous ICH fulfill the eligibility criteria and were included in our study. The mean age of the study cohort was 60.3±12.2 years (range, 27–87 years). Hematoma growth occurred in 69 of 206 patients (33.5%) with intraparenchymal ICH. The median baseline hematoma volume was 12.8 mL (interquartile range, 7.4–20.1 mL). The median time from symptom onset to admission CT scan was 2 hours (interquartile range, 1–4 hours). Follow-up CT scan was performed 17.8 hours (interquartile range, 10.5–22.3 hours) after the admission CT scan. The ICH was lobar in 21 (10.2%), deep in 171 (83%), cerebellar in 8 (3.9%), and brain stem in 6 (2.9%). The demographic and clinical variables including age, sex, hypertension, diabetes mellitus, smoking, and alcohol drinking did not differ significantly between expanders and nonexpanders. Patients who experienced early hematoma growth presented with larger baseline hematoma volume, shorter time to CT...
Black hole sign was found in 30 (14.6%) of 206 patients with ICH on the baseline CT scan. The admission clinical and other imaging variables did not differ significantly between patients with black hole sign and those without the sign (Table 1). The mean baseline hematoma volume was 33.1±23.4 mL in patients with black hole sign when compared with 14.1±10.2 mL in patients without the sign (P<0.001). The black hole sign was more common in patients with hematoma growth (31.9%) than those without hematoma growth (5.8%; P<0.001). The interobserver agreement for evaluation of the presence of black hole sign was excellent between the readers (κ=0.806). The sensitivity, specificity, positive predictive value and negative predictive value of back hole sign in predicting early hematoma growth were 31.9%, 94.1%, 73.3%, and 73.2%, respectively.

In univariate logistic analysis, the time-to-admission CT scan, baseline hematoma volume, and the presence of black hole sign on admission CT scan were associated with hematoma growth (Table 2). The time-to-admission CT scan, baseline hematomata volume, and the presence of black hole sign on admission CT remained significant in multivariate model (Table 3).

Discussion

Our study demonstrated that the black hole sign on nonenhanced CT predicts hematoma expansion in patients with ICH. The black hole sign on admission CT remained significant even adjusted for several of potential predictors. We have also demonstrated that patients with black hole sign are more likely to have larger hematoma volume than those without the sign.

Hematoma heterogeneity has been associated with early hematoma growth in several studies. In a study of 90 patients, Barras et al\(^{17}\) found that large hematomas were more heterogeneous in density and more likely to expand than small hematomas. The authors concluded that density heterogeneity independently predicted hematoma growth in patients with ICH. In another study of 201 patients with acute deep ICH, Takeda et al\(^{18}\) validated the association between hematoma heterogeneity and early hematoma expansion. However, evaluation of hematoma heterogeneity was based on subjective judgment and these studies failed to establish a reliable imaging marker for assessment of heterogeneity of hematoma.

In a recent study, Barras et al\(^{19}\) developed a promising computer-assisted quantitative CT densitometry for assessment of hematoma heterogeneity. The technique is based on several derived parameters of CT densitometry that includes mean attenuation, square root of variance, coefficient of variation, skewness, and kurtosis. Although the CT densitometry helps identify heterogeneous hematomas that are likely to have early hematoma growth, the technique requires manually drawing of region of interests from all obtained CT sections and the use of individualized computer software programs such as Analyze.
and Matlab software. As a result, the technique is time consuming and could not be used in clinical practice. There is an increasing need for establishment of imaging markers that allow easy and rapid assessment of hematoma heterogeneity.

Although heterogeneous hematoma has been associated with early hematoma expansion, the definition of heterogeneous hematoma is subjective and unclear. The degree or extent of heterogeneity was not defined based on the previous definition of heterogeneous hematoma. In our study, we have attempted to develop a CT-based sign that could improve the reliability and subjectivity of the heterogeneous hematoma. We have defined the black hole sign as relatively hypoattenuating area encapsulated by adjacent hyperattenuating area. However, the definition is still subjective, as the assessment is based on identification of relatively hypoattenuation regions within the hematoma. To improve the objectivity of the definition, we have added a stringent degree of heterogeneity criteria for black hole sign. We have refined the definition of heterogeneous hematoma by adding a 28 HU difference between the 2 density regions. The CT densitometry makes sure that only mixed density hematomas with a certain degree of heterogeneity could fulfill the definition of black hole sign.

Our findings suggest that the black hole sign identifies mixed density hematomas with certain degree of heterogeneity sufficient to predict further hematoma growth in patients with ICH. From a pathophysiological point of view, the heterogeneity of the hematoma may reflect different age of the bleeding. The fresh liquid blood seems hypoattenuating on nonenhanced CT scan. After clot retraction, the serum is sequestered out of the hematoma, making the bleed hyperintense on CT scan. The presence of black hole sign within the hematoma may suggest bleeding of different age. This may explain the predictive value of CT black hole sign in patients with intracerebral hemorrhage.

In summary, we have demonstrated that a nonenhanced CT-based black hole sign predicts early hematoma growth in patients with ICH. The CT black hole sign could be used to predict hematoma growth in clinical settings where early CT angiography examination is not available.

Our study has several limitations. First, despite our effort to find the optimal HU threshold for the black hole sign, the selection of 28 HU was still based on clinical experience. We have tried several other HU thresholds and the changes in sensitivity, specificity, and positive predictive value were minimal. Second, evaluation of black hole sign is not completely objective. Third, we have used a 5-mm slice thickness CT scan that may lead to underestimation of hematoma growth in small ICH because of partial volume effect. There might be an interaction between section thickness, ICH size, and the presence of black hole sign. Future studies with large sample

<table>
<thead>
<tr>
<th>Table 1. Comparison of Baseline Characteristics Between Patients With Positive Black Hole Sign and Those Without the Sign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
</tr>
<tr>
<td>Mean age, y (SD)</td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
</tr>
<tr>
<td>Alcohol consumption, n (%)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
</tr>
<tr>
<td>Time to baseline CT (SD)</td>
</tr>
<tr>
<td>Baseline hematoma volume (SD)</td>
</tr>
<tr>
<td>Intraventricular hemorrhage, n (%)</td>
</tr>
<tr>
<td>Baseline GCS score (SD)</td>
</tr>
</tbody>
</table>

CT indicates computed tomography; and GCS, Glasgow Coma Scale.

<table>
<thead>
<tr>
<th>Table 2. Univariate Analysis of Predictors for Early Hematoma Growth</th>
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</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Current smoking</td>
</tr>
<tr>
<td>Alcohol consumption</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Intraventricular hemorrhage</td>
</tr>
<tr>
<td>Glasgow Coma Scale score</td>
</tr>
<tr>
<td>Time to baseline CT</td>
</tr>
<tr>
<td>Baseline ICH volume</td>
</tr>
<tr>
<td>Black hole sign on baseline CT</td>
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</tbody>
</table>

CT indicates computed tomography; and ICH, intracerebral hemorrhage.
size and thin slice thickness should be performed to determine the potential interaction between slice thickness, presence of black hole sign, and hematoma growth.

Acknowledgments
Qi Li and Peng Xie helped in study concept and design. Qi Li, Gang Zhang, Xin-Xiong, Xing-Chen Wang, Wen-Song Yang, Ke-Wei Li, Zhang, Xin-Xiong, Xing-Chen Wang, Wen-Song Yang, Ke-Wei Li, Qi Li and Peng Xie helped in study concept and design. Qi Li, Gang Zhang, Xin-Xiong, Xing-Chen Wang, Wen-Song Yang, Ke-Wei Li, Zhang, Xin-Xiong, Xing-Chen Wang, Wen-Song Yang, Ke-Wei Li, Qi Li, Peng Xie helped in critical revision of the article. Xiao Wei helped in statistical analysis. Qi Li and Xiao Wei helped in drafting the initial article. Xiao Wei helped in data collection. Qi Li and Xiao Wei helped in critical revision of the article. Qi Li helped in obtaining funding.

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Disclosures
None.

References

Table 3. Multivariate Analysis of Predictors for Early Hematoma Growth

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glasgow Coma Scale score</td>
<td>0.95</td>
<td>0.86–1.06</td>
<td>0.371</td>
</tr>
<tr>
<td>Time to baseline CT</td>
<td>0.62</td>
<td>0.49–0.79</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline hematoma volume</td>
<td>1.07</td>
<td>1.03–1.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Black hole sign on baseline CT</td>
<td>4.12</td>
<td>1.44–11.77</td>
<td>0.008</td>
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</tbody>
</table>

CT indicates computed tomography.

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Supplemental Figure I

1. Is there a relatively hypoattenuated area (black hole) within the hyperattenuating hematoma?  
   - Yes: Proceed to step 2.  
   - No: Stop Evaluation.

2. Is the black hole NOT connected with the adjacent brain tissue?  
   - Yes: Proceed to step 3.  
   - No: Negative Black Hole Sign.

3. Does the black hole have an easily identifiable border?  
   - Yes: Positive Black Hole Sign.  
   - No: Proceed to step 4.

4. Is there a >28 Hounsfield unit (HU) difference between the two density regions?  
   - Yes: Positive Black Hole Sign.  
   - No: Stop Evaluation.
ブラックホールサイン：脳内出血における画像マーカー
脳内出血患者の血腫拡大を予測する新たな画像マーカー

Black Hole Sign
Novel Imaging Marker That Predicts Hematoma Growth in Patients With Intracerebral Hemorrhage

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背景および目的：脳内出血後の早期の血腫拡大は致命的な神経合併症である。本研究では、脳内出血患者における血腫拡大の予測に対する CT のブラックホールサインの有用性を評価して報告する。

方法：脳内出血発症後 6 時間以内に施行した入院時の頭部 CT 画像におけるブラックホールサインの有無についてスクリーニングした。ブラックホールサインは高吸収の血腫に囲まれた明確な輪郭の低吸収域と定義した。血腫拡大の予測に対する CT 画像のブラックホールサインの感度, 特異度, 阳性予測値および陰性予測値を計算した。ロジスティック回帰分析でブラックホールサインの存在と早期の血腫拡大を評価した。

結果：登録患者は合計 206 例であった。ベースラインの CT 画像では, 206 例中 30 例 (14.6%) でブラックホールサインが検出された。ブラックホールサインの出現率は血腫拡大例 (31.9%) のほうが非拡大例 (5.8%) より高かった (P < 0.001)。早期の血腫拡大の予測に対するブラックホールサインの感度は 31.9%, 特異度は 94.1%, 陽性予測値は 73.3%, 陰性予測値は 73.2% であった。多変量モデルでは、入院時の CT 検査までの時間をベースラインの血腫量、入院時の CT 画像におけるブラックホールサインは、それぞれ単独で血腫の拡大を予測した。

結論：CT のブラックホールサインは脳内出血患者における早期の血腫拡大を予測する簡単かつ容易に使用できる因子として有用であろう。


### 表 3 早期の血腫拡大の予測因子の多変量解析

<table>
<thead>
<tr>
<th>因子</th>
<th>オッズ比</th>
<th>95%信頼区間</th>
<th>P 値</th>
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CT：コンピュータ断層撮影。