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Accuracy of imaging markers on noncontrast computed tomography in predicting intracerebral hemorrhage expansion

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ABSTRACT

Objectives: Hematoma expansion (HE) is an important factor of unfavorable outcome in patients with intracerebral hemorrhage (ICH). Imaging markers on noncontrast computed tomography (NCCT) provide increasing value in the prediction of HE due to fast and easy-to-use advantages; however, the accuracy of NCCT-based prediction of intracerebral HE remains unclear. We aimed to investigate the predictive accuracy of NCCT markers for the evaluation of HE using a well-characterized ICH cohort.
Methods: We retrospectively analyzed 414 patients with spontaneous ICH, who underwent baseline CT within 6 h after symptom onset and follow-up CT within 24 h after ICH. Hematoma volumes were measured on baseline and follow-up CT images, and imaging features that predicted HE were analyzed. The test characteristics for the NCCT predictors were calculated.
Results: Of the 414 patients investigated, 63 presented blend sign, 45 showed black hole sign, 36 had island sign and 34 had swirl sign. In the 414 patients, 88 presented HE, the incidence was 21.26%. Of the 88 patients with HE, 22 presented blend sign, 11 showed black hole sign, 8 had swirl sign and 7 had island sign. The blend sign showed highest sensitivity (25.00%) and swirl sign showed the highest specificity (92.02%) among the four predictors. We noted excellent interobserver agreement for the identification of HE.
Conclusion: The four NCCT markers can predict HE with limited sensitivity, high specificity and good accuracy. This may be useful for prompt identification of patients at high risk of active bleeding, and prevention of over-treatment associated with HE.

Abbreviations: HE, hematoma expansion; ICH, intracerebral hemorrhage; NCCT, noncontrast computed tomography.

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Intracerebral hemorrhage; hematoma; multidetector computed tomography; biomarker; stroke

Introduction

Intracerebral hemorrhage (ICH) is a common neurological emergency associated with high incidence rates, accounting for 9–13% of strokes in high-income countries, but showing a significant increase up to 25% in China [1]. Compared with other stroke subtypes, ICH patients suffer higher mortality and more severe disability [2,3]. Several risk factors such as hematoma location, initial ICH volume, perihematomal edema and early hematoma growth are significantly associated with unfavorable outcomes in patients with ICH [4–6]. Early hematoma growth is a predictive event compared with hemorrhage location and volume which are unmodifiable on presentation [7]. Therefore, rapid identification of patients at high risk of active bleeding is essential for prompt therapeutic intervention.

There have been several validated imaging findings on computed tomography (CT) which can predict early hematoma expansion (HE) such as spot sign observed on computed tomographic angiography (CTA) source images [8–10] and intrahematoma hypodensities, blend sign as well as island sign showed on non-contrast computed tomography (NCCT) images [11–16]. However, CTA is not part of the routine diagnostic workup of acute ICH in many medical settings, and the accuracy of spot sign for prediction of HE was also shown to be suboptimal [17]. NCCT is a preferred method for patients with ICH since it is fast, safe and widely available. The imaging features on NCCT may predict early HE and then facilitate the evaluation of poor outcomes in ICH patients. Currently, several NCCT predictors of HE have been reported and validated [7,11–16]; however, the conclusions are still inconsistent, and the accuracy of NCCT markers in predicting HE remains unclear.

In this study, we aimed to investigate the accuracy and reliability of multiple NCCT markers in predicting early hematoma expansion in patients with ICH.

Methods

Study population

This study was approved by the Institutional Review Board of Beijing Tiantan Hospital. Written informed

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consent was waived by the Institutional Review Board considering the retrospective nature of the investigation. The data that support the study findings are available from the corresponding author upon reasonable request. This retrospective study was performed in consecutive patients with ICH aged >18 years, who were registered at our hospital from November 2007 to May 2018. We included patients with the following characteristics: (1) spontaneous ICH, (2) ICH diagnosed on baseline CT within 6 h of symptom onset, (3) follow-up NCCT performed within 24 h after the initial CT and (4) no anticoagulation treatment administered. Following were the exclusion criteria for this study: (1) secondary ICH such as vascular malformation and tumor, traumatic and aneurysmal bleeding, (2) hemorrhagic transformation of ischemic stroke and (3) missing data of follow-up NCCT. We recorded the following clinical data: age, sex, medical history, the time interval from symptom onset to baseline CT scan, 3-month mortality and disability rates. Characteristics of the study population are described in the online-only Data Supplement.

Images acquisition and analysis

All patients with ICH underwent a baseline CT and follow-up NCCT scans within 24 h after symptom onset. The baseline and follow-up CT were performed by standard imaging parameters with axial section thickness 5 mm and matrix = 512 × 512. Baseline hemorrhagic volume and hematoma volume on follow-up NCCT were calculated using semi-automated three-dimensional Slicer software. All the CT images were independently analyzed by two experienced reviewers, who were blinded to the clinical information of patients with ICH, to determine the presence of the NCCT predictors such as black hole sign, swirl sign, blend sign and island sign.

HE was defined as relative hematoma growth >33% over the initial volume identified on CT or an absolute increase in hematoma volume >12.5 ml over the baseline ICH volume [12,13]. According to previously described radiological criteria [11–16], black hole sign [13] was defined as (1) an area of relative hypoattenuation encapsulated within the hyperattenuating hematoma, (2) round, oval or rod-like shape without any connection with the adjacent brain parenchyma, (3) an area of hypoattenuation with well-defined margin and (4) a density difference of at least 28 Hounsfield units (Hu) between two areas of differing densities. Swirl sign [14–16] was defined as a swirling hypodense or isodense region inside the hyperdense hematoma compared to the attenuation of brain parenchyma, and that could be connected with the surrounding brain tissue. These regions could vary in shape and could be round, streak-like or irregular. The sign should be observed in both the axial and coronal plane. There was an overlap in the CT attenuation between black hole sign and swirl sign; therefore, we distinguished the two signs based on the CT value of the hypoattenuation areas. A hypodense area with an attenuation of at least 28 Hu compared with a hematoma and density approaching that of the brain parenchyma was assigned to black hole sign. A hypodense region with density lower than that of brain tissue but higher than that of cerebrospinal fluid was allotted to swirl sign. The imaging features of redefined black hole sign and swirl sign are illustrated in Figure 1. Blend sign [12] was defined as (1) blending of areas of relative hypoattenuation with adjacent hyperdense area in a hematoma, (2) a hematoma with an attenuating difference of at least 18 Hu between the two areas of differing densities, (3) a well-defined margin between the two areas and (4) an area of relative hypoattenuation not encompassed by a hyperdense area of the hematoma. Island sign [11] was defined as (1) ≥3 small hematomas, all of which were scattered and separated from the main hematoma or (2) ≥4 small hematomas, some or all of which were connected to the main hemorrhage. Two experienced radiologists who were blinded to the clinical data of ICH patients independently reviewed all

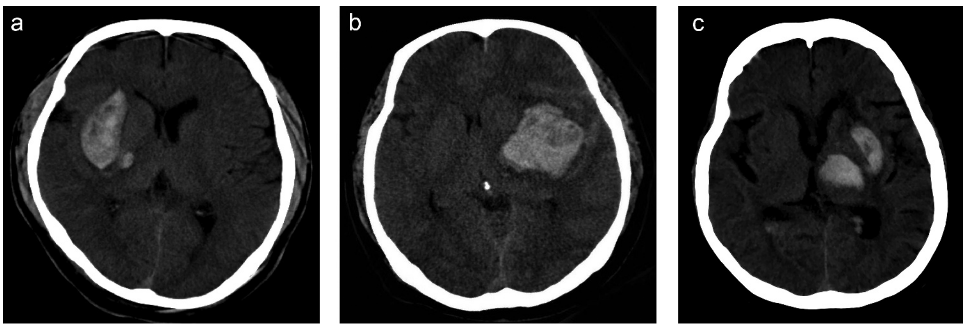

Figure 1. Illustration of redefined black hole sign and swirl sign. Axial non-contrast computed tomography (CT) images. (a) Black hole sign in a patient with right basal ganglia hemorrhage. There are two round hypodense areas encapsulated within the hyperdense hematoma with clear margin and a density difference of 41 Hounsfield units (Hu). (b) Swirl sign in left basal ganglia hematoma. A swirling hypodense region inside the hyperdense hematoma with an CT value of 27 Hu. (c) Swirl sign in another ICH patient, which shows the area of hypoattenuation connected with the adjacent brain parenchyma.

the baseline CT and follow-up NCCT images, and assessed the four aforementioned imaging features. Discrepancies regarding the confirmation of CT features and the presence of the four predictive signs were resolved by consensus through discussion.

Statistical analysis

Continuous variables were presented as medians and interquartile ranges or means ± standard deviation (SD). Categorical data were expressed as percentages. The demographic characteristics and NCCT imaging features (black hole, swirl, blend and island sign) were compared between patients with and without HE using Fisher exact test, student's *t* test, Z test or the Mann-Whitney U test as appropriate. The test characteristics (sensitivity, specificity and positive and negative predictive values) were calculated. The receiver operating characteristic (ROC) curve was plotted, and accuracy (true positive + true negative/sample size) was also calculated. The Cohen κ statistic was used to determine the interobserver reliability of the four NCCT predictive markers evaluated in this study. A probability value <0.05 was considered statistically significant. All statistical analyses were performed using a commercial SPSS software package Version 23.0 (IBM Corporation, Armonk, NY).

Results

Demographic and clinical characteristics

A total of 414 patients with spontaneous ICH were included in this study; no patient underwent surgical operation before follow-up CT was performed. The study included 297 (71.74%) man and 117 (28.26%) women (male: female ratio 2.5:1). The mean patient age was 54.7 ± 11.9 years (range: 19–84 years). The initial hemorrhage was located in the deep region 340 (82.13%), cerebral lobes 58 (14.01%), brain stem 8 (1.93%) and cerebellum 8 (1.93%). The median baseline hemorrhage volume was 20.55 ml. The mean time interval from symptom onset to baseline CT scan was 2.68 h. Significant HE was observed in 88 of 414 patients with ICH who underwent follow-up NCCT within 24 h.

Prevalence and characteristics of the four NCCT markers

A total of 178 (43.00%) ICH patients showed predictive signs on the baseline CT images. Blend sign, black hole sign, island sign and swirl sign were observed in 63 (15.22%), 45 (10.87%), 36 (8.70%) and 34 (8.21%) of the 414 patients with ICH, respectively. In the 414 ICH patients, 88 presented HE on follow-up NCCT (incidence rate of HE was 21.26%). Of the 88 patients with HE, 22 (25.00%) had blend sign, 11 (12.50%) had black hole sign, 8 (9.09%) had swirl sign and 7 (7.95%) had island sign. The baseline demographic and CT imaging characteristics of the patients with and without HE are summarized in Table 1.

The four NCCT imaging markers showed limited sensitivity and high specificity for prediction of HE. Blend sign showed the highest sensitivity of 25% and swirl sign showed the highest specificity of up to 92.02% among the four NCCT markers evaluated in this study. The area under the ROC curve was 0.568 for blend sign, 0.517 for black hole sign, 0.505 for swirl sign and 0.502 for island sign (Figure 2). With regard to the accuracy of the four NCCT markers, swirl sign was relatively high up to 74.40%, and black hole sign was low to 73.19%. The test characteristics of the predictors of early HE investigated in this study are shown in Table 2. There was excellent interobserver agreement for identification of the features of HE on NCCT images, and the kappa value was 0.864, 0.816, 0.814 and 0.808 for swirl, island, black hole and blend sign.

Table 1. Comparison of baseline demographic and CT imaging characteristics between patients with and without hematoma expansion.

	Hematoma expansion		
	Yes (*n* = 88)	No (*n* = 326)	*P*-value
Age, mean (SD)	54.66 (11.60)	54.64 (12.03)	0.194
Sex, *n* (%)			0.004
Male	74 (84.09%)	223 (68.40%)	
Female	14 (15.91%)	103 (31.60%)	
Baseline ICH volume, median, (IQR)	16.27 (7.30–30.06)	15.60 (7.95–29.27)	0.482
ICH location, *n* (%)			0.801
Deep	75 (85.23%)	265 (81.29%)	
Lobar	10 (11.36%)	48 (14.72%)	
Brainstem	2 (2.27%)	6 (1.84%)	
Cerebellum	1 (1.14%)	7 (2.15%)	
IVH, *n* (%)	22 (25.00%)	117 (35.89%)	0.055
Blend sign, *n* (%)	22 (25.00%)	41 (12.58%)	0.004
Black hole sign, *n* (%)	11 (12.25%)	34 (10.43%)	0.580
Swirl sign, *n* (%)	8 (9.09%)	26 (7.98%)	0.735
Island sign, *n* (%)	7 (7.95%)	29 (8.90%)	0.781

ICH indicates intracerebral hemorrhage; IQR, interquartile range; IVH, intraventricular hemorrhage; and SD standard deviation.

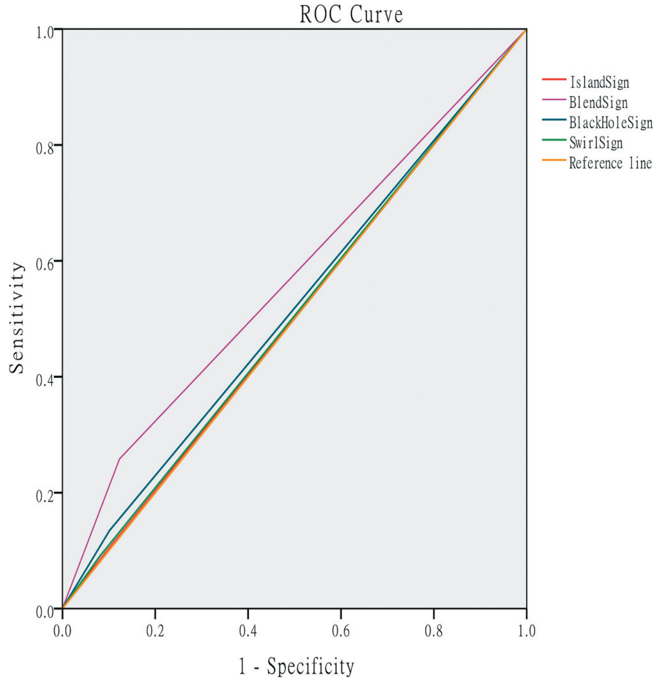

Figure 2. Receiver operating characteristic (ROC) curve showed the area under the curve was 0.568 for blend sign, 0.517 for black hole sign, 0.505 for swirl sign and 0.502 for island sign.

Table 2. Test characteristics of four predictors for early hematoma expansion.

	N	Incidence rate (%)	SE (%)	SP (%)	PPV (%)	NPV (%)	Accuracy (%)
Black hole sign	45	10.87	12.50	89.57	24.44	79.13	73.19
Swirl sign	34	8.21	9.09	92.02	23.53	78.95	74.40
Blend sign	63	15.22	25.00	87.42	34.92	81.20	74.15
Island sign	36	8.70	7.95	91.10	19.44	78.57	73.43

SE indicates sensitivity; SP, specificity; PPV, positive predictive value; and NPV, negative predictive value.

Discussion

The purpose of this study was to investigate the accuracy of NCCT markers in predicting HE using a large spontaneous ICH cohort. We found that the four NCCT imaging markers could predict HE with limited sensitivity, high specificity and good accuracy. These results suggested that NCCT markers are still inadequate in rapid identification of ICH patients at high risk of HE. Therapeutic intervention to minimize unfavorable outcomes associated with HE based on NCCT prediction needs to be carefully considered to avoid overtreatment of patients with ICH.

We evaluated four NCCT markers as predictor of HE in our study. The overall incidence of HE in patients with ICH was 21.26%, which was slightly lower than those reported in recent studies [18,19]. A potential explanation for this was the differences in cohort composition and variables associated with HE and NCCT signs. In this study, a large sample size of ICH patients were registered, and these patients were recruited from the departments of emergency, neurology and neurosurgery rather than from a single stroke unit. Owing to a relatively small bias in sample selection, our results including incidence, sensitivity and specificity are likely to accurately reflect the real-world clinical picture. The NCCT markers investigated in this study are widely available and easy-to-use, and may be rapidly evaluated using baseline NCCT. Just for this reason, our study is clinically important and would significantly contribute to the practical application because most of ICH patients experience HE within the first 6 h after symptom onset.

The CTA spot sign is the strongest predictor in identifying patients at high risk of HE, other CTA-based markers such as spot-and-tail sign and leakage sign have also been validated to be independent predictors of HE [20,21]. However, emergency CTA is not readily available in many hospitals, particularly within the first several hours after ICH onset. In the Antihypertensive Treatment of Cerebral Hemorrhage II clinical trial, Morotti et al. [17] observed that more than 80% of the participants did not undergo CTA examination, and in those who underwent CTA, the diagnostic accuracy of the spot sign was poor than that reported by prior studies. In view of these facts, there is an increasing need for predictive markers on NCCT because of its widely available and easy-to-use in all patients with ICH.

Blend sign is an excellent imaging marker of HE in patients with ICH. In a previous study, Li et al. [12] reported that blend sign was an independent predictor of HE with high sensitivity and specificity. In our study, however, blend sign showed low sensitivity and high specificity. This discrepancy between the two sensitivity may be attributed to the differences in hematoma volume. In their study, the patients with ICH presented a relatively large baseline hematoma volume, and the NCCT-based predictors of HE are more prevalent in large hemorrhages [22].

Black hole sign and swirl sign are NCCT markers that reflect hematoma density heterogeneity for HE prediction. Compared with black hole sign, swirl sign showed a more hypoattenuating area and could be encapsulated by the hematoma or could be connected to the surrounding brain tissue. It is therefore necessary to establish an objective method to distinguish between these signs for better predictive accuracy. In the present study, we redefined black hole sign and swirl sign on the basis of intrahematoma hypodensity using a relatively accurate CT attenuating value to avoid overlap between the two different signs. The intrahematoma hypodensity was a strong predictor of HE, but it showed low specificity for HE prediction because of its unclear definition and lack of strict defining criteria. Our results showed that black hole sign and swirl sign both had high specificity in predicting HE compared with findings reported by previous studies [13–16].

We observed that island sign showed low incidence, sensitivity and high specificity in our study compared with the results reported by previous studies. In a study that included 252 patients with ICH, Li et al. [11] defined a special type of irregular hematoma as island sign, and reported that island sign may accurately predict early HE with 44.5% sensitivity and 98.3% specificity. The discrepancies in sensitivity may reflect differences in sample size, severity of patients and geographic distribution between the two studies. Additionally, island sign remains a nonspecific marker owing to the lack of objective criteria to define this marker.

In our study, the four NCCT markers showed low sensitivity, high specificity and moderate accuracy as predictors of early HE. A predictor of HE showing good specificity may be useful to select the optimal therapeutic strategy to minimize unfavorable HE-induced outcomes in patients with ICH. Notably, the low sensitivity of the NCCT markers evaluated in this study is also important because this finding may provide a hint that overtreatment should be avoided in patients at low risk of HE during the course of clinical treatment of ICH. A recent study [23] reported that patients with homogeneous and regularly shaped small ICH pretend to be safe for less intensive monitoring and may not benefit from therapies aimed at preventing ICH expansion.

Several HE prediction scores that do not require the CTA spot sign evaluation have been published and are used in clinical practice. HE prediction scores may combine multiple NCCT predictors and risk factors of HE for a relatively accurate assessment of HE. Regardless of the Hematoma Expansion Prediction score [24], the clinical prediction algorithm (BRAIN) [25] or BAT score [7], HE risk grading scores are mainly based on NCCT markers as predictors, and currently, there is lack of consistent criteria and consensus regarding the optimal grading of each variable.

HE is a dynamic process that usually occurs within 24 h after ICH onset [2,26]. The HE detection rate is significantly associated with the time when ICH patients arrive at hospital and receive baseline CT scan. The earlier the baseline CT is performed, the higher the detection rate of HE may be found. Therefore, ICH patients should be urgently transferred to a medical institution preferably within 6 h after symptom onset. HE is often regarded as the results of single vessel rupture with continuous bleeding as a tap, or of secondary mechanical shearing of adjacent vessels caused by expansion of initial hemorrhage [27,28]. No matter single or multifocal bleeding, they all may lead to HE and show some characteristics on NCCT images.

Several limitations should be considered in this study. First, we evaluated the accuracy of the four NCCT markers as predictors of HE, and estimated the overall incidence of HE in patients with ICH. However, we did not investigate the association between HE and poor outcomes of ICH patients. Second, there was a little insufficiency in the data consistency because our study cohort included patients with ICH recruited from three different stroke units including the emergency, neurology and neurosurgery departments. In our opinion, the multiple-unit ICH cohort represents a strength of our study because our results accurately reflect the real-world situation in clinical practice. Third, the lack of long-term follow-up CT images and clinical data may affect further studies in the prognostic evaluation of ICH patients. We observed that 40 ICH patients suffered HE; however, without the four signs on NCCT, this part of the data needs to be further analyzed in future studies. CTA spot sign evaluation was not included in this study because CTA examination is not part of the routine diagnostic workup in ICH patients in our institution. In future studies, the incorporation of CTA spot sign and NCCT marker evaluation may play a great role in prediction of HE in patients with ICH [29].

In summary, we evaluated the accuracy of blend sign, black hole sign, swirl sign and island sign as predictors of early HE. The four NCCT markers can predict HE with low incidence, limited sensitivity, high specificity and good accuracy. These predictors are rapidly and widely available and easy-to-use for prediction of HE. This may provide help in rapid identification of patients with ICH at high risk of active bleeding and in precaution of over-treatment associated with HE.

Disclosure statement

The authors report no conflicts of interest.

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Data availability

The computed tomography images of the hemorrhage patients and other measurements are stored in our Dropbox. The data used to support the findings of this study are available from the corresponding author upon request.

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