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The Accuracy of the Spot Sign and the Blend Sign for Predicting Hematoma Expansion in Patients with Spontaneous Intracerebral Hemorrhage

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Statistical Analysis C
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Manuscript Preparation E
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Background: Hematoma expansion is associated with poor outcome in intracerebral hemorrhage (ICH) patients. The spot sign and the blend sign are reliable tools for predicting hematoma expansion in ICH patients. The aim of this study was to compare the accuracy of the two signs in the prediction of hematoma expansion.

Material/Methods: Patients with spontaneous ICH were screened for the presence of the computed tomography angiography (CTA) spot sign and the non-contrast CT (NCCT) blend sign within 6 hours after onset of symptoms. The sensitivity, specificity, and positive and negative predictive values of the spot sign and the blend sign in predicting hematoma expansion were calculated. The accuracy of the spot sign and the blend sign in predicting hematoma expansion was analyzed by receiver-operator analysis.

Results: A total of 115 patients were enrolled in this study. The spot sign was observed in 25 (21.74%) patients, whereas the blend sign was observed in 22 (19.13%) patients. Of the 28 patients with hematoma expansion, the CTA spot sign was found on admission CT scans in 16 (57.14%) and the NCCT blend sign in 12 (42.86%), respectively. The sensitivity, specificity, positive predictive value, and negative predictive value of the spot sign for predicting hematoma expansion were 57.14%, 89.66%, 64.00%, and 86.67%, respectively. In contrast, the sensitivity, specificity, positive predictive value, and negative predictive value of the blend sign were 42.86%, 88.51%, 54.55%, and 82.80%, respectively. The area under the curve (AUC) of the spot sign was 0.734, which was higher than that of the blend sign (0.657).

Conclusions: Both the spot sign and the blend sign seemed to be good predictors for hematoma expansion, and the spot sign appeared to have better predictive accuracy.

MeSH Keywords: Angiography • Hematoma • Intracranial Hemorrhage, Hypertensive

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Background

Spontaneous intracerebral hemorrhage (sICH) is a severe type of stroke with high morbidity and mortality throughout the world [1]. Hematoma expansion is significantly associated with poor outcome in sICH patients [2]. Some indicators could expectantly identify sICH patients with high risk of hematoma expansion and to some extent improve patient prognosis [3]. In 2007, Wada et al. suggested that the spot sign on computed tomography angiography (CTA) was associated with hematoma expansion [4]. Many subsequent studies further confirmed this point [5,6]. The meta-analysis by Du et al. showed that the spot sign seemed to be a reliable neuroimaging predictor for hematoma expansion [7]. The CTA spot sign was also found to be associated with higher risk of intraoperative bleeding, postoperative rebleeding, and large residual sICH volumes in sICH patients undergoing hematoma evacuation [8]. Moreover, the spot sign score was found to be an independent predictor for mortality in hospital and poor outcomes in patients with sICH [9]. Although the spot sign may be a practical indicator, many factors could affect its accuracy, such as hematoma volume, history of anticoagulants, and onset-to-CTA time. However, when CTA was unavailable, potential neuroimaging predictors on non-contrast CT (NCCT) were necessary to predict hematoma expansion. The blend sign on NCCT, which was the blending of the hypoattenuating area and the hyperattenuating region with a clear margin, was introduced as a predictor for hematoma expansion by Li et al. [10]. The blend sign seemed to be an easily identified and highly specific predictor. However, no studies have compared the predictive value of the CTA spot sign and the NCCT blend sign in the same cohort of patients. Thus, we performed this retrospective cohort study to compare the accuracy of CTA spot sign and the NCCT blend sign in predicting hematoma expansion.

Material and Methods

Study design and patients

This was a retrospective study based on the prospective database of the ICH patients at the Department of Neurosurgery of West China Hospital, Sichuan University. This study was approved by the biomedical ethics committee of West China Hospital. All procedures performed in this study were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The inclusion criteria were the following: (1) adult patients had sICH confirmed by CT or MRI scans; (2) CTA was performed within 6 hours after the onset of sICH; and (3) follow-up NCCT scan was performed within 24 hours after the CTA. The patients were excluded if (1) secondary intracerebral hemorrhage was caused by tumor, aneurysm, or arteriovenous malformation (AVM); or (2) there were no available imaging studies, including initial CTA or follow-up NCCT. Patients who received emergency hematoma evacuation before follow-up NCCT was performed were also excluded. The management of blood pressure followed the recommendations of the latest edition of American Heart Association/American Stroke Association (AHA/ASA) and European Stroke Organisation (ESO) guidelines [1,11].

Clinical data

Baseline information including sex, age, admission blood pressure, and medical history were collected. Any of the following histories was recorded: hypertension, diabetes mellitus, previous stroke, previous acute coronary event, smoking, and alcohol abuse. In addition, results of admission coagulation tests including platelet count, prothrombin time (PT), activated partial thromboplastin time (APTT), and international normalized ratio (INR) were also collected.

Image acquisition

CTA was performed when the patients were admitted to the emergency department as a part of standard clinical care on a dual-source 64-slice CT scanner (SOMATOM Definition Flash; Siemens Healthcare Sector, Forchheim, Germany), including NCCT scan (120 kV, 340 mA, contiguous 5-mm axial slices) and CTA scan. For the CTA, 100 mL of ioversol (Iopamidol, Bracco Pharma Co, Shanghai, China; 370 mg I/mL) was intravenously injected at a rate of 4.8 mL/s via a power injector through an intravenous line using the following parameters: 80 kVp; 110 mA; slice thickness, 1 mm; and pitch, 1: 1. NCCT was performed within 24 hours after the first CT to evaluate the hematoma size.

Detection of the spot sign and the blend sign

All the CT scans were reviewed independently by two neuroradiologists who were blinded to the clinical condition of the patients. The initial CTA and follow-up NCCT were evaluated separately. Disagreements about the occurrence of the spot sign or the blend sign were settled by joint discussion of the two readers. Radiological criteria for the spot sign were in accordance with those reported previously: at least 1 focus of contrast pooling within the ICH: high Hounsfield unit (HU) value (>120); discontinuous from normal or abnormal vasculature adjacent to the ICH; and any size and morphology [12,13]. The hematoma blend sign was defined as follows: (1) there is blending of the relatively hypoattenuating area with the adjacent hyperattenuating region within a hematoma; (2) there is a well-defined margin between the hypoattenuating area and the adjacent hyperattenuating region that is easily recognized by the naked eye; (3) the hematoma should have at least an 18 HU difference between the 2 density regions; and

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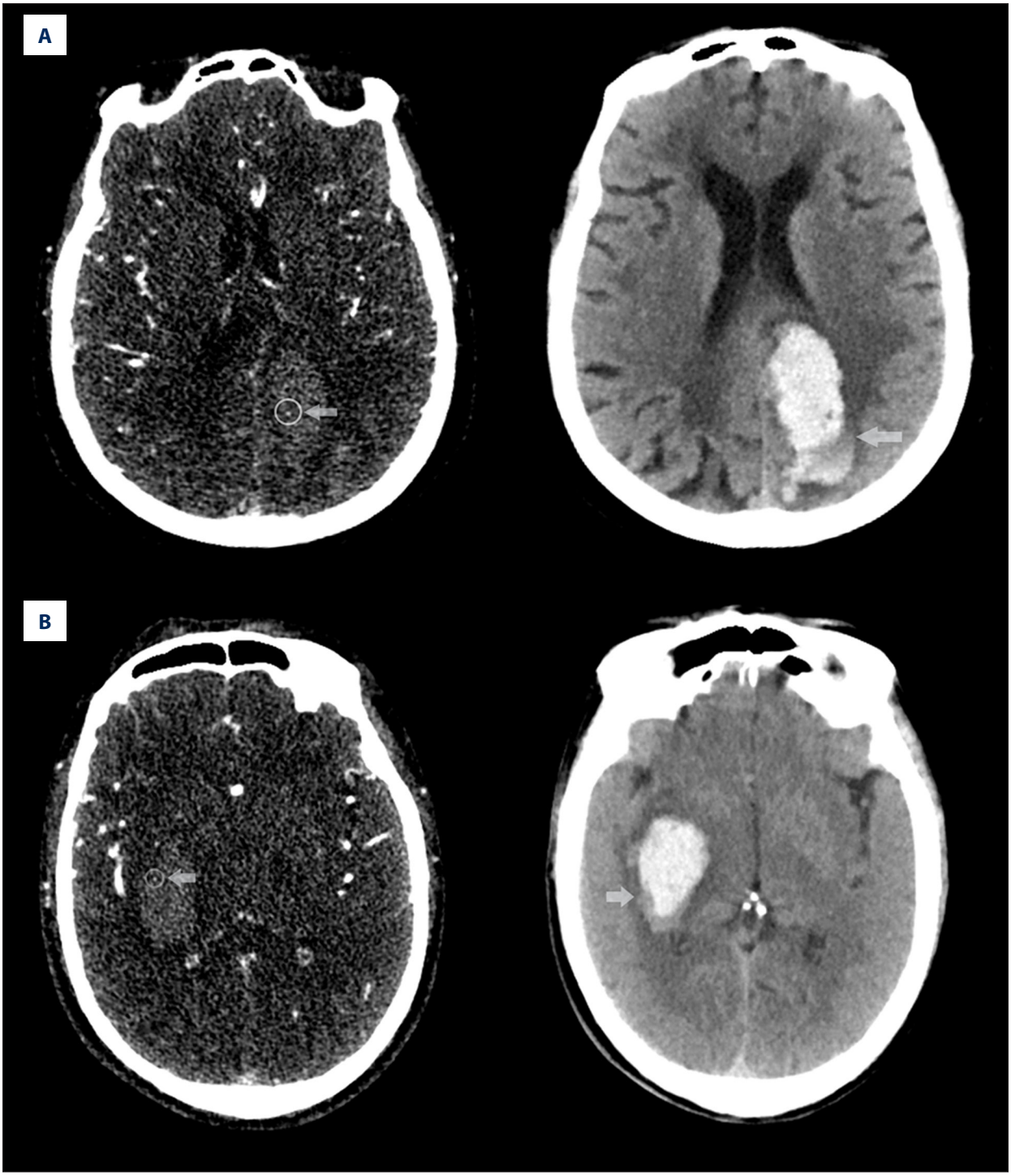
(4) the relatively hypoattenuating area is not encapsulated by the hyperattenuating region [10]. The hematoma has to meet the 4 criteria mentioned above to be defined as blend sign. Illustrative spot sign–positive CTA images and blend sign-positive NCCT images are showed in Figure 1.

Measurement of hematoma volume

Volume of hematoma was calculated from CT scans using the formula A*B*C/2, where A was the largest diameter on the largest hemorrhage slice, B was the maximal diameter perpendicular to A, and C was the vertical hematoma depth [14]. The hematoma expansion was defined as a >33% relative



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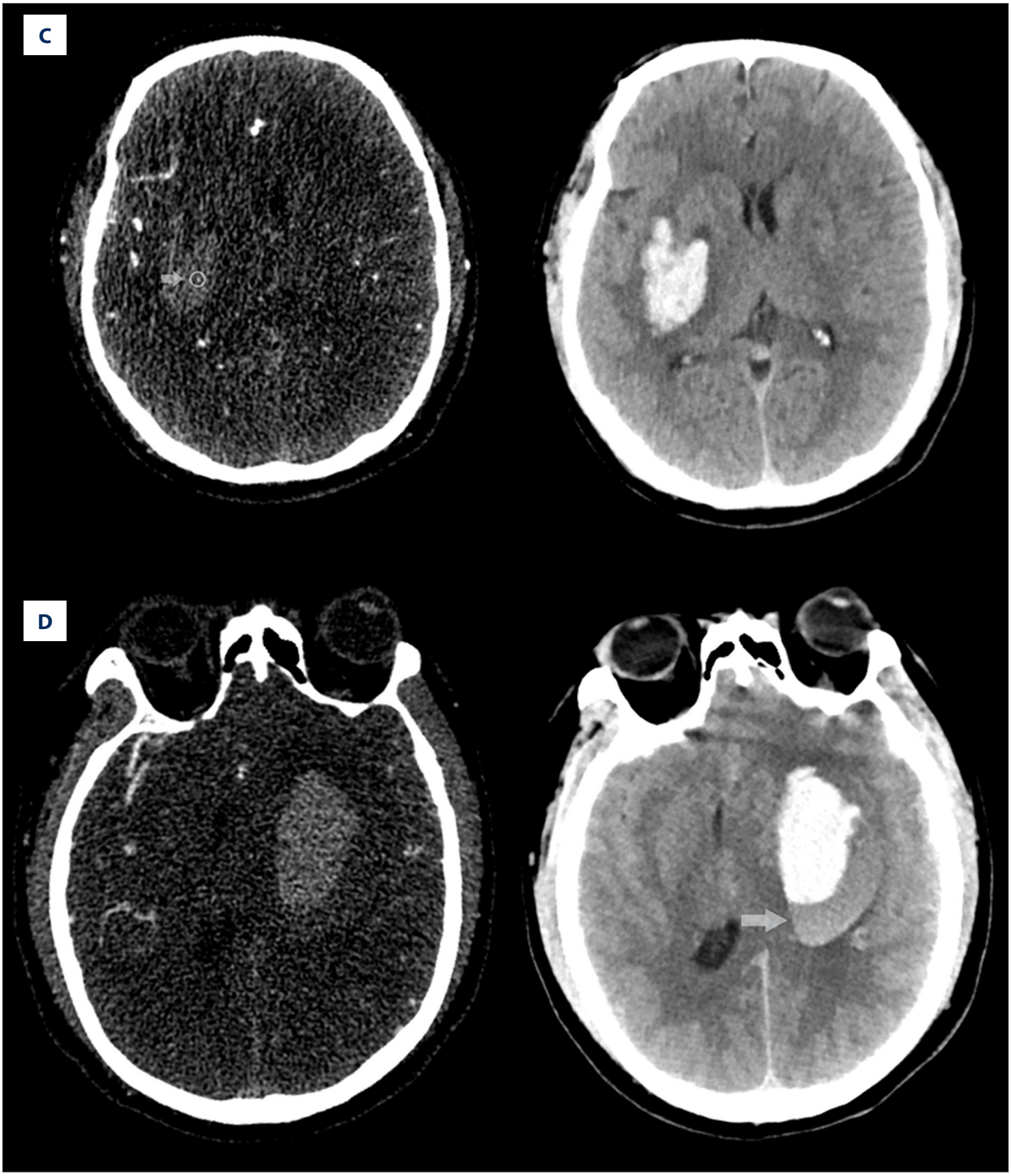

Figure 1. Illustration of the computed tomographic angiography (CTA) spot sign and the non-contrast computed tomographic (NCCT) blend sign. (**A, B**) Different locations of hematoma with spot sign (+) and blend sign (+). (**C**) Spot sign (+) and blend sign (–). (**D**) Spot sign (–) and blend sign (+).

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Table 1. Baseline characteristics.

	Expander (n=28)	Nonexpander (n=87)	P value
Mean age (yrs)	57±12	59±12	0.339
Sex, male	22	62	0.449
Admission SBP (mmHg)	177±30	171±30	0.329
Admission DBP (mmHg)	106±17	99±19	0.063
Hypertension	13	40	0.967
Diabetes mellitus	4	3	0.103
Alcohol consumption	14	30	0.142
Smoking	13	30	0.256
Previous stroke	1	6	0.853
PLT (10^9/L)	145±55	153±54	0.523
PT (s)	10.9±0.8	11.1±1.3	0.474
APTT (s)	27.8±2.3	27.2±5.9	0.408
INR	0.92±0.07	0.94±0.12	0.455
Time to CTA (hrs)	3.32±1.39	3.94±1.35	0.038
Hematoma volume (ml)	31.99±16.60	23.06±22.88	0.059
Spot sign	16	9	<0.001
Blend sign	12	10	<0.001

Data are mean ±SD or number of patients. PLT – platelet count; PT – prothrombin time; APTT – activated partial thromboplastin time; INR – international normalized ratio; CTA – computed tomography angiography.

increase or >12.5 mL absolute increase in hematoma size on follow-up CT scan [15].

Statistical analysis

All the data were analyzed by SPSS 21.0 and EXCEL 2010. Baseline characteristics including demographics, history, admission blood pressure, admission hematoma characteristics, and coagulation tests were compared between patients with hematoma expansion and those without hematoma expansion. Statistical significance was assumed with a probability value of less than 0.05. Continuous values were expressed as mean and standard deviation (SD) and analyzed by the t-test. Discontinuous variable data were expressed as median and interquartile range (IQR) and analyzed by the Wilcoxon rank sum test. The categorical values were analyzed by chi-square analysis. Multivariable logistic regression was performed to adjust the odds ratio (OR) and 95% confidence interval (CI) of the spot sign and the blend sign on hematoma expansion. The value of the spot sign and the blend sign for predicting hematoma expansion was analyzed by receiver-operator analysis. The area under the receiver-operating characteristic (ROC) curves of the spot sign and the blend sign were compared by using the Z test. The interobserver reliability for the identification of the spot sign and the blend sign was determined by calculation of κ values.

Results

From February 2015 to March 2016, a total of 115 consecutive patients met the inclusion criteria and were enrolled in this study. In this study, the median time interval from sICH onset to initial CTA was 4 hours (3, 5 hours). The range of age was between 36 and 83 years (mean 58.8±11.6 years). The mean baseline volume of hematoma was 25.24±21.80 mL. Positions of hematoma included lobar (17, 14.78%), basal ganglia (64, 55.65%), thalamus (14, 12.17%), cerebellum (6, 5.22%), and brain stem (14, 12.17%). Hematoma expansion was observed in 28 out of 115 patients. The mean volume of hematoma expansion was 24.7±23.0 mL. The baseline characteristics of the expander group and the non-expander group are shown in Table 1. In our study, the spot sign was observed in 25 patients, whereas the blend sign was observed in 22 patients. The prevalence of the spot sign and the blend sign was significantly higher in patients with hematoma expansion compared with

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Table 2. Multivariate analysis for hematoma expansion.

Values	Hematoma expansion		
	OR	95% CI of OR	P value
DBP-for every 1mmHg increase	1.026	0.998–1.054	0.064
Time to CTA – for every 1 hrs increase	0.686	0.457–1.031	0.070
Baseline hematoma volume – for every 1 ml increase	1.010	0.986–1.035	0.411
Blend sign	6.498	1.891–22.332	0.003
Spot sign	11.817	3.745–37.285	<0.001

DBP – diastolic blood pressure; CTA – computed tomography angiography.

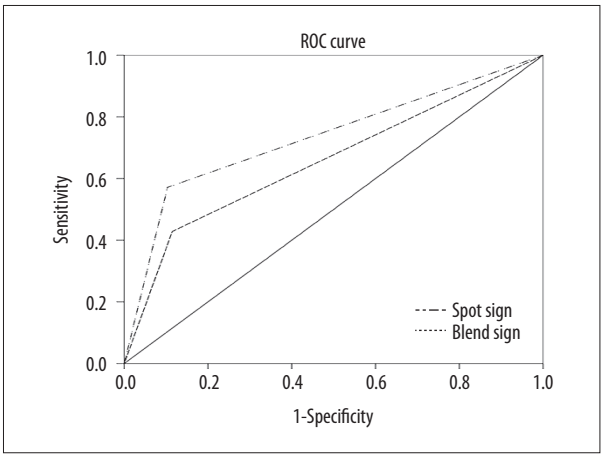

Figure 2. Receiver-operating characteristic (ROC) curve by using a binary definition of hematoma expansion. The area under the curve of the spot sign=0.734 and the area under the curve of the blend sign=0.657; P=0.383.

those without hematoma expansion. Interobserver reliability for the identification of the spot sign and the blend sign was excellent between the two neuroradiologists; the κ was 0.924 and 0.946, respectively. For the multivariable analysis, prevalence of the spot sign and the blend sign was independently associated with hematoma expansion (Table 2).

In this study, the sensitivity, specificity, positive predictive value, and negative predictive value of the spot sign for predicting hematoma expansion were 57.14%, 89.66%, 64.00%, and 86.67%, respectively. By contrast, the sensitivity, specificity, positive predictive value, and negative predictive value of the blend sign were 42.86%, 88.51%, 54.55%, and 82.80%, respectively. The ROC curves of the two procedures for predicting hematoma expansion in sICH patients are shown in Figure 2. No significant difference was found between the area under ROC curves of the spot sign and the blend sign (P=0.383)

Discussion

This is the first study comparing the predictive value of the CTA spot sign with that of the NCCT blend sign in the same cohort of patients with sICH. Both the spot sign and the blend sign had good predictive value for hematoma expansion. Although there was no significant difference in the predictive accuracy of the spot sign and the blend sign, the spot sign seemed to be a better neuroimaging marker for predicting hematoma expansion.

The CTA spot sign was shown to be a potential predictor for hematoma expansion in recent studies [6,7,16,17]. In accordance with previous studies, our study also showed that the CTA spot sign is a good predictor for hematoma expansion. The CTA spot sign was considered to be associated with bleeding from ruptured vessels, but the underlying mechanism is still unclear [12]. Although the results of these studies supported the predictive role of the CTA spot sign in hematoma expansion, the values were different. Wada et al. found the sensitivity, specificity, positive predictive value, and negative predictive value of the spot sign to be 91%, 89%, 77%, and 96% [4]. However, in Demchuk et al.'s study, the sensitivity, specificity, positive predictive value, and negative predictive value of the spot sign were 51%, 85%, 61%, and 78% [5]. Han et al. suggested the sensitivity, specificity, positive predictive value, and negative predictive value of the spot sign to be 57.38%, 90.48%, 74.47%, and 81.43% [18]. The meta-analysis by Du et al. showed the pooled sensitivity of the spot sign was 53% and the specificity was 88% [7]. The difference between sensitivity and specificity in these studies might have various causes. First, prevalence of the spot sign might be interfered with by different hematoma volumes or history of anticoagulant drugs. It has been found that the CTA spot sign can predict expansion of hematoma reliably in patients with hematomas >30 mL [19]. However, small hematomas have a lower prevalence of the spot sign and a lower risk of expansion [20]. ICH patients with a history of warfarin use and the apolipoprotein E epsilon2 allele are more likely to have a spot sign [21].

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Second, it was found that spot signs identified in earlier phases might be associated with greater absolute expansion [22]. With the increase of sICH onset-to-CTA time, the frequency of the CTA spot sign increases and the positive predictive value of the spot sign for hematoma expansion decreases [23]. In spot sign-positive patients, a shorter onset-to-CTA time and higher HU of spot signs are factors for prediction of hematoma expansion [24]. Third, the different scan timing could lead to different prevalence and predictive accuracy of the CTA spot sign [25]. A 90-second delay in time of CTA could improve the sensitivity of the spot sign for predicting hematoma expansion [26]. In addition, the spot sign identified on CTA obtained at high levels of tube was found to have better predictive accuracy for hematoma expansion [27]. Thus, due to these various factors a standardized protocol is necessary to improve the practicability and accuracy of the CTA spot sign.

Unlike the spot sign, the blend sign focused on the heterogeneity of hematoma on NCCT. Compared to the spot sign on CTA, the blend sign is easier to identify. Li et al. were the first to report this novel neuroimaging predictor [10]. In their study, the sensitivity, specificity, positive predictive value, and negative predictive value of the blend sign for predicting hematoma expansion were 39.3%, 95.5%, 82.7%, and 74.1%, respectively, which suggested that the blend sign seemed to be a good predictor for hematoma expansion [10]. In the present study, the sensitivity and the negative predictive value were higher and the specificity and the positive predictive value were lower. Just like the spot sign, many underlying factors might influence the predictive accuracy of the blend sign. The time to baseline CT of our study (3.32 hours in expanders and 3.94 hours in non-expanders) was longer than that in Li et al.'s study (1.67 hours in expanders and 2.76 hours in non-expanders). Moreover, the initial volume of hematoma was larger in our study (31.99 mL in expanders and 23.06 mL in non-expanders) than that in Li et al.'s study (24.31 mL in expanders and 13.12 mL in non-expanders). The difference in baseline CT time and initial hematoma volume might be associated with the difference in predictive accuracy. Further research is needed to investigate the exact factors affecting the predictive value of the blend sign.

Recently, other novel neuroimaging predictors for hematoma expansion were also reported. It was suggested that the CTP dynamic spot sign had a higher predictive value for hematoma expansion than CTA [17]. Fluid levels, density heterogeneity, and margin irregularity on NCCT were found to be associated with hematoma expansion at 24 hours [28]. Hypodensity within ICH on NCCT might be an independent predictor for hematoma expansion [29]. Similarly, the black hole sign on NCCT, which was defined as the hypoattenuating area within the hyperattenuating hematoma with a clear border, was found to be a predictor for hematoma expansion [30]. Although some scoring systems seemed to be effective in hematoma expansion prediction, they did not include these new imaging markers [3]. A comprehensive predictive scoring system including more neuroimaging markers is expected to be built in the future.

There are several limitations in our study. First, this was a single-center retrospective cohort study, and the sample size was relatively small. Moreover, only the CTA spot sign and the blend sign were investigated. Furthermore, the interval between onset and baseline CTA was relatively long, which might influence the predictive accuracy of both signs. Further multi-center prospective studies with larger cohorts and shorter onset-to-CTA time are needed.

Conclusions

Our study compared the predictive value of the spot sign and the blend sign in the same cohort of sICH patients. Both the spot sign and the blend sign seemed to be good predictors for hematoma expansion, and the spot sign appeared to have a better predictive accuracy. Since more and more neuroimaging predictors for hematoma expansion have been developed, it is hoped that a comprehensive predictive scoring system including more neuroimaging markers will be built in the future.

Conflict of interest

The authors declare that they have no conflicts of interest relevant to this work.

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