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ORIGINAL ARTICLE

Eliminating vascular interference from the Spot Sign contributes to predicting hematoma expansion in individuals with spontaneous cerebral hemorrhages

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Abstract

The computed tomography angiography (CTA) Spot Sign is an effective means of predicting hematoma expansion (HE) in the context of spontaneous intracerebral hemorrhage (ICH). We investigated whether continuous CTA source images could differentiate the Spot Sign and blood vessels in the hematoma, and whether it would improve Spot Sign accuracy as an HE predictor. We screened for the presence of CTA Spot Sign in individuals affected by spontaneous ICH within 24 h of symptom development. Based on our findings, we determined the sensitivity, specificity, and positive/negative predictive values of this sign as a predictor of HE both on its own and following the exclusion of blood vessels. In addition, a receiver-operating characteristic approach was used to assess the accuracy of Spot Sign with and without elimination of vascular interference. A total of 265 patients were included in this study. The Spot Sign was observed in 100 patients, including in 29 patients wherein it was confirmed to be blood vessels as determined based upon continuous CTA source images. With respect to predicting HE, Spot Sign sensitivity, specificity, positive predictive values, and negative predictive values were 57%, 71%, 48% and 78%, respectively. Following the exclusion of blood vessels, these values were 57%, 87%, 68% and 81%, respectively. Spot Sign area under the curve after excluding blood vessels was 0.718, which was higher than that of the Spot Sign (0.638). After continuous CTA, source images are used to exclude blood vessels in the hematoma, the Spot Sign is thus more accurate in predicting HE.

Keywords Spontaneous intracerebral hemorrhage · Hematoma expansion · Spot Sign · Computed tomography angiography

Introduction

Spontaneous ICH is the least treatable form of stroke, making up 10–15% of stroke cases in the world [1]. In recent years, several studies have been conducted in an effort to improve outcomes, but the mortality rate is still high, with just 12–39% of survivors remaining able to live on their own after 6 months [2]. HE is linked to negative ICH patient outcomes, and this can potentially be modified if predicted or identified early [3, 4]. Therefore, clarifying why radiological findings are predictive of HE may be of clinical value for ICH patients [4]. In several previous studies, the Spot Sign on CTA had been shown to be an effective indicator of HE [5–7]. The 2015 AHA/ASA Guideline also posit that the CTA can help to identify patients at risk for HE [8]. This sign was found to be associated with higher risk of intraoperative bleeding, postoperative bleeding, as well as to large remainder hematoma volumes in ICH patients via hematoma evacuation [9]. This sign has also been shown to

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predict worse mortality and outcomes in IHC patients [10, 11]. Generally, the Spot Sign is defined as at least 1 focus of contrast pooling within the ICH: high Hounsfield unit (HU) value (> 120); and any size and shape [10, 12]. The Spot Sign is often considered to be the enhancement point that is formed via leakage of contrast medium in hematomas [5]. However, we often find that these enhancement points might also be the cross section of blood vessels or an aneurysm in the hematoma, potentially affecting Spot Sign accuracy. Continuous CTA source images can better identify blood vessels in hematomas, enhancing Spot Sign sensitivity and specificity as a means of predicting HE. We, therefore, performed a retrospective cohort study to explore factors affecting Spot Sign accuracy as an HE predictor.

Materials and methods

Study design and patients

We retrospectively analyzed cases which were recorded in the ICH database between March 2017 and September 2018, Northern Jiangsu People's Hospital. The Biomedical Ethics Committee of Northern Jiangsu People's Hospital approved this study. Inclusion criteria: (1) spontaneous ICH as confirmed via CT scanning; (2) CT and CTA performed upon admission and no more than 24 h following symptom development; (3) age ≥ 18 years; (4) follow-up CT scan was conducted within 24 h after CTA. Exclusion criteria: (1) ICH caused by moyamoya disease, infarction, tumor or trauma; (2) surgical evacuation prior to follow-up scan; (3) unavailable initial CT or follow-up CT; (4) simple intraventricular or subarachnoid hemorrhage. Spontaneous ICH patients underwent treatment in a devoted stroke unit in a manner consistent with the latest guidelines [13, 14].

Clinical data

We gathered basic patient data including age, gender, blood pressure upon admission, time between symptom development and CT, anticoagulant use, medical history (factors including previous strokes, smoking history, diabetes, or hypertension), as well as available laboratory data including platelet levels, activated partial thromboplastin time, international normalized ratios, prothrombin times, fibrinogen levels, and calcium levels.

Imaging acquisition

The CT scans which use a 64-slice Discovery CT750HD scanner were conducted based upon standard clinical parameters using contiguous 5-mm axial slices from the skull base to vertex. For the CTA, 50–100 mL of iodixanol injection (270 mg I/mL) was intravenously injected (5 mL/s) using a power injector as follows: 80 kVp; 375 mA; slice thickness, 0.625 mm. Within 24 h of CTA, a follow-up CT scan was conducted to assess hematoma size.

Imaging marker detection

The images were obtained for neuroradiologists' further evaluation. Two independent individuals experienced in reading such imaged independently assessed images for CTA Spot Sign. Hemorrhages were identified based on their locations in the basal ganglia, brain lobe, brain stem, or cerebellum. The continuous CTA source images were used to assess whether the Spot Sign was due to a cross section of a blood vessel or aneurysm in the hematoma. The specific criteria used for this determination were as follows: if the Spot Sign is of a continuous linear density extending from the surface of the brain or ventricle into the hematoma, it is considered a blood vessel [15]. During the rating process, the two independent neuroradiologists had been blinded to both clinical details and other scans from the same patients. Disagreements between readers were resolved via discussion. We further evaluated other HE predictors, such as satellite sign, blend sign, black hole sign, margin irregularity, and hematoma density heterogeneity as previously described [16–20].

Hematoma volume measurement

The ABC/2 approach was used to determine hematoma volume, with A being the largest diameter of the largest hematoma image, B being the largest diameter perpendicular to A, and C being the hematoma vertical depth [21]. HE was detected based upon hematoma relative growth > 33% or hematoma absolute growth > 6 mL upon follow-up imaging [5, 22].

Statistical analysis

Excel 2016 and SPSS v25.0 were used for all analyses. We compared all collected baseline information between patients. Normal distribution data were present in mean ± standard deviation (SD); non-normal distribution data were present in median and maximum and minimum. Continuous variables were compared via F tests and t tests. Discrete variables are instead given as percentages (%) and were compared via χ^2 tests. Spot Sign odds ratios (ORs) and 95% confidence intervals (CIs) were established via multivariable logistic regression analyses. The variables incorporated into this analysis were those with a $P < 0.05$ in a univariate analysis, and those reported to be linked to HE in past research. The k values were used to analyze the inter-reader reliability. Statistical significance was assumed if $P < 0.05$ (Fig. 1).

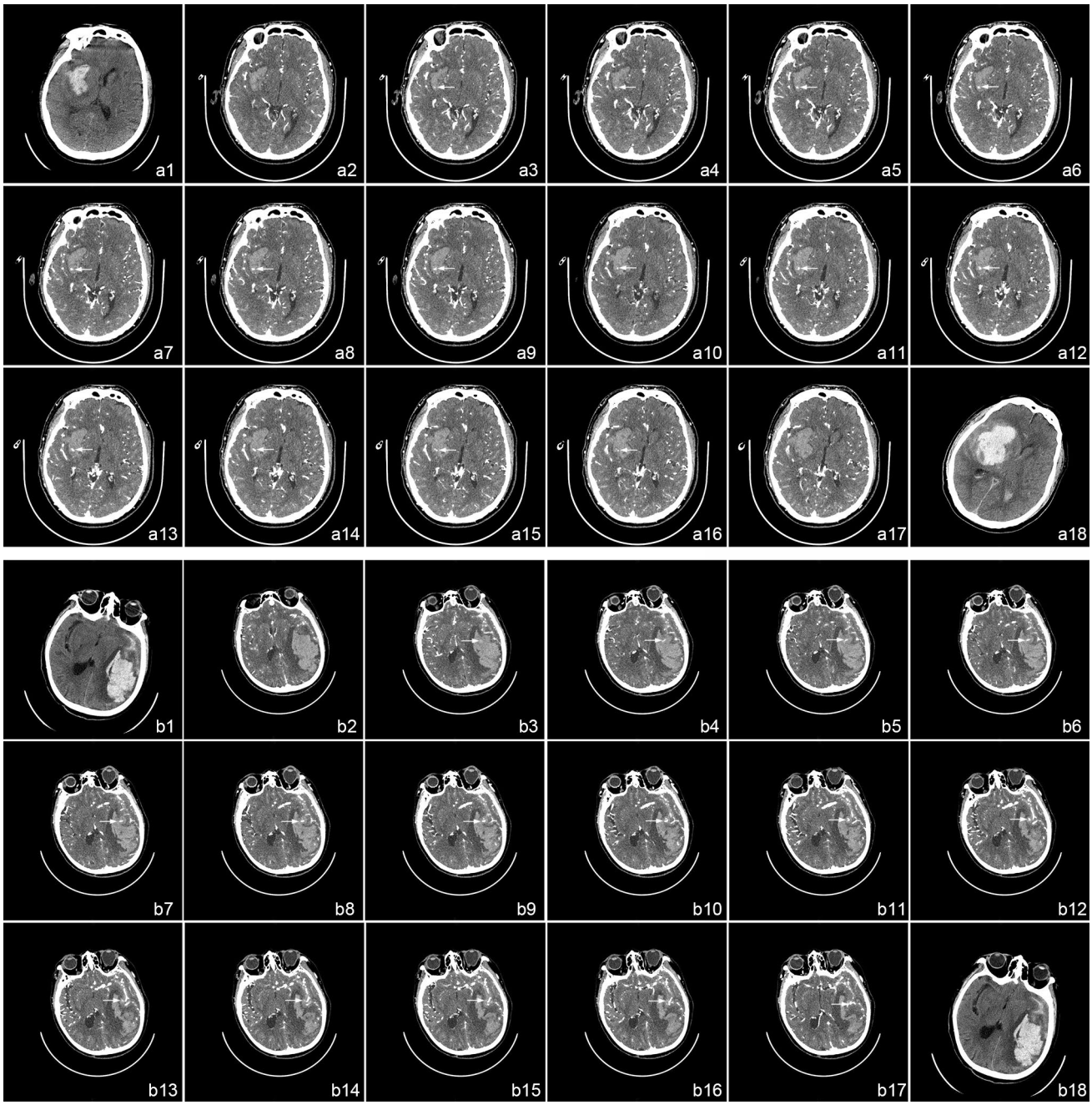

Fig. 1 Illustration of CTA Spot Sign and blood vessels in the hematoma. **a1** The baseline CT image in a patient with basal ganglia hemorrhage. **a2**–**a17** Continuous CTA source images showed the Spot Sign did not extend beyond the hematoma. A small focus of enhancement (white arrow) should be interpreted as a "Spot Sign". **a18** The 24-h follow-up CT image showed the HE. **b1** The baseline CT image in a patient with lobe hemorrhage. **b2**–**b17** Continuous CTA source images showed the Spot Sign extended beyond the hematoma. A small focus of enhancement (white arrow) should not be interpreted as a "Spot Sign". **b18** The 24-h follow-up CT image showed no HE

Results

A total of 265 spontaneous ICH patients (185 men and 80 women) were included in our study. In this study, the time interval from spontaneous ICH onset to initial CT was 2.94 ± 2.73 h. The mean age of these patients was 62.89 ± 12.93 years. The mean baseline hematoma volume was 22.37 ± 23.11 mL. Hematoma locations included the basal ganglia (191, 72.08%), lobar (47, 17.74%), cerebellum (15, 5.66%), and brain stem (12, 4.52%). A total of 85 out of 265 patients experienced HE, with a mean volume of 29.55 ± 29.51 mL. Baseline clinical characteristics of

the HE and non-HE groups are compiled in Table 1. We detected the Spot Sign in 100 patients, including 29 patients in whom it was confirmed to be the result of a blood vessel using continuous CTA source images. Compared to patients without HE, a higher proportion of patients with HE exhibited the Spot Sign. Inter-observer reliability for Spot Sign and hematoma-crossing blood vessels was good between the two neuroradiologists ($k = 0.943$ and 0.925). The univariate and multivariate logistic regression analyses are shown in Tables 2 and 3, respectively. In the univariate analysis, systolic blood pressure at admission, history of diabetes mellitus, time to first CT scan, initial hematoma volume, irregular shape, heterogeneous density, satellite sign, black hole sign, Spot Sign, and the Spot Sign after excluding blood vessels were all associated with HE. Before excluding blood vessels in the hematoma, a multivariate logistic regression analysis determined that having a history of diabetes mellitus (OR 3.631; 95% CI of OR 1.638–8.050; $P = 0.002$), the time to first CT scan(OR 0.751; 95% CI of OR 0.638–0.884; $P = 0.001$), the irregular shape(OR 2.412; 95% CI of OR 1.209–4.810; $P = 0.012$), heterogeneous density (OR 2.125; 95% CI of OR 1.098–4.112; $P = 0.025$), and the satellite sign (OR 1.983; 95% CI of OR 1.021–3.853; $P = 0.043$) independently predicted HE. After excluding blood vessels in the hematoma, the multivariate logistic regression analysis showed that a history of diabetes (OR 3.474; 95% CI of OR 1.547–7.798; $P = 0.003$), the time to first CT scan (OR 0.785; 95% CI of OR 0.675–0.914; $P = 0.002$), the satellite sign (OR 2.442; 95% CI of OR 1.270–4.694; $P = 0.007$), and the Spot Sign after excluding blood vessels (OR 7.112; 95% CI of OR 3.621–13.970; $P < 0.001$) were all independent predictors of HE.

Table 1 Baseline characteristics

Characteristic	HE ($n = 85$)	Non-HE ($n = 180$)	P
Age (year)	67 (29.88)	62.56 ± 12.30	0.540
Sex, male, *n* (%)	66 (77.6)	119 (66.1)	0.056
Admission SBP (mmHg)	179.49 ± 31.47	169.79 ± 28.05	**0.017**
Hypertension *n* (%)	68 (80.0)	158 (87.8)	0.095
Diabetes, *n* (%)	22 (25.9)	18 (10.0)	**0.001**
Stroke history, *n* (%)	23 (27.1)	37 (20.6)	0.238
Smoking, *n* (%)	28 (32.9)	50 (27.8)	0.389
Anticoagulant use, *n* (%)	9 (10.6)	13 (7.2)	0.354
PLT (10^9/L)	179.52 ± 67.79	188.13 ± 64.91	0.321
PT (s)	14.15 ± 11.58	12.25 ± 0.89	0.134
APTT (s)	28.90 ± 10.63	27.52 ± 3.87	0.250
INR	1.25 ± 1.11	1.06 ± 0.08	0.132
Fibrinogen (g/L)	2.50 ± 0.62	2.57 ± 0.61	0.356
Admission calcium concentration (mmol/L)	2.29 ± 0.12	2.28 ± 0.10	0.559
Time to CT (h)	2.05 ± 2.45	3.36 ± 2.76	**< 0.001**
Hematoma volume (mL)	29.55 ± 29.51	18.98 ± 18.53	**0.003**
Location of hematoma, *n* (%)			0.291
Basal ganglia	64 (75.3)	127 (70.6)	
Lobe	11 (12.9)	36 (20.0)	
Cerebellum	4 (4.7)	11 (6.1)	
Brain stem	6 (7.1)	6 (3.3)	
Irregular shape, *n* (%)	65 (76.5)	85 (47.2)	**< 0.001**
Heterogeneous density, *n* (%)	45 (52.9)	45 (25.0)	**< 0.001**
IVH, *n* (%)	38 (44.7)	63 (35.0)	0.129
Satellite sign, *n* (%)	44 (51.8)	43 (23.9)	**< 0.001**
Blend sign, *n* (%)	9 (10.6)	25 (13.9)	0.453
Black hole sign, *n* (%)	58 (68.2)	77 (42.8)	**< 0.001**
Spot Sign, *n* (%)	48 (56.5)	52 (28.9)	**< 0.001**
Spot Sign after excluding blood vessels	48 (56.5)	23 (12.8)	**< 0.001**

Bold values indicate $p < 0.05$

Data are mean ± SD or median and maximum and minimum or *n*/*n* (%)

SBP systolic blood pressure, *PLT* platelet count, *PT* prothrombin time, *APTT* activated partial thromboplastin time, *INR* international normalized ratio, *CT* computed tomography, *IVH* intraventricular hemorrhage

Table 2 Univariable logistic regression analysis of predictors of HE

Variables	OR	95% CI of OR	*P*
Age[a]	1.006	0.986–1.027	0.539
Sex, male	0.562	0.309–1.020	0.058
Admission SBP (mmHg)[a]	1.011	1.002–1.021	**0.013**
History of hypertension	0.557	0.278–1.115	0.098
History of diabetes mellitus	3.143	1.580–6.251	**0.001**
Stroke history	1.434	0.787–2.612	0.239
Smoking	1.277	0.731–2.231	0.390
Anticoagulant use	1.521	0.623–3.712	0.357
PLT (10^9/L)[a]	0.998	0.994–1.002	0.320
PT (s)[a]	1.139	0.993–1.307	0.064
APTT (s)[a]	1.030	0.987–1.075	0.174
INR[a]	4.545	0.951–21.731	0.058
Fibrinogen (g/L)[a]	0.816	0.530–1.256	0.355
Admission calcium concentration (mmol/L)[a]	2.025	0.192–21.365	0.557
Time to CT (h)[a]	0.761	0.654–0.887	**< 0.001**
Hematoma volume (mL)[a]	1.019	1.008–1.031	**0.001**
Location of hematoma			0.301
Lobe vs. basal ganglia	0.606	0.290–1.270	0.185
Cerebellum vs. basal ganglia	0.722	0.221–2.356	0.589
Brain stem vs. basal ganglia	1.984	0.615–6.399	0.251
Irregular shape	3.632	2.033–6.490	**< 0.001**
Heterogeneous density	3.375	1.960–5.811	**< 0.001**
IVH	1.502	0.887–2.541	0.130
Satellite sign	3.419	1.980–5.904	**< 0.001**
Blend sign	0.734	0.327–1.650	0.455
Black hole sign	2.873	1.668–4.950	**< 0.001**
Spot Sign	3.193	1.868–5.460	**< 0.001**
Spot Sign after excluding blood vessels	8.855	4.799–16.341	**< 0.001**

Bold values indicate $p < 0.05$

SBP systolic blood pressure, *PLT* platelet count, *PT* prothrombin time, *APTT* activated partial thromboplastin time, *INR* international normalized ratio, *CT* computed tomography, *IVH* intraventricular hemorrhage, *OR* odds ratio, *CI* confidence interval

[a]Per unit change in regressor

Spot Sign was associated with sensitivity, specificity, positive predictive values, and negative predictive values of 57%, 71%, 48%, and 78%, respectively, as a means of HE detection. When blood vessels were excluded, these same predictive values were 57%, 87%, 68%, and 81%, respectively. The accuracy of other predictors is detailed in Table 4. Results of ROC curve analyses for these two assessments of Spot Sign as a predictor of HE are shown in Fig. 2.

Discussion

Contrast extravasation that is ongoing in CTA source images can be identified as a Spot Sign. In the present study, we detected a Spot Sign incidence rate of roughly 27%, consistent with previous studies identifying a rate between 18 and 72% [23, 24]. The Spot Sign which has been hypothesized to reflect active extravasation of the contrast was termed as a visual manifestation of persistent bleeding [12, 25]. Wada et al. were the first to suggest that there was an association between Spot Sign and the extent of hematoma progression [26]. This was consistent with our finding that there was an association between Spot Sign presence and an elevated HE risk. Similarly, Demchuk et al. [5] also found this Spot Sign to predict HE, and to be a valuable criteria for future trials of hemostatic therapy in spontaneous ICH patients.

Although the CTA Spot Sign is a good predictor of HE, the rates of detection were different in previous studies. Demchuk et al. found the Spot Sign sensitivity, specificity, positive predictive values, and negative predictive values to be 51%, 85%, 61%, and 78%, respectively [5]. In contrast, Wada et al. found these same values to be 91%, 89%,

Table 3 Multivariable logistic regression analysis for HE

Variable	OR	95% CI of OR	*P*
History of diabetes mellitus	3.631	1.638–8.050	**0.002**
Time to CT (h)[a]	0.751	0.638–0.884	**0.001**
Satellite sign	1.983	1.021–3.853	**0.043**
Irregular shape	2.412	1.209–4.810	**0.012**
Heterogeneous density	2.125	1.098–4.112	**0.025**
Spot Sign	1.854	0.965–3.561	0.064
History of diabetes mellitus	3.474	1.547–7.798	**0.003**
Time to CT (h)[a]	0.785	0.675–0.914	**0.002**
Satellite sign	2.442	1.270–4.694	**0.007**
Spot Sign after excluding blood vessels	7.112	3.621–13.970	**< 0.001**

Bold values indicate $p < 0.05$

OR odds ratio, *CI* confidence interval, *CT* computed tomography

[a]Per unit change in regressor

77%, and 96%, respectively, [25] while Han et al. found them to be 57.38%, 90.48%, 74.47%, and 81.43%, respectively [6]. In a previous meta-analysis of Spot Sign, Du et al. calculated a pooled sensitivity of 53% and a specificity of 88% [27]. There may be a range of causes underlying the differences in sensitivity and specificity in these previous studies. For one, the Spot Sign may be affected by different hematoma volumes. Wang et al. found that when the hematoma volumes are > 30 mL; the Spot Sign accuracy for predicting HE is higher [28]. Dowlatshahi et al. found that when the hematoma volumes are small, the probability of Spot Sign is low as is the HE risk [29]. Second, the different timing of scans in previous studies may have yielded different predictive accuracies for the CTA Spot Sign [30]. Ciura et al. found that incorporating a 90-s delay during CTA was sufficient to enhance Spot Sign sensitivity as an HE predictor [31]. Third, Spot Sign positive predictive

Table 4 Predictors on imaging for HE

Variables	SE	SP	PPV	NPV	AUC	95% CI of AUC
Irregular shape	0.77	0.53	0.43	0.83	0.646	0.577–0.716
Heterogeneous density	0.53	0.75	0.50	0.77	0.640	0.566–0.713
Satellite sign	0.52	0.76	0.51	0.77	0.639	0.566–0.713
Black hole sign	0.68	0.57	0.43	0.79	0.627	0.566–0.699
Spot Sign	0.57	0.71	0.48	0.78	0.638	0.565–0.711
Spot Sign after excluding blood vessels	0.57	0.87	0.68	0.81	0.718	0.647–0.789

PPV positive predictive value, *NPV* negative predictive value, *AUC* area under curve, *SE* sensitivity, *SP* specificity, *CI* confidence interval

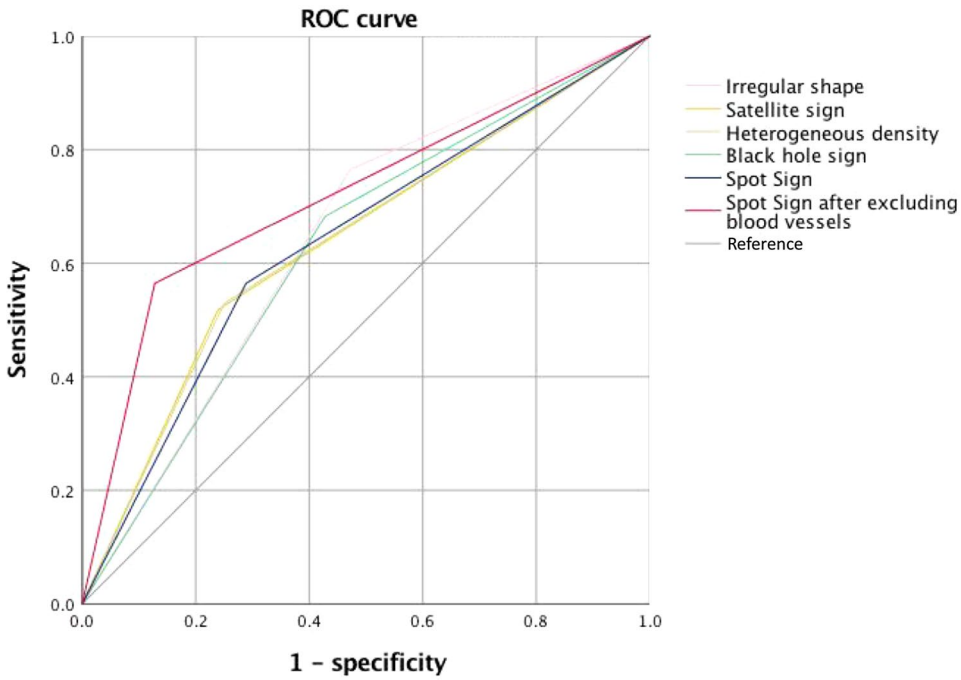

Fig. 2 Receiver-operating characteristic (ROC) curve by using a binary definition of HE. The AUC of the Spot Sign = 0.638, the Spot Sign after excluding blood vessels = 0.718, the irregular shape = 0.646, the satellite sign = 0.639, the heterogeneous density = 0.640 and the black hole sign = 0.627

value for HE decreases as the ICH onset-to-CTA time increases [32]. Finally, the Spot Sign could actually be a cross section of blood vessel or aneurysm in hematoma, which also is one of the possible causes. We differentiated between blood vessels and contrast extravasation in the hematoma using continuous CTA source images, yielding increased Spot Sign specificity, positive predictive values, and negative predictive values of 48%, 78–87%, 68%, and 81%, respectively. At the same time, our study also found that density heterogeneity, irregular shape, satellite sign, and black hole sign can also all predict the expansion of hematoma, consistent with previous work. For example, Blacquiere et al. found that density heterogeneity and irregular shape are associated with HE at 24 h [17]. Li et al. found black hole sign to be predictive of the expansion of hematoma [19]. Zhiyuan et al. found the satellite sign to be predictive of the expansion of hematoma [33]. A multiple indicator-based combined diagnostic strategy can thus be implemented to improve the accuracy of the prediction of HE in the future.

Our study is limited owing to its retrospective nature and single center design. Moreover, the sample size was relatively limited. In addition, the symptom onset-to-CTA time was relatively long, potentially influencing the predictive accuracy of this indicator. Finally, due to CT equipment and subsequent processing, some blood vessels or aneurysm in the hematoma still cannot be identified. To address these issues, future multicenter studies with larger sample populations, better CT machinery/subsequent processing, and a briefer period of time between symptom onset and CTA will be needed.

Conclusions

In summary, the CTA Spot Sign is an effective indicator for predicting the expansion of hematomas in patients with ICH, providing an avenue for defining the basis of patient treatment. Previous studies have detected variations in the utility, sensitivity, and specificity of Spot Sign for HE prediction, potentially for a range of reasons. One such reason is that the cross section of blood vessels or aneurysms in the hematoma can be mistaken for Spot Signs. In our study, a continuous CTA source images silhouette technique was used to distinguish the blood vessels from the hematoma, which improved the accuracy of the Spot Sign prediction for HE and thus increased the value of the Spot Sign in clinical contexts.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of our institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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