The Significance of Contrast Density of the Computed Tomography-Angiographic Spot Sign and its Correlation with Hematoma Expansion

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Background and Purpose: The computed tomography angiographic (CTA) spot sign has been shown to predict hematoma expansion in patients with intracranial hemorrhage (ICH), but the significance of the spot sign density (SSD) and the spot sign ratio (SSR) has not yet been explored. *Methods:* Using the institutional Neurocritical care and Stroke registry, we retrospectively reviewed patients with ICH from January-2013 to June-2017. We selected patients who had baseline CT-head (CTH), CTA with positive-spot sign within 6 hours of last known well and at least one follow-up CTH within 24 hours. Baseline demographics and variables known to affect hematoma-volume were collected. Hematoma-volumes and SSR were calculated using computer-assisted 3D-volumetric measurement and the average of the surrounding hematoma density divided by the SSD, respectively. The 2-sample *t* test and the area-under-the-curve (receiver operating characteristic) were used to detect the association between hematoma expansion and outcome at discharge. *Results:* A total of 320 patients were reviewed; 22 met the inclusion criteria. Significant hematoma expansion (volume expansion ≥12.5 cc or ≥33% compared to baseline) was noted in 14 (64%) subjects. SSD was significantly higher in subjects with hematoma expansion (216 ± 66) than those without (155 ± 52, $P = .036$). With a cut-off SSD of ≥150 HU, we had sensitivity of 86% and specificity of 75%. For SSR, lower ratios suggested a trend toward hematoma expansion, although it was not statistically significant ($P = .12$). There was no significant correlation between SSD or SSR and modified ranking scale at discharge and after 3-6 months. *Conclusion:* SSD might be a good predictor of hematoma growth. Although SSR showed a trend toward expansion, results were not statistically significant.

Key Words: Spot sign—spot sign density—SSD—spot sign ratio—SSR—hematoma expansion

Introduction

Hematoma expansion is a known complication of intracranial hemorrhage (ICH) associated with high morbidity and mortality.[1] The computerized tomography angiography (CTA) contrast extravasation was first noticed by Yamaguchi et al[2] in 1971 and its correlation to hematoma expansion was first described by Murai et al in 1999.[3] Further description of the spot sign and its significance in hematoma

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expansion was provided in 2007 by Wada et al; they defined spot sign as one or more of 1-2 mm foci of enhancement within the hematoma on CTA source images.[4] In 2009, Thompson et al proposed radiological criteria for diagnosis of the CTA "spot sign." They defined the spot sign as a spot-like and/or serpiginous foci of enhancement within the margin of a parenchymal hematoma without connection to outside vessels, measuring >1.5 mm in diameter with a density (in Hounsfield units; HU) at least double that of the background hematoma.[5] Several retrospective and small prospective studies have since evaluated the sensitivity and specificity of the spot sign in relation to hematoma expansion and have reported values with sensitivity of 72%-91%, specificity of 84%-94%, positive predictive value (PPV) of 67%-79%, and negative predictive value (NPV) of 75%-98%.[6-10] In 2012, a large prospective study (PREDICT) reported the predictive value of hematoma expansion in patients with ICH.[11] In this study, the PPV for hematoma expansion in patients with a spot sign was 61% (95% CI 47-73) and the NPV was 78% (71%-84%), with a sensitivity of 51% and a specificity of 85%. A recently published study investigated the significance of CTA spot sign density (in HU) and its correlation with hematoma expansion.[12] Investigators found an estimated sensitivity of 65.4% and specificity of 85.7% with spot sign density $\geq$ 171 HU when expansion was defined as increase in volume of >33% or >6 mL from the baseline using ABC/2 method for volume assessment (n = 47).While some authors have debated the utility of spot sign attenuation or spot sign density as a predictor of hematoma expansion,[13,14] others have used this parameter to develop a predictive score for hematoma expansion.[15-18] Although multiple aspects of the spot sign have been studied to predict hematoma expansion, the spot sign ratio (the ratio of the density of the surrounding hematoma to that of the spot sign; SSR) has not yet been explored. In this study, we investigated the significance of SSR in predicting hematoma expansion. In addition, we explored the spot sign density (SSD) to find the maximal attenuation that is most predictive of hematoma expansion.

Methods

Patient Selection, Image Acquisition and Ratio Calculation

After approval from local institutional review board (IRB), we retrospectively screened all patients in the institutional Neurocritical and Stroke registry between January 2013 and December 2017 to identify patients with ICH who had CT-head (CTH)and CTA upon arrival. We identified patients who had CTH on presentation and at least 1 follow-up CTH between 6-24 hours of presentation. Institutional protocol for CTA contrast injection include use of 100 mL of nonionic iohexol 350, injected at a rate of 4 mL/sec. This is followed by bolus tracking with region of interest (ROI) in the descending aorta.

After the initial screening, 42 patients with positive spot sign were identified. Patients who underwent surgical evacuation prior to obtaining at least 1 follow-up CTH were excluded. Patients with external ventricular drain placed very close to ICH were also excluded as it was difficult to know whether the volume expansion was related to external ventricular drain (EVD) placement. Additionally, patients with cystic encephalomalacia in and around the region of hematoma and patients without a clear hematoma margin for accurate volume measurement were also excluded to avoid false estimation of hematoma volumes. A final list of eligible patients were sent to a staff Neuroradiologist (J.F.) who independently measured the hematoma volumes, confirmed the presence and number of spot signs, measured the SSDs, and calculated the SSRs. The Neuroradiologist followed a predetermined algorithm for retrospective image interpretation using picture archiving and communication system. The algorithm included interpretation of initial CTH followed by follow-up CTH and finally the interpretation of CTA. The Neuroradiologist remained blinded to patients' clinical information. Hematoma volume assessment was done by manually mapping out ROI around the parenchymal hematomas, excluding the intraventricular component, and using a 3D post processing tool (Aquarius iNtuition Edition Version 4.4.12 TeraRacon, Inc., 4000 East 3rd Avenue, Suite 200 Foster City, CA 94404). A semi-automated threshold-based approach with a range of 50-100 HU was used to identify hemorrhage. Where required, manual adjustment was done to delineate the hemorrhage from surrounding tissues. The software adjusts for changes in section thickness and thereby corrects for different CT techniques across centers.[19] Hematoma expansion was defined as >33% and/or >12.5 mL increase from the initial hematoma volume. The maximal HU of the identified spot signs was obtained using a circle ROI. In cases with more than 1 spot sign, all were sampled but the maximal HU value was reported. The average of the hematoma was obtained with circle ROI, excluding the spot signs.

Demographics and Variables

We reviewed the medical records of the enrolled patients and recorded the baseline demographics, imaging findings, and outcome data (Table 1). Recorded variables included spot sign numbers, spot sign greatest axial diameter, spot sign density, spot sign density ratio, and hematoma volumes. Outcomes included hematoma expansion, modified ranking scale (MRS), on discharge, after 3-6 months, MRS change from baseline (premorbid) to discharge, MRS difference from discharge to 3-6 months post discharge. Outcome assessment was done by separate individuals (O.H. and A.A.E.) through review of daily documented exam, physical and occupational therapy notes and telephone conversation with patient and/or family members where post discharge follow-up exam was unavailable on chart (2 patients). The outcome assessor was blinded to imaging findings.

Table 1. *Demographics and variables (spot sign with expansion versus spot sign without expansion). All the variables show no statistically significant difference between the 2 groups (all* P*-values >.05)*

Variables		Spot sign without expansion (n = 8), 36 %	Spot sign with expansion (n = 14), 64 %	*P*-value
Age	Median (range)	58 (46, 85)	64 (36, 79)	.272
HbA1c	Median (range)	5.2 (4.8, 5.7)	5.4 (4.6, 7.8)	.299
NIHSS	Median (range)	16 (9 -32)	22.5 (3, 37)	.157
GCS	Median (range)	10.5 (3, 15)	7.5 (3, 15)	.655
PTT	Median (range)	31.5 (21.0, 51.9)	29.0 (20.9, 36.5)	.206
INR	Median (range)	1.1 (0.9, 3.2)	1.1 (0.9, 2.9)	.783
Number of spots*	Median (range)	2 (1, 3)	1.5 (1-9)	.91
Greatest axial diameter of a spot sign*	Median (range)	4.5 (2, 7)	4 (2, 9)	.97
Initial volume*	Median (range)	27 (6, 91)	22.5 (3, 92)	.762
Gender	Male	5 62.50	8 57.14	1
	Female	3 37.50	6 42.86	
Previous Stroke	+	1 12.50	4 28.57	.613
	-	7 87.50	10 71.43	
Hypertension	+	8 100.00	12 85.71	.515
	-	0 0.00	2 14.29	
Diabetes-Milletus	+	1 12.50	6 42.86	.193
	-	7 87.50	8 57.14	
Smoking	+	5 62.50	5 35.71	.378
	-	3 37.50	9 64.29	
Drugs	+	1 12.50	0 0.00	.364
	-	7 87.50	14 100.00	
Alcohol use	+	3 37.50	4 28.57	1
	-	5 62.50	10 71.43	
Bleeding-disorder	-	8 100.00	14 100.00	1
Coronary artery disease	+	3 37.50	1 7.14	.117
	-	5 62.50	13 92.86	
Chronic kidney disease	+	2 25.00	1 7.14	.527
	-	6 75.00	13 92.86	
Hepatic failure	+	2 25.00	2 14.29	.602
	-	6 75.00	12 85.71	
Underlying vascular-malformation	-	8 100.00	14 100.00	1

Table 1 (*Continued*)

Variables		Spot sign without expansion (n = 8), 36 %	Spot sign with expansion (n = 14), 64 %	*P*-value
Aneurysm**	+	2	0	.121
		25.00	0.00	
	-	6	14	
		75.00	100.00	
Cerebral venous thrombosis	-	8	14	1
		100.00	100.00	
Amyloid angiopathy	-	8	14	1
		100.00	100.00	
On antiplatlets	+	5	9	1
		62.50	64.29	
	-	3	5	
		37.50	35.71	
On anticoagulation	+	2	1	.527
		25.00	7.14	
	-	6	13	
		75.00	92.86	
Final diagnosis	IPH+IVH	1	3	1
		12.50	21.43	
	IPH	7	11	
		87.50	78.57	
Disposition	Death or Hospice	1	5	.108
		12.50	35.71	
	Long-term acute care or skilled nursing facility	2	7	
		25.00	50.00	
	Rehabilitation or home	5	2	
		62.50	14.29	

GCS, glasgow coma scale; HbA1c, hemoglobin A1c (Glycated hemoglobin); INR, international normalized ratio; NIHSS; national institutes of health stroke scale; PTT; partial thromboplastin time.

*There was no difference between the hematoma expansion group and the nonhematoma expansion group when we accounted for the spot sign numbers, greatest axial diameter, and initial volume of the hematoma.

**Two patients in the no expansion group had stable aneurysms away from the site of bleeding (one who had it clipped years before the ICH with no evidence of recurrence; the other had a 2 mm saccular aneurysm remote from the location of ICH).

Statistical Analysis

Patient demographics and characteristics were summarized using descriptive statistics (median and range for the continuous outcomes and frequency for the discrete outcomes). Except for SSR and SSD, continuous variables were compared between patients with and without hematoma expansion using the Wilcoxon test. The fisher's exact test was used to compare the categorical variables (Table 1). The 2-sample *t* test was used to compare SSR and SSD between patients with and without hematoma expansion. ANOVA has been used to assess associations between the MRS parameters and the SSD/SSR. The receiver operating characteristic curve was used for SSD and hematoma expansion, and SSR and hematoma expansion, to determine the optimal sensitivity, specificity, accuracy, PPV, and NPV. *P*-values have been adjusted for multiple comparisons using the Bonferroni method as needed. *P*-values $< .05$ were considered statistically significant. All analyses were conducted in SAS version 9.4 (SAS Institute, Cary, NC).

Results

We screened 519 subjects with ICH who presented to our institution between January 2013 and December 2017. Of those, 320 patients had admission CTH, CTA and at least 1 follow-up CTH within 24 hours. A total of 42 patients were found to have positive spot sign on CTA. We further excluded patients who either died or underwent surgical evacuation prior to follow-up CTH, patients with external ventricular drain placed close to the hematoma, hematomas with cystic encephalomalacia, and patients in whom hematoma margins were not well delineated from the surrounding structures. After applying exclusion criteria, a total of 22 subjects (6.9%) were identified and included in our final analysis.

We defined hematoma expansion as the increase in volume by $\geq$ 33% and/or 12.5 mL from the baseline volume. There were 14 (64%) patients with hematoma expansion and 8 (36%) patients without hematoma expansion. Both groups had comparable baseline demographics as shown in Table 1. None of the patients had underlying cerebral

Table 2. *Comparison of SSR and SSD in subjects with and without hematoma expansion*

	Expansion (n = 14)		No expansion (n = 8)		*P*-value
	Mean	Standard deviation	Mean	Standard deviation	
SSR	0.34	0.09	0.41	0.10	.12
SSD	215.93	66.00	154.63	52.03	.036

SSR, spot sign ratio; SSD, spot sign density.

vascular malformation or aneurysm related to the hemorrhage. Median baseline ICH volume was 22.5 mL (range = 3-92 mL) in spot-sign-positive patients with expansion versus 27 mL (range = 6-91 mL) in spot-sign-positive patients without expansion (P = .762; Table 1).

The median time from last known well to acquisition of the first scan was 4.5 (0.5-23) hours in patients with hematoma expansion and 6 (0.5-14) hours in patients without hematoma expansion. The mean SSD was 216 HU (standard deviation [SD] = 66) in patients with hematoma expansion and 155 HU (SD = 52, P = .036) in patients without hematoma expansion (Table 2). The receiver operating characteristic curve shows that SSD ≥ 150 HU correlates with hematoma expansion with a sensitivity of 86% (95% CI: 56%-97%), specificity of 75% (95% CI: 36%-96%), accuracy of 82% (95% CI: 60%-95%), PPV of 86% (95% CI: 56%-97%), and NPV of 75% (95% CI: 35%-96%) (AUC = 0.79, 95% CI: 0.58-1). When SSD was ≥266 HU, specificity was 100% but sensitivity decreased to 29%. Similarly, when the SSD cut off of 129 HU was considered, sensitivity was 100% with reduced specificity of 37.5% (Figs. 1 and 2).

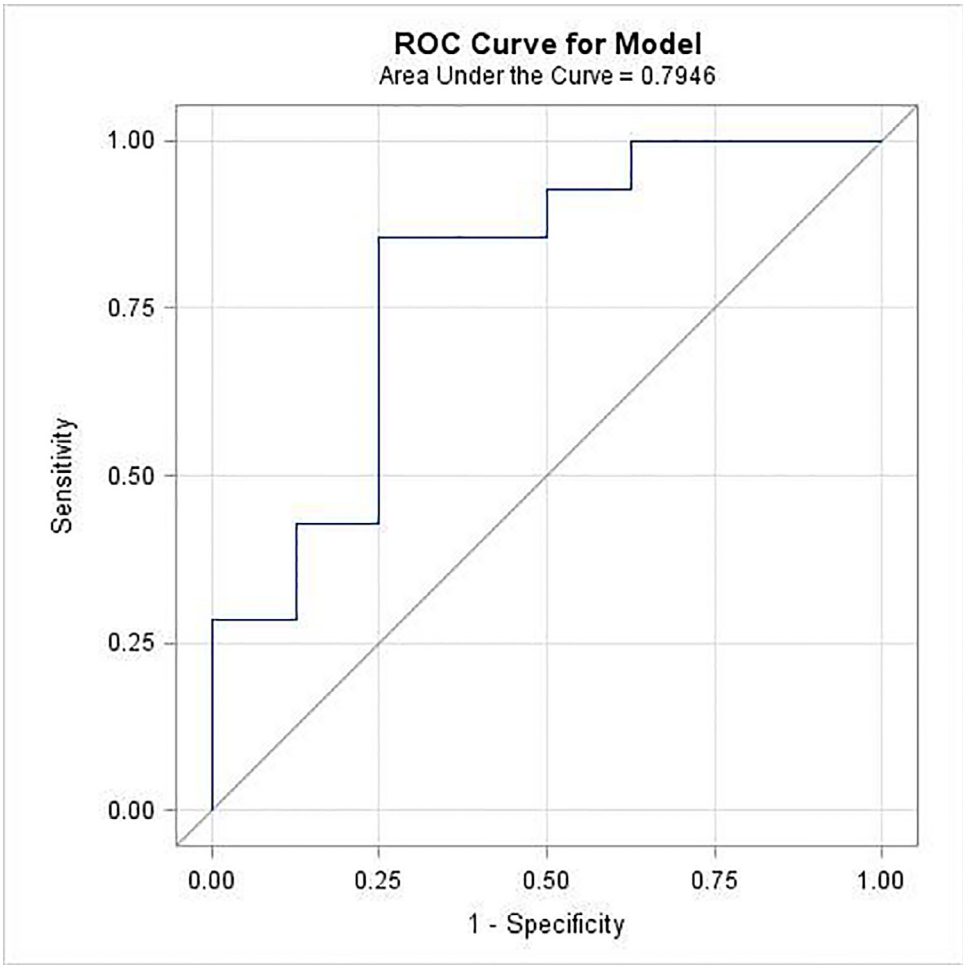

Figure 1. *ROC curve for SSD and hematoma expansion. The best cut-off point for spot density is 150 based on this dataset. SSD ≥ 150 HU corresponds to 86% sensitivity, 75% specificity, 82% accuracy, PPV = 86%, and NPV = 75% for hematoma expansion detection. When SSD was ≥ 266 HU, specificity was 100% and sensitivity was 29%. When the SSD ≥ 129 HU, sensitivity was 100% and specificity was 37.5%. Abbreviations: ROC, receiver operating characteristic; SSD, spot sign density; HU, Hounsfield units.*

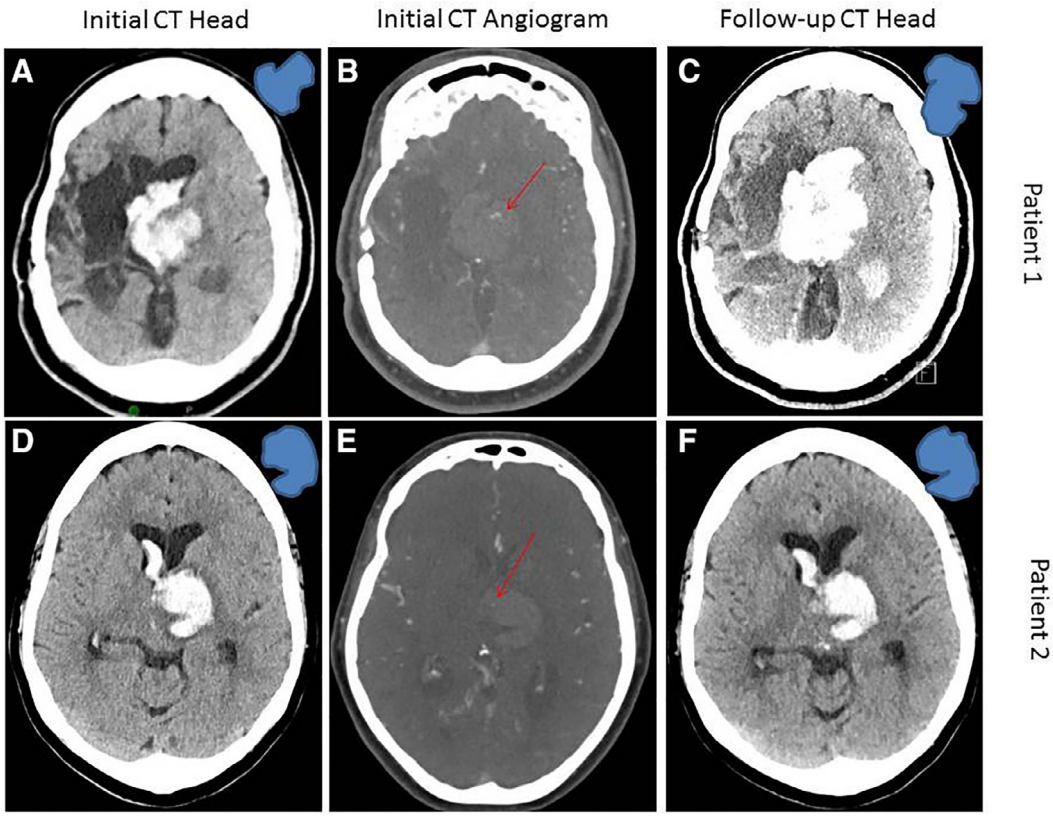

Figure 2. *Comparison between the initial CT-head, CT-angiogram, and follow-up CT-head of 2 patients with intraparenchymal hemorrhage associated with spot signs of different densities. Initial CT head of 2 patients with intraparenchymal right thalamic hematoma (A and D), initial CT angiograms of the same patients showing 2 spot signs in the first patient's hematoma (red arrow) with maximum spot sign density of 282 HU and 1 spot sign in the second patient's hematoma with spot sign density of 102 HU (B and E) and a follow-up CT-head showing hematoma expansion in patient 1 and no hematoma expansion in patient 2 (C and F). Comparison of the initial hematoma 2D size to the follow-up hematoma 2D size is illustrated in blue at the top right corner of the CT head images (A, C, D and F). (Color version of figure is available online.)*

The mean SSR for patients with hematoma expansion was 0.34 (SD = 0.09) and 0.41 (SD = 0.1) for patients without expansion (P = .12; Table 2). Although not statistically significant, lower SSR demonstrated a trend toward expansion. Furthermore, we looked at the correlation of SSR and SSD with clinical outcome using the MRS on discharge, after 3-6 months, MRS difference from preadmission to discharge, MRS difference from discharge to 3-6 month post discharge. We did not find statistically significant outcome association with either SSR or SSD. Additionally, the median length of stay for subjects who had hematoma with expansion was 16.5 days (range: 2-36 days) while for those with hematoma without expansion was 9 days (range: 3-32 days) (Table 3).

Discussion

Hematoma expansion is known to occur in about 35% of patients with ICH.[1] The definition of hematoma expansion has been variable in the literature. Most studies defined hematoma expansion as a percentage increase of >20-33% from the baseline hematoma volume or a volume increase of >6-12.5 mL. The PREDICT trial defined hematoma expansion as an increase of ≥33% and/or 6 mL from baseline volume. The phase IIb recombinant factor VII ICH trial used a cutoff of ≥ 33% and/or 12.5 mL increase from baseline volume. For the purpose of this study, we defined hematoma expansion as an increase in volume of ≥33% and/or 12.5 mL from the baseline. Although different volume parameters used to defined expansion likely does not affect predictive value of spot sign,[10,20-24] we chose the 12.5 cc cut-off since > 12·5 mL volume increase correlated best with clinical outcome.[23]

It is not entirely clear whether spot sign represents active extravasation of blood or the fresh clot (mixed with contrast) formed at the site of hemorrhage. A commonly accepted theory is that spot sign represents continuous leakage of contrast from a micro vessel and hence is predictive of hematoma expansion.[26,27] Some studies have evaluated the cut off value for the contrast density of the spot sign that best correlates with hematoma expansion and noted the attenuation of >171 HU and >180 HU to have significant predictive value.[12,14] In this study, we examined the contrast density that best correlated with hematoma expansion in our study population. We also investigated SSR, a parameter that has not yet been

Table 3. *Association between MRS parameters and SSR/SSD*

MRS		N	SSR			SSD		
			Mean	Std Dev	*P*-value	Mean	Std Dev	*P*-value
MRS on Discharge	**3**	3	0.37	0.10	.52	180.33	74.80	.22
	4	2	0.36	0.03		203.00	5.66	
	5	10	0.40	0.10		166.60	50.44	
	6	7	0.32	0.11		235.29	82.09	
MRS 3-6 months	**3**	4	0.36	0.08	.94	191.50	65.03	.55
	4	8	0.37	0.08		175.25	51.69	
	5	2	0.40	0.09		164.00	19.80	
	6	8	0.35	0.13		220.50	86.75	
MRS change from baseline	**0**	1	0.26	.	.82	266.00	.	.45
	3	3	0.39	0.06		166.67	51.40	
	4	8	0.37	0.08		175.25	51.69	
	5	2	0.40	0.09		164.00	19.80	
	6	8	0.35	0.13		220.50	86.75	
MRS change from discharge	**-2**	1	0.32	.	.15	225.00	.	.37
	-1	6	0.38	0.09		166.00	57.65	
	0	14	0.35	0.09		208.71	69.87	
	1	1	0.57	.		117.00	.	

MRS, modified ranking scale; SSR, spot sign ratio; SSD, spot sign density; N, number of subjects; Std Dev, standard deviation.
The bold value is to highlight the points and levels of comparison.

explored, and have evaluated its significance in the prediction of hematoma expansion. The rationale for this study is discussed below.

1. *Significance of spot sign density in predicting hematoma expansion: Does higher density of spot sign suggest more leakage?* Although a few studies have shown higher spot sign density (in HU) to be correlated with hematoma expansion, there is some controversy in the literature as the density cut off that best correlates with hematoma expansion has been variable.[14,17] Chakraborty et al used dynamic CTA to evaluate spot sign and noted that the spot density has a crescendo pattern through the early and middle scanning phases, which then decreases at the end of the venous phase, likely from dispersion and redistribution of contrast material.[25] This suggests that the timing of image acquisition plays a huge role in observed contrast density of the spot sign. It was also observed that the ability to detect spot sign and its correlation with hematoma expansion improved with CT Perfusion study. The increased sensitivity was mostly attributed to a delay in the appearance of maximal spot attenuation at 30-70 seconds, which appears later than the usual CTA acquisition time of 20-26 seconds.[26] This further emphasizes the importance of the timing of image acquisition (after the initial contrast bolus) in altering spot sign detection as well as density. Furthermore, contrast density of the spot sign is also likely dependent on the contrast injection rate, as suggested by Awai et al. The authors proposed that during CTA, the peak contrast enhancement in the aorta is dependent on the injection rate, provided the contrast dose remains constant.[27] That is, the density of contrast in the vessel rises, as the rate of contrast flow increases, for any given contrast dose. Based on this theory, it is conceivable that the faster the contrast extravasates from the vessel, the brighter (or higher density) the spot sign will appear. In other words, a brighter or denser spot sign may suggest a faster rate of bleeding and hence stronger prediction for hematoma growth. However, given the various external factors that affect the maximal attenuation of the spot sign, the variable contrast density cut-off among various studies is likely due to difference in institutional CTA contrast injection protocols. Validating the contrast density that best correlates with expansion at an institutional level may therefore be valuable in predicting hematoma growth. Furthermore, intrinsic factors, like blood pressure variability, might give an incentive that higher spot sign density might require more aggressive blood pressure control.
2. *The ratio of the density of the hematoma to the density of the spot sign (SSR): Does lower spot sign ratios indicate higher risk of bleeding?* To our knowledge, this parameter has not yet been described in the literature. While the pathophysiology and factors

affecting SSR are similar to that affecting contrast density, we evaluated this parameter to assess whether it improves the sensitivity and specificity of hematoma expansion. However, despite lower SSR showing a trend toward hematoma expansion, it was not statistically significant.

In our patient population, a density of ≥150 HU correlated with reasonable sensitivity of 86% and specificity of 75%. The higher density of 266 HU was 100% specific. This finding does not correlate with previously published cutoffs for predicting hematoma expansion. Since the density or peak enhancement changes with dose (per kg), duration, rate of contrast injection, and timing of image acquisition, this finding is applicable in cases where the hospital protocol mandates standard contrast dose (per kg), duration, and infusion rate for all CT angiograms. Therefore, we believe the optimum contrast density predicting hematoma expansion needs to be validated in each institution.

With regard to the clinical outcomes, neither SSD nor SSR showed significant correlation.

The strength of our study includes strict selection criteria, which allowed a uniform study population with matched variables between patients with and without hematoma expansion. Also, since this was a single center study, standard institutional CTA protocol was used for each patient with constant dose/duration and contrast infusion rate. Our CTA protocol uses a standard dose of 100 mL at 4 mL/sec. Scan timing uses an automated threshold-based trigger, with a threshold of 100 HU and ROI in the descending aorta. We used manually mapped ROIs to calculate hematoma volume, which provided accurate measurement of hematoma volume in comparison to several existing studies that have used calculated volumes using the ABC/2 formula. Furthermore, all images were read and interpreted by a single Neuroradiologist, thereby eliminating inter-rater variability.

Limitations

Our major limitations are the retrospective nature of the study and the small sample size. Although the median time from last known well to acquisition of the first scan was slightly different between the 2 groups (1.5 hours longer for the group without hematoma expansion), both groups had their initial CTH and CTA within a median of 6 hours which is a well-accepted time frame for spot sign detection. Use of the static CTA rather than the dynamic CTA and CT Perfusion imaging for spot sign detection is an additional limitation of the study which likely led to low detection rate of spot signs. Exclusion of patients who underwent surgical evacuation prior to having at least one follow-up CTH were also excluded which further limited our sample size; it is very likely that this group of patients represented the ones with early hematoma expansion.

Blinding of the neuroradiologist to clinical information was done using an honor system given the retrospective nature of the study as described in the methods section. This nontraditional method of blinding may be viewed as a limitation by some. Our outcome measure (MRS) was estimated from the chart review of patient history, exam at discharge, follow-up visits at 3-6 months, and telephone conversation with patients or family members in cases where follow-up visit documentation was not available (2 patients). This could carry a recall bias as they were asked about their MRS 3-6 months following discharge. However, this probably has a limited impact on the results as both the patients had the same MRS at the time of the phone interview.

Although we screened for patients over a 5-year period from our institutional registry, we were only able to include 22 patients in our final analysis due to strict inclusion/exclusion criteria. Strict selection criteria allowed for uniformity among the patient population, however it limited the power of this study. A large-scale collaborative, multicenter study would be helpful to confirm the findings of this study.

Conflict of Interest and Disclosures

All authors of this manuscript report no conflict of interest.

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