Radiology

Multiphase CT Angiography Improves Prediction of Intracerebral Hemorrhage Expansion[1]

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Purpose: To determine the prevalence of the spot sign and the accuracy of using the spot sign to predict intracerebral hemorrhage (ICH) expansion with standardized multiphase computed tomographic (CT) angiography.

Materials and Methods: This prospective observational cohort study included 123 consecutive patients with acute ICH (onset <6 hours). Patients underwent multiphase CT angiography in three automated phases after injection of contrast material. Patients were classified as having one of four patterns (pattern A, B, C, or D) according to the presence of the spot sign in the three phases. Pattern A was the more arterial pattern, and pattern D was the more venous pattern. Ninety-five patients underwent follow-up unenhanced CT 24 hours after symptom onset. Primary outcome was substantial hematoma expansion (>33% or >6 mL) at 24 hours. Associations between the presence of the spot sign and substantial hematoma expansion were assessed by using the Pearson χ^2 test.

Results: The later the phase of CT angiography, the higher the frequency of the spot sign. The spot sign was seen in 29.3% of patients in phase 1, 43.1% of patients in phase 2, and 46.3% of patients in phase 3 ($P < .001$). The presence of the spot sign in any phase was related to substantial hematoma expansion ($P < .001$ for all comparisons; Bonferroni adjusted $\alpha = .0125$), with highest positive predictive value in phase 1 (64.0%) and highest negative predictive value in phase 2 (90.2%). The more arterial the pattern of spot sign presentation, the greater the frequency of substantial hematoma expansion ($P = .013$). Absolute hematoma growth analysis revealed a hierarchical pattern of spot sign presentations, as follows: A > B > C > D > no spot sign ($P = .002$).

Conclusion: Multiphase CT angiography can help differentiate among different forms of spot sign presentation and can help stratify patients at risk for hematoma expansion. The more arterial the spot sign pattern, the greater the frequency and extent of expansion.

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Hematoma expansion is a potentially modifiable determinant of poor outcome in acute intracerebral hemorrhage (ICH) (1,2) and represents a key target for emerging therapies (3). Hemostatic therapy trials with recombinant factor VIIa have demonstrated reductions in hematoma expansion without improvement in clinical outcomes (4), presumably because of the inclusion of a majority of patients unlikely to experience hematoma expansion and, therefore, to benefit from hemostatic therapy (5,6). Hence, the success of future interventions aimed at preventing hematoma expansion and subsequent poor outcome will likely depend on the accurate selection of patients at risk for hematoma expansion (6,7).

The computed tomographic (CT) angiography spot sign is a focus of contrast material enhancement within an ICH that is visible on the source images from CT angiography (8,9). The Predicting Hematoma Growth and Outcome in Intracerebral Hemorrhage Using Contrast Bolus CT (PREDICT) study validated the spot sign as a predictor of hematoma expansion in patients scanned within 6 hours of ICH onset, and those researchers recommended it as an entry criterion for hemostatic trials (6). However, the sensitivity of the spot sign in the prediction of substantial hematoma expansion with use of single-phase CT angiography was 51% in the PREDICT study (6). In a post hoc analysis of the PREDICT study, researchers hypothesized that the low sensitivity observed was likely due to variability in timing of image acquisition after the administration of the bolus of contrast material and suggested that the frequency and diagnostic yield of the spot sign may differ among phases of CT angiography acquisition (10).

Several studies have suggested that the introduction of a delay after the administration of a bolus of contrast material can increase the sensitivity of the CT angiography spot sign in the prediction of hematoma expansion (11–14). However, these studies analyzed retrospectively collected data, and most of them did not have standardized indications for CT angiography or fixed timing for the delayed imaging (11–14). Thus, there is currently no accepted consensus on the timing of CT angiography. Furthermore, the pathophysiologic significance of the spot sign remains unknown, which adds uncertainty about the optimal timing for the acquisition of CT angiograms.

The primary aim of this study was to determine the accuracy of the spot sign in the prediction of hematoma expansion in patients with acute ICH by using standardized multiphase CT angiography. This technique enables the demonstration of additional time points from CT angiography by using the same injection of contrast material and very little additional radiation exposure (15–17). We hypothesized that the more arterial the pattern of spot sign presentation, the greater the frequency and extent of hematoma expansion. Secondarily, we aimed to determine the prevalence of the spot sign by using multiphase CT angiography and to investigate whether multiphase CT angiography can provide additional information on the underlying pathophysiology of the spot sign.

Advances in Knowledge

- Multiphase CT angiography can acquire temporal information of the spot sign without the requirement of additional contrast material.
- The later the phase of multiphase CT angiography, the higher the frequency of the spot sign (29.3% in phase 1, 43.1% in phase 2, and 46.3% in phase 3; $P < .001$).
- Predictive values of the spot sign for substantial hematoma expansion vary across phases of multiphase CT angiography; the highest positive predictive value is observed in phase 1 (64.0%), and the highest negative predictive value is observed in phase 2 (90.2%).
- Multiphase CT angiography can help define predictive patterns from spot sign presentation, from pattern A (with highest degree of hematoma expansion) to pattern D and absence of spot sign (with lowest degrees of hematoma expansion) ($P = .002$).

Implication for Patient Care

- Multiphase CT angiography can be used to predict hematoma expansion in patients with acute intracerebral hemorrhage.

Materials and Methods

Study Design

We conducted a single-center, prospective, observational cohort study of consecutive patients aged 18 years and older with a symptomatic and radiologically confirmed ICH who underwent scanning within 6 hours from symptom onset during a 40-month period (April 1, 2013, to July 31, 2016). Exclusion criteria included known secondary cause of ICH, deep coma (defined as a score of 3–5 on the Glasgow coma scale), known contraindication to CT angiography (eg, renal failure or allergy to iodinated contrast material), and lack of informed consent. Patients or next of kin gave written informed consent. The local ethics committee approved all aspects of the study protocol.

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Abbreviations:
ICH = intracerebral hemorrhage
IQR = interquartile range

Author contributions:
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Conflicts of interest are listed at the end of this article.

Data Acquisition

On admission, we recorded relevant demographic characteristics, medical history, clinical presentation, neurologic status (National Institutes of Health Stroke Scale and Glasgow Coma Scale scores), and results of routine laboratory tests. Time from symptom onset was defined as time of first symptoms or signs of neurologic deficits or the time the patient was last known to be neurologically intact. All patients underwent a standardized acute ICH evaluation at our institution that included unenhanced CT followed by multiphase CT angiography at baseline (<6 hours) and unenhanced follow-up CT at approximately 24 hours (range, 22–30 hours).

All CT examinations were performed from the skull base to the vertex with a multi–detector row CT scanner (Somatom Definition AS; Siemens, Erlangen, Germany). Images were acquired with 1.0-mm-thick sections for unenhanced CT and with 0.6-mm-thick sections for multiphase CT angiography. Multiphase CT angiography was performed in three automated phases after intravenous injection of contrast material. The first phase acquisition was timed to occur during the peak arterial phase, the second during the equilibrium and/or peak venous phase, and the third during the late venous phase (10). The first phase was triggered by monitoring the bolus of contrast material from the descending aorta; scanning started 8 seconds after the CT attenuation value of the aorta reached the threshold value of 120 HU. The second phase was acquired after a delay of 4 seconds, and the third phase after a delay of 15 seconds. Scanning duration of each phase was 3.5 seconds, with an average dose-length product of 300–350 mGy · cm per phase. A total of 80 mL of contrast material (65.2% iodixanol, Visipaque 320; GE Healthcare, Oslo, Norway) was injected at a rate of 5 mL/sec; this was followed by a 30-mL normal saline chase at a rate of 6 mL/sec.

Image Analysis

A stroke neurologist (D.R.L.) with more than 5 years of experience in CT volumetric analysis and who was blinded to the multiphase CT angiographic scans and spot sign status prospectively evaluated baseline and follow-up unenhanced CT scans. ICH volumes were measured by using semiautomatic Hounsfield unit, threshold-based, computerized planimetry software (Syngo, Siemens). ICH location (cerebral lobes, basal ganglia or thalamus, brainstem, or cerebellum), intraventricular extension, and subarachnoid extension were recorded.

A neuroradiologist (P.C.) with more than 5 years of experience in the analysis of spot signs at CT angiography, and who was blinded to follow-up unenhanced CT scans and clinical outcomes, independently interpreted multiphase CT angiographic scans. The spot sign was defined according to previously established criteria (18). The presence and radiologic characteristics of the spot sign, including total number of spot signs, maximum attenuation (in Hounsfield units), and maximum axial diameter, were recorded in each phase of multiphase CT angiography. Patients who were positive for the spot sign were prospectively categorized into one of four predefined patterns of spot sign presentation (Fig 1), as follows: Patients with spot sign present in phase 1 were classified as having pattern A if the spot sign was not present in phase 3 or as having pattern B if the sign was also present in phase 3; patients without spot sign in phase 1 were classified as having pattern C if the sign was present in phase 2 or as having pattern D if the sign was present only in phase 3. Patterns of spot sign presentation were prospectively defined; the intent was to represent the dynamic course of spot signs, from spots that resolve quickly to spots that appear late, as observed in studies of dynamic CT angiography (19,20).

Outcomes

The primary outcome was substantial hematoma expansion at follow-up CT, defined as an absolute volumetric ICH growth of more than 6 mL or relative volumetric ICH enlargement of more than 33% from that at baseline CT (8,21,22). A secondary outcome was absolute volumetric hematoma growth.

Statistical Analysis

Statistical analysis was performed by using software (SPSS, version 17.0; IBM, Chicago, Ill). The categorical variables are presented as absolute values (with percentages) and the continuous variables as means ± standard deviation or medians (with interquartile ranges [IQRs]). Statistical significance for intergroup differences was assessed by using the Pearson χ^2 or Fisher exact test for categorical variables and the Student *t* test, Mann-Whitney *U* test, or Kruskal-Wallis test for continuous variables, as appropriate. Significant differences among the three phases of multiphase CT angiography were assessed with the Cochran *Q* test for the frequency of the spot sign and with the Friedman test (nonparametric repeated-measurements analysis of variance) for the radiologic characteristics of the spot sign. The sensitivity, specificity, predictive values, accuracy, and area under the curve of the spot sign in the three different phases of multiphase CT angiography for the prediction of substantial hematoma expansion were calculated.

Multiple logistic regression analyses were used to test for the association of the spot sign in different phases of CT angiography with substantial hematoma expansion; analyses were adjusted for the covariates age, sex, anticoagulant use, baseline National Institutes of Health Stroke Scale score, time from symptom onset to baseline CT (onset to imaging time), baseline ICH volume, and intraventricular extension. The sample size did not permit the determination of covariates that were associated with outcomes. Results are presented as odds ratios and 95% confidence intervals. Two-sided $P < .05$ was considered to indicate a statistically significant difference. The Bonferroni method was applied to the results of multiple comparison tests (hematoma expansion vs presence of spot sign in phase 1, phase 2, phase 3, or any phase). After Bonferroni correction, the adjusted significance level for multiple comparisons was α of .0125 (0.05/4 = 0.0125).

Figure 1

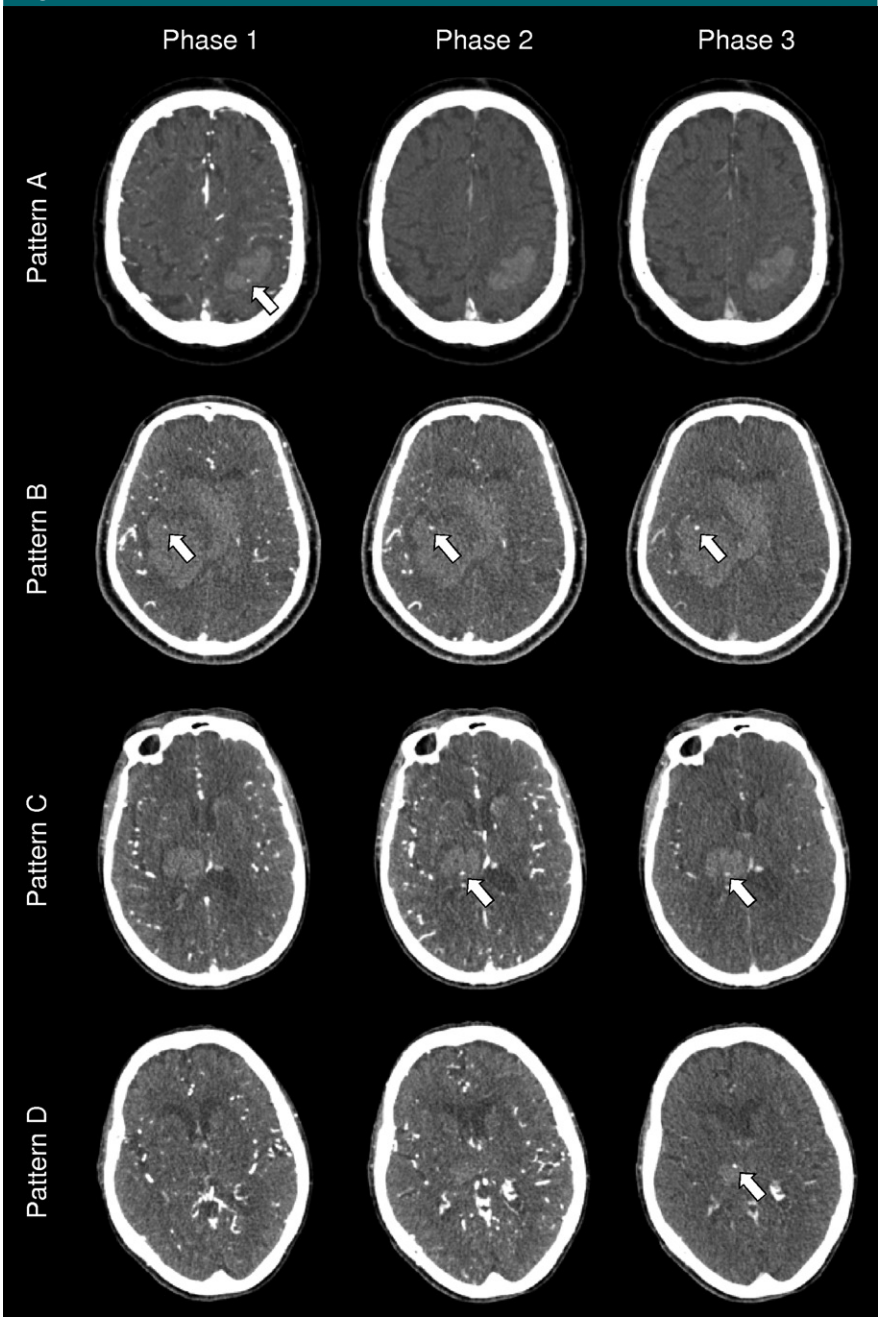

Figure 1: Representative images from CT angiography show the four patterns of spot sign presentation (patterns A, B, C, and D) according to presence of spot sign (arrows) in the three phases of multiphase CT angiography.

Results

Study Population

A total of 123 patients were included in the study, all of whom had undergone multiphase CT angiography within 6 hours from symptom onset (Fig 2). Baseline characteristics are provided in Table 1. The median ICH volume was 16.7 mL (IQR, 5.8–44.3 mL), and the median time between onset and baseline imaging was 159 minutes (IQR, 87–234 minutes).

Hematoma expansion analysis was limited to 95 patients after the exclusion of two patients who underwent surgical hematoma evacuation and 26 patients who did not undergo follow-up CT (20 because of death and six because of withdrawal of care within the first 24 hours) (Fig 2). Patients not included in the hematoma expansion analysis were more likely to be older and have lower Glasgow Coma Scale scores, higher National Institutes of Health Stroke Scale score and ICH volume, a lobar ICH location, intraventricular or subarachnoid extension, and spot sign (Table 2).

Spot Sign Frequency

Overall, 62 of the 123 patients (50.4%) had the spot sign in at least one phase. The spot sign was seen more frequently in the later phases of multiphase CT angiography: in 36 of 123 patients (29.3%) in phase 1, 53 of 123 (43.1%) in phase 2, and 57 of 123 (46.3%) in phase 3 ($P < .001$). Radiologic characteristics of the spot sign according to the different phases of multiphase CT angiography are summarized in Table 3. Spot sign characteristics varied across phases: The later the phase of multiphase CT angiography, the higher the total number and maximum axial diameter and the lower the maximum attenuation.

Pattern A was observed in three of the 62 patients with the spot sign in at least one phase (4.8%); pattern B, in 33 (53.2%); pattern C, in 18 (29.0%); and pattern D, in eight (12.9%). There was no significant difference in the time between onset to baseline imaging with respect to the more arterial pattern ($P = .523$) (Fig 3).

Substantial Hematoma Expansion

Among the 95 patients included in the hematoma expansion analysis, 41 (43.2%) had a spot sign in at least one phase and 25 (26.3%) experienced substantial hematoma expansion (>6 mL or >33%). Substantial hematoma expansion occurred more frequently in patients with spot sign in phase 1 (16 of 25 patients [64.0%] vs nine of 70 patients [12.9%];

Figure 2

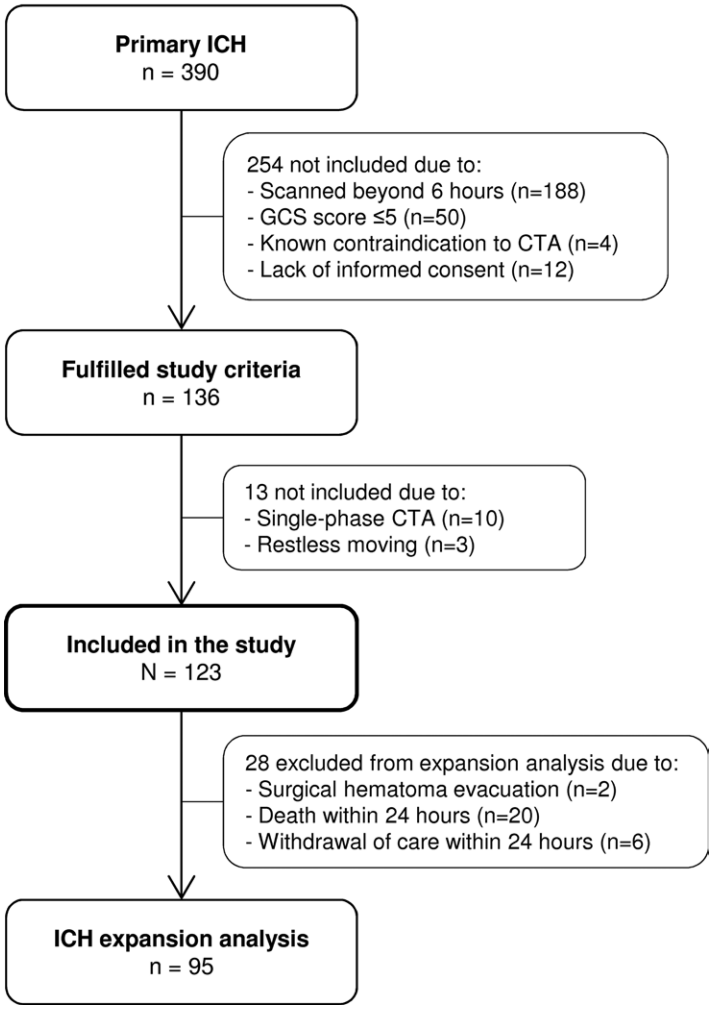

Figure 2: Cohort flowchart. *CTA* = CT angiography, *GCS* = Glasgow Coma Scale.

$P < .001$), phase 2 (19 of 34 patients [55.9%] vs six of 61 patients [9.8%]; $P < .001$), and phase 3 (17 of 36 patients [47.2%] vs eight of 59 patients [13.6%]; $P = .001$) than in patients without spot sign in these phases, as well as in patients with spot sign in any of the three phases (20 of 41 patients [48.8%] vs five of 54 patients [9.3%]; $P < .001$) (Bonferroni adjusted $\alpha = .0125$). The more arterial the pattern of spot sign presentation, the higher the frequency of substantial hematoma expansion: 100% (three of three patients) in pattern A, 59.1% (13 of 22 patients) in pattern B, 40% (four of 10 patients) in pattern C, and 0% (zero of six patients) in pattern D ($P = .013$).

Predictive values varied depending on the acquisition phase (Table 4): Although the highest positive predictive value was observed in phase 1 (64.0% [16 of 25 patients]), negative predictive values were consistently high in all phases; the negative predictive value was highest in phase 2 (90.2% [55 of 61 patients]) of multiphase CT angiography. The association of spot sign presence in phase 1 (odds ratio, 8.1; 95% confidence interval: 2.5, 25.9), phase 2 (odds ratio, 8.2; 95% confidence interval: 2.6, 25.8), phase 3 (odds ratio, 5.0; 95% confidence interval: 1.7, 15.2), or any phase (odds ratio, 6.5; 95% confidence interval: 2.0, 21.0) with the primary outcome remained significant in separate adjusted multiple logistic regression models.

Absolute Hematoma Growth

The median absolute hematoma growth at 24 hours was 0.6 mL (IQR, 0.0–4.6 mL). The presence of the spot sign was associated with higher absolute hematoma growth in phase 1 (8.4 mL [IQR, 0.1–28.9 mL] vs 0.4 mL [IQR, 0.0–1.7 mL]; $P = .001$), phase 2 (5.2 mL [IQR, 0.1–17.7 mL] vs 0.3 mL [IQR, 0.0–1.1 mL]; $P < .001$), and phase 3 (2.8 mL [IQR, 0.0–16.7 mL] vs 0.4 mL [IQR, 0.0–1.7 mL]; $P = .008$), as well in any of the three phases (4.0 mL [IQR, 0.0–16.3 mL] vs 0.3 mL [IQR, 0.0–1.0 mL]; $P = .001$), compared with patients without the spot sign (Bonferroni adjusted $\alpha = .0125$). Absolute hematoma growth analysis revealed a hierarchical pattern of spot sign presentation and hematoma growth, as follows: pattern A > pattern B > pattern C > pattern D > no spot sign ($P = .002$) (Fig 3).

Discussion

The results of this study demonstrate that the more arterial the pattern of spot sign presentation, the greater the frequency and extent of ICH expansion. Furthermore, the frequency of the spot sign varies across phases of multiphase CT angiography, being higher in the later phases. The results of our study also suggest that the different patterns of spot sign presentation in multiphase CT angiography may reflect the pathophysiologic course of ICH expansion, from active hemorrhage to resolved bleeding.

Multiphase CT angiography is an emerging vascular imaging technique that has recently been introduced for the evaluation of acute ischemic stroke (16,23,24). In acute ICH, multiphase CT angiography can acquire temporal information of the spot sign at three data points without the requirement of additional contrast material and with minimal additional radiation over that with single-phase CT angiography (15,17). Several CT modalities were previously proposed for the evaluation of the spot sign in the prediction of hematoma

Table 1

Summary of Baseline Characteristics according to the Presence of the Spot Sign in Any Phase of Multiphase CT Angiography

Variable	All Patients ($n = 123$)	Patients with Spot Sign ($n = 62$)	Patients without Spot Sign ($n = 61$)	*P* Value*
Age (y)	72.0 ± 13.5	76.6 ± 11.0	67.2 ± 14.2	<.001
Men†	79 (64.2)	34 (54.8)	45 (73.8)	.029
Antiplatelet use†	35 (28.5)	22 (35.5)	13 (21.3)	.082
Anticoagulant use†	21 (17.1)	15 (24.2)	6 (9.8)	.034
GCS score‡	15 (14–15)	14 (13–15)	15 (14–15)	.002
NIHSS score‡	16 (8–20)	18 (14–21)	10 (6–17)	<.001
Blood pressure (mm Hg)				
Systolic	172.7 ± 32.7	175.3 ± 33.8	170.1 ± 31.6	.385
Diastolic	90.3 ± 19.8	91.3 ± 21.1	89.3 ± 18.6	.595
Glucose level (mmol/L)	8.2 ± 3.0	8.7 ± 3.4	7.7 ± 2.4	.190
Creatinine level (μmol/L)	78.4 ± 22.6	78.1 ± 21.2	78.6 ± 24.1	.912
Hemoglobin (g/L)	138.7 ± 20.3	134.8 ± 20.9	142.4 ± 19.2	.044
Leukocyte count ($\times 10^3$ cells/μL)	9.9 ± 4.1	10.1 ± 4.4	9.8 ± 3.8	.702
Platelet count ($\times 10^3$ cells/μL)	223.1 ± 71.9	224.9 ± 81.9	221.4 ± 61.7	.793
INR	1.27 ± 0.61	1.43 ± 0.76	1.10 ± 0.36	.019
aPTT (sec)	31.9 ± 5.4	33.1 ± 6.7	30.8 ± 3.5	.022
Time between onset and imaging (min)‡	159 (87–234)	135 (97–232)	184 (83–270)	.489
ICH volume (mL)‡	16.7 (5.8–44.3)	31.2 (13.7–62.7)	6.9 (3.7–21.3)	<.001
ICH location†				.350
Cerebral lobes	38 (30.9)	23 (37.1)	15 (24.6)	
Basal ganglia or thalamus	73 (59.3)	35 (56.5)	38 (62.3)	
Brainstem	5 (4.1)	2 (3.2)	3 (4.9)	
Cerebellum	7 (5.7)	2 (3.2)	5 (8.2)	
Intraventricular extension†	50 (40.7)	37 (59.7)	13 (21.3)	<.001
Subarachnoid extension†	29 (23.6)	22 (35.5)	7 (11.5)	.002

Note.—Except where indicated, data are means ± standard deviations. aPTT = activated partial thromboplastin time, GCS = Glasgow Coma Scale, INR = international normalized ratio, NIHSS = National Institutes of Health Stroke Scale.

**P* values were determined with the Pearson χ^2 test, Student *t* test, or Mann-Whitney *U* test as appropriate.

† Data are numbers of patients, with percentages in parentheses.

‡ Data are medians, with IQR in parentheses.

expansion apart from single-phase CT angiography (6,8,9), including contrast material–enhanced CT, delayed CT angiography, CT perfusion, and dynamic CT angiography (8,11–14,25–32). However, there is no accepted consensus for CT technique or timing of image acquisitions. Studies that introduced second-pass imaging after the initial administration of a bolus of contrast material, termed *postcontrast CT* or *delayed CT angiography* in the literature, have shown divergent results; overall, however, these studies suggest that second-pass imaging can increase both spot sign detection and its sensitivity for predicting hematoma expansion compared with first-pass CT angiography (8,11–14,25–28). However, most of these studies did not have standardized indications for CT angiography (8,11–14,25,26,28), which limits their generalizability, and did not use fixed timing for the delayed imaging (11–14,26–28), which may have altered the ability to detect some spot signs.

Other CT technologies allow for dynamic contrast imaging over 1 minute or longer, producing CT perfusion and dynamic CT angiographic images that provide information about the dynamic changes of the spot sign (28–32). CT perfusion studies have also reported an increase of both spot sign detection and its sensitivity in the prediction of hematoma expansion compared with that of single-phase CT angiography, but with incomplete spatial coverage of ICH volume (29,30). Conversely, studies of dynamic CT angiography did not attempt to predict hematoma expansion (31,32). Multiphase CT angiography has advantages over CT perfusion and dynamic CT angiography, providing dynamic information about the spot sign in a faster and easier manner at a lower dose of radiation and contrast material (16). Multiphase CT angiography may resolve the need for standardization of CT angiography raised by previous studies of contrast-enhanced CT and delayed CT angiography.

Our study demonstrates that the later the phase of multiphase CT angiography, the higher the frequency of the spot sign in patients with acute ICH who systematically underwent a standardized automated multiphase CT angiography protocol with fixed timing for image acquisitions. Nearly half of patients who had the spot sign at one

Table 2

Main Baseline Characteristics according to Inclusion in Hematoma Expansion Analysis

Variable	Patients Included in Analysis ($n = 95$)	Patients Not Included in Analysis ($n = 28$)	*P* Value*
Age (y)†	70.0 ± 13.8	78.6 ± 10.4	.003
Men	62 (65.3)	17 (60.7)	.659
Antiplatelet use	23 (24.2)	12 (42.9)	.055
Anticoagulant use	15 (15.8)	6 (21.4)	.486
GCS score‡	15 (14–15)	11 (7–14)	<.001
NIHSS score‡	13 (6–18)	19 (17–30)	<.001
Blood pressure (mm Hg)†			
Systolic	170.3 ± 26.9	169.9 ± 30.5	.602
Diastolic	94.0 ± 19.9	86.3 ± 19.7	.987
ICH volume (mL)‡	10.4 (5.0–28.4)	71.0 (37.1–104.2)	<.001
ICH location, lobar	24 (25.3)	14 (50.0)	.013
Intraventricular extension	31 (32.6)	19 (67.9)	.001
Subarachnoid extension	14 (14.7)	15 (53.6)	<.001
Spot sign in any phase	41 (43.2)	21 (75.0)	.003

Note.—Except where indicated, data are numbers of patients, with percentages in parentheses. GCS = Glasgow Coma Scale; NIHSS = National Institutes of Health Stroke Scale.

**P* values are from Pearson χ^2 test, Student *t* test, or Mann-Whitney *U* test as appropriate.

† Data are means ± standard deviations.

‡ Data are medians, with IQR in parentheses.

Table 3

Radiologic Characteristics of the Spot Sign in the Different Phases of Multiphase CT Angiography

Variable	Phase 1 ($n = 36$)	Phase 2 ($n = 53$)	Phase 3 ($n = 57$)	*P* Value*
Total no. of spot signs per patient	2 (1–3)	2 (1–4)	3 (1–5)	<.001
Maximum attenuation (HU)	290 (222–358)	261 (193–386)	243 (185–314)	<.001
Maximum axial diameter (mm)	4.7 (3.2–7.7)	5.0 (2.9–7.7)	5.2 (3.4–9.7)	<.001

Note.—Data are medians, with IQR in parentheses.

* Determined with the Friedman test.

or more phases of multiphase CT angiography did not have it at all acquisition phases. This finding supports the need for dynamic evaluation of the spot sign beyond single-phase CT angiography. The influence of the time of imaging acquisition on the prevalence of the spot sign observed in our study confirms the results of previous studies that used nonstandardized second-pass imaging (12–14,25–27).

Although previous authors have hypothesized that the higher frequency of the spot sign being observed in later phases of image acquisition indicates that the arterial phase is too early to allow opacification of contrast material within the hematoma (10–12,25,30), our finding—that the earlier the acquisition, the higher the maximum attenuation of the spot sign—suggests otherwise. Furthermore, the different radiologic outcomes observed according to the patterns of spot sign presentation support the theory that the underlying pathophysiology of the spot sign may differ according to phase pattern (10,12,30,32). Conversely, radiologic characteristics of the spot sign varied across phases of multiphase CT angiography. However, we did not evaluate the influence of these differences on hematoma expansion and therefore cannot conclude that these statistically significant differences are clinically important.

The results of this study confirm that the yield of the spot sign in the prediction of hematoma expansion varies across phases of multiphase CT angiography. Although sensitivity and negative predictive value increased from phase 1 to phase 2, specificity and positive predictive value were higher in phase 1 and decreased in subsequent phases. Multiphase CT angiography can therefore help stratify patients at risk for hematoma expansion in different decision-making scenarios. A higher positive predictive value could help identify patients at higher risk for hematoma expansion and maximize the treatment effect in hemostatic trials (5). Conversely, a higher negative predictive value could help identify patients at lower risk for hematoma expansion, which could aid in avoiding intraoperative bleeding in surgical trials (33). At present, however, in the absence of treatments with consistently demonstrated effectiveness in acute ICH, multiphase CT angiography cannot be recommended as standard clinical practice.

More arterial spot sign patterns were associated with more frequent and greater hematoma expansion. This, along with the different prevalence of the spot sign depending on the phase of acquisition, suggests that different forms of spot sign presentation represent different pathologic entities. Although the general assumption is that the spot sign is a radiologic correlate of active bleeding at the site where arteriolar wall integrity is lost (6–9,32,33), the exact pathophysiologic importance of the various manifestations of the spot sign is not known. Our study suggests that spot signs detected in earlier acquisitions represent active hemorrhaging without hemostasis and those observed in later acquisitions represent pools of blood accumulation that have been sealed off by hemostasis. Thus, the different patterns of spot sign presentation may reflect the pathophysiologic course of ICH expansion, from pattern A (with highest degree

Figure 3

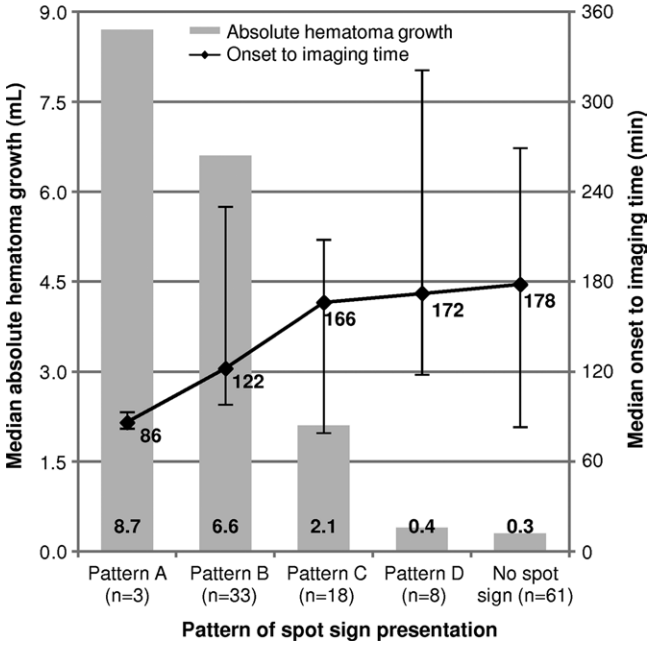

Figure 3: Median time from onset to baseline imaging (error bars are IQR) and median absolute hematoma growth at 24 hours according to pattern of spot sign presentation.

Table 4

Sensitivity, Specificity, Predictive Values, Accuracy, and Area under the Curve of the Spot Sign in Different Phases of Multiphase CT Angiography in the Prediction of Substantial Hematoma Expansion

Spot Sign Positivity	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	AUC
Phase 1	64.0 (16/25)	87.1 (61/70)	64.0 (16/25)	87.1 (61/70)	81.1 (77/95)	0.756
Phase 2	76.0 (19/25)	78.6 (55/70)	55.9 (19/34)	90.2 (55/61)	77.9 (74/95)	0.773
Phase 3	68.0 (17/25)	72.9 (51/70)	47.2 (17/36)	86.4 (51/59)	71.6 (68/95)	0.704
Any phase	80.0 (20/25)	70.0 (49/70)	48.8 (20/41)	90.7 (49/54)	72.6 (69/95)	0.750

Note.—Numbers in parentheses are raw data. AUC = area under the curve, NPV = negative predictive value, PPV = positive predictive value.

of hematoma expansion, corresponding to active hemorrhage) to pattern D and absence of spot sign (with lowest degrees of hematoma expansion, corresponding with resolved bleeding).

Our study has limitations. First, although the technical parameters of multiphase CT angiography were standardized, physiologic variables, such as arterial resistance, circulation time, and intracranial pressure, could have differed among patients and may have influenced the timing of spot sign visualization. Second, we did not find a significant relationship between onset to imaging time and the pattern of spot sign presentation, possibly because of a relatively small sample size. Finally, patients who did not undergo follow-up CT because of death or withdrawal of care within the first 24 hours were more likely to have the spot sign, possibly resulting in underestimation of the predictive value of the spot sign for ICH expansion.

In summary, multiphase CT angiography is a quick and easy-to-use tool for predicting hematoma expansion in patients with acute ICH. Multiphase CT angiography can help differentiate among different forms of spot sign presentation and can help better stratify patients at risk for hematoma expansion in different decision-making scenarios. It might also provide additional information about the pathophysiology of the spot sign, but further studies are needed to elucidate the exact underlying pathophysiology of this imaging biomarker.

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