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Predicting intracerebral hemorrhage growth with the spot sign: the effect of onset to scan time

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Abstract

Background and Purpose—Hematoma expansion following acute intracerebral hemorrhage (ICH) is common and is associated with early deterioration and poor clinical outcome. The CT angiography (CTA) spot sign is a promising predictor of expansion, however frequency and predictive values are variable across studies, possibly due to differences in onset-to-CTA time. We performed a patient-level meta-analysis to define the relationship between onset-to-CTA time and frequency and predictive ability of the spot sign.

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Disclosures

All other authors have nothing to disclose.

Methods—We completed a systematic review for studies of CTA spot sign and hematoma expansion. We subsequently pooled patient-level data on the frequency and predictive values for significant hematoma expansion according to five pre-defined categorized onset-to-CTA times. We calculated spot sign frequency both as raw and frequency-adjusted rates.

Results—Among 2051 studies identified, 12 met our inclusion criteria. Baseline hematoma volume, spot sign status and time-to-CTA were available for 1176 patients, and 1039 patients had follow-up CTs for hematoma expansion analysis. The overall spot sign frequency was 26%, decreasing from 39% within two hours of onset to 13% beyond eight hours ($p<0.001$). There was a significant decrease in hematoma expansion in spot positive patients as onset-to-CTA time increased ($p=0.004$), with positive predictive values decreasing from 53% to 33%.

Conclusions—The frequency of the CTA spot sign is inversely related to ICH onset-to-CTA time. Furthermore, the positive predictive value of the spot sign for significant hematoma expansion decreases as time-to-CTA increases. Our results offer more precise risk-stratification for patients with acute ICH, and will help refine clinical prediction rules for ICH expansion.

Keywords

Spot sign; intracerebral hemorrhage; cerebral hemorrhage; CT-angiography; hematoma expansion

Subject terms

Clinical studies; CT; prognosis; intracranial hemorrhage

INTRODUCTION

Intracerebral hemorrhage (ICH) causes the majority of stroke morbidity and mortality[1,2]. While ICH volume and location are strong predictors of outcome, neither are modifiable at the time of diagnosis[3,4]. However, hematoma expansion occurs in up to 40% of patients, worsens outcome, can potentially be prevented[5–8], and is therefore a therapeutic target of ongoing clinical trials (NCT00810888, NCT01359202, NCT01702636, ISRCTN93732214).

Attempts to mitigate hematoma expansion failed to demonstrate improved outcomes in large randomized controlled trials[7,9–10]. This is partially attributed to the challenge of accurately identifying patients most likely to benefit from interventions targeting hematoma expansion[11]. To date, only one trial demonstrated a shift towards reduced disability with blood pressure lowering, which was achieved with a marginal reduction in hematoma expansion[12]. We can potentially increase the absolute effect of such therapies by using biomarkers to identify patients at highest risk of this expansion. Contrast extravasation following CT angiography (CTA), termed ‘the spot sign’, is a promising radiological marker that predicts hematoma expansion[13–24].

The spot sign is appealing to clinicians and researchers as CTA is a rapid and non-invasive imaging modality used in acute stroke[25,26]. However, the predictive performance of the spot sign is highly variable across studies, with positive predictive values (PPV) ranging from 0.22–1.00[27]. While preliminary data suggests that onset-CTA time may explain some of this variability[28,29], the relationship remains unclear. We therefore performed a systematic

review and patient-level meta-analysis to assess the frequency and predictive performance of the spot sign in relation to onset-to-CTA times in patients presenting with acute ICH.

METHODS

With the assistance of an experienced health sciences librarian (LAU) we searched MEDLINE (1946 to present), EMBASE (1974 to present), Cochrane Central Register of Controlled Trials (CENTRAL), and The Cochrane Library Database of Systematic Reviews (latest issue) for ICH studies reporting the CTA spot sign. We did not restrict the search by language, date or study type. We registered the search strategy with the University of Ottawa, which is available at: http://hdl.handle.net/10393/30685. The search was completed in November 2012 and was updated in September 2013. Additional references were identified from the bibliographies of retrieved articles and by contacting the authors of retrieved articles. Two authors (DD and MS) independently assessed all potential studies identified by the search strategy. Studies that reported CTA assessment of patients with acute primary ICH and initial and follow-up hematoma volumes were included. Review articles and duplicate publications were excluded. Disagreements about inclusion were adjudicated by consensus.

We contacted corresponding authors of all included studies to request patient-level data using a standard data collection form. We requested demographic information, medical history, spot sign status (spot positive or spot negative), baseline and follow-up hematoma volumes, and time from onset to presentation and CTA. We *a priori* categorized onset-to-CTA time into the following five time strata: <120 minutes, 120 – 239 minutes, 240 – 359 minutes, 360 – 479 minutes, and > 480 minutes. Stroke onset time was either a witnessed onset, or a “last seen well” time that could be classified into the five strata. To ascertain the risk of bias in eligible studies, two reviewers independently determined the adequacy of inclusion criteria, clinical and time of onset data, scanning intervals and technique, hematoma measurement technique and selective outcome reporting. Contributing studies were approved by their local institutional research ethics boards.

Statistical analysis

We compared the baseline characteristics of included and excluded patients using Fisher’s exact test, t-test and Mann-Whitney U-test as appropriate. We assessed the heterogeneity of proportions by study and by time strata (I^2). We calculated the overall frequency of spot sign from all patients with baseline CTA and non-contrast CT (NCCT) and reported both raw and frequency-adjusted rates (means weighted by total N). Similarly, we reported absolute hematoma growth and proportion of patients with “significant” hematoma growth from all patients with baseline CTA, baseline NCCT, and follow-up NCCT. We defined significant hematoma expansion as an increase of 6 mL or 33% in parenchymal hematoma volume between baseline and follow-up NCCT[17,24,30,31], and calculated sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios, and the area under the curve (AUC) for the spot sign as a predictor of significant hematoma expansion. We modeled the probability of ICH growth over time, stratified by the spot sign. We used a logistic regression model with time and spot-sign status as covariates and estimated the

predicted probabilities of ICH growth in each stratum. We used SPSS v20 (IBM, Armonk, NY, USA) and STATA (College Station, Tx) for all analyses.

RESULTS

We identified 2051 potential studies in our search of which 11 met our inclusion criteria (table 1). A 12th study was identified by bibliography review[20]. Of these, we were able to obtain patient-level data on eight studies, and to minimize risk of reporting bias, we obtained the full dataset from the authors (N=1343). Spot sign status was identified by the local investigators in all studies, and was considered to be present if high-density contrast material or foci of enhancement was seen within the hematoma without connection to outside vessels[24,27,34]. All studies included first-pass CTAs except one, which included both first and second pass CTA[23]. Hematoma volume was measured in the eight studies with available data by either computer-assisted planimetry (three studies)[17,19,23] or the ABC/2 method (five studies)[14,16,22,24,32].

Of the 1343 patients, 44 did not have a baseline CT scan, 3 did not have spot sign assessment, and 120 could not be classified into time strata due to incomplete time of onset or last seen well information. We were able to obtain baseline hematoma volumes, spot sign status and time-to-CTA for 1176 patients, which formed the spot sign frequency cohort, and had follow-up hematoma volumes for 1039 patients for the hematoma expansion cohort. Patients excluded due to incomplete data were older (mean age 75 versus 67 years), more likely to be female, to use antiplatelets, have lower hemoglobin and higher baseline glucose, and larger hematoma volumes (Table 2). The median time to follow-up NCCT was 22.8 hours [IQR 8.7] for spot negative patients and 22.9 hours [IQR 8.8] for spot positive patients.

There was significant heterogeneity of spot sign frequency between studies (I^2 = 20.67, p=0.004), and this was due to heterogeneity in the 0–2h strata (I^2 = 15.5, p=0.016) and the 2–4h strata (I^2 = 16.5, p=0.011). There was no heterogeneity by study observed at the later time strata. The frequency of the spot sign was 26% for the group as a whole and showed a significant relationship with onset-to-CTA time strata (p<0.001), decreasing from 39% within two hours of onset to 13% after eight hours (Figure 1).

There was no heterogeneity in hematoma expansion between studies (F=0.45, p=0.87) or time strata (F=0.75, p=0.56). In all time intervals the median volume of hematoma expansion was greater for spot positive as compared to spot negative patients, but there was no demonstrable decrease in median hematoma expansion by time-strata in spot positive patients (overall model F=1.28, p=0.14; Supplementary Table I). However, there was a decreasing relationship between spot positivity and significant hematoma expansion (≥6mL or ≥33%) as onset-to-CTA time strata increased (Figure 2, Supplementary Table II). Furthermore, sensitivity and PPV of the spot sign to predict significant hematoma expansion was greatest in the earlier time strata, whereas the specificity and negative predictive value (NPV) of spot sign increased with time (Table 3).

DISCUSSION

We performed a large patient-level meta-analysis and found significant variation in the frequency and predictive value of the CTA spot sign based on onset to CTA time. Frequency of spot sign decreased to a third of its value between the earliest (0–2h) and latest (>8h) onset to scan times. The sensitivity and PPV of the spot sign to predict hematoma expansion was similarly highest in early time strata. While the CTA spot sign is a promising radiological biomarker for prognostication and patient selection for emerging ICH therapies, the onset-to-imaging time should be considered when attempting to identify patients at highest risk for hematoma expansion.

Our study provides important data to optimize patient-selection in ongoing clinical trials, and offers frequency and performance data to inform future trial design. However, we also highlight the limitations of the spot sign: the best sensitivity to detect hematoma expansion was achieved in the first 2 hours from symptom onset and was only 60%. This modest predictive performance precludes the use of the spot sign in isolation, and argues for its inclusion into “expansion prediction scores”. By explaining the variability by time in spot sign performance, our study allows for the refinement of emerging ICH expansion scores and the future development of clinical prediction rules[31,35,36]. Furthermore, we highlight that even in the best-case scenario where patients present hyper-acutely, 40% of those destined for hematoma expansion will not be identified by the spot sign, which supports the need for prediction rules that do not solely rely on CTA[35]. Conversely, our data suggests than in later time-points, the spot sign has a very high specificity and NPV, which may reassure treating clinicians and clinical trialists that spot-negative patients presenting after 6 hours likely have stable hematomas.

Our findings are consistent with the presumed underlying pathology of the spot sign as the source of ICH, and help unify existing theories around its pathophysiology. A recent dynamic CTA study revealed that early spot signs behave in a manner consistent with active extravasation[15]. But as time goes on, endogenous hemostatic mechanisms ultimately stop the bleeding. In the classical ICH pathology series, Dr. Fisher discussed “bleeding globes” consisting of concentric fibrin rings attached to the walls of parenchymal hematomas[37]. These 100–200um globes were thought to be thrombosed sites of vascular rupture, and because they fall within the spatial resolution of CTA, are likely a pathological equivalent to the spot sign[24]. But these autopsy samples would have been acquired many hours after ICH onset, by which time the formation of stable fibrin globes around a ruptured vessel would have reduced the chance of ongoing bleeding; if imaged, these would likely be spot positive yet unlikely to expand. The onset to CTA time relationship in our study fits with the hypothesis that the radiological spot sign initially represents a site of vessel rupture. Indeed, a recent pathological report demonstrated a focal vessel disruption in a spot positive patient undergoing hematoma evacuation[38]. We hypothesize that over time the vessel disruption thromboses, forms concentric fibrin rings, and ultimately achieves hemostasis. Nevertheless, this explanation for late spot sign is speculative; it is entirely possible late spot signs may also represent active extravasation, albeit at a lower rate.

The major strength of this study is the availability of patient-level data from different studies. However, there are several important limitations. Among other missing data, we did not have access to clinical outcome data from all studies and restricted our analysis to radiological outcomes only. We were also unable to access patient-level radiological data from four studies identified in our review representing 563 patients[18,20,21,33], which may have introduced a bias. But we note that the PPV was reported in one of these studies[18], and it consistent with our current findings. There have also been additional spot sign publications since our initial search strategy[39]. This was unavoidable due to the prolonged timelines required to acquire regulatory approvals necessary for access to patient-level data, particularly across national jurisdictions. A second limitation to our study is the different techniques used to measure hematoma volumes. While this can contribute to variability in absolute volumes[40,41], it is less likely to affect the dichotomous hematoma expansion cut-offs (6mL or ≥33%). The third limitation is the relatively low number of spot positive patients in later time windows. Although this may increase variability in point estimates at later time points, the finding of low spot sign prevalence design is in line with previous studies[29] and is nevertheless useful for future studies. A fourth limitation is the different CTA techniques used throughout the different studies included in this analysis, and we cannot exclude the possibility that in some cases, there may have been delays between NCCT and CTA which may contribute to heterogeneity. Finally, we found that patients with incomplete data had markers of poor outcome such as advanced age, and increased glucose and hematoma volumes; it is possible that our estimates of hematoma expansion may be conservative due to their exclusion.

CONCLUSIONS

We demonstrate that spot sign frequencies decreased as onset to scan times increase. While the spot sign remains predictive of hematoma expansion in delayed presentations, PPV and sensitivity decrease and NPV and specificity increase as time-to-CTA increases. Furthermore, the overall performance of the spot sign is modest, suggesting the need for additional clinical and radiological factors to predict hematoma expansion. Our results open a path for more precise risk stratification for patients with acute ICH, and inform ongoing and emerging clinical trials.

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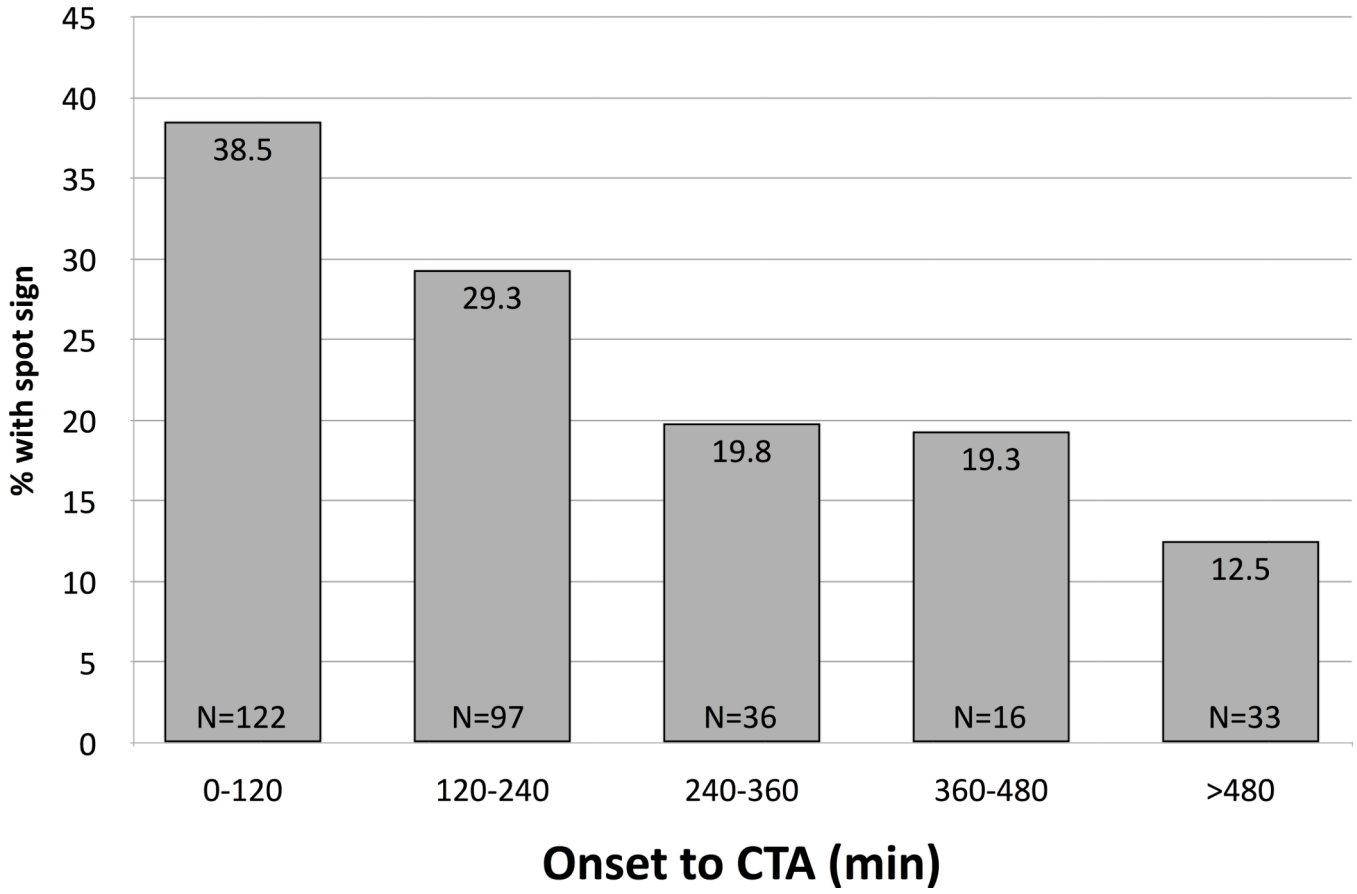

Figure 1.

Frequency of spot sign by time strata (frequency-weighted %); $\mathbf{I^2}$=283.5, p<0.001. The cohort was N=1176, consisting of all patients with baseline CTA spot status.

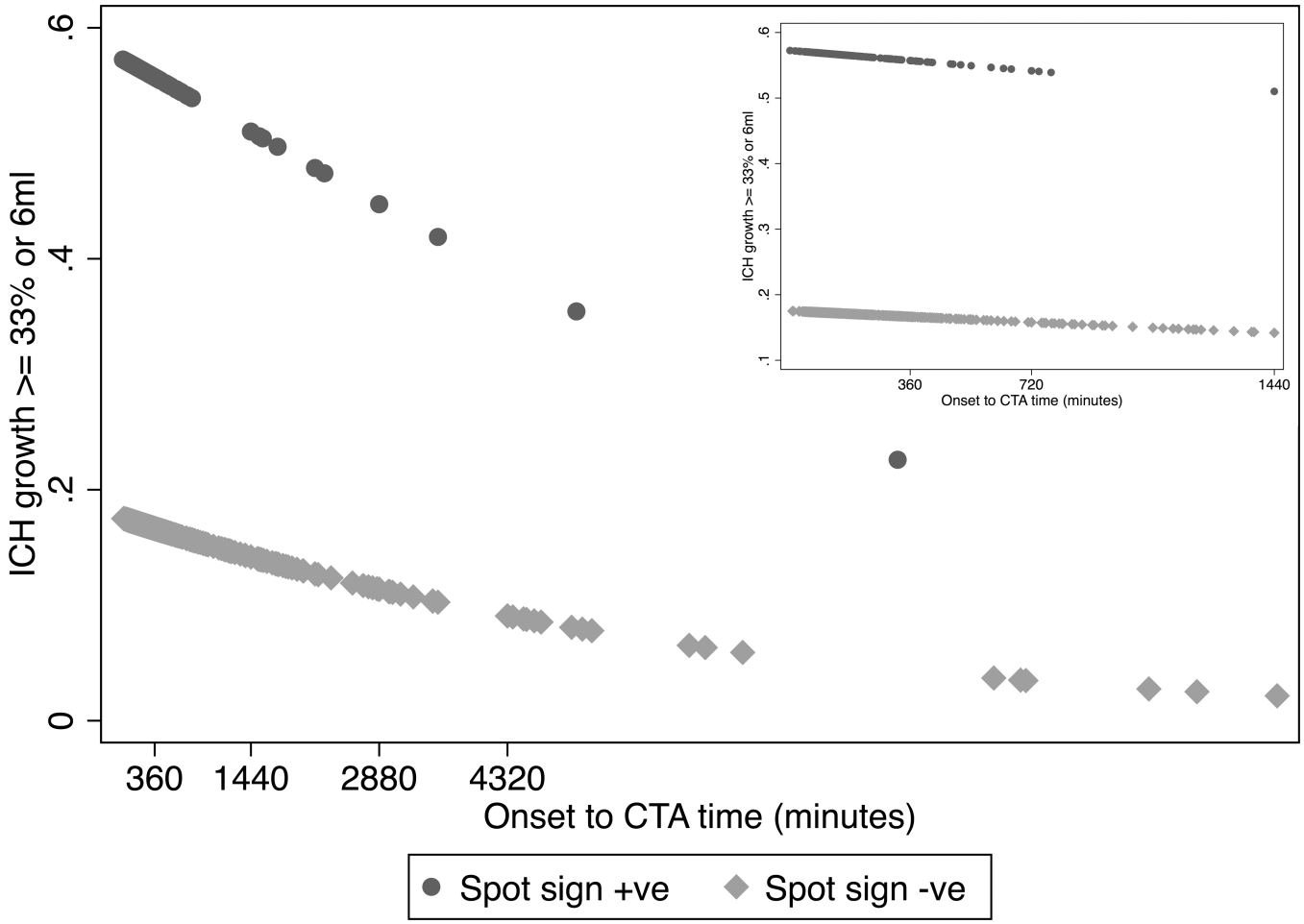

Figure 2.

Modeled probability of significant ICH growth as a function of time from onset to CT angiography. The probability of ICH growth over time was stratified by the spot sign using a logistic regression model with time and spot-sign status as covariates. The inset shows a population restricted to early imaging times.

Table 1

Systematic review results and patient-level data available for meta-analysis.

Study	Country	Year	Enrollment window*	Spot frequency**	PPV	Number of patients+
Demchuk et al.[17]	Multicenter++	2012	< 6 hours	29%	61%	386
Wada et al.[24]	Canada	2007	< 3 hours	33%	77%	126
Goldstein et al.[23]	USA	2007	None	56%	24%	414
Li et al.[19]	China	2011	< 6 hours	22%	79%	139
Murai et al.[32]	Japan	1999	< 12 hours	21%	60%	24
Kim et al.[22]	USA	2008	None	18%	NR	56
Sorimachi et al.[16]	Japan	2013	< 24 hours	21%	NR	141
Rizos et al.[14]	Germany	2013	< 6 hours	27%	59%	57
Becker et al.[33]	USA	1999	None	46%	NR	NA
Park et al.[21]	Korea	2010	< 24 hours	17%	NR	NA
Wang et al.[18]	China	2011	< 3 hours	24%	83%	NA
Hallevi et al.[20]	USA	2010	< 4 hours	41%	100%	NA

*Enrollment window refers to inclusion time windows of published studies.

**Spot prevalence as reported in the initial publications.

+As some studies continued enrollment following publication, number of patients refers to the final number available for pooled analysis.

++Participating centers were in Canada, Spain, Germany, USA, Poland and India.

PPV = positive predictive value; NR = not reported in primary publication; NA = patient-level data not available

Table 2

Baseline Characteristics

	Included patients (n=1039)	Excluded patients (n=304)	P
Demographics			
Age, years (mean, SD)[1]	66 (15)	73 (12)	<0.001
Male sex (%, n/N)[2]	59% (618/1039)	52% (154/295)	0.028
Medical History			
Diabetic (%, n/N)[3]	18% (68/372)	24% (6/25)	0.435
Hyperlipidemia (%, n/N)[3]	23% (86/372)	32% (8/25)	0.333
HTN (%, n/N)[4]	74% (745/1009)	76% (223/292)	0.403
Baseline Systolic BP (median, IQR)[5]	174 (45)	177.5 (45.8)	0.208
Baseline Diastolic BP (median, IQR)[6]	92 (29)	90 (24)	0.074
Medications			
Anticoagulant use (%, n)[7]	10% (97/961)	13% (39/295)	0.134
Antiplatelet use (%, n)[8]	33% (289/879)	41% (122/294)	0.009
Statin use (%, n)[9]	25% (91/360)	27% (69/256)	0.642
Baseline Labs			
INR (median, IQR)[10]	1.02 (0.13)	1.00 (0.13)	0.956
INR >1.7 (%, n)[10]	8% (86)	12% (35)	0.088
Hg (median, IQR)[11]	140 (23)	137 (23)	0.033
Platelets (median, IQR)[12]	224 (90)	230 (91)	0.144
Glucose (median, IQR)[13]	7.1 (2.8)	8.0 (3.4)	<0.001
Creatinine (median, IQR)[14]	77.8 (27.5)	76.9 (30.9)	0.957
Onset to CTA time, min (median, IQR)[15]	199 (253)	180 (251)	0.235
Spot positive (%, n)	24% (252)	29% (85)	0.094
Hematoma volume, mL (median, IQR)[16]	15.5 (208.1)	45.1 (235.6)	<0.001

IQR = interquartile range, HTN = hypertension, INR = international normalized ratio, Hg = hemoglobin

[2] missing 9 values,

[3] missing 946 values,

[4] missing 42 values,

[5] missing 169 values,

[6] missing 193 values,

[7] missing 87 values,

[8] missing 170 values,

[9] missing 727 values,

[10] missing 195 values,

[11] missing 521 values,

[12] missing 169 values,

[13] missing 217 values,

[14] missing 799 values,

[15] missing 190 values,

[16] missing 44 values.

Of the 304 excluded patients, 44 were excluded due to missing baseline CT, 3 for missing spot sign data, 120 due to missing time data precluding assignment to a time strata, and 137 due to missing follow-up CT.

Table 3

Predictive values for spot sign to predict hematoma expansion (≥6mL or ≥33%) by time strata.

	n	Sensitivity	Specificity	PPV	NPV	+LR	−LR	AUC (95% CI)
Overall	1039	0.51	0.85	0.53	0.84	3.31	0.58	0.68 (0.66–0.69)
0–2h	266	0.60	0.76	0.61	0.76	2.56	0.52	0.68 (0.63–0.74)
2–4h	307	0.55	0.84	0.57	0.82	3.37	0.54	0.69 (0.64–0.75)
4–6h	170	0.44	0.91	0.56	0.87	5.01	0.61	0.68 (0.59–0.76)
6–8h	82	0.56	0.92	0.64	0.90	7.41	0.47	0.74 (0.61–0.87)
>8h	214	0.30	0.90	0.33	0.89	3.06	0.78	0.60 (0.52–0.69)

PPV = positive predictive value, NPV = negative predictive value, LR = likelihood ratio, AUC = area under the curve, CI = confidence interval