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CTA Spot Sign Predicts Hematoma Expansion in Patients with Delayed Presentation After Intracerebral Hemorrhage

H. Bart Brouwers,
Center for Human Genetic Research-Rosand Lab, Massachusetts General Hospital, Harvard Medical School, 185 Cambridge Street, CPZN-6818, Boston, MA 02114, USA. Division of Neurocritical Care and Emergency Neurology, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA. Hemorrhagic Stroke Research Group, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA. J. Philip Kistler Stroke Research Center, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Guido J. Falcone,
Center for Human Genetic Research-Rosand Lab, Massachusetts General Hospital, Harvard Medical School, 185 Cambridge Street, CPZN-6818, Boston, MA 02114, USA. Division of Neurocritical Care and Emergency Neurology, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA. Hemorrhagic Stroke Research Group, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Kristen A. McNamara,
Hemorrhagic Stroke Research Group, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA. J. Philip Kistler Stroke Research Center, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Alison M. Ayres,
Hemorrhagic Stroke Research Group, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA. J. Philip Kistler Stroke Research Center, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Alexandra Oleinik,
Hemorrhagic Stroke Research Group, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA. J. Philip Kistler Stroke Research Center, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Kristin Schwab,
Hemorrhagic Stroke Research Group, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA. J. Philip Kistler Stroke Research Center, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Javier M. Romero,

Correspondence to: H. Bart Brouwers, brouwers@chgr.mgh.harvard.edu.

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Neuroradiology Service, Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Anand Viswanathan,
Division of Neurocritical Care and Emergency Neurology, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA. Hemorrhagic Stroke Research Group, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA. J. Philip Kistler Stroke Research Center, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Steven M. Greenberg,
Hemorrhagic Stroke Research Group, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA. J. Philip Kistler Stroke Research Center, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Jonathan Rosand, and
Center for Human Genetic Research-Rosand Lab, Massachusetts General Hospital, Harvard Medical School, 185 Cambridge Street, CPZN-6818, Boston, MA 02114, USA. Division of Neurocritical Care and Emergency Neurology, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA. Hemorrhagic Stroke Research Group, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA. J. Philip Kistler Stroke Research Center, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Joshua N. Goldstein
Division of Neurocritical Care and Emergency Neurology, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA. Hemorrhagic Stroke Research Group, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA. J. Philip Kistler Stroke Research Center, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA. Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

H. Bart Brouwers: brouwers@chgr.mgh.harvard.edu

Abstract

Background—Hematoma expansion after acute intracerebral hemorrhage occurs most frequently in patients presenting within 3 h of symptom onset. However, the majority of patients present outside this window or with an unknown onset time. We investigated the prevalence of hematoma expansion in these patients and assessed the accuracy of the CT angiography (CTA) spot sign for identifying risk of hematoma expansion.

Methods—We analyzed 391 consecutive patients undergoing CTA and a followup CT. CTA spot sign readings were performed by two experienced readers and hematoma expansion was assessed by means of semi-automated software.

Results—Hematoma expansion occurred in 18 % of patients. When stratified by time from symptom onset to initial CT, hematoma expansion rates were: 39 % within 3 h; 11 % between 3 and 6 h, 11 % beyond 6 h (but with known onset), and 20 % in patients with unknown symptom onset. Of patients who developed hematoma expansion, only 38 % presented within 3 h. The accuracy of the spot sign in predicting hematoma expansion was 0.67 for patients presenting within 3 h, 0.83 between 3 and 6 h, 0.88 after 6 h, and 0.76 for patients presenting with an unknown onset time.

Conclusions—A substantial number of patients destined to suffer from hematoma expansion present either late or with an unknown symptom onset time. The CTA spot sign accurately identifies patients destined to expand regardless of time from symptom onset, and may therefore

open a path to offer clinical trials and novel therapies to the many patients who do not present acutely.

Keywords

Intracerebral hemorrhage; CT angiography; CTA spot sign; Hematoma expansion; Late presentation

Introduction

Spontaneous intracerebral hemorrhage (ICH) accounts for 10–15 % of acute stroke cases worldwide and has devastating morbidity and mortality rates [1]. Despite technological advances, overall mortality has not been significantly affected, and 30-day mortality remains approximately 40 % [2]. Hematoma volume is the most potent determinant of outcome [3]. Furthermore, roughly 25 % of ICH patients show significant hematoma expansion during their hospitalization, which further worsens outcome [4, 5]. Therefore, the attenuation of expansion is the current focus of clinical trials (e.g. FAST [6, 7], INTERACT 1 and 2 [8, 9], ATACH-II [10], STOP-IT [11], and SPOTLIGHT [11]).

Since hematoma expansion occurs most frequently in those patients who present within 3 h of symptom onset, prior and ongoing clinical trials have restricted enrollment to patients within this (hyper)acute time window. However, the majority of ICH patients present to the hospital substantially later than 3 h following symptom onset, or without a clear time of onset, and are therefore not candidates for these trials or, presumably, for any successful therapies that might emerge.

In patients with spontaneous ICH, many show evidence of extravasation of contrast into the hematoma on CT angiography (CTA). This finding, termed the “spot sign,” is an independent predictor of hematoma expansion [12–14] and poor clinical outcome [14–16] among patients presenting within the first hours after symptom onset. With this radiographic tool, it may be possible to identify ICH patients who are most likely to expand, even when presenting late or with an unknown onset time (i.e., simply “found down”).

We investigated the frequency of hematoma expansion in ICH patients who present in a delayed or unknown time frame, and determined the accuracy of the CTA spot sign for predicting hematoma expansion in these patients.

Methods

Study Design

This study is a retrospective analysis of prospectively collected data from an ongoing cohort study of consecutive patients with primary ICH at the Massachusetts General Hospital, Boston, USA. All aspects of the study were approved by the hospital’s Institutional Review Board.

Subjects

Consecutive patients who presented to a single urban academic center between December 2000 and November 2010 with primary ICH were approached for enrollment. The current analysis represents data of patients who met the following inclusion criteria: (1) a baseline CT showing primary ICH; (2) a baseline CTA available (standard of care at our institution for all ICH patients since 2007); and (3) a followup CT performed within 48 h of the initial CT. Patients were excluded for traumatic ICH, aneurysmal subarachnoid hemorrhage, hemorrhagic transformation of acute infarction, vascular malformation, brain neoplasm, or

any other suspected cause of secondary ICH. Patients with brainstem hemorrhage or primary intraventricular hemorrhage (IVH) were also excluded. In addition, patients who underwent hematoma evacuation were excluded from the analysis as this intervention precluded accurate assessment of hematoma volumes. Of note, patients with an unknown symptom onset (i.e., "found down") were included in this analysis, unlike all other published cohort studies (Fig. 1).

Clinical Data

Clinical data were prospectively collected through patient interviews (or their families/surrogates) and included age, sex, and medical history including hypertension, atrial fibrillation, coronary artery disease, diabetes mellitus, and hyperlipidemia. Use of warfarin, antiplatelets or statins was also documented. Patient charts were reviewed for admission systolic and diastolic blood pressure, Glasgow Coma Scale (GCS), international normalized ratio, and glucose levels. In addition, time to initial imaging and time between baseline and followup imaging were documented. Mortality and functional clinical outcomes, measured by modified Rankin Scale, were collected by trained study staff at discharge and 3 months post ICH.

CT Analysis

The volumes of both ICH and IVH were assessed for the initial and the first followup CT scan by means of Alice (PAREXEL International Corporation) and Analyze 9.0 (Mayo Clinic, Rochester, Minnesota) software following previously described protocols [17, 18]. Significant hematoma expansion was defined as an absolute increase greater than 6 mL or an increase of greater than 33 % from baseline ICH volume [12, 19, 20].

Two experienced readers, blinded to volume measurements, reviewed CTAs for the presence of spot signs according to previously published, validated criteria [17, 18]. Differences in CTA reading were adjudicated by consensus. All study staff interpreting neuroimaging data were blinded to clinical and outcome measures.

Statistical Analysis

Discrete variables are expressed as count [percentage (%)] and continuous variables as mean [standard deviation (SD)] or median (interquartile range). We assessed the role of the CTA spot sign as a predictor of hematoma expansion through univariate and multivariate logistic regression. Model building for multivariate analysis was carried out as follows: first, stepwise-forward selection with a lenient p value for inclusion of 0.2 was undertaken; second, variables left out in the previous step were re-introduced one at a time and those that modified the point estimate for the main exposure (spot sign) in more than 10 % were kept in the model; third, variables excluded in the previous steps but considered relevant based on biologic knowledge were re-introduced into the final model. Co-linearity among variables included in the final model was evaluated by assessing the changes in standard deviations of each beta when removing one variable at a time. Hosmer–Lemeshow test was applied to test the goodness-of-fit of the final model. The same model was used to assess the relation between spot sign and hematoma expansion in all subjects, and subsequently in the different subgroups based on time from symptom onset to initial CT. For some of the time bins the number of variables in the final model exceeded the number allowed by the rule of one covariate per ten events; therefore, we used propensity score analysis to ascertain the same association, obtaining similar results (Supplementary Table 2). Subsequently, we calculated sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy, by standard methods, to determine the accuracy of the spot sign in predicting hematoma expansion. All statistical analyses were performed by means of Statistical

Analysis Software version 9.3 (SAS Institute Inc. 2011, Cary, NC). A p value of <0.05 was considered statistically significant.

Results

Study Population

Between December 2000 and November 2010, a total of 1769 patients with acute primary ICH presented to our institution. After applying previously described inclusion and exclusion criteria, 551 had a baseline CT and CTA available. Out of these cases, 391 had a followup CT available and were therefore included in the final analysis (Table 1). Patient characteristics of patients without a CTA were not significantly different from those with an available CTA (all $p > 0.20$). Patients lacking a followup CT scan had lower GCS scores at presentation, greater ICH volumes, and higher mortality rates ($p < 0.05$) (Fig. 1).

CT Imaging

Radiographic characteristics are shown in Tables 1 and 2. Overall, hematoma expansion was detected in 71 patients (18 %) on followup CT and was most common in those patients presenting within 3 h of symptom onset (p <0.0001). Among patients with hematoma expansion, the mean increase in ICH volume was 18.5 mL and the mean proportional change was 210 % from baseline ICH volume (baseline ICH volume was considered to be 100 %). We identified at least one spot sign in 74 of 391 patients (19 %) and the frequency of the spot sign was highest in those patients presenting within 3 h ($p < 0.0001$).

Predictors of Hematoma Expansion

Entire Cohort—In order to determine which covariates were associated with hematoma expansion, we first performed a univariate analysis. In the cohort as a whole, hematoma expansion was associated with spot sign presence [odds ratio (OR) 5.91; 95 % confidence interval (95 % CI) 3.34–10.45; $p < 0.0001$]. In addition, hematoma expansion was associated with female sex, history of hypertension, warfarin use, and baseline ICH volume (Table 3).

In multivariate analysis, only spot sign presence [OR 4.66 (95 % CI 2.48–8.77); $p < 0.0001$] and baseline ICH volume [OR 1.01 (95 % CI 1.00–1.02); $p = 0.025$] remained significant (Table 4).

Stratified by Time from Symptom Onset—After stratifying by time from symptom onset, univariate analysis revealed an association between spot sign presence and hematoma expansion in patients who presented within 3 h [OR 3.92 (95 % CI 1.42–10.84); $p = 0.008$], from 3 to 6 h [OR 4.80 (95 % CI 1.15–20.01); $p = 0.031$], and after 6 h [OR 10.03 (95 % CI 2.79–36.05); $p = 0.0004$] from symptom onset. There was a trend toward significance in patients with an unknown symptom onset time [OR 3.00 (95 % CI 0.94–9.60); $p = 0.06$]. In addition, both warfarin use and baseline ICH volume were associated with hematoma expansion, but only in patients who presented within 3 h (Table 3).

In multivariate analysis, spot sign presence remained significantly associated with hematoma expansion in patients presenting: within 3 h [OR 4.00 (95 % CI 1.22–13.18); $p = 0.023$] and after 6 h [OR 8.81 (95 % CI 2.13–36.43); $p = 0.003$] from symptom onset. There was a trend toward significance [OR 3.19 (95 % CI 0.79–12.87); $p = 0.10$] for patients presenting with an unknown time of symptom onset. Baseline ICH volume remained significantly associated with hematoma expansion in patients who presented within 3 h of symptom onset (Table 4).

Because power may have been a limiting factor in the multivariate analysis, we additionally stratified the multivariate analysis by patients presenting within 3 h of symptom onset and those who presented after 3 h. In this analysis, spot sign presence was strongly associated with hematoma expansion in patients presenting after 3 h or with an unknown onset time [OR 4.56 (95 % CI 1.96–10.60); $p = 0.0004$] (Supplementary Table 1). Propensity score analysis showed tightening of the found confidence intervals and approximately the same point estimates as the multivariate analysis (Supplementary Table 2).

CTA Spot Sign Accuracy

For the cohort as a whole, sensitivity of the spot sign for predicting hematoma expansion was 0.46, specificity was 0.87, PPV was 0.45, NPV was 0.88, and overall accuracy was 0.80. Notably, accuracy did not vary across the subgroups stratified according to time from symptom onset to initial CT scan and exceeded 0.67 in all subgroups, including those patients in whom no onset-time could be established (Table 5).

Discussion

The results of our study demonstrate that, although early presentation after ICH occurrence is associated with high risk of hematoma expansion, a substantial number of patients destined to suffer from hematoma expansion present either late or with an unknown time of symptom onset. The CTA spot sign accurately predicted hematoma expansion, regardless of time from symptom onset.

Studies show that up to 40 % of acute ICH patients suffer significant hematoma expansion, and expansion is traditionally thought to occur predominantly in patients presenting early [4, 19, 21]. However, our results suggest that hematoma expansion also occurs in those patients presenting in a delayed fashion or in those who have an unknown time of when their hemorrhage occurred (26 % of patients at our institution). In fact, more than 60 % of patients with expansion presented beyond 3 h and almost half presented beyond 6 h (or with an unknown onset time); the cut-off used for PREDICT [14], the recently published prospective observational study including 268 ICH patients. While early presenters are certainly at higher individual risk, we found that only 18 % of patients (regardless of expansion status) presented within 3 h, and 41 % within 6 h. Thus, more than half of these patients, based solely on their presentation time would be excluded from ongoing therapeutic trials aimed at limiting expansion, including INTERACT2 [9], ATACH-II [10], STOP-IT (ClinicalTrials.gov #NCT00810888), and SPOTLIGHT (ClinicalTrials.gov #NCT01359202). This is especially valid for the high number of patients presenting with an unknown time of symptom onset, who are excluded from all past and current clinical trials.

While prior small studies have suggested that the accuracy of spot sign for prediction of subsequent hematoma growth declines as the time interval between symptom onset and initial CTA rises [11], our data point to a different result—one with important implications for the design of future clinical trials. We demonstrate that the spot sign is equally accurate in predicting hematoma expansion in patients with different times from symptom onset to baseline CT. While other prospective studies have agreed that the spot sign is a good but imperfect predictor of expansion [22], it is important to establish that its performance is equal across different time bins. Therefore, the spot sign may well be applicable to a broader population of ICH patients than currently thought, and can be validated further in current and upcoming clinical trials.

Many investigational therapies in ICH have failed to improve outcome in clinical trials. One of the challenges of such trials has been patient selection. For any given therapy, only a subset of patients is likely to receive a net benefit. For example, in the FAST trial,

recombinant factor VIIa (rFVIIa) reduced the risk of hematoma expansion, but failed to show clinical benefit [6, 7]. One likely explanation is that many subjects had stopped bleeding by the time of enrolment, and were exposed to thromboembolic risks without any potential benefit. The question remains whether selecting only those patients destined to expand would have led to improved patient outcomes [14, 23]. The currently recruiting phase II trials, STOP-IT and SPOTLIGHT, seek to address this question and are using the CTA spot sign to select patients for treatment with rFVIIa. If this strategy proves fruitful, our current results will raise the possibility of expanding the window of these trials beyond the current 6 h from symptom onset. This may prove to be an important development, as only 52 % of patients who suffered from hematoma expansion in our study, and only 59 % of patients with a spot sign on CTA, present within 6 h.

Our study is limited by its retrospective design and the non-standardized timing of followup CT scans. Patients with the largest hematomas, the lowest GCS scores, and with the highest mortality rates disproportionately did not have followup CT scans available due to early death, early surgical interventions, or limitation of care. In addition, as a single center study at a referral center, it may be that our population does not represent the general ICH population.

In conclusion, we demonstrate that while early presentation after ICH is associated with high risk of hematoma expansion, a substantial number of patients destined to expand present in a delayed fashion, or have an unknown time of symptom onset. The CTA spot sign accurately predicts hematoma expansion in those patients presenting late or with an unknown onset time. This observation may open a path to offer clinical trials and novel therapies to the many ICH patients that do not present acutely.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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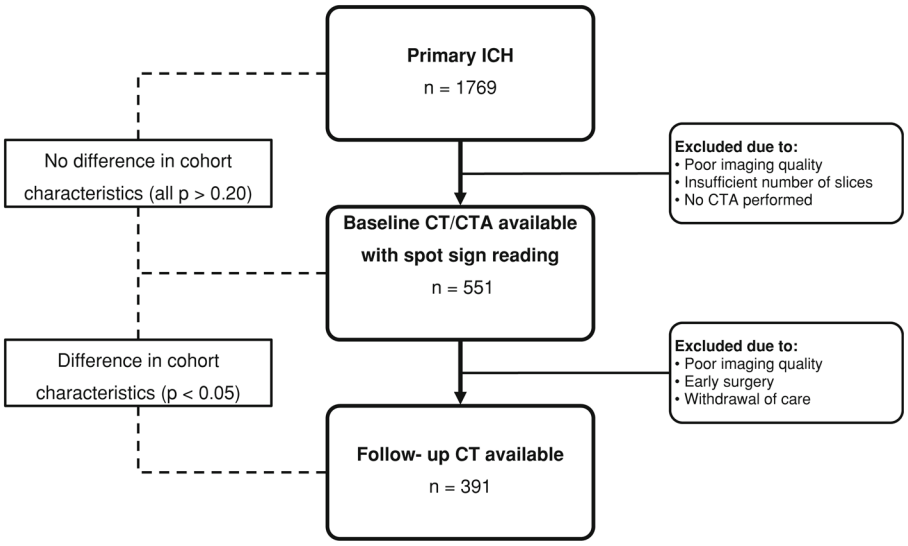

Fig. 1.
Cohort flowchart

Table 1

Cohort characteristics

Variable	All	Time from symptom onset to baseline CT/CT angiography			
	n (%)[a]	0–3 h *n* (%)[a]	3–6 h *n* (%)[a]	>6 h *n* (%)[a]	Unknown *n* (%)[a]
Number of subjects	391 (100.0)	70 (17.9)	92 (23.5)	129 (33.0)	100 (25.6)
Age (mean, SD)	71.9 (13.4)	69.4 (15.8)	73.4 (12.5)	71.3 (12.7)	72.9 (13.0)
Female sex	177 (45.3)	27 (38.6)	47 (51.1)	69 (53.5)	34 (34.0)
Location					
Lobar	192 (49.1)	22 (31.4)	37 (40.2)	74 (57.4)	59 (59.0)
Deep	174 (44.5)	47 (67.1)	48 (52.2)	47 (36.4)	32 (32.0)
Cerebellar	25 (6.4)	1 (1.4)	7 (7.6)	8 (6.2)	9 (9.0)
Hypertension	308 (79.2)	58 (82.9)	78 (84.8)	92 (71.9)	80 (80.8)
Atrial fibrillation	78 (20.3)	14 (20.3)	23 (25.3)	17 (13.3)	24 (24.7)
Statin use	124 (31.7)	18 (25.7)	31 (33.7)	38 (29.5)	37 (37.0)
Antiplatelet therapy	173 (44.6)	26 (38.2)	39 (42.4)	57 (44.2)	51 (51.5)
Warfarin use	68 (17.4)	12 (17.1)	16 (17.4)	18 (14.0)	22 (22.0)
GCS (median, IQR)	15 (10–15)	11 (6–15)	14 (8–15)	15 (14–15)	14 (10–15)
Systolic blood pressure in mm Hg (median, IQR)	174 (153–198)	180 (154–206)	179 (156–200)	174 (154–196)	166 (145–181)
Time from symptom onset to baseline imaging in hours (median, IQR)	6.0 (4.0–12.0)	2.0 (1.0–2.0)	5.0 (4.0–6.0)	14.0 (9.0–29.0)	n/a

n number of patients, *%* percentage, *SD* standard deviation, *GCS* Glasgow Coma Scale, *IQR* interquartile range, *n/a* not applicable

[a]Percentages refer to the percentages in patients with this data point available

Table 2

Radiographic and clinical outcomes

Variable	All	Time from symptom onset to baseline CT/CT angiography			
	n (%)[a]	0–3 h *n* (%)[a]	3–6 h *n* (%)[a]	>6 h *n* (%)[a]	Unknown *n* (%)[a]
Number of subjects	391 (100.0)	70 (17.9)	92 (23.5)	129 (33.0)	100 (25.6)
Baseline ICH volume (median, IQR)	17.0 (6.0–36.7)	22.9 (12.2–45.2)	11.2 (4.8–41.1)	12.8 (5.0–30.7)	22.2 (7.0–39.0)
Follow-up ICH volume (median, IQR)	17.0 (6.0–37.8)	26.6 (12.3–61.6)	12.1 (4.7–38.4)	11.7 (4.4–30.0)	22.0 (6.8–42.7)
Intraventricular extension	164 (41.9)	29 (41.4)	46 (50.0)	40 (31.0)	49 (49.0)
Baseline IVH volume (median, IQR)[b]	5.5 (2.0–18.0)	9.4 (2.1–24.3)	5.0 (1.6–15.0)	4.7 (2.4–14.8)	8.0 (2.0–22.0)
IVH expansion (> 2 mL)[b]	56 (34.1)	16 (55.2)	13 (28.3)	8 (20.0)	19 (38.8)
Interscan time in hours (median, IQR)	17.0 (10.0–24.0)	17.0 (8.0–23.0)	17.0 (9.0–24.0)	16.0 (11.0–23.0)	18.5 (12.0–25.0)
Spot sign presence	74 (18.9)	30 (42.9)	14 (15.2)	14 (10.9)	16 (16.0)
Hematoma expansion	71 (18.2)	27 (38.6)	10 (10.9)	14 (10.9)	20 (20.0)
Mean increase in volume (in mL)	18.5	23.8	8.6	13.1	20.2
Mean proportional change (in %)	209.5	155.4	173.8	149.7	342.1
In-hospital mortality	84 (22.1)	24 (34.3)	19 (21.1)	11 (8.9)	30 (31.3)
Independent at 90 days (mRS 0–2)	101 (34.2)	15 (25.4)	21 (31.3)	53 (51.0)	12 (18.5)

n number of patients, *%* percentage, *IQR* interquartile range, *IVH* intraventricular hemorrhage, *mRS* modified Rankin Scale

[a]Percentages refer to the percentages in patients with this data point available

[b]Data refer only to ICH cases with intraventricular extension

Table 3

Univariate determinants of hematoma expansion

Variable	All (*n* = 391)		Time from symptom onset to baseline CT/CT angiography							
			0–3 h (*n* = 70)		3–6 h (*n* = 92)		>6 h (*n* = 129)		Unknown (*n* = 100)	
	OR (95 % CI)	*p* value	OR (95 % CI)	*p* value	OR (95 % CI)	*p* value	OR (95 % CI)	*p* value	OR (95 % CI)	*p* value
Age	1.01 (0.99–1.03)	0.56	1.02 (0.99–1.06)	0.16	1.03 (0.97–1.09)	0.39	1.00 (0.96–1.05)	1.00	0.99 (0.96–1.03)	0.64
Female sex	**0.56 (0.33–0.96)**	**0.033**	0.90 (0.33–2.43)	0.83	0.21 (0.04–1.03)	0.05	0.62 (0.20–1.90)	0.40	0.80 (0.28–2.30)	0.67
Hypertension	**2.35 (1.08–5.12)**	**0.032**	2.12 (0.52–8.65)	0.30	0.69 (0.13–3.63)	0.66	5.76 (0.73–45.75)	0.10	2.47 (0.52–11.70)	0.26
Antiplatelet therapy	1.30 (0.78–2.19)	0.32	1.71 (0.63–4.67)	0.29	0.55 (0.13–2.27)	0.41	2.51 (0.79–7.97)	0.12	1.19 (0.45–3.19)	0.73
Warfarin use	**2.44 (1.34–4.43)**	**0.003**	**4.11 (1.10–15.36)**	**0.036**	3.89 (0.95–15.86)	0.06	2.89 (0.80–10.46)	0.11	1.24 (0.39–3.88)	0.72
SBP (mm Hg)	1.00 (0.99–1.00)	0.32	1.00 (0.99–1.02)	0.92	1.00 (0.98–1.02)	0.82	1.00 (0.98–1.02)	0.65	0.99 (0.97–1.00)	0.06
Baseline ICH volume (mL)	**1.01 (1.01–1.02)**	**0.0003**	**1.03 (1.01–1.05)**	**0.004**	1.01 (0.99–1.03)	0.46	1.02 (1.00–1.04)	0.06	1.00 (0.98–1.02)	0.77
Spot sign presence	**5.91 (3.34–10.45)**	**<0.0001**	**3.92 (1.42–10.84)**	**0.008**	**4.80 (1.15–20.01)**	**0.031**	**10.03 (2.79–36.05)**	**0.0004**	3.00 (0.94–9.60)	0.06
Interscan time (hours)[a]	0.99 (0.96–1.02)	0.48	1.00 (0.95–1.06)	0.97	0.99 (0.92–1.06)	0.73	0.99 (0.93–1.04)	0.61	0.99 (0.94–1.04)	0.75

n number of patients, *OR* odds ratio, *95 % CI* 95 % confidence interval, *SBP* systolic blood pressure, *ICH* intracerebral hemorrhage

[a]Time interval between baseline and followup CT in hours

Bold values indicate statistically significant results

Table 4

Multivariate analysis of hematoma expansion

Variable	All (*n* = 391)		Time from symptom onset to baseline CT/CT angiography							
			0–3 h (*n* = 70)		3–6 h (*n* = 92)		>6 h (*n* = 129)		Unknown (*n* = 100)	
	OR (95 % CI)	*p* value	OR (95 % CI)	*p* value	OR (95 % CI)	*p* value	OR (95 % CI)	*p* value	OR (95 % CI)	*p* value
Warfarin use	1.55 (0.78–3.09)	0.22	4.86 (0.95–24.91)	0.06	2.67 (0.54–13.17)	0.23	1.59(0.33–7.67)	0.57	0.44(0.10–2.00)	0.29
SBP (mm Hg)	1.00 (0.99–1.00)	0.23	1.00 (0.98–1.02)	0.87	1.00 (0.99–1.02)	0.89	1.00 (0.98–1.02)	0.84	0.98 (0.97–1.00)	0.05
Baseline ICH volume (mL)	**1.01 (1.00–1.02)**	**0.025**	**1.03 (1.01–1.05)**	**0.008**	1.00 (0.98–1.03)	0.98	1.01 (0.99–1.035)	0.38	0.99 (0.98–1.01)	0.51
Spot sign presence	**4.66 (2.48–8.77)**	**<0.0001**	**4.00 (1.22–13.18)**	**0.023**	3.19 (0.53–19.16)	0.20	**8.81 (2.13–36.43)**	**0.003**	3.19 (0.79–12.87)	0.10

n number of patients, *OR* odds ratio, *95 % CI* 95 % confidence interval, *SBP* systolic blood pressure, *ICH* intracerebral hemorrhage

Bold values indicate statistically significant results

Table 5

Spot sign accuracy for the prediction of hematoma expansion

Variable	All	Time from symptom onset to baseline CT/CT angiography			
	n **= 391**	**0–3 h *n* = 70**	**3–6 h *n* = 92**	**>6 h *n* = 129**	**Unknown *n* = 100**
Hematoma expansion (%)[a]	71 (18.2 %)	27 (38.6 %)	10 (10.9 %)	14 (10.9 %)	20 (20.0 %)
Sensitivity	0.46	0.63	0.40	0.43	0.30
Specificity	0.87	0.70	0.88	0.93	0.88
PPV	0.45	0.57	0.29	0.43	0.38
NPV	0.88	0.75	0.92	0.93	0.83
Accuracy	0.80	0.67	0.83	0.88	0.76

n number of patients, *%* percentage, *PPV* positive predictive value, *NPV* negative predictive value

[a] >33 % increase from baseline or an absolute increase of >6 mL