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Predicting Hematoma Expansion After Primary Intracerebral Hemorrhage

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Abstract

IMPORTANCE—Many clinical trials focus on restricting hematoma expansion following acute intracerebral hemorrhage (ICH), but selecting those patients at highest risk of hematoma expansion is challenging.

OBJECTIVE—To develop a prediction score for hematoma expansion in patients with primary ICH.

DESIGN, SETTING, AND PARTICIPANTS—Prospective cohort study at 2 urban academic medical centers among patients having primary ICH with available baseline and follow-up computed tomography for volumetric analysis (817 patients in the development cohort and 195 patients in the independent validation cohort).

MAIN OUTCOMES AND MEASURES—Hematoma expansion was assessed using semiautomated software and was defined as more than 6 mL or 33% growth. Covariates were tested for association with hematoma expansion using univariate and multivariable logistic regression. A 9-point prediction score was derived based on the regression estimates and was subsequently tested in the independent validation cohort.

RESULTS—Hematoma expansion occurred in 156 patients (19.1%). In multivariable analysis, predictors of expansion were as follows: warfarin sodium use, the computed tomography angiography spot sign, and shorter time to computed tomography (≤ 6 vs >6 hours) (P <.001 for all), as well as baseline ICH volume (<30 [reference], 30–60 [P =.03], and >60 [P =.005] mL). The incidence of hematoma expansion steadily increased with higher scores. In the independent validation cohort (n = 195), our prediction score performed well and showed strong association with hematoma expansion (odds ratio, 4.59; P <.001 for a high vs low score). The C statistics for the score were 0.72 for the development cohort and 0.77 for the independent validation cohort.

CONCLUSIONS AND RELEVANCE—A 9-point prediction score for hematoma expansion was developed and independently validated. The results open a path for individualized treatment and trial design in ICH aimed at patients at highest risk of hematoma expansion with maximum potential for therapeutic benefit.

Spontaneous intracerebral hemorrhage (ICH) is the most lethal form of stroke and accounts for approximately 15% of all strokes worldwide.[1–3] Mortality rates at 1 month exceed 40%, and 75% of all patients have died or are severely disabled at 1 year, highlighting the pressing need to improve current therapy.[1–3]

Although hematoma location and volume are strong predictors of outcome, neither factor is modifiable at the time of diagnosis.[4,5] However, significant hematoma expansion occurs in up to 30% of patients and not only worsens outcome but can also be prevented.[3,6–10]

Previous and ongoing clinical trials have focused on the attenuation of hematoma expansion using different medical therapies, including aggressive blood pressure reduction[10–13] and recombinant factor VIIa.[8,9] However, in a recently published phase 3 clinical trial[13] assessing aggressive blood pressure reduction, the primary end point was missed, and rates of substantial expansion were not significantly different between the 2 treatment groups. One compelling explanation is suboptimal patient selection because only a subset of patients

with ICH develops hematoma expansion sufficient to alter outcome.[14,15] To identify prospectively those patients at highest risk of ICH growth, we developed and independently validated a prediction score for hematoma expansion.

Methods

Study Design

Patients with primary ICH seen at a single academic hospital, Massachusetts General Hospital, were prospectively enrolled in an ongoing cohort study. The institutional review board approved all parts of the study. Patients, or their legal health care proxies, signed written informed consent before enrollment, or their consent was waived by protocol-specific allowance. The validation phase of the study was performed at a second academic medical center, Brigham and Women's Hospital, where the local institutional review board approved the matching protocol, and informed consent was obtained from all patients (or their surrogates) before inclusion.

Study Participants

Development Cohort—Consecutive patients seen at Massachusetts General Hospital with primary ICH were screened for eligibility for the ongoing prospective cohort study between September 1, 1994, and April 30, 2011. Patients were eligible for the present retrospective analysis if they were diagnosed as having primary ICH and had available baseline and follow-up computed tomography (CT) of sufficient quality for volumetric analysis. Patients undergoing hematoma evacuation before follow-up CT were excluded. Along with patients having primary intraventricular hemorrhage, patients with a known or suspected secondary cause of their ICH such as trauma, neoplasms, other vascular malformations, aneurysmal subarachnoid hemorrhage, and hemorrhagic transformation of an ischemic stroke were excluded from the study (eFigure in the Supplement).

Validation Cohort—Consecutive patients with primary ICH admitted to the neuroscience intensive care unit at Brigham and Women's Hospital were screened for eligibility between January 1, 2010, and June 30, 2012. The same inclusion and exclusion criteria as in the development cohort were applied for patient selection (eFigure in the Supplement).

All patients in the development cohort were treated according to a standard institutional protocol (available online at http://www2.massgeneral.org/stopstroke/), and none received recombinant factor VIIa. Patients participating in clinical trials assessing blood pressure lowering or treatment with recombinant factor VIIa were excluded from this analysis.

Clinical Data

Medical records were examined, and patients (or their family members) were interviewed to collect clinical data, including age, sex, medication use, and medical history. Admission measures collected were systolic blood pressure, Glasgow Coma Scale score, and time to initial CT and time between baseline and follow-up CT, as well as glucose level and white blood cell count. Trained study staff assessed 3-month mortality by performing telephone interviews with patients or their surrogates, supplemented by the National Death Index if no

contact could be established. The National Death Index is a weekly updated database containing information about individuals whose deaths were reported to the US Social Security Administration.[16]

Imaging Analysis

Neuroradiologists or neurologists (blinded to clinical and outcome data) ascertained hemorrhage locations. The ICH locations were categorized as deep, lobar, cerebellar, or brainstem. For the development and validation cohorts, the ICH volumes of the initial and follow-up CT were calculated by study staff (T.W.K.B. and A.V.) blinded to the data according to standard protocols using available software (Alice; PAREXEL International Corporation[17] and Analyze 10.0; Mayo Clinic[18]). Significant hematoma expansion was defined as a proportional increase of more than 33% or an absolute increase greater than 6 mL from the initial ICH volume.[19–21] Two experienced CT readers (H.B.B. and K.A.M.), blinded to clinical and outcome data, reviewed CT angiographies (CTA) from both institutions for spot sign presence according to previously published methods with high interrater reliability.[18,22]

Statistical Analysis

Continuous variables were summarized using means (SDs) or medians (interquartile ranges [IQRs]) when appropriate, and discrete variables were summarized using counts (percentages). Missing data were imputed per variable if less than 20% of data points were unavailable.[23] Variables with 20% or more missing data points were analyzed as categorical variables with an additional unavailable category.[24] Using univariate logistic regression analyses, clinical and neuroimaging predictors were tested for their potential association with hematoma expansion (dichotomized outcome). Predictors significant at $P < .05$ from the univariate analysis were subsequently tested for an independent association with the outcome in the multivariable logistic regression model. Baseline ICH volume was entered into the model as a categorical variable (<30, 30–60, or >60 mL according to previous studies[4,20,25]), time to initial CT was dichotomized at 6 hours (≤6 vs >6 hours[26]), and the CTA spot sign was entered as present, absent, or unavailable for those patients without a baseline CTA. The CTA spot sign score[18,22] was also tested as a continuous variable and did not improve the C statistic of the model. Consequently, we chose to use the CTA spot sign as a dichotomous variable because it is easier to use for frontline care providers. A prediction score was then created based on the multivariable regression estimates and was subsequently tested in an independent validation cohort from Brigham and Women's Hospital. The predictive ability of the score was assessed using C statistics for the development and independent validation cohorts. The derived prediction score was also tested for association with in hospital and 3-month mortality in the development cohort. Finally, because some clinical studies exclude patients taking anticoagulant medication, a separate score for patients with ICH receiving anticoagulants was created. The threshold for significance was set at $P < .05$. All statistical analyses were performed using available software (SAS version 9.3; SAS Institute Inc).

Results

Study Population

After application of the aforementioned eligibility criteria, 817 of 1890 patients with primary ICH were included in the development cohort (Table 1 and eFigure in the Supplement). At Brigham and Women's Hospital, 195 of 395 screened patients with primary ICH met the inclusion criteria and were enrolled in the independent validation cohort (eFigure and eTable 1 in the Supplement). Patients lacking follow-up CT were more likely to use warfarin sodium and had larger ICH volumes, higher mortality rates, and lower Glasgow Coma Scale scores on presentation (P <.05 for all) (eFigure in the Supplement).

Computed Tomography

Of 817 patients in the development cohort, the ICH was deep in 407 (50.2%), lobar in 342 (42.2%), cerebellar in 41 (5.1%), and brainstem in 21 (2.6%). A minimum of 1 CTA spot sign was present in 19.6%, the median ICH volume at baseline was 16 mL (IQR, 7–37 mL), and the median time from symptom onset to CT was 5.0 hours (IQR, 2.6–8.3 hours). Follow-up CT was performed at a median of 18 hours (IQR, 11–25 hours) after initial CT, and hematoma expansion occurred in 156 patients (19.1%). Other imaging variables, as well as the stratified characteristics, are given in Table 1.

Predictors of Hematoma Expansion

In univariate analysis, warfarin use, CTA spot sign, larger baseline ICH volume, and shorter time to initial CT (≤6 hours) were associated with hematoma expansion (P <.05 for all) (eTable 2 in the Supplement) and remained significant in multivariable analysis (Table 2). The C statistic for model performance was 0.72 for the development cohort, whereas the highest C statistic of the individual components was only 0.63 for the CTA spot sign.

Prediction Score for Hematoma Expansion

A prediction score weighted based on the regression variables (odds ratios [ORs]) of the multivariable logistic regression model was developed. Combined in the 9-point score were warfarin use (no [0 points] or yes [2 points]), shorter time to CT (>6 [0 points] or ≤6 [2 points] hours), CTA spot sign (absent [0 points], present [3 points], or unavailable [1 point]), and baseline ICH volume (<30 [0 points], 30–60 [1 point], or >60 [2 points] mL) (Table 3).

The incidence of hematoma expansion increased steadily with higher scores, reaching 80.0% for patients with the highest score of 9. Only 5.7% of patients had hematoma expansion in the lowest tier. The prediction score also performed well when in-hospital and 3-month mortality were assessed (Table 4). To maximize clinical usefulness of the score, strata combining individual values were created in the following categories: low (score of 0 and incidence rate of 5.7%), medium (score of 1–3 and incidence rate of 12.4%), and high (score of 4–9 and incidence rate of 36.4%).

Exclusion of Warfarin-Related ICH

Because some clinical trials exclude patients taking anticoagulant medication, an analysis was performed excluding warfarin-related ICH (n = 644). A new prediction score was

created, resulting in an 8-point score: CTA spot sign (OR, 3.68; 95% CI, 1.79–7.59; *P* <. 001) (3 points), shorter time to CT (OR, 3.05; 95% CI, 1.53–6.09; *P* =.002) (3 points), and baseline ICH volume (<30 [reference]; 30–60 [OR, 1.81; 95% CI, 1.06–3.09; *P* = .03]; and >60 [OR, 2.35; 95% CI, 1.30–4.26; *P* =.005] mL) (2 points).

Higher scores were associated with greater expansion risk, with an OR of3.22 (95% CI, 2.07–4.99) (*P* <.001) for a high (4–8) vs low (0–3) score. The C statistic was 0.68 (eTable 3 in the Supplement).

External Validation

Independent validation was performed in a consecutive cohort of 195 patients with ICH (eTable 1 in the Supplement). The overall frequency of expansion was 15.9%. Only 5.9% of patients with a score of 0 had hematoma expansion, whereas 32.0% with a score of 4 to 9 had hematoma expansion (Table 5). A high score (4–9 vs 0–3) was strongly associated with increased risk of expansion, with an OR of 4.59 (95% CI, 2.06–10.22) (*P* <.001). The C statistic reached 0.77.

Discussion

A clinical prediction score was developed and externally validated to identify patients with ICH most likely to develop hematoma expansion. The derived 9-point prediction score is easy to use and incorporates information available on initial presentation using clinically relevant categorical measures. Assembled from individual characteristics shown to predict ICH expansion in the present study, as well as prior studies,[17,19–21,27–30] the score is a substantial advance, offering improved accuracy for prediction compared with any of its individual variables. In addition, it is applicable to patients with ICH regardless of time to presentation, rather than the subset seen within the first hours of symptom onset.

From a pathophysiological standpoint, early presentation, anticoagulation use, larger ICH volume, and the presence of a CTA spot sign all add to the theoretical expansion model described by Fisher,[31] in which the initial hematoma displaces and ruptures surrounding vessels, leading to additional bleeding. Early presentation may simply mark those patients early in the course of their disease, offering an opportunity to treat them when bleeding is ongoing. Larger hematomas may lead to additional vessel shearing, adding to the avalanche effect of hematoma expansion.[20,31] Altered coagulation status may increase the risk that surrounding vessels will bleed after injury or will bleed for longer periods.[32] The CTA spot sign, the strongest predictor of subsequent expansion in this study, is an epiphenomenon studied extensively during the past decade and may mark ruptured vessels or the severity of vessel damage.[33]

A validated prediction score for hematoma expansion is a crucial next step toward individualizing treatment and trial design in acute ICH. In the Second Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT2),[13] the largest clinical trial to date aimed at the restriction of hematoma expansion, intensive blood pressure lowering showed a borderline significant effect on reducing the rate of the primary outcome (death and severe disability). A viable explanation for these results is the

indiscriminate enrollment of unselected patients with ICH, resulting in a low rate of significant hematoma expansion, although only patients seen early after their symptom onset were included.[13–15] The INTERACT2 and other large clinical trials[8,9,11,13] enrolled patients solely based on early presentation as a surrogate for hematoma expansion. However, this not only resulted in the inclusion of many patients who did not develop significant expansion but also led to the automatic exclusion of most patients with ICH whose presentation to the emergency department occurred beyond 3 or 6 hours or those whose onset time could not be established. Consequently, up to half of all patients with ICH destined to experience expansion were excluded.[26,34]

As demonstrated in the present study, early presentation is only one of several viable predictors of subsequent expansion. For the targeting of expanders, the 9-point prediction score not only offers improved accuracy over a simple time cutoff but also can be applied to virtually all patients with ICH who are seen in the emergency department, expanding the pool of patients with ICH for clinical trial of anti-expansion therapies. For example, a patient using warfarin (2 points) who is seen at 8 hours from symptom onset (0 points) with a 63-mL ICH (2 points) and a positive CTA spot sign (3 points) (a total of 7 points) has a 55.6% expansion risk (Table 5). This patient would be excluded from ongoing current phase 2 or 3 clinical trials based on presentation time only. The implementation of the 9-point prediction score would extend the enrollment windows of those trials and potentially provide therapeutic benefit to more patients.

In addition to broadening the time window for clinical trial selection, the prediction score identifies patients at highest risk of expansion with improved accuracy. This enrichment of the patient pool may be of pivotal importance to more efficiently design trials and prove efficacy of certain therapies. The proposed score enables the selection of patients with ICH at a 4.5-fold increase in the odds of expansion, tripling the risk of expansion from 9.4% in patients with a low prediction score (range, 0–3) to 32.0% in patients with a high prediction score (range, 4–9). Consequently, the prediction score enriches the patient population in terms of the a priori expansion risk by using readily available clinical factors, without restricting inclusion only to the first hours after symptom onset.

Besides risk stratification and enhanced selection for clinical trials, the prediction score holds clinical potential to stratify which patients need the most intensive care and the most frequent monitoring. Given the results of 2 recent large clinical trials,[13,35] the score may also have a role in selecting patients for blood pressure management or surgical evacuation. In addition, it may help with the daily triaging of patients for floor versus intensive care unit admission because the score not only is a selection tool for those patients most likely to undergo expansion but also allows physicians to predict which patients are unlikely to undergo expansion and treat them accordingly. Because this applies to a substantial group of patients, it may have considerable effect on acute patient flow.

Because not all clinical trials include warfarin-related ICH, a secondary analysis was performed that excluded patients taking warfarin. The subsequently developed prediction score based on 644 patients showed similar weights for 2 of 3 remaining variables (baseline ICH volume and CTA spot sign). The observed 1-point increase for shorter time to CT

reflects the increased risk of expansion among patients seen early after their symptom onset. The prediction score that excluded warfarin use remained strongly predictive of hematoma expansion (OR, 3.22; 95% CI, 2.07–4.99) compared with a 4.5-fold increase in the odds of expansion when warfarin use was included in the score (OR, 4.59; 95% CI, 2.06–10.22) (*P* <.001 for both). As expected, the C statistic was lower for the model that excluded warfarin use (0.68 vs 0.77), a known strong predictor of expansion.[20,27]

The robustness of these results is driven by the large sample size, the prospectively collected data, and the independent validation of the prediction score in a large cohort of patients with primary ICH. Nonetheless, a crucial limitation is the lack of follow-up CT for a subset of patients with ICH, leading to their exclusion from the study. This is a recurring shortcoming of observational studies, in which CT acquisition and timing are driven by clinical care decision making. Because of early death or withdrawal of care, follow-up CT was disproportionately missing for patients using warfarin and for patients having the largest baseline ICH volumes. One could speculate that those adverse effects are partially mediated by hematoma expansion. This would signify a reduced predictive ability of the present model, underestimating its true predictive ability. In addition, the study was performed at 2 teaching hospitals in a metropolitan area, potentially introducing some degree of selection bias.

In conclusion, we developed and independently validated a clinical prediction score for hematoma expansion. The score accurately predicts hematoma expansion and clinical outcome, opening a path for individualized treatment and clinical trial design aimed at patients with ICH at highest risk of hematoma expansion.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of the Development Cohort

Variable	Total (N =817)	No Expansion (n =661)	Expansion (n =156)
Age, mean (SD), y	72 (13)	71 (13)	73 (11)
Female sex, No. (%)	**361** (44.2)	303 (45.8)	58 (37.2)
Hypertension, No. (%)	**645** (78.9)	515 (77.9)	130 (83.3)
Antiplatelet use, No. (%)	**354** (43.3)	286 (43.3)	68 (43.6)
Warfarin sodium use, No. (%)	**173** (21.2)	117 (17.7)	56 (35.9)
Glasgow Coma Scale score, median (IQR)	14 (9–15)	14 (10–15)	14 (9–15)
Systolic blood pressure, median (IQR), mm Hg	179 (154–200)	179 (154–203)	176 (151–196)
White blood cell count, median (IQR), μL	9000 (7000–12 000)	9000 (7000–12 000)	8000 (6000–10 000)
Glucose level, median (IQR), mg/dL	134 (112–167)	134 (111–165)	134 (114–171)
Cerebral amyloid angiopathy, No. (%)	**119** (14.6)	99 (15.0)	20 (12.8)
Apolipoprotein ε2, minor allele frequency	0.09	0.09	0.10
Time to initial CT, h			
Median (IQR)	5.0 (2.6–8.3)	5.5 (3.3–9.2)	2.6 (1.3–5.4)
No. (%)	(n = 573)	(n = 460)	(n = 113)
≤6	**357** (62.3)	268 (58.2)	89 (78.8)
>6	**216** (37.7)	192 (41.7)	24 (21.2)
ICH location, No. (%)	(n = 811)	(n = 657)	(n = 154)
Deep	**407** (50.2)	329 (50.1)	78 (50.6)
Lobar	**342** (42.2)	273 (41.6)	69 (44.8)
Cerebellar	**41** (5.1)	39 (5.9)	2(1.3)
Brainstem	**21** (2.6)	16 (2.4)	5(3.2)
Baseline ICH volume, mL			
Median (IQR)	16 (7–37)	15 (6–33)	25 (9–52)
No. (%)			
<30	**565** (69.2)	476 (72.0)	89 (57.1)
30–60	**156** (19.1)	119 (18.0)	37 (23.7)
>60	**96** (11.8)	66 (10.0)	30 (19.2)
Follow-up ICH volume, median (IQR), mL	17 (7–37)	14 (6–30)	42 (16–78)
Intraventricular extension, No. (%)	**311** (38.1)	246 (37.2)	65 (41.7)
Intraventricular hemorrhage, median (IQR), mL[a]			
Baseline	9(3–22)	9(3–20)	10 (4–29)
Follow-up	9(3–22)	9(2–20)	13 (4–32)
CT angiography spot sign, No. (%)	**74** (19.6)	41 (13.2)	33 (48.5)
In-hospital mortality, No. (%)	**193** (23.6)	123 (18.6)	70 (44.9)
3-mo mortality, No. (%)	**244** (29.9)	159 (24.1)	85 (54.5)

Abbreviations: CT, computed tomography; ICH, intracerebral hemorrhage; IQR, interquartile range.

SI conversion factors: To convert white blood cell count to $\times 10^9$/L, multiply by 0.001; to convert glucose level to millimoles per liter, multiply by 0.0555.

[a] Data refer to patients having ICH with intraventricular extension only (n = 311)

Table 2

Multivariable Analysis of the Prediction Score for Hematoma Expansion

Variable	Adjusted Odds Ratio (95% CI)	*P* Value
Warfarin sodium use	2.61 (1.73–3.95)	<.001
Time to initial CT, ≤6 vs >6 h	2.55 (1.53–4.27)	<.001
Baseline ICH volume, mL		
<30	1 [Reference]	1 [Reference]
30–60	1.64 (1.04–2.59)	.03
>60	2.10 (1.25–3.55)	.005
CT angiography spot sign	3.81 (2.08–6.98)	<.001

Abbreviations: CT, computed tomography; ICH, intracerebral hemorrhage.

Table 3

Individual Components of the Prediction Score for Hematoma Expansion

Variable	Points
Warfarin sodium use	
No	0
Yes	2
Time to initial CT, h	
≤6	2
>6	0
Baseline ICH volume, mL	
<30	0
30–60	1
>60	2
CT angiography spot sign	
Absent	0
Present	3
Unavailable	1
Total	0–9

Abbreviations: CT, computed tomography; ICH, intracerebral hemorrhage.

Table 4

Performance of the Prediction Score for Hematoma Expansion and Mortality

	No. (%)			
Score	**Total (N =817)**	**Expansion (n =156)**	**In-Hospital Mortality (n =193)**	**3-Month Mortality (n =244)**
Individual points				
0	70 (8.6)	4(5.7)	2 (2.9)	4(5.7)
1	108 (13.2)	12 (11.1)	14 (13.0)	22 (20.4)
2	196 (24.0)	15(7.7)	29 (14.8)	31 (15.8)
3	196 (24.0)	35 (17.9)	46 (23.5)	63 (32.1)
4	108 (13.2)	32 (29.6)	36 (33.3)	48 (44.4)
5	82 (10.0)	29 (35.4)	28 (34.1)	35 (42.7)
6	28 (3.4)	15 (53.6)	21 (75.0)	22 (78.6)
7	22 (2.7)	10 (45.5)	10 (45.5)	12 (54.5)
8	2(0.2)	0	2 (100.0)	2 (100.0)
9	5 (0.6)	4 (80.0)	5 (100.0)	5 (100.0)
Categorized score				
0	70 (8.6)	4(5.7)	2 (2.9)	4(5.7)
1–3	500 (61.2)	62 (12.4)	89 (17.8)	116 (23.2)
4–9	247 (30.2)	90 (36.4)	102 (41.3)	124 (50.2)

Table 5

Independent Validation of the Prediction Score for Hematoma Expansion

	No. (%)	
Score	**Total (n =195)**	**Expansion (n =31)**
Individual points		
0	17 (8.7)	1 (5.9)
1	38 (19.5)	2 (5.3)
2	44 (22.6)	1 (2.3)
3	40 (20.5)	9 (22.5)
4	24 (12.3)	2 (8.3)
5	16 (8.2)	10 (62.5)
6	6 (3.1)	0
7	9 (4.6)	5 (55.6)
8	1(0.5)	1 (100.0)
9	0	Not applicable
Categorized score		
0	17 (8.7)	1 (5.9)
1–3	122 (62.6)	12 (9.8)
4–9	56 (28.7)	18 (32.0)