Clinical Prediction Algorithm (BRAIN) to Determine Risk of Hematoma Growth in Acute Intracerebral Hemorrhage

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Background and Purpose—We developed and validated a simple algorithm to predict the risk of hematoma growth in acute spontaneous intracerebral hemorrhage (ICH) to better inform clinicians and researchers in their efforts to improve outcomes for patients.

Methods—We analyzed data from the computed tomography substudies of the pilot and main phases of the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trials (INTERACT1 and 2, respectively). The study group was divided into a derivation cohort (INTERACT2, n=964) and a validation cohort (INTERACT1, n=346). Multivariable logistic regression was used to identify factors associated with clinically significant (≥6 mL) increase in hematoma volume at 24 hours after symptom onset. A parsimonious risk score was developed on the basis of regression coefficients derived from the logistic model.

Results—A 24-point BRAIN score was derived from INTERACT2 (C-statistic, 0.73) based on baseline ICH volume (mL per score, ≤10=0, 10–20=5, >20=7), recurrent ICH (yes=4), anticoagulation with warfarin at symptom onset (yes=6), intraventricular extension (yes=2), and number of hours to baseline computed tomography from symptom onset (≤1=5, 1–2=4, 2–3=3, 3–4=2, 4–5=1, >5=0) predicted the probability of ICH growth (ranging from 3.4% for 0 point to 85.8% for 24 points) with good discrimination (C-statistic, 0.73) and calibration (Hosmer–Lemeshow P=0.82) in INTERACT1.

Conclusions—The simple BRAIN score predicts the probability of hematoma growth in ICH. This could be used to improve risk stratification for research and clinical practice.

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Key Words: clinical trial ■ intracerebral hemorrhage

Clinically significant growth of spontaneous intracerebral hemorrhage (ICH) occurs in about one third of patients who are scanned within 3 hours of symptom onset, but the proportion decreases with time thereafter.[1,2] ICH growth is an important independent predictor of clinical deterioration and outcome.[3–6] Because of its influence on outcome, an ability to accurately predict ICH growth could influence decision-making in clinical management, for example in stratifying patients for surgery and in the design of randomized trials of medical interventions aimed at improving outcomes.

Several associations with the occurrence of ICH growth have been replicated, including larger ICH volume,[2,7] earlier presentation after symptom onset,[1,2] use of oral anticoagulant drugs,[8,9] and the presence of a spot sign on computed tomographic angiography (CTA).[10] Many other individual associations have been described, but the small sample size of many of these studies has often limited the ability to perform multivariable analyses adjusted for known confounders and associations with ICH growth. One recent study with sufficient power was able to develop and validate a prediction model (which included warfarin anticoagulation use, presence of the CTA spot sign, shorter time to computed tomography [CT], and baseline ICH volume),[11] but the retrospective analysis and use of CTA and repeat brain imaging only whenever concern

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for ongoing hemorrhage or hematoma expansion [was] raised or in the setting of clinical deterioration (http://www2.massgeneral.org/stopstroke/protocolAdultHemorrhage.aspx) may limit the generalizability of the findings.

We sought to develop and independently validate a score for the prediction of clinically significant ICH growth, with simple clinical and imaging variables acquired in substudies of the INTERACT (Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial 1 and 2) studies, in which repeat CT was performed without regard to clinical deterioration or suspicion of ICH growth at 24 hours.

Methods

Participants

The design of the INTERACT studies have been described in detail elsewhere.[12–14] In brief, these were international, multicenter, open, assessor-blind, randomized controlled studies in which adult patients with mainly mild–moderate severity, acute spontaneous ICH, and elevated systolic blood pressure (BP; ≥150 to ≤220 mm Hg) were randomly assigned to intensive (target systolic BP <140 mm Hg) or guideline-recommended BP management (systolic BP <180 mm Hg) within 6 hours of ICH symptom onset. INTERACT1 included 404 participants from 44 hospitals in Australia, China, and Korea during 2006 to 2007 and INTERACT2 included 2839 participants from 144 hospitals in 21 countries during 2008 to 2012. The studies were approved by the ethics committees for each hospital and informed consent was obtained from all patients or their relevant surrogates.

Procedures

Demographic and clinical characteristics were recorded at the time of enrollment. Stroke severity was measured using the Glasgow Coma Scale and National Institutes of Health Stroke Scale at baseline, 24 hours, and at day 7 (or earlier on discharge from hospital). In predefined CT substudies, there were 346 and 964 patients of INTERACT1 and 2, respectively, who also underwent brain CT at 24 hours after randomization. For each CT scan, uncompressed digital CT images were collected in DICOM format identified only with the patient's unique study number. ICH volumes were calculated centrally, and blind to clinical data, treatment, and date and sequence of scan, using computer-assisted multisliceplanimetric and voxel threshold techniques in MIStar version 3.2 (Apollo Medical Imaging Technology). For the small number of CT scans received as digital images or plain films, ICH volume was measured manually using the ABC/2 method.[5] In INTERACT1, 2 trained neurologists performed the measurements and their inter-reader reliability was tested by reanalysis of ICH volume on 10% of CT scans (intraclass correlation coefficient 0.97 [95% confidence interval, 0.95–0.98]). INTERACT2 included several trained imaging scientists and inter-reader reliability was checked by periodic reanalysis of 15% of the scans reviewed by each scientist against a gold standard single neurologist to avoid drift (intraclass correlation coefficient, 0.92 for total hematoma volume and 0.96 after removing outlier data with total volumes >50 mL).

Clinically significant ICH growth was defined as an absolute growth of ≥6mL from baseline to 24 hours, as defined elsewhere as indicating both a clinically significant and average degree of growth in a broad range of ICH patients.[3,6,15] Other definitions used were relative growth of >33%, and relative growth >33% or absolute growth of ≥6 mL.

Statistical Analysis

Logistic regression was used to investigate associations with ICH growth in the INTERACT2 CT substudy development cohort. Significant predictors from the univariate analysis and nonsignificant variables chosen for their potential clinical relevance were tested for their association with ICH growth in a multivariable model. We reduced the full model by successively removing the nonsignificant covariates until all the remaining predictors remained statistically significant ($P<0.05$). Collinearity and interaction between variables were checked. We used regression coefficients from the model to generate point scores for predicting the probability of ICH growth.[15,16] We tested the model in the INTERACT1 CT substudy validation cohort. Performance of the final prediction model was assessed using the area under the receiver-operating characteristic curve and concordance C-statistic for discriminative ability, and the Hosmer–Lemeshow goodness-of-fit statistic for calibration using fifths of the fitted risk values.[17] $P<0.05$ was considered statistically significant in all tests. All analyses were performed using SAS version 9.3 (SAS institute, Cary, NC).

Results

All 964 patients in the INTERACT2 substudy, of whom 181 (18.8%) developed clinically significant ICH growth according to our definition of ≥6mL, were included in the development data set (Table 1). All 346 patients in the INTERACT1 CT substudy (43 [12.4%] developed significant ICH growth) were included in the validation data set (Table 2).

Table 1 shows the univariate analysis, where larger baseline ICH volume, recurrent ICH, anticoagulation with warfarin at onset, the presence of intraventricular hemorrhage, fewer hours from symptom onset to baseline CT, and non-Chinese race were significantly associated with ICH growth. These variables were included as covariates in a multivariable logistic regression model, into which other potentially clinically relevant variables were also forced (age, sex, diabetes mellitus, deep location of ICH, and randomization to intensive BP-lowering treatment). After successively removing nonsignificant covariates from the multivariable model, only baseline ICH volume (B), recurrent ICH (R), anticoagulation with warfarin at onset (A), intraventricular hemorrhage (I), and number of hours to baseline CT from onset (N) remained in the final multivariable model (Table 2); no collinearity and interaction were found.

An equation was derived from the multivariable model (Figure I in the online-only Data Supplement) to estimate the probabilities of developing ICH growth by 24 hours after onset. Regression coefficients from the final model (Table I in the online-only Data Supplement) were used to develop the BRAIN prediction algorithm scoring system (Figure 1). The median estimated probability of ICH growth was 16.4% (interquartile range, 7.7%–27.2%), with a range from 3.4% (minimum score of 0) to 85.8% (maximum score of 24). The model had good discriminative ability (C-statistic, 0.73; Figure II in the online-only Data Supplement).

The model demonstrated good discrimination (C-statistic, 0.73; Figure II in the online-only Data Supplement) and calibration (Hosmer–Lemeshow χ^2 statistic 4.35; $P=0.82$) in the independent INTERACT1 data set, where the median probability of ICH growth was estimated to be 9.3% (interquartile range, 5.1%–16.6%). Predicted and observed probabilities of ICH growth in the validation data set corresponded well to over one fifth of predicted probability (Figure 2).

When significant growth was defined as relative growth >33%, only 2 significant variables were identified in univariate analysis—baseline ICH volume and number of hours from onset to baseline CT—which did not allow development of a model. Similarly, using a definition of ≥6 mL or >33% produced on 2 significant variables—anticoagulation with warfarin at onset and number of hours to baseline CT from onset—which was not comprehensive enough to compose a predictive model.

Table 1. Baseline Characteristics and Associations With ICH Growth in the Development Data Set

Characteristics		Hematoma Expansion		Odds Ratio (95% Confidence Interval)	*P* Value
		No (n=783)	Yes (n=181)		
Demographic					
Age, y		67 (57–77)	67 (56–76)	1.00 (0.99–1.01)*	0.775
Sex	Female	300 (38.3)	58 (32.0)	Reference	
	Male	483 (61.7)	123 (68.0)	1.32 (0.93–1.86)	0.116
Chinese	No	459 (58.6)	122 (67.4)	Reference	
	Yes	324 (41.4)	59 (32.6)	0.69 (0.49–0.96)	0.030
Medical history†					
Prior ICH	No	743 (94.9)	162 (89.5)	Reference	
	Yes	39 (5.0)	19 (10.5)	2.23 (1.26–3.97)	0.006
Prior ischemic/undifferentiated stroke	No	700 (89.5)	165 (91.2)	Reference	
	Yes	82 (10.5)	16 (8.8)	0.83 (0.47–1.45)	0.509
Ischemic heart disease	No	753 (96.2)	174 (96.1)	Reference	
	Yes	29 (3.7)	7 (3.9)	1.05 (0.45–2.43)	0.918
Diabetes mellitus	No	680 (86.8)	153 (84.5)	Reference	
	Yes	102 (13.0)	28 (15.5)	1.22 (0.78–1.92)	0.390
Pre-ICH hypertension	No	224 (28.6)	52 (28.7)	Reference	
	Yes	558 (71.4)	129 (71.3)	1.00 (0.70–1.42)	0.982
Medication history					
Antihypertensive therapy	No	383 (49.0)	83 (45.9)	Reference	
	Yes	399 (51.0)	98 (54.1)	1.13 (0.82–1.57)	0.449
Warfarin anticoagulation	No	752 (96.2)	160 (88.4)	Reference	
	Yes	30 (3.8)	21 (11.6)	3.29 (1.84–5.90)	<0.0001
Antiplatelet therapy	No	653 (83.5)	148 (81.8)	Reference	
	Yes	129 (16.5)	33 (18.2)	1.13 (0.74–1.72)	0.574
Clinical features					
Time from symptom onset to CT, h		1.8 (1.3–2.7)	1.7 (1.2–2.4)	0.78 (0.66–0.92)	0.003
Systolic BP, mm Hg		179.4±16.8	180.3±17.4	1.00 (0.99–1.01)	0.498
Diastolic BP, mm Hg		98.5±15.5	99.5±15.7	1.00 (0.99–1.02)	0.432
CT findings					
Deep location of ICH‡	No	131 (16.7)	28 (15.5)	Reference	
	Yes	652 (83.3)	153 (84.5)	1.10 (0.70–1.71)	0.681
Baseline ICH volume, mL		9.3 (4.8–16.6)	17.9 (11.3–29.4)		
	≤10	415 (53.0)	40 (22.1)	Reference	
	10–20	219 (28.0)	61 (33.7)	2.89 (1.88–4.45)	<0.0001
	>20	149 (19.0)	80 (44.2)	5.57 (3.65–8.50)	<0.0001
Intraventricular extension	No	535 (68.3)	93 (51.4)	Reference	
	Yes	248 (31.7)	88 (48.6)	2.04 (1.47–2.83)	<0.0001
Randomized to intensive BP lowering	No	378 (48.3)	95 (52.5)	Reference	
	Yes	405 (51.7)	86 (47.5)	0.85 (0.61–1.17)	0.308

BP indicates blood pressure; CT, computed tomography; and ICH, intracerebral hemorrhage.
*Per year.
†One case was missing these variables.
‡Basal ganglia or thalamus.

Discussion

We developed a simple BRAIN prediction model for estimating the probability of ICH growth using characteristics within the INTERACT2 study that can be routinely assessed in clinical practice. The model demonstrated good discriminative ability and was well calibrated when independently validated in the INTERACT1 data set.

The components of the BRAIN prediction model are pathophysiologically plausible. In particular, a larger baseline ICH may reflect multiple bleeding points from arteries or arterioles

Table 2. Multivariable Analysis of ICH Growth in the Development Data Set

	Cases in Analysis, n	Cases With Expansion, n (%)	Adjusted* Odds Ratio (95% Confidence Interval)	*P* Value
Baseline ICH volume				
≤10	455	40 (8.8)	Reference	
10–20	280	61 (21.8)	2.72 (1.75–4.22)	<0.0001
>20	229	80 (34.9)	4.96 (3.21–7.67)	<0.0001
Recurrent ICH†				
No	905	162 (17.9)	Reference	
Yes	58	19 (32.8)	2.16 (1.16–4.03)	0.015
Anticoagulation with Warfarin at onset†				
No	912	160 (17.5)	Reference	
Yes	51	21 (41.2)	2.79 (1.47–5.30)	0.002
Intraventricular extension				
No	628	93 (14.8)	Reference	
Yes	336	88 (26.2)	1.54 (1.08–2.19)	0.017
Number of hours to baseline CT from symptom onset (per hour)	964		0.81 (0.68–0.96)	0.015

CT indicates computed tomography; and ICH, intracerebral hemorrhage.

*The odds ratio is adjusted for age, sex, Chinese, diabetes mellitus, deep location of ICH, intensive BP-lowering treatment.

†One case was missing this variable.

or under high systemic arterial pressure with further induction of perilesional hemorrhage.[18] Because ICH is a dynamic illness, the earlier a patient is first scanned, the greater the probability of later demonstrating ICH growth. It is also recognized that patients who have been taking warfarin anticoagulation at the time of ICH experience more prolonged bleeding,[8,19] which may persist beyond 24 hours,[8] and result in larger ICH volumes at both presentation and on future assessment.[8,20] In regard to intraventricular hemorrhage, this not only indicates more active hemorrhage but potentially also of more activate inflammatory cytokines and altered systemic homeostatic/fibrinolytic

BRAIN score for prediction of ICH growth at 24 hours	
BRAIN score component	**Poin**
Baseline ICH volume	
≤10ml	0
10-20ml	5
>20ml	7
Recurrent ICH	
No	0
Yes	4
Anticoagulation with Warfarin at onset	
No	0
Yes	6
Intraventricular extension	
No	0
Yes	2
Number of hours to baseline CT from symptom onset	
≤1	5
1-2	4
2-3	3
3-4	2
4-5	1
>5	0

Point total	Probability of ICH growth (%)
0	3.4
1	4.2
2	5.1
3	6.3
4	7.7
5	9.4
6	11.3
7	13.7
8	16.4
9	19.5
10	23.1
11	27.2
12	31.6
13	36.4
14	41.5
15	46.7
16	52.1
17	57.4
18	62.5
19	67.4
20	71.9
21	76.0
22	79.7
23	83.0
24	85.8

Figure 1. BRAIN prediction score and predicted probabilities of intracerebral hemorrhage (ICH) growth in the development model.

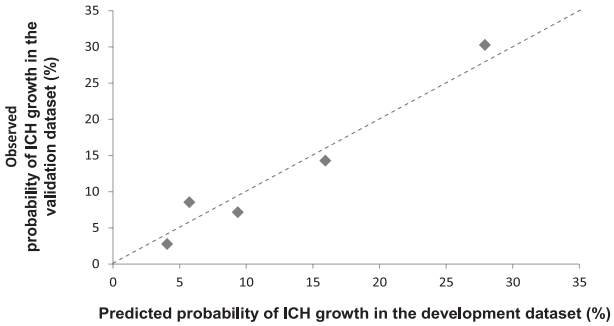

Figure 2. Predicted vs observed probabilities of intracerebral hemorrhage (ICH) growth in the validation model according to fifths of predicted probability in the development model.

pathways, which may in turn lead to a coagulopathic state that further increases the risk of ICH growth.[21] Finally, patients with recurrent ICH are likely to have more severe underlying chronic small vessel cerebrovascular disease,[22] predisposing them to larger and more rapid growth in ICH.[23]

The strongest factors for ICH growth are the presence of warfarin anticoagulation (6 points), large baseline ICH (>20 mL, 7 points) and a short time from onset to first CT (<3 hours, ≈4 points), which alone will have an expected hematoma growth of ≈10%; when combined, however, this outcome occurs in over 50%. Using all variables in this risk model, a patient presenting within 3 hours of onset of a first-ever small supratentorial ICH without intraventricular hemorrhage or prior anticoagulation would have risk of significant hematoma growth of <1 in 10 (8%). Our model may be appropriate for subject selection and risk adjustment in future clinical trials. It may also be useful for triaging patients for more intensive monitoring or intervention.

The strengths of the BRAIN prediction model lie in being derived from a large sample, prospectively collected data, and timely and complete baseline and 24-hour CT acquisition. In addition, the model is based on simple routinely available variables, which underwent independent validation in a large international data set, despite some of the differences in baseline characteristics and directions of association with ICH growth in some subgroups (Table 3). Finally, our approach adhered to the recent PROGRESS statement on prognostic model research.[24] We recognize, however, that there are several limitations. To begin with, we only included ICH patients within 6 hours after the onset of symptoms (although hematoma growth is known to be less likely to occur after this time) and associated elevated systolic BP (although high blood BP is present in over 75% of patients with primary ICH[25,26] and baseline BP was not higher than in other prediction models).[11,27] Second, we did not perform CTA to assess whether the spot sign—which seems to be a strong and independent predictor of ICH growth[10,28]—added further predictive power to our model. However, the C-statistic of a recently published ICH growth prediction model that included CTA spot sign was 0.72 for the development cohort and 0.77 for the validation cohort,[11] which is comparable with the BRAIN score. Finally, as over 90% of subjects were Chinese in the validation cohort, the BRAIN score may need to be further validated in other ethnic populations.

Table 3. Baseline Characteristics in the Validation Data Set

Characteristics		No Expansion (n=303)	Expansion (n=43)
Demographic			
Age, y		64 (53–73)	60 (47–69)
Sex	Female	109 (36)	15 (35)
	Male	194 (64)	28 (65)
Chinese	No	17 (6)	3 (7)
	Yes	286 (94)	40 (93)
Medical history			
Prior ICH	No	268 (88)	38 (88)
	Yes	35 (12)	5 (12)
Prior ischemic/ undifferentiated stroke	No	271 (89)	36 (84)
	Yes	32 (11)	7 (16)
Ischemic heart disease	No	298 (98)	40 (93)
	Yes	5 (2)	3 (7)
Diabetes mellitus	No	276 (91)	41 (95)
	Yes	27 (9)	2 (5)
Pre-ICH hypertension	No	82 (27)	9 (21)
	Yes	221 (73)	34 (79)
Medication history			
Antihypertensive therapy	No	176 (58)	23 (54)
	Yes	127 (42)	20 (46)
Warfarin anticoagulation	No	302 (100)	41 (95)
	Yes	1 (0)	2 (5)
Antiplatelet therapy	No	281 (93)	38 (88)
	Yes	22 (7)	5 (12)
Clinical features			
Hours to baseline CT from symptom onset, h		1.8 (1.1–2.6)	1.4 (1.0–1.8)
Systolic BP, mm Hg		180±18	187±17
Diastolic BP, mm Hg		102±14	107±14
CT findings			
Deep location of ICH*	No	51 (17)	7 (16)
	Yes	252 (83)	36 (84)
Baseline ICH volume			
Median (interquartile range)		8.7 (4.5–14.7)	17.9 (9.1–30.0)
	≤10 mL	173 (57)	11 (26)
	10-20 mL	76 (25)	11 (25)
	>20 mL	54 (18)	21 (49)
Intraventricular extension	No	233 (77)	32 (74)
	Yes	70 (32)	11 (26)
Randomized to intensive BP lowering	No	145 (48)	27 (63)
	Yes	158 (52)	16 (37)

BP indicates blood pressure; CT, computed tomography; and ICH, intracerebral hemorrhage.

*Basal ganglia or thalamus.

In conclusion, we developed and independently validated a simple prediction score for ICH growth, which can be easily assessed and implemented across a range of healthcare settings. In particular, it could be used for shared clinical decision-making in many areas of the world where CTA is not readily available or routinely performed for acute ICH.

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Disclosures

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