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ORIGINAL WORK

Independent Validation of the Hematoma Expansion Prediction Score: A Non-contrast Score Equivalent in Accuracy to the Spot Sign

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Abstract

Background and Purpose: The computed tomography angiography (CTA) spot sign is widely used to assess the risk of hematoma expansion following acute intracerebral hemorrhage (ICH). However, not all patients can receive intravenous contrast nor are all hospital systems equipped with this technology. We aimed to independently validate the Hematoma Expansion Prediction (HEP) Score, an 18-point non-contrast prediction scale, in an external cohort and compare its diagnostic capability to the CTA spot sign.

Methods: We performed a retrospective analysis of the predicting hematoma growth and outcome in intracerebral hemorrhage using contrast bolus CT (PREDICT) Cohort Study. Primary outcome was significant hematoma expansion (≥ 6 mL or ≥ 33%). We generated a receiver operating characteristic (ROC) curve comparing the HEP score to significant expansion. We calculated sensitivity, specificity, positive and negative predictive values (PPV/NPV) for each score point. We determined independent predictors of significant hematoma expansion via logistic regression.

Results: A total of 292 patients were included in primary analysis. Hematoma growth of ≥ 6 mL or ≥ 33% occurred in 94 patients (32%). The HEP score was associated with significant expansion (adjusted odds ratio [aOR] 1.14, 95% confidence interval [CI] 1.01–1.30). ROC curves comparing HEP score to significant expansion had an area under the curve of 0.64 (95% CI 0.57–0.71). Youden's method showed an optimum score of 4. HEP Scores ≥ 4 (n = 100, sensitivity 49%, specificity 73%, PPV 46%, NPV 75%, aOR 1.99, 95% CI 1.09–3.64) accurately predicted significant expansion. PPV increased with higher HEP scores, but at the cost of lower sensitivity. The diagnostic characteristics of the spot sign (n = 82, Sensitivity 49%, Specificity 81%, PPV 55%, NPV 76%, aOR 2.95, 95% CI 1.61–5.42) were similar to HEP scores ≥ 4.

Conclusion: The HEP score is predictive of significant expansion (≥ 6 mL or ≥ 33%) and is comparable to the spot sign in diagnostic accuracy. Non-contrast prediction tools may have a potential role in the recruitment of patients in future intracerebral hemorrhage trials.

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Introduction

Hematoma expansion is a major contributor to the morbidity and mortality associated with intracerebral hemorrhage (ICH) [1]. Current therapeutic approaches have had limited success in preventing hematoma expansion and improving outcomes. As only a proportion of patients experience hematoma expansion, optimizing patient selection to identify those at highest risk of expansion can increase the success of future trials [2].

Several baseline variables are associated with hematoma expansion and have been incorporated into prediction scores for bedside use [3–6]. Prediction scores allow selection of high-risk patients for enrollment in treatment trials and can also help clinicians identify patients at highest risk of deterioration. However, many scores require the use of intravenous (IV) contrast [5]. While the use of computed tomography (CT) has increased worldwide, access to IV contrast remains limited in certain jurisdictions. Most scores also require an accurate measurement of baseline ICH volume, which is a limiting factor for primary stroke centers that may not have 24-h access to neuro-radiological expertise [5–7]. As a result, the wide-spread implementation of these scores for trial recruitment or bedside practice is not always possible, and potentially limited to comprehensive care centers with advanced stroke expertise. An easy-to-use non-contrast prediction tool could be used to improve trial recruitment and may significantly improve triaging and resource allocation for primary stroke centers and acute stroke-ready community hospital systems.

The Hematoma Expansion Prediction (HEP) Score is an 18-point nomogram-derived non-contrast scale based on patient characteristics that can be easily acquired at the bedside [8]. We aimed to independently validate this tool, and to evaluate its predictive potential against the spot sign, a CT-angiogram (CTA) marker of hematoma expansion currently used in ongoing ICH treatment trials [9].

Subjects and Methods

Patients were participants in the predicting hematoma growth and outcome in intracerebral hemorrhage using contrast bolus CT (PREDICT) study [10]. Local research ethics board approval was obtained at all enrolling sites, and written informed consent was obtained from all participants. The dataset is available for access to all PREDICT investigators and qualified researchers trained in human subject confidentiality protocols collaborating with PREDICT investigators.

Patients

Patients were participants consecutively enrolled from June 2006 to July 2012 into PREDICT, a prospective multicenter observational study of patients presenting with spontaneous ICH under 6 h. Patients had baseline CT and CTA, follow-up imaging at 24 h post-event, and serial clinical assessments. Exclusion criteria was ICH > 100 mL, known renal impairment precluding CTA, baseline modified Rankin scale > 3, or terminal illness. For this study, patients who lacked follow-up imaging or information related to HEP scoring were excluded. Also excluded were patients who received recombinant Factor VIIa or had craniotomy for hematoma evacuation or ventricular drainage prior to repeat imaging, as these interventions directly affect final hemorrhage volume at follow-up assessment.

Primary Exposure and Primary Outcome

The primary exposure was the HEP score at initial presentation. The HEP score is an 18-point nomogram that is dependent on six variables: (1) time to CT, (2) dementia history, (3) smoking status, (4) antiplatelet use, (5) Glasgow Coma Scale (GCS), and (6) presence of subarachnoid hemorrhage [8]. The points allocated to each variable are highlighted in Table 1. Five of the six variables were originally collected by PREDICT-ICH investigators during primary data collection at the time of first presentation (time from symptom onset to CT, dementia status, smoking status, antiplatelet use, baseline GCS). Dementia status was not distinguished by sub-type. Authors VY and DD assessed subarachnoid hemorrhage by reviewing baseline imaging data of all enrolled patients. Subarachnoid hemorrhage was defined as the presence of subarachnoid blood either adjacent or distinct to the primary hematoma. HEP scores were then calculated for each patient. The primary outcome of this study was significant hematoma expansion, defined as an absolute ICH growth of ≥ 6 mL or a relative growth of $\geq 33\%$ on follow-up imaging [11]. Because varying definitions of hematoma growth may be used, the performance of the HEP score was also tested with another commonly used definition of hematoma expansion (≥ 12.5 mL or $\geq 33\%$) in a sensitivity analysis.

Table 1 Summary of the Hematoma Expansion Prediction Score

Risk factor	Categories	Point	Occurrence in PREDICT cohort ($n = 292$) (%)
Time to baseline CT < 3 h	No	0	34.9
	Yes	3	65.1
Diagnosis of dementia	No	0	94.5
	Yes	4	5.5
Current smoker	No	0	88.4
	Yes	3	11.6
Antiplatelet drug use	No	0	90.1
	Yes	3	9.9
GCS Score at presentation	3–5	3	0.3
	6–8	2	3.1
	9–11	1	14.7
	12–15	0	81.8
SAH at baseline	No	0	81.2
	Yes	2	18.8

CT computed tomography, *GCS* Glasgow coma scale, *PREDICT* predicting hematoma growth and outcome in intracerebral hemorrhage using contrast bolus CT, *SAH* subarachnoid hemorrhage

Statistical Analysis

A receiver operating characteristic (ROC) curve was generated by comparing HEP scores of each patient to the primary outcome. An area under the curve (AUC) with 95% confidence intervals (95% CI) was computed using stratified bootstrap replicates. We calculated the sensitivity, specificity, positive and negative predictive values (PPV/NPV) for each score point. In addition, the method of Youden was used to derive a mathematically optimal threshold score. Because the optimal cut-point derived from Youden's method is not an integer, several score thresholds were selected for further analysis. Multivariable logistic regression was used to adjust for potential confounding. Candidate covariates were derived with exploratory univariate analysis. Fisher's exact test, ANOVA, or Mann–Whitney *U* tests were used as appropriate ($p < 0.10$). Continuous variables that did not conform to the linearity assumption were re-categorized into dichotomous or ordinal variables [12]. Potential interactions were assessed using Wald or likelihood ratio testing. Baseline ICH volume, anticoagulant use, and spot sign are known major predictors of hematoma expansion [13] and were therefore forced into multivariable models a priori. Dichotomous threshold scores and the overall score (as a continuous variable) were both evaluated. Competing model accuracies expressed as AUCs were compared using deLong's method [14]. To further investigate the generalizability of the HEP score, the occurrence of each individual variable that makes up patient's individual HEP scores was calculated and the associations between each individual variable and hematoma expansion were also explored.

In post hoc analysis, spot sign was compared to the HEP score further by assessing the differences in predictive capability of patients who were spot sign positive but did not have sufficiently high HEP scores, to patients who were HEP ≥ 3 or HEP ≥ 4 and spot sign negative. We looked for a potential biological interaction (synergism) when combining spot sign with high threshold HEP scores through testing of relative excess risk due to interaction, attributable proportion due to interaction, and synergy index measures. In addition, both HEP score (as an ordinal variable) and spot sign were entered into linear regression models to better determine whether either variable is associated with hematoma growth that may be below pre-determined thresholds. Statistical analysis was performed using SPSS v24.0 (IBM, Armonk, NY) and SAS v9.4 (SAS Institute Inc, Cary, NC).

Results

The PREDICT study prospectively enrolled 390 patients presenting with spontaneous ICH. Of these, 98 were excluded from our study: 17 patients were excluded due to delayed presentation or having an alternative diagnosis other than spontaneous ICH (e.g., tumour). Twenty-four patients did not receive baseline or follow-up imaging. Thirty-one patients were treated with recombinant FVIIa treatment or surgical intervention prior to follow-up imaging, and 26 patients lacked data on GCS or subarachnoid hemorrhage status. Our primary analysis population included 292 patients. The occurrence of each variable associated with the HEP score is outlined in Table 1. Presentation within 3 h of symptom onset was observed in 65% of the primary analysis cohort. The presence of the other variables only ranged from 3 to 19%. Baseline patient characteristics are outlined in Table 2. Those excluded were similar to the primary analysis cohort on measured baseline factors. However, patients excluded from this study had larger baseline ICH and intraventricular (IVH) volumes.

Thirty-two percent (94/292) of the PREDICT cohort exhibited significant hematoma expansion. Exploratory analysis revealed associations between the primary outcome and anticoagulant use, history of previous stroke, baseline National Institute of Health Stroke Scale (NIHSS), partial thromboplastin time (PTT), serum creatinine, HEP score, baseline ICH volume, and spot sign status ($p < 0.1$, online-only data supplement). PTT, baseline ICH volume, and baseline NIHSS did not meet linearity assumptions. As such, PTT was re-categorized as a dichotomous variable, > 35 s. Baseline ICH volume was re-categorized as: < 10, 10–30, > 30 mL, reflecting

Table 2 Baseline patient characteristics of the primary analysis cohort

Characteristics	Included (*N* = 292)	Excluded (*N* = 98)	*p*
Age, years (median; IQR)	71 (57–80)	68 (56–78)*	0.47
Male sex (*n*, %)	174 (60%)	55/97 (57%)	0.61
Medical history (*n*, %)			
Hypertension	218 (75%)	59/97 (61%)	0.01
Coronary artery disease	30 (10%)	7/52 (14%)	0.49
Congestive heart failure	5 (2%)	0/52 (0%)	0.34
Atrial fibrillation	29 (10%)	6/52 (12%)	0.83
Hypercholesterolaemia	62 (21%)	15/52 (29%)	0.22
Diabetes mellitus	54 (19%)	7/52 (14%)	0.38
Anticoagulant usage	26 (9%)	11/97 (11%)	0.48
Previous stroke	26 (9%)	8/52 (15%)	0.15
Prior hemorrhage	11 (4%)	3/52 (6%)	0.50
Baseline clinical information (median; IQR)			
Systolic blood pressure (mmHg)	173 (150–196)	172 (147–200)‡	0.89
Diastolic Blood Pressure (mmHg)	93 (80–109)	82 (81–110)‡	0.43
Glucose (mmol/L)	7 (6–9.1)*	7 (6–8.6)§	0.99
National Institute of Health Stroke Scale	14 (7–18)†	14 (7–20)†	0.33
Premorbid modified Rankin Score	0 (0–0)‡	0 (0–0)#	0.18
International normalized ratio	1.0 (1.0–1.1)§	1.0 (0.9–1.2)§	0.92
Partial thromboplastin time (s)	29 (27–32)|	30 (28–34)**	0.02
Platelets (× 10^9 cells per L)	221 (180–272)‡	241 (203–299)h	0.06
Creatinine (µmol/L)	77 (65–92)‡	80 (65–93)i	0.39
Hematoma Expansion Scale characteristics			
Time to CT (min) (median; IQR)	142 (90–223)	130 (80–257)*	0.91
Dementia (*n*, %)	16 (6%)	0/52 (0%)	0.08
Current smoker (*n*, %)	34 (12%)	8/52 (15%)	0.45
Antiplatelet usage (*n*, %)	29 (10%)	10/97 (10%)	0.91
Glasgow Coma Scale (median, IQR)	15 (13–15)	14 (10–15)j	0.02
Subarachnoid hemorrhage (*n*, %)	55 (19%)	25/93 (27%)	0.09
HEP Score (median; IQR)	3 (2–5)	4 (3–6)k	0.03
Imaging (median; IQR)			
ICH volume (mL)	12.1 (6.1–25.9)	18.7 (9.9–44.6)l	< 0.01
IVH volume (mL)	0.0 (0–1.9)	1.0 (0.0–8.4)l	< 0.01
Spot sign positive	82/290 (28%)	34/96 (35%)	0.19

Equal variances not assumed for students *t* tests

CT computed tomography, *HEP* Hematoma Expansion Prediction Score, *ICH* intracerebral hemorrhage, *IQR* interquartile range, *IVH* intraventricular hemorrhage

*Missing 1 value, †Missing 2 values, ‡Missing 3 values, §Missing 4 values, |Missing 7 values, #Missing 49 values, **Missing 11 values, hMissing 5 values, iMissing 50 values, jMissing 51 values, kMissing 55 values, lMissing 8 values

past ICH analysis by Dowlatshahi et al. [15, 16] and large meta-analysis findings by Al-Shahi et al. [13]. Baseline NIHSS was re-categorized as ≤ 5, 6–13, ≥ 14 [17]. Adjusting for the relevant covariates, including spot sign, each 1-point increase in the HEP score was associated with a 14% increased odds of significant hematoma expansion (Table 3). Similar results were observed in a sensitivity analysis using ≥ 12.5 mL or ≥ 33% as the definition of significant expansion (83 expansion events, adjusted odds ratio (aOR) 1.13 per 1-point increase, 95% CI 0.99–1.29). A ROC curve comparing HEP score to significant expansion possessed an AUC of 0.64 (Fig. 1). The discriminative capability of the HEP score was similar to the spot sign (AUC = 0.65, $p = 0.68$).

The calculated sensitivities, specificities, PPV/NPV of each HEP score point are summarized in the online-only data supplement. PPV increased with increasing scores, and sensitivity decreased correspondingly. As per the method of Youden, the mathematically optimal HEP threshold score was at 3.5. This clinically

Table 3 Multivariable-adjusted relationship between HEP Score (as a continuous variable) and significant hematoma expansion

Variable	Adjusted OR	95% CI
HEP Score	1.14	1.01–1.30
Spot Sign	2.71	1.47–5.00
Anticoagulant use	5.01	1.96–12.78
Creatinine	1.01	1.00–1.02
National Institute of Health Stroke Scale		
≤ (Ref)	–	–
6–13	1.44	0.55–3.79
≥ 14	2.93	1.11–7.08
Baseline intracerebral hemorrhage volume		
< 10 mL (Ref)	–	–
10–30 mL	1.13	0.54–2.35
> 30 mL	1.07	0.44–2.57

C-statistic: 0.77, Hosmer and Lemeshow goodness of fit: $p = 0.76$

CI confidence interval, *HEP* Hematoma Expansion Prediction Score, *OR* odds ratio

corresponds to HEP scores of 3 or 4. Two hundred and nineteen (75%) patients had HEP scores ≥ 3. One hundred patients (34%) had HEP scores ≥ 4. After adjusting for the relevant covariates, threshold scores of ≥ 3 and ≥ 4 were associated with significant hematoma expansion (HEP ≥ 3: aOR 2.13, 95% CI 1.04–4.37//HEP ≥ 4: aOR 2.13, 95% CI 1.19–380). The diagnostic performance of spot sign was marginally better than that of the threshold scores (Table 4). The model c-statistics of both HEP ≥ 3 and HEP ≥ 4 were similar to the spot sign (0.73 vs. 0.76, $p = 0.16$; 0.74 vs. 0.76, $p = 0.44$). There was no clear difference in predictive performance when patients who were solely spot sign positive were directly compared to spot sign negative patients with HEP scores ≥ 4 in regression modeling (Table 5). Combining spot sign with the HEP score did not appear to have a synergistic effect on predicting significant hematoma expansion. In a univariate linear model, HEP score was significantly associated with any hematoma expansion (Parameter estimate: 0.88; $p = 0.03$). After adjusting for the relevant covariates, HEP score was not significantly associated with any hematoma expansion. In contrast, spot sign presence was associated

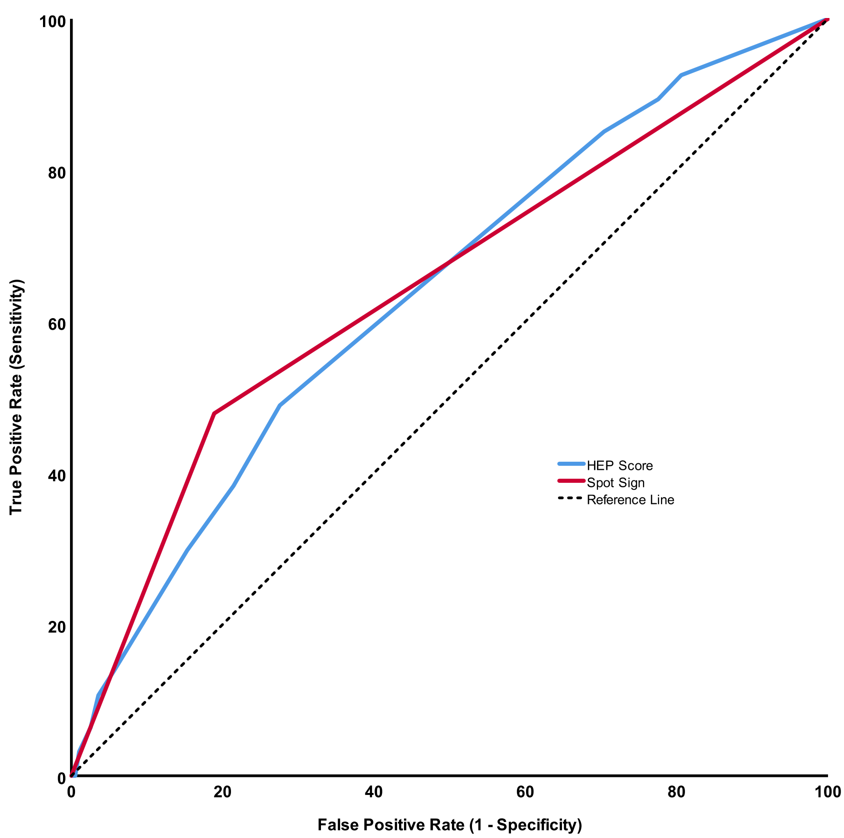

Fig. 1 Receiver operating characteristic curve comparing Hematoma Expansion Prediction (HEP) score and spot sign to significant hematoma expansion (≥ 6 mL or ≥ 33%). HEP Score, area under the curve (AUC): 0.64 (95% CI 0.57–0.71). Youden's Index: 3.5. Spot Sign, AUC: 0.65 (95% CI 0.58–0.72)

Table 4 Diagnostic capabilities of spot sign and HEP Score

	Frequency	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Adjusted OR (95% CI)*	Model C-statistic
Spot Sign	82 (28.3%)[†]	47.9	81.1	54.9	76.4	2.95 (1.61–5.42)	0.76
HEP ≥ 3	219 (75.0%)	85.1	29.8	36.5	80.8	2.14 (1.04–4.41)	0.73
HEP ≥ 4	100 (34.2%)	48.9	72.7	46.0	75.0	1.99 (1.09–3.64)	0.74

CI confidence interval, *HEP* Hematoma Expansion Prediction Score, *OR* odds ratio

*Adjusted for anticoagulant use, serum creatinine, baseline intracerebral hemorrhage volume (< 10 mL, 10–30 mL, > 30 mL), and baseline National Institute of Health Stroke Scale (≤ 5, 6–13, ≥ 14)

[†] Missing 2 values

Table 5 Direct comparisons of Hematoma Expansion (HEP) Score and spot sign

	Adjusted OR (95% CI)*		Adjusted OR (95% CI)*
Spot Sign – & HEP < 3	Ref	Spot Sign – & HEP < 4	Ref
Spot Sign – & HEP < 3	13.38 (2.33–77.01)	Spot Sign + & HEP < 4	3.79 (1.68–8.59)
Spot Sign – & HEP ≥ 3	3.06 (1.22–7.73)	Spot Sign – & HEP ≥ 4	2.56 (1.19–5.51)
Spot Sign + & HEP ≥ 3	7.08 (2.62–19.16)	Spot Sign + & HEP ≥ 4	5.86 (2.45–14.08)
Additive measures (95% CI)			
RERI	– 8.37 (– 30.42 to 13.69)	RERI	0.51 (– 4.43 to 5.36)
AP	– 1.18 (– 4.21 to 1.85)	AP	0.09 (– 0.70 to 0.87)
S Index	0.42 (0.09–1.89)	S Index	1.12 (0.40–3.16)

AP attributable proportion, *CI* confidence interval, *HEP* Hematoma Expansion Prediction Score, *OR* odds ratio, *RERI* relative excess risk due to interaction

*Adjusted for anticoagulant use, serum creatinine, baseline intracerebral hemorrhage volume (< 10 mL, 10–30 mL, > 30 mL) and baseline National Institute of Health Stroke Scale (≤ 5, 6–13, ≥ 14)

with any hematoma expansion, even after adjusting for the relevant covariates (Parameter estimate: 9.86; $p < 0.05$).

Discussion

We aimed to independently validate the HEP score and compare its predictive potential to the commonly used CTA spot sign. Our study used a real-world, pragmatic, observational ICH population with study subjects originating from 6 different countries (Canada, USA, Germany, Poland, Spain, and India) and data collected prospectively at the time of presentation. Our findings show that the HEP score independently predicts significant hematoma expansion and has similar test characteristics to the spot sign.

Our base findings reflect that of Yao and colleagues' original study on the HEP score [8]. Baseline patient characteristics between the development cohort and the primary analysis population were largely similar. There was a higher proportion of warfarin use and a higher median ICH volume reported in the development cohort [8], which is likely due to the exclusion of patients with hemorrhage volumes > 100 mL in the PREDICT study. Thirty-two percent of patients exhibited significant expansion, which is in keeping with prior reports and with the original development cohort [8, 18–20]. We found that HEP scores > 3 were at highest risk of expansion and our calculated c-statistics were similar to that of the development cohort [8]. The consistency in these findings supports the generalizability of the HEP score.

By using the PREDICT study, we were able to compare the performance of HEP to that of the CTA spot sign. Table 4 highlights our key findings and highlights that HEP scores ≥ 4 exhibited similar sensitivities/specificities to that of the spot sign. Spot sign had an improved specificity, but the discriminative capacity, indicated by the model c-statistics, was virtually identical. In addition, our post hoc analysis did not show a superiority in predictive performance between spot sign and HEP score in direct comparison. These findings are in keeping with previous studies [4, 7] and lend support to the notion that non-contrast predictive models have the capability of predicting hematoma expansion with an accuracy that can match the spot sign. Moreover, the proportion of patients observed with HEP scores ≥ 4 was greater than those observed with spot sign (34.2% vs 28.3%, respectively). Given spot sign ICH trials have experienced recruitment challenges (the spot sign for predicting and treating ICH growth study [STOP-IT], NCT00810888/"Spot Sign" selection of intracerebral hemorrhage to guide hemostatic therapy [SPOTLIGHT], NCT01359202), non-contrast tools such as HEP may be a compelling alternative.

Al-Shahi et al. [13] recently identified baseline hemorrhage volume, time to CT, antiplatelet and anticoagulant use, and spot sign, as predictors of hematoma expansion in a large individual patient data meta-analysis. The HEP score complements these findings by utilizing two of the four major variables (antiplatelet use and early time to CT). As baseline hematoma volume assessment and IV contrast use may be challenging in primary stroke centers, the HEP score may act as a suitable substitute tool to use in these particular scenarios. Our findings show that the HEP score was predictive of significant expansion, independent of anticoagulant use. Anticoagulant use is well associated with hematoma expansion, and rapid reversal has already been shown to improve outcomes [21].

The components of the HEP score can be automatically calculated using information available in modern electronic medical records (EMR). This allows for its use as an EMR-based clinical decision rule or an automated clinical support application, analogous to VIZ.ai and MaxQ AI. Such applications can facilitate acute care decision making in the neurocritical care setting.

Our study has several limitations. Unlike the development cohort used by Yao et al. [8], the PREDICT cohort reported significantly lower rates of dementia and antiplatelet use. The former may be explained by the fact that the majority of ICH in the PREDICT cohort were non-lobar (70%), and therefore less likely to be associated with conditions such as amyloid angiopathy or dementia [22, 23]. The incidence of subarachnoid hemorrhage was comparable, but the number of patients with a time to CT < 3 h was significantly higher in the PREDICT population. Further work in a larger dataset is warranted to ensure generalizability. In addition, data around the early withdrawal of care were not available in this cohort. This introduces the potential for bias as these patients can be excluded from analysis due to lack of follow-up imaging. We also could not rule out a selection bias when excluding patients who underwent surgery or received hemostatic agents. Indeed, the primary difference between those included versus excluded from primary analysis was the higher ICH and IVH volumes observed in those, which is an independent predictor of hematoma expansion [13, 15, 24, 25]. Finally, while our study validates the use of HEP score to predict pre-specified hematoma expansion definitions, it does not imply that its components are directly related to the mechanistic aspects or pathophysiology of hematoma expansion. We see evidence of this in our post hoc linear regression analysis, where after adjusting for confounding, the HEP score is not associated with a range of hematoma growth. The HEP score, and the majority of other scores developed, was primarily designed to assess a threshold of hematoma expansion, and these findings provide useful information regarding the limitations of this type of predictive modeling.

Conclusion

In an independent, real-world cohort we confirmed that the HEP score is predictive of significant hematoma expansion. The HEP score is comparable to the spot sign in diagnostic accuracy and frequency when a threshold of significant expansion is used and may have a role in recruitment for future ICH treatment trials. However, the HEP score is limited in predictive capabilities when assessing lesser amounts of hematoma expansion.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s12028-019-00740-5) contains supplementary material, which is available to authorized users.

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Author contributions

This manuscript complies with the instructions provided by ***Neurocritical Care.*** All authors meet the requirements for authorship. Their roles and contributions to this manuscript are listed below: VY and DD were involved in protocol/project development, data analysis, and manuscript writing/editing. TR contributed to data analysis and manuscript writing/editing. AMD, RIA, DR-L, CAM, YSB, ID, AK, J-MB, CL, GG, PS, JR, CSK, RB were involved in data collection or management. MDH contributed to data collection or management and manuscript writing/editing. DF contributed to manuscript writing/editing. MS was involved in protocol/project development and manuscript writing/editing.

Source of support

There was no support for this work.

Conflicts of Interest

Andrew M. Demchuk reports grants from NovoNordisk Canada, during the conduct of the study; Jean-Martin Boulanger reports other from Pfizer, other from Novartis, outside the submitted work; Cheemun Lum has deceased;

Michael D. Hill reports personal fees from Merck, non-financial support from Hoffmann-La Roche Canada Ltd, grants from Covidien (Medtronic), grants from Boehringer-Ingleheim, grants from Stryker Inc., grants from Medtronic LLC, grants from NoNO Inc., outside the submitted work; In addition, Hill has a patent Systems and Methods for Assisting in Decision-Making and Triaging for Acute Stroke Patients pending to US Patent office Number: 62/086,077 and owns stock in Calgary Scientific Incorporated, a company that focuses on medical imaging software, is a director of the Canadian Federation of Neurological Sciences, a not-for-profit group and has received grant support from Alberta Innovates Health Solutions, CIHR, Heart & Stroke Foundation of Canada, National Institutes of Neurological Disorders and Stroke; Magdy Selim reports grants from NIH/NINDS, during the conduct of the study and the remaining authors have nothing to disclose.

Ethical approval/Informed consent

Local research ethics board approval was obtained at all enrolling sites, and written informed consent was obtained from all participants.

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