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Predicting Hemorrhagic Transformation of Acute Ischemic Stroke

Prospective Validation of the HeRS Score

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Abstract: Hemorrhagic transformation (HT) increases the morbidity and mortality of ischemic stroke. Anticoagulation is often indicated in patients with atrial fibrillation, low ejection fraction, or mechanical valves who are hospitalized with acute stroke, but increases the risk of HT. Risk quantification would be useful. Prior studies have investigated risk of systemic hemorrhage in anticoagulated patients, but none looked specifically at HT. In our previously published work, age, infarct volume, and estimated glomerular filtration rate (eGFR) significantly predicted HT. We created the hemorrhage risk stratification (HeRS) score based on regression coefficients in multivariable modeling and now determine its validity in a prospectively followed inpatient cohort.

A total of 241 consecutive patients presenting to 2 academic stroke centers with acute ischemic stroke and an indication for anticoagulation over a 2.75-year period were included. Neuroimaging was evaluated for infarct volume and HT. Hemorrhages were classified as symptomatic versus asymptomatic, and by severity. HeRS scores were calculated for each patient and compared to actual hemorrhage status using receiver operating curve analysis.

Area under the curve (AUC) comparing predicted odds of hemorrhage (HeRS score) to actual hemorrhage status was 0.701. Serum glucose ($P < 0.001$), white blood cell count ($P < 0.001$), and warfarin use prior to admission ($P = 0.002$) were also associated with HT in the validation cohort. With these variables, AUC improved to 0.854. Anticoagulation did not significantly increase HT; but with higher intensity anticoagulation, hemorrhages were more likely to be symptomatic and more severe.

The HeRS score is a valid predictor of HT in patients with ischemic stroke and indication for anticoagulation.

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Abbreviations: aPTT_r = activated partial thromboplastin time, AUC = area under the curve, CT = computerized tomography, eGFR = estimated glomerular filtration rate, HeRS = hemorrhage risk stratification, HI = hemorrhagic infarction, HT = hemorrhagic transformation, ICH = intracerebral hemorrhage, INR =

international-normalized ratio, MRI = magnetic resonance imaging, NIH = National Institutes of Health, PH = parenchymal hematoma, tPA = tissue plasminogen activator.

INTRODUCTION

Hemorrhagic transformation (HT) increases morbidity and mortality of acute ischemic stroke.¹ Ischemia leaves the cerebral vasculature friable, resulting in the highest rate of HT in the days immediately following infarction.^{2–4} Anticoagulants both increase risk of HT,⁵ and worsen degree of bleeding.⁶ There are multiple scores that predict systemic hemorrhage in patients taking anticoagulants for atrial fibrillation,^{7,8} but few include intracerebral hemorrhage, and none address HT of ischemic stroke (Table 1). Patients presenting with acute ischemic stroke often require anticoagulation, most commonly for cardiac etiologies such as atrial fibrillation, reduced ejection fraction, or mechanical valves. There is a known daily risk of stroke when anticoagulation is held; however, risk of HT is poorly characterized. Quantified risk stratification would allow for more appropriate monitoring for HT in high risk patients, and provide a tangible assessment of risk when counseling families of potential complications.

Factors Predicting Hemorrhage

In a previous study, we evaluated factors associated with increased risk of HT in a cohort of patients hospitalized with acute ischemic stroke who also had an indication for anticoagulation ($n = 123$).⁶ Demographic information (gender, race, and age); medical factors (blood pressure, glycemic control, lipid profile, and renal function); information pertaining to anticoagulation status and other medications (prehospital use, indication for anticoagulation, anticoagulation status while hospitalized, peak international-normalized ratio (INR) and PTT_r values, and days to therapeutic anticoagulation poststroke); and information on stroke size and severity (NIHSS score, infarct volume, and Trial of Org 10172 in Acute Stroke Trial classification) were collected and analyzed. Renal function was calculated on admission using the Modification of Diet in Renal Disease (MDRD) Equation⁹, and defined by both linear estimated glomerular filtration rate (eGFR) and category of impairment: normal (eGFR ≥ 60 mL/min/1.73 m²); mild (eGFR 30–59 mL/min/1.73 m²); and moderate (eGFR < 30 mL/min/1.73 m²).⁶ All initial and follow-up neuroimaging obtained during the hospitalization was reviewed for infarct volume and evidence of HT. Hemorrhages were classified as: petechiae versus hematoma; and symptomatic versus asymptomatic. In an adjusted model, advanced age (odds ratio [OR] per 10 years 1.31; 95% confidence interval [CI] 0.98–1.74), renal impairment (1.81 per worsening category of eGFR; 95% CI 1.01–3.26), and larger infarct volume (OR 1.13 per 10 cc; 95% CI

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TABLE 1. Comparison of the Predictive Models of Hemorrhage

Score	N	Type of Bleeding	Time Period	Associated Factors	Hemorrhage Rate	Sensitivity
HAS-BLED Euro Heart Study ⁷	3978 Patients with afib	Intracranial or hospitalization or Hgb decrease >2 g/L and/or transfusion	1 year follow-up period	Hypertension, abnormal liver/renal function, stroke, bleeding history, labile INR, >65 years, drugs/alcohol	53 (1.5%)	C statistic = 0.720
HEMORR ₂ HAGES ⁸	3791 Medicare patients with afib	Hospitalization for any hemorrhage defined by Medicare claims	Up to 1000 days postdischarge	Prior bleed, hepatic or renal disease, ethanol, cancer, >75 years, low platelets, hypertension, anemia, genetics, falls, stroke	162 (4.3%); 25 intracranial (0.7%)	C statistic = 0.670*
HeRS	241 Patients with acute ischemic stroke and indication for anticoagulation	Intracerebral; symptomatic and asymptomatic	Acute hospitalization	Age, infarct volume, eGFR	75 (31%); 19 symptomatic (7.9%)	AUC = 0.701
HeRS plus [†]				Addition of serum glucose, WBC count, and warfarin use on admission		AUC = 0.854

AUC = area under the curve, eGFR = estimated glomerular filtration rate, HeRS = hemorrhage risk stratification, INR = international normalized ratio,

* Anticoagulated group.

† Not yet validated in an independent cohort.

1.05–1.21) were significant predictors of HT.⁶ Interestingly, neither the use of anticoagulation during the hospital stay nor time from stroke onset to initiation of heparin, a heparinoid, or warfarin were significant predictors of hemorrhage, though use was associated with larger more severe hemorrhages.⁶ Regression coefficients from multivariable logistic regression were used to predict odds of hemorrhage. Probability of hemorrhage was then calculated, creating a hemorrhage risk stratification (HeRS) score. Given the complexity of the calculation, we designed an iPhone application to perform this calculation. Search Apple app store: “Johns Hopkins HeRS.”

In this analysis, we validate the HeRS score in a unique, prospectively followed inpatient cohort with acute ischemic stroke and an indication for anticoagulation.

METHODS

Patient Population

This prospective cohort study was approved by the Johns Hopkins School of Medicine’s Institutional Review Board. It was observational in nature and performed as part of a quality assurance initiative using de-identified data stored in the Johns Hopkins Bayview Stroke/Hemorrhage Database (NA_00079956). Therefore, informed consent was not required. Adults (18 years of age and older) presenting to the Johns Hopkins Hospital or Johns Hopkins Bayview Medical Center between June 2011 and March 2014 with: an acute ischemic stroke on head computerized tomography (CT) or diffusion-weighted magnetic resonance imaging (MRI), and a known condition typically requiring treatment with anticoagulation were included in analysis. Patients were excluded from analysis if complete data on infarct volume, age, and eGFR were unavailable (n = 0). Unlike our original cohort, patients were prospectively identified by physicians on our Stroke Service and Neurology Consult Team rather than retrospectively using ICD-9 codes. Indications for anticoagulation included: atrial fibrillation, basilar artery thrombosis, cervical arterial dissection, mechanical valve (aortic or mitral), reduced ejection fraction ($\leq 35\%$), myocardial infarction, apical thrombus, pulmonary embolus or deep vein thrombosis, hypercoagulable state, and high-risk intracranial/extracranial large-vessel stenosis.⁶ Decisions to anticoagulate were made by the primary team caring for the patient. A patient was defined as “anticoagulated” if they received warfarin, unfractionated/low molecular weight heparin (at treatment doses), or one of the new oral anticoagulants.⁶ In nearly 100% of patients, intravenous heparin was used (dosing based on our institution’s unfractionated heparin nomogram: activated partial thromboplastin time [aPTT] goal 1.5–2.0) as a bridge to warfarin therapy. Potential patients were identified by the inpatient stroke attending physician, and charts were reviewed to determine eligibility. A total of 242 patients were identified over the 2.75-year period. Similar to prior analyses, data were collected regarding patient demographics (age, race, and sex), medical profile (admission blood pressure, history of diabetes, statin use, antiplatelet use, anticoagulation status—agent and timing, baseline laboratory values—including eGFR estimated using the MDRD equation⁹), and stroke characteristics (National Institutes of Health [NIH] Stroke Scale, treatment with tissue plasminogen activator [tPA], and infarct volume). Patients were prospectively followed through hospital discharge for HT, defined as bleeding into the area of infarction. Only those with complete data on age, infarct volume, and eGFR were included in the final analysis (n = 241).

Hemorrhage Risk Stratification (HeRS) Score Calculation

Using regression coefficients generated through multivariable logistic regression in our prior study,⁶ the odds of hemorrhage was predicted by exponentiating the equation: $\log(\text{odds}) = -3.823563 + (0.0120706) \times (\text{Volume}) + (0.5939482) \times (\text{eGFR Category}) + (0.0266442) \times (\text{Age})$. Both age (years) and volume (cc) were expressed as continuous variables. eGFR category was defined as: 0 = eGFR ≥ 60 mL/min/1.73 m²; 1 = eGFR 30–59 mL/min/1.73 m²; 2 = eGFR < 30 mL/min/1.73 m². The probability of hemorrhage (HeRS score) was then calculated using the equation: HeRS score = $\text{odds}/(1 + \text{odds})$.

Imaging Data

Patients underwent an initial MRI of the brain as part of their standard stroke evaluation. Neuroimaging was reviewed by 2 board-certified vascular neurologists (EBM, RHL) independent from the clinical record. Imaging was performed on a 1.5 or 3.0 Tesla scanner using a standard quadrature transmit-receive head coil. In the majority of cases, MRI was obtained within 24 to 72 hours of admission. Areas of restricted diffusion were identified on diffusion-weighted imaging. Given its ease of calculation, infarct volume was estimated using the validated equation: $(\text{length} \times \text{width} \times (\text{slice thickness} \times \text{number of slices}))/2$.¹⁰ Patients unable to undergo MRI due to claustrophobia or pacemaker placement (n = 42) had noncontrast CT imaging. Volumes were estimated using the same technique. To determine HT, all follow-up neuroimaging performed during a patient’s hospitalization was reviewed for intracerebral bleeding. No patient experienced isolated hemorrhage outside of the ischemic bed. Hemorrhages were classified as symptomatic (defined as any subjective clinical worsening determined by the treating physicians [no specified change in NIH stroke scale required], with blood on corresponding head imaging¹¹) versus asymptomatic, and were further classified by severity based on European Cooperative Acute Stroke Study criteria (hemorrhagic infarction [HI]1, HI2, parenchymal hematoma [PH]1, PH2).¹² The majority of acute hemorrhages were noted on noncontrast head CT; however, MRI alone was used in a minority of cases. High interrater reliability for hemorrhage severity has been previously demonstrated ($\kappa = 0.76$).¹³

Sample Size Calculation and Statistical Analysis

The sample size for the original retrospective cohort was determined using preliminary data. Given a mean eGFR for individuals with intracerebral hemorrhage (ICH) of 45 mL/min/1.73 m² (standard deviation [SD] 19.5) compared to 52.5 mL/min/1.73 m² (SD 14.2) in those without and a combined symptomatic and asymptomatic hemorrhage rate of 25% we calculated a required sample size of 63 individuals with ICH and 189 without to show primary differences based on eGFR alone. A total of 345 charts were screened given the likelihood many would fail to meet inclusion criteria and an initial analysis was performed to determine the accuracy of our sample size calculation that showed statistically significant results. For the prospective validation cohort, sample size was calculated based on comparison of mean estimated ICH scores from our retrospective cohort showing the required sample size of 36 total individuals to detect a statistically significant difference with 80% power. We chose to recruit a larger overall sample size to guarantee adequate numbers of individuals with brain MRI and complete data.

Univariate analysis was performed using Student's *t*-tests and Chi-square tests. Subsequent multivariable logistic regression, including age, race, sex, and all variables significant in univariate analysis was performed, with HT (combined symptomatic and asymptomatic) as the dependent variable. A secondary analysis was performed investigating factors predictive of symptomatic hemorrhage.

Model validation—a HeRS score was calculated for each individual and compared to actual hemorrhage status using receiver operating curve analysis. The sensitivity, specificity, positive predictive value, and negative predictive value were generated for multiple cutpoints (Table 2).

RESULTS

Validation Cohort

A total of 241 patients were included in the present analysis. They were similar in characteristics to our original cohort (Table 3). Eighty-three percent had anticoagulation initiated during their hospital stay. The most common indications were: atrial fibrillation (36%), reduced ejection fraction (11%), and known hypercoagulable state (10%). Consistent with prior findings, in the validation cohort anticoagulation during the hospitalization was not associated with a higher risk of HT (*P* = 0.797); however, being on warfarin at the time of admission was a significant predictor (*P* = 0.002). The average length of stay was 9.8 days (median 7 days) and the majority (*n* = 64/75) of hemorrhages occurred within the 1st week (mean 4.6 days from admission, median 1 day). Higher peak aPTT (*P* = 0.660) and INR (*P* = 0.703) values were not associated with increased risk. Results for all variables of interest in univariate analysis are outlined in Table 3. Along with warfarin use on admission, worsening eGFR category (*P* = 0.043), larger infarct volume (*P* < 0.001), higher serum glucose (*P* < 0.001), higher NIH Stroke Scale score (*P* < 0.001), treatment with tPA (*P* = 0.005), hemicraniectomy (*P* = 0.017), and elevated white blood cell count (*P* < 0.001) were associated with higher risk of HT.

In multivariable modeling, renal function and infarct volume remained statistically significant predictors of HT; as well as serum glucose, white blood cell count, and warfarin use prior to admission (which had not been evaluated previously⁶). Intraarterial lysis and hemicraniectomy were also significant predictors in this cohort; however, further sensitivity analyses excluding these patients did not impact results.

Validation of the HeRS Score

In the validation cohort, the area under the curve (AUC) comparing predicted odds of hemorrhage (HeRS score) to actual hemorrhage status was 0.701 (Figure 1). A secondary analysis incorporating warfarin use on admission, serum glucose, and white blood cell count improved the AUC to 0.854.

Symptomatic Hemorrhages

Nineteen patients experienced symptomatic HT of their infarct. As the numbers were relatively small, there was no difference in HeRS scores for those with symptomatic versus asymptomatic hemorrhage (*P* = 0.81) and the ability to draw conclusions is somewhat limited; however, patients with symptomatic hemorrhage were more likely to be on warfarin on admission (*P* = 0.024) and in general had higher levels of anticoagulation while in the hospital (mean pTTr values of 1.39 vs 1.02 in those with asymptomatic ICH; *P* = 0.015). When classifying hemorrhages by severity (HI1&2 vs PH1&2), there was also no difference in the average HeRS score (*P* = 0.65); however, patients with more severe hemorrhages were also more likely to have higher pTTr and INR values, and tended to have larger infarct volumes ([mean 91.3 vs 74.2 cc], not statistically significant [*P* = 0.391]). These results are outlined in Table 4.

DISCUSSION

Following acute stroke, the cerebral vasculature is friable, increasing risk of HT. In patients on anticoagulation, even an initially asymptomatic bleed can ultimately result in significant complications, increasing hospital length of stay, and leading to poorer long-term outcomes and higher healthcare costs.¹⁴ Thus, the ability to predict any HT when considering anticoagulation is important. A quantifiable risk estimate such as the HeRS score allows for informed decision-making regarding the appropriate intensity of monitoring to detect HT, particularly in institutions without readily accessible neuroimaging. Further, in some settings the score may influence the agent chosen (a heparin infusion that can be rapidly discontinued vs oral therapy with a longer half-life), and provide a tangible risk estimate of potential complications when counseling families.

Validation of the Hemorrhage Risk Score

We have previously shown that age, infarct volume, and renal impairment (even mild) are predictors of HT. In this study,

TABLE 2. Probabilities of Hemorrhage (Model Vs Cohort), Sensitivity, Specificity, PPV, and NPV for Different Estimated Hemorrhage Odds Cutoffs for the HeRS Score

Odds Cutoff	Probability Equivalent (From Model)	Cohort Probability of Hemorrhage (n ICH Above Cutoff/n Above Cutoff)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
0.10	0.09	72/216 = 33%	0.96 (0.89–0.99)	0.13 (0.09–0.19)	0.33 (0.27–0.40)	0.88 (0.69–0.97)
0.20	0.17	53/136 = 39%	0.71 (0.59–0.81)	0.50 (0.42–0.58)	0.39 (0.31–0.48)	0.79 (0.70–0.86)
0.50	0.33	32/51 = 63%	0.43 (0.31–0.55)	0.89 (0.83–0.93)	0.63 (0.48–0.76)	0.77 (0.71–0.83)
1.00	0.50	16/22 = 73%	0.21 (0.13–0.32)	0.96 (0.92–0.99)	0.73 (0.50–0.89)	0.73 (0.67–0.79)
2.00	0.67	8/12 = 67%	0.11 (0.05–0.20)	0.98 (0.94–0.99)	0.67 (0.35–0.90)	0.71 (0.64–0.77)
5.00	0.83	2/3 = 67%	0.03 (0.003–0.09)	0.99 (0.97–1.0)	0.17 (0.02–0.048)	0.69 (0.63–0.75)

CI = confidence interval, HeRS = hemorrhage risk stratification, NPV = negative predictive value, PPV = positive predictive value.

TABLE 3. Patient Characteristics by Hemorrhage Status for the Original and Validation Cohorts

	Validation Cohort			Original Cohort [†]				
	Overall (N = 241)	No Hemorrhage (n = 166)	Hemorrhage (n = 75)	P-Value*	Overall (N = 123)	No Hemorrhage (n = 93)	Hemorrhage (n = 30)	P-Value*
Age, years, mean (SD)	67.8 (16.4)	68.6 (15.3)	66.0 (18.2)	0.251	63 (17)	62 (18)	67 (16)	0.19
Female, %	48.6	49.4	46.7	0.695	54	52	60	0.53
African American, %	28.2	28.3	28.0	0.960	44	41	53	0.29
Diabetes, %	33.1	29.7	40.5	0.099	30	29	33	0.65
Glucose, mg/dL, mean (SD)	137.5 (57.6)	127.7 (44.9)	159.1 (74.6)	<0.001	50.5 (16)	52.0 (15)	45.1 (19)	0.035
eGFR, mL/min/1.73 m ² , mean (SD)								
eGFR category, %				0.043				
≥60 mL/min/1.73 m ²	67.2	72.3	56.0					
30–59 mL/min/1.73 m ²	27.4	22.9	37.3					
<30 mL/min/1.73 m ²	5.4	4.8	6.7					
Creatinine, mg/dL, mean (SD)	1.12 (0.70)	1.10 (0.78)	1.16 (0.49)	0.580				
LDL, mg/dL, mean (SD)	89.3 (37.3)	89.9 (38.2)	88.1 (35.4)	0.736	86 (39)	88 (38)	79 (42)	0.29
ALT, mg/dL, median (IQR)	21 (15–31)	20 (16–29)	22 (13–36)	0.350				
AST, mg/dL, median (IQR)	21 (16–28)	22 (16–28)	21 (17–31)	0.523				
aPTT, mean (SD)	1.08 (0.39)	1.06 (0.28)	1.11 (0.55)	0.449				
INR, mean (SD)	1.18 (0.36)	1.16 (0.37)	1.23 (0.36)	0.177				
WBC (×10 ³ /mm ³), mean (SD)	9.8 (5.8)	8.8 (3.4)	12.1 (8.6)	<0.001				
Hematocrit, %, mean (SD)	38.2 (6.2)	38.4 (6.0)	37.7 (6.5)	0.427				
Platelet count, ×10 ³ /mm ³ , mean (SD)	241.8 (99.3)	244.8 (98.0)	235.0 (102.6)	0.478				
ESR (mm/hour), median (IQR)	20 (8–40)	19 (9–40)	23 (5–40)	0.212				
Hemoglobin A1c (%), mean (SD)	6.59 (4.4)	6.58 (5.1)	6.61 (1.6)	0.961				
SBP (mmHg), mean (SD)	154.2 (31.4)	154.3 (31.8)	154.2 (30.6)	0.987				
DBP (mmHg), mean (SD)	86.2 (19.3)	86.1 (19.0)	86.4 (20.1)	0.984				
Medication use on admission, %								
Antiplatelet	41.1	42.4	38.4	0.561	35	32	45	0.28
Statin	46.3	47.1	44.6	0.718				
Warfarin	13.0	8.2	23.3	0.002	16	15	20	0.57
Anticoagulation during hospitalization	82.9	82.4	83.8	0.797	80	80	83	0.79
NIH stroke scale (points), mean (SD)	8.7 (7.2)	7.3 (6.7)	11.8 (7.3)	<0.001	9 (7)	8 (7)	11 (6)	0.033
NIH stroke scale (points), median (IQR) [†]	7 (2–14)	5 (2–11)	12 (6–18)	<0.001				
Reason for anticoagulation, %				0.261				
Atrial fibrillation	36.3	37.3	34.6		37	34	47	0.28
Dissection	3.9	4.9	1.9					
Mechanical aortic valve	1.6	1.0	2.8					
Vegetation	0.3	0.0	0.9					
Ejection fraction ≤35%	11.3	10.8	12.1					
Deep vein thrombosis	6.1	5.4	7.5					
Pulmonary embolism	7.7	4.9	13.1					
Known hypercoagulable state	10.0	9.8	10.3					
Other	22.8	26.0	16.8					

	Validation Cohort			Original Cohort ⁶			
	Overall (N = 241)	No Hemorrhage (n = 166)	Hemorrhage (n = 75)	Overall (N = 123)	No Hemorrhage (n = 93)	Hemorrhage (n = 30)	P-Value*
tPA, %							
Intravenous	16.6	14.5	21.3	15	11	27	0.41
Intra-arterial	5.4	3.0	10.7				
Intravenous and intra-arterial	1.7	0.6	4.0				
Volume (cc), median (IQR) [†]	15 (3–45)	6 (1–22)	49 (20–124)				‡OR 1.13 per 10 cc increase; 95% CI 1.05–1.21
Volume category, %							
≤20 cc	58.1	72.9	25.3				
>20–≤100 cc	30.3	22.3	48.0				
>100–≤200 cc	8.7	3.6	20.0				
>200 cc	2.9	1.2	6.7				
Hemicraniectomy, %	2.1	0.6	5.3				0.017

ALT = alanine aminotransferase, aPTT = activated partial thromboplastin time, AST = aspartate aminotransferase, CI = confidence interval, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, ESR = erythrocyte sedimentation rate, INR = international-normalized ratio, LDL = low density lipoprotein, SBP = systolic blood pressure, tPA = tissue plasminogen activator, WBC = white blood cell count.
 * P-value comparing no hemorrhage versus hemorrhage.
 † Median and interquartile range (IQR) are reported for non-normally distributed variables.
 ‡ Volume described in original cohort using odds ratios.

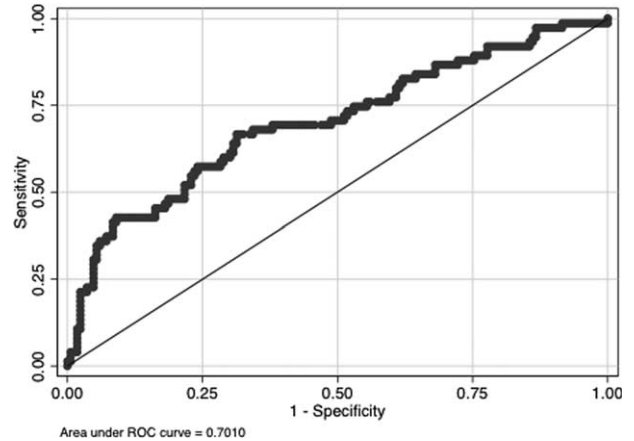


FIGURE 1. ROC curve for estimated hemorrhage based on the HeRS score versus observed hemorrhage. HeRS = hemorrhage risk stratification, ROC = receiver operator characteristics.

we validate the HeRS score (based on these variables) in an independent prospectively collected inpatient cohort. Of the 3 risk factors, infarct volume is the most intuitive and has a significant basis in the literature.¹⁵ The association with age is also consistent with previous studies showing that individuals over the age of 80 who receive intravenous tPA may be at increased bleeding risk.¹⁵ The effect of renal impairment on bleeding is becoming more apparent.^{6,13,16} Several small studies have also shown that patients with renal failure are more likely to experience intracerebral hemorrhage and poor clinical outcomes.^{17–19} ‘‘Uremic platelets’’ are described in end-stage renal disease,^{20,21} though not in milder renal impairment. Renal failure has also been associated with inflammation that may damage the small vessels, leading to increased permeability of the blood brain barrier over time.^{22–26}

Other Significant Variables

In the validation cohort, hyperglycemia and leukocytosis on admission were associated with increased risk of HT, improving the AUC of the HeRS score to predict HT. This will need to be validated in a unique cohort, but is consistent with prior studies. In the literature, hyperglycemia on presentation has been well associated with poor clinical outcomes.^{27–29} Leukocytosis may indicate an upregulated inflammatory state in the setting of ischemia, or a coexisting underlying medical disorder. We suspect that having large strokes with coexisting medical illness may be the greatest predictor of HT.

Although warfarin use on admission was associated with HT, anticoagulation while hospitalized did not significantly increase risk. This may reflect that the majority of our patients were anticoagulated, yielding low power to detect an effect. Marsh et al⁶ and Flaherty et al³⁰ have previously reported a trend toward more severe, symptomatic hemorrhages in those who are anticoagulated, which we did not see in this cohort, likely also because the majority of both symptomatic and asymptomatic hemorrhages were on anticoagulation. However, we did find that a more intense degree of anticoagulation (higher INR and pTTr values) was more likely to result in a hemorrhage that was symptomatic and more severe. Therefore, an alternative explanation is that anticoagulation does not necessarily cause bleeding, but rather increases the likelihood

TABLE 4. Hemorrhages Classified by Severity.⁶

	Symptomatic (n = 19*)	Asymptomatic (n = 56)	P-Value	Severe (PH) (n = 19)	Mild (HI) (n = 56)	P-Value
On warfarin on admission, %	42	17	0.024	32	19	0.253
Anticoagulated in the hospital, %	84	84	0.953	79	85	0.528
INR, mean	1.34	1.19	0.117	1.32	1.20	0.249
aPTTr, mean	1.39	1.02	0.015	1.12	1.10	0.934
Infarct volume (cc), mean	65.4	82.1	0.397	91.3	74.2	0.391
NIHSS (points), mean	9	12	0.075	11	12	0.576

aPTTr = activated partial thromboplastin time, HI = hemorrhagic infarction, INR = international normalized ratio, PH = parenchymal hematoma.
*The group of 19 patients with symptomatic hemorrhage was not entirely identical to that with severe hemorrhage.

that the hemorrhage will be clinically evident. Interestingly, in the literature, warfarin has been associated with larger volumes and higher rates of expansion of intracerebral hemorrhage irrespective of INR and aPTTr values.²⁸ One explanation consistent with both findings is that those presenting on warfarin tend to have atrial fibrillation as their indication for anticoagulation, and atrial fibrillation is associated with larger infarct volumes.³¹ Indeed, patients presenting on warfarin had, on average, 26 cc larger infarcts than those not on warfarin at admission ($P=0.023$). We did not find that larger infarct volumes or higher NIHSS scores were associated with increased likelihood of symptomatic or severe hemorrhage; however, the averages were quite high for both groups and given the small sample size it is likely that we were not adequately powered to find such a difference within the group who bled.

Our study has several limitations. Because of the high acuity of our patient population, not all were able to undergo MRI, and volume measurement is not as precise using CT due to less discrete borders of ischemia. Additionally, we chose to follow patients only to hospital discharge. However, our purpose was to design a tool to aid in clinical management in the acute setting, and the highest rate of HT occurs in the days immediately following stroke.^{2–4} Finally, we caution that our reported predictive values apply only to our particular cohort—a population likely at high overall risk of HT given the number of medical comorbidities and cardioembolic strokes. Our score would likely have different predictive value in other cohorts, though the sensitivities and specificities would remain unchanged.

Importantly, we chose to include asymptomatic hemorrhages in our primary outcome measure. According to European Cooperative Acute Stroke Study, only severe hemorrhages (PH2) were shown to affect clinical outcome;³² however, our prior data suggest that anticoagulation results in larger, more severe hemorrhages.⁶ Therefore, given the potential for worsening of hemorrhage with anticoagulation, we feel it is important to have a reasonable estimate of the risk for all forms of intracerebral bleeding when making decisions regarding clinical management.

Even with these limitations, our data strongly suggest that age, infarct volume, and eGFR are useful predictors of HT. The HeRS score provides a valid calculation of hemorrhage risk for patients with acute ischemic stroke and an indication for anticoagulation. Determination of a specific cut-off point, above which anticoagulation should not be considered, is difficult, as the projected rate of HT is only 1 factor in the decision of whether or not to anticoagulate. We advocate instead that this

score be used to help quantify risk for HT in those who must be on an anticoagulant acutely (ie, the patient with a mechanical valve where the daily risk of recurrent embolization is high), and used to guide therapeutic agent of choice, frequency of subsequent monitoring, and how best to counsel families on complication risk.

CONCLUSIONS

The HeRS score is a valid predictor of HT of ischemic stroke in patients with an indication for anticoagulation.

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