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A Model for Predicting Persistent Elevation of Factor VIII among Patients with Acute Ischemic Stroke

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Abstract

Background and Purpose—Elevated levels of coagulation factor VIII (FVIII) may persist independent of the acute-phase response; however, this relationship has not been investigated relative to acute ischemic stroke (AIS). We examined the frequency and predictors of persistently elevated FVIII in AIS patients.

Methods—AIS patients admitted between July 2008 and May 2014 with elevated baseline FVIII levels and repeat FVIII levels drawn for more than 7 days postdischarge were included. The patients were dichotomized by repeat FVIII level for univariate analysis at 150% and 200% activity thresholds. An adjusted model was developed to predict the likelihood of persistently elevated FVIII levels.

Results—Among 1616 AIS cases, 98 patients with elevated baseline FVIII had repeat FVIII levels. Persistent FVIII elevation was found in more than 75% of patients. At the 150% threshold, the prediction score ranged from 0 to 7 and included black race, female sex, prior stroke, hyperlipidemia, smoking, baseline FVIII > 200%, and baseline von Willebrand factor (vWF) level greater than 200%. At the 200% threshold, the prediction score ranged from 0–5 and included female sex, prior stroke, diabetes mellitus, baseline FVIII level greater 200%, and baseline vWF level greater than 200%. For each 1-point increase in score, the odds of persistent FVIII at both the 150% threshold (odds ratio [OR] = 10.4, 95% confidence interval [CI] 1.63–66.9, $P = .0134$) and 200% threshold (OR = 10.2, 95% CI 1.82–57.5, $P = .0083$) increased 10 times.

Conclusion—Because an elevated FVIII level confers increased stroke risk, our model for anticipating a persistently elevated FVIII level may identify patients at high risk for recurrent stroke. FVIII may be a target for secondary stroke prevention.

Keywords

Ischemic stroke; blood coagulation; biomarker; thrombosis; factor VIII

Introduction

Factor VIII (FVIII), an important cofactor within the coagulation cascade, is activated by thrombin in response to injury. FVIII functions in both the intrinsic and extrinsic clotting pathways through the activation of other clotting factors. Prior research has illustrated an association between FVIII elevation and increased risk of venous thrombosis and recurrent thromboembolic events.^{1–4} Additionally, elevated FVIII is an independent risk factor for acute ischemic stroke (AIS) and coronary artery disease.^{1,5,6}

Recent studies have provided evidence for the association between elevated FVIII levels and worse patient outcomes following ischemic stroke, including recurrent stroke.¹ In the context of ischemic stroke, elevation of FVIII is thought to be a result of the local inflammation produced during the acute phase of stroke.^{1,7} However, recent studies have demonstrated that elevated levels of FVIII may persist independent of the acute-phase response in the setting of venous thromboembolism.⁸ Persistent elevation of FVIII has not been investigated in the context of AIS.

Given the body of evidence implicating FVIII elevation as a risk factor for ischemic stroke, the ability to identify patients at risk for persistent FVIII elevation may be useful in reducing the incidence of recurrent stroke and improving stroke outcomes, if the optimal antithrombotic treatment were known. In this study, we investigated characteristics of AIS patients with initially elevated FVIII levels and examined which patient characteristics were associated with FVIII levels remaining elevated over time. To our knowledge, this is the first study to develop a score that predicts the odds of FVIII remaining persistently elevated rather than resolving after the acute phase of stroke.

Methods

Study Setting and Inclusion/Exclusion Criteria

Consecutive patients who presented to the Stroke Service at Tulane University Medical Center with AIS between July 2008 and May 2014 were identified from our prospective stroke registry.⁹ Patients were excluded if they had a history of coagulopathy, were younger than 18 years of age, did not have initial FVIII levels obtained during stroke admission, or did not have elevated FVIII levels (FVIII > 150%) during stroke admission. Additionally, only patients who completed a follow-up visit and had a repeat FVIII level obtained more than 7 days postadmission were included.¹⁰ Our institutional review board approved this study.

Our data were abstracted from our stroke registry, which was recorded before generation of this research question. Certified examiners determined all National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale scores. Trained researchers collected follow-up FVIII dates, times, and levels via retrospective chart review and coded the patients as having normal or elevated follow-up FVIII levels based on the laboratory-defined 150% and 200% thresholds.

The primary outcome of interest for our study was a comparison of FVIII elevation at baseline and follow-up. At our hospital, the FVIII level is part of a laboratory panel aimed at assessing arterial hypercoagulability that is ordered at the discretion of the treating physician upon initial assessment, generally when no other obvious cause of stroke is identified. Blood samples to determine repeat FVIII levels were collected at the next point of contact with the patient after hospital discharge, typically at the 90-day follow-up appointment. All laboratory assessments were performed in the context of routine clinical care; therefore, the repeat level was only measured in patients with elevated baseline level and only among those who returned for follow-up.

FVIII levels were measured at the on-site coagulation laboratory using spun plasma on the Siemens BCS XP instrument, a validated optical chromogenic method of detection. The laboratory reference range is 50%–150% with FVIII levels greater than 150% classified as elevated and those greater than 200% classified as severely elevated. In the present study, all other thresholds used for laboratory values were based on the laboratory reference ranges.

The patients were divided into 2 groups for statistical analysis: those whose FVIII levels were elevated at baseline but resolved to normal levels at the time of follow-up (transient FVIII elevation) and those whose FVIII levels remained elevated from baseline to follow-up (persistent FVIII elevation).

Statistics

We analyzed whether patients in these groups differed significantly in baseline and clinical variables at both the 150% and 200% laboratory reference thresholds. Pearson's chi-square or Fisher's exact test were used to assess categorical data, where appropriate. Wilcoxon's rank-sum test was used to assess continuous data.¹¹

Univariate logistic regression was used to assess the association between baseline characteristics and persistently elevated FVIII to establish which variables ($P < .2$) should be considered in the development of an elevated FVIII prediction score. All variables that met the P value of .2 or lower were evaluated for the final prediction model using logistic regression models. Model performance was assessed using the c -statistic, corrected for optimism. To correct for optimism, reduce bias, and internally validate the model, we calculated the estimated decrease in the c -statistic that would be expected in an independent dataset using the .632 bootstrap method.¹² This option was chosen over the traditional split-sample modeling because the bootstrap resampling technique has been shown to reduce bias and produce a stable and efficient estimate of predictive accuracy when compared to other methods.¹² For the present study, we created 100 datasets through bootstrap sampling with replacement. The models were fit in each dataset and the average difference in the c -statistic

between the bootstrap dataset (the derivation dataset) and the original dataset (the validation dataset). This value represents the expected optimism in the c -statistic calculated in this study. The points assigned to the variables in the score were assigned based on the beta coefficients from the logistic regression models. A cut-point of the elevated FVIII prediction model was established based on the sensitivity and specificity of the dichotomized score in predicting which patients will remain elevated. All statistical analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC) at a nondirectional alpha of .05.

Results

Among the 1616 AIS patients in our stroke registry, 372 (23.0%) patients had initial FVIII levels obtained at baseline and 266 patients classified as having any elevation in the FVIII level (>150% or higher). Compared to patients who did not have FVIII levels obtained, those with FVIII levels were younger (median age 54 years versus 66 years, $P < .0001$) and had lower frequency of a history of hypertension (74.01% versus 80.20%, $P = .0074$) and atrial fibrillation (4.24% versus 13.07%, $P < .0001$). No significant differences were found with respect to proportion of black race, history of prior stroke, diabetes mellitus, active smoker, and daily alcohol use in tested versus untested patients. Median baseline NIHSS scores were similar in the groups.

Of those with initially elevated FVIII levels, approximately 50.7% presented to our clinic for their standard follow-up appointment. Of those presenting for follow-up, 81.6% had repeat FVIII measurements obtained at follow-up. There was no statistically significant difference between groups in relation to time between baseline and follow-up FVIII measurements (median 96 days in the persistent FVIII elevation group versus 76 days in the transient FVIII elevation group, $P = .5400$). However, patients with baseline FVIII levels greater than 200% were twice as likely to have persistently elevated FVIII levels at the time of follow-up (relative risk = 1.78).

Persistent Elevation Compared to Transient Elevation at 150% threshold

Of the 98 patients with elevated FVIII levels greater than 150% at baseline, 81 (82.7%) had persistent elevation at follow-up. The patients with persistent elevation were older (median age 54 versus 45, $P = .0023$) and more frequently female (65.4% versus 35.3%, $P = .0210$) as compared to those with transient elevation (Table 1). In relation to past medical history, the patients with persistently elevated FVIII levels more frequently had a history of prior stroke (44.4% versus 17.7%, $P = .0266$), diabetes (41.9% versus 11.8%, $P = .0128$), hypertension (75.3% versus 47.1%, $P = .0203$), and hyperlipidemia (41.3% versus 17.7%, $P = .0425$) as compared to those with transient elevation. No significant differences were identified between groups according to the NIHSS score at baseline (median 5 versus 5, $P = .2500$).

With respect to baseline laboratory values, the patients in the persistently elevated group differed significantly according to HbA1C (median 6.0 versus 5.8, $P = .0393$) and von Willebrand factor (vWF) levels (median 239 versus 147, $P = .0242$) as compared to those in the transient elevation group. Furthermore, patients with persistent elevation more frequently had elevated C-reactive protein (CRP) levels (86.1% versus 44.4%, $P = .0149$) and elevated

erythrocyte sedimentation rate (ESR) levels (54.7% versus 15.4%, $P = .0084$) as compared to those with transient elevation.

After identifying significant differences in baseline characteristics, a model was designed to assess which characteristics of patients with elevated FVIII levels greater than 150% at baseline were associated with persistently elevated FVIII levels. The scoring model ranged from 0 to 7, with 1 point assigned to each of the following criteria: black race, female sex, history of stroke, hyperlipidemia, current smoker, baseline FVIII level greater than 200%, and baseline vWF level greater than 200%. According to this model, for every 1-point increase in the score, an individual has 10-fold increased odds of persistently elevated FVIII levels after their stroke event (odds ratio = 10.43, 95% confidence interval 1.63–66.9, $P = .0134$). This model was predictive of persistent elevation of FVIII with an area under the curve (AUC) of .950 (Fig 1). After adjusting for optimism due to internal validation, the AUC for the model was .868. The distribution of the prediction score with respect to transiently versus persistently elevated FVIII levels is displayed in Figure 2.

Persistent Elevation Compared to Transient Elevation at 200% threshold

Of the 70 patients with elevated FVIII levels greater than 200% at baseline, 53 (75.7%) patients exhibited persistent FVIII elevation at the time of follow-up. The patients with persistently elevated FVIII were older (median age 52 versus 46, $P = .0218$) and more frequently female (71.7% versus 35.3%, $P = .0069$) as compared to those with transient elevation (Table 2). In relation to past medical history, the patients in the persistently elevated group more frequently exhibited history of stroke (52.8% versus 17.7%, $P = .0086$), diabetes (45.3% versus 11.8%, $P = .0095$), and hypertension (83.0% versus 52.9%, $P = .0119$) as compared to those in the transient elevation group. No statistically significant differences were detected between groups according to the NIHSS score at baseline (median 6 versus 5, $P = .1400$). With respect to laboratory values, the patients also differed according to HbA1c (median value 6.1 versus 5.4, $P = .0433$) and vWF (median value 271.0 versus 184.0, $P = .0222$) levels.

After identifying significant differences in baseline characteristics, a model was designed to assess which characteristics in patients with elevated FVIII levels greater than 200% at baseline were associated with persistently elevated FVIII levels. The scoring model ranged between 0 and 5, with 1 point assigned to each of the following criteria: female sex, history of stroke, diabetes mellitus, baseline FVIII level greater than 200%, and baseline vWF level greater than 200%. According to this model, for every 1-point increase in the score, an individual has 10-fold increased odds of persistently elevated FVIII after their stroke event (odds ratio = 10.2, 95% confidence interval 1.82–57.5, $P = .0083$). This model was predictive of persistent elevation of FVIII with an AUC of .879 (Fig 1). After adjusting for optimism due to internal validation, the AUC for the model was .786. The distribution of the prediction score with respect to transiently versus persistently elevated FVIII levels is displayed in Figure 3.

Discussion

Given that elevated FVIII level has been previously associated with increased risk of stroke and baseline stroke severity, the ability to anticipate which patients will exhibit persistent elevation based on their baseline characteristics may prove influential in the prevention of secondary stroke and further optimization of AIS patient care.^{1,13} This study proposes a novel model by which clinicians can use patients' baseline characteristics to predict which patients will have persistent elevation of FVIII post-AIS.

In our study, the persistently elevated group did not differ from the transiently elevated group according to time between baseline and follow-up FVIII measurements. Therefore, the results of the present study may be interpreted independent of the time between baseline and follow-up evaluation. Furthermore, given that FVIII has a median half-life of 11.8 hours and our repeat FVIII levels were obtained for a minimum of 7 days post-AIS, we anticipated a return of elevated FVIII levels to within normal range if FVIII is indeed an acute-phase response to stroke, as previous research has suggested.^{1,7,10} However, in our sample, more than 75% of patients experienced persistently elevated FVIII levels at both the 150% and 200% thresholds. This finding suggests that persistent elevation is not rare among patients who present with AIS and elevated FVIII levels at our center and questions whether FVIII is strictly an acute-phase reactant in AIS. We do not know, however, the frequency of elevated FVIII levels and then persistently elevated FVIII levels in patients who were not tested, because levels were not ordered uniformly. The patients tested were younger than those who were not tested and less frequently had pre-existing hypertension and atrial fibrillation. The high proportion of FVIII elevation in our sample suggests either a high level of accuracy in the determination of who to test for FVIII by treating physicians, a very high frequency of elevated FVIII in the acute setting of ischemic stroke, or a very high frequency of constitutional elevation of FVIII in our population. However, even if all of our untested patients were tested and had normal FVIII levels, more than 15% of all AIS patients would have had elevated FVIII levels. Therefore, a prospective trial, in which all ischemic stroke patients have the FVIII measured, and in which all elevated values are repeated remote from the acute phase of stroke, would be needed to confirm the clinical value of measuring FVIII levels in this population.

Interestingly, in our study population at both the 150% and 200% thresholds, persistent elevation was associated with a history of diabetes and elevated HbA1C at baseline with the highest proportion being in the persistently elevated groups. The association between diabetes and elevated FVIII has been well documented in connection with vascular complications.^{13,14} Our research provides unique support of this relationship and suggests that the association between persistent FVIII elevation and diabetes warrants further investigation as it may have unique implications for determining risk in patients with AIS.

Patients with persistently elevated FVIII levels at the 150% threshold had elevated CRP and ESR levels as compared to those in the transient elevation group. If the concurrent elevation in inflammatory markers and FVIII were due to an acute-phase response, we would have expected resolution of elevated FVIII levels in a higher proportion of patients when screened remote from the index stroke. This finding supports previous research that an elevated FVIII

level is more likely in patients with chronic inflammatory states, but has helped to clarify that this association is likely not exclusive to the acute phase of stroke.^{4,13} Given that more than 80% of the patients with elevated CRP and/or ESR levels exhibited persistent FVIII elevation, a relationship may exist between the acute-phase response of stroke and the presentation of persistent elevation.

At both the 150% and 200% thresholds, over half of the patients with persistently elevated FVIII levels had a history of prior stroke. This association supports the idea that elevation of FVIII may persist beyond the acute phase of stroke and may play a role as both a risk factor for incident strokes and a predictor of subsequent strokes. The ability to identify patients who are at greater likelihood for experiencing persistent elevation of FVIII could prove useful in the prevention of future strokes. Furthermore, stroke prevention efforts might offer a particular benefit for patients with elevated FVIII levels given recent evidence for the association between elevated FVIII levels and worse patient outcomes after AIS.¹

At the 150% threshold, our final prediction model included black race, female sex, history of stroke, hyperlipidemia, smoking, baseline FVIII level greater than 200%, and baseline vWF level greater than 200%. At the 200% threshold, our final prediction model included female sex, history of stroke, diabetes mellitus, baseline FVIII level greater than 200%, and baseline vWF level greater than 200%. The factors included in both models have all been independently linked with increased risk for stroke and, according to the results of this study, may be useful in developing patient risk profiles for predicting persistent elevation of FVIII.¹⁵ The differences in the models demonstrate that certain patient characteristics contribute to patient risk in different ways at each threshold.

The present study is limited by a retrospective cross-sectional design and relatively small sample size. Testing of FVIII was not random or universal, which risks selection bias and limits generalizability to AIS patients with suspected hypercoagulable states. Given that our current study design examines FVIII levels obtained after stroke onset, we are unable to determine whether persistent elevation of FVIII is secondary to stroke or is constitutional among these patients. With consideration for these limitations, we report only our observations and acknowledge that prospective studies will be required to clarify this complex relationship.

Conclusion

Our study is the first to explore persistent elevation of FVIII and propose a model by which to predict which patients will have persistent FVIII elevation in the setting of AIS. Our findings may help to establish the usefulness of FVIII levels as a tool to predict and subsequently reduce patient risk for adverse outcomes, ideally before the clinical event. Our study results need to be validated in a prospective study to determine if FVIII elevation exists before stroke or is a product of the clinical course of the disease. Following the determination of temporality, a clinical trial aimed at determining the most appropriate prevention methods (antiplatelet versus anticoagulant) to manage FVIII elevation would be appropriate.

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Figure 1. AUC for prediction models at 150% and 200% thresholds. Abbreviation: AUC, area under the curve.

Figure 2.
Prediction score distribution for predicting persistently elevated FVIII at the 150% threshold. Abbreviation: FVIII, factor VIII.

Figure 3. Prediction score distribution for predicting persistently elevated FVIII at the 200% threshold. Abbreviation: FVIII, factor VIII.

Table 1

Demographic and baseline characteristics of patients with serum FVIII less than 150%

Characteristics	Transiently elevated FVIII 17 (17.4%)	Persistently elevated FVIII 81 (82.7%)	P values
Age	45 (23–61)	54 (28–87)	.0023
Black race	11 (64.7%)	66 (81.5%)	.1600
Female sex	6 (35.3%)	53 (65.4%)	.0210
History of stroke	3 (17.7%)	36 (44.4%)	.0266
Hyperlipidemia	3 (17.7%)	33 (41.3%)	.0425
History of diabetes	2 (11.8%)	34 (41.9%)	.0128
History of hypertension	8 (47.1%)	61 (75.3%)	.0203
History of carotid stenosis	0 (.0%)	5 (6.2%)	.3800
History of atrial fibrillation	0 (.0%)	6 (7.4%)	.3100
Coronary artery disease	2 (11.8%)	16 (19.8%)	.2200
Active smoker	3 (17.7%)	27 (33.3%)	.1100
NIHSS score at baseline	5 (2–21)	5 (0–29)	.2500
Glucose on admission	112.0 (85.0–272.0)	117.0 (66.0–831.0)	.7200
HbA1c	5.8 (4.8–10.2)	6.0 (3.5–13.9)	.0393
Baseline creatinine	1.1 (.6–3.0)	1.2 (.3–7.0)	.8700
PT	10.6 (9.8–18.4)	10.7 (9.6–12.7)	.6300
INR	1.0 (.9–1.9)	1.0 (.8–1.3)	.3900
PTT	23.9 (16.7–34.2)	23.7 (17.0–79.1)	.6000
White blood cell count	8.0 (4.0–14.0)	8.7 (3.6–25.3)	.8400
Hematocrit	39.5 (27.5–49.0)	37.5 (23.3–49.0)	.1900
Platelets	255.0 (78.0–423.0)	246.0 (94.0–541.0)	.7000
Homocysteine abnormal	2.0 (11.8%)	8.0 (11.8%)	.3200
von Willebrand factor	147.0 (109.0–275.0)	239.0 (105.0–569.0)	.0242
DVV	40.3 (32.5–66.3)	37.3 (24.2–123.0)	.0900
Lipoprotein A	14.0 (2.0–157.0)	23.5 (1.0–189.0)	.2700
Fibrinogen	301.0 (72.0–528.0)	410.0 (225.0–685.0)	.1600
Elevated C-reactive protein	4.0 (44.4%)	31.0 (86.1%)	.0149
Elevated erythrocyte sedimentation rate	2.0 (15.4%)	35.0 (54.7%)	.0084

Abbreviations: DVV: Dilute Viper Venom test; FVIII, factor VIII; HbA1c: Glycated Hemoglobin or Hemoglobin A1c; INR: International Normalized Ratio; NIHSS, National Institutes of Health Stroke Scale; PT: Prothrombin Time; PTT: Partial Thromboplastin Time.

Table 2

Demographic and baseline characteristics of patients with serum FVIII greater than 200%

Characteristics	Transiently elevated FVIII	Persistently elevated FVIII	P values
	17 (24.3%)	53 (75.7%)	
Age	46 (35–77)	52 (28–83)	.0218
Black race	11 (64.7%)	43 (81.1%)	.2500
Sex	6 (35.3%)	38 (71.7%)	.0069
History of stroke	3 (17.7%)	28 (52.8%)	.0086
Hyperlipidemia	4 (25.0%)	23 (43.4%)	.1000
History of diabetes	2 (11.8%)	24 (45.3%)	.0095
History of hypertension	9 (52.9%)	44 (83.0%)	.0119
History of carotid stenosis	1 (5.9%)	4 (7.6%)	.4100
History of atrial fibrillation	0 (.0%)	4 (7.8%)	.3200
Coronary artery disease	2 (11.8%)	10 (18.9%)	.2500
Active smoker	4 (23.5%)	15 (28.3%)	.2300
NIHSS score at baseline	6 (0–29)	5 (0–29)	.1400
Glucose on admission	123.0 (85.0–278.0)	126.0 (66.0–831.0)	.4600
HbA1c	5.4 (4.8–11.0)	6.1 (3.5–13.9)	.0433
Baseline creatinine	1.1 (.9–7.0)	1.1 (.3–3.1)	.2300
PT	10.6 (9.8–12.7)	10.6 (9.6–12.4)	.5200
INR	1.0 (.9–1.3)	1.0 (.8–1.2)	.2400
PTT	23.1 (16.7–26.7)	23.5 (17.0–79.1)	.3400
White blood cell count	8.0 (3.7–23.6)	8.6 (3.6–25.3)	.6300
Hematocrit	39.0 (26.2–49.0)	37.0 (23.3–47.7)	.5600
Platelets	230.0 (78.0–524.0)	244.0 (94.0–531.0)	.8500
Homocysteine abnormal	3.0 (18.8%)	4.0 (8.9%)	.1900
von Willebrand factor	184.0 (146.0–316.0)	271.0 (114.0–567.0)	.0222
DVV	38.0 (29.4–66.3)	37.3 (24.2–75.6)	.6800
Lipoprotein A	15.5 (2.0–189.0)	27.0 (1.0–132.0)	.4200
Fibrinogen	336.0 (295.0–528.0)	429.0 (225.0–685.0)	.5600
Elevated C-reactive protein	8.0 (88.9%)	17.0 (80.9%)	.3800
Elevated erythrocyte sedimentation rate	4.0 (30.8%)	22.0 (55.0%)	.0800

Abbreviations: DVV: Dilute Viper Venom test; FVIII, factor VIII; HbA1c: Glycated Hemoglobin or Hemoglobin A1c; INR: International Normalized Ratio; NIHSS, National Institutes of Health Stroke Scale; PT: Prothrombin Time; PTT: Partial Thromboplastin Time.