Symptomatic Intracerebral Hemorrhage after Intravenous Thrombolysis: Predictive Factors and Validation of Prediction Models

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Objective: Thrombolytic therapy with intravenous alteplase (IV-rtPA) has a known risk of symptomatic intracerebral hemorrhage (sICH). We aim to identify factors with a significant association with the development of sICH post-IV-rtPA. We also aim to perform an external validation of sICH predicting scores in our patient population. *Material and Methods:* We performed a retrospective chart review of patients who received IV-rtPA at our tertiary care hospital. We excluded patients who underwent mechanical thrombectomy. We analyzed various factors recorded at presentation such as presenting mean arterial pressure (MAP), blood glucose, National Institutes of Health Stroke Scale (NIHSS) score, verify Aspirin, verify Plavix, age, sex, platelet count, international normalized ratio, prothrombin time, partial thromboplastin time, hemoglobin A1c, low-density lipoprotein, onset to treatment time, weight, sex, and early infarct signs on computed tomography (CT) head and compared them between sICH and non-sICH groups. For validation of sICH scores, we used documented variables to calculate the following scores for each patient: stroke prognostication using age and NIH stroke scale-100 (SPAN-100), DRAGON, CUCCHIARA, hemorrhage after thrombolysis (HAT), SEDAN, totaled health risks in vascular events, and safe implementation of thrombolysis in stroke-symptomatic intracerebral hemorrhage. *Results:* sICH rate in our cohort of 89 patients was 5.62% according to the European-Australasian Cooperative Acute Stroke Study-II (ECASS-II) criteria and 7.86% according to the National Institute of Neurological Disorders and Stroke (NINDS) criteria. In the multivariate regression analysis, MAP (95% CI, .001-.01; *P* .002), blood glucose greater than or equal to 185 mg/dL (95% CI, .12-.45; *P* .001) and presence of early infarct signs (95% CI, .06-.25; *P* .002) had a significant association with the development of sICH with the ECASS-II definition of sICH post-IV-rtPA, whereas, only MAP (95% CI, 1.01-1.18; *P* .025) and verify Aspirin less than 500 (95% CI, .01-.80; *P* .032) had a significant association with the development of sICH with the NINDS definition of sICH post-IV-rtPA. Our study found that HAT (95% CI, .58-.96; *P* .044) and DRAGON (95% CI, .61-.96; *P* .012) scores had the highest area under the curve (AUC) with respect to ECASS-II and NINDS criteria of sICH, respectively. *Conclusions:* We found that presenting MAP, presence of early infarct signs on CT Head and blood glucose greater than or equal to 185 mg/dL upon a patient's presentation have a significant association with sICH post-IV-rtPA when the ECASS-II definition was used, while presenting MAP and verify Aspirin less than 500 upon a patient's presentation have a significant association with sICH post-IV-rtPA when the NINDS definition was used. Our study found that HAT and DRAGON scores had the highest AUC, and they were the most valid in predicting the development of sICH in our independent

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cohort. Patients with these risk factors should receive more intensive neurological monitoring.

Key Words: Acute stroke outcome—stroke emergency cerebrovascular care—tissue plasminogen activator (t-PA)—symptomatic intracerebral hemorrhage (sICH)—ischemic stroke—stroke—thrombolysis

Introduction

In the United States, stroke affects nearly 795,000 people and is one of the leading cause of morbidity and mortality.[1,2] Approximately 80%-87% of strokes are ischemic in nature.[1] Intravenous alteplase (IV-rtPA) is the standard of care for qualifying patients with an acute ischemic stroke.[3] Even though the overall incidence of stroke has been declining, more eligible patients are receiving IV-rtPA.[4-6] Symptomatic intracerebral hemorrhage (sICH) is a feared complication of IV-rtPA.[7-9] In 1995, the National Institute of Neurological Disorders and Stroke (NINDS) study showed better neurological outcomes in patients who receive IV-rtPA within 3 hours at 90 days.[10] The original study also reported an overall risk of intracranial hemorrhage (ICH) in 6.4% of the patients, compared to .6% in the placebo group.[7,10] Only 75% of patients with a suspected acute ischemic stroke, who present within the window receive IV-rtPA.[4] Establishment of risk factors associated with sICH would enable closer neurological monitoring of patients at a higher risk.[11]

Considering the high overall mortality and morbidity of ICH, it is essential to identify patients at a higher risk of developing sICH after IV-rtPA.[12] Various factors such as hypertension, elevated blood glucose, age, and higher National Institutes of Health Stroke Scale (NIHSS) score at presentation have been associated with a higher risk of development of sICH.[13-16] Through this study, we aim to identify the variables associated with the development of sICH after IV-rtPA in our tertiary care hospital.

Predictive tools can help clinicians test the safety of IV-rtPA in eligible patients.[12,17] These predictive tools in the form of computational scores consider the patient's variables at presentation to predict the likelihood of development of sICH after IV-rtPA.[18-23] Some better-known scores include: stroke prognostication using age and NIH stroke scale-100 (SPAN-100)[18], DRAGON[19], CUCCHIARA [20], hemorrhage after thrombolysis (HAT)[21], totaled health risks in vascular events (THRIVE)[16], blood sugar, early infarct signs, [hyper]dense cerebral artery sign, age (SEDAN)[22], and safe implementation of thrombolysis in stroke-symptomatic intracerebral hemorrhage (SITS-ICH) [23]. We aim to perform an external validation of various sICH predicting scores in our cohort.

Material and Methods

We performed a retrospective chart review of patients who received IV-rtPA from 7/1/2014 to 3/31/2018 at University Hospital. All eligible patients were given IV-rtPA after a computed tomography (CT) head and had a confirmation of a new stroke on follow-up neuroimaging during the course of hospitalization. Patients who underwent mechanical thrombectomy or hemicraniectomy were excluded. We used 2 different definitions of sICH for our study: European-Australasian Cooperative Acute Stroke Study-II (ECASS-II)'s definition of sICH, that is, an ICH that causes an increase in NIHSS score by greater than or equal to 4 points within 7 days post-IV-rtPA and the NINDS's definition of sICH, that is, an ICH that causes any neurological worsening post-IV-rtPA. We analyzed various factors recorded upon a patient's presentation such as systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), blood glucose, NIHSS score, verify Aspirin, verify Plavix, presence of early infarct signs on CT head, symptom duration, age, sex, platelet count, international normalized ratio (INR), prothrombin time (PT), partial thromboplastin time (PTT), hemoglobin A1c (Hb A1C), low-density lipoprotein (LDL), onset to treatment time, presence of atrial fibrillation (AF) and weight and compared them between sICH and non-sICH groups. The primary outcome was the development of sICH after IV-rtPA.

Presenting SBP, DBP, MAP, blood glucose, NIHSS score, verify Aspirin, verify Plavix, age, platelet count, INR, PT, PTT, Hb A1C, LDL, onset to treatment time, and weight were considered as continuous variables with presence of ICH, sex, AF and early infarct signs on CTH were considered as categorical variables. Because blood glucose and verify Aspirin levels were only associated with outcome for patients at levels of greater than or equal to 185 mg/dL and less than 500, respectively, they were also analyzed as dichotomous categorical variables with cutoff points at greater than or equal to 185 mg/dL (for blood glucose) and less than 500 (for verify Aspirin), respectively. Student's *t* test was used to compare continuous variables while chi-square was used to compare categorical variables. Statistical analysis was conducted using Microsoft Excel (2016) and IBM SPSS (version 23). The *P* value of less than .05 was considered statistically significant.

After univariable analyses, a multivariate analysis using binary logistic regression was performed to determine variables with a significant association with the development of sICH post-IV-rtPA. For multivariable analysis, only variables with a significant association with the development of sICH post-IV-rtPA in the univariable analysis were included as predictors. For multivariable analysis, MAP

was used instead of SBP and DBP as one predictor, as MAP incorporates the values of both SBP and DBP.

For validation of sICH scores, documented variables were used to calculate the following scores for each patient: SPAN-100, DRAGON, CUCCHIARA, HAT, SEDAN, THRIVE, and SITS-ICH. A receiver operating characteristic (ROC) curve was obtained by plotting sensitivity against false positive rate (1-specificity). An area under the curve (AUC) was calculated using a Riemann sum.

Results

We screened 224 patients, who were given IV-rtPA at University Hospital, Newark, New Jersey, from July 2014 to March 2018. Fifty-one patients had endovascular mechanical thrombectomy or hemicraniectomy and were excluded. Eighty-nine patients met our inclusion criteria. Among them, 61.80% had confirmation of a new stroke on a follow-up MRI, and 38.20% had evidence of a new stroke on a follow-up CTH. 48 (53.93%) patients were male. Mean age of our cohort was 63.4 ± 14.42 years (range, 22-95 years).

First, we evaluated the association of various risk factors at presentation with the development of sICH after IV-rtPA according to the ECASS-II criteria. 5 (5.62%) patients in our cohort developed sICH according to the ECASS-II criteria. Mean age of patients with sICH was 70.2 ± 6.88 years (range, 61-80 years). There was only 1 death, and it was in the sICH group. Mean duration of IV-rtPA administration from the onset was with sICH was 153.4 ± 52.08 minutes. In the univariate analysis, there was no significant difference in the development of sICH with respect to several factors recorded upon a patient's presentation: age (95% CI, −20.43-6.08; *P* .285), gender (95% CI, .34-7.71; *P* .411), blood glucose (95% CI, −96.59-23.73; *P* .232), Hb A1C (95% CI, −1.85-1.73; *P* .947), LDL (95% CI, −43.53-38.82; *P* .91), hemoglobin (95% CI, −.73-2.49; *P* .279), platelet count (95% CI, −78.81-85.62; *P* .935), NIHSS score (95% CI, −7.80-2.47; *P* .304), verify Aspirin (95% CI, −36.71-122.83; *P* .285), verify Plavix (95% CI, −63.88-36.40; *P* .587), INR (95% CI, −.83-1.12; *P* .764), PT (95% CI, −5.82-8.03; *P* .752), PTT (95% CI, −.69-9.40; *P* .088), onset to treatment time (95% CI, −54.42-38.28; *P* .73), AF (95% CI, .19-7.59; *P* .595) and weight (95% CI, −18.24-16.98; *P* .944). There was a significant difference in the development of sICH with respect to several recorded upon a patient's presentation: SBP (95% CI, −60.44--19.21; *P* .004), DBP (95% CI, −56.06--5.72; *P* .001), MAP (95% CI, −55.20--15.51; *P* .001) and presence of early infarct signs (95% CI, 1.02-1.27; *P* .02). Blood glucose and verify Aspirin were also analyzed as dichotomous categorical variables with cutoff points at greater than or equal to 185 mg/dL (for blood glucose) and less than 500 (for verify Aspirin), respectively. Blood glucose greater than or equal to 185 mg/dL (95% CI, 2.06-98.35; *P* .013) and verify Aspirin < 500 (95% CI, 1.10-100.18; *P* .03) were significantly associated with the development of sICH after IV-rtPA. Even though we excluded the patients who underwent endovascular treatment in our study, we found that endovascular treatment was independently associated with the development of sICH (ECASS-II criteria) (OR, 3.57; 95% CI, 1.15-11.08; *P* .022). Univariate analysis showing a comparison of clinical profiles between ICH and non-ICH groups, according to the ECASS-II criteria is shown in Table 1. In the multivariate analysis, there was a significant difference in the development of sICH with respect to MAP (95% CI, .001-.01; *P* .002), blood glucose greater than or equal to 185 mg/dL (95% CI, .12-.45; *P* .001) and presence of early infarct signs (95% CI, .06-.25; *P* .002). Multivariate analysis showing variables with a significant association with the development of sICH according to the ECASS-II criteria is shown in Table 2.

ROC analysis showed that the AUC of the respective sICH scores according to the ECASS-II criteria were: HAT .769 (95% CI, .58-.96; *P* .044), DRAGON .701 (95% CI, .50-.91; *P* .132), SITS-ICH .655 (95% CI, .38-.93; *P* .247), CUCCHIARA .705 (95% CI, .47-.94; *P* .125), SPAN-100 .576 (95% CI, .29-.86; *P* .569), THRIVE .539 (95% CI, .41-.67; *P* .574), and SEDAN .617 (95% CI, .37-.86; *P* .383). ROC curves for our cohort, for respective sICH predictive scores is shown in Table 3. A bar graph comparing area under the receiver operating characteristic (AUROC) curves of respective sICH predictive scores in our cohort is shown in Figure 1.

Second, we evaluated the association of various risk factors at presentation with the development of sICH after IV-rtPA according to the NINDS criteria. 7 (7.86%) patients in our cohort developed sICH according to the NINDS criteria. Mean age of patients with sICH was 69.71 ± 7.11 years (range, 61-80 years). There was only 1 death, and it was in the sICH group. Mean duration of IV-rtPA administration from the onset was with sICH was 148.14 ± 49.63 minutes. In the univariate analysis, there was no significant difference in the development of sICH with respect to several recorded upon a patient's presentation: age (95% CI, −14.21-.56; *P* .067), gender (95% CI, .34-7.71; *P* .411), presence of early infarct signs (95% CI, .56-16.59; *P* .173), blood glucose (95% CI, −70.11-33.36; *P* .482), Hb A1C (95% CI, −1.60-1.35; *P* .868), LDL (95% CI, −48.11-19.67; *P* .407), hemoglobin (95% CI, −1.00-1.77; *P* .579), platelet count (95% CI, −61.52-79.02; *P* .806), NIHSS score (95% CI, −6.87-1.90; *P* .263), verify Plavix (95% CI, −48.32-37.83; *P* .809), INR (95% CI, −.72-.95; *P* .792), PT (95% CI, −5.07-6.77; *P* .776), PTT (95% CI, −11.93-17.45; *P* .71), onset to treatment time (95% CI, −42.23-37.11; *P* .898), AF (95% CI, −.54-12.30; *P* .207), and weight (95% CI, −19.27-10.80; *P* .577). There was a significant difference in the development of sICH with respect to several recorded upon a patient's presentation: SBP (95% CI, −56.06--28.70; *P* < .001), DBP (95% CI, −43.61--13.21; *P* < .001), MAP (95% CI, −47.57--21.58; *P* < .001), while

Table 1. *Univariate analysis of comparison of clinical profiles between ICH and non-ICH groups, according to the ECASS-II criteria*

Variables	Non-sICH	sICH	Confidence intervals with *P* values
Age (yrs)	63.03 ± 14.65	70.2 ± 6.88	95% CI, −20.43-6.08; *P* .285
Sex (male, %)	46 (54.76)	2 (40)	95% CI, .29-11.43; *P* .425
Blood glucose (mg/dL)	136.17 ± 66.51	172.6 ± 30.01	95% CI, −96.59-23.73; *P* .232
Blood glucose ≥185 mg/dL (yes, %)	**8 (9.52)**	**3 (60)**	**95% CI, 2.06-98.35; *P* .013**
SBP (mm Hg)	**161.57 ± 29.16**	**201.4 ± 15.21**	**95% CI, −60.44 - - 19.21; *P* .004**
DBP (mm Hg)	**93.01 ± 19.44**	**124.0 ± 18.37**	**95% CI, −56.06 - - 5.72; *P* .001**
MAP (mm Hg)	**114.45 ± 21.36**	**149.8 ± 14.58**	**95% CI, −55.20 - - 15.51; *P* .001**
Presence of early infarct signs (yes, %)	**37 (44.04)**	**5 (100)**	**95% CI, 1.02-1.27; *P* .02**
Hb A1C (%)	6.27 ± 1.75	6.32 ± 1.49	95% CI, −1.85-1.73; *P* .947
LDL (mg/dL)	110.64 ± 39.61	113 ± 47.55	95% CI, −43.53-38.82; *P* .91
Verify Aspirin*	554.46 ± 86.57	511.4 ± 83.53	95% CI, −36.71-122.83; *P* .285
Verify Aspirin < 500 (yes, %)*	**19 (25.68)**	**4 (80)**	**95% CI, 1.10-100.18; *P* .03**
Verify Plavix*	238.46 ± 55.31	252.2 ± 16.08	95% CI, −63.88-36.40; *P* .587
NIHSS score	9.13 ± 5.43	11.8 ± 7.19	95% CI, −7.80-2.47; *P* .304
Onset to treatment time (min)	145.33 ± 49.97	153.4 ± 52.08	95% CI, −54.42-38.28; *P* .73
INR	1.17 ± 1.09	1.02 ± .10	95% CI, −.83-1.12; *P* .764
PT (s)	14.54 ± 7.69	13.44 ± 1.32	95% CI, −5.82-8.03; *P* .752
PTT (s)	30.42 ± 19.08	26.06 ± 2.68	95% CI, −12.81-21.52; *P* .615
Weight (kg)	84.13-18.70	84.76 ± 23.93	95% CI, −18.24-16.98; *P* .944
Hemoglobin (g/dL)	13.52 ± 1.73	12.64 ± 1.79	95% CI, −.73-2.49; *P* .279
Platelet (×1000 μL)	237.20 ± 90.17	233.8 ± 61.59	95% CI, −78.81-85.62; *P* .935
Atrial fibrillation (yes, %)	30 (35.71)	2 (40.0)	95% CI, .19-7.59; *P* .595

Abbreviations: DBP, diastolic blood pressure; Hb A1C, hemoglobin A1c; INR, international normalized ratio; LDL, low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; PT, prothrombin time; PTT, partial thromboplastin time; SBP, systolic blood pressure; sICH, symptomatic intracerebral hemorrhage.

The significance of bold values are $P < 0.05$.

*Verify aspirin and plavix data were available for only 74 out of the 89 patients.

verify Aspirin (95% CI, .06-134.33; *P* .05) had a borderline significance. Blood glucose and verify Aspirin were also analyzed as dichotomous categorical variables with cutoff points at greater than or equal to 185 mg/dL (for blood glucose) and (for verify Aspirin), respectively. Blood glucose greater than or equal to 185 mg/dL (95% CI, 1.31-36.68; *P* .038) and verify Aspirin less than 500 (95% CI, 1.98-157.26; *P* .003) were significantly associated with the development of sICH after IV r-tPA. Univariate analysis showing a comparison of clinical profiles between ICH and non-ICH groups, according to the NINDS criteria is show in Table 4. In the multivariate analysis, there was a significant difference in the development of sICH with respect to MAP (95% CI, 1.01-1.18; *P* .025) and verify Aspirin less than 500 (95% CI, .01-.80; *P* .032). Multivariate analysis showing variables with a significant association with the development of sICH according to the NINDS criteria is show in Table 5.

Table 2. *Multivariate analysis showing variables with a significant association with the development of sICH according to the ECASS-II criteria*

Variables	Confidence intervals with *P* values
Presence of early infarct signs (yes, %)	**95% CI, .06-.25; *P* .002**
MAP (mm Hg)	**95% CI, .001-.01; *P* .002**
Verify Aspirin <500 (yes, %)	95% CI, −.06-.16; *P* .369
Blood glucose ≥185 mg/dL (yes, %)	**95% CI, .12-.45; *P* .001**

Abbreviations: MAP, mean arterial pressure; sICH, symptomatic intracerebral hemorrhage.

The significance of bold values are $P < 0.05$.

ROC analysis showed that the AUC of the respective sICH scores according to the NINDS criteria scores were: HAT .710 (95% CI, .49-.93; *P* .066), DRAGON .786 (95% CI, .61-.96; *P* .012), SITS-ICH .746 (95% CI, .52-.97; *P* .032), CUCCHIARA .730 (95% CI, .55-.91; *P* .044), SPAN-100 .547 (95% CI, .31-.78; *P* .681), THRIVE .543 (95% CI, .35-.74; *P* .688), and SEDAN .666 (95% CI, .47-.86; *P* .146). ROC curves for our cohort, for respective sICH predictive scores according to the NINDS criteria are shown in Table 6. A bar graph comparing area under the receiver operating characteristic (AUROC) curves of respective sICH predictive scores in our cohort is shown in Figure 2.

Discussion

Meta-analysis of 9 trials comparing placebo vs. IV-rtPA group showed a significant improvement in the IV-rtPA group (mRS ≤ 1) when given within 4.5 hours of

Table 3. *AUROC curves of respective sICH predictive scores according to the ECASS-II criteria in our cohort*

Scores	Variables	P	AUROC (95% CI)
HAT	DM/initial glucose, pre-IV-rtPA NIHHS, and early infarct signs on initial CTH	**.044**	**.769 (95% CI, .58-.96)**
DRAGON	Dense MCA sign/darly infarct on CT, prestroke mRS, glucose, onset of treatment time, and NIHSS	.132	.701 (95% CI, .50-.91)
SITS-ICH	NIHSS, SBP, glucose, weight, onset to treatment time, Aspirin or combined Aspirin and clopidogrel, and HTN	.247	.655 (95% CI, .38-.93)
CUCCHIARA	Age, NIHSS, glucose, and platelet count	.125	.705 (95% CI, .47-.94)
SPAN-100	Age and NIHSS	.569	.576 (95% CI, .29-.86)
SEDAN	NIHSS, SBP, glucose, body weight, stroke onset to treatment time, aspirin or combined aspirin and clopidogrel, and HTN	.383	.617 (95% CI, .37-.86)
THRIVE	Age, NIHSS, HTN, DM, and AF	.574	.539 (95% CI, .41-.67)

Abbreviations: AUROC, area under the receiver operating characteristic; HAT, hemorrhage after thrombolysis; SEDAN, blood sugar, early infarct signs, [hyper]dense cerebral artery sign, age; sICH, symptomatic intracerebral hemorrhage; SITS-ICH, safe implementation of thrombolysis in stroke-symptomatic intracerebral hemorrhage; SPAN-100, stroke prognostication using age and NIH stroke scale-100; THRIVE, totaled health risks in vascular events.

The significance of bold values are $P < 0.05$.

symptom onset in patients with an acute ischemic stroke.[24] Studies show that the benefits associated with the administration of IV-rtPA outweigh the risk associated with sICH.[15,25-27]

There are several definitions of sICH.[8,28] There is a disparity in the definitions of neurological decline, ICH, and the duration between IV-rtPA treatment and onset of ICH.[8] The NINDS study defined sICH as any neurological worsening within 36 hours of IV-rtPA administration, which is attributed to ICH verified on CTH or Magnetic Resonance Imaging (MRI).[10] Safe implementation of thrombolysis in stroke-monitoring study's (SITS-MOST) criteria defined sICH as local or remote parenchymal hemorrhage that occurs on the 22-36 hours post-IV-rtPA, which is associated with worsening of neurological examination by an increase in greater than or equal to 4 points of NIHSS score or death.[29] ECASS-II criteria defined sICH as ICH on imaging associated with an increase of greater than or equal to 4 points of NIHSS score on a neurological examination, within 7 days of intravenous thrombolysis.[30] There is a trend toward lower rates when sICH in studies that use SITS-MOST criteria compared to studies that used the NINDS criteria.[8] Prior studies have shown that the ECASS-II definition has the strongest correlation with the outcome at 3 months.[31] Several studies have found the ECASS-II definition to be more consistent.[32] We used both ECASS-II and NINDS definitions of sICH for our study. As expected, findings had a few differences. In the multivariate regression analysis, presence of early infarct signs on CT Head upon a patient's presentation, MAP and blood glucose greater than or equal to 185 mg/dL had a significant association with the development of sICH with the ECASS-II definition of sICH post-IV-rtPA, whereas, only MAP and verify Aspirin less than 500 had a significant association with the development of sICH with the NINDS definition of sICH post-IV-rtPA. The overall rate of sICH in our study is similar to larger studies.[8,33]

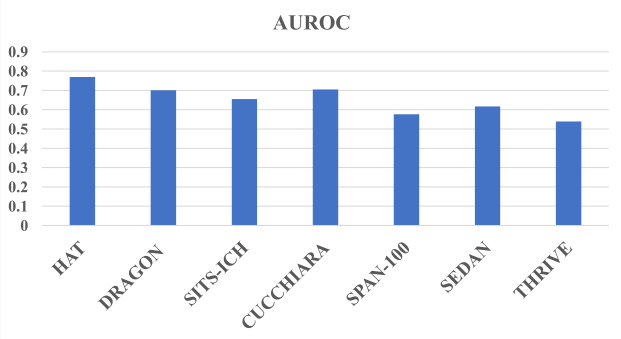

Figure 1. *Bar graph comparing AUROC curves of respective sICH predictive scores according to the ECASS-II criteria in our cohort. Abbreviations: AUROC, area under the receiver operating characteristic; HAT, hemorrhage after thrombolysis; SEDAN, blood sugar, early infarct signs, [hyper]dense cerebral artery sign, age; sICH, symptomatic intracerebral hemorrhage; SITS-ICH, safe implementation of thrombolysis in stroke-symptomatic intracerebral hemorrhage; SPAN-100, stroke prognostication using age and NIH stroke scale-100.*

Our study is the first one which has calculated the risk of sICH with IV-rtPA in patients with verify Aspirin less than 500, However, verify Plavix levels at presentation did not have a significant association with the development of sICH. Most of the variables we report can be easily calculated during the initial assessment and can help identify patients are at a higher risk of developing sICH and should receive more intensive and frequent neurological monitoring. In our cohort, even though the values of presenting NIHSS stroke scale were higher in the groups who developed sICH post-IV-rtPA, the difference was not statistically significant. This finding contrasts with the NINDS investigators. However, it has been reported in studies before by Larrue et al[13] Several other studies have shown that higher NIHSS stroke scales are not necessarily related to increased risk of sICH post-IV-rtPA.[34] Our study also did not find a significant increase in sICH in

Table 4. *Univariate analysis of comparison of clinical profiles between ICH and non-ICH groups, according to the NINDS criteria*

Variables	Non-sICH	sICH	Confidence intervals with *P* values
Age (yrs)	63.89 ± 14.76	69.71 ± 7.11	95% CI, −14.21-.56; *P* .067
Sex (male, %)	45 (54.88)	3 (50)	95% CI, .34-7.71; *P* .411
Blood glucose (mg/dL)	136.77 ± 67.20	155.14 ± 37.70	95% CI, −70.11-33.36; *P* .482
Blood glucose ≥185 mg/dL (yes, %)	**8 (9.76)**	**3 (42.86)**	**95% CI, 1.31-36.68; *P* .038**
SBP (mm Hg)	**160.48 ± 28.65**	**202.86 ± 13.06**	**95% CI, −56.06 - - 28.70; *P* <.001**
DBP (mm Hg)	**92.59 ± 19.38**	**121.0 ± 16.60**	**95% CI, −43.61 - - 13.21; *P* <.001**
MAP (mm Hg)	**113.71 ± 21.10**	**148.29 ± 12.75**	**95% CI, −47.57 - - 21.58; *P* <.001**
Presence of early infarct signs (yes, %)	37 (45.12)	5 (71.42)	95% CI, .56-16.59; *P* .173
Hb A1C (%)	6.26 ± 1.76	6.38 ± 1.33	95% CI, −1.60-1.35; *P* .868
LDL (mg/dL)	109.78 ± 39.55	124.0 ± 43.71	95% CI, −48.11-19.67; *P* .407
Verify Aspirin*	557.91 ± 85.28	490.71 ± 79.13	95% CI, .06-134.33; *P* .05
Verify Aspirin <500 (yes, %)*	**17 (22.97)**	**6 (81.08)**	**95% CI, 1.98-157.26; *P* .003**
Verify Plavix*	238.90 ± 55.74	244.14-26.40	95% CI, −48.32-37.83; *P* .809
NIHSS score	9.08 ± 5.44	11.8 ± 7.19	95% CI, −6.87-1.90; *P* .263
Onset to treatment time (min)	145.58 ± 50.16	148.14 ± 49.63	95% CI, −42.23-37.11; *P* .898
INR	1.17 ± 1.10	1.06 ± .13	95% CI, −.72-.95; *P* .792
PT (s)	14.55 ± 7.78	13.70 ± 1.39	95% CI, −5.07-6.77; *P* .776
PTT (s)	30.39 ± 19.31	27.63 ± 3.53	95% CI, −11.93-17.45; *P* .71
Weight (kg)	83.84 ± 18.52	88.07 ± 23.86	95% CI, −19.27-10.80; *P* .577
Hemoglobin (g/dL)	13.50 ± 1.75	13.11 ± 1.72	95% CI, −1.00-1.77; *P* .579
Platelet (×1000 μL	237.70 ± 91.21	229.0 ± 52.82	95% CI, −61.52-79.02; *P* .806
Atrial fibrillation (yes, %)	28 (34.15)	4 (57.14)	95% CI, −.54-12.30; *P* .207

Abbreviations: DBP, diastolic blood pressure; Hb A1C, hemoglobin A1c; INR, international normalized ratio; LDL, low-density lipoprotein.; NIHSS, national institutes of health stroke scale; PT, prothrombin time; PTT, partial thromboplastin time; SBP, systolic blood pressure; sICH, symptomatic intracerebral hemorrhage.

The significance of bold values are $P < 0.05$.

*Verify Aspirin and Plavix data were available for only 74 out of the 89 patients.

IV-rtPA treatment groups, with age or onset to treatment time, unlike some other studies.[15] This may be because the association between presenting variables with the risk of sICH post-IV-rtPA may be cumulative and multifactorial rather than unifactorial, with presenting blood pressure being associated with a higher risk of development of sICH post-IV-rtPA, relative to other factors, in our cohort.

Prognostic information can assist in clinical decision making and in informing families of a likely outcome.[12,17] Efforts have been underway for some time to develop a predictive model for the development of sICH after IV-rtPA. In our study, we also calculated the validity of 7 scores (SPAN-100, DRAGON, CUCCHIARA, HAT, SEDAN, THRIVE, and SITS-ICH) developed to predict sICH after IV-rtPA in our external cohort.[18-23] Some of these scores were generated using the NINDS definition of sICH, while others used ECASS-II and SITS-MOST definitions of sICH. Lack of consensus on the criteria for sICH has reduced reproducibility and comparability of these scores.[11] Majority of these sICH predicting scores considered the patient's age, NIHSS score, blood pressure, the presenting blood glucose to predict the development of sICH. Some scores also considered prestroke modified Rankin score (mRS), AF, and the presence of a dense MCA sign. We used both the ECASS-II and NINDS criteria of sICH. Overall the scores were more valid to predict sICH when the NINDS criteria were used. We found that the HAT score had the highest area under the curve (AUC) and it was the most valid in predicting the development of sICH when the ECASS-II criteria were used, while DRAGON was more useful in predicting sICH when NINDS' definition was used. SPAN-100 score and THRIVE scores had the poorest results across both definitions of sICH. We conclude that the HAT and DRAGON scores are the most accurate and reliable predictor of sICH development after IV-rtPA.

Our study had several limitations, first, it was a retrospective analysis performed at a single center and comprises a relatively small sample size. Second, we only

Table 5. *Multivariate analysis showing variables with a significant association with the development of sICH according to the NINDS criteria*

Variables	Confidence intervals with *P* values
MAP (mm Hg)	**95% CI, 1.01-1.18; *P* .025**
Verify Aspirin <500 (yes, %)	**95% CI, .01-0.80; *P* .032**
Blood glucose ≥185 mg/dL (yes, %)	95% CI, .05-8.56; *P* .745

Abbreviations: MAP, mean arterial pressure; sICH, symptomatic intracerebral hemorrhage.

Values with $P < 0.05$ are highlighted in bold.

Table 6. *AUROC curves of respective sICH predictive scores according to the NINDS criteria in our cohort*

Scores	Variables	*P*	AUROC (95% CI)
HAT	DM/initial glucose, pre-IV-rtPA NIHHS, and early infarct signs on initial CTH	.066	.710 (95% CI, .49-.93)
DRAGON	Dense MCA sign/early onfarct on CT, prestroke mRS, glucose, onset of treatment time, and NIHSS	**.012**	**.786 (95% CI, .61-0.96)**
SITS-ICH	NIHSS, SBP, glucose, weight, onset to treatment time, Aspirin or combined Aspirin and clopidogrel, and HTN	**.032**	**.746 (95% CI, .52-0.97)**
CUCCHIARA	Age, NIHSS, glucose, and platelet count	**.044**	**.730 (95% CI, .55-0.91)**
SPAN-100	Age and NIHSS	.681	.547 (95% CI, .31-.78)
SEDAN	NIHSS, SBP, glucose, body weight, stroke onset to treatment time, aspirin or combined aspirin and clopidogrel, and HTN	.146	.666 (95% CI, .47-.86)
THRIVE	Age, NIHSS, HTN, DM, and AF	.688	.543 (95% CI, .35-.74)

Abbreviations: AUROC, area under the receiver operating characteristic; HAT, hemorrhage after thrombolysis; SEDAN, blood sugar, early infarct signs, [hyper]dense cerebral artery sign, age; sICH, symptomatic intracerebral hemorrhage; SITS-ICH, safe implementation of thrombolysis in stroke-symptomatic intracerebral hemorrhage; SPAN-100, stroke prognostication using age and NIH stroke scale-100; THRIVE, totaled health risks in vascular events.

The significance of bold values are $P < 0.05$.

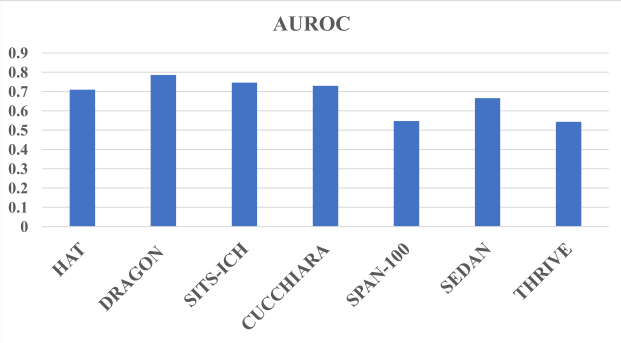

Figure 2. *Bar graph comparing AUROC curves of respective sICH predictive scores according to the NINDS criteria in our cohort. Abbreviations: AUROC, area under the receiver operating characteristic; SEDAN, blood sugar, early infarct signs, [hyper]dense cerebral artery sign, age; sICH, symptomatic intracerebral hemorrhage, HAT, hemorrhage after thrombolysis, SITS-ICH, safe implementation of thrombolysis in stroke-symptomatic intracerebral hemorrhage, SPAN-100, stroke prognostication using age and NIH stroke scale-100.*

used the ECASS-II and NINDS definitions of sICH in our study. Even though these 2 criteria are the most strongly associated with the 3-month outcome and the most consistent among other sICH predictive scores, there is still a discrepancy in a clinical definition and a questionable inter-rater agreement rate.[31,32] In our study depending on the criteria, SBP, DBP, MAP, blood glucose greater than or equal to 185 mg/dL and verify Aspirin less than 500 were significantly associated with the development of sICH after IV-rtPA, the values had wide confidence intervals, likely due to small sample size. Another limitation of our study was the exclusion of patients who underwent endovascular treatment. This was done to ensure uniformity in patient selection. Further studies involving a larger number of patients may confirm our findings.

Conclusions

We found that presenting MAP, presence of early infarct signs on CT Head and blood glucose greater than or equal to 185 mg/dL upon a patient's presentation have a significant association with sICH post-IV-rtPA when the ECASS-II definition was used, while presenting MAP and verify Aspirin less than 500 upon a patient's presentation have a significant association with sICH post-IV-rtPA when the NINDS definition was used. Patients with these risk factors should receive more intensive neurological monitoring. Our study found that HAT and DRAGON scores had the highest AUC, and they were the most valid in predicting the development of sICH in our independent cohort.

Author Disclosures

Taha Nisar: None; Rajanigandhi Hanumanthu: None; Priyank Khandelwal: None.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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