

Risk Scores for Predicting Post-thrombolysis Intracerebral Hemorrhage

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Abstract

Post-thrombolysis hemorrhage is a major concern for physicians treating acute ischemic stroke. Two scoring systems that incorporate factors associated with post-thrombolysis hemorrhage have been developed in an attempt to estimate the risk of developing post-thrombolysis hemorrhage among stroke patients. In this article we discuss these scoring systems and their utility in the clinical assessment of stroke patients.

Keywords

Stroke, recombinant tissue plasminogen activator (rt-PA), thrombolysis, hemorrhage, symptomatic intracerebral hemorrhage, risk score

Disclosure: The authors have no conflicts of interest to declare.

Received: February 11, 2009 **Accepted:** July 14, 2009 *DOI:* 10.17925/USN.2010.05.02.39

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Intracerebral hemorrhage (ICH) is the most dangerous and dreaded complication of thrombolytic therapy for acute ischemic stroke (AIS). The risk for symptomatic ICH (SICH) after AIS was increased from 0.6 to 6.4% after treatment with recombinant tissue plasminogen activator (rt-PA) compared with placebo in the National Institute of Neurological Disorders and Stroke (NINDS) trial.¹ Despite this increased risk for ICH, treatment with rt-PA was associated with significantly better clinical outcomes at three months and one year after stroke.^{1,2} These results led to approval of rt-PA by the US Food and Drug Administration (FDA) for the treatment of AIS in 1996. Almost two decades after the NINDS trial reported the benefit of thrombolytic therapy, fewer than 5% of stroke patients receive rt-PA despite aggressive community and physician education.³ While there are several factors limiting its utility, fear surrounding hemorrhagic complications has undoubtedly played a significant role in limiting the clinical use of rt-PA.

Definitions of Post-thrombolysis Intracerebral Hemorrhage

Post-thrombolysis ICH can be classified based on radiographic criteria alone or on the combination of a clinical change in a patient's neurological status in conjunction with evidence of ICH on brain imaging studies. Both approaches have strengths and weaknesses. Use of a classification scheme incorporating clinical changes (i.e. symptomatic versus asymptomatic ICH) is subject to imprecision given the fact that observed neurological changes may or may not be causally related to visualized ICH, and the criteria used to establish a change in neurological status may be variable. On the other hand, ICH associated with neurological deterioration (SICH) may be most relevant to patients and physicians as this is directly related to an observable clinical

change. Radiographic criteria for defining ICH may be more objective and reliable, but may have less direct clinical relevance.

At present, the most common radiographic classification scheme divides post-thrombolysis ICH into hemorrhagic infarction (HI) and parenchymal hemorrhage (PH).⁴ In the NINDS trial, HI was defined as punctuate or patchy hyperdensity with an indistinct border, and PH was described as a hyperdensity with a sharply demarcated border with or without edema or mass effect.¹ The European Cooperative Acute Stroke Study (ECASS) further expanded this scheme, with the subclasses of HI1 for small petechiae at the borders of an infarct, HI2 for confluent petechiae without mass effect within an infarct, PH1 for hematomas occupying <30% of the infarct with mass effect, and PH2 for hemorrhages occupying >30% of the infarcted territory with mass effect.^{5,6} PH, and in particular PH2, has been shown to worsen clinical outcomes.⁷⁻⁹

Classification of post-thrombolysis ICH based on the association (or lack thereof) with neurological deterioration has varied considerably across studies. In the NINDS trial, SICH was defined as any clinical worsening temporally associated with radiographic evidence of hemorrhage in the view of the treating clinician.¹ In the ECASS III study, SICH was defined as hemorrhagic transformation causally associated with a clinical worsening of ≥ 4 points on the National Institutes of Health (NIH) Stroke Scale (NIHSS) or death.¹⁰ ECASS II used a similar definition to ECASS III; however, a causal relationship between the hemorrhage and clinical deterioration or death was not necessary.⁶ The SITS-MOST study defined SICH as local or remote PH2 on imaging obtained 22–36 hours after treatment associated with a ≥ 4 -point increase in baseline or best NIHSS or death.¹¹ The choice of definition has a notable impact on observed hemorrhage rates. For

Table 1: Score Assignments in the HAT Score

History of Diabetes or Admission Hyperglycemia >200mg/dl	
No	0
Yes	1
Pre-treatment NIHSS	
<15	0
15–20	1
≥20	2
Presence of Hypodensity on Initial Head CT Scan	
No	0
<1/3 of MCA territory	1
>1/3 of MCA territory	2

CT = computed tomography; HAT = Hemorrhage After Thrombolysis; MCA = middle cerebral artery; NIHSS = National Institute of Health Stroke Scale.

Table 2: Risk of Post-thrombolytic Hemorrhage Based on the HAT Score in a Combined Analysis of NINDS and Prospective Cohorts (n=400)

Cumulative Score	Number of Patients	Total ICH Rate (%)	SICH Rate (%)
0	153	6	2
1	121	16	5
2	84	23	10
3	33	36	15
>3	9	78	44

HAT = Hemorrhage After Thrombolysis; ICH = intracerebral hemorrhage; NINDS = National Institute of Neurological Disorders and Stroke; SICH = symptomatic intracerebral hemorrhage.

instance, in ECASS III the rate of SICH was 2.4% in the rt-PA group using the ECASS III protocol definition, but 7.9% using the NINDS definition.¹⁰ Studies evaluating predictors of post-thrombolytic ICH have used various definitions, which may account for some of the variability in identified predictors of post-thrombolysis ICH between studies.

Risk Factors for Post-thrombolysis Intracerebral Hemorrhage

Lansberg et al. recently performed a systematic review of the literature and reported several risk factors consistently associated in multiple studies with post-thrombolysis SICH.¹² In 12 studies that met their inclusion criteria, early computed tomography (CT) hypodensity, elevated serum glucose or history of diabetes, and symptom severity as defined by the NIHSS were the factors most consistently associated with an increased risk of post-thrombolysis SICH.^{12–22} Numerous other risk factors have been reported in individual studies, including advanced age, longer time to treatment, high systolic blood pressure, low platelet count, history of congestive heart failure, low plasminogen activator inhibitor levels, prior antiplatelet use, non-smoking status, low-density lipoprotein levels, imaging characteristics on magnetic resonance imaging (MRI), and deviations from treatment protocols.^{12,19–21,23–29} However, the association between these factors and risk for ICH remains uncertain given the variable results across studies. For instance, advanced age was independently identified to increase SICH risk in a secondary analysis of ECASS II.¹⁹ Age was also identified as a potential risk factor for SICH in the pooled analysis of the NINDS, ECASS, and ATLANTIS trials and by the Multicenter rt-PA Stroke Study Group as

Table 3: Score Assignments in the Score Reported by the Multicenter Stroke Survey Scale

Multicenter Stroke Survey Scale (n=481)	
Age (years)	
≤60	0
>60	1
Pre-treatment NIHSS	
≤10	0
>10	1
Admission Glucose (mg/dl)	
≤150	0
>150	1
Platelet Count	
>150,000	0
≤150,000	1

NIHSS = National Institute of Health Stroke Scale.

Table 4: Risk of Post-thrombolytic Hemorrhage Based on the Score Reported by the Multicenter Stroke Survey Scale

Cumulative Score	Number of Patients	asICH Rate (%)	SICH Rate (%)	PH Rate (%)
0	39	0	0	0
1	163	5	5	3
2	192	11	4	5
≥3	87	20	18	18

asICH = asymptomatic intracerebral hemorrhage; PH = parenchymal hemorrhage; SICH = symptomatic intracerebral hemorrhage.

an independent predictor of ICH in multivariate analysis.^{20,30} However, in the Multicenter rt-PA study the association of age and ICH disappeared when baseline CT and laboratory changes were included in the statistical model. The variability between risk factors across studies is likely in part due to differences in baseline patient characteristics and statistical modeling between and within studies, as well as the increased power of pooled analysis of multiple studies.

Despite the identification of numerous factors associated with an increased risk for post-thrombolysis ICH, it is unclear how to incorporate these factors into a risk assessment for individual stroke patients. Factors such as the presence or extent of early changes on neuroimaging, age, elevated glucose or diabetes, and degree of neurological impairment defined by NIHSS may all, to some extent, reflect stroke severity and therefore not be truly independent variables. Even when independent, it is difficult to quantify the incremental additive risk associated with the presence of multiple risk factors in the individual patient. The development of clinical risk scores attempts to fill this need. Two recent publications have incorporated some of the above variables into scoring systems to better predict SICH and allow risk stratification of patients receiving thrombolytic therapy for acute ischemic stroke.^{31,32}

The Hemorrhage After Thrombolysis Score

The Hemorrhage After Thrombolysis (HAT) Score was developed by analyzing the reported odds ratios from publications of predictors of post-thrombolysis ICH.³¹ Receiver–operator characteristic (ROC) curves were developed and the predictive ability of various combinations of

risk factors measured using the area under the ROC curve, quantified by the c-statistic. The ROC curves integrate the sensitivity and specificity of the variables tested. An ideal predictive model produces a c-statistic of 1.00, while a model with a predictive ability no better than chance gives a c-statistic of 0.50. Various combinations of risk factors were studied and the combination that produced the highest predictive value was reported. Using this method the authors identified a history of diabetes or admission hyperglycemia >200mg/dl, pre-treatment NIHSS, and obvious early CT hypodensity as the most important factors for determining bleeding risk after thrombolysis. These risk factors were then categorized and assigned a value of 0, 1, or 2 based on their determined import, with a maximum cumulative score of 5 (see *Table 1*). The HAT score was evaluated in rt-PA-treated patients in the NINDS trial (n=302) and in a small prospective cohort (n=98) of patients treated clinically at the authors' institution. SICH was defined differently in the two groups: the NINDS definition was used in the retrospective cohort, but the ECASS III definition was used in the prospectively collected group of patients.

The rate of total ICH and SICH increased with increasing HAT scores in the NINDS trial group and in the prospective cohort. In the combined analysis of both groups, the total risk for ICH was 6, 16, 23, 36, and 78% for HAT scores of 0, 1, 2, 3, and >3, respectively, and the risk for SICH was 2, 5, 10, 15, and 44% for HAT scores of 0, 1, 2, 3, and >3, respectively (see *Table 2*). The c-statistics (95% confidence interval [CI]) for the combined analysis was 0.72 (0.65–0.79; p<0.001) and 0.74 (0.63–0.84; p<0.001) for total ICH and SICH, respectively, indicating that the HAT score can be used to reasonably predict risk for post-thrombolytic ICH. There were no other combinations of reported risk factors that improved the reliability of the model using c-statistics. It should be noted that the derivation and refinement of the HAT score appears to have utilized the larger NINDS data set in which the score was also tested, such that the score has only truly been independently validated in the single small cohort of patients at the authors' own institution.³¹

The Multicenter Stroke Survey Scale

The Multicenter rt-PA Stroke Survey group has also developed and published a clinical risk score for predicting ICH after rt-PA.³² The Multicenter Stroke Survey Scale used variables identified in the initial Multicenter Stroke Survey publication in multivariate analysis as independent risk factors for post-thrombolysis ICH. Further refinement of the score involved selecting variables that were easily and reliably measured in clinical practice. The factors utilized in this scale include age >60 years, NIHSS >10, admission serum glucose >150mg/dl, and platelet count <150,000. If present, each of these factors was assigned a score of 1 point (see *Table 3*). This scoring system was both developed from and tested in the data from the Multicenter rt-PA Stroke Survey Group data set in which there were complete data for all variables (n=481). Asymptomatic intracerebral hemorrhage (asICH), SICH, and PH risks were reported using the definitions from the NINDS rt-PA trial. The ability of this rating scale to predict post-thrombolytic ICH was also assessed using c-statistics.

Using the Multicenter Stroke Survey scale, the rate of asICH, SICH, and PH correlated with increasing scores (see *Table 4*). The rate of asICH was 0, 5, 11, and 20% for a score of 0, 1, 2, and ≥3, respectively. The rate of SICH was 0, 5, 4, and 18% for a score of 0, 1, 2, and ≥ 3, respectively.

The rate of PH was 0, 3, 5, and 18% for a score of 0, 1, 2, and ≥3, respectively. The c-statistics were 0.67, 0.68, and 0.72 for asICH, SICH, and PH, respectively, indicating reasonable ability of the model to predict hemorrhage. Inclusion of other variables failed to improve the discriminatory capability of the model. One of the potential strengths of this scoring system is the relative simplicity of its variables, in particular not requiring radiographic interpretation, compared with the HAT score. However, this scoring system has not been validated in an independent cohort and thus must undergo further study before its validity and generalizability can be determined.³²

Clinical Implications

If confirmed in validation studies, these clinical risk scores would provide clinicians and patients with a useful tool to estimate the risk for hemorrhagic complications following treatment with thrombolytic agents. This information might be useful to align patient and family expectations about short-term treatment complications with probable outcomes, help select patients for differing levels of intensive monitoring, and potentially be used in decisions about when to start antithrombotic therapy post-thrombolysis. Furthermore, these scores might be useful in research studies of future thrombolytic agents to ensure balance between treatment and control arms in terms of risk for hemorrhagic transformation. Finally, these scores might serve as a benchmark to assess the supplemental value of alternative predictors of post-thrombolysis ICH, such as those based on laboratory or radiological parameters.^{33,34} However, it is critically important to recognize that these scores do not provide information about the risk–benefit calculation for thrombolytic therapy because they do not provide any meaningful assessment of the potential benefit of thrombolysis. In other words, a patient with a severe stroke may have an extremely elevated risk for SICH, but may still have a better chance of neurological recovery when treated with thrombolytic therapy than if it is withheld. Indeed, even those patients at highest risk for bleeding benefited from treatment in the NINDS rt-PA trial.¹³

In conclusion, post-thrombolysis hemorrhage will continue to be a major concern for physicians treating patients with AIS. If validated in future studies, risk scores such as the HAT score and Multicenter Stroke Survey Scale will provide clinicians with additional tools in the evaluation and treatment of stroke patients. ■



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