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Defining Clinically Relevant Cerebral Hemorrhage After Thrombolytic Therapy for Stroke: Analysis of the NINDS-tPA Trials

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Abstract

Background and Purpose—Several definitions have been proposed to distinguish clinically relevant from incidental cerebral hemorrhagic transformation after thrombolytic therapy for acute ischemic stroke. We investigated which definition best identifies cerebral hemorrhages that alter long-term functional outcome in The National Institute of Neurological Disorders and Stroke (NINDS) tPA Trials.

Methods—We analyzed four candidate hemorrhage definitions for which The NINDS tPA Trials public data set had relevant data. For each, we identified tPA-treated patients having that hemorrhage type and compared their actual functional outcomes at 90 days to their predicted outcomes had they not received tPA and not had the hemorrhage. Projected outcomes without tPA were based on a 17 variable prognostic model derived from The NINDS tPA Trials placebo group.

Results—Among the 312 patients treated with IV tPA, 33 (10.6%) experienced any radiologic intracerebral hemorrhage within 36 hours of treatment, 16 (5.1%) a radiologic parenchymal

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Disclosures

Neal Matsumori Rao - reports no disclosures

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hematoma, 20 (6.4%) an NINDS defined symptomatic intracerebral hemorrhage (SICH), 12 (3.8%) an ECASS 2 defined SICH, and 6 (1.9%) a modified (m)SITS-MOST defined SICH. The ECASS2 and mSITS-MOST definitions identified the largest hemorrhage-related change in 90 day modified Rankin Scale scores (2.26–0.32=1.94, p=0.0001 and 2.81–0.63=2.18, p=0.0002 respectively). These definitions also distinguished the largest hemorrhage-related change in 90 day mortality (64.7%–7.6%=57.1%, p=0.0004 for ECASS2 and 68.4%–19.5%=48.9%, p=0.0152 for mSITS-MOST).

Conclusions—The ECASS 2 and mSITS-MOST SICH definitions, which combine radiologic features and occurrence of substantial early neurologic deterioration, best identify tPA hemorrhages that alter final patient outcome.

Keywords

Stroke; Cerebrovascular Disorders; Thrombolysis; Cerebral Ischemia; Hemorrhage

Introduction

One of the most important issues a clinician must consider when treating an acute ischemic stroke patient with intravenous tissue plasminogen activator (IV tPA) is the risk of a clinically important intracerebral hemorrhage (ICH). Estimating this risk has been confounded by the various definitions of clinically important ICH proposed (online supplemental Table I). Some definitions consider only radiologic extent of the hemorrhage. However, sometimes even large parenchymal hematomas may occur asymptomatically and without final clinical consequence. Other definitions identify hemorrhages that produce early symptomatic worsening, based on temporal coincidence with change in neurologic deficits or on relatedness by clinical judgment. However, it is challenging to delineate hemorrhages that cause early worsening, as deficit progression may arise from other causes than the ICH. Furthermore, patients who have early clinical worsening due to their hemorrhage may not have their final clinical outcome altered by the ICH.

The NINDS tPA Trials were instrumental in generating data on hemorrhagic transformation after IV tPA.[1] In these trials, symptomatic ICH (SICH) was defined as any hemorrhagic transformation temporally related to any worsening in neurologic condition. The neurologic worsening could be minor, insufficient to alter the patient's National Institutes of Health Stroke Scale (NIHSS). In the nearly two decades since the NINDS tPA Trials, this definition of SICH was recognized as potentially over-inclusive. Among the 20 cases defined as SICH in the NINDS trials, there are several in which the ICH was minimal and unlikely to have altered long term patient outcome (Figure 1).

Many processes other than ICH may cause small fluctuations in the NIHSS in a clinically stable patient, including inter-rater variability, patient fatigue, new medications, and infections. Consequently, some subsequent studies used a more stringent criterion of increase by 4 or more points on the NIHSS to define early neurologic deterioration [2–6]. Others advocate that pure radiologic analysis of ICH should be emphasized to avoid noise introduced by the multiplicity of processes that may affect early neurologic clinical course.

Which of the contending definitions of clinically important ICH to cite with patients and families is a challenge for clinicians. Taking a patient-centered perspective, the most relevant definition is the one that identifies ICH that will alter the final clinical outcome of the patient, affecting their long term functioning. Asymptomatic or transiently symptomatic ICHs are of much less importance to patients and their families. We undertook this study to determine which definition of clinically important ICH best predicts a patient's long-term neurological outcome.

Methods

We computationally analyzed the National Institute of Neurological Disorders and Stroke (NINDS) tPA trials available through the public data set, which provides a record of the presence and timing of ICH and NIHSS as judged by the NINDS site investigators and central adjudicators. We included only ICH occurring within the first 36 hours of tPA administration. 24 hour NIHSS was used to determine neurologic deterioration. The following candidate definitions for clinically relevant ICH were analyzed: 1) parenchymal hematomas (PH), 2) The NINDS tPA Study definition of SICH, 3) the European-Australian Cooperative Acute Stroke Study 2 (ECASS 2) SICH definition, and 4) a modified version of the Safe Implementation of Thrombolysis in Stroke Monitoring Study (mSITS-MOST) SICH. [1–3] As there was no distinction between PH1 and PH2 available in the public dataset, the mSITS-MOST definition included all PH as opposed to only PH2 in the original definition. These four definitions included one pure radiologic and three mixed clinical-radiologic (Table 1).

We tested these definitions to determine which best identified clinically relevant ICH, defined as ICH that altered long term global disability assessed by the modified Rankin Scale (mRS) at 3 months. In a secondary analysis, we also analyzed which ICH definition best identified ICH that altered mortality at 3 months post-stroke.

As described previously, a model predicting final disability outcome under supportive care based on demographic and clinical features at trial entry was developed from the 312 patients in the placebo groups of The NINDS tPA trials.[7] The ordinal logistic model for 90 day mRS used the following 17 baseline variables identified in previous studies of the NINDS Study and other acute ischemic stroke trials as important prognostic determinants: age, sex, pretreatment NIHSS, age–NIHSS interaction, history of hypertension, diabetes, smoking, time from onset to treatment, mean arterial pressure, pretreatment serum glucose, hyperdense artery sign on CT, hypodensity on CT, mass effect on CT, preexisting disability, stroke subtype, side of brain lesion, side of brain lesion-NIHSS interaction.[8–12] Performance of the logistic model was evaluated with the C (concordance) statistic and maximum rescaled R square statistic.

Next, for each ICH definition, two clinical outcome distributions were compared: 1) the observed, actual 3 month mRS outcomes among those patients who experienced the defined ICH after receiving tPA, and 2) the projected 3 month mRS outcome those patients would have experienced had they not received tPA, based on the ordinal logistic regression model.

The predicted 3-month modified Rankin Scale (mRS) values without tPA treatment were derived by entering baseline patient covariate values into the model. In the main analysis, regression imputation was utilized in the case of missing ordinal logistic model variables. In sensitivity analysis, only patients with complete data available were analyzed.

For each ICH definition, the 33 patients with any radiologic ICH within 36 hours of treatment were divided into those who fit the definition and those who did not. The candidate definition with the largest difference (differential) in the observed minus expected mRS distribution between the two groups, was considered the most predictive definition. That is, if Δ_{met} is the observed minus expected mRS distribution in the group that meets the candidate definition, and Δ_{notmet} is the observed minus expected mRS distribution in those patients with hemorrhage who do not meet the candidate definition, we defined the differential as the difference between between Δ_{met} and Δ_{notmet}. We considered the most predictive definition to be the one that maximizes the mean differential. In other words, the criterion for the optimal definition was that ICH patients meeting the definition had substantially worse final outcomes with tPA and ICH than they would have had without tPA, while patients not meeting the definition had equivalent final outcomes with tPA and ICH as they would have had without tPA.

We believe this method to compare the change between observed mRS with tPA and predicted mRS without tPA is preferable to performing separate regression analyses for each definition, which would result in a new and possibly different expected mRS for the same person in each regression. With our method, the expected mRS with no tPA will not change for a given patient regardless of the definition of ICH used to classify that patient.

For comparison of variables across definition groups, p values for comparing categorical variables such as gender were computed using Fishers exact test. The p values for comparing continuous variables that did not follow the normal such as NIHSS were computed using the Wilcoxon rank sum test and the p value for comparing continuous variables that follow the normal such as age were computed with t tests (Table 2).

Differences in the observed minus expected mRS distributions were summarized using the mean difference. Mean values were used because, while mRS is an ordinal scale, the median difference is not as good a single number summary in this dataset because it does not indicate small differences/shifts in the distribution. The confidence bounds and p values for mRS mean differences were computed non-parametrically using non-parametric resampling (bootstrap) methods (Table 3 – 90 day mRS). Confidence bounds and p values for mortality were computed using the exact binomial distribution and Fisher's exact test (Table 3 - Mortality).

Results

Among the 312 patients treated with IV tPA, 33 (10.6%) experienced any radiologic ICH within 36 hours of treatment, including 16 (5.1%) with a radiologic parenchymal hematoma and 17 (5.4%) with a radiologic hemorrhagic infarction. Among the candidate SICH definitions, 20 (6.4%) experienced an NINDS Study-defined SICH, 12 (3.8%) experienced

an ECASS 2-defined SICH, and 6 (1.9%) experienced an mSITS-MOST-defined SICH. The patients meeting each ICH definition are displayed graphically (online supplemental figure I).

The baseline clinical characteristics of patients with PH and the three clinical-radiographic candidate SICH categories are shown in table 2, compared to control patients who did not receive tPA. Patients meeting the NINDS Study definition group were older, had higher pretreatment NIHSS scores, and more often showed mass effect than patients in the other groups. Mean arterial pressure was higher in patients meeting the mSITS-MOST definition.

In the prognostic model derived from the NINDS Study placebo groups, the ordinal logistic model for predicted outcome had a Concordance (c) statistic of 0.76 and a max rescaled R square of 0.40.

The quantitative differences between actual and predicted 90 day mean mRS are shown in Table 3. The ECASS2 and mSITS-MOST definitions had the largest mRS point differentials (2.26–0.32=1.94 mRS points, p=0.0001 and 2.81–0.63=2.18 mRS points, p=0.0002 respectively). Similar results were seen in the mortality analysis (Table 3). These same two definitions had the largest differentials in percent mortality (64.7%–7.6%=57.1%, p=0.0004 for ECASS2 and 68.4%–19.5%=48.9%, p=0.0152 for mSITS-MOST). Sensitivity analysis confined to patients that did not have missing data revealed similar results (results not shown).

A graphic representation of the actual and predicted day 90 mRS distributions for symptomatic and asymptomatic ICH patients using the NINDS, ECASS 2 and mSITS-MOST definitions are shown in figure 2. This visual display highlights the superiority of the mSITS-MOST and ECASS 2 definitions in stratifying patients. Patients with ICH meeting these definitions had the largest differences between actual and predicted outcome, while patients with ICH not meeting these definitions had the smallest difference between actual and predicted outcome.

Discussion

This study of four candidate definitions for the most clinically relevant SICH after IV tPA in acute ischemic stroke patients found that the ECASS 2 and mSITS-MOST definitions had the best performance characteristics. Patients with ICH fitting these definitions had substantial and significant differences in their actual 3 month functional outcome from their expected 3 month outcome without tPA, while patients not meeting these definitions had the greatest concordance of their actual 3 month function outcome with their expected 3 month outcome.

Compared with the best-performing definitions, each of the other candidate definitions showed limitations. The NINDS Study definition was less precise. In the patients it identified as having clinically relevant ICH, the ICH had less impact on final outcome than in the better predictor definitions. In the patients it identified as not having clinically relevant ICH, the ICH tended to have more impact on final outcome than in the better

definitions. A similar lack of precision was observed with the pure radiologic parenchymal hematoma definition.

Between the two best-performing definitions, there were differences in performance characteristics, although these did not reach statistical significance. The ECASS 2 definition identified twice as many patients as having clinically relevant ICH than the mSITS-MOST definition (which itself is more inclusive than the standard SITS-MOST definition). This greater inclusiveness of the ECASS 2 definition did not come at a cost, and tended to come with greater specificity. Among patients not meeting the definitions, alterations in final outcome compared with expected outcome were nominally lower for the ECASS 2 definition. If these findings became statistically significant in a larger dataset, it would indicate an advantage of the ECASS 2 definition over the mSITS-MOST definition in both sensitivity and specificity in detecting ICH that worsen 90 day disability and mortality.

The findings of this study are consonant with those of prior investigations. They validate the intuition of the developers of the ECASS 2 and SITS-MOST definitions that the NINDS Study definition was overly inclusive, and that more stringent classification algorithms should be formulated.[13,14] This study accords with and extends the work of Strbian and colleagues.[13] In a single center cohort of tPA-treated patients, they found the ECASS 2 definition outperformed the NINDS Study and the SITS-MOST definitions in identifying hemorrhages making the largest contribution to worst outcomes in both integrated discrimination improvement and receiver operating characteristic curve analysis. That both studies converge upon the ECASS 2 definition as best-performing provides strong evidence for its utility.

This study provides insight into the population impact of ICH after IV tPA. Considering the ECASS 2 definition, among 1,000 patients matching the NINDS Study population who are treated with IV tPA, 38 will have a potentially clinically important ICH, among whom 25 will die as a result of the ICH. These adverse outcomes must be balanced against the 320 patients who will have a better outcome as a result of receiving tPA.[15] For every 1 patient harmed by tPA, 10 are helped.

Our study has several limitations. Due to the constraints of the publicly available data, we could only analyze a subset of the definitions of clinically important ICH that have been proposed. We must also rely on the NINDS investigator's judgment of the NIHSS and type of ICH. Also limited by this data set, we have no record of the exact NIHSS at the time the ICH was discovered, and must use the 24 hour NIHSS as the closest surrogate. Furthermore, the public data set did not distinguish parenchymal hematoma (PH) type 1 from PH2, did not state the lowest NIHSS between treatment and 24 hours, and did not state investigator judgment of causal relatedness between an ICH and early worsening. As a result, analysis of additional candidate definitions could not be performed, including the unmodified SITS-MOST SICH definition, the ECASS 3 trial SICH definition, and a radiologic-only PH2 definition. The sample size of patients experiencing radiologic hemorrhagic transformation after IV tPA was modest, limiting study power. More restrictive definitions of ICH (e.g. mSITS-MOST) were further limited by fewer patients who met the criteria. Predictive modeling was utilized so that SICH could be analyzed within the context of potential

clinical benefit from the administration of tPA. However, the possibility of error is inherent when comparing a calculated outcome to an actual one. The expected mRS values assuming no tPA under the logistic model assume all relevant factors are represented correctly, and our results are tempered by the accuracy of our predictive model, which had a c statistic of 0.76. Association is not causation, and our study of which definition identified ICH most strongly associated with worse 90 day outcome may not be identifying the ICHs actually causing worse long term outcome.

Reperfusion therapy for acute ischemic stroke is a dynamic research arena with many ongoing studies of thrombolytics and endovascular thrombectomy techniques. It is critical to accurately quantify clinically important ICH in a standardized manner across studies. Indeed, future trials are likely to test agents specifically aimed at reducing ICH rates, requiring uniform definition of the key endpoint variable. To identify the subset of ICH that are most important to patients, clinicians, and society, our study supports the use of a mixed radiologic-clinical definition that includes patients with substantial, but not minimal, early worsening.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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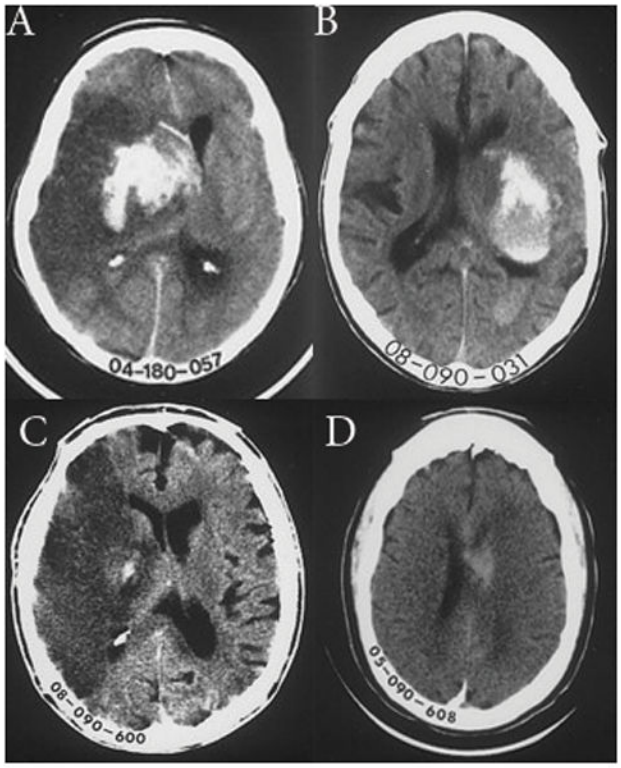

Figure 1.

Axial CT images from 4 of the 20 patients designated as having SICH in the NINDS tPA trials. A and B are examples of patients with parenchymal hematomas producing mass effect and likely to cause both early neurologic deterioration and worse final outcome. C and D are patients with relatively small areas of petechial hemorrhage within the territory of infarction. While these hemorrhages were temporally associated with early worsening, they are unlikely to have been the cause of the early worsening and very unlikely to have altered final functional outcome. (Modified with permission from Stroke 1997;28:2109–2118.)

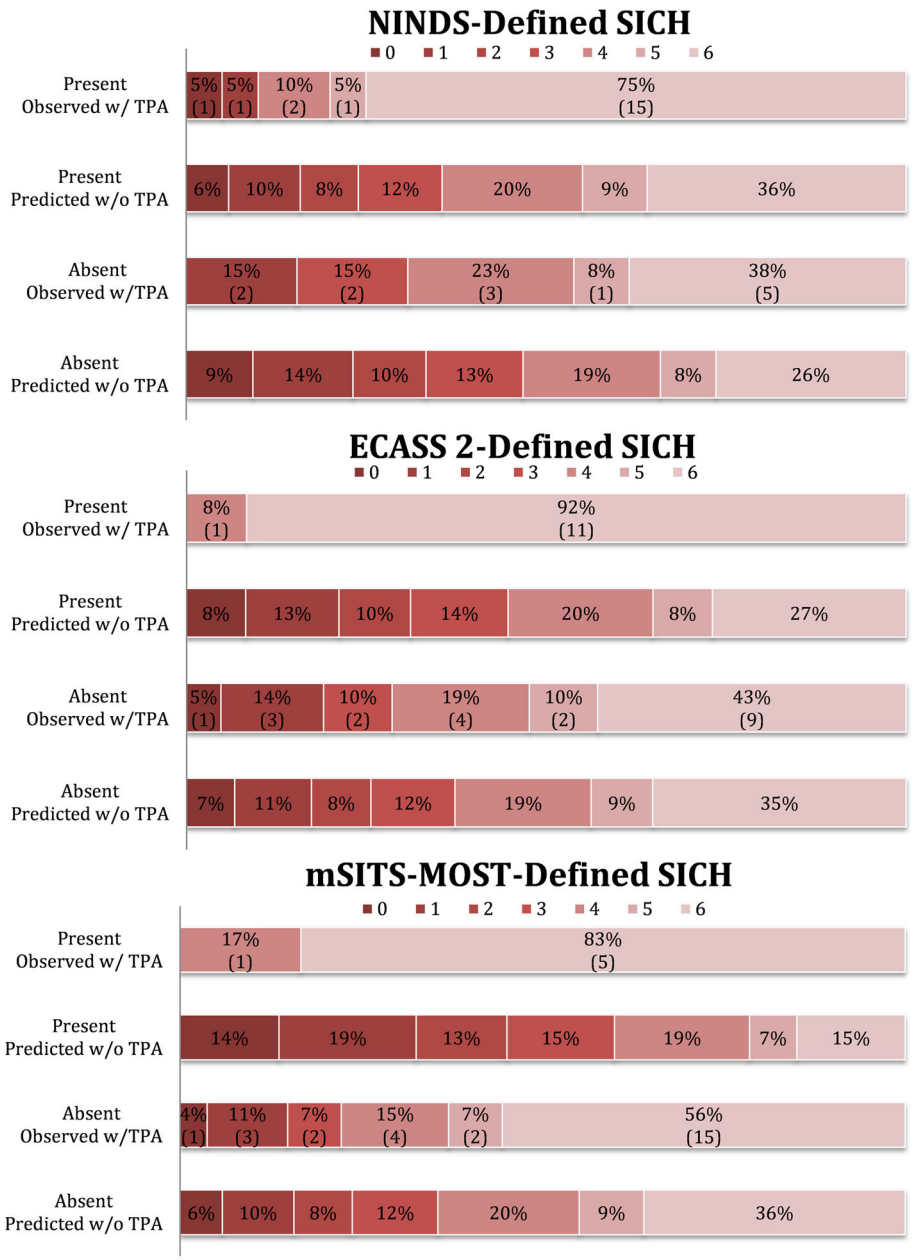

Figure 2.

Day 90 mRS distributions for the NINDS Study, ECASS 2 and modified SITS-MOST definitions of SICH. Actual and predicted outcomes for patients with clinical important and clinically unimportant hemorrhages under each candidate definition are compared. Percentages were rounded to the nearest whole number. The number of patients contributing to each observed mRS category is given in brackets.

Table 1

Candidate definitions for clinically important hemorrhage

	Clinical	**Radiologic**
PH	None	PH only
NINDS Study	Any worsening	Any ICH
ECASS 2	Only ≥ 4 NIHSS	Any ICH
mSITS-MOST	Only ≥ 4 NIHSS	PH only

HI - hemorrhagic infarction, PH - parenchymal hemorrhage, NINDS - National Institute of Neurological Disorders and Stroke, ECASS - European-Australian Cooperative Acute Stroke Study 2, mSITS-MOST - modified Safe Implementation of Thrombolysis in Stroke Monitoring, ICH – intracerebral hemorrhage, NHISS - National Institutes of Health Stroke Scale

Table 2

Clinical characteristics of patients in the placebo group compared with patients meeting different hemorrhage definitions after tPA

	Control (Placebo)	PH	NINDS Study SICH	ECASS II SICH	mSITS-MOST SICH
Number	312	16	20	12	6
Sex (Female)	41%	50%	50.0%	50.0%	50.0%
Age [mean (SD)]	65.9 (±11.9)	72.6 (±10.3)*	72.8 (±10.6)**	71.2 (±13.7)	70.3 (±14.3)
Pretreatment NIHSS [median (IQR)]	15 (9.5–20)	16.5 (11–23)	21 (15–25.5)*	16.5 (14–23)	15 (7–16)
Hypertension	65.7%	62.5%	65.0%	75.0%	66.7%
Diabetes	20.3%	18.8%	20.0%	8.3%	0.0%
Smoking	35.8%	13.3%	15.8%	18.2%	20.0%
Time to treatment (min)	120	118	118	121	131
Mean arterial pressure [mean (SD)]	111.9 (±17.4)	118.2 (±19.5)	115.9 (±19.8)	120.9 (±20.0)	129.6 (±13.2)*
Hypodensity on baseline CT	9.1%	12.5%	15.0%	25.0%	16.7%
Hyperdense vessel sign	17.8%	25.0%	20.0%	16.7%	0.0%
Mass effect on CT	4.2%	12.5%	20.0%*	16.7%	16.7%
Glucose at baseline (mean)	150.6 (±77.9)	171.9 (±103.7)	173.7 (±93.2)	147.4 (±63.5)	140.2 (±73.6)
Preexisting disability	7.7%	0.0%	0.0%	0.0%	0.0%
Small Vessel Disease	9.7%	6.3%	5.0%	8.3%	16.7%
Cardio embolism	38.6%	68.8%*	60.0%	58.3%	50.0%
Large vessel atherosclerosis	21.4%	6.3%	10.0%	0.0%	0.0%
Bilateral stroke	6.1%	0%	0%	0%	0%
Left sided stroke	45.0%	37.5%	30.0%	41.7%	50.0%

SICH – symptomatic intracerebral hemorrhage.

* p value less than or equal to 0.05,

** p value less than or equal to 0.01, when compared to control

Table 3

Modified Rankin Scale global disability scores and mortality at 90 days

Day 90 mRS						
Definition	**Present**	**N**	**Observed**	**Expected**	**Difference (95% CI)**	**P value**
PH	Yes	16	4.81	3.57	1.24 (0.31–1.92)	0.4565
	No	17	4.82	4.00	0.82 (0.03–1.69)	
NINDS Study SICH	Yes	20	5.20	4.00	1.20 (0.35–2.16)	0.4542
	No	13	4.23	3.48	0.75 (0.06–1.63)	
ECASS 2 SICH	Yes	12	5.83	3.57	2.26 (1.70–3.01)	0.0001
	No	21	4.24	3.92	0.32 (−0.28–0.96)	
mSITS-MOST SICH	Yes	6	5.67	2.85	2.81 (2.01–3.73)	0.0002
	No	27	4.63	4.00	0.63 (−0.04–1.14)	

Day 90 Mortality						
Definition	**Present**	**N**	**Observed**	**Expected**	**Difference (95% CI)**	**P value**
PH	Yes	16	62.5%	28.0%	34.5% (13.4–55.6)	0.4713
	No	17	58.8%	36.2%	22.6% (0.4–44.9)	
NINDS Study SICH	Yes	20	75.0%	36.0%	39.0% (20.1–58.0)	0.0833
	No	13	38.5%	26.4%	12.1% (−11.6–35.8)	
ECASS 2 SICH	Yes	12	91.7%	26.9%	64.7% (47.2–82.3)	0.0004
	No	21	42.9%	35.2%	7.6% (−8.5–23.8)	
mSITS-MOST SICH	Yes	6	83.3%	14.9%	68.4% (38.4–98.4)	0.0152
	No	27	55.6%	36.0%	19.5% (3.8–35.2)	