Comparison of Risk-scoring Systems in Predicting Symptomatic Intracerebral Hemorrhage After Intravenous Thrombolysis

Sheng-Feng Sung, MD; Solomon Chih-Cheng Chen, MD, PhD; Huey-Juan Lin, MD, MPH; Yu-Wei Chen, MD; Mei-Chiun Tseng, PhD; Chih-Hung Chen, MD

Background and Purpose—Various risk score models have been developed to predict symptomatic intracerebral hemorrhage (SICH) after intravenous thrombolysis for acute ischemic stroke. In this study, we aimed to determine the prediction performance of these risk scores in a Taiwanese population.

Methods—Prospectively collected data from 4 hospitals were used to calculate probability of SICH with the scores developed by Cucchiara et al, the Hemorrhage After Thrombolysis (HAT) score, the Safe Implementation of Thrombolysis in Stroke-SICH risk score, the Glucose Race Age Sex Pressure Stroke Severity score, and the Stroke Prognostication using Age and National Institutes of Health Stroke Scale-100 index. We used logistic regression to evaluate the effectiveness of each risk model in predicting SICH and the c statistic to assess performance.

Results—A total of 548 patients were included. The rates of SICH were 7.3% by the National Institute of Neurological Diseases and Stroke definition, 5.3% by the European-Australasian Cooperative Acute Stroke Study II definition, and 3.5% by the Safe Implementation of Thrombolysis in Stroke-Monitoring Study definition. The Cucchiara score, the HAT score, and the Safe Implementation of Thrombolysis in Stroke-SICH risk score were significant predictors of SICH for all 3 definitions, whereas the Glucose Race Age Sex Pressure Stroke Severity score and the Stroke Prognostication using Age and National Institutes of Health Stroke Scale-100 index predicted well only for 1 or 2 definitions of SICH. The c statistic was highest for the HAT score (range, 0.69–0.73) across the definitions of SICH.

Conclusions—The Cucchiara score, the HAT score, and the Safe Implementation of Thrombolysis in Stroke-SICH risk score predicted SICH reasonably well regardless of which SICH definition was used. However, only the HAT score had an acceptable discriminatory ability. (Stroke. 2013;44:1561-1566.)

Key Words: AIS ■ intracerebral hemorrhage ■ intravenous thrombolysis ■ prognosis ■ risk score

Intravenous thrombolytic therapy with tissue-type plasminogen activator (tPA) is the standard treatment for acute ischemic stroke despite its risk of symptomatic intracerebral hemorrhage (SICH).1 A variety of baseline factors, such as older age, higher stroke severity as assessed by the National Institutes of Health Stroke Scale (NIHSS), higher glucose level, prior antiplatelet use, the presence of atrial fibrillation, congestive heart failure, renal impairment, and early ischemic changes on pretreatment brain imaging, are associated with SICH.2 SICH potentially increases the risk of poor and fatal outcome,3 and consequently influences the net benefit from thrombolysis. Many emergency physicians were reluctant to use thrombolysis for acute ischemic stroke in fear of SICH, with mean upper limit of tolerable risk being 3.4%.4 Several models of risk stratification were proposed to improve the identification of patients at high risk of SICH in thrombolysis, including Cucchiara et al,5 the Hemorrhage After Thrombolysis (HAT) score,6 the iScore,7 the Safe Implementation of Thrombolysis in Stroke (SITS)-SICH risk score,8 the blood Sugar, Early infarct signs and hyperDense cerebral artery sign, Age, and NIHSS (SEDAN) score,9 the Glucose Race Age Sex Pressure Stroke Severity (GRASPS) score,10 and the Stroke Prognostication using Age and NIHSS (SPAN)-100 index.11 These clinical risk scores may have potential advantages, such as to facilitate treatment by nonspecialists or to help select patients in clinical trials.8 They also provide patients and families concrete information on the risk associated with thrombolysis,10 and may assist clinicians...
to partner with patients to enhance informed decision making. However, before these risk scores can be implemented in populations or settings that differ from the derivation sample, they need to be externally validated.12

In Taiwan, ≈1.5% of patients with acute ischemic stroke were treated with intravenous tPA according to a nationwide registry.13 One of the reasons for this low treatment rate might be the stringent criteria on eligibility set up by the Bureau of National Health Insurance,14 which is the single payer of the universal and mandatory health insurance program in Taiwan. However, the presence of single exclusion criterion, such as age >80 years, baseline NIHSS scores >25, or combination of prior stroke and diabetes mellitus, is not necessarily associated with an increased risk of SICH.15 Hopefully, applying risk score models to identify low-risk patients might increase the number of patients with stroke who could benefit from intravenous thrombolytic therapy.

In this study, we aimed to determine whether these risk scores could be used to predict SICH after intravenous thrombolysis in a Taiwanese population.

Methods

Study Population
As a joint initiative of 4 Taiwan stroke centers (Landseed Hospital, National Cheng Kung University Hospital, Chi-Mei Medical Center, and Chia-Yi Christian Hospital), we identified all consecutive stroke patients treated with intravenous tPA within 3 hours of symptom onset between January 2007 and June 2012. Eligibility for tPA treatment was determined following the guidelines of the American Heart Association,16 and included off-label use (aged >80 or NIHSS score >25). Variable dosing (0.6–0.9 mg/kg) were recommended according to the current Taiwan guidelines.17 Each study hospital maintained a stroke registry in accordance with the design of the nationwide Taiwan Stroke Registry,13 which prospectively registered all stroke patients presenting within 10 days of onset. Stroke severity of each patient was assessed by the NIHSS at baseline and at discharge. All thrombolysis patients underwent computed tomography (CT) or MRI between 24 and 36 hours after thrombolysis and additional scans in case of clinical deterioration. Results of the official neuroradiology report were used to determine the presence and the size of visible hypodensity on initial head CT scan and the presence of ICH on follow-up scans. Radiologists were blinded to the risk score variables. The study protocol was approved respectively by the Landseed Hospital Institutional Review Board (IRB), National Cheng Kung University Hospital IRB, Chi-Mei Medical Center IRB, and Chia-Yi Christian Hospital IRB.

Outcome Measures
The primary outcome was the presence of SICH after intravenous tPA treatment. Because different definitions of SICH were used among the various risk models, we used 3 definitions of SICH per the NINDS.10,15 The SPAN-100 index, created using the data from the NINDS tPA trials, aimed to predict clinical response and risk of ICH after thrombolysis.11 We included the SICH risk score, developed using data from the SITS-MOST (27804 patients), was intended to predict large cerebral parenchymal hemorrhages associated with severe clinical deterioration.4 The GRASPS score was constructed using data from the Get With The Guidelines-Stroke (10242 patients) to predict SICH per NINDS.10 The SICH model includes demographic factors, medical history (such as congestive heart failure, cancer, and kidney disease on dialysis), which may not be easily accessed in the hyperacute stroke management.

Statistical Analysis
Continuous variables were summarized as mean±SD or median (interquartile range), and categorical variables as counts and percentages and were compared with χ² test or Fisher exact test. We calculated the risk scores and the predicted probability of SICH for each patient according to each risk model. To assess the prediction performance of each risk model, we performed a univariate logistic regression on SICH by entering each risk score as a continuous variable. The model fit was measured with the Hosmer–Lemeshow goodness-of-fit statistic. The trend of SICH incidence across the increasing score values was assessed by the χ² test for trend. The discriminatory ability of each risk model was evaluated using the area under the receiver operating characteristic curve (c statistic). We compared the c statistic for each pair of the scores using the DeLong method.20 We considered P value <0.05 (2-tailed) statistically significant. All analyses were performed using MedCalc for Windows, version 12.3.0.0 (MedCalc Software, Mariakerke, Belgium).

Results

A total of 548 consecutive patients at study hospitals underwent intravenous tPA treatment of acute ischemic stroke within 3 hours of stroke onset (Landseed Hospital, n=39; National Cheng Kung University Hospital, n=202; Chi-Mei Medical Center, n=170; Chia-Yi Christian Hospital, n=137). Characteristics of the study population are shown in Table 1. The median dose administered was 0.86 mg/kg. The baseline NIHSS scores between the study hospitals were different (Table II in the online-only Data Supplement). The proportions of SICH among the study hospitals ranged from 4.0% to 10.2% (Fisher exact test, P=0.075) per NINDS, 2.6% to 8.8% (P=0.111) per ECASS II, and 2.5% to 5.8% (P=0.398) per SITS-MOST. The overall rates of SICH were 7.3% (95% confidence interval, 5.2%–9.9%) per NINDS, 5.3% (3.5% to 7.6%) per ECASS II, and 3.5% (2.1% to 5.4%) per SITS-MOST. The rate of SICH per NINDS was overpredicted by the GRASPS score (observed 7.3%, predicted 10.9%), whereas the rate of SICH per SITS-MOST was underpredicted by the SITS SICH risk score (observed 3.5%, predicted 1.6%; Table 2).
The abilities of these 5 risk models to predict SICH according to different definitions of SICH are summarized in Table 3. The Cucchiara score, the HAT score, and the SITS-SICH risk score effectively predicted the occurrence of SICH. However, the GRASPS score and the SPAN-100 index inadequately forecasted SICH in our patients. The SPAN index (namely, age in years plus NIHSS) also lacked good performance (odds ratio, 1.02, \( P = 0.063 \) per NINDS; odds ratio, 1.02, \( P = 0.069 \) per ECASS II; and odds ratio, 1.03, \( P = 0.082 \) per SITS-MOST). The observed rates of SICH according to different risk score models are shown in the Figure. The trend of increasing SICH incidence across rising score values was significant for risk scores across the definitions of SICH except the SPAN-100 index. The rates of SICH were not significantly different between patients with SPAN-100 index \( \geq 100 \) and those <100 regardless of the definitions of SICH. Overall, the \( c \) statistic was highest for the HAT score and lowest for the SPAN-100 index (Table 3). Significant differences in the \( c \) statistics were observed between the HAT score and the Cucchiara score for SICH per NINDS (\( P = 0.007 \)), between the HAT score and the GRASPS score for SICH per NINDS (\( P = 0.030 \)) and per SITS-MOST (\( P = 0.036 \)). Discrepancy was also noted between the HAT score and the SPAN-100 index for SICH per NINDS (\( P < 0.001 \)), SICH per ECASS II (\( P = 0.002 \)), and SICH per SITS-MOST (\( P = 0.003 \)).

**Discussion**

We found that the Cucchiara score, the HAT score, and the SITS-SICH risk score could reasonably predict SICH regardless of the definitions of SICH. Of them, the HAT score had the best ability to discriminate between patients with and without SICH because its \( c \) statistics were above or approaching an acceptable threshold of 0.7.\(^{22}\) The Cucchiara score and the SITS-SICH risk score showed a slightly lower ability of discrimination with \( c \) statistics ranging from 0.6 to 0.7. The predictive ability of the GRASPS score and the SPAN-100 index was inadequate because their predictive value was poor regardless of SICH definition. In addition, the SPAN-100 index had the lowest discriminatory ability.

Although the rates of SICH per NINDS and per ECASS II in our cohort were in agreement with those predicted by the SITS-SICH risk score, the probability of SICH per SITS-MOST (3.5%; 95% confidence interval, 2.1%–5.4%) was notably higher than expected (1.6%; Table 2). Identification of SICH might be subject to inter-rater variability and the variation in SICH rates was found to be highest across studies that reported SICH rates using the SITS-MOST criteria.\(^{23}\) Nevertheless, the rates of SICH according to various definitions in our cohort were comparable to those of an earlier multicenter study in Taiwan (Table 2).\(^{21}\) The distinct discrepancy between the observed and predicted rates of SICH might be subject to inter-rater variability and the variation in SICH rates was found to be highest across studies that reported SICH rates using the SITS-MOST criteria.\(^{23}\) Nevertheless, the rates of SICH according to various definitions in our cohort were comparable to those of an earlier multicenter study in Taiwan (Table 2).\(^{21}\)
incidence of SICH per SITS-MOST in our population might be attributed to patient characteristics (SICH after tPA tended to happen earlier or caused more marked worsening of neurological symptoms), apart from inter-rater variability in assessment.

To be clinically practical and easily applied at the bedside, a risk score using information easily available before the administration of thrombolysis to estimate the risk of SICH is favored. Of the available scoring models, the HAT score and the SEDAN score incorporated early infarct signs on the pretreatment head CT scan in addition to clinical parameters. Although extensive cerebral ischemia substantially increased the risk of SICH, lack of agreement among physicians in interpreting early infarct changes on CT probably limits its independent predictor of SICH and had an even higher weight than blood glucose. However, this finding may not be conclusive. We speculate that the inclusion of Asian race as one of the predictors may explain the overestimation of SICH risk by the GRASPS score in our population.

SICH is a disastrous thrombolysis-related complication and often associated with poor outcomes. It is still unclear which definition of SICH is best correlated with stroke outcomes. The NINDS definition considers any CT-documented hemorrhage that is temporally related to any clinical deterioration as SICH, and tends to be confounded by deterioration caused by infarct edema and inconsistency in judgment between clinicians. Studies showed that the ECASS II definition had the highest inter-rater agreement and the largest contribution to worst outcomes. Patients with SICH per SITS-MOST was also found to have the highest risk for death and poor outcome.

A proportion of our patients were treated with a lower dose of intravenous tPA. Whether the incidence of SICH is similar between standard dose and low-dose regimens remains unclear. A systematic review on intravenous thrombolysis in Asians found that both standard dose and low-dose regimens were associated with rates of SICH comparable with those seen in the NINDS and SITS-MOST studies. Furthermore, an open-label study found no difference in the occurrence of SICH between the standard-dose group and low-dose group (0.7 mg/kg). Our study reflects the real world of current practice.
A limitation of our study is that the determination of symptomatic versus asymptomatic hemorrhage may be influenced by the inter-rater variability between participating investigators. However, the stroke neurologists and the radiologists were blinded to the risk score variables when interpreting the data. Second, we did not explore hospital characteristics that might potentially alter the incidence of SICH (eg, the quality of patient care after thrombolysis). Notably, the baseline stroke severity might largely explain hospital variations in SICH rates. Third, all risk models evaluated are predominantly developed and validated in patients from European-American ancestry. To what extent the different performance of these risk scores is attributable to racial differences remains to be explored. Fourth, caution should be taken in generalizing our findings in light of the small proportion of stroke patients who received intravenous tPA in Taiwan.

Conclusions
Our study suggests that in selected models of risk score, the Cucchiara score, the HAT score, and the SITS SICH risk score were reasonably predictive of SICH after thrombolysis independent of the SICH definition used. Predictive performance of the GRASPS score and the SPAN-100 index was less satisfactory in our patients. Moreover, only the HAT score had an acceptable discrimination. Further refinement of these scores to increase their discriminatory ability may be warranted.

Disclosures
None.

References


Comparison of Risk-scoring Systems in Predicting Symptomatic Intracerebral Hemorrhage After Intravenous Thrombolysis
Sheng-Feng Sung, Solomon Chih-Cheng Chen, Huey-Juan Lin, Yu-Wei Chen, Mei-Chiun Tseng and Chih-Hung Chen

Stroke. 2013;44:1561-1566; originally published online April 30, 2013; doi: 10.1161/STROKEAHA.111.000651
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/44/6/1561

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2013/04/30/STROKEAHA.111.000651.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/
Title

Comparison of risk-scoring systems in predicting symptomatic intracerebral hemorrhage after intravenous thrombolysis.

Supplemental Tables

Table S1. Comparison of risk score models.

<table>
<thead>
<tr>
<th>Model</th>
<th>Variables used</th>
<th>Cut-off points</th>
<th>Definition of SICH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cucchiara score</td>
<td>Age, NIHSS, Glucose, Platelet count</td>
<td>&gt;60 y, &gt;10, &gt;150 mg/dL, &lt;150,000 /mm³</td>
<td>NINDS</td>
</tr>
<tr>
<td>HAT score</td>
<td>NIHSS, Glucose, Hypodensity on CT, History of diabetes</td>
<td>&lt;15, 15-20, &gt;20, &gt;200 mg/dL, &lt;1/3 of MCA territory, ≥1/3 of MCA territory</td>
<td>NINDS&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>SITS SICH risk score</td>
<td>Age, NIHSS, Glucose, SBP, Weight, OTT, Aspirin monotherapy, Aspirin + clopidogrel, History of hypertension</td>
<td>≥72 y, 7-12, ≥13, ≥180 mg/dL, ≥146 mm Hg, ≥95 kg, ≥180 min</td>
<td>SITS-MOST</td>
</tr>
<tr>
<td>GRASPS score</td>
<td>Age, NIHSS, Glucose, SBP, Ethnicity, Gender</td>
<td>≤60, 61-70, 71-80, &gt;80 y, 0-5, 6-10, 11-15, 16-20, &gt;20, &lt;100, 100-149, ≥150 mg/dL, &lt;120, 120-149, 150-179, ≥180 mm Hg, Non-Asian, Asian</td>
<td>NINDS</td>
</tr>
<tr>
<td>SPAN-100 index</td>
<td>Age + NIHSS</td>
<td>≥100</td>
<td>NINDS</td>
</tr>
</tbody>
</table>


<sup>a</sup>The definition of SICH used by the HAT score is not exactly the same as that in the NINDS study.
Table S2. The baseline NIHSS score, risk scores to predict SICH, and incidence of SICH.

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>LH</th>
<th>NCKUH</th>
<th>CMMC</th>
<th>CYCH</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>548</td>
<td>39</td>
<td>202</td>
<td>170</td>
<td>137</td>
<td></td>
</tr>
<tr>
<td>Baseline NIHSS, median (IQR)</td>
<td>13 (8-20)</td>
<td>10 (6-13)</td>
<td>11 (8-20)</td>
<td>13 (9-18)</td>
<td>15 (10-22)</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Risk scores, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cucchiara score</td>
<td>1.77 (0.93)</td>
<td>1.46 (0.97)</td>
<td>1.71 (0.95)</td>
<td>1.81 (0.86)</td>
<td>1.91 (0.95)</td>
<td>0.037&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>HAT score</td>
<td>1.18 (1.07)</td>
<td>1.03 (1.09)</td>
<td>1.07 (1.05)</td>
<td>1.23 (1.09)</td>
<td>1.34 (1.07)</td>
<td>0.111&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>SITS SICH risk score</td>
<td>3.92 (1.61)</td>
<td>3.33 (1.31)</td>
<td>3.88 (1.65)</td>
<td>3.85 (1.59)</td>
<td>4.24 (1.61)</td>
<td>0.011&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>GRASPS score</td>
<td>80.8 (8.4)</td>
<td>76.6 (8.1)</td>
<td>80.5 (8.6)</td>
<td>81.4 (8.3)</td>
<td>81.7 (8.1)</td>
<td>0.006&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>SPAN-100 index</td>
<td>80.8 (15.5)</td>
<td>72.7 (13.8)</td>
<td>81.8 (16.5)</td>
<td>80.2 (13.5)</td>
<td>82.3 (16.3)</td>
<td>0.004&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>SICH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per NINDS</td>
<td>7.3%</td>
<td>5.1%</td>
<td>4.0%</td>
<td>9.4%</td>
<td>10.2%</td>
<td>0.075&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Per ECASS II</td>
<td>5.3%</td>
<td>2.6%</td>
<td>3.0%</td>
<td>5.9%</td>
<td>8.8%</td>
<td>0.111&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Per SITS-MOST</td>
<td>3.5%</td>
<td>2.6%</td>
<td>2.5%</td>
<td>2.9%</td>
<td>5.8%</td>
<td>0.398&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>


<sup>a</sup>Kruskal-Wallis test
<sup>b</sup>ANOVA
<sup>c</sup>Fisher’s exact test