# Accuracy of clinical risk scores in predicting post-rtPA intracerebral hemorrhage in a Thai cohort

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# Accuracy of Clinical Risk Scores in Predicting Post-rtPA Intracerebral Hemorrhage in a Thai Cohort

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***Objective***: Several prediction scores for post-rtPA symptomatic intracerebral hemorrhage (SICH) have been developed based on western datasets. The authors compared the accuracy of eight clinical risk scores to predict post-rtPA SICH in the Thai population.

***Materials and Methods***: The authors applied eight risk scores to a retrospective cohort of acute ischemic stroke patients who received IV rtPA between 2005 and 2015 in a tertiary care center (Siriraj Hospital, Mahidol University, Thailand). The main outcomes were SICH defined according to the ECASSII and the NINDS definitions. All risk scores were then compared using ROC curve, sensitivity, specificity, NPV and PPV, and the LR+ and LR–.

***Results***: Four hundred five patients were included. The rates of SICH-ECASSII and SICH-NINDS definition were 7.1% and 11.1%, respectively. Among the eight risk scores, the DRAGON score, the HAT score, and the GRASPS score were the three best scores for predicting by SICH-ECASSII definition. The DRAGON score achieved 66% sensitivity and 58% specificity (AUC 0.60, PPV 11%, NPV 96%, LR+ 1.56, LR– 0.59), the HAT score had 72% sensitivity, 50% specificity (AUC 0.65), while GRASPS score reached 79% sensitivity, but only 40% specificity (AUC 0.63).

***Conclusion***: The present study demonstrates that the existing SICH risk scores did not perform well in the studied population.

***Keywords***: Risk scores, Post-rtPA intracerebral hemorrhage, Predicting, Stroke, Thai patients

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Clinical practice guidelines according to the American Heart Association and the American Stroke Association (AHA/ASA) in 2007, and the American College of Chest Physicians in 2008 have recommended the thrombolytic agent recombinant tissue plasminogen activator (rtPA) for the treatment of acute ischemic stroke (AIS) in eligible patients[1,2].

However, symptomatic intracerebral hemorrhage (SICH) is a serious complication of intravenous (IV) thrombolysis treatment associated with high mortality and increased risk of poor functional outcome. In Thailand, a previous study that included 192 patients with AIS who were treated with IV rtPA found that SICH occurred in 5.7% of patients and asymptomatic ICH in 13.0%[3]. Other studies[4,5] suggested that post-rtPA ICH incidence was slightly increased among Asian ethnic groups.

Many clinical scores have been developed to predict SICH in stroke patients undergoing rtPA therapy. However, these models were mostly developed from western populations and may not be applicable in Thai patients. After an extensive literature review, the authors found 10 clinical risk scores developed to predict SICH after rtPA therapy. They are Post-thrombolysis Risk Score (PRS)[6], the Hemorrhage After Thrombolysis (HAT) score[7], the iScore[8], the Safe Implementation of Thrombolysis in Stroke (SITS)-SICH risk score[9], the blood Sugar,

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**Table 1.** The existing clinical scores and its components

| Score | Components |
|---|---|
| PRS | Age, admission NIHSS, glucose, platelet count |
| HAT | Diabetes mellitus or glucose, admission NIHSS, early CT hypodensity |
| iScore | Age, sex, admission CNS or NIHSS, stroke subtype, risk factor (atrial fibrillation, congestive heart failure, previous myocardial infarction, current smoker), comorbid condition (cancer, renal dialysis), preadmission disability, glucose |
| SITS-SICH | Age, weight, hypertension, aspirin/clopidogrel, admission NIHSS, initial SBP, glucose, OTT |
| SEDAN | Age, NIHSS, glucose, HDMCA sign, early CT infarct |
| GRASPS | Glucose, race, age, sex, initial SBP, NIHSS |
| SPAN-100 | Age, admission NIHSS |
| ASTRAL | Age, admission NIHSS, OTT, decreased level of consciousness, visual field defects, glucose |
| Stroke-TPI | Age, NIHSS, gender, SBP, OTT, glucose, history of diabetes, history of stroke |
| DRAGON | Age, prestroke mRS, HDMCA or early CT infarct, glucose, OTT, admission NIHSS |

PRS=post-thrombolysis risk score; HAT=hemorrhage after thrombolysis score; SITS= Safe Implementation of Thrombolysis in Stroke; SICH=symptomatic intracerebral hemorrhage; SEDAN=blood Sugar, Early infarct signs and hyperDense cerebral artery sign, Age, and NIHSS score; GRASPS=Glucose Race Age Sex Pressure Stroke Severity score; SPAN-100=stroke prognostication using age and NIHSS-100 index; ASTRAL=Acute Stroke Registry and Analysis of Lausanne; Stroke-TPI=stroke-thrombolytic predictive instrument; DRAGON=Dense cerebral artery prestroke modified Rankin scale Age Glucose Onset-to-treatment time NIHSS score; NIHSS=National Institute of Health Stroke Scale; CT=computed tomography; CNS=Canadian Neurological Scale; SBP=systolic blood pressure; OTT=onset-to-treatment time; HDMCA=hyperdense middle cerebral artery; mRS=modified Rankin Scale

Early infarct signs and hyperDense cerebral artery sign, Age, and NIHSS (SEDAN) score[10], the Glucose Race Age Sex Pressure Stroke Severity (GRASPS) score[11], the Stroke Prognostication using Age and NIHSS (SPAN)-100 index[12], the Acute Stroke Registry and Analysis of Lausanne (ASTRAL) score[13], the Stroke-Thrombolytic Predictive Instrument (Stroke-TPI)[14], and the Dense cerebral artery prestroke modified Rankin scale Age Glucose Onset-to-treatment time NIHSS score (DRAGON)[15]. Each score and its components are shown in Table 1.

## Objective

In the present study, the primary objective was to evaluate and compare the accuracy of existing clinical risk scores in predicting post-rtPA intracerebral hemorrhage in AIS in Thais. The secondary objective is to evaluate the prevalence of SICH and functional outcome in Thai stroke patients who had undergone rtPA therapy. In addition, the authors hoped to identify other significant risk factors for SICH after rtPA that might be able to be included in predictive tools to be developed in the future.

## Materials and Methods

### *Study population*

The authors identified all the AIS patients that received IV rtPA between August 2005 to December 2015 in a tertiary care center (Siriraj Hospital, Mahidol University, Thailand). All patients were eligible for IV rtPA according to Siriraj's stroke fast track protocol with the dosage between 0.6 and 0.9 mg/kg. All patients were admitted to the stroke unit for at least 24 hours for close neurological monitoring and treated according to the national guideline. An NIHSS and a computed tomography (CT) brain scan were performed prior to and at 24 hours after receiving thrombolysis in all patients. Patients who did not complete the total calculated dose of rtPA, had at least one component of the clinical risk scores missing, or underwent other treatment for ischemic stroke other than rtPA administration such as mechanical thrombectomy within 24 hours, were excluded. The study protocol was approved by the Siriraj Institutional Review Board (134/2558:EC1).

### *Outcome measures*

The primary outcome was the presence of SICH after rtPA therapy. SICH was defined per the National Institute of Neurological Diseases and Stroke (NINDS) and the European-Australasian Acute Stroke Study II (ECASSII) definition. SICH per NINDS definition was defined as any neurological decline and any cerebral hemorrhage in less than 36 hours following rtPA administration attributed to ICH and verified by CT or magnetic resonance imaging

(MRI)[16]. SICH per ECASSII definition was defined as any intracranial bleed and 4 points or more clinical decline on the NIHSS within seven days following the rtPA administration[17]. The secondary outcome was the functional outcome after the rtPA therapy categorized by the modified Rankin Score (mRS) as 4 or greater for a catastrophic outcome.

### *Statistical analysis*

Categorical variables were presented as counts and percentages and continuous variables were summarized in mean ± standard deviation (SD). The prevalence of post-rtPA SICH in AIS patients that underwent rtPA therapy was evaluated and presented with the 95% confidence interval. Risk scores and the predicted probability of SICH and catastrophic outcome (mRS of four points or more) for each patient were calculated according to each risk model. The authors believe that practical scores should be easy to use and assess, and their components should not involve sophisticated investigation. Visual field defects, which are a component of the ASTRAL score, may be inaccurate in severely compromised patients. The Stroke-TPI requires the ASAT tool to be calculated, which may be difficult in clinical practice. These two scores were excluded from the present study. The accuracy of each score was analyzed and presented with sensitivity and specificity along with positive predictive value (PPV), negative predictive value (NPV), and the likelihood ratios (LR+ and LR–). Risk factors were compared between those with and without SICH-ECASSII using the Chi-square or Fisher's exact test (for categorical risk factors) and independent t-test for continuous risk factors. All analysis was conducted using the R statistical package (V3.2.1, R core team, 2016) and a significance level of 0.05 was used throughout all analysis.

## Results

Four hundred sixty-three patients were registered in the Siriraj's IV rtPA stroke fast track registry as shown in Figure 1. Eight of them were excluded due to non-stroke diagnosis and protocol violation. Fifty more cases were excluded according to the exclusion criteria. Only 405 cases were included in the present study. The baseline characteristics of the study population are outlined in Table 2. The rates of SICH-ECASSII and SICH-NINDS were 7.16% (n = 29) and 11.11% (n = 45), respectively. Catastrophic outcome at discharge (mRS of four points or more) was 54.07% (n = 219). Accuracy of each score in predicting post-rtPA ICH was compared according to both the ECASSII and NINDS definitions as shown in Table 3. Among the eight risk scores, the DRAGON score, HAT score, and GRASPS score were the three best scores for predicting SICH according to the ECASSII definition. The DRAGON score achieved 66% sensitivity and 58% specificity (AUC 0.59), the HAT score had 72% sensitivity, 50% specificity (AUC 0.65), while GRASPS score had 79% sensitivity, but had only 40% specificity (AUC 0.63). In terms of SICH according to the NINDS definition, PRS (sensitivity 67%, specificity 78%), DRAGON (sensitivity 67%, specificity 59%) and HAT (sensitivity 73%, specificity 51%) were the most accurate scores. Although the SITS-SICH and SPAN-100 scores had high specificity, they both had low sensitivity for predicting post-rtPA SICH according to both definitions. The SITS-SICH score achieved only 17% sensitivity, 95% specificity (AUC 0.68) whereas SPAN-100 had a sensitivity of 7% and 89% specificity (AUC 0.53).

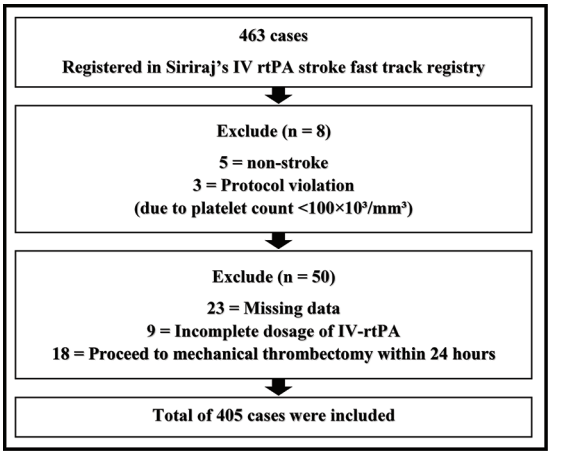


**Figure 1.** Diagram showing the total number of patients included in study.

IV, intravenous; rtPA, recombinant tissue plasminogen activator

## Discussion

The present study demonstrated comparatively poor accuracy of the existing eight clinical risk scores in predicting post-rtPA ICH in the Thai population. The authors showed these scores, along with their recommended cut-points, failed to accurately predict the ECASSII and NINDS SICH outcomes in the present population.

The present study results differed from previous western studies[18,19]. David et al (2014) found that DRAGON and HAT score were among the four best-performing scores, achieving considerably better

**Table 2.** Baseline characteristics of the study population

| Factors | SICH-ECASSII, n (%) | | p-value |
|---|---|---|---|
| | No (n = 376) | Yes (n = 29) | |
| Sex: male | 187 (49.7) | 10 (34.5) | 0.16 |
| Race: Asian | 375 (99.7) | 29 (100) | 1 |
| Age (years), Mean±SD | 66.0±14.5 | 66.2±13.1 | 0.91 |
| Weight (kg), Mean±SD | 62.7±12.9 | 68.2±11.8 | 0.02* |
| Door time (minutes), Mean±SD | 95.9±54.3 | 107.1±63.2 | 0.37 |
| CT time (minutes), Mean±SD | 114.7±54.1 | 122.5±58.1 | 0.49 |
| OTT (minutes), Mean±SD | 159.9±53.1 | 165.4±57.9 | 0.63 |
| ASPECTS, Mean±SD | 8.4±1.6 | 7.2±2.4 | 0.01* |
| NIHSS, Mean ± SD | 13.5±6.5 | 15.6±6.0 | 0.08 |
| Initial SBP (mmHg), Mean±SD | 150.2±29.0 | 157.72±37.3 | 0.30 |
| Initial DBP (mmHg), Mean±SD | 84.4±18.1 | 91.6±26.8 | 0.17 |
| rtPA SBP (mmHg), Mean±SD | 143.4±22.2 | 149.1±25.8 | 0.25 |
| rtPA DBP (mmHg), Mean±SD | 80.8±14.6 | 85.4±16.6 | 0.16 |
| Glucose (mg/dl), Mean±SD | 148.1±60.3 | 163.4±58.4 | 0.18 |
| Platelets ($\times 10^3/mm^3$), Mean±SD | 244±85 | 209.6±63 | 0.01* |
| Total dose rtPA (mg) Mean±SD | 47.3±13.0 | 50.2±10.1 | 0.15 |
| Diabetes mellitus | 112 (29.8) | 13 (44.8) | 0.14 |
| Hypertension | 250 (66.5) | 25 (86.2) | 0.05* |
| Atrial fibrillation | 100 (26.6) | 14 (48.3) | 0.02* |
| Smoker | 55 (14.6) | 2 (6.8) | 0.38 |
| Coronary artery disease | 74 (19.7) | 10 (34.5) | 0.10 |
| Hyperlipidemia | 135 (35.9) | 12 (41.3) | 0.70 |
| Congestive heart failure | 34 (9.0) | 3 (10.3) | 1 |
| Chronic kidney disease | 46 (12.3) | 6 (20.7) | 0.31 |
| Cancer | 18 (4.8) | 2 (6.9) | 0.95 |
| Prior stroke | 67 (17.8) | 3 (10.3) | 0.44 |
| Anterior circulation | 359 (95.5) | 29 (100) | 0.05* |
| HDMCA | 119 (31.6) | 15 (51.7) | 0.05* |
| Early infarct on CT | | | <0.01* |
| No | 153 (40.7) | 11 (37.9) | |
| <1/3 | 209 (55.6) | 9 (31.0) | |
| >1/3 | 14 (3.7) | 9 (31.0) | |

CT=computed tomography; OTT=onset-to-treatment time; ASPECTS=Alberta stroke program early CT score; NIHSS=National Institute of Health Stroke Scale; SBP=systolic blood pressure; DBP=diastolic blood pressure; rtPA=recombinant tissue plasminogen activator; HDMCA=hyperdense middle cerebral artery; SD=standard deviation

* p-value <0.05

results than in the present study (AUCNINDS 0.76 and 0.70, respectively). Another retrospective cohort study in Belgium[19] demonstrated the reliability of five clinical prediction scores for SICH both per NINDS and ECASSII definitions. All of the five scores (PRS, HAT, SITS-SICH, SEDAN, GRASPS

**Table 3.** Accuracy of each scores in predicting post-rtPA ICH by ECASSII definition and NINDS definition

| Score | SICH-ECASSII | | | | | | | SICH-NINDS | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Sen (%) | Spec (%) | PPV (%) | NPV (%) | AUC | LR+ | LR– | Sen (%) | Spec (%) | PPV (%) | NPV (%) | AUC | LR+ | LR– |
| DRAGON >6 | 66 | 58 | 11 | 96 | 0.60 | 1.56 | 0.59 | 67 | 59 | 17 | 93 | 0.64 | 1.63 | 0.56 |
| HAT ≥2 | 72 | 50 | 10 | 96 | 0.65 | 1.46 | 0.55 | 73 | 51 | 16 | 94 | 0.68 | 1.51 | 0.52 |
| GRASPS ≥80 | 79 | 40 | 9 | 96 | 0.63 | 1.33 | 0.52 | 80 | 41 | 15 | 94 | 0.67 | 1.36 | 0.49 |
| PRS ≥3 | 37 | 79 | 5.7 | 87.5 | 0.62 | 1.85 | 0.78 | 67 | 78 | 28 | 95 | 0.63 | 3.08 | 0.43 |
| SEDAN ≥4 | 34 | 78 | 11 | 94 | 0.59 | 1.64 | 0.84 | 38 | 79 | 19 | 91 | 0.61 | 1.84 | 0.78 |
| iScore ≥200 | 21 | 82 | 8 | 93 | 0.58 | 1.14 | 0.97 | 31 | 83 | 19 | 91 | 0.64 | 1.87 | 0.83 |
| SITS-SICH ≥8 | 17 | 95 | 22 | 94 | 0.68 | 3.6 | 0.87 | 13 | 95 | 26 | 90 | 0.64 | 2.82 | 0.91 |
| SPAN-100 >100 | 7 | 89 | 5 | 93 | 0.53 | 0.62 | 1.05 | 16 | 90 | 16 | 89 | 0.59 | 1.51 | 0.94 |

SICH=symptomatic intracerebral hemorrhage; NINDS=National Institute of Neurological Diseases and Stroke; ECASSII=European-Australasian Acute Stroke Study II; Sen=sensitivity; Spec=specificity; PPV=positive predictive value; NPV=negative predictive value; AUC=area under curve; LR+=positive likelihood ratio; LR–=negative likelihood ratio; DRAGON=Dense cerebral artery prestroke modified Rankin scale Age Glucose Onset-to-treatment time NIHSS; HAT=hemorrhage after thrombolysis; GRASPS=Glucose Race Age Sex Pressure Stroke Severity; PRS=post-thrombolysis risk score; SEDAN=blood Sugar, Early infarct signs and hyperDense cerebral artery sign, Age, and NIHSS; SITS=Safe Implementation of Thrombolysis in Stroke; SPAN-100= stroke prognostication using age and NIHSS-100 index

score) demonstrated better performance compared to the present study (AUCNINDS ranging 0.66 to 0.70 and AUCECASSII ranging 0.69 to 0.86). Surprisingly, the SITS-SICH score also performed well in their study (AUCNINDS 0.68 and AUCECASSII 0.76), in contrast to the present study (AUCNINDS 0.64 and AUCECASSII 0.68) with additional low sensitivity (range from 13% to 17%) across both definitions. This supports the evidence that the western clinical risk scores might not be accurate when applying to Asians.

A previous study in an Asian population demonstrated quite different results for the performance of these scores in predicting post-rtPA SICH. In a prospective Chinese cohort study[20], which included data from 67 stroke centers and 811 patients who underwent IV rtPA, the PRS score achieved considerably better accuracy for both the SICH-NINDS and SICH-ECASSII definitions (AUCNINDS 0.71 and AUCECASSII 0.73). However, the study focused on only four scores, the PRS, GRASPS, SEDAN, and SITS-SICH. The latter two also performed poorly in the present study. However, since Li et al (2015) did not include several well-established risk scores, including those identified as performing well, the authors feel their results are inconclusive[20].

Another prospective cohort study in Taiwan[5] that included 548 patients from four hospitals showed similar results to the present study. The study included the PRS, HAT, SITS-SICH, GRASPS, and SPAN-100 score. The former two scores had similar results for AUC compared to the present study for predicting post-rtPA SICH according to both definitions (range from 0.6 to 0.7). It should be noted that only the HAT score had an acceptable discriminatory ability with the highest c-statistic (range 0.69 to 0.73) across the definitions of SICH (ECASSII, NINDS, and SITS-MOST definitions) in the Taiwanese population.

However, a recent analysis in a western population[21] from the third International Stroke Trial (IST-3) evaluated the HAT, SEDAN, GRASPS, DRAGON, Totaled Health Risks in Vascular Events (THRIVE), and a model with the National Institutes of Health Stroke Scale and age. The study demonstrated that these scores performed modestly in predicting SICH (AUC ranging between 0.56 to 0.68), a result similar to the present study. It was concluded that clinical prediction models were unable to predict patients who have high-risk for SICH, and those predicted to be at high-risk for post-rtPA SICH still benefited from receiving thrombolysis. The authors feel that the variability in the performance of the existing clinical risk scores may be because recommended cut-points for each score cannot be generalizable across all populations. However, the purpose of the scores should be for risk assessment in the consent discussion before giving rtPA treatment, and not to exclude patients from the therapy.

A possible explanation for the less accuracy of post-rtPA SICH in the present population could be due to the difference between Asian versus Caucasian

ethnic characteristics. There is evidence showing the higher overall proportion of ICH in Asian stroke patients[22]. Supporting data point out that hypertension is one of the major etiologies for ICH. A study in Thailand also found that less than half of Thai patients had an awareness of their hypertension comorbidity and achieved well-controlled blood pressure[23]. Another explanation for poorer accuracy in the present population is because some other significant risk factors had not been included in those scores, such as the ASPECT score and cortical microbleeds. Particularly, the latter factor had a higher prevalence among the Asian population[24]. Therefore, further studies are needed to develop better predictive tools for predicting post-rtPA SICH for Asian stroke patients.

The present study did have some limitations. First, as SICH is a relatively rare condition, the present study cohort was collected over quite a lengthy period. During this period, there may have been improvements in treatment and/or more effective protocols implemented, resulting in substantial reductions in door-to-needle times and changes in the risk of ICH over the course of data collection. In the beginning of the study, according to Siriraj's stroke fast track protocol, the rtPA dosage of 0.6, 0.75, and 0.9 mg/kg/dose were used in patients who came within 151 to 180, 91 to 150, and less than 90 minutes after the onset of the symptoms, respectively. The protocol was changed to the current guideline in December 2013, when all AIS patients within 4.5 hours onset-time window received a 0.9 mg/kg/dose. Second, the present study was based on data from a single large center and might not be generalizable to the Asian population, or even, to the Thai population. Given the low prevalence of SICH in AIS patients, the present sample of 405 patients is relatively modest. Further studies in larger samples may be required.

The present study also had some strengths. First, the authors considered eight different models. Additionally, the authors demonstrated that the more complex models had no better utility compared to simple ones for predicting post-rtPA SICH.

## Conclusion

The present study demonstrated that existing SICH risk scores did not perform well in the Thai population. Further study is needed to develop a new model to better predict SICH post IV rtPA among Asians in general, and Thais in particular.

## What is already known on this topic?

Several prediction scores for post-rtPA SICH have been developed but most of them have been derived from western datasets. The clinical utility for those prediction scores among Asian population is questionable.

## What this study adds?

The authors compared as many as eight clinical risk scores in their accuracy and clinical utility to predict post-rtPA SICH in the Thai population. These findings demonstrate that the existing clinical risk scores did not perform well in a Thai population, supporting the need of a new model to better predict post-rtPA SICH in South East Asian populations.

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## Conflicts of interest

The authors declare no conflict of interest.

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