Prediction of Symptomatic Intracranial Hemorrhage after Intravenous Thrombolysis in Acute Ischemic Stroke: The Symptomatic Intracranial Hemorrhage Score

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Background: Symptomatic intracranial hemorrhage (sICH) is common after intravenous thrombolysis in acute ischemic strokes (AISs). Available predictive scoring systems were derived mostly in the Western countries. *Methods:* Retrospective data in 1 provincial and 4 regional hospitals in the northern part of Thailand were reviewed. Patients with AIS, to whom recombinant tissue plasminogen activator (rt-PA) had been prescribed, were classified into 3 groups: no intracranial hemorrhage (no ICH), asymptomatic intracranial hemorrhage (asICH) and sICH. Coefficients under the multilevel ordinal logistic model were transformed into item scores and sum scores. Measures of discrimination, calibration, and internal validation were analyzed. *Results:* Among 1172 patients, there were 78.8% with no ICH (n = 923), 13.1% with asICH (n = 154), and 8.1% with sICH (n = 95). The final model was named "SICH score" and included 6 variables: valvular heart diseases, use of aspirin, systolic blood pressure prior to thrombolysis that is 140 mmHg or higher, National Institutes of Health Stroke Scale scores higher than 10 and 20, a platelet count lower than 250,000 cell/mm^3, and use of intravenous antihypertensive drugs during thrombolysis, with an Area under Receiver Operating Characteristic of .75 (95% confidence interval, .71-.80). *Conclusion:* The SICH score could be an assisting tool to predict an individual risk of sICH after intravenous thrombolysis for AIS in Thai patients.
Key Words: Stroke—thrombolytic therapy—tissue plasminogen activator—intracranial hemorrhage—clinical prediction rule—prognosis.

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Introduction

Intravenous recombinant tissue plasminogen activator (rt-PA) in acute ischemic stroke (AIS) is the only proved treatment with the number needed to benefit of 6.1 (95% confidence interval [CI], 5.6-6.7), but its complication, symptomatic intracranial hemorrhage (sICH), is still high, leading to severe disability or death with the number needed to harm of 37.5 (95% CI, 34.6-40.5).[1] Many physicians were reluctant to use thrombolysis for AIS in fear of sICH previously reported with the mean upper limit of tolerable risk of 3.4%.[2] A systematic review and meta-analysis of 55 studies tried to quantify the diversities of variables and their association with post-rt-PA intracranial hemorrhage (post-rt-PA ICH).[3] To date, there was no single variable to prognosticate such complications.

Many scoring systems have been constructed to predict the risk of sICH following thrombolysis, including the Hemorrhage After Thrombolysis (HAT) score[4]; the Multicenter Stroke Survey (MSS) score[5]; the Safe Implementation of Thrombolysis in Stroke–symptomatic intracerebral hemorrhage (SITS-SICH) risk score[6]; the blood Sugar, Early ischemic infarct signs, hyperDense cerebral artery sign, Age, and the National Institutes of Health Stroke Scale (NIHSS) (SEDAN) score[7]; and the glucose at presentation, race, age, sex, systolic blood pressure, and severity of stroke (GRASPS) score.[8] The predictive abilities varied from fair to good (AuROC, .68-.77) using different domains, outcome definitions, and score modelings.

Asian ethnicity was mentioned as an important factor associated with sICH (odds ratio [OR], 2.12; 95% CI, 1.28-3.50; $P = .004$)[8] that could be explained by different blood coagulation-fibrinolysis factors.[9] Most of these scoring systems were derived from Western countries. The GRASPS score is the only scoring system that comprised Asian patients, but the percentage was very small (2.3%).[8] In Thailand, we previously found a different set of prognostic parameters that differed from the Western ones.[10,11] This study aimed to develop a simple scoring system by using prognostic parameters obtained from Thai patients to predict post-rt-PA ICH before starting the treatment, which may be more suitable to generalize to Thai or possibly other Asian populations.

Methods

Patients

A retrospective cohort design was conducted in 1 provincial and 4 regional hospitals in the northern part of Thailand during January 2008 to September 2016. All AIS patients to whom standard dose with 0.9 milligram per kilogram body weight of intravenous rt-PA had been prescribed were reviewed. Following the routine protocol of The Thai Stroke Society and The National Health Security Office, 24 hours after rt-PA administration, the follow-up brain imaging (computed tomography or CT) was done to evaluate complications. The medical files, laboratory data, CT findings, and final end points were extracted. Patients without follow-up CT according to the protocol, receiving incomplete precalculated doses due to immediate complications or some contraindications encountered later, and strokes caused by some other determined etiology such as vasculitis, systemic lupus erythematosus, human immunodeficiency virus, protein C, protein S deficiency, septic emboli, tumor, or neurosyphilis were excluded. Variables measured before rt-PA administration were collected.

The study has been approved by The Human Research Ethics Committee, Faculty of Medicine, Thammasat University, and all the ethics committees of the participating hospitals.

Definitions of post-rt-PA ICH: an outcome of interest

We classified final clinical outcomes into 3 groups—no intracranial hemorrhage (no ICH), asymptomatic intracranial hemorrhage (asICH), and sICH—based on the following definitions:

1) No ICH were patients in whom no hemorrhage was found on follow-up CT brain within 24 hours after treatment and were clinically stable within the next 7 days.
2) asICH were patients in whom intracranial hemorrhage was found on follow-up CT brain within 24 hours after treatment but without clinical deterioration and were clinically stable within the next 7 days.
3) sICH were patients in whom intracranial hemorrhage was defined as symptomatic (if the patients had clinical deterioration causing an increase in the NIHSS score of more than or equal to 4 points and if the hemorrhage was likely to be the cause of clinical deterioration).[12] However, in case of doubt whether edema or hemorrhage was the leading pathology, an association of the hemorrhage with the deterioration was assumed. The time window was also 7 days.

Deteriorated patients in whom follow-up CT brain showed brain edema without intracranial hemorrhage were classified as the “no ICH” group.

Deteriorated patients in whom follow-up CT brain showed brain edema but with small hemorrhage were classified as “asICH” group.

To improve the reliability of the outcomes and to reduce biases, the final clinical outcomes were assessed by 2 of 3 experts (1 emergency physician and 2 internists) under blinding approaches.

Predictive Parameters

Prognostic factors were retrieved from various aspects: demographic data, medical histories, clinical findings, laboratory investigations, and specific treatments. In most