Derivation and Validation of a Scoring System for Intravenous Tissue Plasminogen Activator Use in Asian Patients

Leonard L. L. Yeo, MD,* Shih-Chao Chien, MD,¶ Jr-Rung Lin, PhD,† Chia-Wei Liow, MD,‡ Jiann-Der Lee, MD,§ Tsung-I Peng, MD, PhD,‖ Teoh Hock Luen, MD,* Vijay Sharma, MD,* Bernard Chan, MD,* and Tsong-Hai Lee, MD, PhD¶ for the SRICHS Group

Background and Purpose: As Chinese Asian populations have an increased risk of intracerebral hemorrhage (ICH) after intravenous tissue plasminogen activator (IV tPA), we aimed to design a rapid, clinically applicable risk scoring system to predict ICH and functional outcomes after IV tPA treatment in Asian ischemic stroke patients. *Methods:* From January 2009 to December 2012, consecutive acute ischemic stroke patients treated with IV tPA recruited from the Stroke Registry in Chang Gung Healthcare System (SRICHS) in Taiwan and the National University Hospital of Singapore (NUHS) acute stroke database were used to create and validate a scoring system. Nomogram was created for ICH and 3-month mortality. *Results:* In total, 932 patients were included in the study: 386 from SRICHS for the derivation of scoring system and 546 from NUHS to validate it. We used nomograms to assign weightage to the scoring system. The presence of atrial fibrillation, glucose level, and the National Institutes of Health Stroke Scale (NIHSS) score were significantly associated with the risk of ICH. Age, NIHSS score, hyperlipidemia, and the presence of post-tPA ICH were significantly associated with mortality. The areas under the curve of derivation and validation cohorts were .663 and .662 for ICH, and .808 and .790 for mortality, respectively. *Conclusions:* The scoring system using nomograms can provide a fast, practical, and user-friendly tool that allows physicians to predict the risk of ICH and functional outcomes with IV tPA treatment in a clinical setting. **Key Words:** intracerebral hemorrhage—tissue plasminogen activator—nomograms—stroke—prognosis—critical care.

From the *Division of Neurology, Department of Medicine, National University Health System, Singapore; †Clinical Informatics and Medical Statistics Research Center, Chang Gung University, Taoyuan, Taiwan; ‡Department of Neurology, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan; §Department of Neurology, Chiayi Chang Gung Memorial Hospital, Chiayi, Taiwan; ‖Department of Neurology, Keelung Chang Gung Memorial Hospital, Keelung, Taiwan; and ¶Stroke Center and Department of Neurology, Linkou Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taoyuan, Taiwan.

Received January 30, 2017; revision received March 8, 2017; accepted March 23, 2017.

Grant support: The study received funding from Chang Gung Memorial Hospital (Grant Numbers: CMRPG35072, 35073, 39082, 39083, CMRPG3B0611, CMPRG3A0352, and CMRPG3B0111).

Address correspondence to Tsong-Hai Lee, MD, PhD, Stroke Center and Department of Neurology, Linkou Chang Gung Memorial Hospital, Chang Gung University College of Medicine, 5 Fu-Hsing St., Kueishan, Taoyuan 33333, Taiwan. E-mail: thlee@adm.cgmh.org.tw.

1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2017.03.033

Introduction

Thrombolytic therapy in acute ischemic stroke using intravenous tissue plasminogen activator (IV tPA) can lead to better functional outcomes; however, it is not without its inherent dangers.[1] The risk of intracerebral hemorrhage (ICH) is supposedly higher in Asian populations at standard doses.[2,3] At lower doses of .6 mg/kg, the recent ENCHANTED trial demonstrated this lower dose was also associated with fewer deaths, less ICH, and less fatal ICH than the standard dose.[4] Recent studies in Taiwan and Japan showed that lower doses may have safety profiles and efficacy similar to those of the standard dose in Japanese and Han-Chinese populations.[5,6] These all point to the fact that risk factors for complications from IV tPA cannot be generalized but should be specifically determined based on the race of the patient.

Although a lower dose of IV tPA may help reduce the rate of ICH, discerning patient selection is also essential to reduce the risk of complications. Many scoring systems such as the Multicenter Stroke Survey (MSS)[7]; hemorrhage after thrombolysis (HAT)[8]; blood sugar and early infarct signs ([hyper]dense cerebral artery sign, age, and the National Institutes of Health Stroke Scale [NIHSS] [SEDAN (blood Sugar [glucose] on admission, Early infarct signs and [hyper]Dense cerebral artery sign on admission computed tomography [CT] head scan, Age, and NIHSS) score])[9]; glucose on presentation, race (Asian), age, sex (male), systolic blood pressure (BP) on presentation, and NIHSS (GRASPS (Glucose at presentation, Race (Asian), Age, Sex (male), systolic blood Pressure at presentation, and Severity of stroke at presentation (NIHSS)))[10]; safe implementation of thrombolysis in stroke (SITS)[11]; SPAN-100 (stroke prognostication using age and NIHSS) positive index (stroke prognostication using age and NIHSS)[12]; and iScore have been developed in western countries to objectively quantify the selection procedure.[13] Importantly, the Asian subgroup in these studies was small.

Considering the ethnic difference, a scoring system specific for Asian population is needed. The present study aims to identify factors predictive of post-tPA ICH and 3-month mortality to form a scoring system that can be used for rapid decision making in an emergency setting.

Methods

Patient data were retrospectively collected from the Stroke Registry in Chang Gung Healthcare System (SRICHS) in Taiwan and the National University Hospital of Singapore (NUHS) acute stroke database. SRICHS is an electronic chart-based stroke registry system used in the 4 branch hospitals of the Chang Gung Healthcare System.[14] As the International Classification of Diseases (ICD-9) coding system has been used as a standard disease diagnosis system by the Bureau of National Health Insurance in Taiwan, SRICHS used ICD-9 codes (430-437) to ensure the recruitment of every stroke patient. Ethical approval for this study was obtained from the local institutional review board of Linkou Chang Gung Memorial Hospital.

Patient Recruitment and Data Collection

From January 2009 to December 2012, data of all consecutive acute ischemic stroke patients receiving tPA were analyzed. Patients who underwent endovascular treatment were excluded. All laboratory data, including biochemistry and complete blood count, and clinical profiles including vital signs, disease history, and drug history, were obtained from SRICHS and NUHS acute stroke database. Pretreatment nonenhanced computed tomographic scans of the brain were performed on all patients. Inclusion criteria for IV thrombolysis followed the same guidelines for both institutions. In addition, computed tomographic scans or magnetic resonance images were performed on all patients at 24-36 hours after tPA treatment or in case of neurologic deterioration. The brain images were evaluated for evidence of ICH by experienced radiologists. ICH was defined by the European Cooperative Acute Stroke Study-2 criteria. Hemorrhagic transformation was small punctate hemorrhage (HI 1) or confluent petechiae within the area of infarct (HI 2); this was also considered symptomatic if the NIHSS increased by 4 or more. Hematomas occupying less than 30% of the infarct with mild mass effect (PH1) and more than 30% with significant mass effect (PH2) were also considered symptomatic if the NIHSS increased by 4 or more. The Taiwanese cohort was chosen for risk score derivation, and the Singapore cohort was used for validation.

The primary outcome measures were ICH and 3-month mortality after tPA injection. The modified Rankin scale was not chosen as the Taiwan cohort consistently measured this on discharge whereas the Singapore cohort measured it at 3 months. In total, 11 candidate variables that could be reliably measured and readily available at the point of presentation in both cohorts were selected for the diagnostic model. These covariates included demographics (age and sex), systolic BP, presence of vascular risk factors (hypertension, diabetes, hyperlipidemia, atrial fibrillation [AF], and smoking), onset-to-treatment time, NIHSS score, premorbid modified Rankin scale score, and serum glucose.

Patients with a history of hypertension or hyperlipidemia on medication or lifestyle changes were considered as having hypertension or hyperlipidemia on admission. For patients without pre-existing hypertension, systolic BP ≥140 mm Hg or diastolic BP of ≥90 mm Hg demonstrated on 2 recordings within 24 hours of symptom onset was considered hypertension. For patients with no pre-existing hyperlipidemia, a serum cholesterol level that is 220 mg/dL or higher and triglyceride that is 150 mg/dL or higher was considered hyperlipidemia. Patients with a history of diabetes on medication or dietary modification