An Analysis of Long-Term Ischemic Stroke Risk in Survivors of Septicemia

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Introduction: Sepsis increases the long-term incidence of ischemic stroke (IS). The chances for long-term IS in patients who are discharged after sepsis are unclear. Our aim was to demonstrate long-term risk chances of IS after septicemia discharge. We used a nomogram to identify those septicemia survivors with the higher risk of developing IS. *Methods:* Inpatient data were used from the Taiwan Longitudinal Health Insurance Database, from 2001 to 2003. The event was IS rehospitalization after discharge of septicemia. We used multivariate Cox proportional regression of the risk factors for IS in septicemia survivors to create a nomogram. *Results:* There were 642 IS incidents in this study. The risk factors for IS in survivors of septicemia were advanced age (hazard ratio [HR] 1.035 [95% confidence interval (CI) 1.029-1.042]), new-onset atrial fibrillation (HR 1.875 [95% CI 1.327-2.651]), hypertension (HR 2.042 [95% CI 1.687-2.471]), diabetes mellitus (HR 1.735 [95% CI 1.469-2.05]), coronary artery disease (HR 1.661 [95% CI 1.408-1.96]), chronic kidney disease (HR 1.264 [95% CI 1.071-1.49]), chronic obstructive pulmonary disease (HR 1.201 [95% CI 1.016-1.421]), and local hospital admission (HR 1.414 [95% CI 1.155-1.731]). The model showed good calibration and discrimination, with a bootstrap-corrected concordance index of .785. *Conclusion:* With this prognostic nomogram, we found age with the strongest factor for IS. There was increased IS incidence with more comorbid conditions in advance-aged septicemia survivors. Physicians must identify high IS–risk patients and control risk factors to prevent adverse events in the clinical setting. **Key Words:** Ischemic stroke—septicemia—risk—nomogram.

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Introduction

Unstable hemodynamic status and atrial fibrillation (AF) associated with sepsis may induce ischemic stroke (IS).[1] A previous study found that septicemia carried with the risk of stroke, including IS and cerebral hematoma, within the first 6 months.[2] Long-term survival of septicemia is associated with long-term death and major adverse cardiovascular events in Taiwan.[3] A previous study has found that older sepsis survivors with AF in the United States suffered increased long-term incidence of IS, congestive heart failure, and death over a 5-year period.[4] The chances for long-term IS in sepsis-discharged patients are unclear. Our aim was to construct an easy-to-use scale system to calculate IS chances in septicemia survivors.

Most stroke patients have atherosclerosis factors,[5] but some do not. It is important to discover the nontraditional factors for IS in this group. The mortality rate for sepsis decreases according to the guideline treatment.[6] As Taiwanese society ages, there will be greater chances for infection and its evolution into septicemia among the elderly. It provides an opportunity to survey interactions between IS occurrence and risk factors for septicemia survivors in the general population using the National Health Insurance Research Database (NHIRD) in Taiwan.

A nomogram, based on statistically significant factors, is here used for disease prognosis and estimated event probability.[7-9] The nomogram provides a point value for each risk factor. After totaling the point value sum, the probabilities for an individual patient may be estimated. It is useful to have a 1-page nomogram for predicting the risk of a disease's outcome.[10] The nomogram for the prediction of acute IS outcomes after 3 months has been fitted to a logistic regression.[8]

This study focused on the relationship between risk factors and IS for a period of 6 years. By developing the nomogram, we make it easy to reference the individual probabilities of IS occurrence in Asian survivors of septicemia.

Methods

The National Health Insurance is a unified government insurance system. It was implemented in 1995 and covers majority of residents in Taiwan. The NHIRD contains the majority of health-care information in Taiwan. All medical care providers must submit computerized claims data for medical insurance payment. The data contain each patient's age, gender, comorbid conditions, IS codes, and times of events.[11]

We used an inpatient data set including information from January 1, 2001, to December 31, 2003. The data had up to 5 diagnostic codes and 5 operational codes. Because the NHIRD data set for payments records the diagnostic codes for hospital discharge, it does not discriminate which order sepsis and IS occurred during hospitalization. Therefore, we designed this study to cover septicemia survivors after discharge from the hospital. The first occurrence of septicemia was retrieved via the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 038, 003.1, and 036.1, and sepsis diagnosis in the NHIRD was used for verification.[2,3,12] Nonsepticemia patients were defined as no septicemia codes during 2001-2003. AF was determined through the ICD-9-CM code of 427.3x; when this occurred during or after septicemia within 3 months, we defined this as new-onset AF. The event was followed by rehospitalization for IS (ICD-9-CM of 433-437) following discharge for septicemia or until December 31, 2009. Patients with prior stroke (ICD-9-CM of 430-437), AF before first septicemia, and stroke or death during first hospitalization for septicemia were excluded. For comparison of different age adult IS incidence, age groups were divided into older (more than 65 years old), middle-aged (between 45 and 65 years old), and youth (between 18 and 45 years old). The diagnostic codes of comorbid conditions were based on a previous study by Walkey et al.[13] Comorbid conditions mapped by ICD-9-CM codes included hypertension (401-405), diabetes mellitus (250), coronary heart disease (410-414), congestive heart failure (428), hyperlipidemia (272), chronic kidney disease (582-586, 588), and chronic obstructive pulmonary disease (490-496). The study flowchart is described in Figure 1. This study was approved by the Tri-Service General Hospital Ethics Institutional Review Board.

Student's *t*-test and the chi-square test were used to evaluate the factors for difference; the difference between the cumulative incidences of the 2 groups was compared via the log-rank test, using Kaplan–Meier curves. Predictor variables for IS were identified using a multivariate Cox proportional hazard regression model with forward selection procedure, and the statistical significance was set as $P < .05$. All statistical analyses were performed using SPSS software version 21 (International Business Machines Company, Armonk, NY).

The nomogram for chance of IS was constructed based on the Cox regression model, using the rms package of the R software. Each risk factor's 0- to 100-point scale is determined by drawing directly upward from the appropriate place on the factor's scale. Total points are added together from the points for each risk factor. The probability of IS-free survival over a 6-year period is determined by drawing downward to the IS-free survival axes from the Total Points axis. An internal validation was performed 200 times, with a resampling bootstrap for overfitting corrected to discriminate the event-free times of individual patients (concordance index [C-index]). The criterion of risk groups was according to the mean total points of IS and non-IS groups of septicemia survivors.[7,10] Another method for internal validation is the analysis that we did on a Kaplan–Meier curve, and a log-rank test for cumulative incidence of IS was used to compare the