ORIGINAL ARTICLE

Neurologic and Non-neurologic Predictors of Mortality in Ischemic Stroke Patients Admitted to the Intensive Care Unit

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Background/Purpose: Patients with severe strokes may have different associated medical comorbidities from those with mild strokes. This study evaluated the neurologic and non-neurologic medical predictors of mortality in patients with severe cerebral infarction in the acute stage.

Methods: Patients admitted to a neurologic intensive care unit (ICU) due to cerebral infarction were included. Neurologic and non-neurologic predictors for in-unit mortality were determined by logistic regression analyses. Two models using (A) neurologic factors and (B) combined neurologic and non-neurologic factors as mortality predictors were developed. The performance of the models in predicting overall, neurologic and non-neurologic mortalities was compared by areas under the receiver-operating characteristic curves (AUC) of the derived regressive equations.

Results: Of 231 patients with cerebral infarction admitted to the ICU, 34 (14.7%) died during ICU stay. Conscious state and acute physiologic abnormalities were significant predictors of mortality. The length of ICU stay in patients with non-neurologic mortality was longer than in those with neurologic mortality ($p = 0.044$). The AUC of Model B was larger than that of Model A in predicting overall (0.768 ± 0.045 *vs.* 0.863 ± 0.033, $p = 0.005$) and non-neurologic mortalities (0.570 ± 0.073 *vs.* 0.707 ± 0.074, $p = 0.009$), while there was no difference in predicting death from neurologic causes (0.858 ± 0.044 *vs.* 0.880 ± 0.032, $p = 0.217$).

Conclusion: Impaired consciousness and acute physiologic abnormalities are independent predictors of mortality for severe ischemic stroke during the acute stage. Neurologic factors predict early mortality from intrinsic cerebral dysfunction, while non-neurologic factors, especially the associated physiologic abnormalities, predict late mortality from medical complications. [*J Formos Med Assoc* 2006;105(8):653–658]

Key Words: cerebral infarction, consciousness, mortality, receiver-operating characteristic curve

Despite recent advances in acute treatment, stroke is still a leading cause of mortality and severe morbidity in heavily afflicted patients. Reliable outcome prediction at the acute stage is thus the basis on which feasibility of aggressive management is judged and effectiveness of therapeutic methods is compared. Several scoring systems, either disease- or setting-specific, are now available to objectively quantify disease severity and provide prognostic information. For ischemic stroke, the most widely used disease-specific systems include the National Institutes of Health Stroke Scale and the Scandinavian Stroke Scale. Although both scales have been validated in predicting intermediate and long-term prognosis in previous studies,[1–3] their role in predicting prognosis at

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the acute stage has not yet been determined. Focusing on neurologic deficits, these scales do not include non-neurologic factors that potentially affect prognosis. The Acute Physiology and Chronic Health Evaluation (APACHE) system was originally designed for patients admitted to intensive care units (ICU).[4] By including age, acute physiologic (including neurologic) and chronic systemic variables, this system gives a wider scope of consideration in evaluating the impact of disease.

In addition to prominent neurologic deficits, patients with more severe strokes may differ from those with milder disorders in frequent associations with medical complications.[5–7] In this study, we utilize the configuration of the APACHE system to evaluate whether the addition of non-neurologic factors to neurologic variables may improve prediction of survival outcomes for ischemic stroke patients in the ICU. Contributions of neurologic and non-neurologic factors to mortality in the subsets of patients and their related characteristics were also explored.

Methods

Patient population and data collection

Consecutive patients with acute ischemic stroke admitted to the neurologic ICU during December 2000 and May 2002 were included. Criteria for ICU admission included conditions warranting intensive monitoring and management, such as impaired consciousness, prominent bulbar (e.g. impaired upper airway clearance and choking) or motor dysfunction (unable to lift proximal limbs against gravity unilaterally or bilaterally), deteriorating neurologic conditions, or life-threatening medical comorbidities.[8,9] Patients with the following conditions were excluded: (1) transient ischemic attacks; (2) strokes associated with vasculitis, substance abuse or hypertensive encephalopathy; or (3) receiving thrombolytic therapy.

Based on the APACHE system with modifications, we selected age, neurologic, acute physiologic and chronic systemic variables as the possible mortality predictors. The locations of cerebral infarctions were recorded for all patients. Assessment of consciousness was based on the Reaction Level Scale (RLS) proposed by Starmark et al.[10] This is an eight-grade single line scale in which "fully conscious" is given a score of 1 and "comatose" is coded as score 8. Characterized by its direct evaluation of global responsiveness, the scale can be used more reliably than the Glasgow Coma Scale (GCS) in situations such as endotracheal intubation, severe dysarthria or motor aphasia. Scores of RLS upon ICU admission were used for analysis. Acute physiologic derangement was quantified with a scoring system modified from the Acute Physiology Score in APACHE II[4] (modified APS) consisting of body temperature, heart rate, mean arterial pressure, respiratory rate, arterial pressure of oxygen, arterial pH, serum sodium, potassium and creatinine, hematocrit, and white blood cell count. The worst set of data for these items throughout the first 24 hours of admission was chosen to determine an aggregate score. Chronic systemic failure was defined as the presence of one of the following conditions: New York Heart Association class 3 or 4 cardiac failure;[11] chronic respiratory failure with mechanical ventilation or oxygen use; chronic hepatic failure with Child-Pugh class B or C;[12] chronic dialysis, malignancy, or current usage of immunosuppressive agents for more than 6 months.

Patients were classified as nonsurvivors or survivors during the period of ICU stay. Nonsurvivors were further classified into neurologic or non-neurologic mortality groups according to the cause of death. Patients in the neurologic mortality group died of brain failure due to brain herniation or extensive brain stem dysfunction, while patients in the non-neurologic mortality group died from medical complications such as sepsis or ischemic heart disease. Length of neurologic ICU stay (LOS) and cause of death were also recorded.

Statistical analysis

Univariate analyses were performed with χ^2 and *t* tests as required. The Mann–Whitney U test was used for comparing RLS score and LOS.

Two predictive models were constructed by logistic regression using in-unit mortality as the dependent variable. Model A included two variables, location of the cerebral infarction (carotid or vertebrobasilar system) and the RLS score, while Model B contained, in addition to the variables in Model A, three additional variables of age, modified APS and chronic systemic failure. The odds ratios (OR), 95% confidence intervals, and p values were calculated for each variable in the presence of the others in the final models. A p value of less than 0.05 was considered statistically significant. The assessment of fit of predictive mortality to observed mortality was analyzed by using the Hosmer–Lemeshow goodness-of-fit statistic.[13]

To evaluate the performance of the two models in discriminating survivors and nonsurvivors, areas under the receiver-operating characteristic (ROC) curves (AUCs) of derived regression equations were computed. Comparison of AUCs was performed according to the method proposed by Hanley et al.[14] The test calculates the critical ratio z with the following equation:

$$z = \frac{A_2 - A_1}{\sqrt{SE_1^2 + SE_2^2 - 2rSE_1SE_2}}$$

where A_i represents the AUC, SE represents the standard error of the area, and r represents the correlation coefficient between the two areas. A one-tailed test was conducted to determine the p values. Discriminations of the neurologic and non-neurologic mortalities by Models A and B were also tested by this method.

Results

A total of 547 patients were admitted to the neurologic ICU during the study period and 272 (49.7%) had acute cerebral infarction. Of 231 patients entered in the final analysis according to the criteria for case selection, 34 died during ICU stay (14.7%). Univariate analyses comparing baseline characteristics between survivors and nonsurvivors showed that the latter group had more severe consciousness impairment, higher APS, and more frequent association with chronic systemic dysfunctions (Table 1). Among the nonsurvivors, 20 patients died from neurologic causes, and 14 died from medical causes. The causes of death are listed in Table 2. The median LOS was 4 days (interquartile range, 1–7) in the neurologic mortality group and 11 days (interquartile range, 3–21) in the non-neurologic mortality group ($p = 0.044$).

The associations of each variable with the outcomes in the two predictive models are shown in

Table 1. Comparison of baseline characteristics between survivors and nonsurvivors

	Survivors ($n = 197$)	Nonsurvivors ($n = 34$)	p
Demographic features			
Male (%)	56	47	0.355
Age (yr)*	68 ± 11	71 ± 12	0.162
Medical history (%)			
Diabetes mellitus	39	36	0.515
Hypertension	55	71	0.280
Atrial fibrillation	18	18	0.651
Chronic systemic failure	9.7	23	0.037
Stroke characteristics (%)			
Recurrent stroke	29	29	0.982
Carotid system infarction	62	67	0.701
RLS score†	2 (1–3)	4 (2–5)	< 0.001
Modified APS*	4.0 ± 3.3	9.2 ± 6.3	< 0.001

**Mean ± SD; †median (interquartile range). RLS = Reaction Level Scale; APS = Acute Physiology Score.*

Table 2. Neurologic and non-neurologic causes of death

Mortality	Causes of death	Case no. (%)
Neurologic		20 (59)
	Brain herniation	16
	Brain stem failure	4
Non-neurologic		14 (41)
	Sepsis	5
	Adult respiratory distress syndrome	3
	Acute renal failure	3
	Cardiogenic shock	2
	Massive gastric bleeding	1

Table 3. Two mortality-predicting models including different sets of variables developed by logistic regression

	Odds ratio (95% CI)	*p*
Model A		
Carotid system infarction	0.70 (0.29–1.68)	0.424
RLS score	1.83 (1.45–2.30)*	<0.001
Model B		
Carotid system infarction	0.58 (0.21–1.59)	0.286
Age	1.00 (0.96–1.04)	0.987
RLS score	1.74 (1.33–2.27)*	<0.001
Modified APS	1.24 (1.13–1.36)*	<0.001
Chronic systemic failure	0.50 (0.16–1.55)	0.229

**Per point increment. RLS = Reaction Level Scale; APS = Acute Physiology Score.*

Table 4. Comparison of areas under receiver-operating characteristic (ROC) curves (mean ± SE) by two different models to discriminate between surviving and deceased patients

Mortality	Model A	Model B	*r*	*z*	*p*
Overall	0.768 ± 0.045	0.863 ± 0.033	0.59	2.55	0.005
Neurologic	0.858 ± 0.044	0.880 ± 0.032	0.77	0.78	0.217
Non-neurologic	0.570 ± 0.073	0.707 ± 0.074	0.68	2.33	0.009

r = correlation coefficients between two ROC areas; z = test statistic of ROC area difference.

Table 3. In Model A, RLS on admission was the independent predictor to in-unit mortality. Model B found that both RLS (OR 1.74) and modified APS (OR 1.24 for each point increment) were the independent predictors. The Hosmer–Lemeshow statistic of 6.73 (df = 5, $p = 0.24$) in Model A and 9.13 (df = 8, $p = 0.33$) in Model B suggested that both models fit the derived data well. In discriminating survivors and nonsurvivors, however, Model B was better than Model A as shown by a significantly larger AUC (Table 4 and Figure). The ability of the two models to discriminate survivors from patients with neurologic or medical mortality was further tested. In predicting neurologic mortality, there was no difference in the AUCs between the two models. However, the AUC of Model B was significantly larger than that of Model A in predicting medical death. For both models, the largest AUC was noted for neurologic mortality, and the smallest AUC was noted for non-neurologic mortality. The largest AUC was found in Model B for neurologic mortality (0.880), and

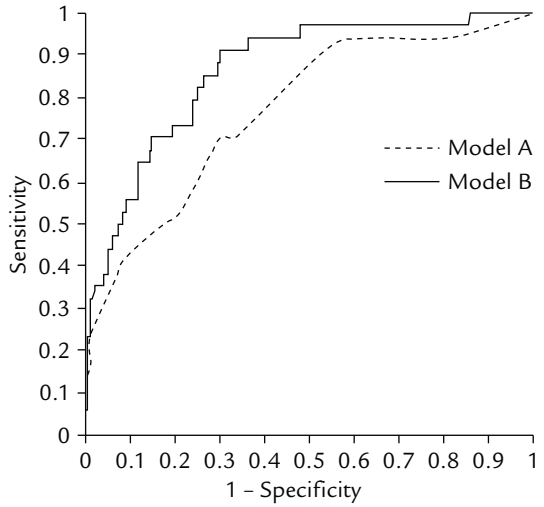

Figure. Receiver-operating characteristic curves for Models A and B in predicting intensive care unit mortality in the study patients.

the AUC of Model A for discriminating non-neurologic mortality was the smallest (0.570).

Discussion

This study showed that conscious level on admission was a significant predictor of in-unit mortality in ischemic stroke patients admitted to the ICU. Previous studies also demonstrated comparatively high predictability of conscious levels among other clinical parameters in the prognosis of patients with ischemic or hemorrhagic stroke.[15,16] For patients with hemispheric infarct, brain edema with midline structure shift or brain stem compression is the major cause of mortality.[17] Patients with large cerebral infarction, especially complicated with brain edema, often present with impaired and deteriorating consciousness.[18–20] Similarly, extensive brain stem infarct tends to cause prominent impairment of consciousness. These patients usually carry unfavorable prognosis due to the involvement of the vital centers in the brain stem or development of respiratory complications.[21–23]

In this study, acute non-neurologic physiologic abnormality was an independent predictor of survival outcome. Previous studies in patients with acute ischemic stroke indicated that cardiac comorbidities,[24] elevated body temperature,[25,26] leukocytosis,[26] and hyperglycemia[27,28] were associated with survival or functional outcomes. Rordorf et al[26] assessed acute physiologic abnormalities in stroke patients using the APACHE II score and they found that body temperature, serum creatinine, and white blood cell counts were the main predictors of in-hospital mortality. All of these findings indicate the importance of systematized assessments and proper management of coexisting medical complications in treating stroke patients, especially for those with more prominent disease severity.

Comparison of two models for predicting overall mortality in this study showed that the model (Model B) combining non-neurologic and neurologic variables performed better than the model (Model A) containing neurologic factors only. In predicting specific causes of mortality, both models performed just as well in predicting which patients would have neurologic causes of death. However, Model B was significantly better than Model A in predicting medical causes of death. Patients with medical mortality had longer LOS in the ICU than those who died from neurologic causes. These findings indicate the differences in clinical courses and the roles of neurologic and non-neurologic factors in mortality. Neurologic factors generally reflect the severity of stroke and are thus more related to death from intrinsic cerebral conditions early in the acute stage. In contrast, non-neurologic factors composed of acute or chronic physiologic derangements contribute to mortality from medical complications in the latter stage. Distinctions between the two kinds of factors in outcome determination have also been reported in other acute brain disorders such as head injury.[29,30]

In conclusion, disturbances of consciousness and acute physiologic abnormalities are independent predictors of mortality during the acute stage in patients with severe ischemic stroke. For these patients, intrinsic cerebral dysfunction is the major cause of early mortality, while associated non-neurologic factors contribute to late mortality from medical complications. Although stroke patients may benefit from recent progress in

disease-specific treatments, clinicians must be alert to the development of medical comorbidities and apply proper management techniques to improve survival and functional reserve in these patients.

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