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Full Length Research Paper

A new prognostic model and score to predict short term outcome after intracerebral hemorrhage

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Spontaneous intracerebral hemorrhage (ICH) accounts for the highest mortality of all strokes. An early and reliable prognostic indication in ICH patients is potentially useful for initiating individual treatment and for informing patients and families. The published predictive models are largely based on neurological features; however, a part of them need to be judged with the subjective viewpoint of physician. Recently, we reviewed the data of 716 patients of ICH within 30 days. By univariate analysis and receiver operating characteristic (ROC) curves, four independent predictors for death outcome were identified from 11 laboratorial items and patient's basic information, such as blood glucose (Glu), white blood cell count (WBC), lactate dehydrogenase (LDH) and age. With the AUC of 0.769, the prognostic model was developed by logistic regression. When the threshold of prediction index was set to 0.106, the sensitivity (88.9%) and specificity (55.6%) for death outcome were obtained by ROC curves. Furthermore, a simple predictive score was developed, whose AUC was 0.745. On a range from 0 - 4, the score of ≥3 could predict death outcome with good sensitivity (71.4%) and specificity (72.3%). The objective regression model and score had perfect discriminatory power for the prognosis of ICH within 30 days without the subjective judgment of physicians. It should be easily used by both neurological specialists and community doctors.

Key words: Intracerebral hemorrhage, prognosis, regression model, predictive score

INTRODUCTION

Stroke remains a major cause of mortality and disability worldwide among middle-aged and elder people. Spontaneous intracerebral hemorrhage (ICH) accounts for 10 - 20% of all strokes (Keir et al., 2002), and has a higher morbidity and mortality than cerebral infarction or subarachnoid hemorrhage (Caplan, 1992; Broderick et al., 1993; Jorgensen et al., 1995; Qureshi et al., 2001). Short term prognosis of patients with ICH is poor, approximately 35 - 50% of them die within the first month after bleeding (Poungvarin and Viriyavejakul, 1990; Nilsson et al., 2002). It is very important to predict the outcome in patients with ICH for two main purposes (Ariesen et al., 2005): (i) to differentiate between patients who might still benefit from intensive care and those who have such a poor prognosis that they will not benefit from intensive care any more; (ii) to inform patients and families about

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Abbreviations: AUC, Area under curve; **CI,** confidence interval; **Glu,** glucose; **HDL-c,** high density lipoprotein cholesterol; **ICH,** intracerebral hemorrhage; **LDH,** lactate dehydrogenase; **LDL-c,** low density lipoprotein cholesterol; **OR,** odds ratio; **ROC,** receiver operating characteristic; **SD,** standard deviation; **TC,** total cholesterol; **TG,** triglyceride; **UA,** uric acid; **WBC,** white blood cell count

the chance of survival. A reliable model for outcome of ICH will help to enhance the physician-patient communication and decrease the conflict between the physicians and patients.

Several prognostic models for mortality after ICH have been proposed and validated (Raymond et al., 2003; Weimar et al., 2006a, b). These models were usually developed by neurologist from their standpoint on the basis of the status of consciousness, neurological features, and other clinical features. In published models, the level of consciousness on admission, neurological features, and hematoma volume are the most significant predictors. The objective results from clinical laboratories play less of a role in those models. Unfortunately, only an experienced neurologist could properly judge those significant clinical predictors, and different conclusions might be drawn by different estimators because of subjective factors. Besides, some published prognostic models involved complex algebraic calculations. To our knowledge, these are rarely used for triage in clinical practice. Additionally, no grading scale for ICH is consistently used for triage and acute intervention in either clinical care or clinical research (Hemphill et al., 2001).

The aim of this study was to develop a reliable prognostic model and a simple predictive score for ICH mainly based on objective laboratorial results.

MATERIALS AND METHODS

We reviewed the data of patients with ICH under the permission of the Research Ethics Committee of Chongqing Medical University. During 1st May 2005 to 30th September 2009, 825 patients were admitted to the neurology department of the First Affiliated Hospital of Chongqing Medical University. Those patients were diagnosed as ICH with both neurological features and cephal computerized tomography scanning or magnetic resonance imaging. Patients whose hematomas were caused by head trauma, anticoagulant or thrombolytic drugs, brain tumor, saccular arterial aneurysm or vascular malformation were excluded from the study. The outcome was assessed within 30 days after onset. According to the outcome, these patients were classified into the following two groups: the death outcome group and the survivor outcome group.

All the venous fasting blood samples were collected in the following morning after admission. The biochemical items were tested by AUTOMATIC BIOCHEMICAL ANALYZER AU640 (Olympus, Japan), which included serum total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c), lactate dehydrogenase (LDH), uric acid (UA) and glucose (Glu). The blood routine tests were performed by AUTOMATIC BLOOD CELL ANALYZER XE-2100 (Sysmex, Japan). The white blood cell count (WBC), neutrophils (NEU), red blood cell count (RBC), and platelet (PLT) were selected as candidates among the parameters of blood routine test.

All statistical analysis were performed with SPSS (version 13.0), and $P<0.05$ (2-tailed) was taken to infer statistical significance. First, we compared the statistical difference of each variable between groups (chi-square test for categorical variables, and the student's t-test for numerical variables), and calculated the area under curve (AUC) with receiver operating characteristic (ROC) curves. An AUC of 1 corresponds with a perfect prediction and an AUC of 0.5 with no discriminatory power at all. The screening criteria ($P<0.05$ and AUC≥0.6) was set, and the independent predictors were selected from these candidates to develop a regression model for predicting the death outcome within 30 days after ICH. Secondly, the prognostic power of this model was estimated by ROC curves again. Furthermore, on the basis of these independent predictors, a simple predictive score of ICH was created, which prognostic power for ICH was estimated by ROC curves.

RESULTS

Basic information of patients with ICH

Of 825 patients who were presented with ICH during the study period, 109 patients were excluded because of incomplete record. The remaining 716 patients were analyzed. The mean age of patients was 59.7±14.9 years and 473(66.6%) patients were male. 576 patients (80.4%, mean age 58.4±14.7 years) were in the survivor outcome group, and 140 patients (19.6%, mean age 64.8±14.6 years) were in the death outcome group. There were no statistical difference ($P>0.05$) in gender between the death outcome group (male 64.3%) and the survivor outcome group (male 66.5%).

Developing the regression model to predict the death outcome of ICH

Compared with patients in survivor outcome group, the patients in death outcome group were older with statistical significance ($P<0.01$), and had higher concentrations of Glu, UA, LDH, lower WBC, NEU, PLT, all with statistical significant ($P<0.01$). The AUC of each candidate was calculated by ROC curve. The statistical results were listed in Table 1.

Using the screening criteria of $P<0.05$ and AUC ≥0.6, such variables as age, Glu, LDH, WBC, and NEU were selected from 11 laboratorial candidate and the basic information of patients. Then a regression model was developed to predict the outcome within 30 days after ICH through forward LR logistic regression analysis (Table 2). But the NEU could not enter into the equation for that the P value was greater than 0.05 ($P = 0.080$).

The discriminatory power of the regression model was evaluated using ROC curve, the AUC of this model was 0.768 (Figure 1). The prediction index of ≥0.106 or <0.106 could provide the best Youden's index of prognostic in this model for death outcome and survivor outcome, respectively. In this threshold of prediction index, the sensitivity and specificity were 88.9% and 51.6%, respectively for predicting death outcome.

Developing the predictive score for the death outcome of ICH

As a result of the complex algebraic calculations, this

Table 1. The comparative result between two groups and the AUC of variables.

Parameters	Survivor outcome group (n = 576)	Death outcome group (n = 140)	*P*	AUC
Age (years)	58.4±14.7	64.8±14.6	<0.01	0.623
Gender: male (%)	383 (66.5%)	90 (64.3%)	0.62	0.511
TC (mmol/L)	4.73±1.06	4.70±1.28	0.84	0.509
TG (mmol/L)	1.47±1.05	1.43±1.16	0.79	0.445
HDL-c (mmol/L)	1.33±0.43	1.46±0.53	0.43	0.587
LDL-c (mmol/L)	2.71±0.83	2.59±0.92	0.22	0.468
UA (umol/L)	302.86±111.36	347.88±138.72	<0.01	0.590
Glu (mmol/L)	6.78±2.47	8.77±3.66	<0.01	0.718
LDH (U/L)	346.02±400.08	457.67±438.63	0.02	0.611
RBC ($\times10^{12}$/L)	4.40±0.64	4.33±0.94	0.38	0.495
WBC ($\times10^{9}$/L)	9.32±3.88	12.80±6.06	<0.01	0.678
NEU($\times10^{9}$/L)	7.94±7.38	10.97±5.79	<0.01	0.674
PLT ($\times10^{9}$/L)	159.18±70.23	139.41±62.86	<0.01	0.522

Note: Numbers with percentages of subtotal in parentheses are used for categorical variables, and mean ± SD are used for numerical variables.

Table 2. Regression model for death outcome within 30 days.

Variables	β	S.E.	Odds ratio	95%CI	*P*
Age	0.044	0.011	1.045	1.022-1.069	<0.001
Glu	0.150	0.046	1.162	1.063-1.270	0.001
LDH	0.001	0	1.001	1.000-1.001	0.033
WBC	0.102	0.032	1.107	1.040-1.178	0.001
Intercept	-6.894	0.981			

Regression model for death outcome: Log (PI) = 0.044 × Age + 0.150 × Glu + 0.001 × LDH + 0.102 × WBC - 6.894. Note: β, regression coefficient; S.E, standard error; CI, confidence interval; PI, prediction index.

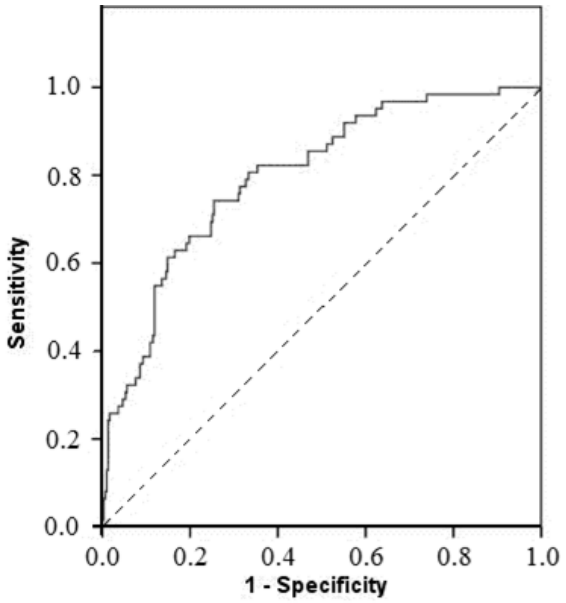

Figure 1. ROC curve of the regression model for predicting death outcome within 30 days after ICH. Note: the AUC of the regression model was 0.768.

regression model may be inconvenient for clinicians. Therefore, a simple predictive score for the outcome of ICH patients should be created. According to the best Youden's index, the cut-off value of age, Glu, LDH, WBC for prognostic score were obtained (Table 3).

ROC curve of this predictive score is shown in Figure 2. The AUC obtained was 0.745. On a range of 0~4, this score could predict fatality when the score was no less than 3, the sensitivity and specificity were 71.4% and 72.3%, respectively.

DISCUSSION

Proper judgment of the prognosis of ICH is very important for both clinical treatment and communication with patients or their relatives. The published predictive models are based on more neurological features (Raymond et al., 2003; Weimar et al., 2006a, b); however, only the experienced neurologist could judge these important predictors properly. For community doctor, it is difficult to judge such predictor as the levels of coma. By now, the predictive model based on the laboratorial

Table 3. Prognostic score of each predictor for death outcome following ICH.

Independent predictors	Prognostic score
Age (years)	<64.5 = 0; ≥64.5 = 1
Glu (mmol/L)	<7.35 = 0; ≥7.35 = 1
LDH (U/L)	<200.5 = 0; ≥200.5 = 1
WBC ($\times 10^9$/L)	<8.75 = 0; ≥8.75 = 1

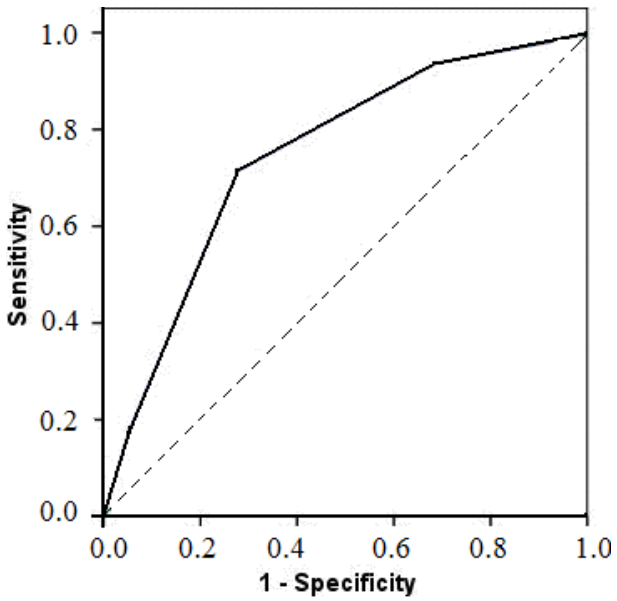

Figure 2. ROC curve of the predictive score for predicting death outcome within 30 days after ICH.
Note: the AUC of the predictive score was 0.745.

results mainly has not been found.

In this study, the mean age of patients was younger (59.7±14.9 years) than that of a report from western countries (65±16 years) (Ariesen et al., 2005). The mortality (19.6%) was also lower than the report from Ariesen (40%) (Ariesen et al., 2005) and Dennis (40 - 45%) (Dennis, 2003). However, the mean age and mortality of present study were close to the Asian Stroke Advisory Panel's report collaborated by seven Asian countries (mean age: 59.5±14.3 years; mortality: 25.7%) (Poungvarin et al., 2006). It indicated the patients enrolled into this study were typical of samples.

The roles of laboratorial candidates in the prognosis of ICH

In previous studies, some candidate parameters were considered to be associated with prognosis of patients with ICH. Among them, hypertension and atherosclerosis are considered as the main causes (Inagawa, 2007). Several prospective studies have showed that higher level of TC increase the risk of stroke (Zhang et al., 2003; Horenstein et al., 2002). But Karagiannis reported that lower level of TC and the absence of hyperlipidemia were associated with the occurrence of death (Karagiannis et al., 2007). However, another research reported that TC concentrations were not an independent predictor of 30-day fatality in acute stroke (Bhatia et al., 2004). Consequently, the relationship between TC and stroke seems debatable. This confusion may be caused by different endpoints of observation and different samples. In present study, with large sample analysis, the concentrations of lipid profile (including TC, TG, HDL-c, LDL-c) were similar in two groups and were excluded by the inclusion criteria (P<0.05 and AUC≥0.6).

After ICH, hyperglycemia is a common condition as a stress response to the bleeding (Tetri et al., 2009). Because cerebral glucose increased only at blood levels >7.8 mmol/L, blood glucose levels >7.8 mmol/L independently predicted unfavorable outcome (Schlenk et al., 2009). A prospective observational follow-up study showed that the relationship between Glu concentrations at admission and mortality was continuous, without any detectable threshold. Each 1.0 mmol/l increase in Glu concentration above 5.0 mmol/L was associated with a 33% mortality increase in the likelihood of experiencing a fatal event (OR: 1.33; 95%CI: 1.22-1.46; P < 0.01) (Godoy et al., 2008). In present study, hyperglycemia was selected as an independent predictor of death outcome within 30 days after ICH (AUC = 0.718). The pathogenesis may be that hyperglycemia aggravate the intracellular acidosis after ICH, damage nerve cells, and also dilate blood vessels, which should aggravate brain edema, increase intracranial pressure, and ultimately intensify brain damage.

In present study, the serum UA in the death outcome group was significantly higher than that in the survivor outcome group (P<0.01), which was similar to previous reports (Karagiannis et al., 2007; Newman et al., 2006). As a predictor of outcome, UA concentration was considered to be associated with hematoma volume and severity of ICH. But Chamorro has reported that high level of UA may be neuroprotective in patients with acute stroke, resulting in better functional outcome (Chamorro et al., 2002). However, UA concentration was not selected to develop the regression model because the AUC was 0.59 (the inclusion criteria was AUC≥ 0.6).

LDH is present in the cytoplasm and mitochondria of neurons. It was released into the intercellular space and cerebrospinal fluid when nerve cell degeneration and

necrosis happened after ICH, then spread into the blood through the damaged blood-brain barrier and caused the increase of blood LDH (Bakcy and Word, 2003). In present study, LDH activity of death outcome group was higher than that of survivor outcome group with statistical significance ($P<0.05$). It entered the regression model ($P = 0.033$) as an independent predictor (AUC = 0.611).

As parameters of the blood routine test, WBC and PLT had statistical difference between the two groups in this study. After ICH, meningeal irritation by hematoma may stimulate white blood cells to release from bone marrow. The increased white blood cells in the peripheral blood could aggravate the cerebral tissue lesion by disturbing microcirculation (Gong et al., 2000), releasing inflammatory factors (Holmin and Mathiese, 2000), inducing oxidative stress (Park et al., 2008, 2009) and lipid peroxidation in brain. In this study, the WBC count in death outcome group was higher than those in survivor outcome group ($P<0.05$). It was an independent predictor of poor outcome (AUC = 0.678). In addition, the PLT count in death outcome group was less than that in the survivor outcome group with statistical significance ($139.41\pm62.86 \times 10^9$/L *v.s* $159.18\pm70.23 \times 10^9$/L, $P<0.01$), but it did not enter the regression model because the AUC was less than 0.6 (AUC = 0.522). Perhaps this is a consumptive decrease as previously reported by O'Malley et al. (1995).

It was universally acknowledged that the body was in a hypercoagulable state with decreasing fibrinolytic activity in acute ICH (Gong et al., 2008). So blood coagulation profile may become a possible candidate predictor. But the results of blood coagulation profile may be inconsistent in different blood taking time because of their rapid change resulting from consumed clotting factors over time (Antovic et al., 2002). And it was difficult to make uniform in blood taking time in present retrospective study. It is pity that the blood coagulation profile was not taken into account.

The prognostic regression model and predictive score

A large sample of 716 patients with ICH was studied in this research. According to the pathophysiologic theory and previous reports, gender, age and 11 laboratorial items were chosen as candidate predictor. Focusing on death outcome and survivor outcome within 30 days after ICH as endpoints of primary interest, four items were obtained as the independent predictor by statistical analysis and ROC curve. Next, a regression model and a predictive score were developed to predict the death outcome within 30 days after ICH with a reasonable AUC value, closer to one than to zero. Prediction index of ≥0.106 in the regression model or the score of ≥3 in the predictive score could predict the death outcome of ICH with good sensitivity and specificity.

In contrast to previous regression models and ICH scores (Weimar et al., 2006b; Ruiz-Sandoval et al., 2007; Castellanos et al., 2005; Rost et al., 2008), this model and score based on laboratorial candidates mainly were more objective. It kept out subjective judgment from different physicians, such as levels of consciousness and neurological features.

The present study does have some limitations. The regression model and predictive score have excluded some important clinical information, such as hematoma volume, the levels of coma, which might lead to a slight lower predictive ability than other models (AUC 0.768 or 0.745 *v.s* NIHSS 0.863 (Weimar et al., 2006b)). But as an objective model and a simple score, the present predicting system provides an operable way for both experienced neurologist and community doctor. We think it deserves to be validated in other ICH cohorts.

Conclusion

An objective model and a simple score were developed mainly based on the laboratorial candidates for predicting the short outcome of ICH. Its easy applicability and objective judgment render it useful for both neurological specialist and community doctor.

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