Development and validation of the hypertensive intracerebral hemorrhage prognosis models

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Abstract

To develop and validate the prognosis model of hypertensive intracerebral hemorrhage based on admission characteristics, which would be applied to predict the 3-month outcome.

For developing the prognosis models, we studied data from 325 patients with retrospectively consecutive hypertensive intracerebral hemorrhage admitted between 2012 and 2016. The predictive value of admission characteristics was tested in logistic regression models, presenting 3-month outcome as the primary outcome. The performance of the models was tested by discrimination and calibration. After development, internal and external validations were used to test the function.

The multivariate analysis of logistic regression indicated that age, Glasgow coma scale score, pupillary light reflex, hypoxemia, intracerebral hemorrhage volume, blood glucose, and D-dimer level were independent factors of the hypertensive intracerebral hemorrhage prognosis model. The prognosis model based on those admission risk factors worked well. The receiver operating characteristic curve was used to analyze the discriminant ability of model A, model A + B, and model A + B + C. Specifically, the area under the receiver operating characteristic curve increased from 0.816 (model A; 95% CI, 0.760–0.872) to 0.913 (model A + B + C; 95% CI, 0.881–0.946), and the models were not overoptimistic and were applicable confirmed by internal and external validations respectively.

This prognosis model could be used to predict the prognosis of patients with hypertensive intracerebral hemorrhage early, simply and accurately, contributing to the clinical treatment eventually.

**Abbreviations:** AUC = area under the receiver operating characteristic curve, BP = blood pressure, CI = confidence interval, CT = computed tomography, EF = ejection fraction, GCS = Glasgow coma scale, GFR = glomerular filtration rate, HE = hematoma expansion, HICH = hypertensive intracerebral hemorrhage, H-L = Hosmer–Lemeshow, ICH = intracerebral hemorrhage, IQRs = interquartile ranges, IVH = intraventricular hemorrhage, LDL = low-density lipoprotein, mRS = modified Rankin scale.

**Keywords:** high blood pressure, intracerebral hemorrhage, prediction

1. Introduction

Intracerebral hemorrhage (ICH) is the deadliest form of stroke that accounts for approximately 10% to 30% of all strokes.\textsuperscript{11} And the reported 30-day case fatality rate of ICH was around 40% to 50%.\textsuperscript{2–3} As we all known, high blood pressure (BP) can lead to spontaneous intracerebral hemorrhage which is also known as hypertensive intracerebral hemorrhage (HICH). The best clinical management of HICH remains unclear due to unproven therapies, such as craniotomy, craniectomy, and hyperosmolar agents. Therefore, HICH is still short of effective treatments. In this respect, it can be a serious public health affair which would increase the burden of social economy.\textsuperscript{2}

Therefore, it is of great importance to explore and identify the prognostic risk factors of HICH and establish a HICH prognosis model with excellent performance, which can assist clinicians to make the accurate diagnosis as well as further treatments for HICH patients. Various and complex prognosis models have been reported depending on different parameters,\textsuperscript{14–7} but the results were not satisfactory. In this study, we tried to develop a suitable prognosis model of HICH, based on the established ICH treatment database of Shaoxing Central Hospital from 2012 to 2016 and relevant clinical data. The data of patients with HICH in Shaoxing Second Hospital from 2016 to 2017 were used as the external validation to test the predictive performance of this prognosis model.

2. Methods

2.1. Patient selection and study design

In this retrospective cohort study, we reviewed medical records of all spontaneous ICH patients admitted to Shaoxing Central Hospital between January 1, 2012 and December 31, 2016 to develop the prognosis model. Patients were eligible for the study if the baseline nonenhanced computed tomography (CT) scan was performed within 6 hours after symptoms onset. A follow-up CT scan was performed within 30h after the initial CT scan. The exclusion criteria were: patients who had secondary ICH due to arteriovenous malformation, intracranial aneurysm rupture, traumatic brain injury, brain tumor, or hemorrhagic infarction; patients who had primary intraventricular hemorrhage (IVH);
patients with anticoagulant associated ICH; and patients who refused to follow-up clinical assessment after being discharged from hospital. Collected data also included demographic information, medical history, initial evaluation (including vital signs, laboratory data, and radiographic findings) and hospital course.

The primary outcome was assessed by the modified Rankin scale (mRS) for 3 months. The outcome was dichotomized as favorable and poor outcomes from the 3-month mRS score. And the poor outcome was defined by an mRS score of 4 to 6 according to previous definitions. Hypertension was defined by systolic BP ≥ 140 mm Hg, or diastolic BP ≥90 mm Hg. Admission BP was modulated according to the guideline recommendations. Also hypoxemia was defined by PaO₂ < 60 mm Hg. ICH was diagnosed with noncontrast CT examinations with 5-mm sections. Besides, hematoma volume was measured by the ABC/2 formula, where A, B, and C represent the dimensions of the maximum level of hematoma in 3 perpendicular axes.

In total, 352 patients were enrolled into the database in this study, providing information and data to develop the prognosis model. In addition, we reviewed medical records of patients by using the same selected criteria, who were treated at the Shaoxing Second Hospital for the external validation between January 2015 and October 2017.

All aspects of this study were approved by Institutional Review Board. Direct patient identifiers were not collected as part of the data setting due to privacy considerations. Because our study did not address patient care intervention, it was not necessary to obtain written informed consents.

2.2. Model development and validation

The initial evaluated data were used to develop our prognosis models for the outcome prediction of HICH. Three prognosis models were developed based on different independent risk factors. Model A was based on the clinical condition on admission (GCS score and pupil light reflex) together with patient age. Model B was built based on the amount of extravasated blood from CT scan. Model C was built based on the result of laboratory data.

The discriminative performance was described by an area under the receiver operating characteristic curve (AUC) with a corresponding 95% confidence interval (CI). The calibration of the models was evaluated by using the Hosmer–Lemeshow (H-L) goodness-of-fit test, which was considered as reliable if \( P > .2 \).

Meanwhile, we internally validated our models with bootstrapping techniques, that is, in each bootstrap sample, the entire modeling process was repeated to correct the overestimation. In addition, we evaluated both discrimination and calibration of the risk chart in the validation cohort.

2.3. Statistical analysis

The categorical variables were divided into 2 groups (mRS > 3 and mRS ≤ 3), and the baseline characteristics were summarized appropriately as mean ± SD or as median and interquartile ranges (IQRs). Continuous variables were compared by using Student’s \( t \)-test, and categorical variables were compared by using Pearson’s chi-squared test. The variables that were significantly related to 3-month outcome in univariate analysis were entered within the logistic regression model by using a forward stepwise selection. The maximum likelihood method was used after adjusting for confounding factors and identifying independent predictors of 3-month outcome. All statistical analyses were performed by using the SPSS software package version 19.0 (IBM Corporation, Armonk, NY), and \( P < .05 \) was considered to be statistically significant.

3. Results

A total of 325 patients, including 198 males (60.9%) with mean age of 60.9, were recruited in the developmental cohort. All patients had a history of high blood pressure, the mean systolic BP on arrival at hospital was 203 ± 45 mm Hg (range, 55–364 mm Hg) and the mean heart rate was 98 ± 24 bpm (range, 52–180 bpm). Depending on the mRS score, 239 (73.5%) patients had the good outcome, 86 (26.5%) patients had the poor outcome. Main characteristics of the cohort were summarized in Table 1. In general, the average age, ICH volume, blood glucose, D-dimer, and fibrinogen level in the poor prognosis group were higher than those in the good prognosis group (\( P < .05 \)), whereas the average scores of GCS, the level of blood magnesium, total cholesterol, and low-density lipoprotein (LDL) in the poor prognosis group were lower than those in the good prognosis group (\( P < .05 \)). Furthermore, the proportions of manual worker, smoking, hypoxemia, brainstem hemorrhage, IVH, and midline shift ≥ 5 mm in the poor prognosis group were higher than those in the good prognosis group (\( P < .05 \)). And surgery was considered as a risk factor for the poor prognosis.

Significant risk factors selected by univariate analyses were further evaluated by logistic regression analyses with forward, stepwise selection procedures. Only 8 predictors, including age ≥ 60, GCS score ≤ 12, the absence of pupillary light reflex, ICH volume ≥ 25 ml, the presence of IVH, hypoxemia, higher blood glucose (≥ 10 mmol/L), and D-dimer (≥ 2.5 mg/L) were identified as significant and independent predictors of the 3-month poor outcome (Table 2).

3.1. Prognostic models

As described above, model A was based on 3 predictors of age, GCS score and pupillary light reflex on admission. Model B was built based on amount of extravasated blood from CT scan result including ICH volume and the presence of IVH. Model C was built based on the independent risk facts of laboratory data, such as hypoxemia, blood glucose, and D-dimer. The receiver operating characteristic curve was used to analyze the discriminant ability of model A, model A + B, and model A + B + C. With the increase of risk factors evolved in the analysis, the discriminant ability of the prognosis model was enhanced (Table 3 and Fig. 1). Concretely, the AUC increased from 0.816 (model A; 95% CI, 0.760–0.872) to 0.913 (model A + B + C; 95% CI, 0.881–0.946).

Table 4 showed that old age, GCS score, pupillary light reflex, ICH volume, IVH, hypoxemia, blood glucose, and D-dimer were risk facts of the poor outcome in the validation cohort. Moreover, Table 5 showed that the internal validity of these models was high, and there was no over optimism. Meanwhile, when applying the prognostic models to the validation cohort, the external validity of model A, model A+B, and model A+B+C was very high. Besides, the H-L goodness-of-fit test, that was used to test the calibration ability, indicated that each prognosis model had a good performance and a high applicability. Thus, these prognosis models could be clinically applied to accurately and effectively predict the prognosis of patients with ICH.
4. Discussion

The prognosis model is a statistical model combined with various risk factors to predict, assist, and improve the prognosis of patients, which would be more accurate and effective than clinicians’ own experience. Recently, prognosis models based on statistical methods have been developed rapidly; several scholars have put forward their prognosis models about predicting the death and short-term outcome of ICH patients. In 2001, Hemphill raised a 6-point scoring system that included the factors of GCS score, age, infratentorial origin of ICH, ICH volume, and presence of IVH, showing the 30-day mortality increasing from 13% (1 point) to 97% (5 point).\(^{[4]}\) Furthermore, other studies introduced new parameters such as NIHSS score, IVH score, history of hypertension, subarachnoid extension and serum glucose into the model, which could improve the predictive performance of the new models.\(^{[15-17]}\) These models presented a good predictive performance during the internal and external validations. At present, there are plenty of researches focusing on the prognostic risk factors of spontaneous HICH. However,
suitable prognosis models that can be widely applied for clinical prognosis have not been studied clearly to date. In this study, we systematically analyzed the risk factors of admission, and selected significant risk factors to develop different prognosis models. After development, we performed internal and external validations to test their function, and eventually confirmed that the prognosis models were applicable to the clinical practice.

Predictive risk factors were the basis of prognosis models. In the multivariate analysis, we found that old age, lower GCS score, the absence of pupillary light reflex, ICH volume ≥ 25 mL, the presence of IVH, hypoxemia, higher blood glucose, and D-dimer level were independent factors of the patient prognosis. Specifically, age ≥ 60, GCS score ≤ 12 and the absence of pupillary light reflex indicated a poor prognosis. Moreover, CT examination was usually used as an important assistant examination for diagnosis within HICH patients. In addition to ICH volume and IVH, subarachnoid dilatation, cisterna ambiens compression and midline shift were also defined as significant risk factors of the poor prognosis.

Likewise, laboratory examination also provided the clinical data in the early stage, and clinicians could correct the abnormal values during the laboratory examination in order to improve the patient prognosis. However, it had been controversial to consider blood glucose as a prognostic factor for a long time. Some studies showed that high blood glucose could have a biologically plausible association with poor outcomes in ICH patients, while other study showed patients with or without HE had similar blood glucose (179 ± 68 mg/dL vs 153 ± 71 mg/dL) and diabetes incidence (14% vs 25%). Some studies showed the deleterious effect of hyperglycemia was attributed to its secondary promotive effects of acidosis, free radical formation, and inflammatory cytokines release. Those secondary effects accelerated the BBB breakdown, impaired the integrity of adjacent vessels surrounding the initial bleeding sites, and promoted emerging or continuous bleeding.

Previous studies had demonstrated that blood glucose levels between 3.7 and 7.3 mmol/L were significantly associated with favorable functional outcomes in acute ischemic stroke, and higher blood glucose variability was reported to be significantly associated with poor outcomes in subarachnoid hemorrhage. However, the pool of available evidence pertaining to blood glucose and ICH was still limited. Thus, further studies should investigate the association between blood glucose levels and functional outcomes with multiple time points and variability of blood glucose. Importantly, our study also proved that D-dimer level was responsible for the prognosis of HICH patients. Among ICH patients, the high level of D-dimer in the early phase was related with the progressive hemorrhagic

Table 3

| Prognosis model | AUC (95%CI) | Sensitivity | Specificity |
|-----------------|------------|------------|------------|
| A               | 0.816 (0.760–0.872) | 0.782 | 0.756 |
| A+B             | 0.884 (0.842–0.925) | 0.820 | 0.814 |
| A+B+C           | 0.913 (0.881–0.946) | 0.862 | 0.826 |

Figure 1. Receiver operating characteristic curves of each combinatorial prognosis model for predicting 3-month outcome.
The performance of prognosis models.

| Model                  | Model A | Model A + B | Model A + B + C |
|------------------------|---------|-------------|-----------------|
|                        | Internal validation | External validation | Internal validation | External validation | Internal validation | External validation |
| AUC (95%CI)             | 0.801 (0.763–0.852) | 0.823 (0.792–0.854) | 0.875 (0.813–0.982) | 0.881 (0.844–0.949) | 0.921 (0.878–0.967) | 0.947 (0.911–0.985) |
| $P^2$                  | .451    | .451        | .451            | .325               | .138               | .138               |

1 H-L goodness-of-fit test.

2 Bootstrap sample is 200.
5. Conclusions
The prognosis models based on the risk factors on admission can predict the prognosis early, simply and accurately, which is convenient for clinical practice. Clinicians can operate this predictive tool to make a prognosis of patients with HICH, lead to the correct clinical decision, make a good use of medical resources, and eventually provide the best treatment for patients.

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