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A nomogram to predict early hematoma expansion of hypertensive cerebral hemorrhage

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Abstract

Early hematoma expansion of hypertensive cerebral hemorrhage is affected by various factors. This study aimed to clarify the risk factors and develop a nomogram to predict early hematoma expansion.

A retrospective analysis was carried out in patients with hypertensive cerebral hemorrhage admitted to our institution between January 1, 2012 and December 31, 2018; the patients were divided into 2 groups according to the presence of early hematoma expansion. Univariate and multivariate analyses were performed to analyze the risk factors of hematoma expansion. The nomogram was developed based on a multivariate logistic regression model, and the discriminative ability of the model was analyzed.

A total of 477 patients with hypertensive cerebral hemorrhage and with a baseline hematoma volume <30 ml were included in our retrospective analysis. The hematoma expansion rate was 34.2% (163/477). After multivariate logistic regression, 9 variables (alcohol history, Glasgow coma scale score, total serum calcium, blood glucose, international normalized ratio, hematoma shape, hematoma density, volume of hematoma on initial computed tomography scan, and presence of intraventricular hemorrhage) identified as independent predictors of hematoma expansion were used to generate the nomogram. The area under the receiver operating characteristic curve of the nomogram was 0.883 (95% confidence interval 0.851–0.914), and the cutoff score was −0.19 with sensitivity of 75.5% and specificity of 87.3%.

The nomogram can accurately predict the risk of early hematoma expansion.

Abbreviations: AUC = the area under the ROC curve, CRP = C-Reactive Protein level, CT = computed tomography, DBP = diastolic blood pressure, GCS = Glasgow coma scale, HE = hematoma expansion, HICH = hypertensive intracerebral hemorrhage, ICH = intracerebral hemorrhage, INR = international normalized ratio, MAP = mean arterial pressure, Mg^{++} = Serum magnesium level, ROC = receiver operating characteristic, SBP = systolic blood pressure, tCa = total serum calcium.

Keywords: hematoma expansion, hypertensive cerebral hemorrhage, nomogram, risk factors

1. Introduction

Intracranial hemorrhage is a common form of stroke, accounting for 10% to 30% of all strokes.[1] Hypertensive intracerebral hemorrhage (HICH) is the least treatable form of intracerebral hemorrhage (ICH) and is associated with high mortality.[2,3] Clinical studies have found that hematoma expansion (HE) is common in patients with ICH and leads to poor outcomes. Brott et al performed an observational study using serial computed tomography (CT) scans to determine the extent of HE in 103 ICH patients.[4] That study found that 38% of patients had significant hematoma growth, defined as >33% enlargement of the hematoma compared with baseline. Previous studies have determined that HE following HICH significantly affects patients' prognosis, including survival, disability, and mortality rates.[5,6] Therefore, it is important to predict and evaluate the risk factors for HE in the early stages of HICH. Although several studies have investigated early HE in patients with ICH, the underlying mechanism remains unclear.

Several studies have described better performance by nomograms compared with scores that use risk grouping. Using a continuous score, a nomogram is a graphical statistical instrument that calculates the continuous probability of a particular outcome for an individual patient.[7–9] Nomograms are important components of modern medical decision-making and have been used in an extensive array of applications, including cancer, surgery, and other specialties.[10–12] The purpose of this study was to develop a nomogram to predict the probability of HE for patients with HICH.

2. Materials and methods

2.1. Patient selection

We conducted a retrospective analysis of HICH patients admitted to the Neurology and Neurosurgery Department of our hospital

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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(Affiliated Huzhou FuYin Hospital of Huzhou University) from January 1, 2012 to December 31, 2018. Inclusion criteria were as follows:

1. an accurate history of hypertension, defined as office systolic blood pressure (SBP) ≥140 mm Hg and/or diastolic blood pressure (DBP) ≥90 mm Hg[13];
2. typical bleeding sites including the basal ganglia, ventricle, thalamus, brainstem, and cerebellum;
3. a baseline CT scan performed within 6 hours of hemorrhage and a follow-up CT scan performed within 24 hours.

Exclusion criteria were as follows:

1. traumatic brain injury;
2. secondary cerebrovascular disease detected by CT angiography;
3. patients with leukemia, aplastic anemia, thrombocytopenic purpura, hemophilia, and other blood diseases;
4. brain tumors or cavernous vascular malformations and other diseases detected by early (within 72 hour) or late (2–3 weeks after full absorption of hematoma) enhanced magnetic resonance imaging;
5. previous use of anticoagulant or antiplatelet drugs such as aspirin or clopidogrel.

In addition, patients with a baseline hematoma volume of more than 30 ml and those who received immediate surgical treatment after baseline CT scan were excluded from our study. A flowchart of the case screening process is shown in Figure 1. Our research was approved by the hospital ethics committee, and informed consent was obtained from all patients.

2.2. Data collection

Baseline clinical and demographic information included age; gender; smoking history; alcohol history; diabetes history; previous history of hypertensive cerebral hemorrhage; SBP, DBP, and mean arterial pressure (MAP) at admission; Glasgow coma scale (GCS) score; renal dysfunction (urea nitrogen or

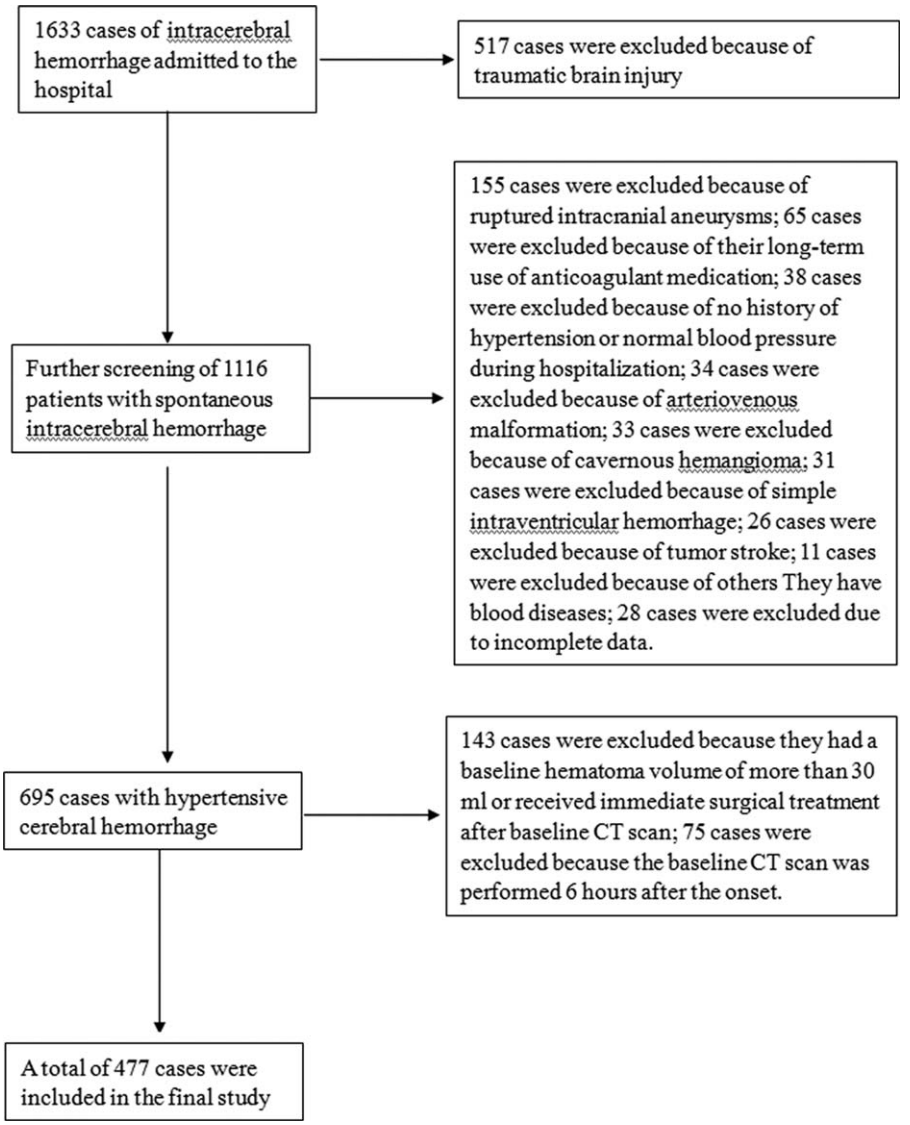

Figure 1. A flowchart of the case screening process.

creatinine level higher than normal) and hyperlipidemia at admission; time from onset to the first CT scan; record at admission of total serum calcium (tCa), blood glucose level, high density lipoprotein level, low density lipoprotein level, Serum magnesium level, C-Reactive Protein level and coagulation function indices obtained from the peripheral blood; location, volume, shape, and density of the hematoma on the first CT scan; and presence (yes/no) of intraventricular hemorrhage. Coagulation indices included platelet count, prothrombin time, activated partial thromboplastin time, international normalized ratio (INR), and fibrinogen.

Hematoma volume was estimated by a simplified method from CT scans on admission.[14] Briefly, the cubic content of the hematoma was calculated from the maximum width (X), length (Y), and height (Z), as seen on the CT scans; the 3 dimensions (X, Y, and Z) were multiplied together, and half of that value was used to estimate the hematoma volume ($X \times Y \times Z \times \pi/6$). Hemorrhage within the ventricular system was not measured. HE was defined as an increase of ≥6 ml or ≥33% of hematoma volume observed between the initial and follow-up CT scan at 24 hours or the closest one.[15,16] Hematomas were divided into 2 categories according to shape:

1. Regular: the hematoma was round-like or oval, had a clear boundary, was smooth and regular, there were no scattered small hematomas; and
2. Irregular: the hematoma was shapeless, irregular, with a fuzzy boundary or with scattered small hematomas.[17]

Hematomas were also divided into 2 categories according to density:

1. mixed density: composed of 2 density components, the boundary between the 2 components was obvious (easily distinguished by the naked eye), and the difference between the 2 densities measured by CT was at least 18 Hu; and
2. uniform density: hematoma density was uniform.[18]

Some imaging examples are shown in Figure 2. All data were analyzed by 2 experienced researchers. In cases of a difference of opinion, a third researcher was consulted.

2.3. Statistical analysis

The patients were divided into HE and non-HE groups. According to the GCS score, the patients were divided into 2 groups: low (GCS score ≤12), moderate to severe change of consciousness; and high (GCS score 13–15), no or mild change of consciousness. Baseline clinical and demographic information of all patients was compared between groups. Categorical variables, shown as numbers, were tested by Chi-Squared or Student *t* test. Continuous variables, presented as mean ± SD, were tested by one-way analysis of variance (the Student–Newman–Keuls test was used when one-way analysis of variance was significant). To generate the nomogram, multivariate binary logistic regression analysis was performed to predict the probability of HE using a forward stepwise method that included all variables with probability values <.05 in the univariate analysis. Receiver operating characteristic (ROC) curves were used to determine the cutoff value and evaluate the discriminative ability of the model. All statistical analyses were two-tailed, and *P* values <.05 were considered statistically significant. The nomogram ROC curves were generated using R (http://www.R-project.org) and EmpowerStats software (www.empowerstats.com, X&Y Solutions, Inc., Boston, MA). Other analyses were performed using SPSS software (ver. 24.0; IBM Corp., Armonk, NY).

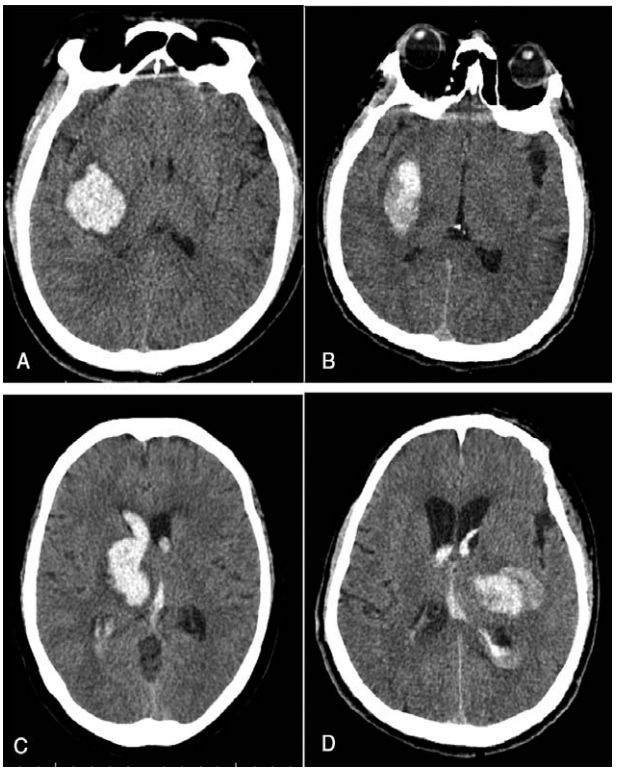

Figure 2. Imaging examples describing the shape and density of hematoma. A: regular shape, uniform density of hematoma, and without intraventricular hemorrhage; B: regular shape, mixed density of hematoma, and without intraventricular hemorrhage; C: irregular shape, uniform density of hematoma, and with intraventricular hemorrhage; D: irregular shape, mixed density of hematoma, and with intraventricular hemorrhage.

3. Results

A total of 477 patients (326 males and 151 females) with HICH were included in the study. Baseline data and clinical characteristics of all patients are shown in Table 1. The rate of HE in this study was 34.2% (163/477). Table 1 provides the results of univariate analysis; 20 variables showed significant differences between the 2 groups. These 20 variables were subjected to regression analysis, and 9 independent risk factors for the expansion of hypertensive cerebral hemorrhage were obtained: alcohol history (β = 0.746, odds ratio [OR] = 2.11, 95% confidence interval [CI] 1.22–3.64, *P* = .007); GCS score (β = 0.790, OR = 2.20, 95% CI 1.28–3.78, *P* = .004), tCa (β = −2.056, OR = 0.13, 95% CI 0.03–0.50, *P* = .003), blood glucose (β = 0.163, OR = 1.18, 95% CI 1.05–1.32, *P* = .004), INR (β = 3.314, OR = 27.50, 95% CI 4.67–161.77, *P* < .001), hematoma shape (β = 1.012, OR = 2.75, 95% CI 1.31–5.78, *P* = .007), hematoma density (β = 1.155, OR = 3.17, 95% CI 1.88–5.36, *P* < .001), hematoma volume on initial CT (β = 0.101, OR = 1.11, 95% CI 1.07–1.15, *P* < .001), and presence of intraventricular hemorrhage (β = 0.811, OR = 2.25, 95% CI 1.34–3.77, *P* = .002) (Table 2). No significant statistical collinearity was observed for any of the 9 variables (Table 3).

The nomogram includes a preliminary score for each of the 9 predictors, which range from 0 to 10; these scores are summed to

Table 1

Comparison and results of univariate analysis between patients with and without HE.

Characteristics	HE Group (n = 163)	Non-HE Group (n = 314)	*P* value
Age, years, (mean ± SD)	60.07 ± 13.11	59.75 ± 13.33	.08‡
Sex, male, n (%)	124 (76.1%)	202 (64.3%)	.009*
Medical history, n (%)			
smoking history	57 (35%)	75 (23.9%)	.01*
alcohol history	61 (37.4%)	77 (24.5%)	.003*
diabetes history	41 (25.2%)	54 (17.2%)	.039*
history of HICH	6 (3.7%)	18 (5.7%)	.33*
Admission record			
SBP, mm Hg, (mean ± SD)	186.52 ± 25.95	176.08 ± 23.46	<.001‡
DBP, mm Hg, (mean ± SD)	103.93 ± 15.31	100.48 ± 15.06	.019‡
MAP, mm Hg, (mean ± SD)	130.99 ± 18.24	125.08 ± 16.88	<.001‡
Renal dysfunction, n (%)	13 (8%)	34 (10.8%)	.32*
Hyperlipidemia, n (%)	33 (20.2%)	61 (19.4%)	.83*
tCa, mmol/L, (mean ± SD)	2.15 ± 0.22	2.24 ± 0.16	<.001‡
HDL, mmol/L, (mean ± SD)	1.36 ± 0.43	1.46 ± 0.40	.009
LDL, mmol/L, (mean ± SD)	2.27 ± 0.80	2.52 ± 0.68	<.001‡
Blood glucose, mmol/L, (mean ± SD)	8.42 ± 2.73	7.08 ± 2.04	<.001‡
Mg^{++}, mmol/L, (mean ± SD)	0.78 ± 0.13	0.81 ± 0.13	.006‡
CRP, mg/L, (mean ± SD)	21.70 ± 33.93	12.55 ± 22.91	<.001‡
GCS score, n (%)			
High group (13–15)	38 (23.3%)	185 (58.9%)	<.001*
Low group (≤12)	125 (76.7%)	129 (41.1%)	
Coagulation function indexes			
PLT count, (*10^9 / L), (mean ± SD)	146.06 ± 61.37	166.91 ± 53.83	<.001‡
PT, seconds, (mean±SD)	11.22 ± 1.64	11.00 ± 1.55	.16‡
APTT, seconds, (mean ± SD)	28.16 ± 4.86	28.58 ± 4.60	.35‡
INR, (mean ± SD)	1.03 ± 0.18	0.96 ± 0.11	<.001‡
FIB, mmol/L, (mean ± SD)	3.24 ± 1.11	3.35 ± 0.95	.26‡
Time from onset to initial CT, hours, (mean ± SD)	1.74 ± 1.14	1.96 ± 1.24	.06†
Shape of hematoma, n (%)			
regular	12 (7.4%)	116 (36.9%)	<.001*
irregular	151 (92.6%)	198 (63.1%)	
Density of hematoma, n (%)			
Uniform density	73 (44.8%)	245 (78%)	<.001*
Mixed density	90 (55.2%)	69 (22%)	
Volume of hematoma on initial CT, ml, (mean ± SD)	19.95 ± 6.47	11.77 ± 7.42	<.001‡
Presence of intraventricular hemorrhage, n (%)			
yes	98 (60.1%)	114 (36.3%)	<.001*
no	65 (39.9%)	200 (63.7%)	
Location of hematoma			
basal ganglia	126 (77.3%)	197 (62.7%)	<.001*
thalamus	6 (3.7%)	64 (20.4%)	
cerebellum	6 (3.7%)	8 (2.5%)	
brainstem	0 (0%)	6 (1.9%)	
frontal lobe	0 (0%)	3 (1%)	
temporal lobe	17 (10.4%)	23 (7.3%)	
parietal lobe	3 (1.8%)	4 (1.3%)	
occipital lobe	5 (3.1%)	9 (2.9%)	

SBP = systolic blood pressure, DBP = diastolic blood pressure, MAP = mean arterial pressure, GCS = Glasgow coma scale, tCa = total serum calcium, HDL = high density lipoprotein, LDL = low density lipoprotein, PLT = platelet, PT = prothrombin time, APTT = activated partial thromboplastin time, INR = international normalized ratio, FIB = fibrinogen, Mg^{++} = Serum magnesium level, CRP = C-Reactive Protein level.

* Chi-Squared test.

† Student *t* test.

‡ 1-way analysis of variance.

P values <.05 were deemed statistically significant.

obtain the total score, which translates into the individual probability (0%–100%) of HE in hypertensive cerebral hemorrhage. In this study, the expression outcomes (β) from the multivariate logistic model were used to construct the model for estimation of the risk of HE. The scoring model was as follows: −4.64658 + 0.74637 * (existing alcohol history = 1) + 0.78989 * (low GCS score [≤12] = 1) − 2.05616 * tCa (mmol/L) + 0.16311 * blood glucose (mmol/L) + 3.31400 * INR + 1.01196 * (irregular shape = 1) + 0.10084 * volume of hematoma on initial CT (ml) + 1.15513 * (mixed density = 1) + 0.81077 * (presence of intraventricular hemorrhage yes = 1) (Fig. 3). The performance of the nomogram was measured using ROC curves; the area under

Table 2

Multivariate binary logistic regression analysis of independent risk factors indicating hematoma expansion.

Variables	β	OR (95% CI)	*P* value
Alcohol history	0.746	2.11 (1.22–3.64)	.007
GCS score	0.790	2.20 (1.28–3.78)	.004
tCa, mmol/L	−2.056	0.13 (0.03–0.50)	.003
Blood glucose, mmol/L	0.163	1.18 (1.05–1.32)	.004
INR	3.314	27.50 (4.67–161.77)	<.001
Shape of hematoma	1.012	2.75 (1.31–5.78)	.007
Density of hematoma	1.155	3.17 (1.88–5.36)	<.001
Volume of hematoma on initial CT, ml	0.101	1.11 (1.07–1.15)	<.001
Presence of intraventricular hemorrhage	0.811	2.25 (1.34–3.77)	.002

GCS = Glasgow coma scale, tCa = total serum calcium, INR = international normalized ratio, β = Regression coefficient, OR = Odds Ratio, CI = Confidence Interval.

Table 3

Collinearity of combinations of variables in the HE group.

variables	Tolerance	VIF
Alcohol history	0.983	1.017
GCS score	0.811	1.233
tCa, mmol/L	0.967	1.034
Blood glucose, mmol/L	0.908	1.102
INR	0.949	1.054
Shape of hematoma	0.811	1.233
Density of hematoma	0.861	1.161
Volume of hematoma on initial CT, ml	0.704	1.420
Presence of intraventricular hemorrhage	0.918	1.089

All values of variation inflation factors (VIF) were <2.

the ROC curve (AUC) was 0.883 (95% CI 0.851–0.914) in the model based the on observed data. The cutoff score was −0.19, with sensitivity of 75.5% and specificity of 87.3% (Fig. 4). The predictive accuracy of the nomogram was also measured using

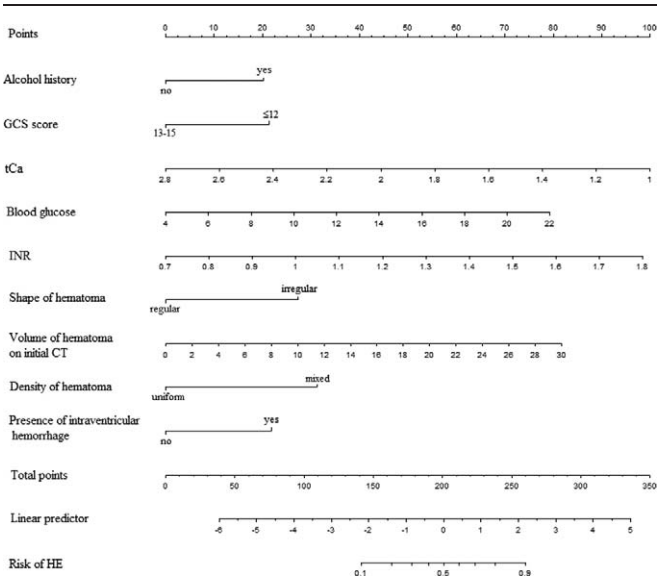

Figure 3. Nomogram for predicting the probability of hematoma expansion definition. To use the nomogram, find the position of each variable on the corresponding axis, draw a line to the points axis for the number of points, add the points from all of the variables, and draw a line from the total points axis to determine the HE probabilities at the lower line of the nomogram. tCa = total serum calcium, INR = international normalized ratio.

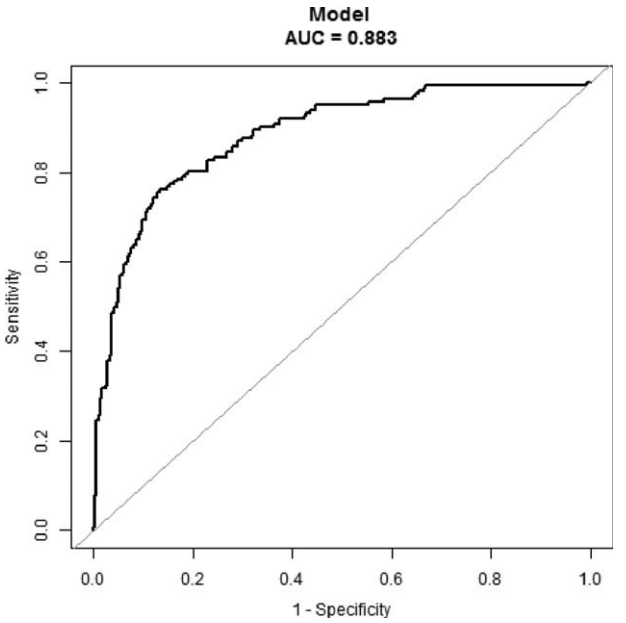

Figure 4. The AUC of the model from observed data (nomogram) was 0.884. The cut-off value was −0.37 with a sensitivity of 78.5% and a specificity of 85.0%. AUC = area under ROC.

the bootstrap (1000 replicates) method, and the AUC of the model with this method was similar (AUC=0.869, 95% CI 0.835–0.907).

4. Discussion

Hypertensive cerebral hemorrhage is a spontaneous non-traumatic cerebral hemorrhage disease that is the most common cerebrovascular disease in middle-aged and older individuals. The rates of disability and death due to this disease are high, and the population with the disease is getting younger.[19,20] In hypertensive cerebral hemorrhage, toxic substances such as thrombin and hemoglobin are released by the hematoma, causing damage to the surrounding tissues and resulting in HE in the early stage of hemorrhage.[21] HE further increases the mortality and disability rates. Therefore, predicting HE and determining risk factors are of great clinical significance for the treatment of hypertensive cerebral hemorrhage.

Previous studies have shown many risk factors for HE. Ohwaki et al suggested that the risk of HE is greatly reduced by maintaining systolic blood pressure below 150 mm Hg;[22] they suggested that hypertension was associated with hematoma enlargement in the early stage of primary cerebral hemorrhage. Flibotte et al revealed a higher likelihood of early HE in patients with abnormal liver function or long-term history of alcohol abuse.[23] Significant early HE is more common in patients with prior warfarin use and abnormal coagulation function.[24] Morotti et al suggested that a tCa level lower than 2.1 mmol/L was independently associated with a greater hematoma volume at admission and hematoma growth.[25] Zhang et al found that a lower serum iCa level (<1.12 mmol/L) was associated with a greater risk of early HE.[26] Qureshi et al[27] analyzed the relationship between blood glucose concentration and HE in 60 patients with ICH and found that the risk of HE in patients with hyperglycemia was more than twice that of patients with

hypoglycemia. Huynh et al[28] conducted a retrospective study of 301 patients with primary or anticoagulant-related cerebral hemorrhage and found that the international standardized ratio of >1.5 was an important predictor of HE in ICH. Barras et al showed that a hematoma volume greater than 30 ml was more likely to cause early HE than those were small hematomas.[29] In their another study, hematoma shape was proposed as an important independent risk factor for early hematoma enlargement.[30] In the present study, we found relationships of HE with alcohol history, GCS score, liver dysfunction, total serum calcium, blood glucose, INR, hematoma shape, hematoma density, hematoma volume on initial CT, and presence of intraventricular hemorrhage.

We observed that previous studies tended to determine the best threshold for their prediction of HE for continuous or discrete variables such as blood glucose level, hematoma volume, INR, and tCa, and then to classify the variables into 2 categories, such as hematoma volume <30 ml, INR >1.5, and TCA <2.1 mmol/L. We believe that the process of dividing these variables into 2 or 3 risk groups is usually statistically inefficient and may reduce prediction accuracy. The first issue caused by continuous variable classification is information loss. For several groups, the information loss is small; however, with only 2 groups, information loss is more significant. Another important disadvantage of dichotomizing is that it does not use all of the information in a given category. Everyone above (or everyone below) the threshold is treated equally, although their prognoses differ greatly. The characteristics of individuals who are close to the tangent point but on the opposite sides are regarded as very different from one another rather than as very similar. Therefore, in our prediction model, we retain the characteristics of these continuous or discrete variables by using nomograms, thereby clarifying the statistical effects of these variables. The nomogram in the present study showed good performance in predicting the risk of HE (AUC = 0.883).

As for smoking history; diabetes history, high density lipoprotein level, low density lipoprotein level, Serum magnesium level, C-Reactive Protein level and platelet count, several study have shown that they have a certain relationship with HE of intracerebral hemorrhage.[3–6,31,32] In our study, the results of univariate analysis showed there is a significant significance with them, but the results of multivariate analysis did not observe significant connection, which may be related to both historical records and sample size are related. In addition, for the 2 indicators of Serum magnesium level and C-Reactive Protein level, there are other possibilities. Jafari et al considered there is a difference between the serum total magnesium and the serum magnesium level as a physiological active component[31]; clinical CRP assays that only measure the portion of total CRP in plasma in the soluble pentameric form, the insoluble component of CRP, ative pentameric CRP (npCRP), and monomeric CRP (mCRP) is not currently measured in clinical settings.[32,33] However, these indicators should be further verified in large samples and more accurate experiments.

This study has several limitations. First, this was a retrospective study conducted in a single center. Second, data were obtained by reviewing medical records, which could have compromised data quality through the accumulation of inappropriate data. Third, for commonly recognized features that can predict hematoma enlargement, such as the black hole sign, the island sign on enhanced CT, and micro hemorrhages on magnetic resonance imaging, not all of these examinations were carried out for all patients due to their condition and economic limitations; thus, their indices were not included in the prediction model. In addition, the biomarkers matrix metalloproteinase-9 and interleukin-6 have been considered independent risk factors for HE. In future prospective studies, it will be necessary to evaluate and integrate these indicators and biomarkers to improve the accuracy of nomogram prediction. In addition, the prediction of hematoma enlargement after intracerebral hemorrhage is important, but it should ultimately serve the patients. Therefore, these factors are necessary to study the prognosis of hypertensive intracerebral hemorrhage in the future.

5. Conclusions

In patients with hypertensive cerebral hemorrhage, HE may be related to alcohol history, GCS score, total serum calcium, blood glucose, INR, hematoma shape, hematoma density, hematoma volume on initial CT, and presence of intraventricular hemorrhage. The nomogram can help to predict the risk of early hematoma expansion.

Author contributions

Conceptualization: Si Hu, Zhang Rui Han.
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Formal analysis: Guo Wen Sheng.
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Methodology: Bin Li, Qiang Ma.
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Supervision: Zhang Rui Han.
Writing – original draft: Si Hu.
Writing – review & editing: Guo Wen Sheng, Yi Hu, Zhang Rui Han.

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