Predicting Recurrent Hypertensive Intracerebral Hemorrhage: Derivation and Validation of a Risk-Scoring Model Based on Clinical Characteristics

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■ OBJECTIVE: **To develop and validate a risk-scoring model for predicting recurrent hypertensive cerebral hemorrhage (RHCH) occurring within 1 year after initial hypertensive cerebral hemorrhage and to facilitate preemptive clinical intervention for the prevention of secondary hemorrhage.**

■ METHODS: **Patient gender, age, blood pressure, Glasgow Coma Scale (GCS) score, location of cerebral hemorrhage, surgery, past medical history, blood biochemical parameters, and Glasgow Outcome Scale score were analyzed using logistic regression analysis to determine independent predictors of RHCH. A risk-scoring model was constructed by assigning coefficients to each predictor and validating it in another independent cohort. The accuracy of the model was then assessed by the area under the receiver operating characteristic curve (AUC), and the calibration ability of the model was assessed by the Hosmer-Lemeshow test.**

■ RESULTS: **Of 520 patients in the derivation cohort, 38 developed RHCH within 1 year after discharge. Independent risk factors of RHCH were age >60 years; stage 3 hypertension at admission; GCS score 9–12 (admission); GCS score 3–8 (discharge); history of cerebral ischemic stroke, smoking, alcoholism; and plasma homocysteine (Hcy) level ≥10 μmol/L. The recurrence rates for the low-risk (0–13 points), intermediate-risk (14–26 points), and high-risk (27–39 points) groups were 1.73%, 6.11%, and 57.14%, respectively ($P < 0.001$). The corresponding rates in the validation cohort, of whom 10/107 (9.35%) developed RHCH, were 3.45%, 7.14%, and 71.43%, respectively ($P < 0.001$). The risk-scoring model showed good discrimination in both the derivation and validation cohorts, with an AUC of 0.802 versus 0.863. The model also showed good calibration ability (the Hosmer-Lemeshow *P* values of the two cohorts were 0.532 vs. 0.724).**

■ CONCLUSIONS: **This model will help identify high-risk groups for RHCH in order to facilitate and improve preemptive clinical intervention.**

INTRODUCTION

As of 2010, the age-standardized incidence of stroke in China exceeded 336/100,000, ranking it first in the world. The number of patients who died of stroke reached 1.7 million each year, ranking it first among the national causes of death.[1] Hypertensive cerebral hemorrhage (HICH) is one of the most important subtypes of stroke. It has a sharp onset and poor prognosis. The mortality of patients can reach approximately 38%–43%, and the disability rate is >90%,[2]

Key words
- Hypertensive intracerebral hemorrhage
- Recurrent
- Risk-scoring model
- Secondary prevention

Abbreviations and Acronyms
AUC: Area under the receiver operating characteristic curve
BP: Blood pressure
CI: Confidence interval
CT: Computed tomography
DP: Diastolic pressure
GCS: Glasgow Coma Scale
GOS: Glasgow Outcome Scale
Hcy: Homocysteine
HDL: High-density lipoprotein
HICH: Hypertensive cerebral hemorrhage
H-L: Hosmer-Lemeshow
LDL: Low-density lipoprotein
n: number
OR: Odds ratio
RHCH: Recurrent hypertensive cerebral hemorrhage
ROC: Receiver operating characteristic
SP: Systolic pressure
TC: Cholesterol
TG: Triglyceride

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Table 1. Glasgow Outcome Scale[11]

	Glasgow Outcome Scale Score				
Category	1	2	3	4	5
Meaning	Death	Vegetative state	Severe neurological deficit	Mild neurologic deficit	Premorbid level of functioning or completely recovery

which seriously threatens health and quality of life. Although most patients can get better by conservative treatment or surgical treatment, there are still many patients who experience recurrent HICH (RHCH) after treatment. The destruction of brain tissue as a result of RHCH increases cumulatively, and the disability rate after hemorrhage is significantly higher than that of initial cerebral hemorrhage.[3] Therefore, it is critical to have effective prevention of RHCH in clinical practice.

Hypertension is the most important risk factor of HICH and RHCH. In addition, other factors are reported to affect RHCH, including cerebral amyloidosis[4]; homocysteine (Hcy); age; gender; history of previous cerebral ischemic stroke, smoking, excessive drinking, and surgeries; and other factors. Because of the different evaluative and inclusion criteria of different research centers, the results may be controversial. Current research mostly focuses on specific risk factors and the impact of these risk factors on RHCH. There are few reports, either locally or globally, that use risk factors to construct a risk-scoring model to predict RHCH. Furthermore, previous studies have not considered the predictive value and impact of these risk factors in the context of predictive models.

Some studies have reported[5,6] that the incidence of RHCH is highest in the first year after initial onset. Moreover, RHCH is the leading cause of death in patients with cerebral hemorrhage after 1 year.[7] Therefore, the risk-scoring model constructed in our study was set up to mainly predict RHCH within 1 year after initial HICH onset. We hope that our study can provide new ideas for secondary prevention after initial HICH and contribute to better prevention methods combined with other methods.

METHODS

Patient Population

We browsed data from all patients with HICH admitted to the neurosurgery department of Lianyungang First People's Hospital from August 2015 to January 2018 and then selected appropriate patients. We communicated with patients or their families before discharge and signed informed consent was required to include them in this study. Clinical data were recorded using the electronic medical record system of the hospital (MandalaTDoqlei 2009, MandalaT Software Corporation, China). Radiographic images were reviewed using the radiographic system of the hospital (GE Healthcare Centricity RIS CE, General Electric Company, USA). Clinical data of patients from August 2015 to August 2017 were collected as a derivation cohort, and data from September 2017 to January 2018 were collected as a validation cohort. For this study, adult patients who were diagnosed with cerebral hemorrhage by computed tomography (CT) scan and had a previous history of hypertension were included in the study. To avoid interference, we excluded the following patients: 1) those with cerebral hemorrhage caused by other causes (e.g., aneurysm, vascular malformation, and tumor stroke); 2) those with a history of HICH; 3) those with unstable vital signs at discharge or life expectancy of <1 year; 4) those with incomplete clinical data or missing follow-up.

Patient Management

Immediately after admission, all patients were evaluated with an initial CT scan and were followed with serial neurologic examinations. All the imaging studies were technically adequate and reviewed by the staff of the radiology department. Patients were evaluated and treated during hospitalization according to well-accepted guidelines.[8,9] The indications for surgery during hospitalization were: 1) supratentorial hemorrhage >30 mL and submucosal hemorrhage ≥10 mL; 2) displacement of brain midline structure ≥1 cm; 3) ventricle and cerebral cistern deformed or disappeared; 4) unequal pupils, pupillary light reflex is slow, or the pupils are scattered and the light reflex disappears; and 5) the patient's state of consciousness deteriorates to restlessness, lethargy, or even coma. The surgical approaches include cerebral hematoma removal (adding decompressive craniectomy if needed), or puncture and drainage. The choice of surgical approach was determined according to the specific conditions of the disease and communication with the patient's family. CT was dynamically reviewed after admission, and another CT scan was performed to assess for any clinical deterioration. For each patient, CT scans were obtained at least twice during hospitalization. Patients without surgical indications underwent conservative management, including controlling blood pressure, intracranial pressure, body temperature, blood sugar, and preventing epilepsy. Patients with stable intracranial conditions were recommended for early rehabilitation.

HICH Diagnosis

HICH is not difficult to diagnose using CT and other imaging techniques, according to clinical signs and symptoms such as sudden onset, severe headache, vomiting, and neurologic dysfunction. However, there is no gold standard for the diagnosis of primary cerebral hemorrhage, especially HICH. In addition, it is necessary to rule out various kinds of secondary cerebral hemorrhage diseases and avoid misdiagnosis. According to Chinese expert consensus,[10] the final diagnosis must meet all the following criteria: 1) a history of hypertension; 2) typical hemorrhage sites (including basal ganglia, ventricles, thalamus, brainstem, and cerebellar hemispheres); 3) digital subtraction angiography, CT angiography, and magnetic resonance angiography exclude secondary cerebrovascular diseases; 4) early (72 hours) or advanced (after 3 weeks of hematoma disappearance) enhanced magnetic resonance imaging to exclude diseases such as brain tumors or cavernous vascular malformation; and 5) other coagulopathy diseases have been ruled out.

Patient Follow-Up

We followed-up with patients with HICH who had signed the informed consent through a telephone call up to 1 year after

Table 2. Clinical Characteristics of Patients in the Derivation Cohort and Univariate Analysis of Association Between Potential Risk Factors and Recurrent Hypertensive Cerebral Hemorrhage

Characteristics	Category	Total Patients, n (%)	Recurrent Hypertensive Cerebral Hemorrhage, n (%)	Non-Recurrent Hypertensive Cerebral Hemorrhage, n (%)	*P* Value
Gender	Male	351 (67.5)	31 (81.6)	320 (66.4)	0.054
	Female	169 (32.5)	7 (18.4)	162 (33.6)	
Age	<60 years	287 (55.2)	12 (31.6)	275 (57.1)	0.002
	≥60 years	233 (44.8)	26 (68.4)	207 (42.9)	
Blood pressure at admission	Normal	27 (5.2)	2 (5.3)	25 (5.2)	0.008
	Stage 1	100 (19.2)	15 (39.5)	85 (17.6)	
	Stage 2	139 (26.7)	5 (13.2)	134 (27.8)	
	Stage 3	254 (48.8)	16 (42.1)	238 (49.4)	
Glasgow Coma Scale score at admission	13–15	308 (59.2)	15 (39.5)	293 (60.8)	0.026
	9–12	125 (24.0)	12 (31.6)	113 (23.4)	
	3–8	87 (16.7)	11 (28.9)	76 (15.8)	
Blood pressure at discharge	Normal	266 (51.2)	10 (26.3)	256 (53.1)	0.003
	Stage 1	230 (44.2)	27 (71.1)	203 (42.1)	
	Stage 2	23 (4.4)	1 (2.6)	22 (4.6)	
	Stage 3	1 (0.2)	0	1 (0.2)	
Glasgow Coma Scale score at discharge	13–15	450 (86.5)	29 (76.3)	421 (87.3)	0.000
	9–12	60 (11.5)	5 (13.2)	55 (11.4)	
	3–8	10 (1.9)	4 (10.5)	6 (1.2)	
Hemorrhage location	Basal ganglia	269 (51.7)	16 (42.1)	253 (52.5)	0.483
	Thalamus	68 (13.1)	7 (18.4)	61 (12.7)	
	Cerebellum	35 (6.7)	2 (5.3)	33 (6.8)	
	Brainstem	32 (6.2)	1 (2.6)	31 (6.4)	
	Ventricles	36 (6.9)	3 (7.9)	33 (6.8)	
	Cerebral lobe	80 (15.4)	9 (23.7)	71 (14.7)	
Surgery or not	No	388 (74.6)	24 (63.2)	364 (75.5)	0.092
	Yes	132 (25.4)	14 (36.8)	118 (24.5)	
Surgery approach	No	388 (74.6)	24 (63.2)	364 (75.5)	0.402
	Puncture and drainage	83 (16.0)	9 (23.7)	74 (15.4)	
	Cerebral hematoma removal	22 (4.2)	2 (5.3)	20 (4.1)	
	Cerebral hematoma removal + decompressive craniectomy	27 (5.2)	3 (7.9)	24 (5.0)	
History of diabetes	No	481 (92.5)	32 (84.2)	449 (93.2)	0.09
	Yes	39 (7.5)	6 (15.8)	33 (6.8)	
History of cerebral ischemic stroke	No	472 (90.8)	30 (78.9)	442 (91.7)	0.009
	Yes	48 (9.2)	8 (21.1)	40 (8.3)	
History of smoking	No	271 (52.1)	11 (28.9)	260 (53.9)	0.003
	Yes	249 (47.9)	27 (71.1)	222 (46.1)	
History of alcoholism	No	357 (68.6)	15 (39.5)	342 (71.0)	0
	Yes	163 (31.4)	23 (60.5)	140 (29.0)	

Continues

Table 2. Continued

Characteristics	Category	Total Patients, n (%)	Recurrent Hypertensive Cerebral Hemorrhage, n (%)	Non-Recurrent Hypertensive Cerebral Hemorrhage, n (%)	*P* Value
History of coronary heart disease and abnormal electrocardiogram	No	469 (90.2)	33 (86.8)	436 (90.5)	0.661
	Yes	51 (9.8)	5 (13.2)	46 (9.5)	
Triglyceride	<1.7 mmol/L	388 (74.6)	29 (76.3)	359 (74.5)	0.35
	1.7 ≤ X < 2.3 mmol/L	75 (14.4)	3 (7.9)	72 (14.9)	
	≥2.3 mmol/L	57 (11.0)	6 (15.8)	51 (10.6)	
Cholesterol	<5.2 mmol/L	396 (76.2)	28 (73.7)	368 (76.3)	0.504
	5.2 ≤ X < 6.2 mmol/L	96 (18.5)	9 (23.7)	87 (18.0)	
	≥6.2 mmol/L	28 (5.4)	1 (2.6)	27 (5.6)	
High-density lipoprotein	<1 mmol/L	185 (35.6)	10 (26.3)	175 (36.3)	0.215
	≥1 mmol/L	335 (64.4)	28 (73.7)	307 (63.7)	
Low-density lipoprotein	<3.4 mmol/L	421 (81.0)	34 (89.5)	387 (80.3)	0.303
	3.4 ≤ X < 4.1 mmol/L	83 (16.0)	4 (10.5)	79 (16.4)	
	≥4.1	16 (3.1)	0	16 (3.3)	
Homocysteine	<10 mmol/L	174 (33.5)	6 (15.8)	168 (34.9)	0.016
	≥10 mmol/L	346 (66.5)	32 (84.2)	314 (65.1)	
Glasgow Outcome Scale score 3 months after discharge	2	19 (3.7)	3 (7.9)	16 (3.3)	0.375
	3	137 (26.3)	12 (31.6)	125 (25.9)	
	4	113 (21.7)	8 (21.1)	105 (21.8)	
	5	251 (48.3)	15 (39.5)	236 (49.0)	

Normal: Systolic pressure (SP) < 120 mmHg and diastolic blood (DP) pressure < 80 mmHg; Stage 1 hypertension: 140 ≤ SP < 159 mmHg and/or 90 ≤ DP < 99 mmHg; Stage 2 hypertension: 160 ≤ SP < 179 mmHg and/or 100 ≤ DP < 109 mmHg; Stage 3 hypertension: SP ≥ 180 mmHg and/or DP ≥ 110 mmHg.

discharge. There were 3 follow-ups at 3, 6, and 12 months after discharge. The main purpose of follow-up was to confirm whether RHCH recurred and to use the Glasgow Outcome Scale (GOS) to evaluate the prognosis of patients 3 months after discharge (Table 1).

Clinical Variables Obtained

The data were obtained mainly from clinical medical records and radiology databases. The variables included gender; age; blood pressure at admission and discharge; Glasgow Coma Scale (GCS) score at admission and discharge; cerebral hemorrhage location; surgery; history of diabetes, cerebral ischemia, smoking, alcoholism, coronary heart disease, and abnormal electrocardiogram; triglycerides; cholesterol; high-density lipoprotein; low-density lipoprotein; plasma Hcy level; and GOS score 3 months after discharge. The blood pressure at admission refers to the blood pressure of patients with HICH taken for the first time in the emergency room of our hospital. The blood pressure at discharge refers to the blood pressure measured the last time before discharge. The GCS scores at admission and discharge refer to the first and last scores evaluated by the neurosurgery doctors after patients were admitted to the neurosurgical ward. The hemorrhage location was confirmed by imaging data such as CT and then verified again by surgical results. Surgical approaches included cerebral hematoma removal (and decompressive craniectomy if needed), or puncture and drainage. Data about blood lipids, Hcy, and other blood indicators were gained through patients' clinical data of blood examination outcomes during hospitalization. The GOS score was obtained at the 3-month follow-up by a telephone call.

Derivation and Validation of the Risk-Scoring Model

The risk-scoring model was derived using a stepwise logistic regression, with RHCH as the prediction, and the clinical variables analyzed as independent risk factors or predictors. To develop a practical prognostic score, the weighted scores were

Table 3. Multivariate Logistic Analysis of the Derivation Cohort and the Risk-Scoring Model for the Prediction of Recurrent Hypertensive Cerebral Hemorrhage

Predictors	Category	Odds Ratio	95% Confidence Interval	*P* Value	β-Regression Coefficient	Scores
Age	≥60 years	2.463	1.12—5.44	0.026	0.901	4
Blood pressure at admission	Stage 3	4.302	2.84—12.65	0.034	1.459	6
Glasgow Coma Scale score at admission	9—12	3.161	1.28—7.79	0.012	1.151	5
Glasgow Coma Scale score at discharge	3—8	9.687	1.65—57.01	0.012	2.271	10
History of cerebral ischemic stroke	Yes	3.343	1.18—9.49	0.023	1.207	5
History of smoking	Yes	3.522	1.53—8.13	0.003	1.259	5
History of alcoholism	Yes	2.838	1.33—6.08	0.007	1.043	5
Homocysteine level	≥10 μmol/L	2.421	1.35—6.81	0.041	0.884	4

Assignment of points to risk factors was based on a linear transformation of the corresponding β-regression coefficient: the coefficient of each variable was divided by 0.884 (the lowest β-value, corresponding to Hcy ≥ 10 μmol/L), multiplied by a constant (4), and rounded to the nearest integer.

assigned to each risk factor proportional to the β-regression coefficient values and rounding to the nearest integer. A risk score was then calculated by adding each predictor's score together for each patient, and the population was divided into 3 categories according to the score percentile: low risk (0—33rd percentile), intermediate risk (34th—67th percentile), and high risk (68th—100th percentile) for RHCH. Validation was performed to evaluate the accuracy of this scoring system. The construction of our model drew on some successful experiences and advantages of other similar prediction models.[12,13]

Statistical Analysis

SPSS version 19.0 (IBM Corp., Armonk, New York, USA) was used for data analysis. The Pearson χ^2 test or Fisher exact test was used for univariate analysis of categorical variables. Variables associated with RHCH in the univariate analysis ($P < 0.05$) were included in a logistic regression model to identify independent risk factors (predictors) of RHCH and were retained in the final model if the P value from the χ^2 test indicated an increasing trend in the incidence of RHCH across the 3 risk categories. A receiver operating characteristic (ROC) curve and area under the ROC curve (AUC) were used to evaluate the discriminatory power of the risk-scoring model, which was classified into good (AUC >0.8), moderate (AUC 0.7—0.8), and low (AUC 0.6—0.7) predictive ability. Furthermore, a Hosmer-Lemeshow (H-L) test was used to assess the calibration ability of the model.

RESULTS

Patients' Characteristics in the Derivation Cohort

A total of 557 patients with HICH were analyzed to derive the prognostic model, according to the inclusion and exclusion criteria. Thirty-seven patients were excluded because of incorrect numbers, unanswered calls, and patients' family members unwilling to provide information during follow-up after discharge. In the end, we obtained complete clinical data and follow-up data from 520 patients. The patient characteristics in the derivation cohort are shown in Table 2. During the 12-month follow-up period, 38 patients (7.31%) developed RHCH. The statistical analysis outcome showed that there were no significant differences between the RHCH group and non-RHCH group regarding gender; hemorrhage location; surgery; history of diabetes,

Table 4. Observed Incidence of Recurrent Hypertensive Cerebral Hemorrhage in the Derivation and Validation Cohorts According to Risk Stratification

		Derivation Cohort (n = 520)		Validation Cohort (n = 107)	
Risk Category	Score	n (%)	Recurrent Hypertensive Cerebral Hemorrhage, n (%)	n (%)	Recurrent Hypertensive Cerebral Hemorrhage, n (%)
Low	0—13	347 (66.73)	6 (1.73)	58 (54.21)	2 (3.45)
Intermediate	14—26	131 (25.19)	8 (6.11)	42 (39.25)	3 (7.14)
High	27—39	42 (8.08)	24 (57.14)	7 (6.54)	5 (71.43)
χ^2 for trend		113.832		17.332	
P value for trend		<0.001		<0.001	

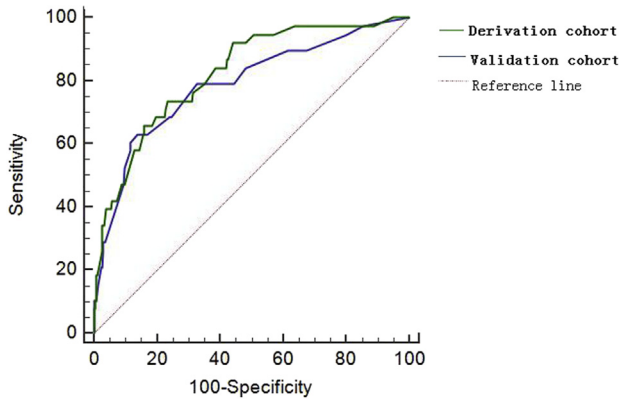

Figure 1. ROC curves for the risk scoring model in the derivation cohort (AUC = 0.802) and validation cohort (AUC = 0.863).

coronary heart disease, and abnormal electrocardiogram; blood lipids; and GOS score 3 months after discharge. Among the 38 patients with RHCH, hemorrhage location included the basal ganglia in 16 (42.11%), thalamus in 6 (15.79%), cerebral lobe in 9 (23.68%), cerebellum in 2 (5.26%), ventricles in 4 (10.53%), and brain stem in 1 (2.63%). Fourteen patients underwent surgical treatment and the remainder received conservative treatment.

Blood pressure values were classified as follows: normal, systolic pressure (SP) <120 mm Hg and diastolic pressure (DP) <80 mm Hg; stage 1 hypertension, SP 140–159 mm Hg and/or DP 90–99 mm Hg; stage 2 hypertension, SP 160–179 mm Hg and/or DP 100–109 mm Hg; and stage 3 hypertension, SP ≥180 mm Hg and/or DP ≥110 mm Hg.

Construction of the Risk-Scoring Model

The univariate analysis showed significant correlations between the occurrence of RHCH and age; blood pressure at admission and discharge; GCS scores at admission and discharge; history of cerebral ischemic stroke, smoking, alcoholism; and Hcy. Table 3 shows the independent risk factors (predictors) identified by multivariable logistic regression analysis for RHCH. After the exclusion of variables with a poor predictive performance and those showing multicollinearity, the variables including age >60 years (odds ratio [OR], 2.46; 95% confidence interval [CI], 1.12–5.44); stage 3 hypertension at admission (OR, 4.30; 95% CI, 2.84–12.65); GCS score of 9–12 at admission (OR, 3.16; 95% CI, 1.28–7.79); GCS score of 3–8 at discharge (OR, 9.69; 95% CI, 1.65–57.01); history of cerebral ischemic stroke (OR, 3.34; 95% CI, 1.18–9.49), smoking (OR, 3.52; 95% CI, 1.53–8.13), or alcoholism (OR, 2.84; 95% CI, 1.33–6.08); and plasma Hcy level ≥10 μmol/L (OR, 2.42; 95% CI, 1.35–6.81) maintained their prognostic significance and were included in the final model. A risk-stratification scoring model that could be used to predict RHCH was then developed based on this logistic regression model, assigning each predictor a number of points proportional to its regression coefficient (Table 4). A risk score was calculated for each patient by adding together the points corresponding to the patient's risk factors. The patients were then divided into 3 subgroups based on the risk score: low-risk group (0–13 points), intermediate-risk group (14–26 points), and high-risk group (27–39 points). The incidence of RHCH in these 3 groups was 1.73%, 6.11%, and 57.14%, respectively, in the derivation cohort (Table 4).

Assignment of points to risk factors was based on a linear transformation of the corresponding β-regression coefficient: the coefficient of each variable was divided by 0.884 (the lowest β value, corresponding to Hcy level ≥10 μmol/L), multiplied by a constant (4), and rounded to the nearest integer (Table 3).

Validation of the Risk-Scoring Model

The validation cohort data included 107 patients with HICH, 10 (9.35%) of whom developed RHCH. By applying our risk stratification, the RHCH rates in the 3 risk groups (low to high) were 3.45%, 7.14%, and 71.43%, respectively. The observed incidence of RHCH increased significantly with an increasing risk score in the derivation and validation cohorts (both χ^2 for trend P values <0.001, Table 4). To further evaluate the accuracy of predicting RHCH, we created ROC curves and calculated the AUC (Figure 1). The AUC for the derivation data was 0.802 (95% CI, 0.691–0.867), with a sensitivity of 75.8% and a specificity of 78.9%, indicating that the model showed good predictive power for RHCH. The results of the H-L test (P = 0.532) were indicative of good calibration. Appling the scoring system in the validation cohort, the model had an AUC of 0.863 (95% CI, 0.759–0.974), with a sensitivity of 80.2% and a specificity of 82.6%, and a P value of 0.724 (H-L test), indicating that the risk

Table 5. Some Studies of Recurrent Hypertensive Cerebral Hemorrhage in China

Study	Province, Country/Setting	Initial Cerebral Hemorrhage, n	Time Interval	Recurrence of Cerebral Hemorrhage, n	Rate (%)
Li et al., 2011[14]	Neimenggu, China/multicenter	1060	1990.11–2007.07	72	6.79
Liu et al., 2007[15]	Guangdong, China/single-center	677	1993.10–2005.10	35	5.17
Dou et al., 2007[16]	Liaoning, China/single-center	1257	1996.01–2005.12	62	4.93
Yang et al., 2008[17]	Sichuan, China/single-center	601	1997.02–2006.12	60	9.98
Liu, 2009[18]	Henan, China/single-center	1200	2005.01–2008.12	68	5.67
Qi et al., 2016[19]	Shanxi, China/single-center	1800	2010.01–2013.10	274	15.22

Table 6. Some Studies of Recurrent Hypertensive Cerebral Hemorrhage in Other Countries

Study	Country/Setting	Initial Cerebral Hemorrhage, n	Follow-Up (Months)	Recurrence of Cerebral Hemorrhage, n	Rate (%)
Kang et al., 2012[20]	South Korea, multicenter	97	38–47	9	9.28
Imaizumi et al., 2013[21]	Japan, single-center	188	31.6 ± 22.2	24	12.77
Biffi et al., 2010[22]	United States, single-center	104	34.3	29	27.88
Jeon et al., 2007[23]	South Korea, single-center	63	23.3	7	11.11
Naka et al., 2006[24]	Japan, single-center	83	18.8 ± 7.6	10	12.05
Imaizumi et al., 2004[25]	Japan, single-center	199	22.5 ± 13.1	5	2.51

score system also discriminated and calibrated well with the validation data.

DISCUSSION

Recurrence Rate of HICH

RHCH is one of the most serious complications after initial HICH, which is the main cause of disability and death of survivors. Because of different research backgrounds, diagnosis and treatment conditions, population characteristics, and other factors, the recurrence rate of HICH varies from different regions and different studies but generally tends to be between 5% and 15% (Tables 5 and 6). In this study, we observed a recurrence rate of 7.66% (48/627) via 3 telephone follow-ups after discharge. Although there is increasing clinical emphasis on RHCH and continuous improvement of treatment, RHCH is still easily overlooked during rehabilitation, and the consequences of diagnostic and therapeutic delay are seriously destructive. Therefore, early prediction of RHCH can help to assess the status of patients with HICH and improve outcomes.

Risk Factor Analysis

In this study, we developed a risk-scoring model to predict RHCH within 1 year of discharge; the model is simple to calculate and construct from variables that are easily assessed and can be generated from demographic characteristics and clinical findings. This model provided good discrimination of RHCH risk in both the derivation and validation cohorts, with AUCs indicative of a good predictive power. The prognostic factors in the risk-scoring model included age >60 years; stage 3 hypertension at admission; GCS score of 9–12 at admission; GCS score of 3–8 at discharge; history of cerebral ischemic stroke, smoking, and alcoholism; and plasma Hcy level ≥10 μmol/L.

Hypertension is the most important independent risk factor for initial HICH and RHCH.[26] There have been many studies on their mechanism, so there is no need to repeat that information. In this study, patients with stage 3 hypertension were the majority, and RHCH patients were also the majority, as shown in Figure 2.

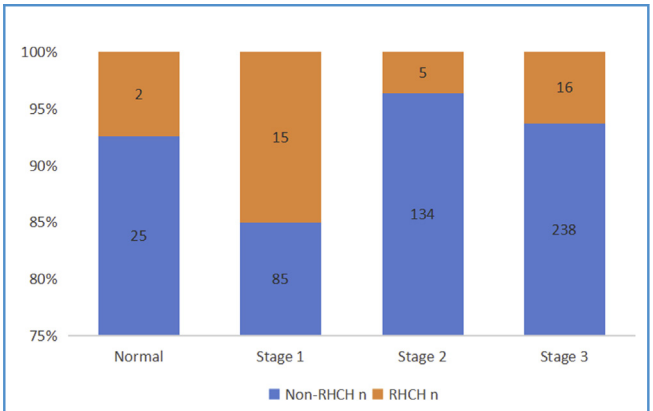

Figure 2. Stratification of hypertension at admission.

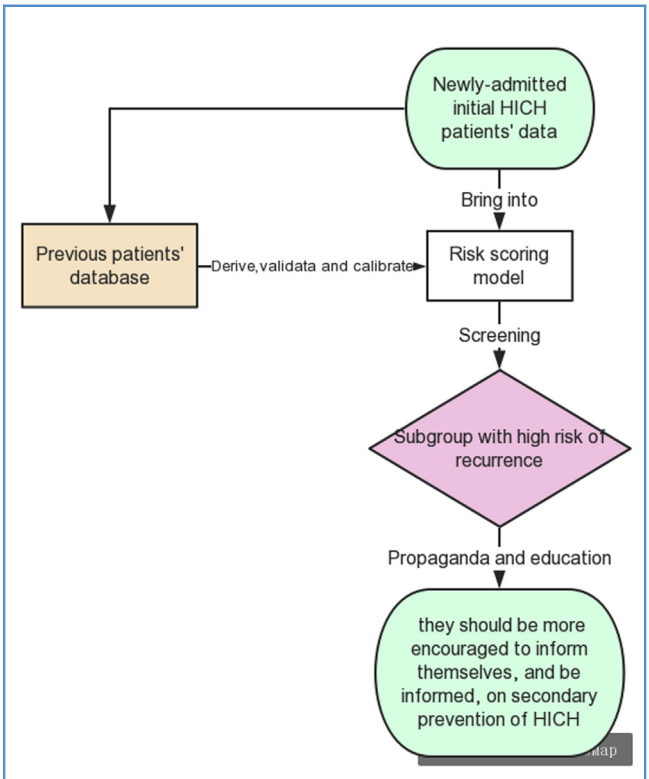

Figure 3. Flow chart of model construction and action.

Unexpectedly, the total number of patients with stage 1 hypertension was less than that of patients with stage 2 hypertension, but patients with RHCH who had stage 1 hypertension were significantly more in number than those with stage 2 group. The reason may be that the sample size limitation of this study led to a bias in the results; on the other hand, according to the basic data of this study, the patients with stage 1 hypertension took regular medications, and their blood pressure was better (compared with patients with stage 2 hypertension), but their situation was poor in terms of other risk factors, which may have caused more recurrent events.

The GCS score includes 3 aspects: blink response, language response, and limb movement. The scores for each of the 3 aspects can help determine the coma index. The coma index is assessed clinically and is an indicator of a patient's degree of coma. Several previous studies[27-29] have reported that GCS scores are associated with enlargement of the hematoma. The deeper the patient's consciousness disorder, the lower the GCS score and the more serious the brain damage. It is easy for those patients to have convulsions, vomiting, frequent irritations, and increase in blood pressure, which may lead to the expansion of hematoma. In this study, GCS scores (9–12) at admission and GCS scores (3–8) at discharge were independent risk factors for RHCH. Both were low and support our conclusions.

History of cerebral ischemic stroke, smoking, and alcoholism are important risk factors for HICH and RHCH. These topics have been discussed in previous studies and are not discussed here.

Hcy is an independent risk factor for HICH that has been proposed in recent years. STONE (Shanghai Trial of Nifedipine in the Elderly) and Syst-CHINA (Systolic Hypertension Study in China), which were carried out among the Chinese population with hypertension, showed that the ratio of stroke and myocardial infarction events was 13.0 and 6.6, respectively.[30] However, the corresponding ratio from the national intervention cooperative study carried out in Japan is 5.0,[30] and the ratio of other European and American countries is <2.0.[30] The result indicates that the relationship between hypertension and stroke is closer in the Asian population, especially the Chinese population. However, traditional risk factors, including hypertension, are not sufficient to explain the high morbidity and mortality of stroke in China. Studies also suggest that simply controlling blood pressure does not mean control of stroke in our population. Previous studies[31-33] have shown that high Hcy and low folic acid levels are common in the Chinese population with hypertension. Therefore, the team of Professor Huo Yong (Peking University) pointed out that plasma Hcy levels may be a unique risk factor for stroke in the Chinese population.[34] According to relevant data, Chinese Hcy levels are 1.3–1.5 times those of Americans. High Hcy levels and hypertension not only have interactions but also contribute to the occurrence of stroke synergistically.[35,36] A study with a sample size of 40,000 and a mean follow-up of >6 years showed that the rate of strokes in patients with hypertension only versus high Hcy level only was 3.6 times and 8.2 times greater, respectively, than that of healthy people (no significant abnormalities in blood pressure and Hcy level), but when hypertension and high Hcy levels were combined, the incidence of stroke in patients significantly increased to 12.1 times that of healthy people.[37] The current mainstream perspective is described earlier, but some scholars believe that the relationship between hypertension and Hcy is not so simple; whether plasma Hcy level is the cause of the disease or whether it is only an additional effect of the disease remains to be studied and discussed.[38]

Clinical Significance of the Model

The high mortality and disability rate of HICH suggest that effective prevention is more important than treatment. However, domestic reports show that Chinese population with hypertension and HICH includes most middle-aged and elderly people. The awareness rate of hypertension and HICH prevention is not high, the rate of regular drug treatment is low, and so is the proportion of regular monitoring and control. Therefore, screening, propaganda, and education are important in primary and secondary prevention of HICH. We should pay more attention to screening to find high-risk patients who may be more likely to have RHCH. Then we should emphasize the harmfulness and severity of the condition, and the importance of regular monitoring. We also should improve patients' compliance in HICH prevention and treatment. All these factors require methods of effective screening. In clinical practice, neurosurgeons used patient's previous data and hospitalized clinical data of initial HICH to derive and validate the risk-scoring model. Then, the data of newly admitted patients with initial HICH were brought into the model to screen out the subgroup with higher risk of recurrence. These patients' data were included with the previous patients' data and the database was expanded to calibrate the model. The selected subgroup had a higher recurrence rate than did other populations with HICH (57.14% in the high-risk group of our study vs. 5%–15% in the literature). Therefore, this group should be informed as early as possible about prevention of HICH. The prevention activities must be practiced to avoid the poor prognosis resulting from low compliance, as shown in **Figure 3**. Although this model cannot directly improve the prognosis of HICH, the effectiveness of HICH secondary prevention can be improved to some extent through the described procedure.

There are other reasons and implications for screening and education. China's large population leads to a large population with HICH. The treatment and prevention of HICH require considerable medical input. If each patient with HICH receives the same medical and human resources, it will be a huge burden and consumption of resources. Moreover, the efficiency and benefits may not be good. Therefore, the strategy of highlighted key matters and hierarchic treatment and prevention may be a better choice. Hierarchic treatment and prevention means focusing on serious diseases and giving them most of the clinical attention and limited resources and treating common diseases normatively with the remaining resources. This is also the medical strategy practiced in China. What our risk-scoring model can do is to highlight some key matters. The model can select people with a high risk of recurrence, which means that this group of people may need to receive more clinical attention and preventive resources than do other patients with HICH.

The statistical calculation process of this model is not particularly complicated for neurosurgeons, who often write articles or have gained some statistical knowledge. It is relatively easy to create models after understanding the whole process. Perhaps the most difficult part of the construction is obtaining the informed consent of patients and data entry.

Advantages and Limitations

Our study has the following merits. First, it may be the first study, both in China and worldwide, to apply the risk-scoring model in RHCH. Few relevant studies have been reported. We are in the era of digital big data, and big data computing has penetrated every aspect of life. It is obviously not sensible for the hospital clinical system to simply record patient clinical data during hospitalization and not to use those data to generate some information prospectively. We should make use of the available advances in technology to use the patients' clinical data to derive, improve, and validate the risk-scoring model to predict diseases. Second, the research factors included in our study are more numerous than in other similar studies (20 factors were included). In addition, there were different stratifications for different factors and the stratification was based on Chinese recognized guidelines, for which a theoretic basis is sufficient. Blood pressure was stratified based on 2013 Chinese guidelines for the education of hypertensive patients.[39] The blood lipid levels were stratified based on 2016 Chinese guidelines for the management of dyslipidemia in adults.[40] The Hcy level was stratified based on the definition of Hcy widely accepted by Chinese scholars.[41] Finally, the statistical analysis of the study is rigorous. In the most important aspect of validation, the χ^2 test was used to evaluate whether there was an increasing trend in the rate of RHCH in the 3 risk category groups; the ROC and AUC were used to access the discriminatory power of the model; the H-L test was used to evaluate the calibration ability of the model. The triple test fully shows the validity of the model.

In contrast, our study also has several limitations. First, the patient population included in the study is mainly from the neurosurgery department in our hospital within 3 years, so there is inevitably a limit on the sample size, particularly for the small number of patients with RHCH, which may cause some bias in the results. Second, the population included in our study is mainly from Lianyungang City, Jiangsu Province, China. Therefore, the results may also contain some regional limitations and bias. Third, Our predictive model is an immature model that needs more improvement. The final form of our risk-scoring model should include patients' physical information and all clinical data during hospitalization and self-improve by bringing new indicators in and self-calibrate, to predict the prognosis of many diseases. This strategy involves questions about ethics, privacy, and technology. It is obvious that a predictive model in a mature form will not be completed soon.

CONCLUSIONS

HICH and RHCH are complex pathophysiologic processes and apparently result from a variety of factors. This is the first attempt to derive and validate a risk-scoring model for predicting RHCH. We show that the risk of RHCH can be predicted by age >60 years; stage 3 hypertension at admission; GCS score of 9–12 at admission; GCS score of 3–8 at discharge; history of cerebral ischemic stroke, smoking, or alcoholism; and plasma Hcy level ≥10 μmol/L. A subgroup of high-risk patients who may be more likely to have RHCH can be selected by our model and they should be encouraged to inform themselves, and be informed, on secondary prevention of HICH. Also, preventive activities must be emphasized to avoid the poor prognosis resulting from low compliance. The model cannot improve the prognosis of patients directly but can improve the efficiency and results of secondary prevention of HICH by screening for a high-risk population, facilitating hierarchic prevention, and allowing for more attention to be paid to the high-risk subgroup. Whether these high-risk patients with RHCH could benefit from more intensive forms of surveillance and therapies remains to be confirmed. Moreover, the predictive model cannot replace clinical assessment of an individual patient and the prediction should be regarded with care and not directly applied when making clinical decisions.

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