Journal of Inflammation Research

Dovepress
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ORIGINAL RESEARCH

A Novel Nomogram for Predicting the Risk of Pneumonia After Intracerebral Hemorrhage

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Background: Pneumonia is among the most dangerous complications of infection after intracerebral hemorrhage. We aimed to create a novel nomogram for pneumonia after intracerebral hemorrhage.

Methods and Results: The data from the Chinese Cerebral Hemorrhage: Mechanism and Intervention (CHEERY) study was analyzed. Thirty percent of qualified patients were placed in the validation group (n=763) while seventy percent of them were randomly placed in the training group (n=1784). In the multivariate analysis, ten variables were included in the model: age (β= 0.023, P<0.001), hospital days (β=0.392, P<0.001), baseline mRS score (β=0.484, P<0.001), baseline GCS score (β=−0.285, P<0.001), hs-CRP (β=0.328, P<0.001), hematoma volume (β=0.376, P<0.001), brainstem hemorrhage (β=0.956, P=0.002), intraventricular hemorrhage (β=0.629, P=0.001), and β-blocker (β=0.899, P<0.001) In the training subset, the areas under curve were 0.805 (95% CI, 0.773–0.833). The model was subsequently examined in the validation group, with the area under curve 0.767 (95% CI, 0.716–0.807). There was strong agreement between the anticipated and actual survival rates in the nomogram calibration curves for both the training and validation groups. The clinical value of the model is assessed by means of Decision Curve Analysis. In addition, we validated other models with this cohort, which showed that our model had better discrimination. Moreover, the area under the curve of the catboost model established using the above nine variables in the training set and the validation set is 0.87(95% CI, 0.80–0.90) and 0.77 (95% CI, 0.72–0.80).

Conclusion: We have established a simple and easy predictive tool. By evaluating the incidence of pneumonia after intracerebral hemorrhage, we can identify high-risk groups early. At the same time, our study also suggests that doctors should be cautious in the use of β-blocker in clinical decision-making.

Keywords: pneumonia, inflammation, intracerebral hemorrhage, nomogram, β-blocker

Background

Intracerebral hemorrhage (ICH) constitutes only 10% to 15% of strokes; however, it is associated with significant mortality and morbidity, making it one of the most severe stroke types.[1,2] A neuroinflammatory process begins in the brain immediately following a hemorrhagic stroke, making patients susceptible to infections. The most prevalent infection is pneumonia, occurring in approximately 10% of the hemorrhagic stroke patients.[3,4] As the major complication of a hemorrhagic stroke, pneumonia has increased mortality and has the worst impact on functional outcomes.[5]

Previous research has identified several risk factors of stroke-associated pneumonia, including age, modified Rankin Scale (mRS), fasting blood glucose (FBG), National Institutes of Health Stroke Scale admission score (NIHSS), Glasgow Coma Scale score (GCS), C-reactive protein, Chronic Obstructive Pulmonary Disease (COPD), and current smoking, Dysphagia.[6–10]

According to previous studies, the prediction of stroke-associated pneumonia includes post-intracerebral hemorrhage pneumonia and post-ischemic stroke pneumonia. The current prediction models for pneumonia following intracerebral

Received: 22 September 2024
Accepted: 22 January 2025
Published: 30 January 2025

hemorrhage include the Intracerebral Hemorrhage-Associated Pneumonia Score (ICH-APS), ICH-LR2S2, ISAN, and PASS. Their respective areas under the curve are 0.75, 0.749, 0.71, and 0.82.[6,11–14] These models have some limitations. ICH-APS did not record the exact date of pneumonia, so that it could not distinguish whether SAP caused mechanical ventilation or mechanical ventilation caused pneumonia.[12] Although ICH-LR2S2 is a simple and easy prediction tool, it does not use additional imaging data or additional medication history information.[6] ISAN is also not included in the drug history (for example, statins, proton pump inhibitors or angiotensin converting enzyme inhibitors), and because the state of dysphagia is indirectly derived, it is not included in the model construction. The factors not reflected in the pneumonia score, such as the level of consciousness and the location of stroke, may play an important role in the occurrence and development of pneumonia. In addition, more detailed risk factors such as age and neurological deficits were not considered for stratification.[11] PASS is an open-label, blind endpoint study. Physicians are aware of the allocation of treatment, which may influence decisions about diagnosis and unplanned treatment. There may be some implementation risks and detection bias.[14]

Preventive antibiotics decrease the likelihood of stroke-associated pneumonia. Advocating for the routine use of prophylactic antibiotics following an acute stroke is, however, not supported by sufficient data.[15,16] Neurologists urgently need a tool to predict the possibility of post-stroke pneumonia in patients with cerebral hemorrhage. It contributes to define risk variables and has some guiding influence in the prevention and diagnosis of Stroke-associated pneumonia.

In the Chinese Cerebral Hemorrhage: Mechanism and Intervention (CHEERY) study, we developed a nomogram for pneumonia after ICH based on demographic data, clinical presentations, biochemical tests, and imaging findings.

Methods

Study Population

The data supporting the findings of this study can be obtained from the corresponding author upon reasonable request. We conducted an analysis of the data from the CHERRY investigation. Between December 2018 and June 2021, 31 hospitals admitted consecutive patients with spontaneous ICH (Registration number:ChiCTR1900020872). Patients were included if they were hospitalized within seven days following the start of symptoms, diagnosed with spontaneous ICH using computed tomography, and aged more than eighteen years.

If any of the following criteria were met, patients were excluded: (1) hemorrhages generated from trauma, initial subarachnoid hemorrhage, hemorrhagic conversion from ischemic stroke, or thrombolysis; (2) no imaging or baseline data was available. The number of training set data generally accounts for 2 / 3 to 4 / 5. In practical applications, based on the size of the entire data set data, the division ratio of the training set data and the test set data can be 7: 3 or 8: 2. Since the incidence of pneumonia in the final cohort was only 13.9%, and the final cohort had a total of 2547 samples, the use of an 8: 2 ratios may cause the model to overfit and avoid performance evaluation bias due to the small test set. Results with significant differences between the test set and the training set. The ratio of 7:3 helped all qualified patients to be split into training and validation cohorts. Research ethics committee of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China (ethical permission number: 2018-S485) approved the study plan. Before enrolling, each participant provided a written informed consent.

Imaging and Clinical Data Collection

There was a collection of clinical variables and demographic characteristics, including time from onset to diagnosis of pneumonia, hospital days, dysphagia, age, male, history of smoking, medical history (hypertension, hyperlipidemia, ischemic stroke, ischemic heart disease, diabetes, chronic obstructive pulmonary disease), medication history (angiotensin converting enzyme inhibitors (ACEI), Angiotensin receptor blocker (ARB), calcium channel blockers (CCB), and β-blockers), admission vitals (onset-to-admission time, baseline systolic blood pressure (SBP), baseline mRS score, baseline GCS score and baseline NIHSS score), imaging data (hematoma location and hematoma volume), and laboratory tests (time from stroke symptoms to blood draw, white blood cell (WBC), fasting blood glucose (FBG), lymphocytes (LY), Neutrophils (Neu), neutrophil to lymphocyte ratio (NLR), and high-sensitivity C-reactive protein (hs-CRP). Medication history was characterized as ICH patients on antihypertensive medicines (ACEI, ARB, CCB or

β-blockers). Admission NIHSS scores and admission mRS scores were utilized to measure baseline neurological impairments. Admission GCS score was utilized to determine the degree of coma. Experienced neurologists conducted imaging studies based on the first computed tomography scan, which calculated the hematoma volume using the ABC/2 equation.

Collectively, general practitioners, hospital records, patients, and their families assembled all pertinent information.

Diagnostic Criteria for Pneumonia

Stroke-associated pneumonia is the emergence of new pneumonia within seven days of the commencement of stroke in patients who are not treated with mechanical ventilation.

At least one of the following criteria: (1)Fever (body temperature > 38 ° C); (2)Leukopenia (<$4x10^9$ / L);(3)Aged ≥ 70 years old; and at least in line with the following criteria in any of the two: (1) new sputum, or within 24 hours of sputum traits change or respiratory secretions increase or need to increase the number of sputum,(2) new or aggravated cough or dyspnea or shortness of breath (respiratory rate > 25 times / min);(3) lung auscultation found that rales or bursts or bronchial breathing sound;(4) gas exchange disorders (such as hypoxemia, increased oxygen demand). Chest imaging examination has at least one new or progressive infiltration shadow, consolidation shadow or ground glass shadow in the following manifestations (patients without previous cardiopulmonary basic diseases, a single chest imaging examination can have any one of the above manifestations).

Pneumonia after ICH can be diagnosed by the therapist according to the PISCES (Pneumonia in Stroke ConsEnsuS).[17]

Statistical Analysis

For univariate analyses, continuous variables were evaluated using the student *t* test for normally distributed variables and the Mann–Whitney *U*-test for nonnormally distributed variables. Continuous variables were presented as means with standard deviations or medians with interquartile range. Categorical variables were analyzed using the $\chi 2$ test for frequency and percentages. All variables with a P-value of less than 0.05 in the univariate analysis were included in the multivariate logistic regression analysis. Based on the Akaike information criterion minimum, the variables were selected for inclusion in the nomogram by stepwise regression. The final nomogram for predicting pneumonia contained non-normally distributed continuous variables (baseline mRS score, baseline GCS score, hematoma volume, hospital days, hs-CRP) grouped by quartiles that remained significant in the multivariate model.

The nomogram form of the pneumonia prediction model shows Hosmer-Lemeshow test was used to evaluate calibration by means of goodness of fit. We compared the area under the curve (AUC), accuracy, positive predictive rate, negative predictive rate, specificity and sensitivity between different models. Clinical advantages and utility of training cohort and validation cohort were assessed using decision curve analysis (DCA). All results were two-tailed. A significance threshold of $P < 0.05$ was determined. SPSS software (version 26.0; IBM, Armonk, NY) and R software (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria) were employed to carry out statistical analyses. In addition, we also use python to analyze the data to establish machine learning models.

Results

Patient Characteristics

The CHEERY trial comprised 4248 patients who experienced an ICH episode between December 1, 2018 and June 30, 2021. In order to facilitate the final analysis, 1701 patients were excluded (25 for non-spontaneous ICH, 87 for an onset to admission period exceeding 7 days, 469 patients excluded for onset to blood draw time>7d, and 1120 for the absence of imaging and clinical data). This left 2547 patients for the final analysis (Figure 1). The median age was 62 years (interquartile range, 53–71 years), and 68.5% of them were men. After ICH, 353 (13.9%) patients suffered from pneumonia after ICH. Randomly, the training cohort was allocated 1784 eligible patients, while the validation cohort was assigned 763 patients.

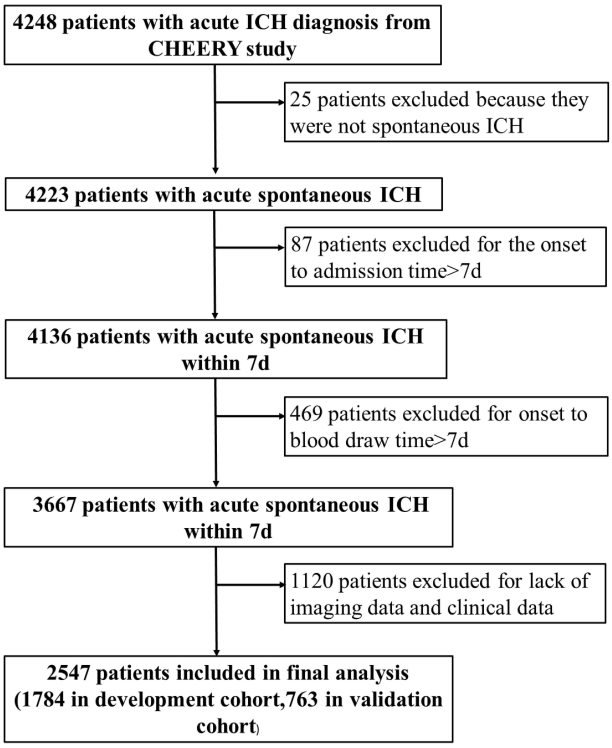

Figure 1 The flowchart of patient selection.

Table 1 shows the clinical traits of the training and validation cohorts' members. Patients in the two cohorts showed no appreciable variations. In the training cohort, 13.3% of the patients had pneumonia; in the validation cohort, the figure was 15.2% (Table 1).

Predictors of Pneumonia After ICH

Several factors (age, onset-to-admission time, hospital days, baseline NIHSS score, baseline mRS score, baseline GCS score, hs-CRP, FBG, hematoma volume, thalamus hemorrhage, brainstem hemorrhage, intraventricular hemorrhage, β-blocker, dysphagia) were identified as related with pneumonia after ICH in univariate analysis. (Table 2).

Nine variables remained statistically significant in the multivariate logistic regression analysis: age (β= 0.023, P<0.001), hospital days (β=0.392, P<0.001), baseline mRS score (β=0.484, P<0.001), baseline GCS score (β=−0.285,

Table 1 Baseline Characteristics and Outcomes of the Study

Characteristics	Training Cohort (N=1784)	Validation Cohort (N=763)	P value*
Post-ICH pneumonia	237(13.3)	116(15.2)	0.222
Onset-to-pneumonia time, h	74 (39–158)	80 (40.5–130.5)	0.002
Onset to blood draw time, h	22.5(13–42)	23(14–42)	0.607
Demographic data			
Age, years	62(53–70)	62(52–71)	0.165
Male	1211(67.9)	533(69.9)	0.349
Hospital days	15(10–21)	15(10–21)	0.734

(*Continued*)

Table 1 (Continued).

Characteristics	Training Cohort (N=1784)	Validation Cohort (N=763)	P value*
Medical history			
Smoking history	544(30.5)	231(30.3)	0.95
COPD	68 (3.8)	29 (3.8)	0.975
Ischemic stroke	190(10.7)	80(10.5)	0.957
Ischemic heart disease	72(4.0)	23(3.0)	0.258
Hypertension	1161(65.1)	508(66.6)	0.494
Diabetes	163(9.1)	73(9.6)	0.788
Hyperlipidemia	53(3.0)	18(2.4)	0.467
Clinical presentations			
Onset-to-admission time, h	4(2–19)	4(2–20)	0.555
SBP, mm Hg	168(150–187)	168(150–189)	0.68
Baseline NIHSS	8(3–15)	8(3–14)	0.552
Baseline mRS	4(2–5)	4(2–5)	0.561
Baseline GCS	14(11–15)	14(12–15)	0.407
Dysphagia	449(25.2)	216(28.3)	0.001*
Imaging findings			
Hematoma volume, cm3	12(5.2–21.0)	12(5–23.2)	0.585
Basal ganglia hemorrhage	893(50.1)	366(48.0)	0.357
Lobar hemorrhage	352(19.7)	154(20.2)	0.835
Brainstem hemorrhage	127(7.1)	61(8.0)	0.489
Cerebellar hemorrhage	126(7.1)	47(6.2)	0.457
Thalamus hemorrhage	370(20.7)	163(21.4)	0.763
Intraventricular hemorrhage	290(16.3)	150(19.7)	0.043*
Laboratory values			
WBC, *109/L	8.32(6.42–10.97)	8.4(6.45–10.87)	0.264
Neu, *109/L	6.65(6.64–9.32)	6.28(4.45–9.39)	0.001*
Lymphocytes, *109/L	1.19(0.85–1.72)	1.16(0.84–1.60)	0.488
NLR	5.19(2.98–9.93)	5.58(3.09–9.93)	0.201
hs-CRP, mg/L	4.05(0.5–22.13)	4.60(0.5–23.49)	0.309
FBG, mmol/L	6.17(5.24–7.43)	6.18(5.29–7.65)	0.252

(*Continued*)

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Table 1 (Continued).

Characteristics	Training Cohort (N=1784)	Validation Cohort (N=763)	P value*
Medication history during hospitalization			
ACEI	232(13.0)	91(11.9)	0.494
CCB	1220(68.4)	527(69.1)	0.769
β-blocker	162(9.1)	75(9.8)	0.602
ARB	160(9.0)	57(7.5)	0.245

Notes: Continuous variables were reported as mean ± SD or median (IQR), and categorical variables were presented as n (%). *$P<0.05$.
Abbreviations: SD, standard deviation; IQR, interquartile.

Table 2 Univariate Analysis Comparing Patients With and Without Pneumonia in the Training Cohort

Characteristics	Without Pneumonia	Pneumonia	P value*
Post-ICH pneumonia	1548(86.7)	236(13.3)	
Demographic data			
Age, years	62(53–70)	64(54–74)	0.007*
Male	1039(67.2)	172(72.6)	0.115
Hospital days	14(9–20)	20(12–29)	<0.001*
Medical history			
Smoking history	462(29.9)	82(34.6)	0.184
COPD	59(3.8)	9(3.8)	0.999
Ischemic stroke	157(10.1)	33(13.9)	0.082
Ischemic heart disease	66(4.3)	6(2.5)	0.216
Hypertension	998(64.5)	163(68.8)	0.211
Diabetes	147(9.5)	16(6.8)	0.179
Hyperlipidemia	46(3.0)	7(3.0)	0.996
Clinical presentations			
Onset-to-admission time, h	4(2–24)	4(2–10)	0.009*
SBP, mm Hg	168(150–187)	170(150–194)	0.155
Baseline NIHSS	7(3–13)	15(8–22)	<0.001*
Baseline mRS	4(2–5)	5(4–5)	<0.001*
Baseline GCS	15(12–15)	11(7–14)	<0.001*
Dysphagia	360(23.3)	89(37.4)	<0.001*

(*Continued*)

Table 2 (Continued).

Characteristics	Without Pneumonia	Pneumonia	P value*
Imaging findings			
Hematoma volume, cm3	10.70(5–20)	17.50(10–40)	<0.001*
Basal ganglia hemorrhage	779(50.4)	114(48.1)	0.485
Lobar hemorrhage	304(19.7)	48(20.3)	0.783
Brainstem hemorrhage	102(6.6)	25(10.5)	0.027*
Cerebellar hemorrhage	113(7.3)	13(5.5)	0.303
Thalamus hemorrhage	308(19.9)	62(26.2)	0.027*
Intraventricular hemorrhage	226(14.6)	64(27.0)	<0.001*
Laboratory values			
WBC, *109/L	8.08(6.28–10.60)	10.24 (7.54–12.64)	0.119
Neu, *109/L	6.17(4.35–9.20)	8.39(5.46–11.18)	0.783
Lymphocytes, *109/L	1.22(0.88–1.74)	1.01(0.65–1.49)	0.004*
NLR	4.88(2.89–9.16)	7.50(4.53–14.25)	<0.001*
hs-CRP, mg/L	3.35(0.34–20.30)	10.00 (2.13–40.13)	<0.001*
FBG, mmol/L	6.17(5.22–7.32)	6.69(5.65–8.52)	<0.001*
Medication history during hospitalization			
ACEI	195(12.6)	37(15.6)	0.191
CCB	1053(68.1)	167(70.5)	0.501
β-blocker	119(7.7)	43(18.1)	<0.001 #x002A;
ARB	138(8.9)	22(9.3)	0.968

Notes: Continuous variables were reported as mean ± SD or median (IQR), and categorical variables were presented as n (%). *$P<0.05$.
Abbreviations: SD, standard deviation; IQR, interquartile.

P<0.001), hs-CRP (β=0.328, P<0.001), hematoma volume (β=0.376, P<0.001), brainstem hemorrhage (β=0.956, P=0.002), intraventricular hemorrhage (β=0.629, P=0.001), and β-blocker (β=0.899, P<0.001) (Table 3). As the boundary value of the continuous variable, the value that corresponds to the quartile is rounded to the closest integer. After ICH, these nine factors were identified as independent predictors of pneumonia and subsequently employed to generate a nomogram.

The Pneumonia Nomogram

The nomogram was created based on logistic regression analysis of the training group (n=1784) (Figure 2). The stepwise regression findings indicate that the model including age, hospital days, baseline mRS score, baseline GCS score, hs-CRP, hematoma volume, intraventricular hemorrhage, brainstem hemorrhage, and β-blocker had the lowest AIC value in the training group. We developed a nomogram based on the selected variables.

The C statistic for the training subgroup was 0.805 (95% CI, 0.773–0.833), and the Hosmer-Lemeshow goodness of fit test yielded a P value of 0.590. The model was subsequently assessed in the validation cohort, demonstrating excellent

Table 3 Multivariate Analysis for Factors Associated With Pneumonia in the Training Cohort

Predictor Variable	β	P value	OR	95% C.I.for OR	
				Lower	Upper
Age, years	0.023	<0.001*	1.023	1.01	1.036
Baseline mRS score	0.484	<0.001*			
0–1		0.002*			
2–4	−1.134	<0.001*	0.322	0.173	0.6
5	−0.331	0.074	0.718	0.5	1.032
Baseline GCS score	−0.285	<0.001*			
3–8		<0.001*			
9–11	0.896	<0.001*	2.449	1.565	3.832
12–14	0.007	0.982	1.007	0.546	1.86
15	0.232	0.408	1.261	0.728	2.184
Hospital days	0.392	<0.001*			
0–9		<0.001*			
10–14	−1.315	<0.001*	0.269	0.174	0.413
15–20	−0.615	0.006*	0.541	0.349	0.838
>21	−0.742	<0.001*	0.476	0.315	0.72
hs-CRP, mg/L	0.328	<0.001*			
0–0.5		<0.001*			
0.6–4	−1.161	<0.001*	0.313	0.196	0.501
5–22	−0.357	0.089	0.7	0.464	1.056
>22	−0.205	0.306	0.815	0.551	1.205
Hematoma volume, cm3	0.376	<0.001*			
0–5		<0.001*			
6–12	−0.958	<0.001*	0.383	0.226	0.651
13–22	−0.875	<0.001*	0.417	0.281	0.619
>22	−0.565	0.013*	0.568	0.363	0.89
Beta blockers	0.956	<0.001*	2.6	1.668	4.053
Brainstem hemorrhage	0.89	0.002*	2.435	1.372	4.32
Intraventricular hemorrhage	0.669	0.001*	1.953	1.339	2.847
Constant	−2.211	<0.001*	0.11		

Note: *P<0.05.

calibration with a Hosmer-Lemeshow goodness of fit P value of 0.484 and a C statistic of 0.767 (95% CI, 0.716–0.807) (Figure 3). The calibration curves of the nomogram exhibited significant agreement between the observed and predicted survival probabilities in both the training and validation groups. (Figure 4).

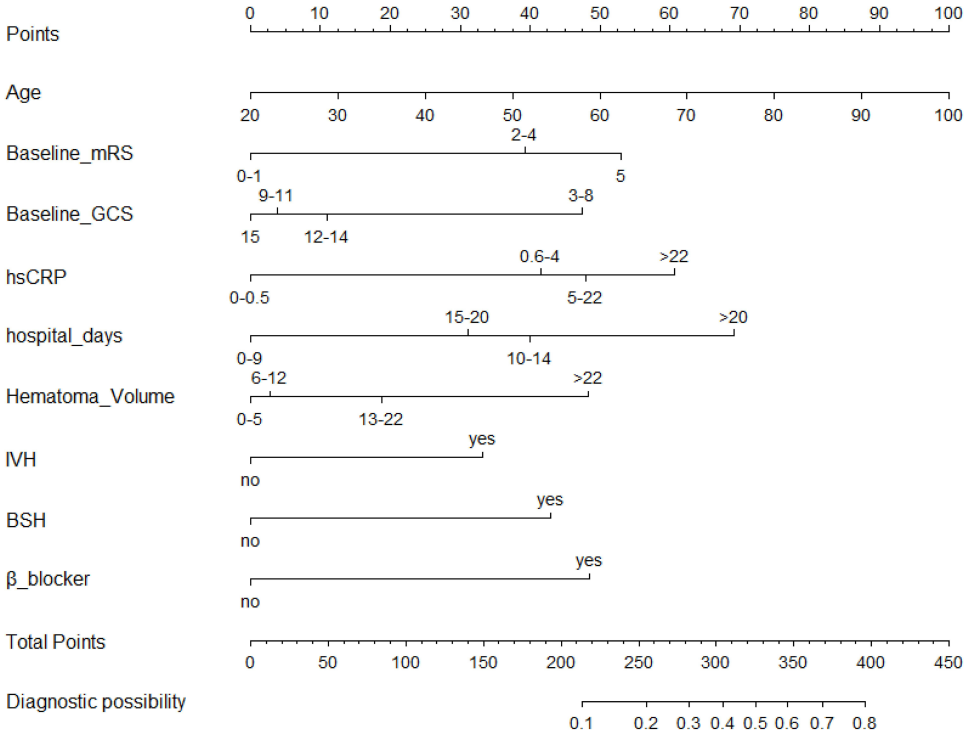

Figure 2 A nomogram for predicting the risk of pneumonia after intracerebral hemorrhage.
Abbreviation: hsCRP, high-sensitivity C-reactive protein; IVH, intraventricular hemorrhage; BSH, Brainstem hemorrhage.

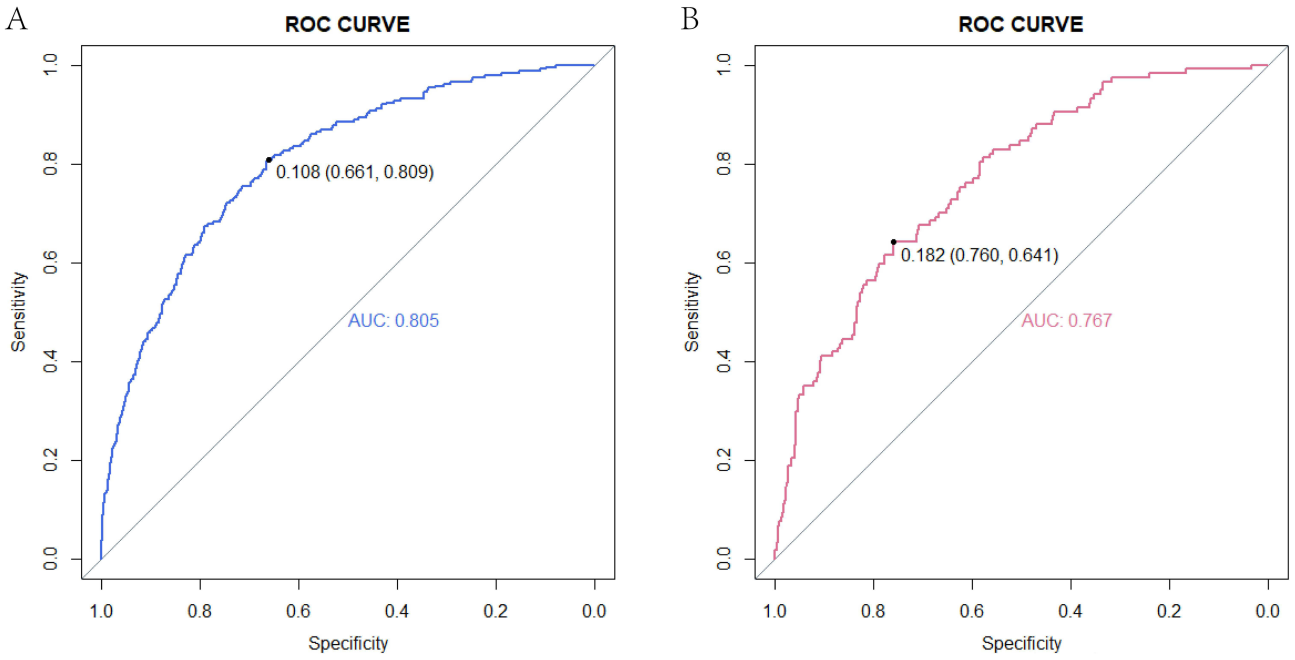

Figure 3 The area under the curve of the training set and the validation set. (**A**)The C value for the training set was 0.805 (95% CI: 0.773–0.833). (**B**)The model was then tested on the validation group, and the C statistic was found to be 0.767 (95% CI, 0.716–0.807). The coordinate points on the figure represent the optimal critical point (Youden index), and the corresponding index value is the optimal threshold.

https://doi.org/10.2147/JIR.S490064

The clinical value of the model is assessed with reference to Decision Curve Analysis. The ordinate of the decision analysis curve is the net benefit rate, which represents the difference between the income of the true positive patients diagnosed with pneumonia after intracerebral hemorrhage after clinical intervention and the income of the false positive patients after clinical intervention. The abscissa is the high-risk threshold, which represents the risk threshold for positive pneumonia after intracerebral hemorrhage. If a solid line (None) parallel to the abscissa is drawn with the ordinate of 0, it represents the net benefit rate of clinical intervention when all patients have no outcome event (pneumonia after intracerebral hemorrhage). The slash "All" represents the net benefit rate of clinical intervention after all patients had an outcome event (pneumonia after intracerebral hemorrhage), and the red or blue solid line represents the net benefit rate based on the prediction model (Figure 5). Within a certain high-risk threshold, after clinical intervention for patients with pneumonia after intracerebral hemorrhage based on the prediction model, the higher the net benefit rate, the more clinical value, that is, the larger the area under the curve, the more sufficient the clinical decision. In the training set, when the risk threshold is 0.1–0.6, clinical intervention for patients with positive pneumonia after cerebral hemorrhage based on the prediction model can benefit the patients, indicating that the prediction model has better performance. In the validation set, it was found that when the risk threshold was 0.1–0.5, the performance of the prediction model was better, which could benefit the patients with positive pneumonia after cerebral hemorrhage. The above results show that the application of this model will benefit patients with pneumonia after intracerebral hemorrhage.

Furthermore, we validated the ICH-LR2S2, ICH-APS, PASS, the Pneumonia Score, ISAN with this cohort, In the training set, the AUC of ICH-LR2S2 is 0.763, while that of ICH-APS is 0.741, PASS is 0.716, the Pneumonia Score is 0.710, and ISAN is 0.724; in the validation set, the AUC of ICH-LR2S2 is 0.719, ICH-APS is 0.719, PASS is 0.687, the Pneumonia Score is 0.690, and ISAN achieves an AUC of 0.696, indicating superior discriminatory performance for our model. (Figure 6).

Machine Learning Model

We used multivariate regression analysis to screen nine variables and established nine machine learning models, namely catboost model, xgboost, KNeighbors (KNN), Multilayer Perceptron (MLP), lightgbm, Byes, RandomForest (rf), GradientBoosting (GDBT), DecisionTree. In the validation set, by comparing the accuracy, specificity and sensitivity, as well as the positive predictive rate and negative predictive rate, and the area under the curve, the catboost model performed best, with an AUC of 0.77, a specificity of 0.9845, and an accuracy of 0.8545. (Table 4, Figure 7). In order to

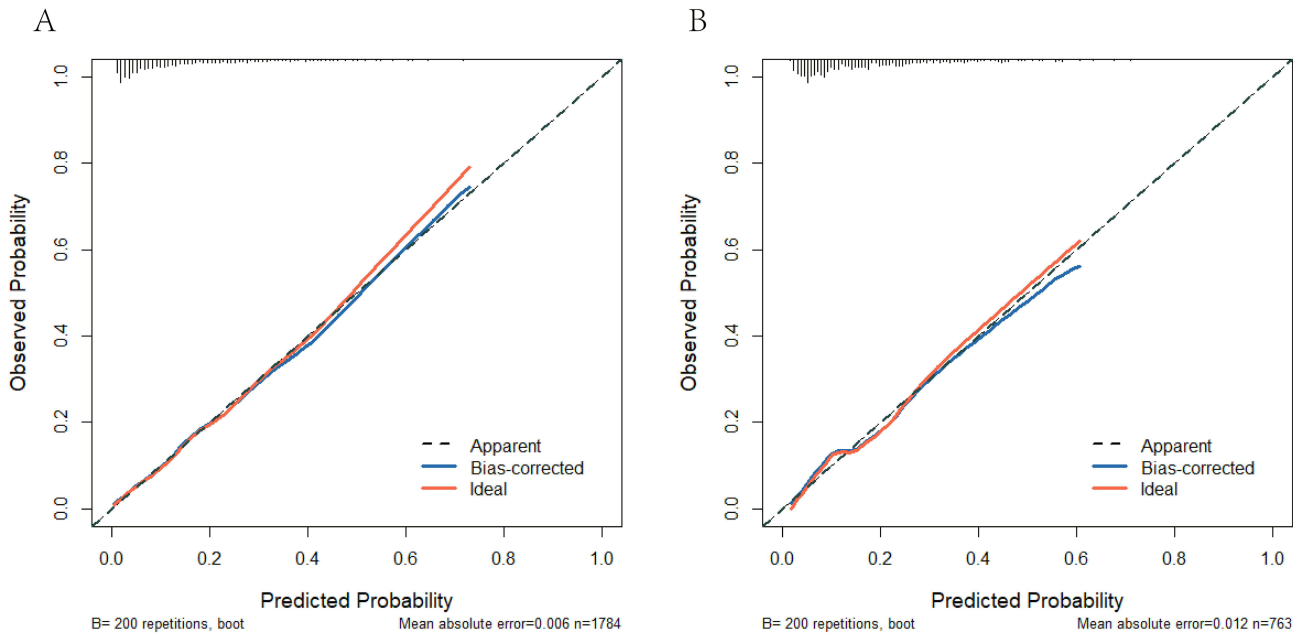

Figure 4 Calibration curves of training set and validation set. The calibration curves of the nomogram demonstrated strong consistency between the anticipated and actual survival probabilities in both the training (**A**) and validation groups (**B**).

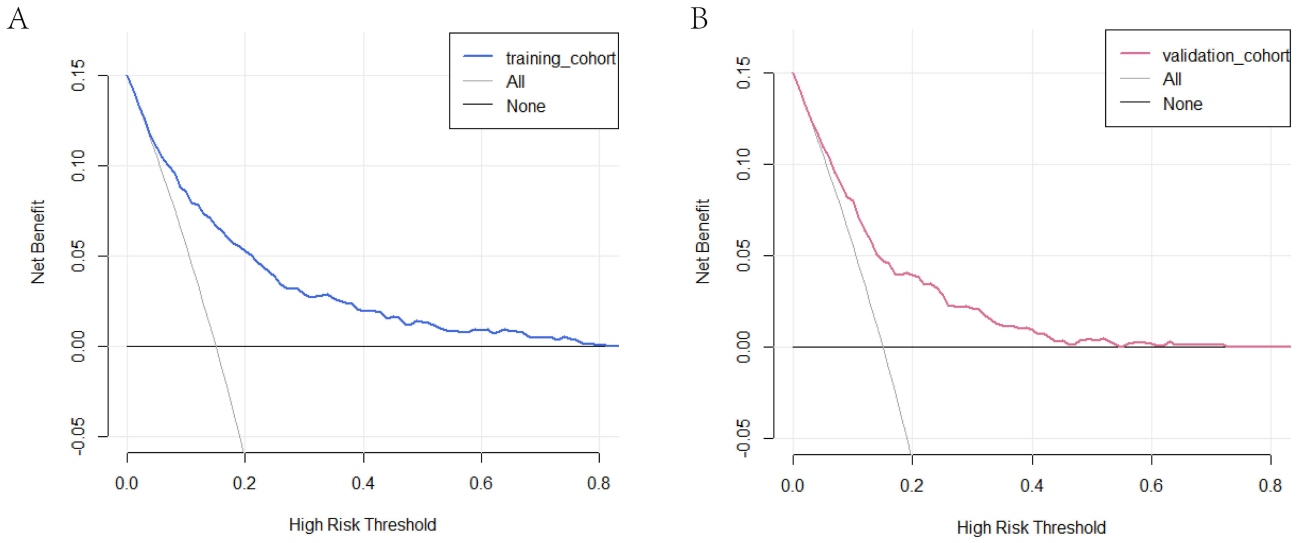

Figure 5 Decision Curve Analysis of training set and validation set. The ordinate of the decision analysis curve is the net benefit rate, which represents the difference between the income of the true positive patients diagnosed with pneumonia after intracerebral hemorrhage after clinical intervention and the income of the false positive patients after clinical intervention. The abscissa is the high-risk threshold, which represents the risk threshold for positive pneumonia after intracerebral hemorrhage. If a solid line (None) parallel to the abscissa is drawn with the ordinate of 0, it represents the net benefit rate of clinical intervention when all patients have no outcome event (pneumonia after intracerebral hemorrhage). The slash "All" represents the net benefit rate of clinical intervention after all patients had an outcome event (pneumonia after intracerebral hemorrhage), and the red or blue solid line represents the net benefit rate based on the prediction model. (**A**)In the training set, when the risk threshold is 0.1–0.6, clinical intervention for patients with positive pneumonia after cerebral hemorrhage based on the prediction model can benefit the patients, indicating that the prediction model has better performance. (**B**)In the validation set, it was found that when the risk threshold was 0.1–0.5, the performance of the prediction model was better, which could benefit the patients with positive pneumonia after cerebral hemorrhage.

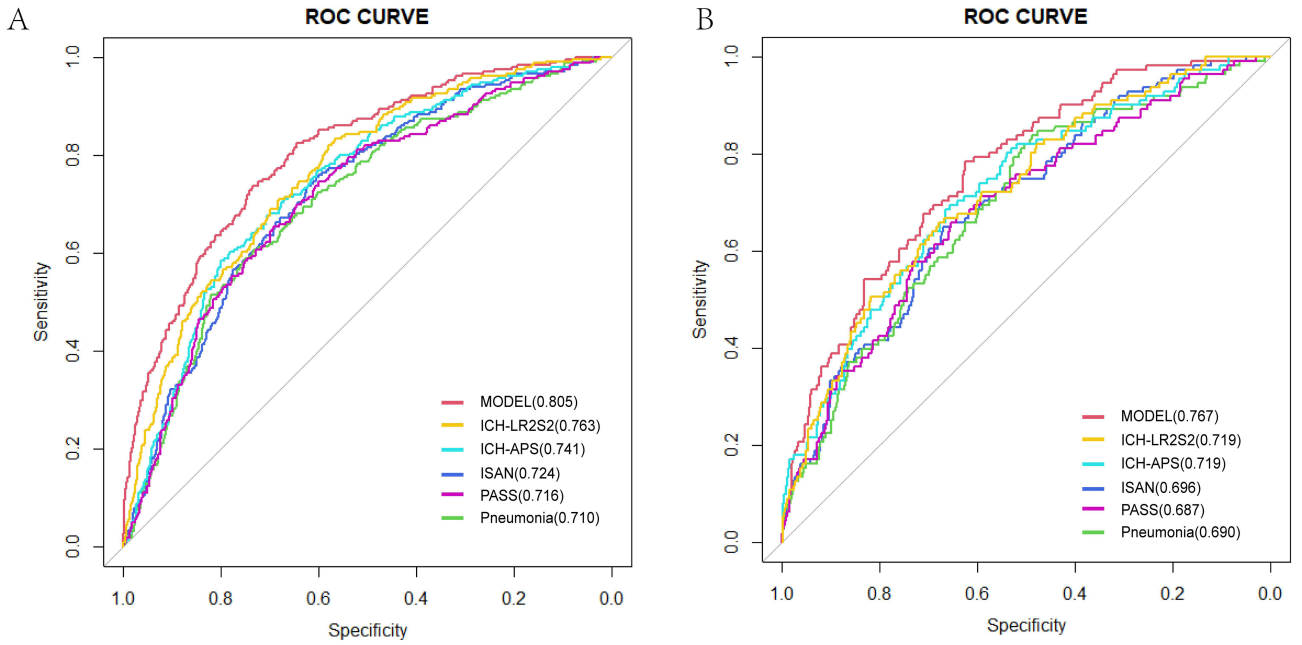

Figure 6 The area under the curve of training set and validation set. (**A**) In the training set, the AUC of ICH-LR2S2 is 0.763, while that of ICH-APS is 0.741, PASS is 0.716, the Pneumonia Score is 0.710, and ISAN is 0.724; (**B**) in the validation set, the AUC of ICH-LR2S2 is 0.719, ICH-APS is 0.719, PASS is 0.687, the Pneumonia Score is 0.690, and ISAN achieves an AUC of 0.696, indicating superior discriminatory performance for our model.

further increase the interpretation of the machine learning model, we used the shap model to explain the machine learning model. Among them, mRS and GCS accounted for the highest proportion, 17.5% and 17.6%, respectively, and brainstem hemorrhage accounted for the lowest proportion, 3.1% (Figure 8).

https://doi.org/10.2147/JIR.S490064

Table 4 Comparison of Predictive Power Between Different Models

	Sensitivity		Specificity		Negative Predictive Value		Positive Predictive Value		Accuracy		AUC	
	Training	Validation	Training	Validation	Training	Validation	Training	Validation	Training	Validation	Training	Validation
catboost	0.2034	0.1368	0.9942	0.9845	0.8911	0.8630	0.8421	0.6154	0.8896	0.8545	0.870	0.768
xgboost	0.8983	0.2393	1.0000	0.9582	0.9847	0.8743	1.0000	0.5091	0.9865	0.8480	1.000	0.737
knn	0.2797	0.1368	0.9800	0.9551	0.8992	0.8593	0.6804	0.3556	0.8873	0.8296	0.898	0.634
mlp	0.2839	0.1111	0.9787	0.9799	0.8950	0.8697	0.7215	0.4898	0.8873	0.8453	0.856	0.737
Bayes	1.0000	0.2564	1.0000	0.9489	1.0000	0.8757	1.0000	0.4762	1.0000	0.8427	1.000	0.735
lightgbm	0.4237	0.4359	0.8805	0.8591	0.9093	0.8937	0.3509	0.3592	0.8201	0.7942	0.773	0.740
rf	1.0000	0.1624	1.0000	0.9814	1.0000	0.8651	1.0000	0.6207	1.0000	0.8558	1.000	0.759
GBDT	0.5085	0.1880	0.9974	0.9644	0.9301	0.8677	0.9677	0.4889	0.9327	0.8453	0.947	0.747
DecisionTree	0.9661	0.3077	0.9994	0.8947	0.9949	0.8803	0.9956	0.3203	0.9950	0.7864	0.999	0.601
Logistic	0.6625	0.7755	0.8093	0.5812	0.2671	0.3192	0.9579	0.9109	0.8672	0.8480	0.805	0.767
ISAN	0.6195	0.5898	0.7500	0.7094	0.2311	0.2385	0.9420	0.9181	0.6368	0.6081	0.724	0.696
Pneumonia	0.6576	0.7415	0.6864	0.5556	0.2341	0.2802	0.9322	0.9021	0.6614	0.7130	0.71	0.69
ICH-APS	0.7925	0.6703	0.6102	0.6667	0.3097	0.2680	0.9302	0.9174	0.7684	0.6697	0.741	0.719
PASS	0.6731	0.4985	0.6780	0.8034	0.2402	0.2249	0.9320	0.9333	0.6738	0.5452	0.716	0.687
ICH-LR2S2	0.5801	0.6855	0.8202	0.6306	0.2300	0.2642	0.9547	0.9120	0.6120	0.6772	0.763	0.719

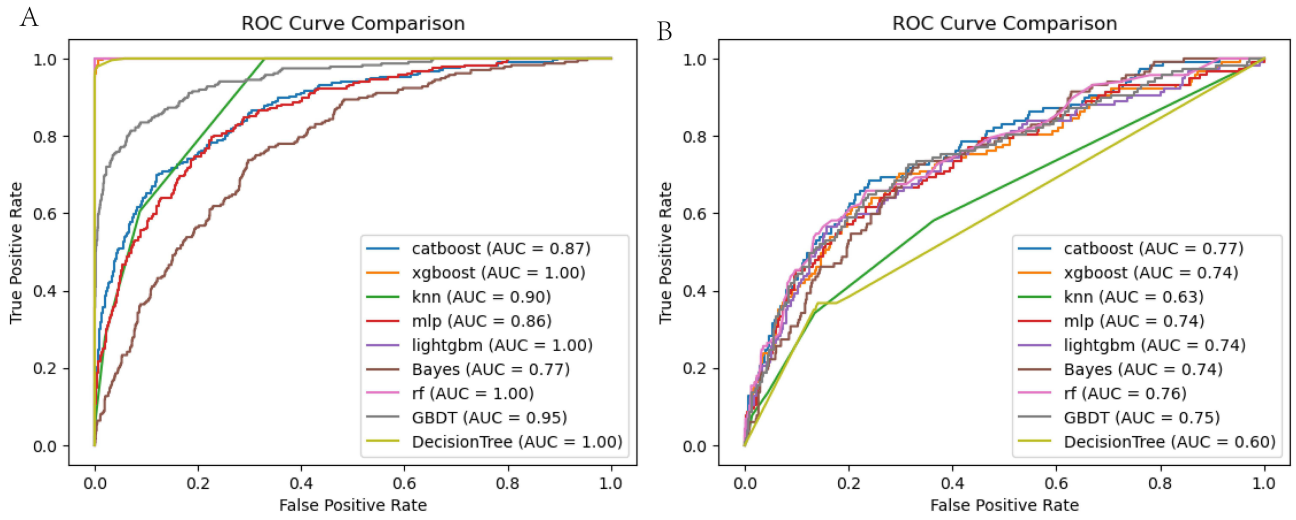

Figure 7 The area under the curve of different machine learning models in the training set and the validation set. (**A**) We used multivariate regression analysis to screen nine variables and established nine machine learning models, namely catboost model, xgboost, KNeighbors (KNN), Multilayer Perceptron (MLP), lightgbm, Byes, RandomForest (rf), GradientBoosting (GDBT), DecisionTree. (**B**) In the validation set, by comparing the accuracy, specificity and sensitivity, as well as the positive predictive rate and negative predictive rate, and the area under the curve, the catboost model performed best, with an AUC of 0.7, a specificity of 0.9845, and an accuracy of 0.8545.

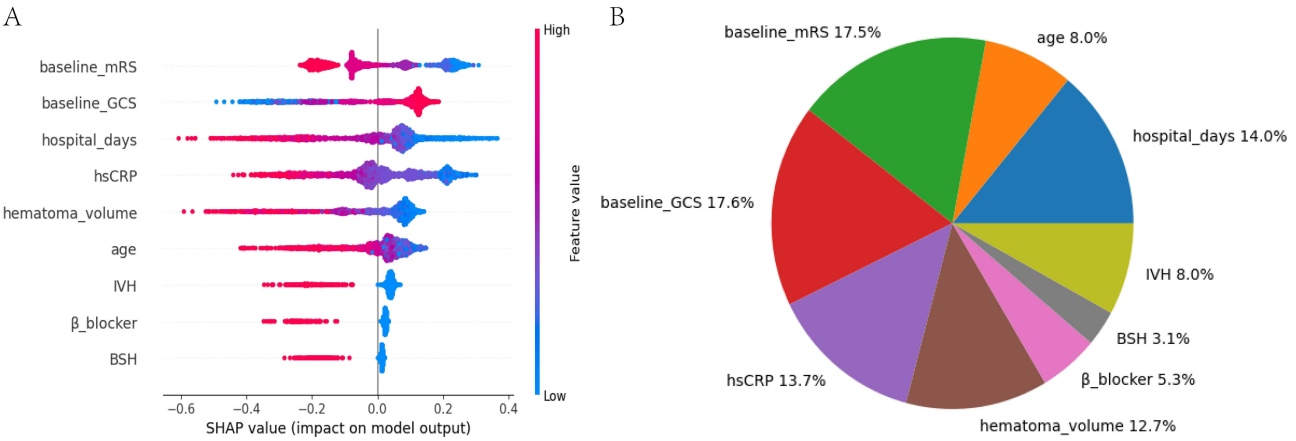

Figure 8 The catboost model uses the summary plot and pie chart displayed by the shap model. (**A**) In order to further increase the interpretation of the machine learning model, we used the shap model to explain the machine learning model (catboost). (**B**) Among them, mRS and GCS accounted for the highest proportion, 17.5% and 17.6%, respectively, and brainstem hemorrhage accounted for the lowest proportion, 3.1%.

Discussion

Based on the literature, the prevalence of stroke-associated pneumonia is reported to be 12.3%. The prevalence of stroke-related pneumonia in the contemporary era (post-2011) appears to have remained consistent with previous years. It is noteworthy that, despite major improvements in acute therapy and stroke care, there is no evidence of a drop in the prevalence of stroke-associated pneumonia over time, indicating that it remains a major clinical challenge.[18]

To predict pneumonia following ICH, we designed and validated a nomogram using age, hospital days, baseline mRS score, baseline GCS score, hs-CRP, hematoma volume, intraventricular hemorrhage, brainstem hemorrhage, and β-blocker. The predictive model, further validated in the validation cohort, demonstrates exceptional discriminative and calibrated performance in the derivation group, suggesting that it has considerable potential as an easy-to-use treatment tool.

https://doi.org/10.2147/JIR.S490064

Compared with the machine learning model, the performance of the model established by logistic regression analysis was slightly worse. The accuracy rates in the training set and the validation set were 0.8672 and 0.8480, respectively, while the catboost model was 0.8896 and 0.8545. CatBoost is a GBDT framework based on oblivious trees, which has fewer parameters, supports categorical variables and high accuracy. It can deal with categorical features efficiently and reasonably. In addition, CatBoost also solves the problems of Gradient Bias and Prediction shift, thus reducing the occurrence of over-fitting and improving the accuracy and generalization ability of the algorithm. Through the deep machine learning model, it is proved that the model also has certain superior performance, but the machine learning model also has certain inexplicability. In order to better explain the catboost model, we use the shap model to explain the proportion of each variable in the model, but this can only be used to explain the model, the model still lacks certain practicability, so we use multiple logistic regression analysis to establish the nomogram.

This nomogram can integrate nine risk factors to predict the risk of patients. By marking the specific information of patients on the nomogram, the risk probability of pneumonia in patients can be calculated, which is convenient for early identification of high-risk patients (such as those with dysphagia). At the same time, early and timely intervention, including antibiotic treatment, respiratory support and preventive care (such as aspiration prevention). For patients with different risks, doctors can formulate more accurate treatment plans for each patient based on the prediction results provided by the nomogram, and improve clinical decision-making ability.

From the standpoint of pathogenesis as well as clinical features, the present findings are reasonable. The baseline features and the incidence of pneumonia after ICH[18,19] are comparable to earlier investigations. For the first time, the nomogram identified β-blocker as an independent risk factor for pneumonia following intracerebral hemorrhage. Multivariate analysis includes β-blocker. This is also consistent with our results and the latest research on this topic in the PASS experiment. The authors found that the use of any β-blocker within the first 3 days after admission to ischemic stroke was associated with an increased risk of infection.[20] As is known to all, the β receptor is an adrenaline receptor. The β1 receptor is mostly found in the heart and can enhance myocardial contractility, auto rhythmicity, and conduction performance. The β2 receptor, found in bronchial smooth muscle, vascular smooth muscle, and myocardium, has a role in relaxing bronchial smooth muscle and promoting vasodilation. The β3 receptor is found mostly in white and brown adipose tissue, where it affects energy consumption, cardiac negative muscular strength, and vascular smooth muscle relaxation.[21,22] Taking β-blocker affects bronchial smooth muscle, leading to blood vessel contraction and decreased lung function, making patients more susceptible to pneumonia. Wong et al demonstrated in a mouse model that the β-blocker propranolol inhibited the natural killer T (iNKT) inflammatory response after medial cerebral artery occlusion (MCAO). However, it is not clear which receptors are involved in mediating this immunosuppressive effect.[23] The results confirmed that metoprolol specifically blocked neutrophil migration through β1AR and reduced circulating neutrophil-platelet co-aggregation in mice with ischemic stroke, reducing the infiltration of neutrophils in the brain of mice and the inflammatory response.[24]

The results of these animal experiments are not consistent with the results in our cohort. We believe that it may be because most of them are verified on animal models of cerebral infarction, and the physiological mechanism of β-blocker is not verified on cerebral hemorrhage models. It may also be related to the different definitions of' treatment' of β-blocker. Some studies only classify a single dose of β-blocker as treatment, while others include various doses, dosing regimens, specific drugs, and treatment days. Although these results undoubtedly prove the suspicion of the idea of prophylactic use of β-blocker after intracerebral hemorrhage, the conclusion that β-blocker lead to an increased risk of infection may be premature. Our study questioned the effectiveness of these findings and even found that the use of β-blocker was associated with an increased risk of infection. It seems reasonable to conduct prospective modern RCTs to address the potential benefits and risks of β-blocker therapy after intracerebral hemorrhage. This is a reminder for clinicians that patients with intracerebral hemorrhage and patients with underlying diseases of hypertension need to carefully consider taking β-blockers to control blood pressure.

The morbidity and mortality associated with spontaneous intracerebral hemorrhage (ICH) remain high, and there is currently no definitive treatment beyond supportive care.[25] Increasing experimental evidence indicates that cerebral hemorrhage triggers an inflammatory response mediated by microglia and T cells in the brain.[26] This inflammatory response is linked to perihematomal edema, cytokine release, blood-brain barrier disruption, and subsequent infiltration

of white blood cells,[27] potentially leading to adverse outcomes following ICH. It has been demonstrated that the risk factors in the model correlate with pneumonia following ICH. For example, high-sensitivity C-reactive protein and lymphocytes may indicate the activated inflammatory response after ICH, and the lymphocyte count of patients with pneumonia becomes less, which may be caused by the consumption of T lymphocytes after infection with pneumonia, and high-sensitivity C-reactive protein increases instead.[4,28,29]

Although lymphocytes, and neutrophil / lymphocyte ratios were shown to be related to the occurrence of pneumonia after cerebral hemorrhage in univariate analysis, which was consistent with some research results,[10] these variables were excluded when multivariate analysis was included in the model, and lymphocytes were considered to be more stable in the model.

In this study, we use the SHAP interpretation model to explain the catboost machine learning model, and the results show that mRS and GCS account for the largest proportion (Figure 8). The mRS score at admission may be due to patients with worse neurological function, which leads to a higher risk of pneumonia during hospitalization. It is worth mentioning here that the GCS score at admission is grouped according to the clinical diagnostic criteria, which represents coma, severe disturbance of consciousness, moderate disturbance of consciousness, and mild disturbance of consciousness. The results of the nomogram show that the worse the patient ‘s level of consciousness, the more prone to pneumonia.[6,11,30] This may be because patients with poor consciousness are more likely to stay in bed. Bedridden patients have poor sputum drainage, weakened pharyngeal reflexes, and dysphagia. There are also people who have hidden aspirations into their lungs while sleeping at night, resulting in lung deposits that are not emptied, making them susceptible to pulmonary infection.

Our analysis reveals several strengths. The factors we included in the cohort are clinically accessible data, and the index of drug factors is added, which is no longer a simple scoring index, and is more comprehensive than the previous scoring system. Consecutive individuals from both main care providers and big teaching hospitals were included based on a large-sample multicenter study. The statistics show little variability because all of the included subjects had distinct ICH clinical features and had not participated in any prior clinical studies. New independent predictors, including β-blocker were added into the risk prediction model. This can remind clinicians to use β-blockers more cautiously in clinical practice. In order to further test our model, we also added a machine learning model and a shap interpretation model, which can better indicate the proportion of different factors in the model.

The score has considerable limitations.[13,31] Due to the lack of clinical data and imaging data, we excluded 1120 data. We compared the baseline data of the original cohort and the final cohort (Table 5). The results showed that there was no statistically significant difference between most of the baseline data except fasting blood glucose between the two cohorts, which may also be a reason why our model was not included in fasting blood glucose. In the follow-up study, we need to further consider incorporating fasting blood glucose into our model (Table 5). Unmeasured confounding factors may influence the outcomes of this observational study. Most external cohorts do not contain β-blockers as a variable, resulting in a lack of independent validation for an additional cohort. Only the outcome of pneumonia during hospitalization was considered, and no pneumonia follow-up was conducted on patients after release. This cohort

Table 5 Baseline Characteristics of the Original and Final Queues

Characteristics	Original Cohort (N=4248)	Final Cohort (N=2547)	P value*
Post-ICH pneumonia	610(14.4)	353(13.9)	0.567
Demographic data			
Age, years	62(53–70)	62(53–71)	0.122
Male	2854(67.2)	1744(68.5)	0.284
Hospital days	15(9–21)	15(10–21)	0.117

(*Continued*)

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Table 5 (Continued).

Characteristics	Original Cohort (N=4248)	Final Cohort (N=2547)	P value*
Medical history			
Smoking history	1453(30.7)	775(30.4)	0.356
COPD	162 (3.8)	97 (3.8)	0.664
Ischemic stroke	407(9.6)	270(10.6)	0.116
Ischemic heart disease	158(3.7)	95(3.7)	0.654
Hypertension	2690(63.3)	1669(65.5)	0.434
Diabetes	381(9.0)	236(9.3)	0.665
Hyperlipidemia	116(2.7)	71(2.8)	0.569
Clinical presentations			
SBP, mm Hg	165(147–185)	168(150–188)	0.226
Baseline NIHSS	8(3–15)	8(3–15)	0.243
Baseline mRS	4(2–5)	4(2–5)	0.435
Baseline GCS	14(11–15)	14(12–15)	0.564
Dysphagia	1322(27.3)	665(26.1)	0.435
Imaging findings			
Hematoma volume, cm3	11(5–24)	12(5–26.9)	0.233
Basal ganglia hemorrhage	2106(49.6)	1259(49.4)	0.915
Lobar hemorrhage	912(21.5)	506(19.9)	0.117
Brainstem hemorrhage	309(7.3)	188(7.4)	0.896
Cerebellar hemorrhage	269(6.3)	173(6.8)	0.455
Thalamus hemorrhage	817(19.2)	533(20.9)	0.095
Intraventricular hemorrhage	767(18.1)	440(17.3)	0.418
Laboratory values			
WBC, *109/L	8.5(6.5–11.23)	8.36(6.43–10.93)	0.266
Neu, *109/L	6.62(4.60–9.60)	6.38(4.52–9.38)	0.869
Lymphocytes, *109/L	1.15(0.80–1.66)	1.18(0.84–1.69)	0.261
hs-CRP, mg/L	4.03(0.5–22.33)	4.60(0.5–21.49)	0.268
FBG, mmol/L	6.17(5.22–7.60)	6.17(5.22–7.60)	0.018*
Medication history during hospitalization			
ACEI	629(13.0)	323(12.7)	0.657
CCB	3244(67.4)	1747(68.6)	0.342
β-blocker	436(9.1)	237(9.3)	0.611
ARB	435(9.1)	217(8.5)	0.549

Notes: Continuous variables were reported as mean ± SD or median (IQR), and categorical variables were presented as n (%).
Abbreviations: SD, standard deviation; IQR, interquartile. *$P<0.05$.

lacks data on the use of antibiotics, and it is hoped that this element can be added to the subsequent cohort when it is included. Our cohort is only a study of Chinese patients, which has certain limitations. In the future, it is necessary to apply the nomogram to different cohorts and populations in different countries to determine the predictive ability of the prediction model.

Conclusions

In conclusion, we have established a simple and easy predictive tool. By evaluating the incidence of stroke pneumonia after intracerebral hemorrhage, we can identify high-risk groups early. At the same time, our study also suggests that doctors should be cautious in the use of β-blockers in clinical decision-making. In order to verify the practicability of the prediction model, it needs to be further verified in the external queue.

Abbreviations

ICH, intracerebral hemorrhage; CHEERY, Chinese cerebral hemorrhage: mechanism and intervention study; mRS, the modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; GCS, Glasgow Coma Scale; LY, lymphocytes; hs-CRP, high-sensitivity C-reactive protein; WBC, white blood cell count; NLR, neutrophil lymphocyte ratio; PLT, platelet; AST, aspartate aminotransferase; ALT, glutamic pyruvic transaminase; INR, international normalized ratio; FBG, fasting blood-glucose; TC, triglycerides; LDL-C, low-density lipoprotein cholesterol; IVH, intraventricular hemorrhage; ACEI, angiotensin converting enzyme inhibitors; ARB, Angiotensin receptor blocker; CCB, calcium channel blockers; SBP, systolic blood pressure; AUC, area under the curve; ICH-APS, Intracerebral Hemorrhage-Associated Pneumonia Score; PISCES, Pneumonia in Stroke ConsEnsuS; DCA, Decision curve analysis.

Data Sharing Statement

The data that support the findings of this study are available on request from the corresponding author (Quanwei He) upon reasonable request.

Ethics Approval and Consent to Participate

The study was approved by the Research Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China (ethical approval number:2018-S485). Informed consent was obtained from all participants prior to the enrollment. The study complies with the Declaration of Helsinki.

Acknowledgments

Yuanyuan Sun and Lei Zhang are co-first authors for this study. We indeed appreciate Prof. Yongjun Wang and Prof. Xingquan Zhao for their kindly technical and statistical support, and also all the other participants and investigators in the CHEERY study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the National Natural Science Foundation of China (NO. 82071335 to QWH, NO. 81820108010 to BH).

Disclosure

The authors declare that they have no competing interests in this work.

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