Development and Validation of a Nomogram Prediction Model for Delayed Cerebral Edema After Intracerebral Hemorrhage Based on Serum Inflammatory Markers and Hemodynamics

Keywords
Hemodynamics, Delayed cerebral edema, Serum inflammatory factors, hypertensive cerebral hemorrhage

Abstract

Introduction
To explore the risk prediction model of delayed cerebral edema after hypertensive cerebral hemorrhage based on serum inflammatory factors and hemodynamics and its clinical application value.

Material and methods
Multivariate Logistic regression was used to analyze the risk factors of postoperative bleeding and build a nomogram prediction model, and ROC curve and calibration curve were drawn to evaluate the prediction efficiency of nomogram model, which was verified in the verification set.

Results
The results of univariate analysis showed that there were significant differences in L-6, TNF-α, IL-1β, MIP-1α, CBF, CVR, HMGB1 and CRP between patients with edema and those without edema in training ($P<0.05$). Logistic regression analysis showed that L-6, TNF-α, IL-1β, CBF, CVR, HMGB1 and CRP were independent risk factors for bleeding ($P<0.05$). The nomogram model has good calibration and fitting degree between prediction and reality in training set and verification set (C-index index is 0.792 and 0.799). The results of HosmerLemeshow test are $\chi2=16.582$, $P =0.035$ and $\chi2=7.472$, $P = 0.487$. The ROC curve is shown in the training set and the validation set. The AUC of the nomogram model in predicting delayed cerebral edema is 0. 794 and 0. 796.

Conclusions
The nomogram prediction model of delayed cerebral edema after hypertensive cerebral hemorrhage based on serum inflammatory factors (IL-6, TNF-α, IL-1β), hemodynamic parameters (CBF, CVR) and other related factors (HMGB1, CRP) was successfully established. The model can effectively predict the risk of delayed cerebral edema in patients with hypertensive cerebral hemorrhage.

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Development and Validation of a Nomogram Prediction Model for Delayed Cerebral Edema After Intracerebral Hemorrhage Based on Serum Inflammatory Markers and Hemodynamics

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Abstract

Objective: To explore the risk prediction model of delayed cerebral edema after hypertensive cerebral hemorrhage based on serum inflammatory factors and hemodynamics and its clinical application value.

Methods: Multivariate Logistic regression was used to analyze the risk factors of postoperative bleeding and build a nomogram prediction model, and ROC curve and calibration curve were drawn to evaluate the prediction efficiency of nomogram model, which was verified in the verification set.

Results: The results of univariate analysis showed that there were significant differences in L-6, TNF-α, IL-1β, MIP-1α, CBF, CVR, HMGB1 and CRP between patients with edema and those without edema in training ($P<0.05$). Logistic regression analysis showed that L-6, TNF-α, IL-1β, CBF, CVR, HMGB1 and CRP were independent risk factors for bleeding ($P<0.05$). The nomogram model has good calibration and fitting degree between prediction and reality in training set and verification set (C-index index is 0.792 and 0.799). The results of HosmerLemeshow test are $\chi^2=16.582$, $P=0.035$ and $\chi^2=7.472$, $P = 0.487$. The ROC curve is shown in the training set and the validation set. The AUC of the nomogram model in predicting delayed cerebral edema is 0. 794 and 0. 796.

Conclusion: The nomogram prediction model of delayed cerebral edema after hypertensive cerebral hemorrhage based on serum inflammatory factors (IL-6, TNF-α, IL-1β), hemodynamic parameters (CBF, CVR) and other related factors (HMGB1, CRP) was successfully established. The model can effectively predict the risk of

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delayed cerebral edema in patients with hypertensive cerebral hemorrhage.

Keywords: Serum inflammatory factors; Hemodynamics; Delayed cerebral edema; hypertensive cerebral hemorrhage

1 Introduction

With the acceleration of social aging, hypertensive cerebral hemorrhage, as a common and dangerous cerebrovascular disease, has an increasing trend year by year, posing a serious threat to human health on a global scale [1]. This disease has a sudden onset and rapid progress, which often causes irreversible damage to the patient's brain tissue in a short time [2]. Hypertensive cerebral hemorrhage will not only cause physical damage to local brain tissue, but also trigger a series of complex pathophysiological changes [3]. Among them, delayed cerebral edema, as one of the common and extremely harmful complications after operation, seriously affects the prognosis of patients. It usually develops gradually after cerebral hemorrhage for a period of time, which makes the intracranial pressure continue to rise, then oppresses the surrounding brain tissue, affects cerebral perfusion, and may even lead to the formation of cerebral hernia, which is an important cause of disability and death of patients [4].

At present, in clinical practice, the prediction method of delayed cerebral edema after hypertensive cerebral hemorrhage is not perfect. Doctors mostly rely on their own clinical experience and some conventional imaging examination methods to make judgments, but these methods have obvious shortcomings. Although clinical

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experience is valuable, it is subjective, and there may be differences among different doctors. However, traditional imaging examination can only be found when brain edema has occurred or developed to a certain extent, which has limited value for early prediction, which makes us often in a passive situation in the face of delayed cerebral edema and unable to take timely and effective preventive measures [5].

In recent years, more and more studies show that serum inflammatory factors and hemodynamic changes play a key role in the pathophysiological process after cerebral hemorrhage. As an important marker of inflammatory reaction, serum inflammatory factors have changed significantly during the initiation and development of local inflammatory reaction after cerebral hemorrhage [6-7]. They can affect the function of cerebral vascular endothelial cells, the permeability of blood-brain barrier and the survival state of neurons in many ways. The abnormal expression of inflammatory factors may induce the chemotaxis and activation of white blood cells, release more inflammatory mediators, and further aggravate the damage and edema of brain tissue [8-9]. At the same time, the change of hemodynamics is also a factor that can not be ignored. The change of hemodynamic parameters such as cerebral blood flow and cerebrovascular resistance is directly related to the perfusion of brain tissue [10]. After the occurrence of cerebral hemorrhage, the automatic regulation mechanism of cerebral blood vessels may be damaged, leading to the decrease of cerebral blood flow and the increase of cerebral vascular resistance. This abnormal blood flow state will lead to ischemia and hypoxia of brain tissue, which will further promote a series of pathophysiological chain

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reactions and create conditions for the occurrence of delayed cerebral edema [11-13].

Therefore, it is of great significance to conduct in - depth research on the relationship between the changes in serum inflammatory factors, hemodynamics, and delayed cerebral edema. The aim of this study is to construct an accurate and effective prediction model, provide a strong basis for clinical treatment and intervention, and improve the prognosis of patients with hypertensive intracerebral hemorrhage.

2 Data and methods

2.1 Research object

From January 2022 to January 2024, 300 patients with hypertensive intracerebral hemorrhage in our hospital were selected as the research subjects, and all of them informed and agreed to participate in this study voluntarily, which was approved by the ethics Committee of our hospital. Patients were randomly divided into training set (n=210) and verification set (n=90) according to the ratio of 7:3, and general data were collected simultaneously. Data can be provided upon request. The follow-up period was 10 months.

2.2 Inclusion exclusion criteria

2.2.1 Inclusion criteria

Patients should clearly meet the diagnostic criteria of hypertensive cerebral hemorrhage; The age is between 40 and 80 years old; The time from onset to admission is within 24 hours; The patient or family members sign the informed consent form. Ethical Approval Date: December 20, 2021, Ethical Approval Number: KY2023126, Research Protocol (Version Number: Y1.0; Version Date: December 6,

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2023), Informed Consent Form (Version Number: V1.0; Date: December 6, 2023).

2.2.2 Exclusion criteria

Exclude patients with other serious craniocerebral trauma, brain tumor and other diseases; Patients with severe heart, liver and renal insufficiency; The clinical data is incomplete.

2.3 Detection methods

2.3.1 Detection method of serum inflammatory factors (enzyme-linked immunosorbent assay, ELISA)

Collect patient's venous blood in a vacuum blood collection tube without anticoagulant, and centrifuge at the speed of 3000-3500rpm for 15 minutes after the blood naturally coagulates to obtain serum. Transfer the serum to a clean EP tube, and store the sample at -20℃ or lower if it is not detected immediately. Before testing, thaw the sample at room temperature and mix it gently. Select the corresponding ELISA kit according to the measured serum inflammatory factors, and check the status of each reagent in the kit. According to the instructions, the standard is prepared into a suitable concentration gradient with diluent. Add 50μL of standard solution and 50μL of serum sample to the microplate coated with specific antibody in turn, and set up multiple wells for each sample and standard. Gently shake the microplate to make the liquid fully mixed, then seal the microplate with a sealing film and incubate at room temperature for 1.5 hours. After the incubation, the liquid in the well was discarded, and the microplate was washed with washing liquid for 5 times, soaking for 2 minutes each time to remove unbound substances. Then, enzyme-labeled

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secondary antibody (100μL per well) was added, and the plate was sealed again and incubated at room temperature for 60 minutes. After that, repeat the washing step, and then add the substrate solution, 100μL per hole, and develop color in the dark. When the color is developed to an appropriate degree, the reaction is terminated by adding a termination solution. Finally, the absorbance of each hole was measured by enzyme-labeled instrument at the wavelength of 450nm, Each sample is measured three times. Based on the average value of the absorbance obtained from the three measurements, the concentration of inflammatory factors in the sample is calculated in combination with the standard curve.

2.3.2 Detection method of hemodynamic parameters (TCD)

Patients take supine position or sitting position, and keep quiet and relaxed. Examiners apply a proper amount of coupling agent to the transcranial Doppler ultrasound probe to ensure good contact between the probe and the skin and reduce air interference. Firstly, the temporal window is found in the temporal part, which is a common part of transcranial Doppler ultrasound examination. Generally, the appropriate ultrasonic signal is found by adjusting the angle and depth of the probe. When clear blood flow signals are obtained, the blood flow spectra of main cerebral vessels such as middle cerebral artery (MCA), anterior cerebral artery (ACA) and posterior cerebral artery (PCA) are identified. For the middle cerebral artery, the probe is usually placed in the temporal window, and the depth is adjusted to about 30-65mm to find signals with typical blood flow spectrum characteristics, that is, the systolic blood flow velocity is relatively fast, the diastolic blood flow velocity is

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relatively low, and the blood flow spectrum is three peaks (S1, S2 and D peaks). The blood flow velocity parameters of each major cerebral blood vessel need to be measured repeatedly 5 times at different time points. The blood flow velocity parameters of major cerebral vessels, including peak systolic blood flow velocity (Vs), end diastolic blood flow velocity (Vd) and average blood flow velocity (Vm), can be directly read on the instrument or calculated by measuring spectral envelope line. At the same time, the blood pressure was recorded, and combined with the measured blood flow velocity, the hemodynamic parameters such as cerebrovascular resistance (CVR) and cerebral blood flow (CBF) were calculated according to the formula (such as CVR = (mean arterial pressure-intracranial pressure)/CBF, in which CBF can be calculated from blood flow velocity and other parameters through a specific formula). During the inspection, it is necessary to adjust the angle and depth of the probe to obtain the best signal quality, and measure the average value for many times at different time points to improve the accuracy of the measurement. If the detection of temporal window is not ideal, we can try to check it through other parts such as orbital window or occipital window.

2.3.3 Challenges Encountered During the Measurement Process and Their Solutions During the measurement process, some patients are unable to remain quiet and relaxed. This can lead to head movement or vasospasm, causing the position of the probe during measurement to change. As a result, the measured blood flow velocity values fluctuate significantly, failing to accurately reflect the true hemodynamic state and affecting the accuracy of subsequent parameter calculations.

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Before the examination, fully explain the examination process and precautions to the patients to relieve their nervousness. For patients who have difficulty cooperating, appropriate psychological comfort can be provided or sedative medications can be used (subject to the doctor's assessment and permission). At the same time, during the measurement, use a fixation device to assist in fixing the patient's head to reduce errors caused by head movement.

If the TCD instrument is not calibrated regularly, there may be errors in the basic data it measures, directly affecting the measured values of blood flow velocity. Consequently, the hemodynamic parameters calculated based on these data lose their reliability. Moreover, if unstable conditions such as signal drift occur during the use of the instrument, it will also render the measurement results unreliable.

We have established a strict instrument calibration system. In accordance with the requirements of the instrument operation manual, the TCD instrument is calibrated and maintained regularly. Before each use, warm up and self - check the instrument to ensure it is in a stable working condition. If abnormal conditions such as signal drift are detected during the measurement, stop the measurement immediately, check the instrument connections and settings, and if necessary, recalibrate the instrument before resuming the measurement.

2.4 Statistical methods

All data were imported into SPSS 26.0 software for analysis. Categorical data were described by frequency and percentage, and the chi-square test was used. Measurement data with a normal distribution were expressed as mean±standard

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deviation, and the independent-samples t-test was applied. A model was established through Logistic regression analysis, and the rms package in R language (R4.0.0) was used to visualize the model. The Receiver Operating Characteristic (ROC) curve of the model was plotted to determine the sensitivity, specificity, Youden index, and optimal cut-off value of the model. The discrimination of the model was evaluated by the Area Under the Curve (AUC) of the ROC curve. The larger the value, the better the discrimination. The calibration of the model was evaluated using the calibration curve or Hosmer-Lemeshow test. The Decision Curve Analysis (DCA) was plotted to test the practical application efficiency of the model.

3 Results

3.1 Comparison of delayed cerebral edema rate and clinical characteristics between training set and verification set.

100 cases (47.62%) of 175 patients in the training set developed delayed cerebral edema, and 42 cases (46.67%) of 90 patients in the verification set developed delayed cerebral edema. There was no significant difference in the incidence and clinical characteristics between the training set and the verification set ($P > 0.05$), as shown in Table 1.

3.2 Comparison of clinical features between edema group and non-edema group

In the training concentration, the results of univariate analysis showed that there were significant differences in L-6, TNF-α, IL-1β, MIP-1α, CBF, CVR, HMGB1 and CRP between the patients with edema and those without edema ($P < 0.05$), as shown in Table 2.

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3.3 Risk factors analysis of delayed cerebral edema after cerebral hemorrhage

The occurrence of edema was taken as the dependent variable (0= none, 1= yes), and the factors in univariate analysis ($P < 0.05$) were taken as the covariate. Further multivariate Logistic regression analysis showed that L-6, TNF-α, IL-1β, CBF, CVR, HMGB1 and CRP were independent risk factors for bleeding ($P < 0.05$), as shown in Table 3.

3.4 Establishment of nomogram prediction model for delayed cerebral edema after cerebral hemorrhage

Based on the independent risk factors identified by multivariate Logistic regression analysis, the nomogram prediction model of delayed cerebral edema after cerebral hemorrhage was constructed, and the independent risk factors in the model were assigned, and the total score for predicting delayed cerebral edema after cerebral hemorrhage was calculated, which was reflected by the prediction probability of bleeding. The higher the total score, the higher the accuracy of predicting delayed cerebral edema after cerebral hemorrhage. See figure 1.

3.5 Evaluation and validation of the prediction model of delayed cerebral edema after cerebral hemorrhage

In the training set and verification set, the C-index index of nomogram model is 0.792 and 0.799, respectively. The average absolute error of the coincidence degree between the predicted value and the real value in the calibration curve is 0.188 and 0.182, respectively, and the results of HosmerLemeshow test are χ^2=16.582, P =0.035 and χ^2 =7.472, P = 0.487, respectively. The ROC curve is shown in the training set

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and the validation set. The AUC of the nomogram model in predicting delayed cerebral edema is 0. 794(95% CI: 0. 722-0. 865) and 0. 796(95% CI: 0. 688-0.904), and the sensitivity and specificity are 0.629 and 0. 804, respectively. See Figure 2 for the calibration curve and Figure 3 for the ROC curve.

3.6 Analysis of decision curve of nomogram prediction model for delayed cerebral edema after cerebral hemorrhage

The decision curve shows that when the threshold probability is between 0. 05 and 0. 95, the nomogram model constructed in this study has more clinical benefits in predicting postoperative bleeding. See Figure 4.

4 Discussion

Delayed cerebral edema after hypertensive cerebral hemorrhage seriously affects the prognosis of patients, and there is no effective prediction method in clinic at present. The nomogram prediction model constructed in this study is of great significance. Serum inflammatory factors play a key role in the inflammatory response after cerebral hemorrhage. As important proinflammatory factors, IL-6, TNF-α and IL-1β can activate a series of inflammatory cascade reactions[14-15]. IL-6 can induce the activation and proliferation of immune cells, promote the production of adhesion molecules by vascular endothelial cells, increase vascular permeability, and make plasma components seep into the brain tissue space, leading to brain edema [16]. TNF-α can directly damage vascular endothelial cells, destroy the integrity of blood-brain barrier and induce chemotaxis and infiltration of inflammatory cells [17].

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IL-1β activates endothelial cells in the early stage of inflammation, promotes the expression of inflammatory cell adhesion molecules, and further intensifies the inflammatory reaction. These inflammatory factors interact and jointly promote the development of brain edema [18]. The changes of hemodynamic parameters CBF and CVR are also closely related to delayed cerebral edema [19]. The decrease of CBF means insufficient perfusion of brain tissue, which will cause ischemia and hypoxia of brain tissue, energy metabolism disorder of cells, increase anaerobic metabolism, produce a large amount of lactic acid accumulation, lead to intracellular acidosis, and then cause imbalance of ion balance inside and outside cells and edema of cells [20]. At the same time, ischemia and hypoxia can also activate inflammation-related signal pathways, promote inflammatory cells to release more inflammatory mediators, and aggravate brain edema. The increase of CVR reflects the spasm or stenosis of cerebral vessels, which will hinder the normal blood perfusion, further reduce CBF, and interact with CBF, becoming an important hemodynamic factor in the occurrence of cerebral edema [21]. As an injury-related molecular model molecule, HMGB1 is released from injured cells after cerebral hemorrhage. It can activate the signal pathways of various immune cells, induce inflammatory cells to produce more inflammatory factors, such as IL-6 and TNF-α, and form positive feedback, continuously amplify the inflammatory response, increase the permeability of blood-brain barrier and promote the formation of brain edema [22-23]. As an acute phase reaction protein, the increase of CRP level reflects the activation degree of inflammatory reaction, which can activate the complement system, enhance the

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function of phagocytes, lead to vascular endothelial damage, promote the destruction of blood-brain barrier and create conditions for brain edema[24].

The nomogram model constructed in this study is excellent in forecasting efficiency. From the point of calibration and fitting degree, the C- index index is 0.792 and 0.799, respectively, which shows that the model has good prediction accuracy and discrimination ability. The average absolute error of the calibration curve is small, which is 0.188 and 0.182 respectively, indicating that the predicted value is in high agreement with the real value. Hosmer-Lemeshow test results further support the goodness of fit of the model in the training set (P = 0.035) and the verification set (P = 0.487). ROC curve analysis shows that the AUC of the training set and the validation set are 0.794 and 0.796, respectively. This result shows that the model has good discrimination and can effectively distinguish patients with and without delayed cerebral edema. The sensitivity and specificity of the model are 0.629, 0.805, 0.633 and 0.786, respectively, which shows that the model is reliable in accurately identifying whether patients will have delayed cerebral edema. Compared with traditional forecasting methods, this model has obvious advantages. Traditional methods rely on doctors' experience or single examination index, which is subjective and limited. However, this model comprehensively considers many factors closely related to the occurrence of cerebral edema, organically combines serum inflammatory factors and hemodynamic parameters, and more comprehensively reflects the complex pathophysiological state after cerebral hemorrhage. The form of nomogram is intuitive and easy to understand. Clinicians can easily calculate scores

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according to patients' specific indicators, quickly assess the risk of patients with delayed cerebral edema, and help to identify high-risk patients early in clinical practice.

Although some achievements have been made in this study, there are still some limitations. First of all, although the sample size has reached 300 cases, it may be necessary to further expand the sample size for this complex clinical situation to improve the stability and accuracy of the model. A larger sample size can better cover patients with different severity and individual differences, and reduce the errors caused by sample deviation. Secondly, there may be other factors that have not been taken into account in the process of model construction, which have an impact on delayed cerebral edema. For example, the genetic polymorphism of patients may play a role in the inflammatory reaction and the development of brain edema after cerebral hemorrhage, but this study does not involve this aspect. In addition, factors such as patients' lifestyle and drug use may also be related to the occurrence of brain edema. Future research can further improve the model and include these potential factors. In terms of research design, this study is a retrospective study. Although the relationship between related factors and delayed cerebral edema can be analyzed to some extent, there may be problems such as information bias. Prospective research can be carried out in the future to further verify the application value of the model in clinical practice, and at the same time, the whole process from cerebral hemorrhage to delayed cerebral edema can be observed more accurately, and more comprehensive data can be collected. In this study, the specific application processes, application scenarios of the

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model in clinical practice, as well as the adaptation methods to the existing clinical workflow have not been clarified yet. One of the key focuses of future research work lies in developing the nomogram into software or clinical tools. This can provide intuitive and efficient support for clinical decision - making, enhance the accessibility and practicality of the model in clinical practice, promote its true integration into the clinical decision - making process, and improve the quality of medical services.

In a word, the nomogram prediction model based on serum inflammatory factors and hemodynamics provides a new and effective tool for predicting delayed cerebral edema after hypertensive cerebral hemorrhage. Through further research and improvement, it is expected to continuously optimize the model, better serve the clinic and improve the prognosis of patients with hypertensive cerebral hemorrhage.

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Authors' contributions

Conception and design: Fuqiang Zhai and Jixin Shou. Method: Haidong Gao and Jianye Wang. Data Collection: Haidong Gao and Jianye Wang. Manuscript Writing: Fuqiang Zhai. Manuscript revision: Jixin Shou and Peng Yang. Research supervision: Jixin Shou and Peng Yang. All authors contributed to the article and approved the submitted version.

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Data Availability

The simulation experiment data used to support the findings of this study are available from the corresponding author upon request.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Fifth Affiliated Hospital of Zhengzhou University (No. KY2023126), and informed consent was obtained from all patients. This study was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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441 Table 1 Comparison of clinical characteristics between training set and verification set

clinical features		Training set (n=210)	Verification set (n=90)	statistical values	P value
Age (years)		61.70±7.22	62.31±6.87	0.682	0.496
gender	man	118（56.19）	49（54.44）	0.078	0.780
	woman	92（43.81）	41（45.56）		
BMI（kg/m2）		23.00±3.08	22.41±2.86	1.568	0.118
Course of hypertension (year)		7.88±4.01	7.06±4.21	1.590	0.113
Smoking history	have	79（37.62）	36（40.00）	0.151	0.698
	without	131（62.38）	54（60.00）		
Drinking history	have	68（32.38）	27（30.00）	0.165	0.685
	without	142（67.62）	63（70.00）		
IL-6（pg/mL）		27.41±10.32	26.48±9.46	0.735	0.463
TNF-α（ng/mL）		1.13±0.49	1.04±0.37	1.825	0.069
IL-1β（pg/mL）		13.39±4.95	14.04±5.21	1.014	0.311
IL-8（pg/mL）		17.41±6.05	17.25±6.11	0.201	0.840
IL-10（pg/mL）		14.73±3.84	14.07±2.72	1.704	0.090
MCP-1（ng/mL）		4.82±2.09	4.57±2.11	0.973	0.331
MIP-1α（ng/mL）		3.43±1.59	3.71±1.68	1.379	0.169
CBF（mL/(100g·min|)）		38.49±8.19	37.88±7.26	0.613	0.540
CVR（(mmHg·min)/mL）		1.31±0.40	1.34±0.37	0.511	0.610
HMGB1（ng/mL）		11.09±3.87	11.86±3.75	1.610	0.108
CRP（mg/L）		7.06±2.78	7.21±2.44	0.468	0.640

442 Note:BMI：Body Mass Index；IL-6：Interleukin-6；TNF-α：Tumor Necrosis Factor-α；
443 IL-1β：Interleukin-1β；IL-8：Interleukin-8；IL-10：Interleukin-10；MCP-1：Monocyte
444 Chemoattractant Protein-1；MIP-1α：Macrophage Inflammatory Protein-1α；CBF：
445 Cerebral Blood Flow；CVR：Cerebrovascular Reactivity；HMGB1：High-Mobility
446 Group Box 1 Protein；CRP：C-reactive Protein

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Table 2 Comparison of clinical characteristics between edema group and non-edema group

clinical features		Edema (n=100)	No edema (n=110)	statistical values	P value
Age (years)		62.34±7.55	61.12±6.88	1.227	0.221
gender	man	60（60.00）	58（52.73）	1.125	0.289
	woman	40（40.00）	52（47.27）		
BMI（kg/m2）		22.88±3.21	23.12±2.98	0.563	0.574
Course of hypertension (year)		8.23±4.12	7.57±3.89	1.194	0.234
Smoking history	have	44（44.00）	35（31.82）	3.312	0.069
	without	56（56.00）	75（68.18）		
Drinking history	have	38（38.00）	30（27.27）	2.753	0.097
	without	62（62.00）	80（72.73）		
L-6（pg/mL）		29.67±10.23	25.35±10.02	3.082	0.002
TNF-α（ng/mL）		1.23±0.54	1.02±0.42	3.307	0.001
IL-1β（pg/mL）		14.56±5.12	12.34±4.56	3.320	0.001
IL-8（pg/mL）		18.23±6.78	16.67±5.23	1.855	0.065
IL-10（pg/mL）		14.19±3.45	15.23±4.12	1.972	0.050
MCP-1（ng/mL）		5.13±2.12	4.56±2.03	1.955	0.052
MIP-1α（ng/mIL）		3.67±1.89	3.23±1.23	1.984	0.049
CBF（mL/(100g·min)）		36.56±8.12	40.23±7.89	3.320	0.001
CVR（(mmHg·min)/mL）		1.40±0.45	1.24±0.32	3.075	0.002
HMGB1（ng/mL）		12.03±4.32	10.23±3.21	3.423	0.001
CRP（mg/L）		7.63±3.12	6.56±2.34	2.795	0.006

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Table 3 Logistic regression analysis of risk factors of delayed cerebral edema after cerebral hemorrhage

factor	B	S.E.	Wald	P	OR	95%CI
L-6	0.054	0.017	10.167	0.001	1.056	1.021-1.092
TNF-α	1.002	0.368	7.407	0.006	2.724	1.324-5.606
IL-1β	0.109	0.037	8.766	0.003	1.115	1.037-1.198
MIP-1α	0.205	0.111	3.427	0.064	1.228	0.988-1.525
CBF	-0.065	0.021	9.316	0.002	0.937	0.899-0.977
CVR	1.292	0.433	8.906	0.003	3.639	1.558-8.498
HMGB1	0.110	0.043	6.475	0.011	1.116	1.025-1.214
MIP-1α	0.156	0.062	6.241	0.012	1.169	1.034-1.320
constant	-6.416	1.532	17.536	0.002		

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Figure Legends

Figure 1 Nomogram of delayed cerebral edema prediction model after cerebral hemorrhage. Note: X1-X7 are L-6, TNF-α, IL-1β, CBF, CVR, HMGB1 and CRP respectively.

Figure 2 Calibration curve of postoperative bleeding prediction model (A is training set and B is verification set).

Figure 3 ROC curve (A is training set and B is verification set).

Figure 4 Decision Curve (A is training set and B is verification set).

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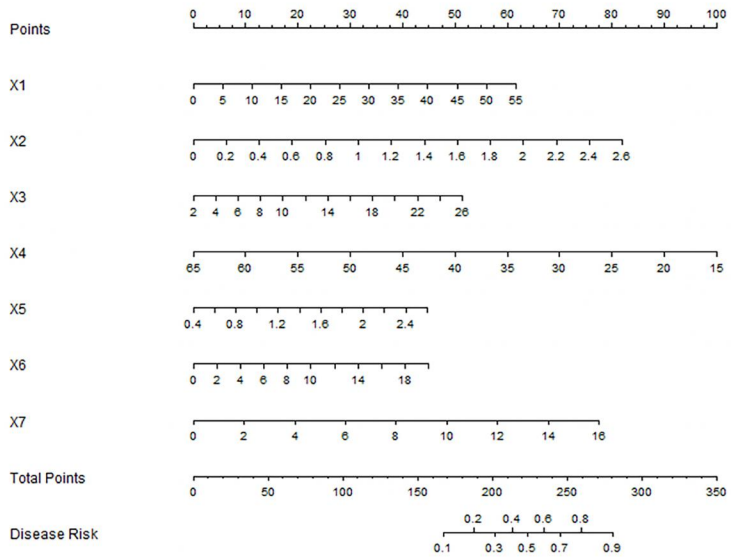
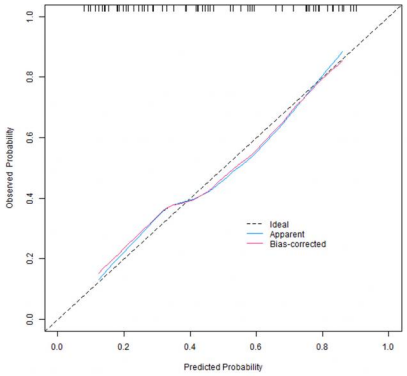
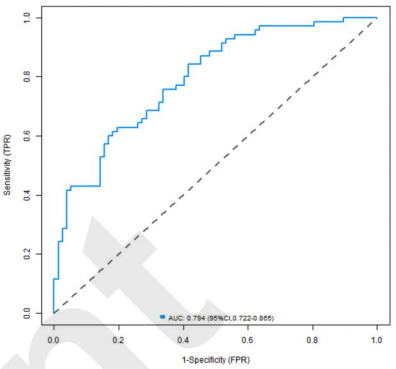

Points
0 10 20 30 40 50 60 70 80 90 100
X1
0 5 10 15 20 25 30 35 40 45 50 55
X2
0 0.2 0.4 0.6 0.8 1 1.2 1.4 1.6 1.8 2 2.2 2.4 2.6
X3
2 4 6 8 10 14 18 22 26
X4
65 60 55 50 45 40 35 30 25 20 15
X5
0.4 0.8 1.2 1.6 2 2.4
X6
0 2 4 6 8 10 14 18
X7
0 2 4 6 8 10 12 14 16
Total Points
0 50 100 150 200 250 300 350
Disease Risk
0.2 0.4 0.6 0.8
0.1 0.3 0.5 0.7 0.9


Observed Probability
Predicted Probability
Ideal
Apparent
Bias-corrected


Sensitivity (TPR)
1-Specificity (FPR)
AUC: 0.794 (95%CI:0.722-0.865)

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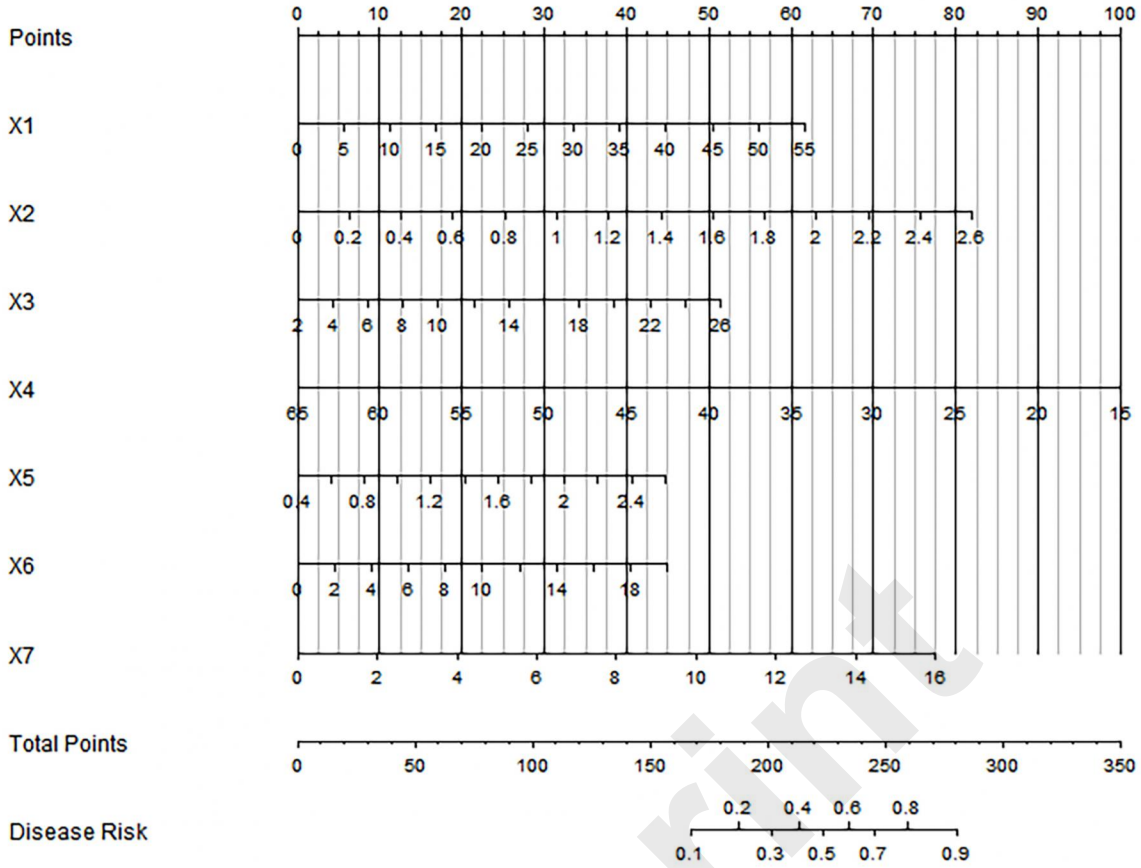

Figure 1 Nomogram of delayed cerebral edema prediction model after cerebral hemorrhage.
Note: X1-X7 are L-6, TNF-α, IL-1β, CBF, CVR, HMGB1 and CRP respectively.

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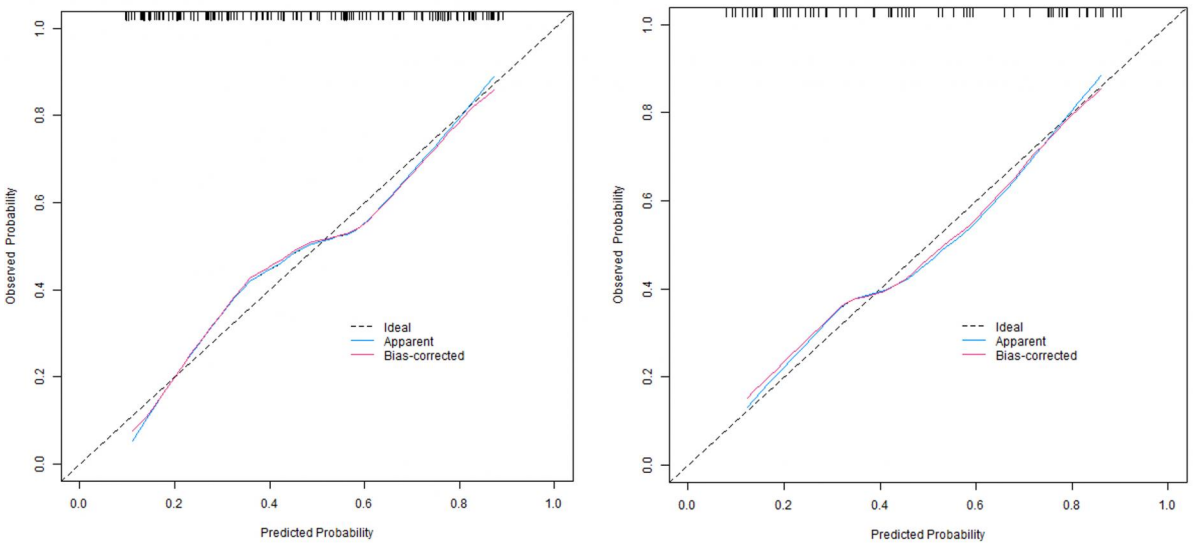

Figure 2 Calibration curve of postoperative bleeding prediction model (A is training set and B is verification set).

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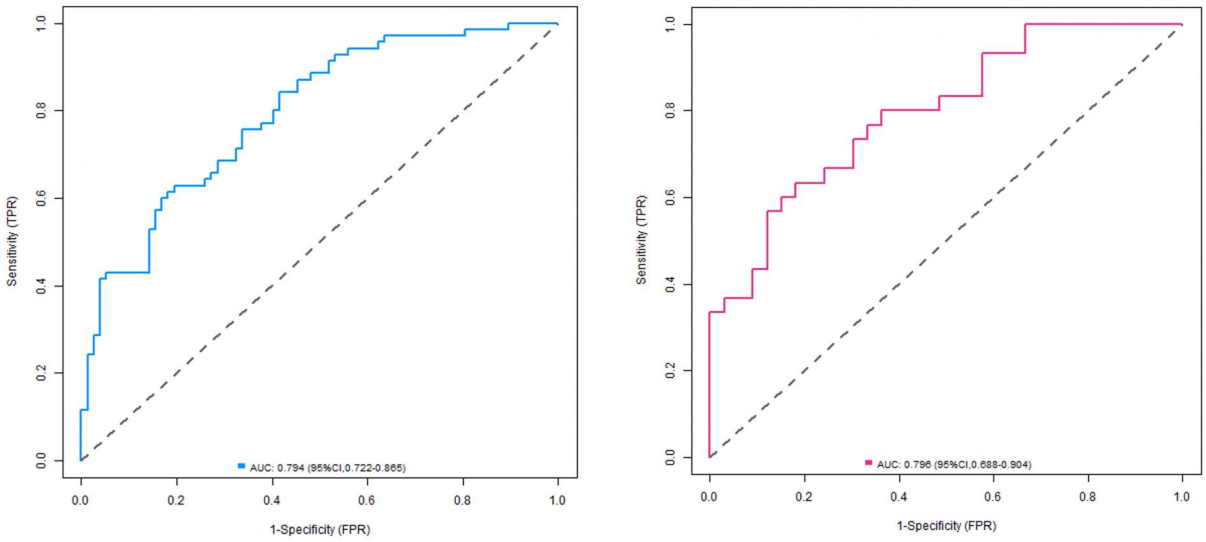

Figure 3 ROC curve (A is training set and B is verification set).

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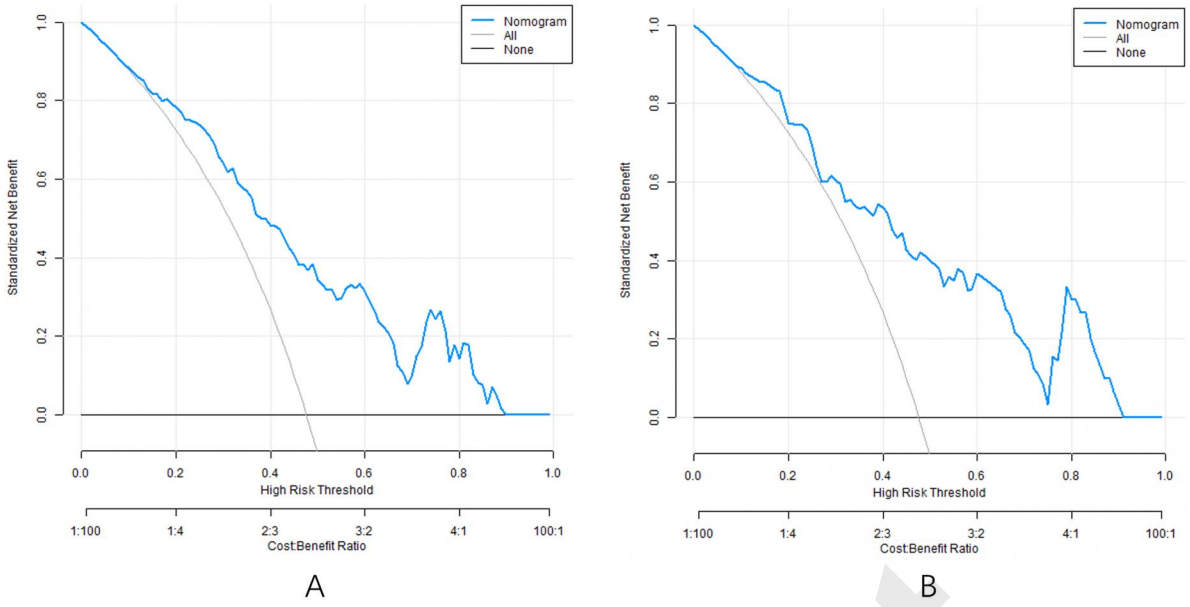

Figure 4 Decision Curve (A is training set and B is verification set).

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