A 6-month prognostic nomogram incorporating hemoglobin level for intracerebral hemorrhage in young adults

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Abstract

Objective—Intracerebral hemorrhage (ICH) is the second most common subtype of stroke with higher mortality and morbidity, and it lacks effective 6-month prognostic markers,especially in young patients.The aim of this research is to construct a newly valuable prognostic nomogram model incorporating hemoglobin level for young patients with ICH.

Method—Patients aged between 18 and 50 years with first-ever intracerebral hemorrhageselected from Tongji Hospital affiliated to Tongji Medical College of Huazhong University of Science and Technology from January1,2012 to December 31,2018.We retrospectively analyzed 565 young patients with ICH. The independent factors of prognosis were identified by univariate and multivariate logistic regression analysis. Then based on independent risk factors,a new nomogram model was further constructed and validated. Its clinical value was subsequently explored utilizing decision curve analysis and clinical impact curve.

Results—A total of 565 patients were enrolled in this study.There were 117 patients (20.7%) who developed unfavourable prognosis. Infratentorial lesion(adjusted odds ratio [aOR]=3.708,95%confidence interval [CI],1.490-9.227; P=0.005)was most significant with unfavourable outcome.Age([aOR]=1.054;95%CI,1.014-1.096;P=0.008),hematoma volume(aOR=1.014,95%CI,1.002-1.027;P=0.024),hemoglobin(aOR=0.981,95% CI,0.969-0.993;P=0.002),blood glucose(aOR=1.135,95%CI,1.037-1.241; P=0.005)and NIHSS(aOR=1.105,95%CI,1.069-1.141;P<0.001) were independent rish factors.Based on these 6 factors,a reliable nomogram was constructed for the prediction of unfavourable prognosis in our study(C-index=0.791). Decision curve analysis and clincal impact curve showed showed an increased net benefit for utilizing the nomogram.

Conclusion—The hemoglobin level at admission may be an easily overlooked factor in clinical work.This new nnomogram model could be a promising and convient tool to predict the early functional prognosis of in young people with ICH.In addition, more prospective multicenter studies are needed to cestimate these findings.

Summary

In this study, we recruited consecutive patients of acute ICH from January 2012 to December 2018 in the neurology department of Tongji Hospital affiliated with Tongji Medical College of Huazhong University of Science and Technology and followed up for at least one year unless the occurrence of a death. We evidenced that hemoglobin level may be a overlooked factor for ICH patients.And we established a convient and novel nomogram to evaluate 6-month unfavourable prognosis in young patients with ICH.The performance of nomogram model was better than ICH-FOS and ICH score.

1. Introduction

Intracerebral hemorrhage (ICH) is a devastating stroke subtype,accounts for 10–27% in all strokes. [1]The overall incidence of ICH is about 24.6 affected individuals per 100,000 person-years,and it increases with age.[2]Due to the high mortality rate and disability rate of ICH[3], more attention should be paid to functional outcome of young adults to avoid consequent increase of the socioeconomic burden.Several studies reported only 34.9%–39.9% of the young patients reach a favourable short-term outcome,and 39.0–59.5% of patients had attained a long-term favourable outcome.[4–8]

Many studies conducted in the young adults had explored numberous common risk factors related to functional outcome,such as age,increasing initial NIH Stroke Scale scores and ventricular extension of the haemorrhage.[9–11]Meanwhile,a meta-study found hemoglobin is closely associated with mortality in patients with intracerebral hemorrhage,suggests that it may be a neglected blood indicator.[12]However, none of them failed to integrate both those common risk factors and hemoglobin -related data into a systematic assessment methodology applied to young adults.Therefore, such a systematic prognostic model applied to young adults is needed to risk-stratification guidelines for treatment and rehabilitation.

At present,nomogram is a useful statistical tool for assessing and calculating the precise risk of individual patients for both short-term and long-term outcomes.[13]While,there is no nomogram that has been practiced in young adults with intracerebral hemorrhage.To better distinguish important and overlooked predictors of unfavourable outcomes, we conducted a retrospective study that covered multiple dimensions of risk factors,and established a novel and comprehensivel nomogram model.And decision curve analysis (DCA) and clinical impact curve(CIC)were used to validated the clinical usefulness and applicability net benefits of the model.

2. Materials And Methods

2.1 Patients

This study retrospectively analyzed the nontraumatic first-ever ICH patients between 18 and 50 years of age treated in Tongji Hospital affiliated to Tongji Medical College of Huazhong University of Science and Technology from January1,2012 to December 31,2018.ICH was diagnosed according to the WHO criteria and confirmed by brain noncontrast CT.[14]We excluded ICH patients caused by trauma,tumours,primary subdural/epidural/subarachnoid hemorrhage,and post infarct hemorrhagic transformation.Our study was approved by the institutional ethics Committee of Tongji Medical College of Huazhong University of Science and Technology.The enrollment flow chart is shown in Fig. 1.

2.2 Data collection

Baseline data including age,sex,history of diseases,smoking and drinking status,hematoma features,laboratory test data,systolic and diastolic blood pressure(BP),treatment and clinical assessment scales on admission were collected.Hematoma features were consisted of hematoma volume(caculated for ABC/2 method[15]),hematoma location,intraventricular extension and subarachnoid space extension.Laboratory test data included WBC counts,hemoglobin level,PLT counts,liver function,kidney function and blood glucose on admission.Treatment means conservative treatment and surgical treatment,including ventricular drainage ,craniotomy or minimal invasive hematoma evacuation.

When patients were on admission,we recorded 4 clinical assessment scales which contained National Institutes of Health Stroke Scale (NIHSS),ICH score, GCS(Glasgow Coma Scale) and ICH-FOS score. [16–18]

Patients were followed through the death date or the last follow-up date (August,31, 2019) by telephone interview.We use the modified Rankin Scale (mRS) to evaluate the patient's outcome at 6-month.favourable and unfavourable functional outcome were defined as mRS $\leq$ 3 and mRS 3, respectively.

2.3 Statistical analysis

Continuous variables were reported as the mean ± SD, median (IQR).Categorical variables were reported as n(%).Differences between the two groups were assessed by the Mann-Whitney U-test or Student t test for continuous variables and Fisher's exact test or the χ 2 test for categorical variables.All variables with a probability value < 0.1 in the univariate analysis were entered into a multivariate logistic regression analysis.

The nomogram model was established on those pre-predictors in multivariate analysis with package "rms" in R.To verify the performance of the nomogram model,calculation of the area under curve (AUC) of the receiver-operating characteristic(ROC)and Harrell's concordance index (C-index) were conducted.Calibration curves were constructed to evaluate the model's predictive accuracy by comparing the predicted probability with the observed probability in our study. The calibration curve was regarded as appropriate if curve on the calibration plot was close to a 45°diagonal line.

Decision curve analysis(DCA) and clinical impact curve(CIC) was conducted to quantified the net benefits of different threshold proabilities to evaluate the clinical value of the nomogram.The CIC was developed using the bootstrap resampling method (times = 1,000).

The statistical analysis was carried out using SPSS version 26.0(IBM Corporation, Armonk, NY, USA)and the statistical software package R,version 3.5.2(R Development Core Team, Auckland, New Zealand).P value < 0.05 was indicated a statistically significant difference.

3. Results

3.1 Patient Characteristics

In this cohort,a total of 565 subjects were retrospectively recruited((male: 68.1%; mean age:42.6 ± 7.1years; Fig. 1).The baseline data including clinical, history of diseases, and laboratory data of the patient cohort was exhibited according to the different clinical outcomes (Table 1).We compared the baseline characteristics and mRS scores at 6-month,favourable and unfavourable functional outcome were defined as mRS $\leq$ 3 and mRS>3. At the significant level of $p = 0.05$, age,gender,hematoma volume,history of hypertesion,blood glucose,WBC counts,hemoglobin,AST and surgical treatment were related with unfavourable outcome (Table 1).For the prognostic scores, NIHSS,GCS,ICH score and ICH-FOS score divided cases into different functioncal outcome groups with highly statistically significant.

Table 1
Baseline characteristics and univariate analysis to identify the independent predictors of functional outcome in young adults at 6month

	All patients (n = 565)	Favourable outcome (n = 448)	Unfavourable outcome (n = 117)	P value
Demographics				
age (ys)	42.6 ± 7.1	42.2 ± 7.3	44.2 ± 6.5	<0.001*
Male sex	385(68.1%)	317(70.8%)	68(58.1%)	0.009*
History of diseases				
hypertension	331(58.6%)	253(56.5%)	78(66.7%)	0.046*
Diabetes mellitus	29(5.1%)	23(5.1%)	6(5.1%)	0.998
Coronary heart disease	11(2.0%)	9(2.0%)	2(1.7%)	1
Atrial fibrillation	2(0.4%)	25(5.6%)	3(2.6%)	0.306
Oral anticoagulation	8(1.4%)	5(1.1%)	3(2.6%)	0.459
Previous stroke	45(8.0%)	35(7.8%)	10(8.5%)	0.795
Lifestyle				
Heavy smoking	178(31.5%)	143(31.9%)	35(29.9%)	0.678
Alcohol abuse	157(69.6%)	130(29%)	27(23.1%)	0.201
Hematoma volume(ml)	13.7(5.8–29.6)	12.1(4.9–26.3)	21.6(8.4–41.4)	<0.001*
Hematoma location				
Lobar lesion	164(29.0%)	127(28.3%)	37(31.6%)	0.487
Basal ganglion lesion	145(25.66%)	113(25.2%)	32(27.4%)	0.639
Infratentorial lesion	38(6.73%)	26(5.8%)	12(10.3%)	0.087
Multiple hemorrhages	6(1.0%)	4(0.9%)	2(1.7%)	0.443
Intraventricular extension	146(25.8%)	109(24.3%)	37(31.6%)	0.304
Subarachnoid space extension	45(8.0%)	33(7.4%)	12(10.3%)	0.109
Systolic blood pressure (mmHg)	152(135–171)	152(133–171)	152(137–177)	0.606

Abbreviations: AST,aspartate aminotransferase;NIHSS, National Institutes of Health Stroke Scale;GCS,Glasgow Coma Scale.

	All patients (n = 565)	Favourable outcome (n = 448)	Unfavourable outcome (n = 117)	P value
Diastolic blood pressure (mmHg)	94(81–107)	94(81–107)	94(82–108)	0.926
Laboratory data at admission				
Blood glucose (mmol/L)	6.2(5.3–7.5)	6(5.2–7.2)	7.2(5.8–9.3)	<0.001*
WBC(10^9/L)	10.0(7.4–12.9)	9.7(7.3–12.3)	11.9(8.5–15.1)	<0.001*
hemoglobin	144(132–154)	144(133–154)	143(126–151)	0.05*
PLT(10^9/L)	207(175–245)	205(175–245)	207(162–249)	0.997
AST(U/L)	19(15–26)	19(15–24`)	22(16–31)	0.003*
eGFR, mL/min/1.73m^2	102.4(82.2-114.2)	102.7(83.5-115.7)	97.7(67.2-112.3)	0.105
Surgical treatment	172(30.44%)	123(27.5%)	49(41.9%)	0.003*
GCS	14(10–15)	14(12–15)	10(7–14)	<0.001*
NIHSS	11(4–16)	9(3–15)	18(11–25)	<0.001*
ICH score	1(1–2)	1(1–2)	2(1–3)	<0.001*
ICH-FOS	3(1–5)	3(1–5)	6(3–8)	<0.001*
Abbreviations: AST,aspartate aminotransferase;NIHSS, National Institutes of Health Stroke Scale;GCS,Glasgow Coma Scale.				

3.2 Development and Validation of the Nomogram

In multivariate logistic regression analysis (Table 2), infratentorial lesion(adjusted odds ratio [aOR] = 3.708,95%confidence interval [CI],1.490–9.227; P = 0.005)was most significant with unfavourable outcome.Age ([aOR] = 1.054; 95%CI,1.014–1.096;P = 0.008),hematoma volume(aOR = 1.014,95% CI,1.002–1.027;P = 0.024),hemoglobin(aOR = 0.981, 95% CI,0.969–0.993; P = 0.002),blood glucose (aOR = 1.135, 95% CI,1.037–1.241; P = 0.005)and NIHSS(aOR = 1.105,95%CI,1.069–1.141;P < 0.001) remained significant($p < 0.05$)after adjusting for confounders.These variables were independent of each other.

Table 2
Multivariable logistic regression analysis to identify the independent predictors of functional outcome in young adults at 6-month

	OR	95%CI	P-value
Age	1.054	1.014–1.096	0.008
Hematoma volume	1.014	1.002–1.027	0.024
Blood glucose	1.135	1.037–1.241	0.005
Infratentorial lesion	3.708	1.490–9.227	0.005
Hemoglobin	0.981	0.969–0.993	0.002
NIHSS	1.105	1.069–1.141	<0.001*
*P < 0.05			
Abbreviations:NIHSS, National Institutes of Health Stroke Scale.			
Multivariable logistic regression adjusted for age,male sex,history of hypertension, hematoma volume,infratentorial lesion,WBC count,blood glucos,PLT,AST,eGFR,systolic blood pressure,suigical treatment,NIHSS and GCS.			

Base on these above six independent risk factors, we estabilised a nomogram to estimate prognosis for intracerebral hemorrhage in young adults at 6-month(Fig. 2).Validation of the nomogram was accomplished by 200 bootstrap.For the logistic binary variable model,the C-index is equivalent to the area under the ROC curve.The C-index of nomogram was 0.791 (95% CI, 0.743–0.840) higher than the AUC of NIHSS 0.742 (95% CI,0.688–0.795),ICH-FOS 0.764(95% CI,0.691–0.801) and ICH score 0.672(95% CI,0.619–0.726)(Fig. 3).Furthermore,the calibration curve revealed fully fit of the nomogram to predict the actual-risk of a unfavourable outcome,indicated that the prediction results were accurate(Fig. 4).

3.3 Decision Curve Analysis and Clinical Impact Curve for the Nomogram

In the last step,DCA showed that,between the threshold probabilities of 10–60%, the net benefit for nomogram model was approximatly larger then ICH score and ICH-FOS (Fig. 5). Based on the DCA,the outcome was verified by a clinical impact curve(Fig. 6).

4. Discussion

To our knowledge, the present study is the first to establish a scientific and reasonable nomogram model to predict a 6-month prognosis among young adults with ICH.In this consecutive series of young individuals with ICH, age,hematoma volume,bood glucose,infratentorial lesion,hemoglobin and the NIHSS were significant prognostic factors in the univariate logistic regression analysis and confirmed as an independent risk factor for functional prognosis.Based on those predicting parameters, we constructed a nomogram model for evaluating. We incorporated several common clinical factors and an easily overlooked blood indicator into our model.The performance of the present nomogram was strictly assessed and internally validated,and its net benefit was also explored by DCA and CIC, compared with other prognostic scores commonly used in clinical practice.In addition, our study demonstrates that clinical applicability of this nomogram is feasible for ICH in young adults.

Hemoglobin level is a part of automated blood analysis of blood cells at no additional cost, establishing an important link with the undesirable prognosis of stroke.[19]In recent years, several studies have found a positive correlation between anemia and higher mortality in stroke patients.[12,20]In 2018,a meta-analysis identified seven cohort studies with 7,328 ICH patients, including 1,546 patients with anemia,revealed that anemia was associated with an increased risk of poor outcome in patients with ICH (OR = 2.29 for 3-month outcome,95% CI 1.16 to 4.51; OR = 3.42 for 12-month outcome,95% CI 0.50 to 23.23).[12]Another recent study reported a large meta-analysis that pooled data from the ATACH-2, FAST, and ERICH studies,also found higher admission Hb levels were associated with better outcomes.[20]David J. Roh et al reported that such a result may occur because theses patient had a hematologic disorder that causes the hematoma,and eventually a poor prognosis.[21]Lower erythrocyte counts may result in less efficient radial transport of platelets toward the vessel wall, preventing the platelet endothelial interaction vital to hemostasis initiation. In addition, erythrocytes themselves may be implicated in hemostasis through their adhesion to the injured vessel wall in addition to their interaction withplatelets and fibrinogen leading to blood clot contraction.[22]David J. Roh et al also suggested hyperacute transfusion of pRBC can be considered in preventing the early occurrence of HE to improve outcomeBut the timing of red blood cell transfusions still needed more research to be clear.[21]

Previous studies suggested hyperglycemia was associated with mortality in ICH patients.[23,24] A meta-analysis of 16 studies reinforced this view: high blood glucose was significantly associated with poor functional outcome in ICH patient.[25]previous animal studies identified an evident association between hyperglycemia and perihematomal neuronal apoptosis in rat models.[26] In ICH models, hematoma with high blood glucose was found to lead to neurological injury and decreased autophagy.[27] High blood glucose can increase superoxide production in ICH induced by tissue plasminogen activator.[28]

A 2013 study showed that age could affect the prognosis of intracerebral hemorrhage in young people, and the INTERACT-2 study also showed that age is a strong predictor of a poor prognosis for intracerebral hemorrhage, consistent with the results of this study.[1110]The reason for this may be that young people have better physical condition than the old. Their vascular atherosclerosis is mild, and they can establish collateral circulation in a short period of time, so that angioedema is relatively mild, neurological deficits are lighter, and young patients have a strong sense of health care and actively carry out secondary prevention.[29]

The GCS and NIHSS scores are commonly used in stroke scales, with GCS scores assessing a patient's state of consciousness, and NIHSS scores assessing not only the state of consciousness but also the patient's neurological deficits.A 2003 study found that the NIHSS score was superior to the GCS score in predicting the prognosis of patients with intracerebral hemorrhage, which was consistent with the results of the univariate analysis of this study that the NIHSS score and GCS score affected the prognosis at the time of univariate analysis, while the NIHSS score was independent of the influencing factors in the multivariate regression analysis.[30]

We found that certain outcomes were consistent with former studies. Using continuous variables,a nomogram cooperating hemoglobin with acceptable discrimination (C-index = 0.791) and calibration was established for predicting an unfavourable outcome, and it seems to possess more power efficiency than currently utilized prognostic tools.The decision curve suggested that when the probability ranges from 20–40%,the net benefits of the nomogram were higher than ICH-score and ICH-FOS. Moreover, the outcome was verified by a clinical impact curve.

In this study,the nomogram has novelity and certain advantages. Firstly, we integrated and internally validated a new nomogram model that combined clinical score and laboratory data. The nomogram can be employed to predict early functional prognosis with high accuracy (AUC 0.791). Secondly, the DCA and CIC were used to evaluate the clinical performance of the new model cretively. Finally, the data required for the nomogram model is readily available for clinical work,without adding additional workload.

However, there were still some limitations. Firstly,it was a retrospective study in a single center and not a randomized controlled trial (RCT).As a results, selection bias caused by single-center data may result in a lack of representation of results.And accuracy of clinical valuation may be attenuated by its retrospective nature.External validations in other institutions is warranted.Moreover,our model covered many types of clinical data variables, but the lacked detailed neuroimaging and therapeutic data that may lead to an unavoidable systemic bias to weaken its discriminative performance of the nomogram model.Finally,we have collected a limited number of cases and have a 30% loss-of-follow rate,that may affect the credibility of the results.Despite these limitations, we made a first attempt to establish and validate a nomogram model to predict a 6-month functional prognosis in young ICH patients.

5. Conclusion

In summary, the study shows the age,hematoma volume,bood glucose,infratentorial lesion,hemoglobin and the NIHSS are associated with unfavourable outcome of young ICH patients. The hemoglobin level at admission may be an easily overlooked factor.

The nomogram constructed from these data could be a promising and convient tool to predict the early functional prognosis of in young people with ICH.In addition, more prospective multicenter studies are needed to cestimate these findings.

Abbreviations

ICH=intracerebral hemorrhage; NIHSS=National Institutes of Health Stroke Scale score;GCS=Glasgow Coma Scale;DCA=decision curve analysis;CIC=clinical impact curve;mRS=modified Rankin Scale;AUC=area under curve.

Declarations

Ethics approval and consent to participate

The studies involving human participants were reviewed and approved by the Ethics Committee of Tongji Medical College Huazhong University of Science and Technology. The patients/participants provided their written informed consent to participate in this study.We stated that all methods were performed in accordance with the 1964 Helsinki declaration and its later amendments.

Consent for publication

All the data involved in this article was agreed to be published by the participants.

Availability of supporting data

The datasets presented in this article are not readily available because further data mining is ongoing. Requests to access the datasets should be directed to wangfurong.china@163.com.

Competing interests

All authors report no conflicts of interest.

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Authors' contributions

Yuyan Yang: Data curation (equal); Methodology (equal); Writing original draft(lead) Shanshan Huang: Methodology (equal); Yuchao Jia:Data curation (supporting). Guini Song: Data curation (supporting). Xiaodong Ye: Data curation (supporting). Kai Lu: Data curation (supporting). Guo Li: Conceptualization (lead); Data curation (equal); Funding acquisition (equal); Supervision (equal);. Furong Wang: Conceptualization (equal); Funding acquisition (equal); Project administration (lead); Supervision (lead):Suiqiang Zhu: Conceptualization (equal); Funding acquisition (equal); Project administration (lead); Supervision (lead).

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Disclosures

None.

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Figures

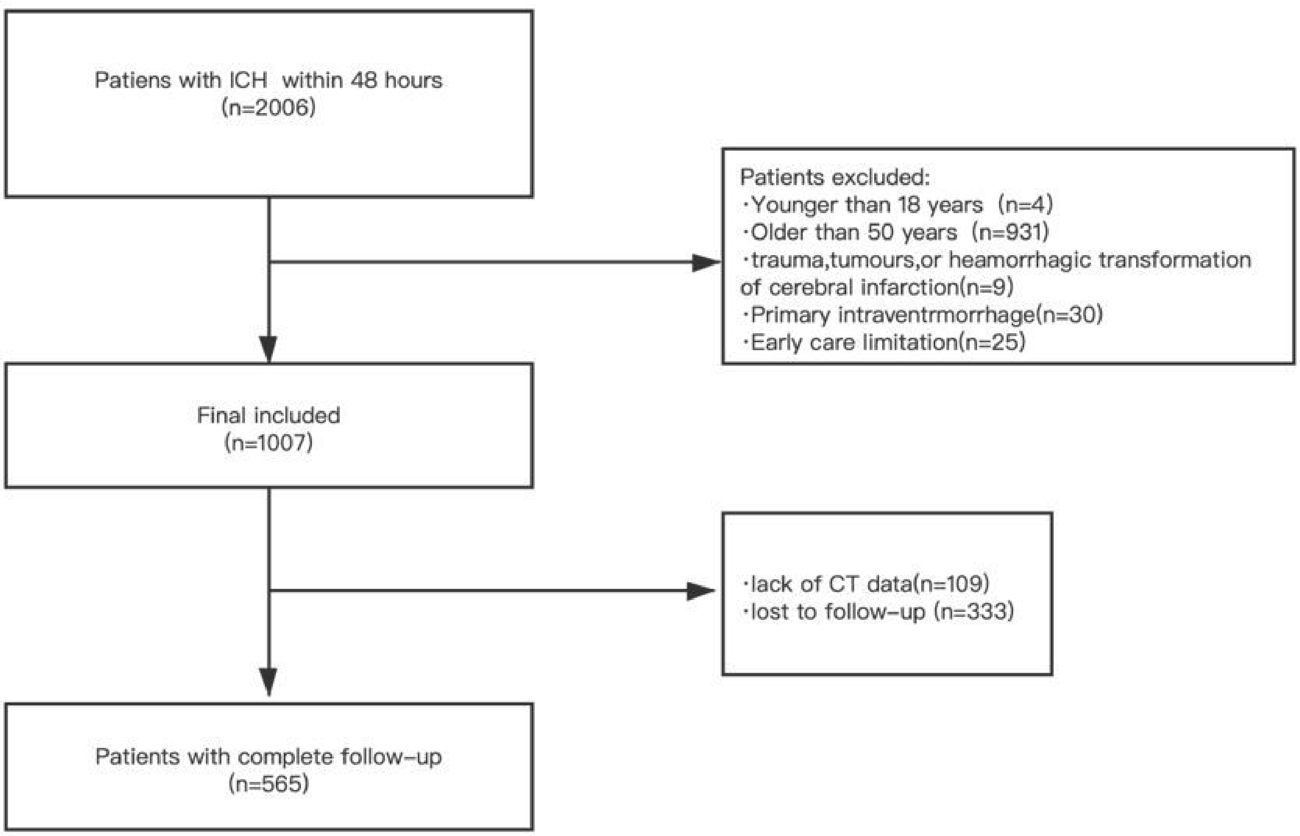

Figure 1

Enrollment flow chart of study cohort.

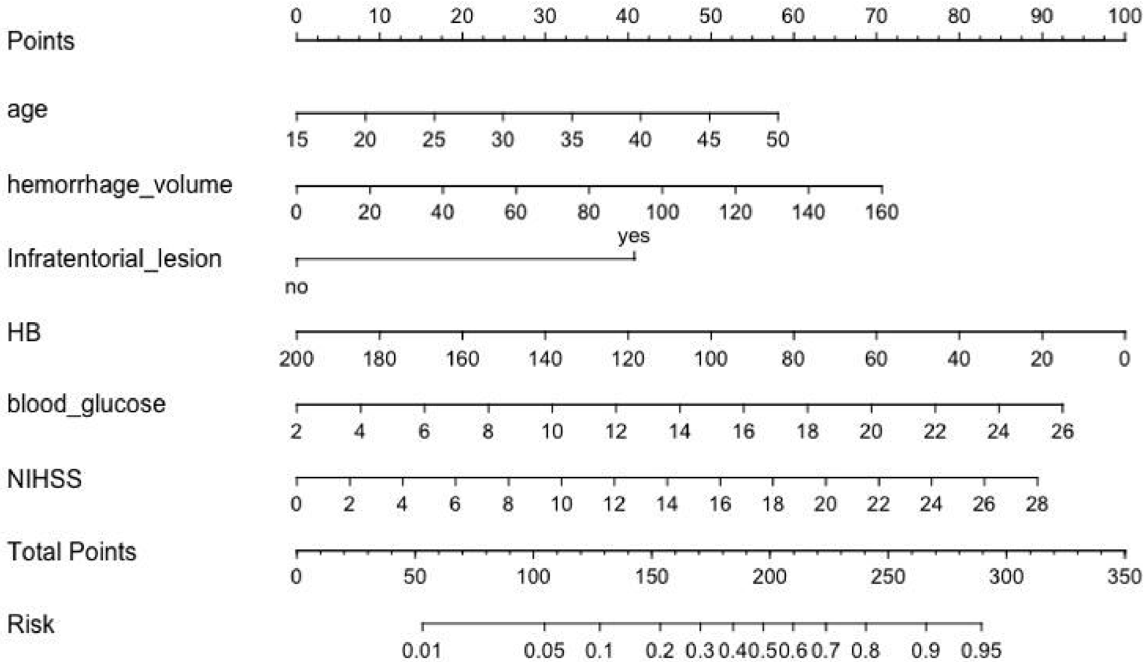

Figure 2

Nomogram of the study population to predict poor functional outcome of intracerebral haemorrahage at 6-month

Abbreviations:NIHSS, National Institutes of Health Stroke Scale;HB,hemoglobin level.

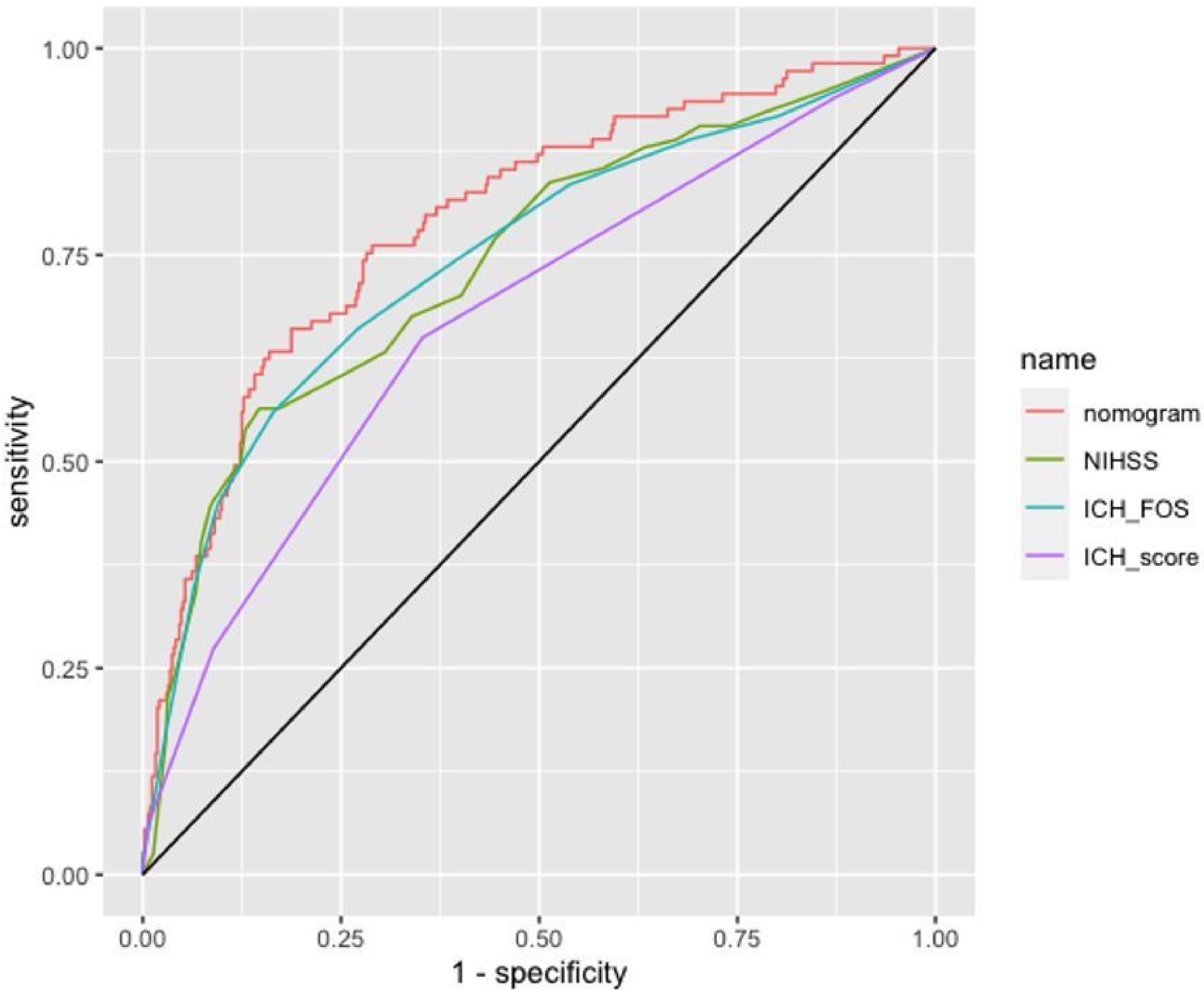

Figure 3

Area under the receiver operating characteristic curve (AUROC), which is representative of predictive accuracy,compared with NIHSS,ICH-FOS and ICH score.

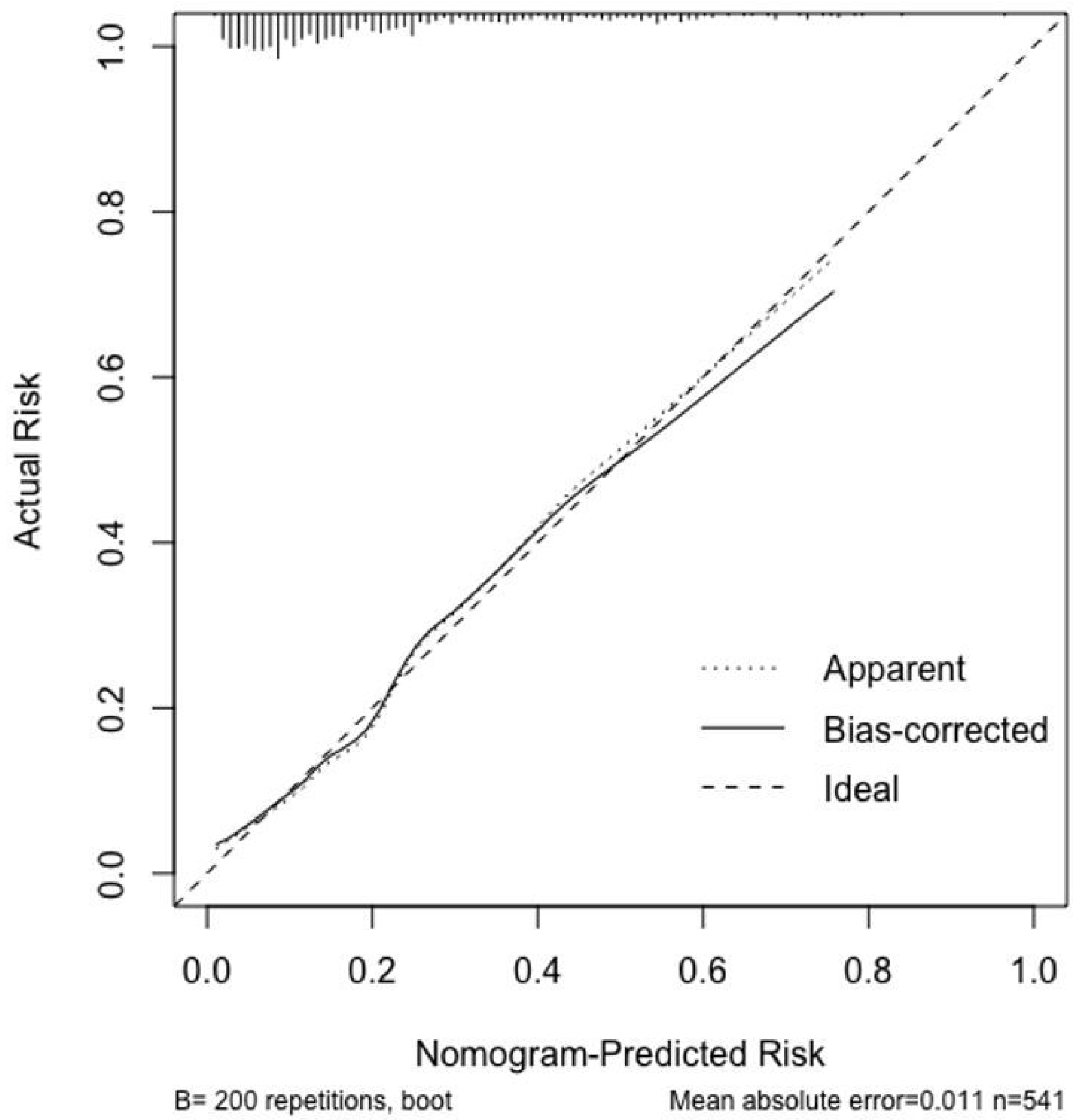

Figure 4

Calibration curve for the nomogram. Dashed line is reference line where an ideal nomogram would lie. Dotted line is the performance of nomogram, while the solid line corrects for any bias in nomogram

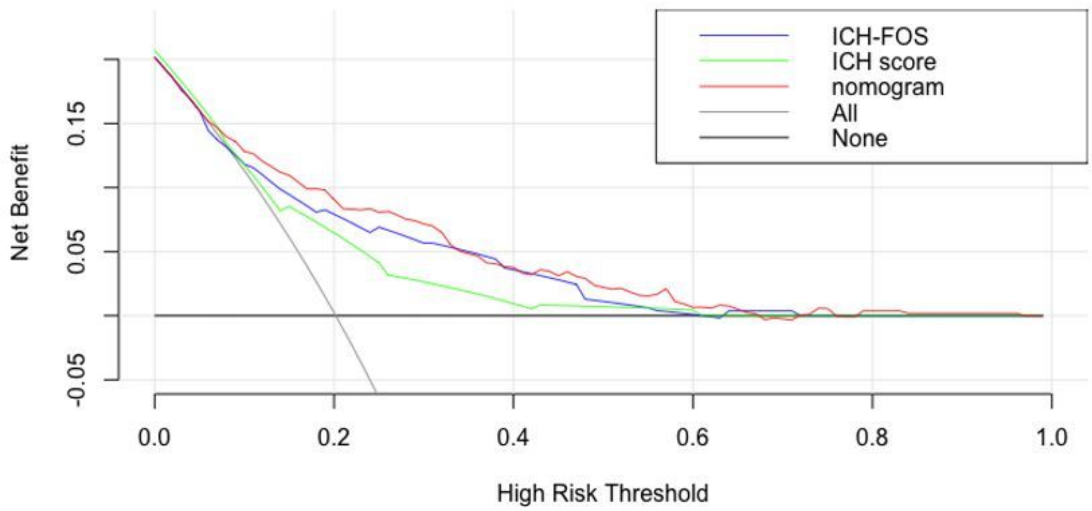

Figure 5

Decision curve analysis of the nomogram compared with NIHSS,ICH-FOS and ICH scoreX-axis indicates the threshold probability for critical care outcome and Y-axis indicates the net benefit.

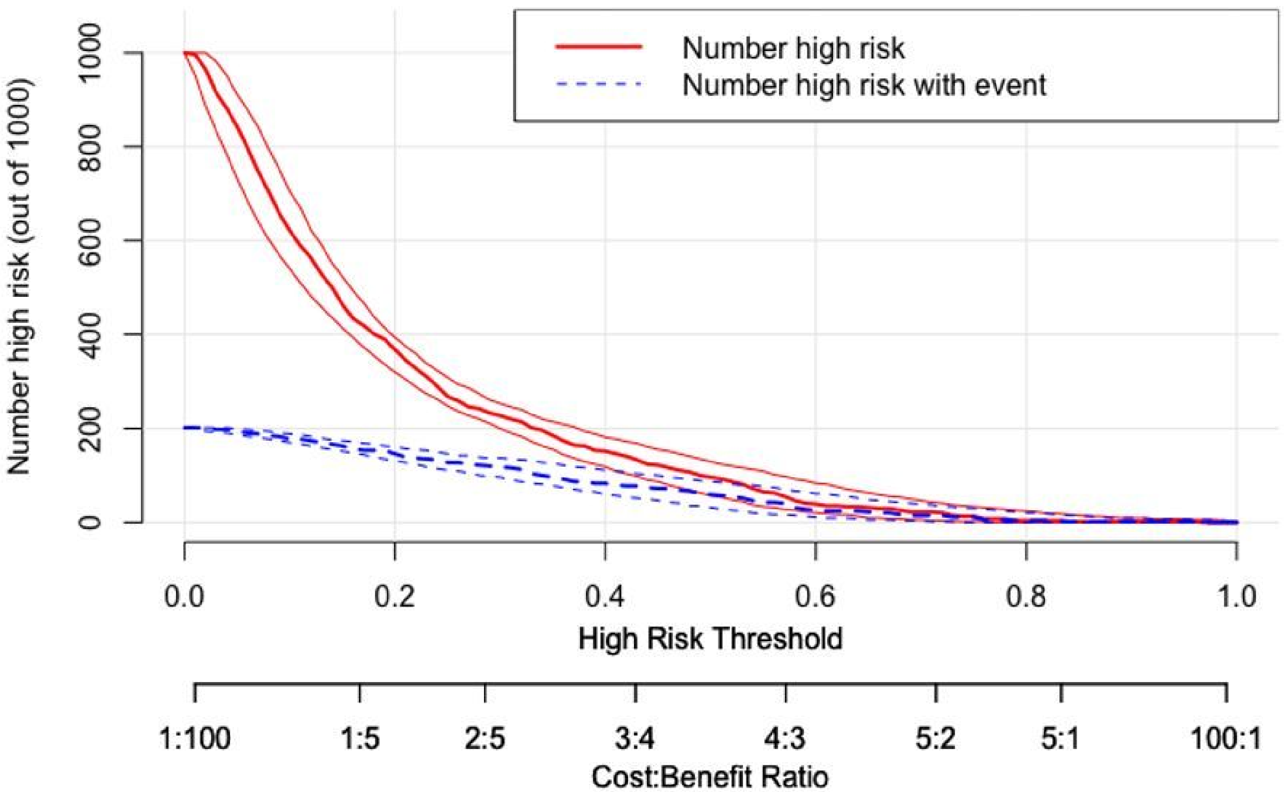

Figure 6

Clinical impact curve (CIC) of nomogram model. The red curve (number of high-risk individuals) indicates the number of people who are classified as positive (high risk) by the model at each threshold probability; the blue curve (number of high-risk individuals with outcome) is the number of true positives at each threshold probability. CIC visually indicated that nomogram conferred high clinical net benefit and confirmed the clinical value of the nomogram model