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ORIGINAL RESEARCH

A Novel Nomogram to Predict Symptomatic Intracranial Hemorrhage in Ischemic Stroke Patients After Intravenous Thrombolysis

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Objective: This study aimed to create and validate a novel nomogram to predict the risk of symptomatic intracranial hemorrhage (sICH) in patients with acute ischemic stroke (AIS) who underwent intravenous thrombolysis (IVT).

Methods: In this retrospective study, 784 patients with AIS who received IVT were enrolled. The patients were randomly divided into two groups: a training set (n=550, 70%) and a testing set (n=234, 30%). Utilizing multivariable logistic regression analysis, relevant factors for the predictive nomogram were selected. The performance of the nomogram was evaluated using various metrics, including the area under the receiver operating characteristic curve (AUC-ROC), the Hosmer-Lemeshow goodness-of-fit test, calibration plots, and decision curve analysis (DCA).

Results: Multivariable logistic regression analysis showed that specific factors, including National Institutes of Health Stroke Scale (NIHSS) scores, Early infarct signs (EIS), and serum sodium, were identified as independent predictors of sICH. Subsequently, a nomogram was constructed using these predictors. The AUC-ROC values of the nomogram were 0.864 (95% CI: 0.810–0.919) and 0.831 (95% CI: 0.770–0.891) in the training and the validation sets, respectively. Both the calibration plots and the Hosmer-Lemeshow goodness-of-fit test showed favorable agreement in both the training and the validation sets. Additionally, the DCA indicated the practical clinical utility of the nomogram.

Conclusion: The novel nomogram, which included NIHSS, EIS and serum sodium as variables, had the potential for predicting the risk of sICH in patients with AIS after IVT.

Keywords: ischemic stroke, symptomatic intracranial hemorrhage, thrombolysis, nomogram

Introduction

Acute ischemic stroke (AIS) continues to be a major global cause of mortality and disability, imposing a significant burden on both families and society.[1,2] Currently, the most effective treatment for ischemic stroke within 4.5 hours of onset is intravenous thrombolysis (IVT) using recombinant tissue-plasminogen activator (rt-PA).[3] However, some patients may experience a worsened condition due to symptomatic intracerebral hemorrhage (sICH) after rt-PA thrombolysis.[4,5] Consequently, it becomes imperative to identify patients at risk of post-thrombolysis sICH for better management.

Numerous scoring systems[6–10] are available to predict sICH risk following thrombolysis. However, many of these models transform continuous variables into categorical ones, leading to potential information loss.[6–9,11] Although several prognostic nomograms have been developed for sICH events in AIS patients undergoing thrombolysis,[12–20] some limitations remain. Firstly, certain examinations are either unavailable in most medical centers or require a long time for the results to be obtained,[12–16] limiting their widespread applicability. Secondly, many studies overlook the impact of baseline neuroimaging before IVT.[16–20] Admittedly, Yang[13] has already integrated early infarct sign (EIS) on non-contrast computed tomography (NCCT) before IVT into their prognostic nomogram. Nonetheless, given the various types of early brain infarction signs on NCCT,[21] subgroup analysis is meaningful.

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The objective of this study is to identify the independent pre-thrombolytic factors associated with sICH in stroke patients receiving IVT. Additionally, the goal is to develop and validate a nomogram that combines neuroimaging and readily available laboratory variables to accurately predict the likelihood of sICH following IVT in ischemic stroke patients.

Materials and Methods

Study Design and Participants

Consecutive ischemic stroke patients who underwent IVT treatment in the department of emergency at Dongyang People's Hospital between July 1, 2017, and April 30, 2023, were included in this retrospective observational study. The study was ethically approved by the Ethics Committee of Dongyang People's Hospital (Dong Ren Yi 2023-YX-234) and adhered to the principles of the Declaration of Helsinki. Informed consent from patients was waived due to the retrospective observational design. During the data collection and analysis process, patient's names and other identity information were concealed to fully protect patient privacy.

Patients received thrombolytic therapy in the emergency department and were subsequently admitted to the neurology ward after treatment. Within 22–36 hours after thrombolysis, no anticoagulants or antiplatelet drugs were administered. Blood pressure was maintained within 180/100 mmHg during this period, and oral or intravenous antihypertensive treatment was provided if blood pressure exceeded this range. Blood glucose levels were kept between 7.7–10.0 mmol/L during this period. If blood glucose levels fell below this range, oral or intravenous glucose solution supplementation was given, and if blood glucose levels rose above this range, insulin or oral antidiabetic medication was administered to control blood glucose. During this period, the patients are placed under 24-hour electrocardiogram monitoring and instructed to remain in bed for rest. The study enrolled participants based on the following inclusion criteria: (1) age 18 years or older, (2) diagnosed with acute ischemic stroke without any evidence of intracranial hemorrhage on NCCT, and (3) patients treated with alteplase thrombolysis within 4.5 hours from the onset of stroke symptoms. Exclusion criteria consisted of: (1) patients who underwent endovascular treatment after IVT, and (2) patients with incomplete clinical data.

Clinical Data Collection

At admission, demographic characteristics, medical history, and clinical data were collected. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) scores. Laboratory data, including baseline blood glucose, neutrophil-to-lymphocyte ratio (NLR), and platelet count and other relevant parameters, were also recorded. The method for obtaining the patient's vascular risk factors is through inquiries with the patients and their family members. All clinical data and test results were obtained prior to thrombolysis. The early infarct signs on NCCT were categorized into four groups. Two experienced clinicians independently reviewed the cerebral NCCT scans, and the agreement between them for early infarct signs was evaluated using the kappa statistic, yielding a value of 0.783. Disagreement was resolved through discussion.

The classification of early infarct signs on cerebral CT is as follows: Group 1: No infarct sign observed in cerebral CT. Group 2: Presence of any one or multiple of the following NCCT manifestations: obscuration of lentiform nucleus, loss of differentiation between gray and white matter in the basal ganglia, focal hypoattenuation in basal ganglia, brainstem, thalami, or any other white matter region. Group 3: Presence of any one or multiple of the following NCCT manifestations: cortical sulcal effacement, loss of insular ribbon, obscuration of the sylvian fissure, and focal hypoattenuation in the cerebellum or any other cortical area. Group 4: Imaging manifestations described in both group 2 and group 3 are observed simultaneously, or there is the presence of hyperdense cerebral vessel sign.

Definition of sICH

In this study, all enrolled patients underwent follow-up CT or magnetic resonance imaging (MRI) within 22–36 hours after intravenous thrombolysis. Additionally, if there was any neurological deterioration, another CT scan was performed. Symptomatic intracranial hemorrhage (sICH) was defined, according to the European Cooperative Acute Stroke Study II criteria,[22] as any type of intracranial hemorrhage(ICH) detected on posttreatment imaging after the initiation of

thrombolysis, along with an increase of 4 points or more in the National Institutes of Health Stroke Scale (NIHSS) scores from baseline or resulting in death. All images and clinical scores were independently assessed by two experienced neurologists.

Statistical Analysis

In this study, continuous variables were presented as medians with interquartile ranges (IQRs) as all continuous variables did not conform to a normal distribution based on Kolmogorov–Smirnov test, while categorical variables were described as numbers with percentages. As the continuous variables did not follow a normal distribution, differences between groups with and without sICH were assessed using the Mann–Whitney *U*-test. For categorical variables, differences between the two groups were analyzed using Fisher's exact test or the $\chi 2$ test, as appropriate. Variables with a P-value <0.05 in the univariate analyses were further subjected to multivariable analysis. Restricted cubic splines (RCS) are used to test the linear relationship between continuous variables and the outcome variable. Collinearity between each variable was assessed by evaluating the tolerance (<0.2 considered significant) and variation inflation factors (>5 considered significant).

The forward-selection method was employed to select the final prediction model for the development of a prognostic nomogram. The discriminative performance of the nomogram was evaluated using the area under the receiver operating characteristic curve (AUC-ROC) in both the training and the validation sets. Calibration of the nomogram model, indicating concordance between predicted and observed probabilities, was assessed using the Hosmer-Lemeshow goodness-of-fit test (P >0.05) and a calibration plot with 500 bootstrap resamples. To evaluate the clinical validity of the nomogram, decision curve analysis (DCA) was performed in both the training and validation sets. Statistical analyses were conducted using IBM SPSS (version 26.0) and R statistical software (version 3.5.1). Two-tailed significance values were applied, and statistical significance was defined as P <0.05.

Results

Baseline Characteristics

Initially, a total of 888 patients with AIS were included in this study. After excluding 104 patients who did not meet the criteria, the final analysis comprised 784 patients. Comparison between excluded and included cases shows no statistically significant differences. Among the 784 patients, 550 individuals were assigned to the training set, and the remaining 234 individuals formed the validation set in a 7:3 ratio (Figure 1). Table 1 displays the baseline characteristics of the patients in both sets. In the training set, the median age of the patients was 70 years (with an interquartile range of 59–78), and 352 patients (64.0%) were male. Meanwhile, in the validation set, the median age was 69 years (with an interquartile range of 59–79), and 150 patients (64.1%) were male. Overall, 47 patients (6.0%) experienced sICH among the total cohort. The percentages of patients with sICH were 6.7% in the training set and 4.3% in the validation set. All variables were found to be balanced between the two groups, with p-values exceeding 0.05, indicating no significant differences.

As depicted in Table 2, the results of the univariate analysis demonstrated significant associations between sICH and the following variables: age, hypertension, atrial fibrillation (AF), National Institutes of Health Stroke Scale (NIHSS) scores, early infarct signs, prothrombin time (PT), blood urea nitrogen (BUN), creatinine, and serum sodium (P < 0.05). We further established restricted cubic splines (RCS) to conduct linear test between the continuous variables and sICH (Supplementary Figure 1). All continuous variables exhibit a linear relationship with sICH (*P* overall <0.05, *P* nonlinear >0.05), indicating the reliability of incorporating predictor variables in the form of continuous variables into the development of model. In the multivariable analysis, no significant collinearity was observed among all the variables (Table 3).

Following the multivariate logistic regression analysis, three factors were identified as independent predictors for sICH after intravenous thrombolysis in patients with ischemic stroke. These predictors included early infarct signs (Group 2 OR,2.879; 95% CI, 0.601–10.409; P=0.134. Group 3 OR, 3.547; 95% CI, 1.399–8.941; P=0.007. Group 4 OR,11.063; 95% CI, 3.191–36.939; P<0.001), NIHSS scores (OR, 1.047; 95% CI, 1.002–1.092; P = 0.034), and serum sodium levels (OR, 0.884; 95% CI, 0.811–0.953; P = 0.002).

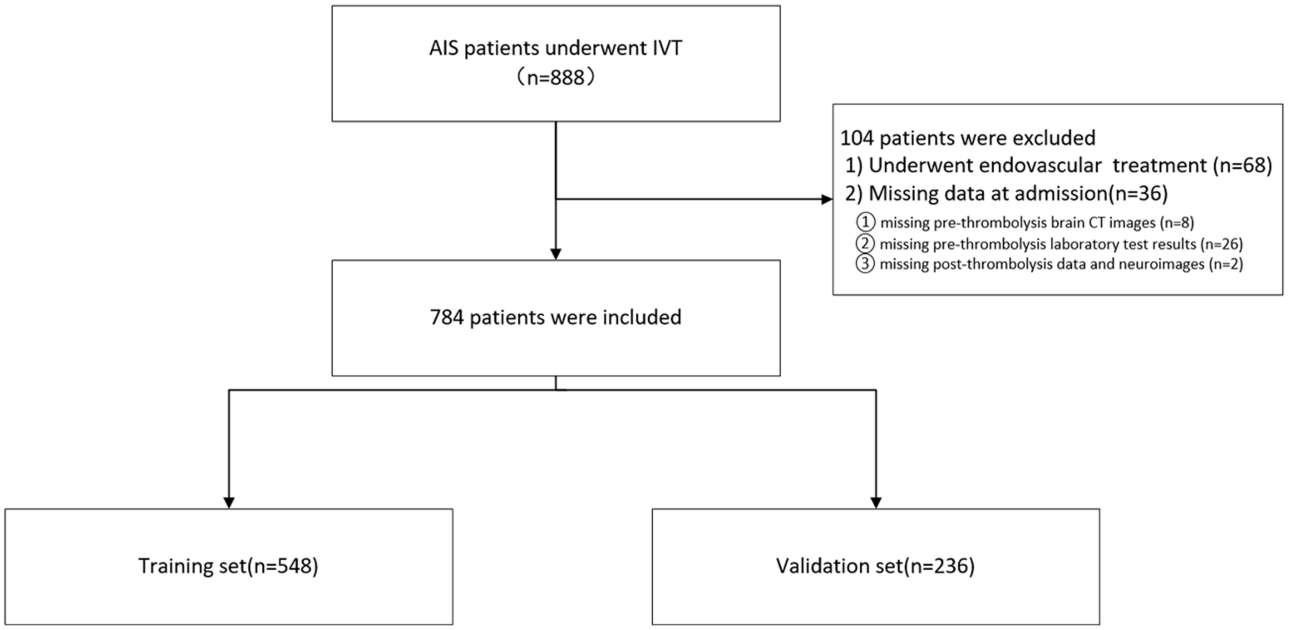

Figure 1 Flow chart of patient inclusion.
Abbreviations: IVT, intravenous thrombolysis; CT, Computer Tomography.

Predictive Model Development

The novel nomogram (Figure 2) was developed using all the identified independent predictors for sICH after intravenous thrombolysis. The nomogram comprises the preliminary values of the predictors, their corresponding preliminary score ranges, the total score, and the probability of ICH.

To use the nomogram, one must first locate the value of each predictor for a specific patient on the corresponding axis. Next, a line is drawn vertically downward from each preliminary value to the preliminary score axis, where the corresponding preliminary score is identified. The preliminary scores for all the predictors are then added together to obtain the total score for that patient. Finally, by drawing a line upward from the total score on the probability axis, the individual probability of experiencing sICH after intravenous thrombolysis is determined.

Nomogram Validation

The discriminative performance of the nomogram was assessed using the area under the receiver operating characteristic curve (AUC-ROC), which indicated a moderate predictive power in both the training set (AUC, 0.864; 95% CI, 0.810–0.919) (Figure 3A) and the validation set (AUC, 0.831; 95% CI, 0.770–0.891) (Figure 3B).

Furthermore, the goodness-of-fit of the nomogram was evaluated using the Hosmer-Lemeshow test, demonstrating good concordance between the predicted and observed probabilities in both the training set (P = 0.606) and the validation set (P = 0.488). The calibration plots for the training set exhibited excellent agreement between the predicted probability of ICH and the actual observations (Figure 4A), and similar optimal concordance was observed in the validation set (Figure 4B).

To evaluate the clinical usefulness of the nomogram, decision curve analysis (DCA) was performed. The DCA results suggested that the threshold probabilities ranged from 4.0% to 55.8% in the training set (Figure 5A) and from 4.0% to 45.8% in the validation set (Figure 5B). These findings indicate that the nomogram has practical clinical utility for predicting the risk of sICH after intravenous thrombolysis in patients with ischemic stroke.

Discussion

In this retrospective single-center study, we successfully developed and validated a novel nomogram that relies on easily and quickly obtainable predictors, namely the NIHSS score, early infarct signs, and serum sodium levels, prior to

Table 1 Baseline Characteristics of AIS Patients with IVT in the Training and Validation Sets

Variables	All Patients (n=784)	Training Set (n=550)	Validation Set (n=234)	*p*-value
sICH (%)	47 (6.0)	37 (6.7)	10 (4.3)	0.185
Demographic data				
Age(years), median (IQR)	70 (59–78)	70 (59–78)	69 (59–79)	0.81
Female, n (%)	282 (36.0)	198 (36.0)	84 (35.9)	0.978
Vascular risk factors, n (%)				
Hypertension	537 (68.5)	378 (68.7)	159 (67.9)	0.83
Diabetes mellitus	141 (18.0)	98 (17.8)	43 (18.4)	0.852
Hyperlipidemia	54 (6.9)	37 (6.7)	17 (7.3)	0.786
IHD	116 (14.8)	84 (15.3)	32 (13.7)	0.564
CHF	27 (3.4)	21 (3.8)	6 (2.6)	0.378
AF	130 (16.6)	94 (17.1)	36 (15.4)	0.557
History of smoking	97 (12.4)	73 (13.3)	24 (10.3)	0.241
Current smoking	140 (17.9)	98 (17.8)	42 (17.9)	0.965
History of stroke	106 (13.5)	67 (12.2)	39 (16.7)	0.093
Antiplatelet agents	119 (15.2)	85 (15.5)	34 (14.5)	0.741
Statin	99 (12.6)	73 (13.3)	26 (11.1)	0.404
Baseline data				
OTT (min), median (IQR)	145 (100–190)	150 (100–192)	140 (100–185)	0.359
NIHSS scores, median (IQR)	4(2–8)	4(2–8)	3(2–8)	0.346
SBP (mmHg), median (IQR)	152 (139–167)	152 (140–166)	154 (139–168)	0.865
DBP (mmHg), median (IQR)	84 (75–94)	85 (75–95)	84 (74–92)	0.117
Early infarct signs, n (%)				0.078
Group 1	586 (74.7)	404 (73.5)	182 (77.8)	
Group 2	53 (6.8)	43 (7.8)	10 (4.3)	
Group 3	122 (15.6)	83 (15.1)	39 (16.7)	
Group 4	23 (2.9)	20 (3.6)	3 (1.3)	
Laboratory data, median (IQR)				
WBC (*10^9/L)	7.20 (5.99–8.79)	7.17 (6.00–8.79)	7.28 (5.96–8.68)	0.911
Neutrophil (*10^9/L)	4.38 (3.50–5.77)	4.34 (3.51–5.78)	4.52 (3.46–5.76)	0.999
Lymphocyte (*10^9/L)	1.85 (1.40–2.53)	1.82 (1.37–2.56)	1.98 (1.47–2.49)	0.291
RBC (*10^{12}/L)	4.62 (4.26–4.95)	4.63 (4.26–4.95)	4.60 (4.28–4.95)	0.798
RDW (%)	12.80 (12.30–13.30)	12.80 (12.30–13.28)	12.90 (12.40–13.30)	0.293
Hemoglobin (g/L)	143 (131–154)	142 (131–154)	144 (132–154)	0.274
Platelet (*10^9/L)	205 (165–242)	206 (166–243)	200 (165–238)	0.296
PT (s)	13.10 (12.60–13.70)	13.10 (12.70–13.70)	13.05 (12.60–13.60)	0.665
APTT (s)	34.05 (31.60–36.70)	34.15 (31.60–36.80)	33.85 (31.72–36.50)	0.591
Fibrinogen (g/L)	3.21 (2.76–3.72)	3.20 (2.74–3.70)	3.27 (2.84–3.79)	0.516
Potassium (mmol/L)	3.81 (3.56–4.05)	3.82 (3.57–4.07)	3.80 (3.56–3.99)	0.517
Sodium (mmol/L)	139 (137–141)	139 (137–141)	139 (137–141)	0.856
Calcium (mmol/L)	2.28 (2.23–2.35)	2.29 (2.23–2.36)	2.28 (2.22–2.34)	0.09
BUN (mmol/L)	5.80 (4.80–7.20)	5.90 (4.80–7.20)	5.80 (4.62–7.20)	0.625
Serum creatinine (μmol/L)	73.00 (61.00–87.00)	73.00 (62.00–86.75)	72.00 (61.00–87.00)	0.867
Blood glucose level (mmol/L)	6.92 (5.98–8.54)	6.92 (5.96–8.39)	6.97 (6.06–8.91)	0.512
NLR	2.29 (1.55–3.50)	2.36 (1.55–3.55)	2.23 (1.54–3.37)	0.439

Abbreviations: AIS, acute ischemic stroke; IVT, intravenous thrombolysis; sICH, symptomatic intracranial hemorrhage; IHD, ischemic heart disease; CHF, congestive heart failure; AF, atrial fibrillation; OTT, onset-to-treatment; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; RBC, red blood cell; RDW, red blood cell distribution; PT, prothrombin time; APTT, active partial thromboplastin; BUN, blood urea nitrogen; NLR, neutrophil-to-lymphocyte.

intravenous thrombolysis. The nomogram demonstrated excellent performance in both the training set (AUC-ROC, 0.864) and the validation set (AUC-ROC, 0.831), indicating its robust predictive capabilities. Furthermore, the calibration capability of our nomogram was also found to be excellent, as the predicted risk closely aligned with the actual risk in both the training and validation sets. This suggests that our nomogram provides accurate and reliable risk estimations

Table 2 Univariable and Multivariable Analysis of sICH in AIS Patients with IVT in the Training Set

Variables	Univariable Analysis			Multivariable Analysis		
	OR	95% CI	*P*-value	OR	95% CI	P-value
Demographic data						
Age(years), median (IQR)	1.039	1.011–1.071	0.008	1.020	0.990–1.054	0.209
Female, n (%)	1.054	0.506–2.115	0.884			
Vascular risk factors, n (%)						
Hypertension	0.509	0.260–1.009	0.05	0.536	0.244–1.186	0.119
Diabetes mellitus	1.082	0.426–2.408	0.856			
Hyperlipidemia	0.368	0.020–1.782	0.331			
IHD	1.586	0.656–3.450	0.27			
CHF	1.486	0.231–5.404	0.604			
AF	3.746	1.832–7.486	<0.001	1.327	0.530–3.236	0.537
History of smoking	0.558	0.132–1.608	0.344			
Current smoking	1.082	0.426–2.408	0.856			
History of stroke	1.137	0.378–2.789	0.798			
Antiplatelet agents	1.562	0.646–3.396	0.286			
Statin	1.58	0.618–3.554	0.298			
Baseline data						
OTT (min), median (IQR)	0.997	0.991–1.003	0.336			
NIHSS scores, median (IQR)	1.088	1.053–1.124	<0.001	1.047	1.002–1.092	0.034
SBP (mmHg), median (IQR)	0.999	0.982–1.017	0.898			
DBP (mmHg), median (IQR)	1.019	0.994–1.045	0.144			
Early infarct signs, n (%)						
Group 1						
Group 2	2.089	0.468–6.739	0.262	2.879	0.601–10.409	0.134
Group 3	5.173	2.309–11.536	<0.001	3.547	1.399–8.941	0.007
Group 4	15	5.001–43.060	<0.001	11.063	3.191–36.939	<0.001
Laboratory data, median (IQR)						
WBC (*10^9/L)	1.001	0.863–1.141	0.993			
Neutrophil (*10^9/L)	1.02	0.867–1.170	0.792			
Lymphocyte (*10^9/L)	0.865	0.582–1.230	0.446			
RBC (*10^{12}/L)	0.778	0.443–1.408	0.395			
RDW (%)	1.25	0.935–1.603	0.097			
Hemoglobin (g/L)	0.994	0.975–1.013	0.51			
Platelet (*10^9/L)	0.997	0.991–1.002	0.279			
PT (s)	1.802	1.233–2.666	0.002	1.253	0.762–1.976	0.352
APTT (s)	0.953	0.870–1.040	0.293			
Fibrinogen (g/L)	1.346	0.953–1.838	0.073			
Potassium (mmol/L)	1.334	0.614–2.776	0.454			
Sodium (mmol/L)	0.896	0.827–0.963	0.004	0.884	0.811–0.953	0.002
Calcium (mmol/L)	0.099	0.003–3.016	0.189			
BUN (mmol/L)	1.149	1.022–1.282	0.014	1.021	0.847–1.210	0.814
Serum creatinine (μmol/L)	1.006	1.000–1.012	0.024	1.006	0.996–1.014	0.180
Blood glucose level (mmol/L)	1.023	0.916–1.118	0.65			
NLR	1.037	0.912–1.146	0.52			

Abbreviations: AIS, acute ischemic stroke; IVT, intravenous thrombolysis; sICH, symptomatic intracranial hemorrhage; OR, odd ratio; CI, confidence interval; IHD, ischemic heart disease; CHF, congestive heart failure; AF, atrial fibrillation; OTT, onset-to-treatment; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; RBC, red blood cell; RDW, red blood cell distribution; PT, prothrombin time; APTT, active partial thromboplastin; BUN, blood urea nitrogen; NLR, neutrophil-to-lymphocyte.

for post-thrombolysis symptomatic intracranial hemorrhage. Lastly, the decision curve analysis (DCA), a tool utilized to assess the clinical usefulness of a nomogram, reaffirmed the significance of our predictive model.

Table 3 Collinearity of Combinations of Variables in the Training Set

Variable	Tolerance	Variation Inflation Factor
Age	0.819	1.221
NIHSS scores	0.790	1.266
Hypertension	0.964	1.038
BUN	0.634	1.567
Serum creatinine	0.668	1.496
Serum sodium	0.993	1.007
EIS	0.862	1.160
AF	0.779	1.284
PT	0.863	1.159

Notes: All values of tolerance were > 0.2 and variation inflation factor were < 5.
Abbreviations: NIHSS, National Institutes of Health Stroke Scale; BUN, blood urea nitrogen; EIS, early infarct signs; AF, atrial fibrillation; PT, prothrombin time.

Our study's findings were consistent with previous research,[6–20] as we also identified NIHSS scores as predictors for sICH in patients undergoing rt-PA intravenous thrombolysis. This finding helped explain why patients with posterior circulation stroke (PCS) experienced a lower risk of sICH after intravenous thrombolysis when compared to those with anterior circulation stroke (ACS).[23,24] This was due to the fact that the NIHSS scoring system assigned higher weight to

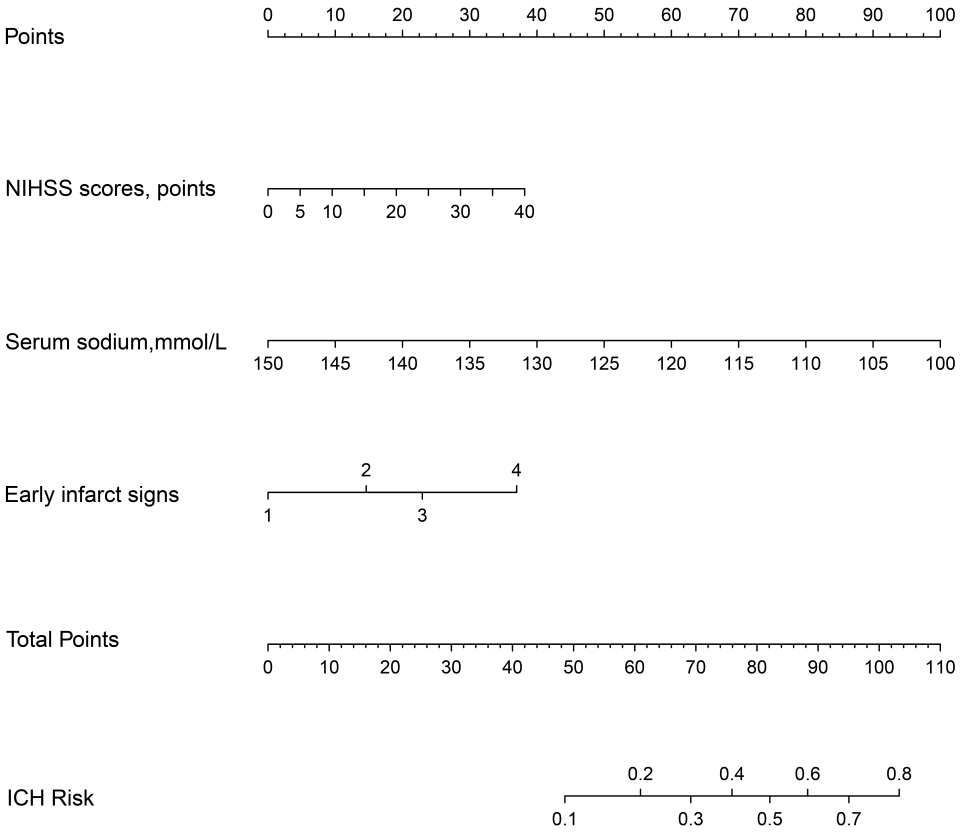

Figure 2 Nomogram for predicting sICH in patients experiencing IVT. The nomogram consists of three predictors, each of which is given a preliminary score (0–100). The total score is obtained by summing all the preliminary score of each of the three predictors. The classification of EIS: 1: No infarct sign observed in cerebral NCCT. 2: Presence of any one or multiple of the following NCCT manifestations: obscuration of lentiform nucleus, loss of differentiation between gray and white matter in the basal ganglia, focal hypoattenuation in basal ganglia, brainstem, thalami, or any other white matter region. 3: Presence of any one or multiple of the following NCCT manifestations: cortical sulcal effacement, loss of insular ribbon, obscuration of the sylvian fissure, and focal hypoattenuation in the cerebellum or any other cortical area. 4: Imaging manifestations described in both group 2 and group 3 are observed simultaneously, or there is the presence of hyperdense cerebral vessel sign.
Abbreviations: sICH, symptomatic intracranial hemorrhage; IVT, intravenous thrombolysis; NIHSS, national institutes of health stroke scale; NCCT, non-contrast computed tomography.

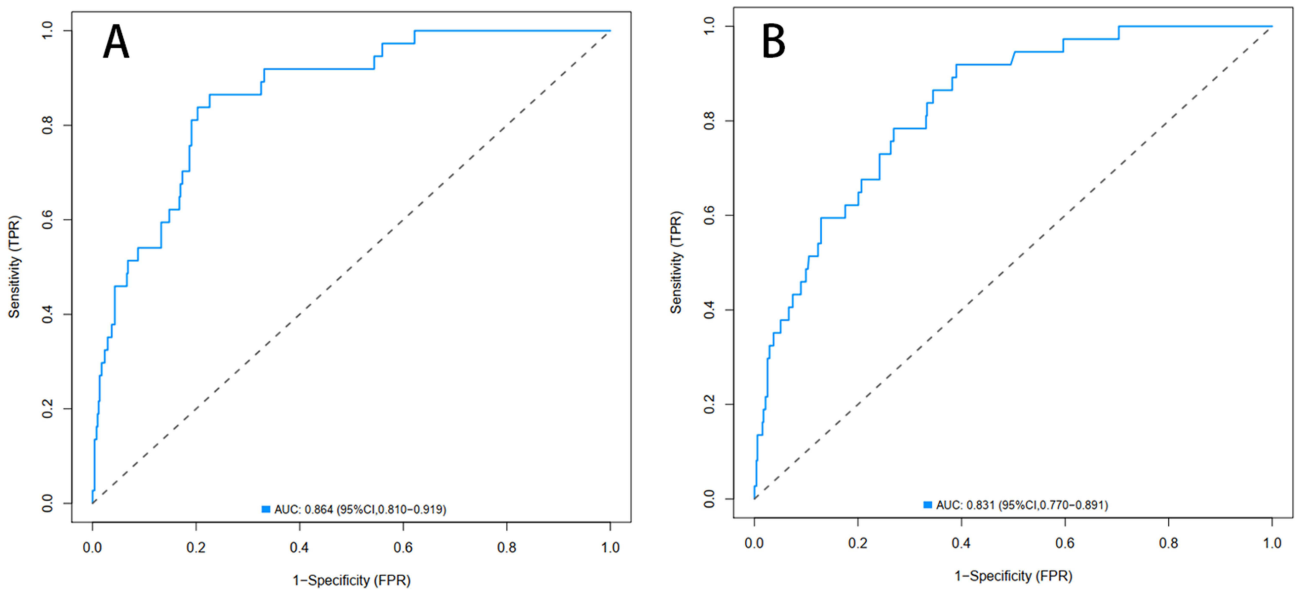

Figure 3 The receiver operating characteristic curve of the nomogram for predicting symptomatic intracranial hemorrhage in the training set (**A**) and the validation set (**B**). The value of area under curve is 0.864 in the training set and 0.831 in the validation set.

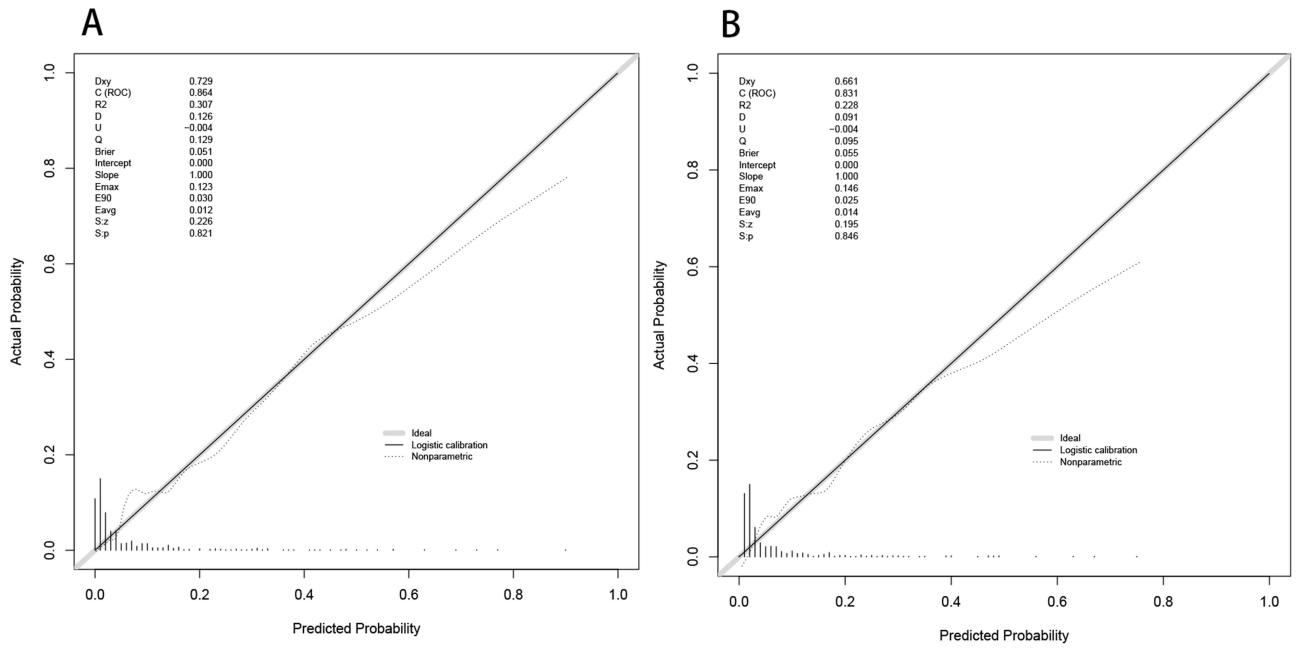

Figure 4 Calibration plot for predicting symptomatic intracranial hemorrhage after intravenous thrombolysis in the training set (**A**) and the validation set (**B**).

deficits commonly seen in ACS, such as aphasia and hemiparesis, while signs of PCS, like bulbar deficits and ataxia, received fewer points.[25]

Our study also revealed that early infarct signs was an independent risk factor for sICH as many previous studies did.[6,9,11,13] However, different from previous studies, where EIS was always incorporated into prediction model with dichotomous variable, we divided EIS into four different subgroups based on the region and type of infarct signs on NCCT in this study. We found that the risk of post-thrombolysis sICH was varied in different regions and types of infarct signs. We hypothesized that the finding was attributed to the volume of cerebral infarction. Numerous prior studies have demonstrated a positive correlation between the risk of sICH after thrombolysis and the size of the identified cerebral

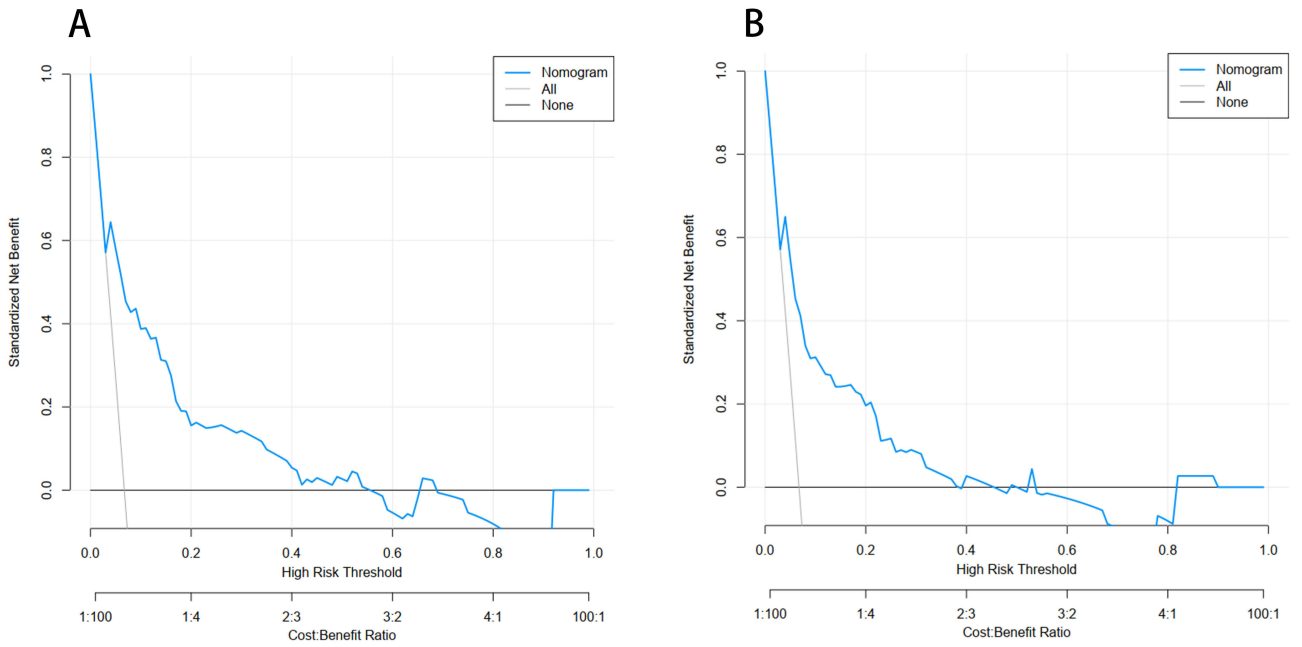

Figure 5 Decision curve analysis (DCA) of the nomogram predicting symptomatic intracranial hemorrhage after intravenous thrombolysis in the training set (**A**) and the validation set (**B**). The x-axis demonstrates the threshold probability. The y-axis indicates the net benefit. The black line displays all patients are negative and have no treatment, the net benefit is zero. The gray line means all patients who accept intravenous thrombolysis will develop symptomatic intracranial hemorrhage. The blue line indicates the net benefit of the nomogram.

infarction.[14,26,27] In group 4, infarct signs appearing in both central and peripheral regions of brain meant a relatively large infarct volume. Additionally, the presence of hyperdense cerebral vessel sign indicated major cerebrovascular occlusion, often accompanied by massive cerebral infarction.[28] Consequently, the risk of post-thrombolysis sICH in group 4 was the highest among the four groups. Comparing group 2 to group 3, the regions in group 3 contained a higher proportion of gray matters. Previous researches have demonstrated that gray matters were much more vulnerable than white matters to ischemia.[29–31] This implied that infarct signs in gray matters might appeared prior to the white matters theoretically. Therefore, infarct signs in gray matters might suggest potential ischemia in adjacent white matters, whereas infarct signs in white matters did not necessarily indicate concurrent ischemia in nearby gray matters. This interpretation implied that the actual infarct volume in group 3 could be larger than what is apparent on cerebral CT, potentially leading to a higher risk of post-thrombolysis sICH compared to group 2. To further validate this hypothesis, future studies could conduct volume and area comparisons between pre-IVT CT imagining and subsequent diffusion-weighted imaging (DWI).

Notably, our study ascertained that serum sodium might act as a protective factor for post-thrombolysis sICH in patients with ischemic stroke. Serum sodium was barely taken into account in scoring systems building or nomogram establishing in the past. He[32] have reported that hyponatremia was associated with post-thrombolysis hemorrhagic transformation. Several previous studies have implicated the disruption of the blood-brain barrier (BBB) and rt-PA-induced reperfusion injury as potential mechanisms behind ICH after rt-PA intravenous thrombolysis.[33,34] The BBB played a vital role in maintaining cerebral homeostasis,[35] and in conditions of hyponatremia, alterations in solute and water transfer could lead to volume perturbations and compromise the integrity of tight junctions and endothelial cells. This disruption of the BBB might ultimately lead to intracranial hemorrhage.[36]

While our study identified serum sodium as a potential protective factor, the exact mechanism behind its relationship with post-thrombolysis sICH remained to be fully investigated. Given that serum sodium level was a modifiable predictor, it merits further attention. One intriguing question was whether timely and proper management of serum sodium levels, particularly in patients with hyponatremia, could potentially reduce the risk of sICH after intravenous thrombolysis. To answer this question definitively, further investigation and research were required.

Our study has some limitations. First, the data for our study were obtained from a single-center retrospective analysis, which might introduce potential biases and limit the statistical power of the results. Second, our model has not been validated in external data. Further external validation is essential to assess the robustness of the nomogram in different patient populations.

Conclusion

In conclusion, the novel nomogram that includes NIHSS scores, early infarct signs and serum sodium may predict the risk of sICH after IVT in AIS patients.

Abbreviations

sICH, symptomatic intracranial hemorrhage; AIS, acute ischemic stroke; IVT, intravenous thrombolysis; AUC-ROC, area under the receiver operating characteristic curve; DCA, decision curve analysis; NIHSS, National Institutes of Health Stroke Scale; EIS, early infarct signs; rt-PA, recombinant tissue-plasminogen activator; NCCT, non-contrast computed tomography; NLR, neutrophil-to-lymphocyte ratio; OR, odd ratio; CI, confidence interval; IHD, ischemic heart disease; CHF, congestive heart failure; AF, atrial fibrillation; OTT, onset-to-treatment; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; RBD, red blood cell; RDW, red blood cell distribution; PT, prothrombin time; APTT, active partial thromboplastin; BUN, blood urea nitrogen; IQRs, interquartile ranges; BBB, blood-brain barrier.

Data Available Statement

The raw data supporting the conclusions of this article will be made available from the corresponding author, without undue reservation.

Ethics Statement

In accordance with national legislation and institutional requirements, the Ethics Committee of Dongyang People's Hospital reviewed and approved the studies involving human participants. Written informed consent from the participants was not necessary for this study.

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Disclosure

All authors report no conflicts of interest in this work.

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