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Construction and validation of a nomogram model to predict symptomatic intracranial hemorrhage after intravenous thrombolysis in elderly population with severe white matter lesions

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Abstract

Background and Objective: Elderly people are at high prevalence of atherosclerotic cerebral infarction. Cerebral white matter lesions (WMLs) increase the risk of bleeding after intravenous thrombolysis (IVT) although they may also require the IVT. The aim of this study is to develop a clinical nomogram model for post-IVT symptomatic intracranial hemorrhage (sICH), with the aim to prevent sICH in elderly patients with severe WMLs when IVT is being considered. *Methods:* This is a large single-center retrospective analysis study of elderly patients with severe WMLs receiving IVT from January 2018 to December 2022. Univariate and multi-factor logistic regression analysis were used to construct nomogram model, and a series of validations were performed on the model. *Results:* More than 2,000 patients with IVT were screened for inclusion in this study after cranial magnetic resonance imaging evaluation. Out of these, 163 elderly patients had cerebral WMLs, and 25 had sICH. In univariate analysis, history of hypertension (p=0.037), hyperlipidemia (p<0.001), NIHSS score before IVT (p<0.001), low-density lipoprotein levels (p=0.016), cholesterol levels (p=0.020), platelet count (p=0.006), systolic blood pressure (p<0.001), diastolic blood pressure (p<0.001) were significantly associated with sICH. In a multifactorial analysis, the NIHSS score before IVT (OR 42.056 CI 7.308-242.012, p<0.001), and diastolic blood pressure (OR 1.050 CI 1.002-1.100, p=0.040) were found to be significantly associated with sICH after IVT. The four most significant risk factors from logistic regression are subsequently fitted to create a predictive model. The accuracy was verified using calibration curves, decision curves, and clinical impact curves, and the model was considered to have strong stability.

Conclusions: The NHISS score before IVT and diastolic blood pressure are independent risk factors for sICH after IVT in elderly patients with severe WMLs. The models are highly accurate and can be applied clinically to provide a reliable predictive basis for IVT in elderly patients with severe WMLs.

Keywords: Severe white matter lesions, intravenous thrombolysis (IVT), symptomatic intracranial hemorrhage (sICH), nomogram model, elderly population

INTRODUCTION

As the basal metabolism of the elderly decreases, there is less lean body tissue and more adipose tissue in the body, making the elderly more susceptible to cerebrovascular disease.[1] According to previous studies, elderly population aged 60 to 70 years old has a high prevalence of cardiovascular diseases, and the incidence of atherosclerotic cerebral infarction (ACI) is significantly higher especially in people over 65 years old.[2,3] Intravenous thrombolysis (IVT) is currently an indispensable and important treatment of acute cerebral infarction and is considered to be the main therapeutic measure within the appropriate time window.[4] However, IVT can be fatal for some elderly stroke patients. Exogenous

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rt-PA can increase the permeability of the blood-brain barrier, thereby increasing the risk of early symptomatic intracranial haemorrhage (sICH) transformation, which may result in more harm than conservative treatment.[5] The incidence of bleeding after IVT is higher in the elderly population. In early studies of IVT, >80 years of age was considered a contraindication, although age is currently considered to be not a limiting factor for IVT.[6] Studies on IVT outcome have shown that many factors are associated with the development of sICH after IVT, including advanced age, hypertension, cerebral white matter lesions (WMLs), and others.[7,8]

WMLs is considered to be a long-term chronic ischemic changes in the paraventricular and deep white matter, mainly manifesting as white matter demyelination and gliosis.[8,9] Recent studies have confirmed that the occurrence of WMLs is closely related to the damage to the blood brain barrier.[10,11] Some previous studies have shown that patients with WMLs have an increased risk of sICH after IVT.[12] However, many national (USA, Europe, China, and Japan) guidelines do not recommend that WMLs should be a limiting factor against the use of IVT.[13-16] There is an increasing number of elderly people with cerebral WMLs undergoing IVT. Some have continue to use IVT in the context of severe WMLs, while others have not.

In our previous study, we found hyperlipidaemia and National Institutes of Health Stroke Scale (NHISS) scores before IVT as risk factors for sICH transformation in patients with severe WMLs.[17] In this study, we focus on the elderly population of more than 65 years with severe WMLs, the risk factors for sICH when undergo IVT, and establish a prediction model based on the risk factors. It is hoped that the result of this study will be able to guide clinicians when treating elderly patients with WMLs using IVT, to avoid sICH.

METHODS

This was a single-center, retrospective study. Patients who visited or were referred to the Second Affiliated Hospital of Nanchang University for cerebral infarction and underwent IVT were enrolled from January 2018 to December 2022 were enrolled in this study. This study was approved by the Ethics Committee of the Second Affiliated Hospital of Nanchang University.

We included people older than 65 years of age in our study. The patient information and laboratory tests were collected in the hospital's complete medical record system by physicians unaware of the study. The information collected included basic patient information (age, sex, race), past medical history (hypertension, diabetes, heart disease), lifestyle habits (smoking, alcohol consumption), and laboratory tests (blood counts, electrolytes, liver function, kidney function). The IVT infusion information, including the time of IV infusion after the onset of illness, NIHSS at the time of IV infusion, and blood pressure at the time of infusion. We excluded patients whose important information are missing and those who refused consent at the time of the visit.

All patients were screened for sICH according to the guidelines[18], including when no hemorrhage was found on completion of cranial CT or when a diffusion-weighted imaging sequence of cranial magnetic resonance imaging (MRI) was definitive for cerebral infarction. rt-PA was administered after evaluation by an experienced emergency neurologist. rt-PA was given at a dose of 0.9 mg/kg body weight, with the maximum dose did not exceed 90 mg. Ten percent of the infusion was given as a bolus followed by the rest as an infusion lasting 60 minutes.

The NIHSS was used to assess the neurological function of patients in the neurological emergency department by a medical professional. After completion of IVT, the patient was admitted to the neurology intensive care unit (ICU) for observation, where blood pressure, heart rate, and respiration were monitored in real time. Symptomatic treatment was given, including antihypertensive treatment for systolic blood pressure above 180 mmHg and diastolic blood pressure above 120 mmHg. A cranial CT was ordered 24 hours after IVT (also ordered if there is a sudden change in condition within 24 hours). Hemorrhagic transformation was assessed using the European Cooperative Acute Stroke Study II (ECASS II) guidelines.[19,20] sICH is defined as a deterioration in the patient's neurological function (≥4-point increase in NIHSS score) or death and hemorrhage observed on CT within 24 hours after IVT. Monitoring for 24 hours after IVT was performed by a physician specializing in the neurological ICU. According to the guidelines, no antiplatelet aggregation or anticoagulation drugs were administered during this 24-hour period. WMLs were diagnosed with 3T brain MRI. The Fazekas scale was used to evaluate the paraventricular and deep white matter with fluid-attenuated inversion recovery (FLAIR) on T2-weighted imaging.[21] The absence of any lesions in the paraventricular region was indicated as '0'; cap-shaped or pencil-like thin layer lesions were represented by a '1'; smooth halo lesions were rated as ‘2’; and irregular high signal extending into deep white matter was scored as ‘3’. A deep white matter score of 0 indicated the absence of disease; a score of 1 point indicated punctate disease; 2 points indicated merging lesions; and 3 points indicated a large area of fusion. The total score range is 0 to 6, divided into paraventricular and deep regions, with each region having a maximum score of 3. The specific scoring criteria are shown in Figure 1.[8,22] Based on other studies, we also defined a score equal to 4 or more as severe WMLs.[23,24] This work was performed by two imaging physicians who had no knowledge of the study.

Statistical analyses

The final population included consisted of patients with severe WMLs who had undergone IVT. Patients were divided into two groups based on the presence or absence of sICH transformation. Categorical variables were usually statistically analyzed by the $\chi 2$ test. To detect differences between two groups of continuous variables, the independent samples t test was used for normally distributed variables; the Mann-Whitney U test was used for variables that did not conform to a normal distribution. To assess the effect of all collected variables on the results, univariate and multiway logistic regression analyses were performed. Variables considered risk factors in the univariate analysis were included in the regression models, and ORs and 95% confidence intervals were calculated. Variables with P less than 0.15 in the multifactorial model were included in the prediction modeling. The incidence of outcome was 15.56%, and the total sample size was calculated to be at least 100[25]. The screened risk factors were plotted in a column line graph prediction model by the R language software car, rms package. To evaluate the accuracy of the developed prediction models, C-indices, calibration curves, and clinical decision curves

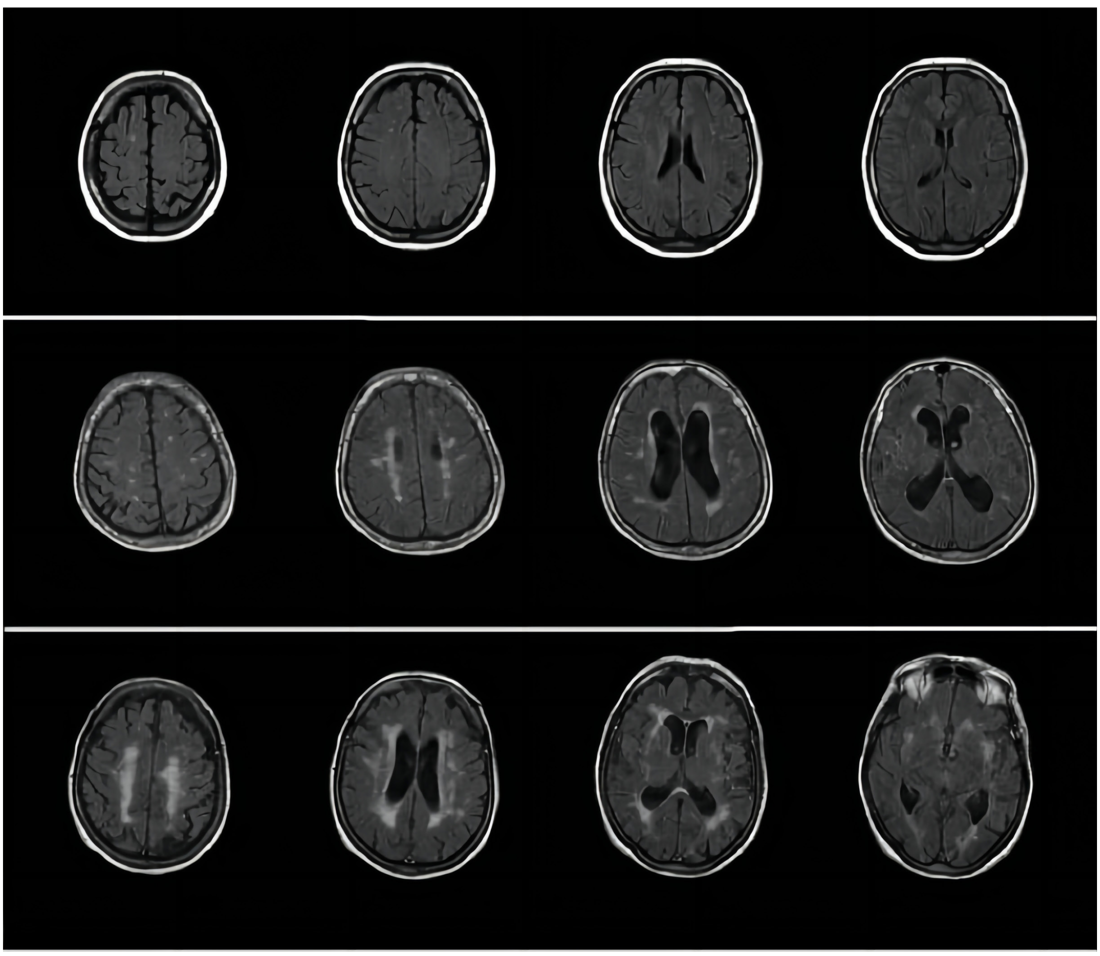

Figure 1. The first line of imaging pictures with a score of 0 or 1, the second line has a score of 2 and the third line is 3.

produced by R software were used to evaluate the models simultaneously. To make the established model better for clinical use, it was validated by decision curve analysis (DCA) to determine whether the model performs well in clinical work, where a larger area under the decision curve indicates a higher net clinical benefit for the patient. The calibration curve has a 45° diagonal line, and the closer the other line is to this diagonal line, the better the model is.[26] $P<0.05$ was considered statistically significant. Preliminary statistics were performed using IBM SPSS Statistics V.25.0 software. The prediction model and verification process were performed using R software (version 4.2.2).

RESULTS

After two neurologists reviewed the relevant cases, the hospital had nearly 2,000 patients treated with IVT after cerebral infarction in the past 5 years. In these patients, the imaging physicians evaluated the patients' cranial MRIs, and 163 patients had WML scores that met the study requirements and were ultimately included in our study. The mean age of the 163 patients was 76.25 years and included 101 (61.96%) males and 62 (38.04%) females. Of these 163 patients, 25 (15.34%) presented with sICH. The baseline information of the patients is fully presented in Table 1.

The data were analyzed according to sICH (presence or absence). In the univariate analysis, hyperlipidemia ($p<0.001$), history of hypertension ($p=0.037$), NIHSS score before IVT ($p<0.001$), cholesterol levels ($p=0.020$), low-density lipoprotein levels ($p=0.016$), platelet count ($p=0.006$), systolic blood pressure ($p<0.001$), and diastolic blood pressure ($p<0.001$) were significantly associated with sICH. In the multifactorial analysis, the NIHSS score before IVT (OR 42.056 CI 7.308-242.012, $p<0.001$) and diastolic blood pressure (OR 1.050 CI 1.002-1.100, $p=0.040$) were considered to be significantly associated with sICH conversion after IVT as risk factors for the occurrence of sICH (Table 2).

We fitted the four factors (hyperlipidemia, the NIHSS score before IVT, low-density lipoprotein and diastolic blood pressure) with $P<0.15$ among the multiple factors to construct the model and drew the nomogram graph using R software (Figure 2). As shown, the NHISS score and diastolic blood pressure had the greatest impact on prognosis. The total score of the four items predicts bleeding risk.

Then, we carried out a series of validations on the constructed prediction model. The calibration curve (Figure 3) showed that the predicted probabilities of the constructed prediction model were in high agreement with the actual probabilities (average absolute error of 0.031). The decision curve (Figure 4) showed that the highest net benefit of the four-factor prediction model and the one-factor prediction model at different threshold probabilities was 0.2. When the threshold probability was ≥0.2, the four-factor prediction model curve showed a higher net clinical benefit than any of the one-factor models. The clinical impact curves (Figure 5) show further hazard stratification using the newly constructed model to predict 1000 patients, with a line plot of the number of positive cases screened indicated by the red curve and the actual situation indicated by the blue curve, suggesting that a higher degree of compliance with the event between theory and practice can be obtained with a higher degree of clinical effectiveness with a risk threshold greater than 0.35.

DISCUSSION

The pathogenesis of ACI in the elderly is due to acute thrombosis or embolism resulting in localized vascular obstruction in the brain. To avoid permanent brain tissue necrosis, the obstructed vessels should be recanalized as soon as possible to restore brain tissue reperfusion.[27] IVT is believed to significantly improve the clinical prognosis of ACI patients.[28] However, numerous studies have shown that the outcome of IVT in the elderly is influenced by many factors.[29,30] However, cerebral WMLs are also an important factor affecting the outcome of IVT.[12] Therefore, in the present study, we used an elderly population with severe WMLs as the study population, and a series of univariate and multivariate analyses were conducted. A predictive model system was constructed and tested, which was considered to be highly accurate and applicable to clinical work.

The higher the NIHSS score before IVT in cerebral infarction patients, the more severe the neurological deficit and the larger the infarct area and cerebral edema, resulting in more pronounced vascular compression ischemia, poorer vascular wall permeability and vascular integrity, and significant reperfusion injury after IVT to dissolve the thrombus.[31] The degree of neurological deficits reflected by the NIHSS is an important factor in hemorrhagic transformation after IVT. The American Heart Association/American Stroke

Table 1: Baseline patient characteristics

Characteristics	No sICH (n=138)	sICH (n=25)	*P* value
Sex, n (%)			0.044
Male	90 (55.2%)	11 (6.7%)	
Female	48 (29.4%)	14 (8.6%)	
Age, median (IQR)	75.5 (72, 82)	77 (70, 80)	0.793
Hypertension, n (%)			**0.037**
Yes	100 (61.3%)	23 (14.1%)	
No	38 (23.3%)	2 (1.2%)	
Diabetes, n (%)			0.554
Yes	47 (28.8%)	7 (4.3%)	
No	91 (55.8%)	18 (11%)	
CHD, n (%)			0.856
Yes	17 (10.4%)	4 (2.5%)	
No	121 (74.2%)	21 (12.9%)	
Atrial fibrillation, n (%)			0.118
Yes	44 (27%)	12 (7.4%)	
No	94 (57.7%)	13 (8%)	
Hyperlipidemia, n (%)			**< 0.001**
Yes	22 (13.5%)	12 (7.4%)	
No	116 (71.2%)	13 (8%)	
Previous cerebral infarction, n (%)			0.952
Yes	45 (27.6%)	8 (4.9%)	
No	93 (57.1%)	17 (10.4%)	
NIHSS, n (%)*			**< 0.001**
1	92 (56.4%)	0 (0%)	
2	42 (25.8%)	19 (11.7%)	
3	4 (2.5%)	4 (2.5%)	
4	0 (0%)	2 (1.2%)	
Time from onset to thrombolysis, median (IQR)	2.5 (1.5, 3)	2.5 (1.5, 3)	0.649
D-dimer, median (IQR)	1.135 (0.64, 2.55)	1.15 (0.7, 3.19)	0.311
Low-density lipoprotein (SD)	2.4371 ± 0.8139	2.8564 ± 0.68073	**0.016**
Apolipoprotein (IQR)	35.975 (25.925, 52.593)	44 (30.02, 56.23)	0.148
Cholesterol (SD)	4.1489 ± 1.0074	4.664 ± 0.99968	**0.020**
Platelet count (IQR)	182 (140.25, 226.75)	139 (119, 174)	**0.006**
Platelet distribution width (IQR)	12.25 (10.825, 14.1)	14.6 (12.8, 16.3)	**0.001**
Sodium ion (IQR)	139 (137.2, 140.31)	140.51 (138.41, 141.33)	0.028
Systolic blood pressure (IQR)	153 (130, 166.75)	174 (164, 180)	**< 0.001**
Diastolic blood pressure (SD)	84.029 ± 15.657	99 ± 19.835	**< 0.001**

Values are numbers (%). P-values are not adjusted; SD, standard deviation; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; IVT: Intravenous thrombolysis; sICH: symptomatic intracranial hemorrhage; *: NHISS score of 1-10 is 1, 11-20 is 2, 21-30 is 3, and above 30 is 4. Each value is reserved for three decimal places.

Association guidelines recommend that patients with cerebral infarction with an NIHSS score >25 within 4.5 h of onset are at high risk for post thrombolytic hemorrhage and should be treated cautiously with IVT[6]. In addition, many studies have concluded that the NHISS score is the main factor affecting the prognosis of patients[31], which is the same as the results of this study, so a comprehensive assessment of the risk of sICH should be performed in critically ill patients in

Table 2: Multivariate logistic regression model for the predictors of sICH

Variable	*P* value	OR	95% CI
Platelet count	0.056	0.987	(0.974, 1.000)
NHISS	**<0.001**	42.056	(7.3088, 242.012)
Low-density lipoprotein	0.147	2.821	(0.693, 11.478)
Diastolic blood pressure	**0.040**	1.050	(1.002, 1.100)

NIHSS, National Institutes of Health Stroke Scale; sICH, symptomatic intracranial hemorrhage

clinical practice, and IVT should be administered with caution.

Cerebral WMLs are demyelinating changes in the white matter of the brain that are mostly caused by autoimmune diseases, cerebral hypoxia, ischemia, and cerebral perfusion deficits; pathologically, people with cerebral leukomalacia have intracranial small arteriosclerosis, high permeability of the blood-cerebrospinal fluid barrier, interstitial changes, and endothelial damage, all of which can lead to cerebral infarction and an increased risk of hemorrhagic transformation after IVT.[32] Fazekas grading is an imaging-based specific index of the degree of cerebral white matter osteoporosis, and the results of this study found that the incidence of sICH was significantly higher in elderly patients with moderate-to-severe cerebral WMLs than in the general population, in which the incidence was 4%.[14] It is currently believed that the main reason for this is that exogenous rt-PA triggers the cleavage of high relative molecular mass kininogenase by mediating the release of large amounts of bradykinin from fibrinolysin, activated coagulation factor XII, and plasma kininase; bradykinin can be involved in the production of inflammatory mediators and the activation of microglia, which increase vascular permeability and lead to the opening of the blood-brain barrier, thus exacerbating brain injury; moreover, plasma kinin also interferes with collagen-induced platelet activation, increasing the risk of sICH.[33,34] Therefore, it is necessary to pay attention to this group of people.

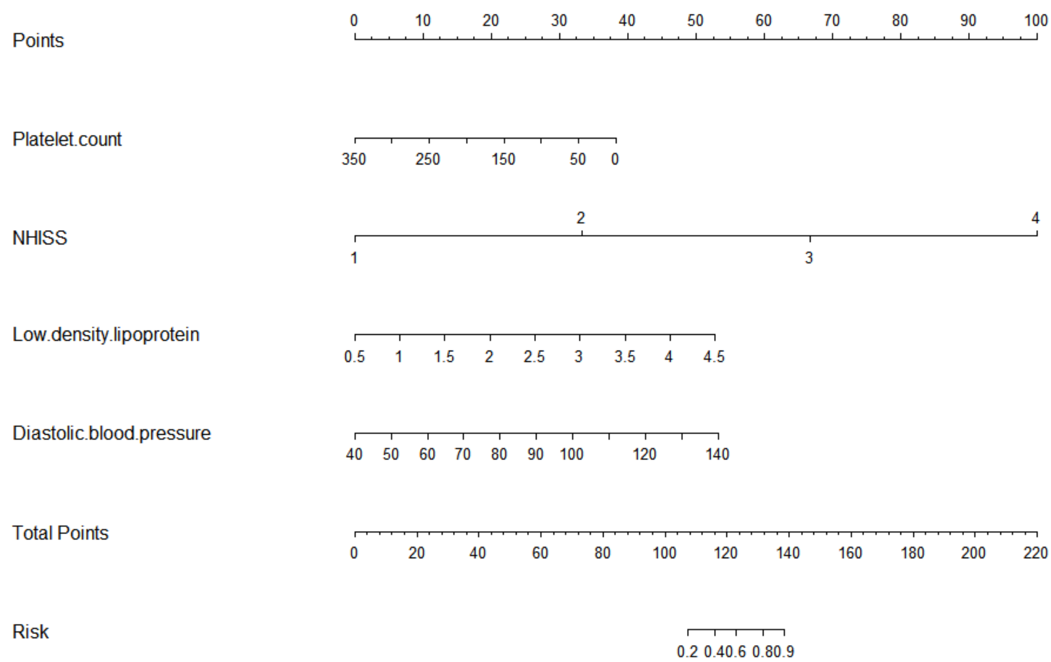

Figure 2. Nomogram graph. Each individual clinical indicator receives a corresponding score at the top, and after assessing all the clinical indicators, the sum is added to the total score that appears on the total scale bar, which corresponds to the risk of the corresponding event occurring.

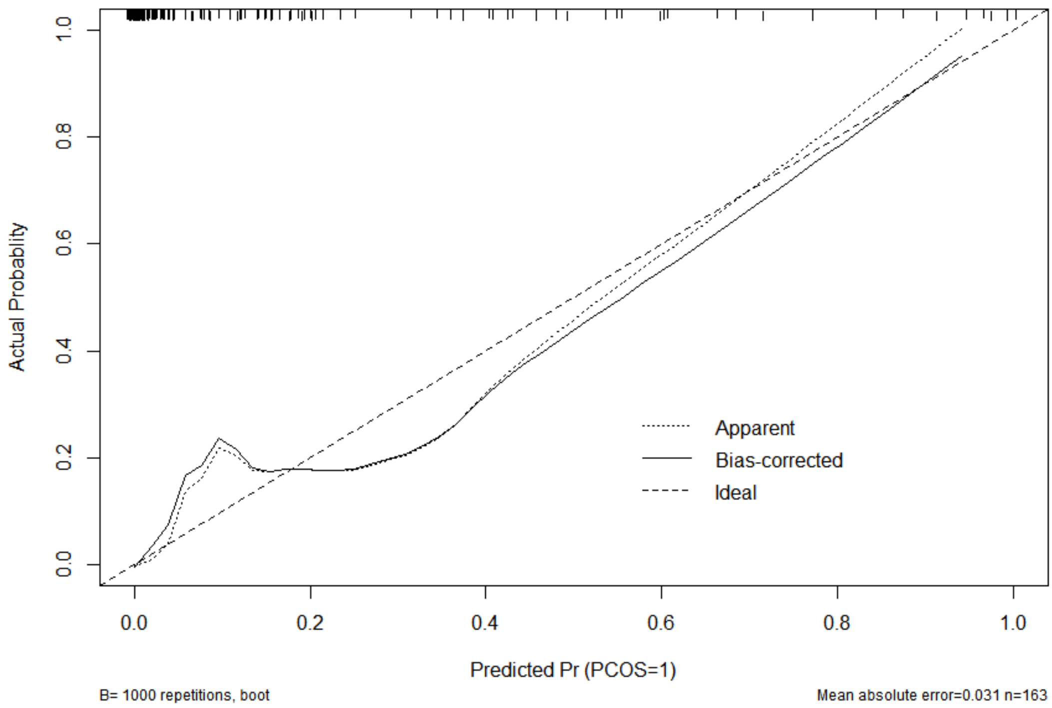

Figure 3. Calibration curve. The calibration curve has a 45° diagonal line, and the closer the other line is to this diagonal line, the better the model is.

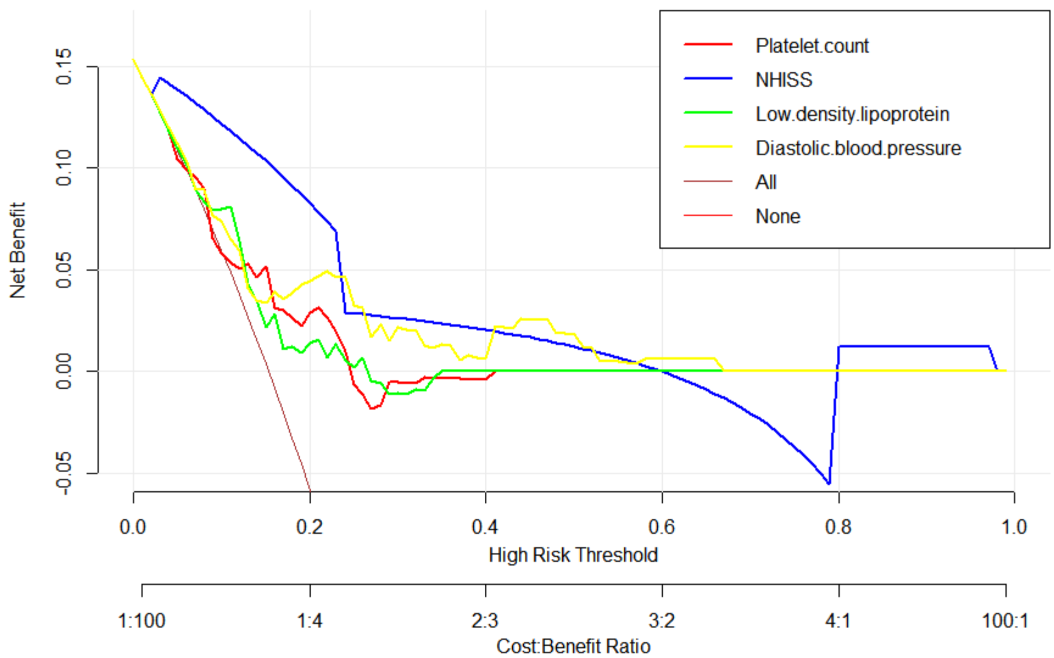

Figure 4. The decision curves. The highest net benefit of the four-factor prediction model and the single-factor prediction model within different threshold probabilities was 0.2. When the threshold probability was ≥0.2, the four-factor prediction model curves showed a higher net clinical benefit than any single-factor model.

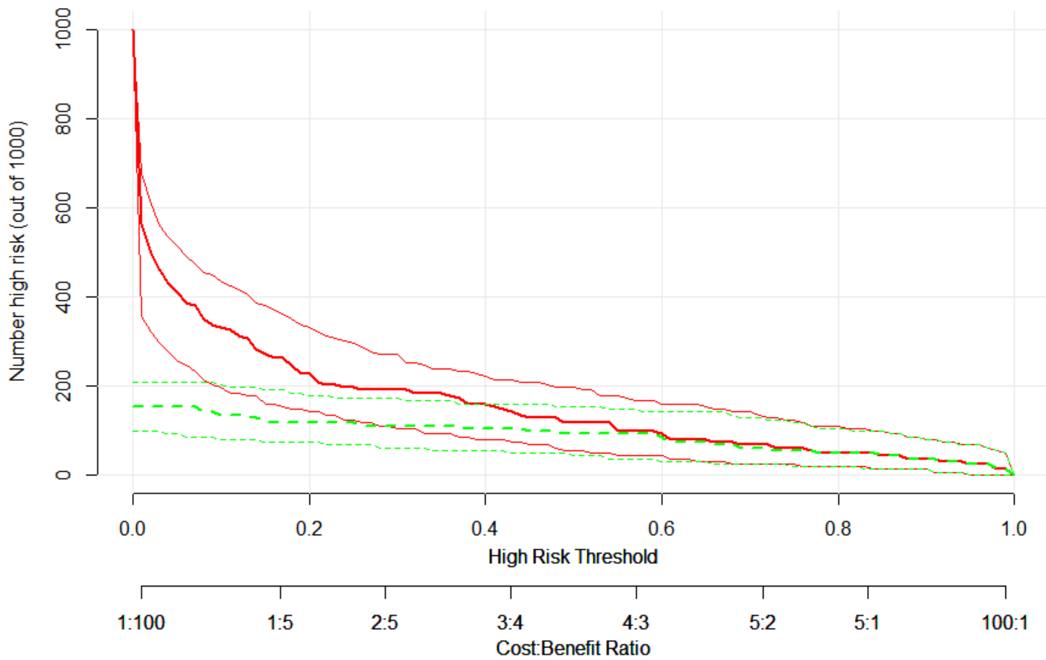

Figure 5. Clinical impact curve. The red curve indicating the number of positive cases screened by the line graph and the blue curve indicating the number of actual cases, shows that a higher degree of compliance between theoretical and actual events can be obtained with a higher degree of clinical validity at risk thresholds greater than 0.35.

Our study also concluded that diastolic blood pressure is a risk factor for predicting sICH in elderly patients undergoing IVT, suggesting that blood pressure control before IVT in general is necessary. Other studies have concluded that systolic blood pressure prior to IVT is strongly associated with sICH in the normal population, which is slightly different from our study.[34] However, we believe this is because most of our included patients had already involved small vessels, and diastolic blood pressure is more closely associated with small vessels. In elderly patients, the incidence of post thrombolytic complications is higher due to decreased organ function, which seriously affects the recovery of patients after IVT. Muchada *et al*. found that elderly ACI patients who underwent IVT had better clinical outcomes and better prognosis than those who did not, so IVT is still the main pharmacological treatment for elderly patients when their conditions allow.[35]

Our study establishes a prediction model, which is encouraging and has been shown to be reliable in multiple assessments. To our knowledge, this is the first study to construct a predictive model based on risk factors for IVT in an elderly population with severe cerebral WMLs. The limitations of this study are also obvious: 1. The sample size included in this study is still not optimistic and still falls short of the thousands of constructed model studies of common diseases, but we believe that this is the result of performing a rigorous imaging assessment. 2. The data used in this study were derived from a single center and were not externally validated. 3. As this study was retrospective, this study is subject to the unavoidable biases associated with retrospective studies. For example, it is difficult to achieve consistency in the treatment of patients, which is reflected in the control of patients' blood pressure and blood glucose. We plan to conduct a prospective study in our center to provide more accurate clinical guidance for these patients.

In conclusion, our study draws some relatively reliable conclusions that controlling diastolic blood pressure can reduce the occurrence of sICH on an existing basis when the severity of onset cannot be controlled (the NIHSS score before IVT). In addition, we constructed a relatively reliable and simple prediction model for the prediction of sICH in elderly patients with severe WMLs undergoing IVT. The NHISS score before IVT and diastolic blood pressure are independent risk factors for sICH after IVT in an elderly population with severe WMLs. The models have high accuracy and can be applied clinically to provide a reliable predictive basis for IVT in an elderly population with severe WMLs.

DISCLOSURE

Data availability: All relevant data are described within the paper. Deidentified data can be requested via the corresponding author.

Ethics: The research was approved by ethics committee of the second affiliated hospital of Nanchang University (No. [2016] 096).

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Conflicts of interest: None

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