

A Nomogram to Predict the Probability of Relapse during Hospitalization after Minor Ischemic Stroke in Chinese Patients.

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Abstract

Background: Predicting the risk of recurrence during hospitalization in patients with minor ischemic stroke (MIS) is of great significance for clinical and treatment. Compared with early models and prognostic scores, nomogram is a better visualization tool for predicting clinical outcomes. It combines different factors to develop a graphical continuous scoring system, and accurately calculates the risk probability of adverse outcomes based on individual characteristics. Our goal is to develop and validate a nomogram for individualized prediction of hospitalization recurrence in patients with mild ischemic stroke in the Chinese population.

Methods: Based on retrospective collection, a single center study was conducted in the first affiliated Hospital of Anhui Medical University from January 2014 to December 2019. The subjects were stroke patients with NIHSS \leq 5. In order to generate the nomogram, age, systolic blood pressure, previous heart disease, serum total bilirubin, ferritin and smoking were integrated into the model. The predictive accuracy of the nomogram model to predict the probability of unfavorable outcome was assessed by calculation of the area under the receiver operating characteristic curve (AUC–ROC). Calibration of the risk prediction model was assessed by the plot comparing the observed probability of unfavorable outcome against the predicted, and by using the Hosmer–Lemeshow test.

Results: Age at admission (OR,0.946; 95% CI,-0.002 to 0.048), SBP (OR,0.012,95%CI,0.000 to 0.024), previous heart disease (OR,0.867,95%CI, 0.084 to 1.651), UA (OR,-0.003,95%CI,-0.006 to 0.001), serum total bilirubin (OR,-0.022,95%CI,-0.036 to -0.008), ferritin (OR,0.004,95%CI, 0.002 to 0.005), smoking (OR,0.494,95%CI,-0.115 to 1.103) are significant predictors of in-hospital recurrence in Chinese patients with minor ischemic stroke. The model shows good discrimination, the AUC-ROC value is 0.737 (95%CI:0.676-0.798), and has perfect calibration performance. Calibration was good ($p=0.1457$ for the Hosmer-Lemeshow test), which could predict the risk of recurrence of MIS patients during hospitalization.

Conclusion: The nomogram developed and validated in this study can provide individualized, intuitive and accurate prediction of recurrence in Chinese patients with minor ischemic stroke during hospitalization.

Background

Stroke is the third leading cause of disability and the second leading cause of death in the world.[1] MIS refers to ischemic stroke with minor symptoms and mild neurological impairment. The prevalence of MIS is high in China.[2] One out of every three patients with acute ischemic cerebrovascular disease is MIS. While symptoms of MIS is minor, its prognosis is not optimistic. Studies[3,4] have shown that the risk of recurrent stroke is up to 10% in the week after a transient ischaemic attack (TIA) or minor stroke. It has been shown that 25% ~ 50% of MIS patients still leave varying degrees of disability at 90 days after onset.[5,6]

In-depth understanding of factors affecting the recurrence of MIS will not only help to predict the prognosis of patients, but also provide a feasible reference for the clinical management and treatment of MIS. With the increase in the number of the elderly and the extension of life expectancy, the number of patients with disabilities caused by MIS is expected to further increase in the future. Therefore, it is of great significance to

be able to establish a formal statistical model and provide a formal prediction of adverse outcomes after recurrence of MIS during hospitalization combined with clinical experience.

Disease prediction is an important part of medicine. Nomogram is considered as a means to improve disease prediction. It is a visualized graphic statistical tool, which is used to calculate the continuous probability of a specific outcome of a single patient, and can provide an estimated numerical prognosis for each patient; it can combine different data to form a continuous scoring system to predict the risk of the individual. Nomogram is an important part of modern medical decision-making. It has become a risk stratification tool used in routine clinical practice, including cancer and medical and surgical diseases. [7,8] However, to the best of our knowledge, there is no nomogram that can predict the probability of recurrence of stroke after MIS in Chinese patients during hospitalization. The purpose of this study is to develop and validate a nomogram based on multi-parameter integration to predict the possibility of adverse outcomes such as recurrence during hospitalization in Chinese MIS patients.

Methods

Data source

Patients with MIS were retrospectively identified from the database of the Stroke Center of the Department of Neurology of the first affiliated Hospital of Anhui Medical University (China). A total of 2216 patients with MIS from January 2014 to December 2019 were selected. The diagnostic criteria of MIS are according to the guidelines for the diagnosis and treatment of High-risk non-disabling Ischemic Cerebral artery events compiled by the Chinese Stroke Association in 2016: NIHSS ≤ 5 [9]. With those who received endovascular therapy such as thrombolysis and stenting were excluded from the study. All patients with signs of intracranial hemorrhage, age <18 or >100 , progressive stroke and unknown NIHSS in baseline CT were excluded from the analysis.

At admission, a detailed list of all clinical parameters, demographic and laboratory characteristics of each patient was recorded. Data of age, sex, baseline NIHSS score, creatinine, fasting blood glucose, hypertension, diabetes, previous heart disease, smoking and drinking were collected. All patients were evaluated with Magnetic Resonance Imaging (MRI) after admission to determine whether there was any recurrence or aggravation during hospitalization. The baseline NIHSS and the 3-month MRS are conducted by assessors who have received training and certification in the use of these tools.

Of the 2216 registered patients, those were excluded if they received intravascular therapy ($n=165, 7.4\%$), NIHSS was unknown ($n=146, 6.6\%$), imaging confirmed that there were intracranial hemorrhage ($n=195, 8.8\%$), age <18 or >100 ($n=229, 10.3\%$) and progressive stroke ($n=247, 11.1\%$).

This retrospective investigation did not require individual consent based on the institutional guidelines for waiving consent, was performed according to local ethical committee regulation, in accord with the Helsinki declaration, and was finally cleared by the Institutional Review Board as no-risk retrospective study.

Statistical Analysis

Mann-Whitney U test was used for bivariate analysis of continuous and ordered distribution variables. Fisher's exact test was used for bivariate analysis of classified variables. The nomogram model was generated to predict the probability of recurrence during hospitalization in patients with mild ischemic stroke in study population. In univariate analysis, all variables with probability < 0.20 entered the selection range, and the likelihood ratio test with Akaike's information criterion (AIC) [10] as the termination rule was used for a forward stepwise method, and the predictive variables with non-zero coefficient characteristics were screened out by lasso regression to compare the results. Regression coefficients and odds ratios (OR) with two-sided 95% confidence intervals (CI) for each of the variables included in the models were finally calculated.

The nomogram enables discrimination of patients with favorable outcome from those with unfavorable outcome, the predictive accuracy of the nomogram model was assessed by calculation of the area under curve (AUC) of the receiver-operating characteristic. The model confusion matrix is listed and the error rate is calculated. The R package used in the study is reported in **"Supplemental Information"**. All tests were two-sided and $P < 0.05$ was considered statistically significant.

The statistical analysis was carried out using the statistical software package R version 3.6.2 (R Foundation for Statistical Computing; <https://www.r-project.org/>) and STATA 15.0 (StataCorp Texas, USA).

Construction and validation of a nomogram

We included the patients in the first four years (2014-2017) as the training cohort and the patients in the last two years (2018-2019) as the validating cohort. The nomogram is constructed by using the regression coefficient obtained from the multivariable Logistic regression model and the RMS package in the R software. Nomogram is a graphical representation of complex mathematical formulas. Medical nomogram uses laboratory tests and clinical variables such as blood glucose, uric acid and patient age to graphically describe statistical prognostic models that generate the probability of clinical events (such as disease recurrence or death) for a given individual. Rapid calculation through an intuitive digital interface, coupled with higher accuracy and easier to understand prognosis, can seamlessly combine the prognosis obtained by nomogram to help clinical decision-making.

The performance of the model is evaluated by discrimination (the ability of the proposed model to distinguish patients with different outcomes) and calibration (the relative distance between the prediction and the actual results). The predictive accuracy of the nomogram model to predict the probability of unfavorable outcome was assessed by calculation of the area under the receiver operating characteristic curve (AUC-ROC). Calibration of the risk prediction model was assessed by the plot comparing the observed probability of unfavorable outcome against the predicted, and by using the Hosmer-Lemeshow test. Calibration was carried out using a calibration plot, in which the predicted probabilities were plotted against the frequency of the observed unfavorable outcome. The prediction of a well-calibrated model should be mirrored by a 45° diagonal line.

Results

As a result, the final study population included 1234 patients whose clinical features, demographic and laboratory data were shown in **Table 1**. All the 27 clinical features, demographic and laboratory data were reduced to 7 potential predictors on the basis of information of patients in the training cohort (**Figure 1A and 1B**). These features were nonzero coefficients in the LASSO logistic regression model. Finally, the predictive variables screened by lasso regression are highly consistent with the stepwise regression method, and the variables of seven constructing models were obtained (**Table 2**), age (OR, 0.946; 95% CI, -0.002 to 0.048), SBP (OR, 0.012; 95% CI, 0.000 to 0.024), previous heart disease (OR, 0.867; 95% CI, 0.084 to 1.651), UA (OR, -0.003; 95% CI, -0.006 to 0.001), SBIL (OR, -0.022; 95% CI, -0.036 to -0.008), ferritin (OR, 0.004; 95% CI, 0.002 to 0.005), smoking (OR, 0.494; 95% CI, -0.115 to 1.103). No significant statistical collinearity was observed for any of the seven independent risk factors that entered the multivariate logistic regression analysis. The result of Logistic regression model was: $\text{LOG} (p [x] / 1-p [x]) = -5.715 + (0.946 * \text{age}) + (0.867 * \text{previous heart disease}) + (0.494 * \text{smoking}) + (-0.003 * \text{UA}) + (-0.022 * \text{SBIL}) + (0.004 * \text{ferritin}) + (0.012 * \text{SBP})$, where $p (X)$ was the probability of recurrence in MIS patients during hospitalization.

Table 1 Characteristics of hospitalization of patients with Minor Ischemic Stroke in China

Training Dataset				Validation Dataset			
Factor	statu = 0	statu = 1	p-value*	Factor	statu = 0	statu = 1	p-value*
N	844	56		N	329	5	
age, median (IQR)	63 (52, 70) (n=844)	65 (59.5, 74) (n=56)	0.07	age, median (IQR)	63 (52, 70) (n=329)	64 (62, 71) (n=5)	0.71
sex			0.65	sex			1.00
0	245 (29.0%)	14 (25.0%)		0	104 (31.6%)	1 (20.0%)	
1	599 (71.0%)	42 (75.0%)		1	225 (68.4%)	4 (80.0%)	
hypertension			0.89	hypertension			0.17
0	325 (38.5%)	22 (39.3%)		0	118 (35.9%)	0 (0.0%)	
1	519 (61.5%)	34 (60.7%)		1	211 (64.1%)	5 (100.0%)	
diabetes			0.45	diabetes			1.00
0	611 (72.4%)	38 (67.9%)		0	234 (71.1%)	4 (80.0%)	
1	233 (27.6%)	18 (32.1%)		1	95 (28.9%)	1 (20.0%)	
FPG, median (IQR)	5.485 (4.95, 7.16) (n=844)	5.45 (4.66, 6.445) (n=56)	0.25	FPG, median (IQR)	5.62 (5, 7.35) (n=329)	4.57 (4.35, 7.22) (n=5)	0.30
cardiopathy			0.02	cardiopathy			1.00
0	777 (92.1%)	46 (82.1%)		0	297 (90.3%)	5 (100.0%)	
1	67 (7.9%)	10 (17.9%)		1	32 (9.7%)	0 (0.0%)	
smoke			0.09	smoke			0.33
0	631 (74.8%)	36 (64.3%)		0	254 (77.2%)	3 (60.0%)	
1	213 (25.2%)	20 (35.7%)		1	75 (22.8%)	2 (40.0%)	
UA, median (IQR)	298 (243, 360) (n=844)	290 (204, 334) (n=56)	0.13	UA, median (IQR)	308 (234, 360) (n=329)	267 (243, 331) (n=5)	0.74

UN, median (IQR)	5.3 (4.44, 6.54) (n=844)	4.97 (3.88, 6.33) (n=56)	0.27	UN, median (IQR)	5.59 (4.5, 7.1) (n=329)	3.81 (3.78, 5) (n=5)	0.06
hcy, median (IQR)	13.93 (10.86, 19.02) (n=844)	14.6 (10.01, 18.52) (n=56)	0.49	hcy, median (IQR)	14.1 (10.69, 17.46) (n=329)	16.43 (10.25, 58) (n=5)	0.40
CRP, median (IQR)	1.4 (.52, 5.655) (n=844)	1.325 (.605, 3.9) (n=56)	0.46	CRP, median (IQR)	1.76 (.56, 5.77) (n=329)	2.21 (1.56, 2.99) (n=5)	0.69
TC, median (IQR)	4.39 (3.76, 5.16) (n=844)	4.64 (3.82, 5.26) (n=56)	0.28	TC, median (IQR)	4.5 (3.94, 5.09) (n=329)	5.31 (3.24, 5.75) (n=5)	0.65
TG, median (IQR)	1.5 (1.06, 2.1) (n=844)	1.69 (1.095, 2.255) (n=56)	0.68	TG, median (IQR)	1.5 (1.09, 2.09) (n=329)	1.19 (.92, 2.45) (n=5)	0.62
LDLC, median (IQR)	2.59 (2.02, 3.19) (n=844)	3.03 (2.3, 3.37) (n=56)	0.08	LDLC, median (IQR)	2.63 (2.17, 3.28) (n=329)	3.33 (2.09, 3.71) (n=5)	0.41
soft_plaque			0.78	Vulnerable_plaque			1.00
0	538 (63.7%)	37 (66.1%)		0	200 (60.8%)	3 (60.0%)	
1	306 (36.3%)	19 (33.9%)		1	129 (39.2%)	2 (40.0%)	
Hard_plaque			0.21	Stable_plaque			1.00
0	389 (46.1%)	31 (55.4%)		0	167 (50.8%)	3 (60.0%)	
1	455 (53.9%)	25 (44.6%)		1	162 (49.2%)	2 (40.0%)	
drink			0.31	drink			0.65
0	560 (66.4%)	33 (58.9%)		0	226 (68.7%)	3 (60.0%)	
1	284 (33.6%)	23 (41.1%)		1	103 (31.3%)	2 (40.0%)	
HDLC, median (IQR)	1.1 (.93, 1.36) (n=844)	1.145 (.9, 1.285) (n=56)	0.64	HDLC, median (IQR)	1.12 (.96, 1.37) (n=329)	1.1 (1.08, 1.13) (n=5)	0.94
APOA,	1.35	1.415	0.65	APOA, median	1.37	1.51	0.65

median (IQR)	(1.205, 1.55) (n=844)	(1.19, 1.525) (n=56)		(IQR)	(1.23, 1.55) (n=329)	(1.26, 1.53) (n=5)	
APOB, median (IQR)	.91 (.73, 1.08) (n=844)	1 (.76, 1.18) (n=56)	0.14	APOB, median (IQR)	.94 (.75, 1.11) (n=329)	1.02 (.8, 1.1) (n=5)	0.57
LP.a., median (IQR)	203.5 (109, 340) (n=844)	151 (124, 344.5) (n=56)	0.59	LP.a., median (IQR)	189 (109, 345) (n=329)	151 (145, 343) (n=5)	0.91
Cr, median (IQR)	55 (14.31, 71.9) (n=844)	67.95 (48.6, 80) (n=56)	<0.01	Cr, median (IQR)	56 (15.04, 70.1) (n=329)	73 (47.4, 77.9) (n=5)	0.26
TBIL, median (IQR)	17.97 (11.795, 58.5) (n=844)	15.57 (11.7, 19.03) (n=56)	0.04	STBL, median (IQR)	17.23 (11.7, 58.5) (n=329)	15.57 (13.52, 15.7) (n=5)	0.34
Ferritin, median (IQR)	214.46 (136.245, 321.8) (n=844)	253.6 (212.7, 426.1) (n=56)	<0.01	Ferritin, median (IQR)	211.64 (131.2, 326.5) (n=329)	241.3 (236.03, 255) (n=5)	0.44
GHb, median (IQR)	6.4 (5.6, 7.7) (n=844)	6.655 (5.045, 8.139999) (n=56)	0.70	GHb, median (IQR)	6.51 (5.51, 7.94) (n=329)	5.91 (5.6, 6.3) (n=5)	0.52
SBS, median (IQR)	141 (130, 158) (n=844)	146 (137, 163) (n=56)	0.06	SBP, median (IQR)	141 (130, 156) (n=329)	150 (142, 154) (n=5)	0.57
DP, median (IQR)	82 (75, 91) (n=844)	85.5 (81, 90) (n=56)	0.11	DBP, median (IQR)	82 (74, 91) (n=329)	89 (82, 90) (n=5)	0.41

*Continuous variables were compared using Mann-Whitney U test and categorical variables were compared using Fisher's exact test.

included into the multiple logistic regression models ($P < 0.2$) and Additionally traditional stroke risk factors such as Hypertension, diabetes and cardiopathy were added into the model.

Table 2. Predictors of Relapse during Hospitalization after Minor Ischemic Stroke in Chinese Patients

Intercept and Variable	β	OR (95% CI)	P
Intercept	-5.715	-	-
Age	-0.023	1.023(0.998 to 1.049)	=0.073
Cardiopathy	0.867	2.380(1.087 to 5.210)	=0.030
Smoke	0.494	1.639(0.892 to 3.012)	=0.112
UA	-0.003	0.997(0.994 to 1.000)	=0.058
STBL	-0.022	0.978(0.965 to 0.992)	=0.002
Ferritin	0.004	1.004(1.002 to 1.005)	<0.001
SBP	0.012	1.012(1.000 to 1.024)	=0.054
Area under roc curve	-		
Training Dataset		0.737(0.676 to 0.798)	
Validation Dataset		0.706(0.532 to 0.881)	

Multivariate analysis

UA,Uric Acid;STBL,Serum Total Bilirubin;OR,odds ratio; 95% CI,95% confidence of interval

The nomogram was created by assigning a graphic preliminary score to each of the seven predictors with a point range from 0 to 10, which was then summed to generate a total score, finally converting it into the individual risk of recurrence of MIS patients during hospitalization (from 0% to 100%).The higher total score of nomogram, the higher possibility of adverse outcome. The AUC-ROC of the Nomogram of the training cohort is 0.737 (95%CI 0.676-0.798) (**Figure 2**). In the validating cohort, the AUC-ROC value is 0.706 (95%CI 0.532-0.881) (**Figure 3**).The confusion matrix of the model in the training cohort is shown in the figure , and the error rate is 0.06; the confusion matrix of the model in the validating cohort is shown in the figure, and the error rate is 0.015(**Table 3**).The calibration curve of the nomogram model shows that there is sufficient consistency between the predicted values calculated by the nomogram and the actual results. Hosmer-Lemeshow goodness-of-fit test showed that the nomogram was well corrected (p=0.1457), which could predict the risk of recurrence of MIS patients during hospitalization.

Table 3. Summary of the Confusion matrix for the training dataset and testing dataset.

A—2×2 Table—Confusion matrix for the training dataset

		Actual Outcome	
		Non Relapse during Hospitalization	Relapse during Hospitalization
Predicted Outcome	Non Relapse during Hospitalization	844	54
	Relapse during Hospitalization	0	2

B—2×2 Table—Confusion matrix for the testing dataset

		Actual Outcome	
		Non Relapse during Hospitalization	Relapse during Hospitalization
Predicted Outcome	Non Relapse during Hospitalization	329	5
	Relapse during Hospitalization	0	0

Note: The rows in a confusion matrix correspond to what the logistic algorithm predicted and the columns correspond to the known truth. Since there are only two categories to choose from: “Non Relapse during Hospitalization” or “Relapse during Hospitalization”. Then the top left corner contains True Negatives. The True Positives are in the bottom right-hand corner. The accuracy (Number of correct predictions divided by total predictions) is 94.0% and 98.5% in the training and testing dataset, respectively.

Discussion

Studies have shown that [11], among MIS patients, the risk of stroke recurrence within 90 days is 10%-19% (average 15%) while the risk of recurrence of acute ischemic stroke within 90 days is 2%-7% (average 5%), which is significantly lower than that of MIS. MIS is a relatively urgent emergency. More importantly, although MIS attacks do not usually lead to immediate functional or cognitive decline, patients have a significantly increased risk of ischemic events in the future, more frequently in the days or weeks after the initial relief of symptoms [12]. Because of these evidences, post-MIS disability has now become a public health care problem. Therefore, it is of great significance to propose a more accurate and valuable predictive model through the early prevention and identification of MIS, through reliable predictors.

This is the first time that the probability of adverse events which can better predict the recurrence of Chinese MIS patients during hospitalization was proposed through the comprehensive influence of a variety of variables (such as age and total bilirubin, previous heart disease and smoking, etc.). That is, age, SBP, previous heart disease, UA, SBIL, ferritin, and smoking were independently associated with the incidence of cerebral infarction in previous studies. Therefore, we developed and validated a nomogram containing these seven variable combinations, which can relatively accurately predict the probability of relapse during the hospitalization of MIS patients (AUC=0.706).

When we use R to generate nomogram, we find an interesting phenomenon. When inputting seven variables into R software, we get the original version of nomogram (**Figure 4**). But when we interacted between age and a previous heart disease, the regenerated nomogram (**Figure 5**), results caught our eyes. Under the condition of previous heart disease (cardiopathy=0 or cardiopathy=1), age is no longer simply significantly positively correlated with the recurrence of MIS, but the younger patients with heart disease, the higher incidence of adverse events. A study of atrial fibrillation may explain our results, which showed that cerebral infarction was closely related to cardiovascular disease and was the most common cause of cardiovascular death. However, all-cause mortality was the highest in young patients with atrial fibrillation and decreased with age. The effect of atrial fibrillation on mortality varies with age. The absolute mortality (death toll) is lower in young patients with atrial fibrillation, but the effect of atrial fibrillation on mortality is higher than that in elderly patients. In contrast, the absolute mortality rate of elderly patients with atrial fibrillation is higher, although standardized mortality ratio (SMR) is observed to be lower than that of young patients with atrial fibrillation, indicating that the effect of atrial fibrillation on mortality decreases with age. As individuals without atrial fibrillation get older, they will develop complications other than atrial fibrillation, which may increase mortality and thus weaken the impact of atrial fibrillation on patients.[13] There is also a warning role to remind young people at risk of high-risk diseases that they should pay more attention to prevention, actively improve lifestyle behavior and seek medical treatment in time in daily life, and preventive drug treatment if necessary.

Blood pressure (BP) level is closely related to stroke mortality. We already know that early antihypertensive therapy is beneficial to patients with acute intracranial hemorrhage and ischemic stroke.[14] Tan's study also proved that systolic blood pressure can be used as an independent risk factor for MIS.[15] Some studies have shown that BP can distinguish between MIS and non-cerebrovascular events in the population, and early and accurate diagnosis of MIS is particularly important to reduce the risk of recurrence and disability.[16] We found that elevated SBP can be used as a warning indicator by physicians in the short term, as our nomogram shows, the higher the SBP, the higher the corresponding score, and the higher the total score, indicating a higher risk of the disease. This reminds doctors to further examine the neurological symptoms and imaging features of patients in order to make treatment decisions in a timely manner.

Previous studies have shown that the level of serum uric acid is an independent protective factor for cognitive impairment in patients with MIS, and the lower the level of uric acid is, the more disadvantageous it is to the cognitive function of patients. [17] Serum uric acid is a good antioxidant and will increase rapidly after acute cerebral infarction. An animal study shows that in the establishment of rat middle cerebral artery occlusion model, apoptosis and brain tissue injury will produce reactive oxygen species, and after the addition of appropriate high concentration of uric acid, the degree of brain tissue injury is reduced and the production of reactive oxygen species is reduced. However, low concentration uric acid can not improve the cell survival rate, so in a certain range, the increase of uric acid level has a certain neuroprotective effect. [18] Our study shows that there is a negative correlation between high concentration of uric acid and recurrence of MIS, which further confirms this view. The clinical studies of Zhang et al have shown that UA plays a neuroprotective role in acute ischemic stroke, and appropriate high concentration of uric acid is beneficial to the prognosis of adolescent stroke.[19] The meta-analysis of Wang supports that serum uric acid level has a protective effect on neurological prognosis after acute ischemic stroke, and high uric acid

level at onset is a biomarker with better prognosis in patients with acute ischemic stroke.[20]Therefore, an appropriate high level of serum uric acid can prevent the recurrence of MIS.

It can be seen from nomogram that ferritin is closely related to the progression of the disease. Ferritin is an iron-binding plasma protein. It is also an acute phase reactant that increases after proinflammatory stimulation. The high concentration of plasma ferritin is related to clinical deterioration. This suggests that the excitotoxicity of iron free radicals may be one of the reasons for the progression of the disease. Some studies have pointed out that the increase of ferritin concentration in plasma and cerebrospinal fluid within 24 hours after the onset of ischemic stroke is related to the deterioration of early neurological function, and the increase of iron reserve may lead to stroke progression by enhancing the cytotoxic mechanism of cerebral ischemia. This study is consistent with our findings, that is, there is a positive correlation between ferritin and recurrence of MIS.[21]

Bilirubin, as an antioxidant, can always oxidize lipids and lipoproteins and play a certain role in preventing atherosclerosis. Bilirubin reduces oxidative stress by scavenging free radicals, thus improving endothelial dysfunction. The improvement of endothelial function will prevent the progression of atherosclerosis. Therefore, higher physiological levels of serum bilirubin have a protective effect on vascular events[22]. Studies have shown that higher levels of total bilirubin are associated with lower risk of asymptomatic cerebral infarction.[24] Tan et al [17]also proved that total bilirubin can be used as an independent risk factor for MIS. Indeed, as nomogram shows, it is reasonable that higher levels of bilirubin can prevent the recurrence of cerebral infarction to some extent.

The view that smoking is harmful to vascular health has been around for a long time. The impact of smoking on the disease is mainly manifested in three points: the first is the thickening and stiffness of the blood vessel wall; the second is the slow blood flow; and the third is the increase of blood viscosity. [25]Smoke also contains a lot of nicotine, these toxic substances will cause the body to increase the secretion of adrenaline and thyroxine, can make the heartbeat faster, blood pressure rise, resulting in adverse consequences. Quitting smoking as soon as possible plays an important role in preventing the recurrence of mild stroke. Quitting smoking is not only the most economical intervention to reduce the risk of stroke, but also one of the important measures to prevent cerebrovascular disease. Therefore, smoking is also one of the important risk factors for MIS.[26]

Nomogram is an important part of modern medical decision-making. The well-constructed nomogram is designed to answer a focus question, which, when properly explained and applied, can be of great value to clinicians and patients. However, they must undergo rigorous scrutiny and need to be aware of their performance and limitations before using them in clinical decisions. Only in this way, nomogram can better predict patients health outcomes. Despite these limitations, as far as we know, this is the first attempt to construct and verify a nomogram to predict the possibility of recurrence of MIS.

We have to admit that the current research also has some limitations. First, this is an inherent weakness of any single-center exploratory study, such as collection and entry bias, and possible residual confusion, whose clinical value may be diminished by flaws in its experimental design. Secondly, these methods can prevent over-interpretation of data, but can not eliminate all deviations caused by overfitting that may be

inherent in the selection of variables and thresholds. Third, the group of patients with limited race or geographical area has always been a concern in the development of predictive models.[27]In consequence, external verification, especially in completely different patient cohorts, is necessary.[28]

Conclusion

Before hospitalization of MIS patients, we use this nomogram for individual risk assessment to identify high-risk patients and provide them or their relatives with more detailed risk information to support sound decision-making. In the future, a multicenter clinical test should be conducted to verify whether the model can help patients prevent adverse events and promote their understanding. This is essential to provide a reasonable method of patient management and to help patients and their families understand the process of the disease, and clinicians and patients can also take more necessary measures in lifestyle monitoring and medical intervention.

Abbreviations

MIS Minor ischemic stroke

AUC Area under the curve

ROC Receiver operating characteristic

TIA Transient ischaemic attack

MRI Magnetic Resonance Imaging

AIC Akaike's information criterion

OR Odds ratios

CI Confidence intervals

SBP Systolic Blood Pressure

STBL Serum total bilirubin

Declarations

Ethics approval and consent to participate

This retrospective investigation did not require individual consent based on the institutional guidelines for waiving consent, was performed according to local ethical committee regulation, in accord with the Helsinki declaration, and was finally cleared by the Institutional Review Board as no-risk retrospective study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analysed during the current study are not publicly available due to protection of patients' privacy but are available from the corresponding author on reasonable request.

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Competing Interests

The authors declare that they have no conflicts of interest.

Author Contributions

(I) Conception and design: XFY, WWY

(II) Administrative support: ZWS

(III) Provision of study materials or patients: WZ, YX

(IV) Collection and assembly of data: CJH,XY

(V) Data analysis and interpretation: XFY, WWY,XZ

(VI) Manuscript writing: All authors

(VII) Final approval of manuscript: All authors

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Figures

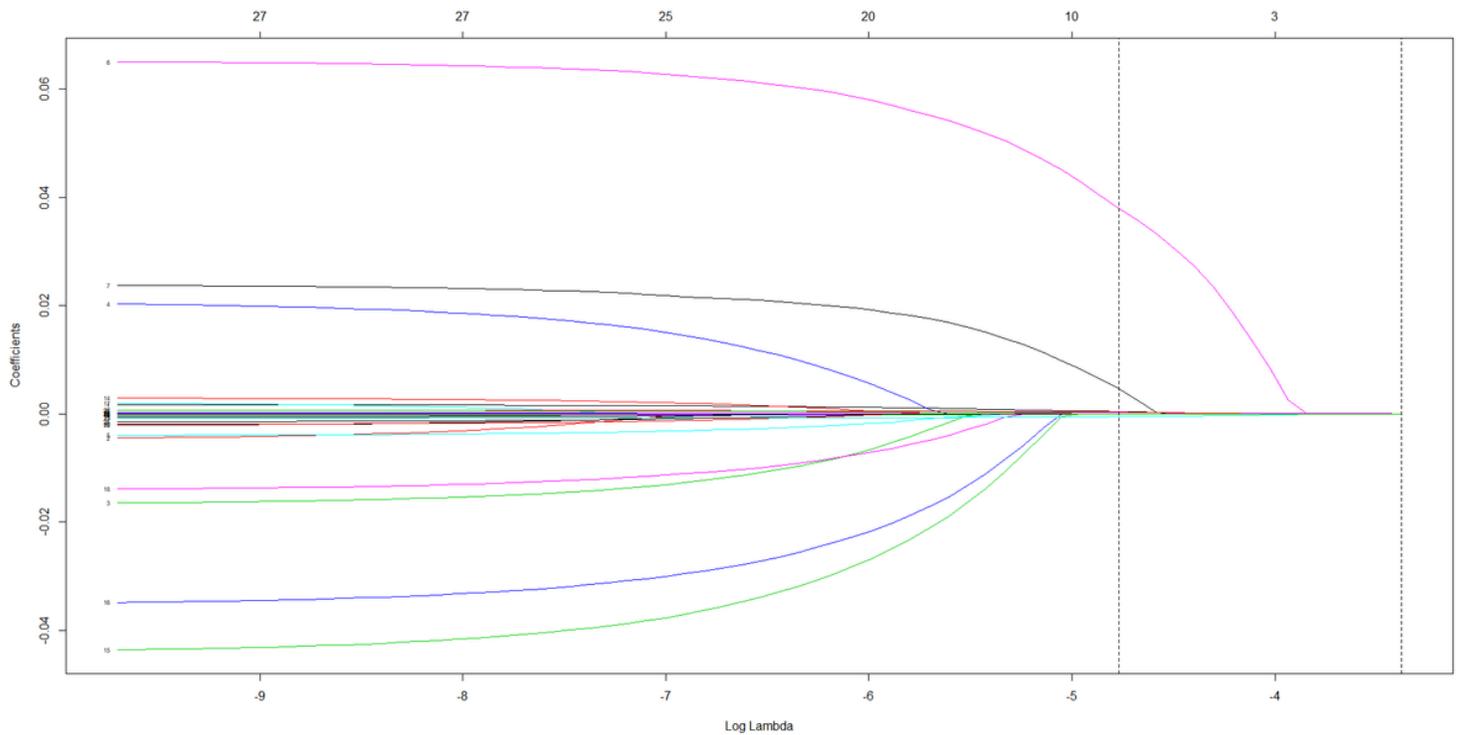


Figure 1

Demographic and clinical feature selection using the LASSO binary logistic regression model. Notes: (A) Optimal parameter (lambda) selection in the LASSO model used fivefold cross-validation via minimum criteria. The partial likelihood deviance (binomial deviance) curve was plotted versus log(lambda). Dotted vertical lines were drawn at the optimal values by using the minimum criteria and the 1 SE(standard error) of the minimum criteria (the 1-SE criteria).

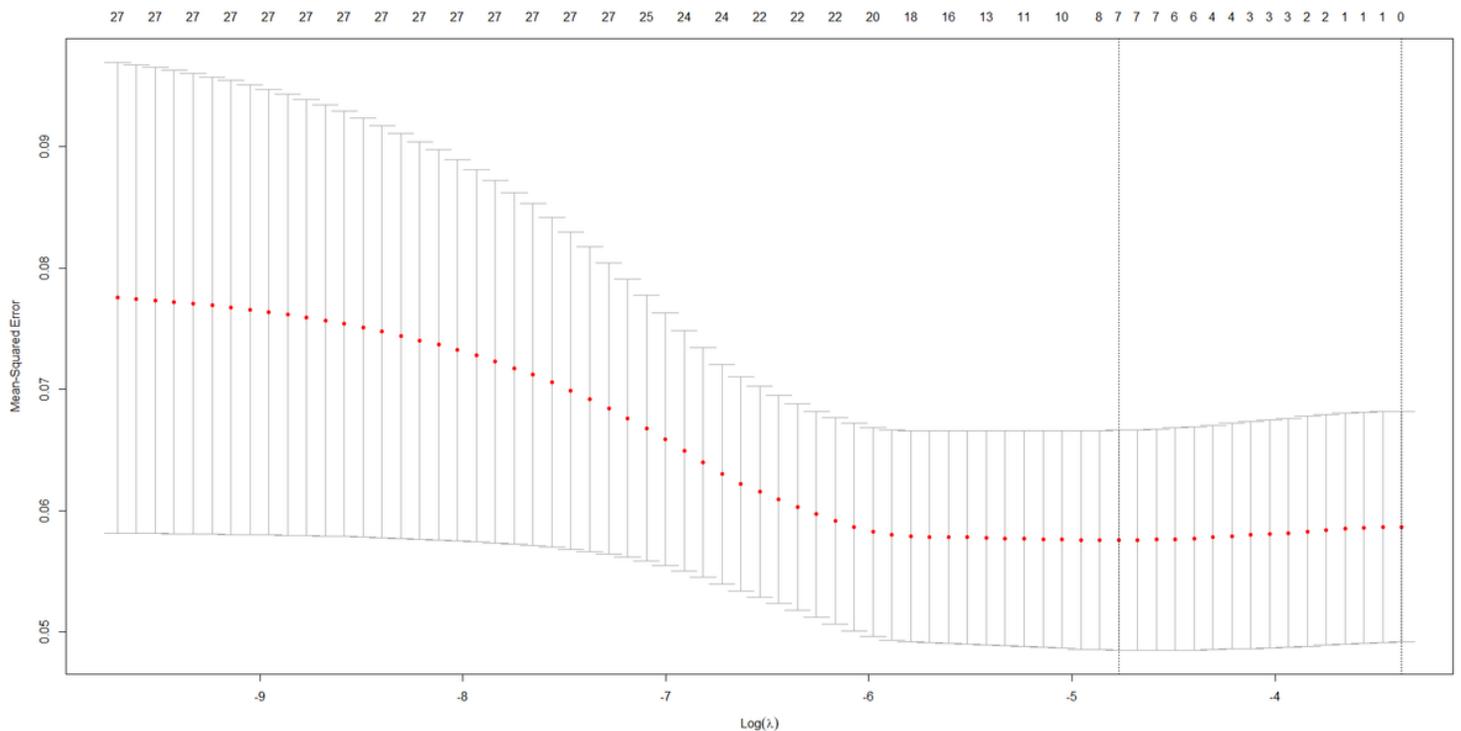


Figure 2

Demographic and clinical feature selection using the LASSO binary logistic regression model. Notes: (B) LASSO coefficient profiles of the 27 features. A coefficient profile plot was produced against the $\log(\lambda)$ sequence. Vertical line was drawn at the value selected using fivefold cross-validation, where optimal λ resulted in seven features with nonzero coefficients.

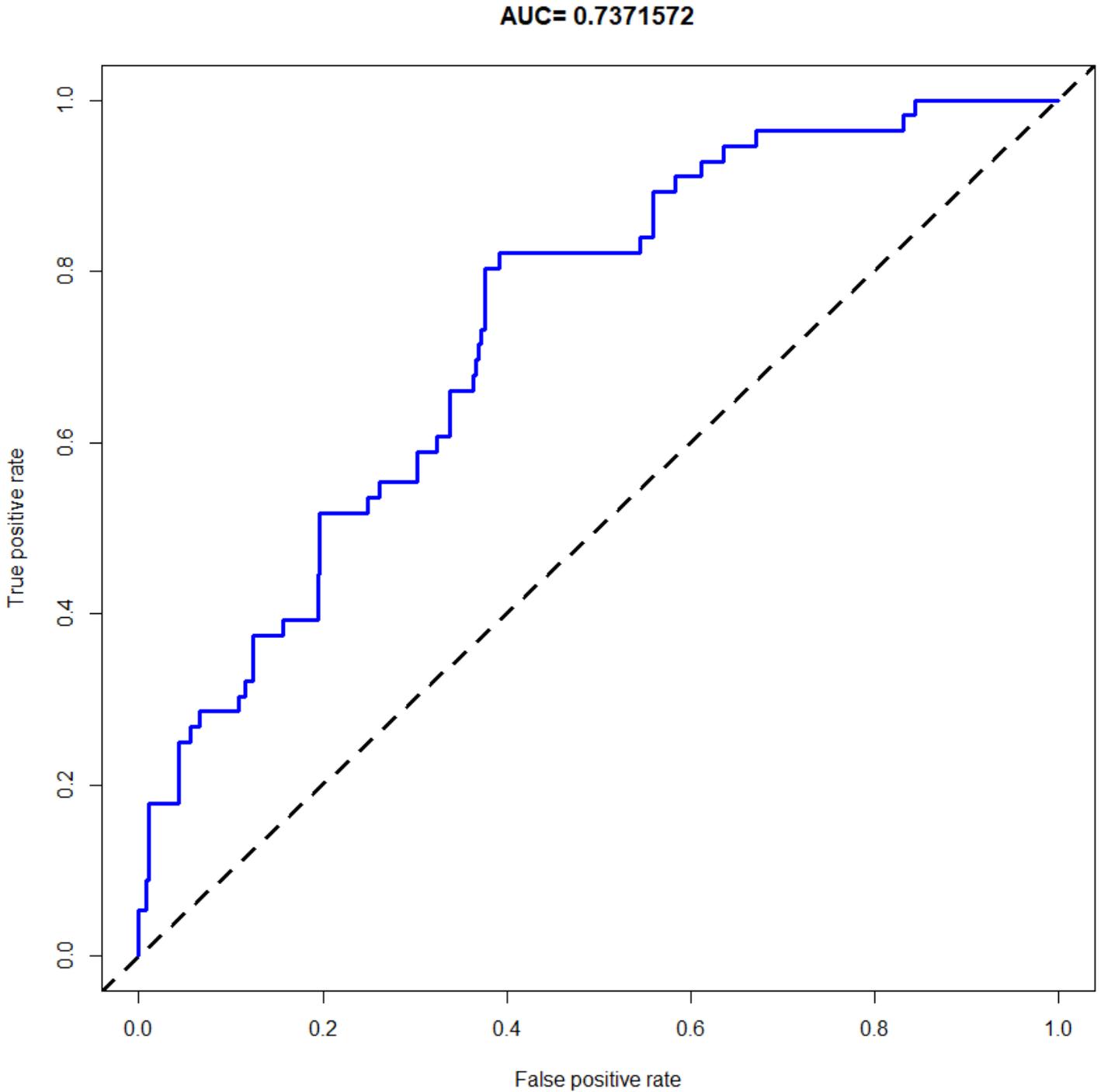


Figure 3

The AUC-ROC of the Nomogram of the training cohort

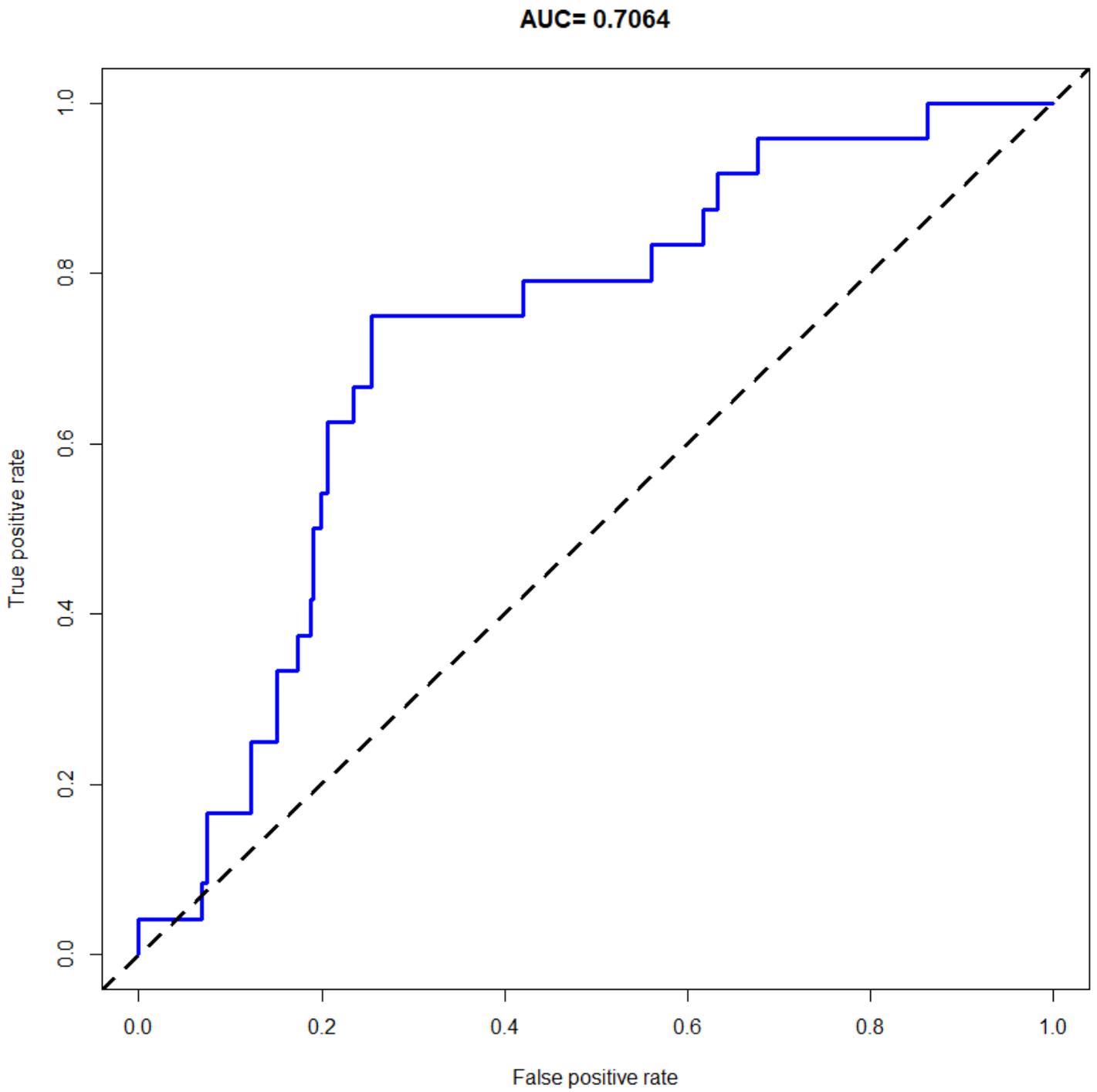


Figure 4

The AUC-ROC of the Nomogram of the validating cohort

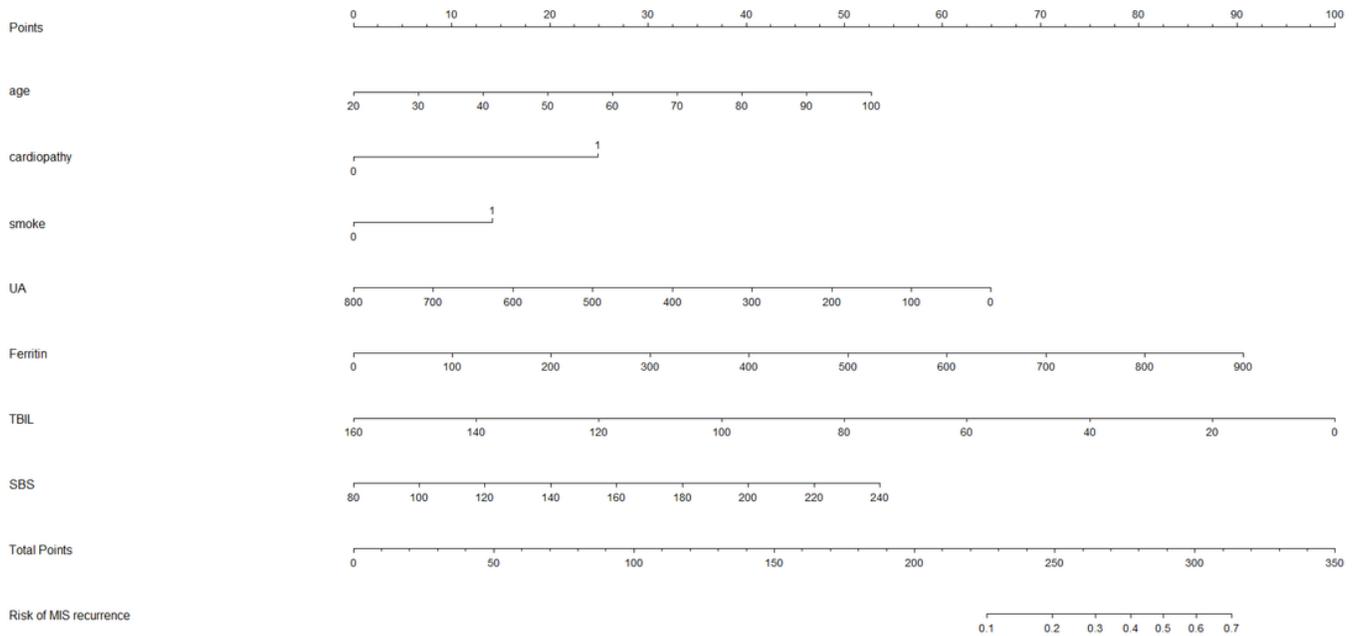


Figure 5

Nomogram of The Original Version The nomogram for Predicting of Relapse during Hospitalization after Minor Ischemic Stroke in Chinese Patient

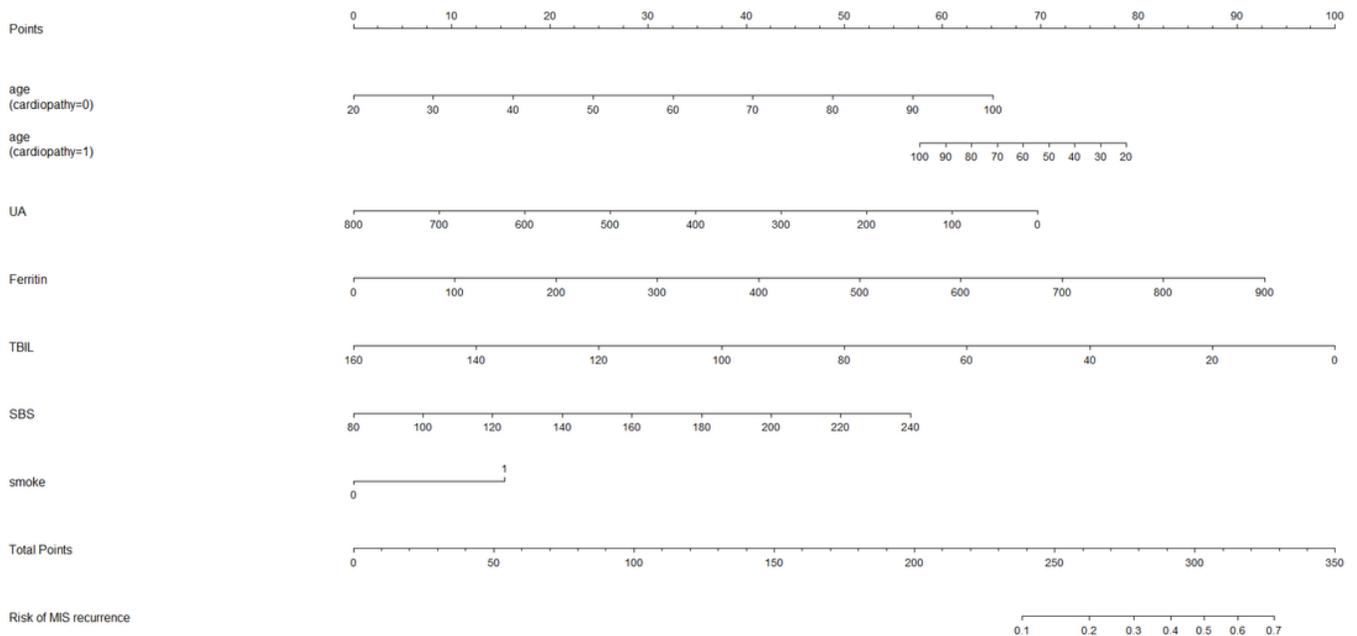


Figure 6

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