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ORIGINAL RESEARCH

Development and Validation of a Nomogram for Predicting Lacunar Infarction in Patients with Hypertension

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Background: A considerable proportion of hypertensive patients may experience lacunar infarction. Therefore, early identification of the risk for lacunar infarction in hypertensive patients is particularly important. This study aimed to develop and validate a concise nomogram for predicting lacunar infarction in hypertensive patients.

Methods: Retrospectively analyzed the clinical data of 314 patients with accurate history of hypertension in the Second Affiliated Hospital of Wannan Medical College from January 2021 to December 2022. All the patients were randomly assigned to the training set (n=220) and the validation set (n=94) with 7:3. The diagnosis of lacunar infarction in patients was confirmed using cranial CT or MRI. The independent risk factors of lacunar infarction were determined by Least absolute shrinkage and selection operator (LASSO) regression and multivariable logistic regression analysis. The nomogram was built based on the independent risk factors. The nomogram's discrimination, calibration, and clinical usefulness were evaluated by receiver operating characteristics (ROC) curve, calibration curve, and decision curve analysis (DCA) analysis, respectively.

Results: The incidence of lacunar infarction was 34.50% and 33.00% in the training and validation sets, respectively. Five independent predictors were made up of the nomogram, including age (OR=1.142, 95% *CI*: 1.089–1.198, *P*<0.001), diabetes mellitus (OR=3.058, 95% *CI*: 1.396–6.697, *P*=0.005), atrial fibrillation (OR=3.103, 95% *CI*: 1.328–7.250, *P*=0.009), duration of hypertension (OR=1.130, 95% *CI*: 1.045–1.222, *P*=0.002), and low-density lipoprotein (OR=2.147, 95% *CI*: 1.250–3.688, *P*=0.006). The discrimination with area under the curve (AUC) was 0.847 (95% *CI*: 0.789–0.905) in the training set and was a slight increase to 0.907 (95% *CI*: 0.838–0.976) in the validation set. The calibration curve showed high coherence between the predicted and actual probability of lacunar infarction. Moreover, the DCA analysis indicated that the nomogram had a higher overall net benefit of the threshold probability range in both two sets.

Conclusion: Age, diabetes mellitus, atrial fibrillation, duration of hypertension, and low-density lipoprotein were significant predictors of lacunar infarction in hypertensive patients. The nomogram based on the clinical data was constructed, which was a useful visualized tool for clinicians to assess the risk of the lacunar infarction in hypertensive patients.

Keywords: lacunar infarction, nomogram, hypertension, lasso regression, predictive model

Introduction

Stroke is the second leading cause of death worldwide, including large arterial disease, cardiogenic cerebral infarction, and small lacunar vessel disease.[1] Lacunar infarction (LI) accounts for 20–30% of ischemic strokes and is ignored due to its atypical clinical presentation.[2] However, the asymptomatic infarct is primarily responsible for cognitive impairment, acute ischemic stroke, and depression, especially in middle-aged and elderly people.[3,4] Therefore, early recognition of lacunar infarction needs to be widely concerned by society.

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Hypertension was the main cardiovascular risk factor in cerebral infarction only for lacunar strokes and atherothrombotic infarctions,[5] which impaired the structural and functional integrity of cerebral microcirculation, and aggravated cerebral microvascular endothelial dysfunction.[6] The incidence of cerebral infarction in hypertensive patients was significantly increased, even with stable blood pressure control.[7] Early identification of lacunar infarction in hypertensive patients was crucial, as it allowed clinicians to implement timely interventions, thereby improving patient outcomes and decreasing the incidence of long-term complications. In addition, accumulating studies indicated that age, diabetes, insulin resistance, and male gender have been the potential risk factors for lacunar infarction.[8–10] However, there was no concise predictive model for lacunar infarction in hypertensive patients. Hence, it is essential to investigate the associated risk factors and construct a predictive model to assist clinicians in the early identification of lacunar infarction in hypertensive patients.

In this study, we aimed to find the sociodemographic, clinical predictors, and available biomarkers to screen the potential risk factors for lacunar infarction, using a retrospective cohort of hypertensive patients. Compared to other predictive models, the nomogram offered a visual representation, making it easier for medical professionals to apply in clinical practice. Therefore, we build a nomogram for clinicians to make a visualized and quick assessment to predict the possibility of lacunar infarction in hypertensive patients.

Methods

Study Design and Patients

This retrospective study enrolled 415 patients in the Second Affiliated Hospital of Wannan Medical College from January 2021 to December 2022. All patients were not required to agree with the use of their medical records. The clinical data of patients were strictly confidential. The study was approved by the Medical Ethics Committee of the Second Affiliated Hospital of Wannan Medical College and conducted in accordance with the principles of the Declaration of Helsinki (No. WYEFYLS202205). The ethics committee waived the requirement for patient informed consent due to the retrospective study design. All patient medical records were anonymized and strict confidentiality measures were implemented.

The inclusion criteria with patients were as follows: (1) age>18 years; (2) accurate history of hypertension; (3) completed a cranial computed tomography (CT) scan or magnetic resonance imaging (MRI) examination during the hospitalization; (4) patient with National Institute of Health Stroke Scale (NIHSS score) <5 on admission. The exclusion criteria were as follows: (1) incomplete medical records; (2) acute ischemic stroke or cerebral hemorrhage; (3) any other diagnosed inflammatory or infectious disorders of the neurological system; (4) malignancy or hematological disorders; (5) severe liver disease or chronic kidney failures.

According to the inclusion and exclusion criteria, a total of 314 patients were included in this study. Subsequently, we randomly assigned 220 patients to the training set and 94 patients to the validation set (the split ratio was 7:3) for nomogram construction and validation (Figure 1).

Observation Indicators and Definition

All patients completed a routine clinical evaluation, including age, gender, body mass index (BMI), comorbidities (diabetes mellitus, atrial fibrillation, coronary heart disease, chronic heart failure, and chronic obstructive pulmonary disease), and blood pressure monitoring. Clinical data included clinical symptoms (headache, vertigo, limb weakness), length of stay, and duration of hypertension. Laboratory examinations included red blood count (RBC), white blood count (WBC), hemoglobin (HB), platelet (PLT), total cholesterol (TC), low-density lipoprotein (LDL), triglyceride (TG), albumin (ALB), total bilirubin (TBIL), creatinine (CREA), blood urea nitrogen (BUN), uric acid (UA), alanine transaminase (ALT), serum potassium, serum sodium, and serum calcium. Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP)≥90 mmHg.[11] BMI was calculated as dividing body weight (kg) by height (m^2).[12]

Imaging

All enrolled patients underwent CT or MRI examinations within 24 hours of admission. The CT examinations were performed using a 64-section multidetector-row CT scanner (Model: Brilliance, Philips, The Netherlands). The scanning

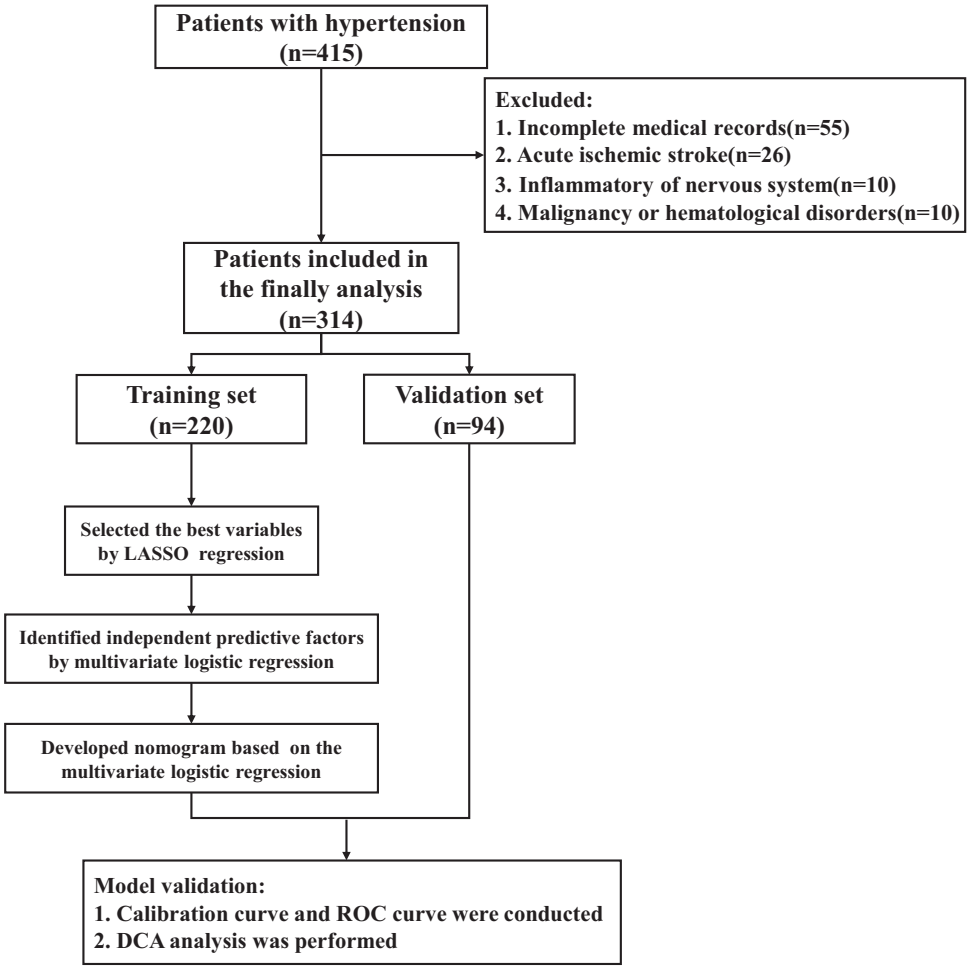

Figure 1 Flow chart with the study.

parameters were as follows: tube voltage of 120 kV, tube current ranging from 150 to 400 mA, slice thickness of 5 mm, pitch of 0.984, and a rotation time of 0.5 seconds. Image reconstruction was done using a standard algorithm with a reconstruction slice thickness of 1 mm.

The MRI examinations were performed using a 1.5-T MR scanner (Model: Optima MR360, GE healthcare, American). The scanning parameters were as follows: For T1-weighted imaging (T1WI), the parameters were TR (repetition time) =500 ms, TE (echo time) =10 ms, slice thickness =5 mm, and interslice gap=1 mm. For T2-weighted imaging (T2WI), the parameters were TR =3000 ms, TE =80 ms, slice thickness =5 mm, and interslice gap =1 mm. For FLAIR imaging, the parameters were TR=9000 ms, TE=120 ms, slice thickness=5 mm, and interslice gap=1 mm.

Lacunar infarction was characterized by a hypodense lesion measuring less than 2 cm in diameter, predominantly located in the basal ganglia, thalamus, or brainstem on CT scans, and appeared as hyperintense lesions on T2-weighted and FLAIR sequences, and hypointense lesions on T1-weighted sequences on MRI scans.[13] The diagnosis of lacunar infarction was confirmed by experienced radiologists and neurologists.[14]

Statistical Analysis

Statistical analysis was performed with SPSS 25.0 (IBM Corporation, 2020, USA) and R software (version 3.6.2, http://www.r-project.org). The normal distribution for all continuous variables was tested using the Kolmogorov–Smirnov (K-S) method. Continuous variables with normal distribution were presented as mean± standard deviation, which was examined by using the independent samples *t*-test. The median (interquartile range) was used to present for continuous variables which were not

normally distributed and were evaluated by the Mann–Whitney *U*-test. Categorical variables were expressed as frequency (percentage) and were examined by the chi-square test.

The least absolute shrinkage and selection operator (LASSO) method[15] was used to select the best variables of risk factors to predict lacunar infarction in hypertensive patients. LASSO regression incorporated an L1 regularization term in the regression model, effectively shrinking some feature coefficients to zero. Variables with nonzero features were selected in the LASSO regression model. Independent predictive factors were identified by multivariate logistic regression analysis. Based on the results of multivariate logistic regression analysis, a predictive nomogram was developed to predict lacunar infarction. A calibration curve was drawn to assess the fitting degree between the actual and nomogram-prediction by using a calibration plot with bootstraps of 1000 resamples. The receiver operating characteristics (ROC) curve was used to evaluate the diagnostic value of the nomogram for discriminating. The net-benefit of the decision curve analysis (DCA) curve was further performed to estimate the clinical value of the nomogram. All statistical results performed were two-sided and regression coefficients reported 95% confidence intervals (*CI*). $P<0.05$ was considered statistically significant.

Results

Demographics and Clinical Data of Patients in the Training and Validation Sets

In total, 314 patients with hypertension were retrospectively included in this study, of which 220 constituted the training set and 94 constituted the validation set. 76(34.50%) patients in the training set and 31(33.00%) patients in the validation set were diagnosed with lacunar infarction, respectively. The characteristics and clinical data of the patients in the training set and the validation set were no significant differences ($P>0.05$) (Table 1).

Table 1 Demographics and Clinical Characteristics with Patients of the Training and Validation Sets

Variables	Total (n=314)	Training Set (n=220)	Validation Set (n=94)	*P* value
Demographic characteristics				
Age, years†	56.30±8.11	56.37±8.37	56.13±7.53	0.807
Male, n (%)‡	158(50.30)	110(50.00)	48(51.10)	0.863
BMI, kg/m²§	20.81(18.36, 23.49)	20.99(18.36, 23.79)	20.21(18.34, 23.40)	0.713
Clinical data				
Headache, n (%)‡	49(15.60)	36(16.40)	13(13.80)	0.571
Vertigo, n (%)‡	62(19.70)	44(20.00)	18(19.10)	0.862
Limb weakness, n (%)‡	66(21.00)	47(21.40)	19(20.20)	0.819
Length of stay, day§	8(6, 10)	8(6, 9)	8(6, 11)	0.080
Duration of hypertension, years§	9(7, 12)	9(7, 12)	8(6, 12)	0.462
Comorbidities				
Diabetes mellitus, n (%)‡	91(29.00)	63(28.60)	28(29.80)	0.837
Atrial fibrillation, n (%)‡	62(19.70)	38(17.30)	24(25.50)	0.092
Coronary heart disease, n (%)‡	81(25.80)	54(24.50)	27(28.70)	0.438
Chronic heart failure, n (%)‡	72(22.90)	49(22.30)	23(24.50)	0.672
COPD, n (%)‡	55(17.50)	36(16.40)	19(20.20)	0.411
Laboratory examination				
RBC, $\times10^{12}$/l†	3.82±0.75	3.78±0.73	3.91±0.78	0.166
WBC, $\times10^{9}$/l§	6.46(5.11, 8.72)	6.49(5.03, 8.69)	6.27(5.24, 8.83)	0.765
HB, g/l§	117.00(102.00, 131.25)	119.00(103.25, 132.00)	115.00(100.00, 130.00)	0.226
PLT, $\times10^{12}$/l§	131.00(95.50, 182.25)	135.00(96.75, 184.75)	114.50(85.00, 176.25)	0.105
TC, mmol/l†	3.80±1.09	3.79±1.11	3.80±1.06	0.971
LDL, mmol/l†	1.71±0.68	1.71±0.69	1.71±0.67	0.928
TG, mmol/l†	1.11±0.69	1.14±0.75	1.04±0.53	0.258
ALB, g/l†	36.45±4.66	36.14±4.57	37.18±4.83	0.069

(*Continued*)

Table 1 (Continued).

Variables	Total (n=314)	Training Set (n=220)	Validation Set (n=94)	*P* value
TBIL, μmol/l[§]	19.70(14.20, 27.90)	19.65(14.23, 28.28)	20.05(14.05, 27.43)	0.756
CREA, μmol/l[§]	84.05(64.85, 108.78)	83.45(63.90, 110.08)	85.60(67.53, 106.18)	0.465
BUN, mmol/l[§]	7.36(5.78, 10.32)	7.36(5.87, 10.42)	7.43(5.66, 9.79)	0.500
UA, mmol/l[§]	440.50(357.75, 549.50)	452.50(358.25, 562.75)	422.50(354.75, 517.50)	0.106
ALT, u/l[§]	22.50(15.00, 32.25)	22.50(15.00, 31.00)	22.50(15.75, 35.00)	0.511
Serum potassium, mmol/l[§]	3.86(3.52, 4.35)	3.87(3.51, 4.35)	3.79(3.52, 4.36)	0.597
Serum sodium, mmol/l[§]	139.00(136.38,141.00)	139.05(136.15, 141.20)	139.00(136.63, 141.00)	0.871
Serum calcium, mmol/l[§]	2.28(2.19, 2.41)	2.28(2.20, 2.41)	2.28(2.17, 2.38)	0.369
Lacunar infarction, n (%)[‡]	107(34.10)	76(34.50)	31(33.00)	0.788
Subtypes of lacunar infarction				0.215
Pure motor hemiparesis, n (%)[‡]	62(19.70)	44(20.00)	18(19.10)	
Pure sensory stroke, n (%)[‡]	69(22.00)	54(24.50)	15(16.00)	
Sensorimotor syndrome, n (%)[‡]	75(23.90)	54(24.50)	21(22.30)	
Ataxic hemiparesis, n (%)[‡]	38(12.10)	27(12.30)	11(11.70)	
Dysarthria clumsy, n (%)[‡]	29(9.20)	18(8.20)	11(11.70)	
Atypical lacunar syndromes, n (%)[‡]	41(13.10)	23(10.50)	18(19.10)	

Notes: [§]Mann–Whitney *U*-test; [†]Independent-samples *t*-Test; [‡]Pearson's χ^2 test.
Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; RBC, red blood count; WBC, white blood count; HB, hemoglobin; PLT, Platelet; TC, total cholesterol; LDL, low-density lipoprotein; TG, Triglyceride; ALB, albumin; TBIL, total bilirubin; CREA, creatinine; BUN, blood urea nitrogen; UA, uric acid; ALT, Alanine transaminase.

Variable Selection in the LASSO Regression and Multivariate Logistic Regression Analysis

Of the demographic characteristics, clinical data, comorbidities, and laboratory examinations, 5 potential variables were selected from 29 clinical features with nonzero coefficients in the LASSO binary logistic regression analysis. These factors included age, diabetes mellitus, atrial fibrillation, duration of hypertension, and low-density lipoprotein (Figure 2). Multivariate logistic regression analysis revealed that age (OR=1.142, 95% *CI*: 1.089–1.198, *P*<0.001), diabetes mellitus (OR=3.058, 95% *CI*: 1.396–6.697, *P*=0.005), atrial fibrillation (OR=3.103, 95% *CI*: 1.328–7.250, *P*=0.009), duration of hypertension (OR=1.130, 95% *CI*: 1.045–1.222, *P*=0.002), low-density lipoprotein (OR=2.147, 95% *CI*: 1.250–3.688, *P*= 0.006) were key predictors of lacunar infarction risk in patients with hypertension (Table 2).

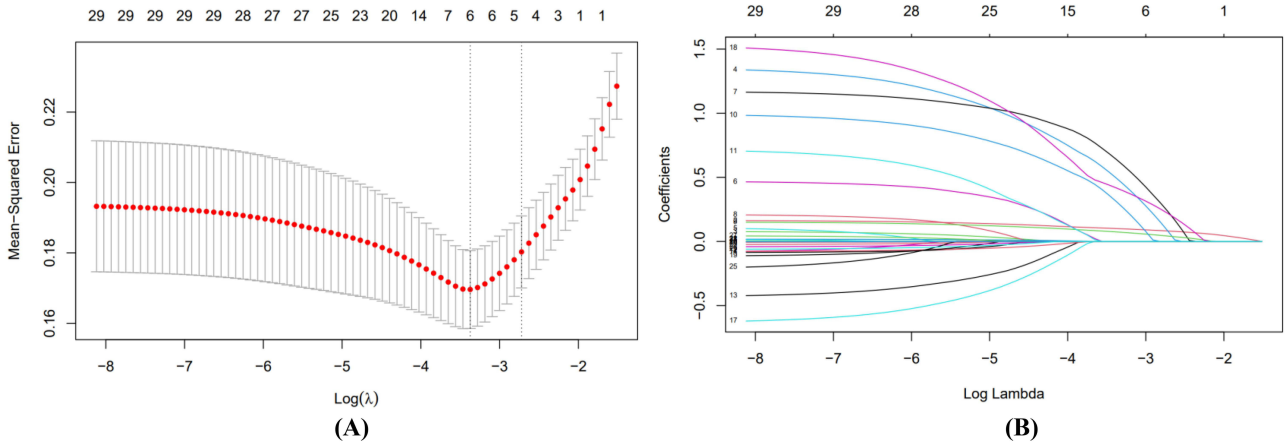

Figure 2 Variable of demographic and clinical data selection using the LASSO binary logistic regression model.
Notes: (**A**) Optimal parameter (lambda) selection of the LASSO model were obtained via 10-fold cross-validation. Dotted vertical lines were drawn at the optimal values based on the minimum criteria and the one standard error of the minimum criteria. Five variables with nonzero coefficients were selected based on the one standard error of the minimum criteria (lambda.1se =0.0658). (**B**) LASSO coefficient profiles of the 29 features. A coefficient profile plot was produced against the log (lambda) sequence. LASSO, the least absolute shrinkage, and selection operator.

Table 2 Multivariate Analysis of Risk Factors for Lacunar Infarction in Patients with Hypertension

Variables	Multivariate Logistic Regression		
	β	Odds Ratio (95% *CI*)	*P*-value
Age	0.133	1.142(1.089–1.198)	<0.001
Diabetes mellitus	1.118	3.058(1.396–6.697)	0.005
Atrial fibrillation	1.132	3.103(1.328–7.250)	0.009
Duration of hypertension	0.122	1.130(1.045–1.222)	0.002
Low-density lipoprotein	0.764	2.147(1.250–3.688)	0.006

Development of a Predictive Nomogram

A clinical nomogram was developed for predicting the probability of lacunar infarction based on the results from the multivariate logistic regression analysis, which included 5 variables (Figure 3). Drew a vertical line up to the "Point" axis to calculate the score of each variable, and the total score was summarized by the preliminary scores. Locate the total score on the "Total Points" axis, then the corresponding predicted probability of lacunar infarction could be located on the bottom axis. The higher the sum of points with each variable in the nomogram, the higher the risk of lacunar infarction.

The Discrimination of the Nomogram by ROC Curve

The AUC for the nomogram was 0.847 (95% *CI*: 0.789–0.905) in the training set (Figure 4A) and was confirmed to be 0.907 (95% *CI*: 0.838–0.976) in the validation set (Figure 4B), which demonstrated the model's good discrimination. By contrast, the nomogram had high efficacy in detecting lacunar infarction in the training cohort, with accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 0.847, 0.803, 0.819, 0.701, and 0.887, respectively (Table 3).

Subgroup analysis revealed that the AUC of the nomogram for predicting lacunar infarction was 0.846 (95% *CI*: 0.778–0.913) in male patients (Figure 4C), and 0.893(95% *CI*: 0.837–0.949) in female patients (Figure 4D).

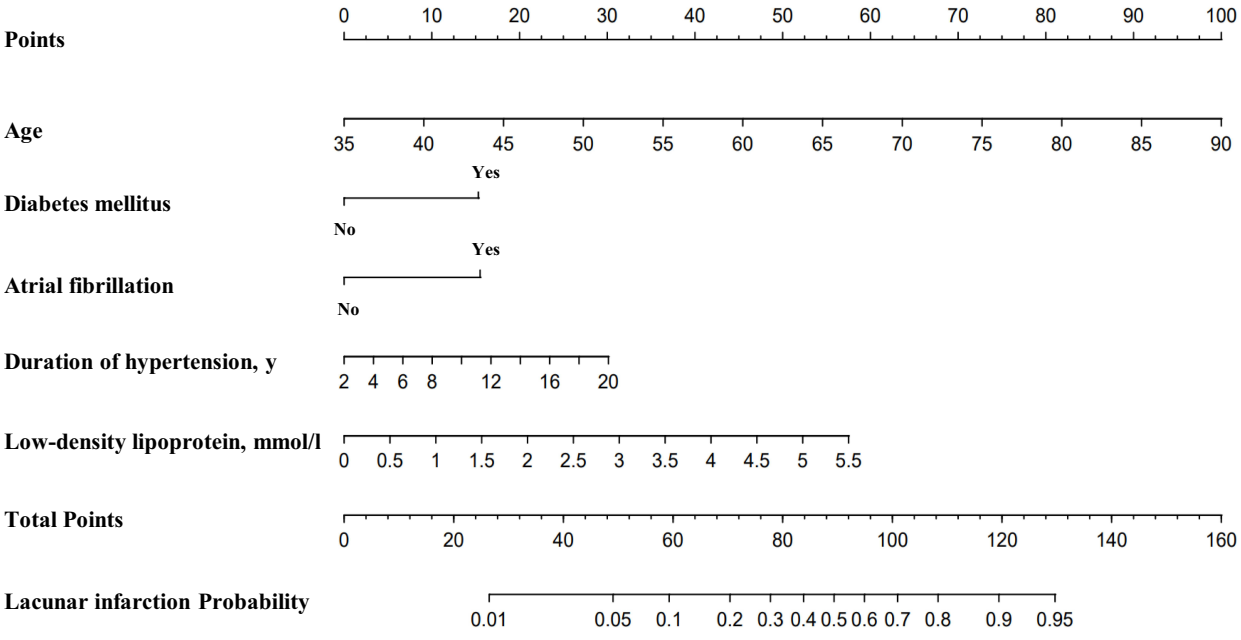

Figure 3 Development of a predictive nomogram. Notes: The lacunar infarction risk nomogram was developed using 5 predictors, including age, diabetes mellitus, atrial fibrillation, duration of hypertension, and low-density lipoprotein.

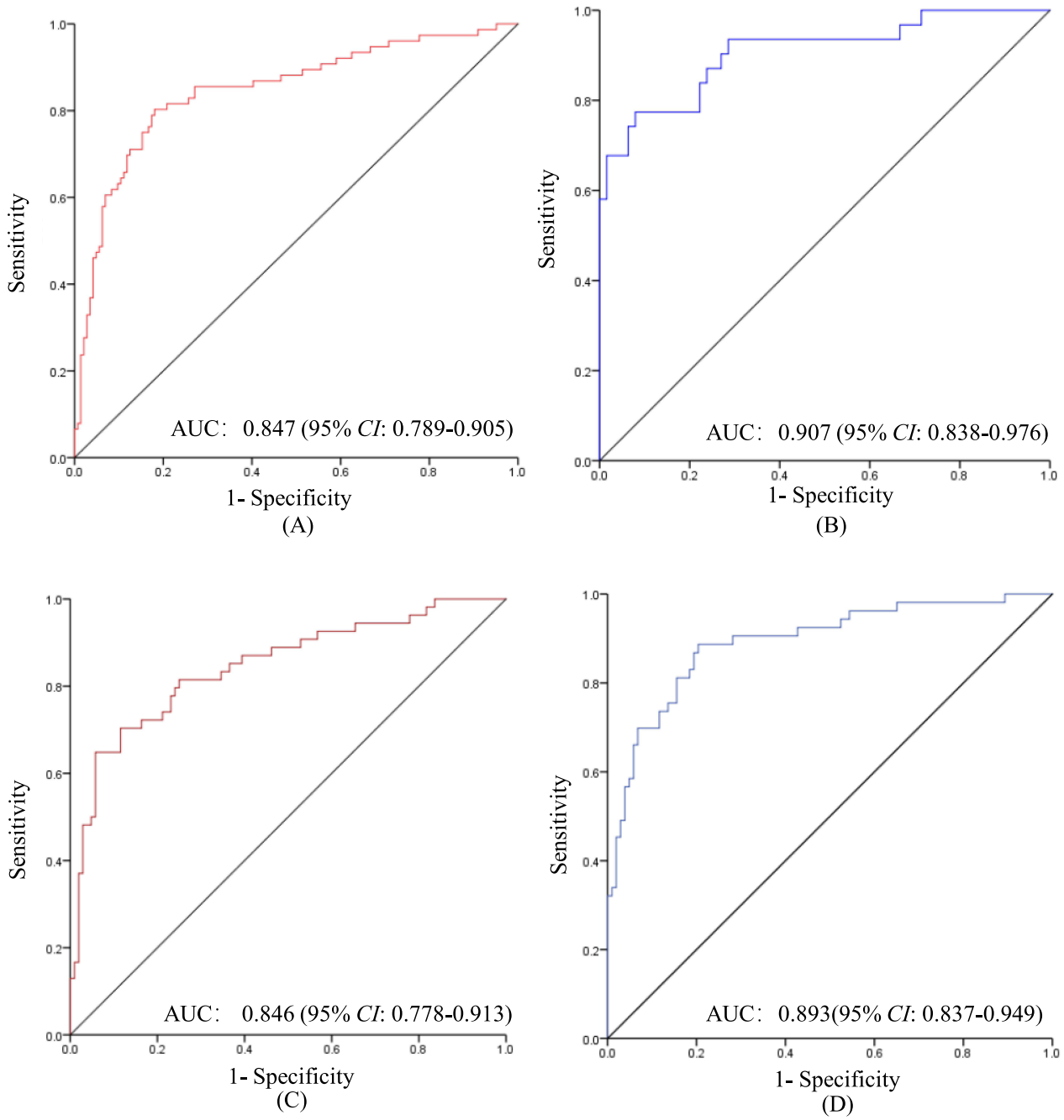

Figure 4 ROC curves of nomogram.
Notes: (**A**) ROC in the training set; (**B**) ROC in the validation set; (**C**) ROC in male patients; (**D**) ROC in female patients.

The Performance of the Nomogram

The performance of the nomogram was evaluated using the calibration curve. The calibration curves of the nomogram in the training set (Figure 5A) and validation set (Figure 5C) were plotted, which demonstrated a good agreement in both sets.

Clinical Use

The decision curve analysis for the nomogram showed that the use of this nomogram to predict the lacunar infarction risk yielded more net benefit than the scheme when the threshold probabilities of lacunar infarction in patients with

Table 3 Diagnostic Performances of Predictive Factors and Nomogram in the Training Set

	AUC (95% *CI*)	Sensitivity, % (95% *CI*)	Specificity, % (95% *CI*)	PPV, % (95% *CI*)	NPV, % (95% *CI*)
Age	0.772(0.699–0.846)	60.53(48.6–71.6)	95.83(91.2–98.5)	88.50(76.6–95.6)	88.5(76.6–95.6)
Diabetes mellitus	0.583(0.502–0.664)	39.47(28.4–51.4)	77.08(69.3–83.7)	47.6(34.9–60.6)	70.7(62.9–77.7)
Atrial fibrillation	0.579(0.497–0.661)	27.63(18.0–39.1)	88.19(81.8–93.0)	55.3(38.3–71.4)	69.8(62.5–76.4)
Duration of hypertension	0.662(0.582–0.742)	73.68(62.3–83.1)	55.56(47.1–63.8)	46.7(37.5–56.0)	80.0(70.8–87.3)
Low-density lipoprotein	0.636(0.558–0.714)	42.11(30.9–54.0)	82.64(75.4–88.4)	56.1(42.4–69.3)	73.0(65.5–79.7)
Nomogram	0.847(0.789–0.905)	80.26(69.5–88.5)	81.94(74.7–87.9)	70.1(59.4–79.5)	88.7(82.1–93.5)

Abbreviations: AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value.

hypertension ranged from 10% to 82% in the training set (Figure 5B), and 10% to 99% in the validation set (Figure 5D). These results indicated the predictive nomogram to be clinically useful.

Discussion

Lacunar infarction is a small deep infarction caused by penetrating arterial embolism, accounting for about 30% of all strokes.[16,17] Early identification of risk factors for lacunar infarction was critical to stroke prevention.[18] In this study, we investigated the risk factors of lacunar infarction in hypertensive patients. Several pivotal results were found in this study. First, the prolonged duration of hypertension had significantly associated with lacunar infarction. Second, we proved

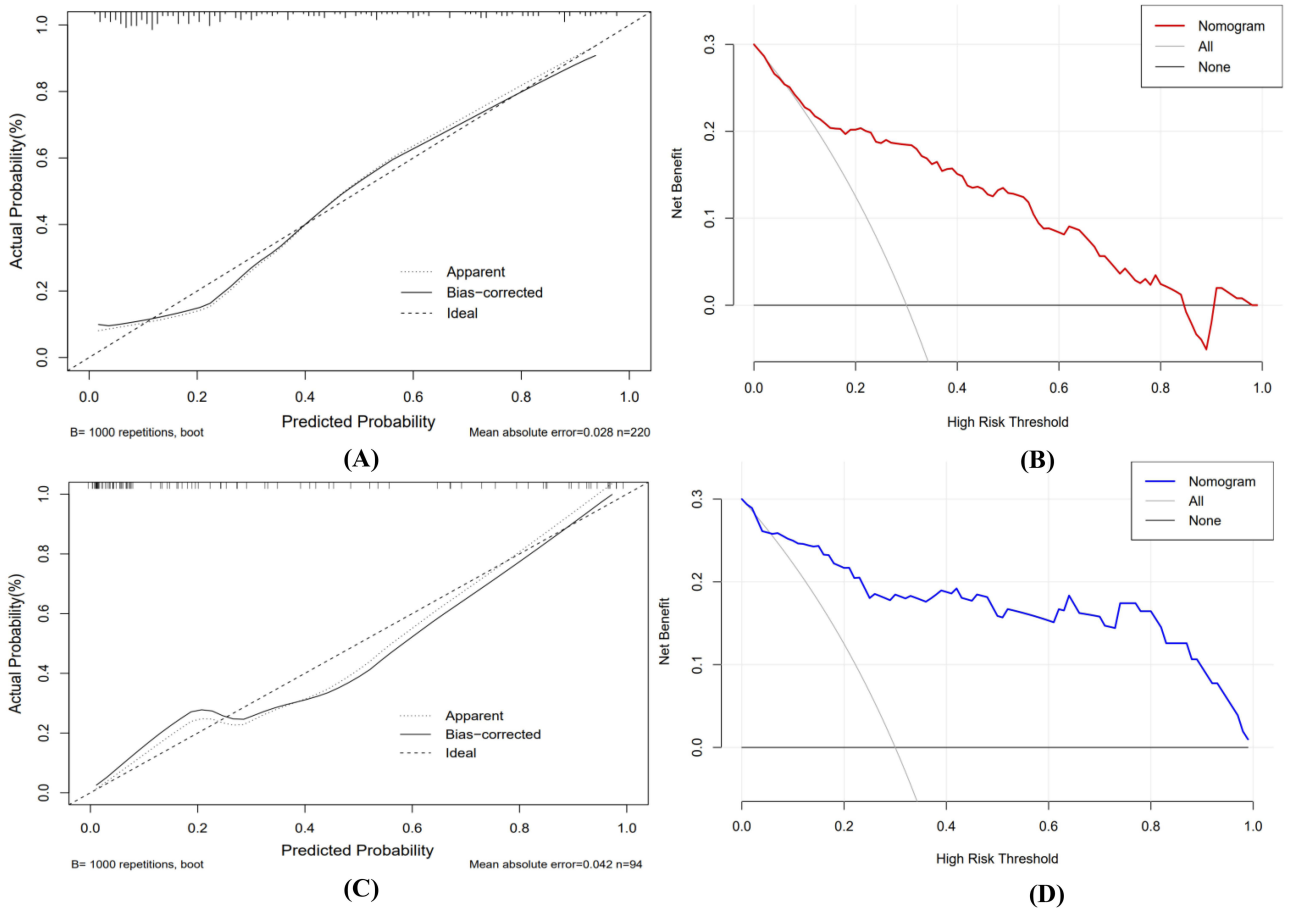

Figure 5 Calibration curves and decision curve analysis (DCA) for the lacunar infarction risk nomogram.
Notes: (**A**) Calibration curve to measure the coherence of nomogram in the training set (mean absolute error=0.029). (**B**) Calibration curve to measure the coherence of nomogram in the validation set (mean absolute error=0.044). (**C**) The DCA of nomogram in the training set. (**D**) The DCA of nomogram in the validation set. The red line represents the lacunar infarction risk nomogram. The y-axis represents the net benefit. The grey slash line represents the assumption that all hypertensive patients had lacunar infarction. The horizontal black line represents the assumption that no patients had lacunar infarction events.

several traditional risk factors, such as age, diabetes mellitus, atrial fibrillation, and low-density lipoprotein were also independently associated with lacunar infarction. Third, we draw a nomogram model based on the traditional risk factors that can effectively predict lacunar infarction in hypertensive patients.

Lacunar infarcts are common in elderly patients with hypertension, with an annual incidence of 1,500,000 to 2,000,000 new cases in China.[19] One study carried out in Dutch found the prevalence of lacunar infarction in people over 45 years old was 5.6%.[20] In addition, the existing evidence found that the older the age, the higher the probability of lacunar infarction.[21] Moreover, the probability of lacunar infarction increased with age in both males and females.[22] The reason may be related to the long-term exposure to risk factors such as hypertension, arteriosclerosis, and diabetes as they grow older.[23,24]

Hypertension is the main cause of lacunar infarction and affects nearly half of Chinese adults.[25,26] Hypertension-induced arteriolar hyaline degeneration, atherosclerosis, and fibrinoid necrosis ultimately leaded to lacunar infarction.[26–28] Sun's study showed that an increased incidence of lacunar infarction was associated with a longer duration of hypertension, which was consistent with our findings.[26] In addition, they found that left atrial enlargement was closely associated with hypertension and was a risk factor for lacunar infarction. The longer duration of hypertension, the larger the diameter of the left atrium, and the higher the probability of lacunar infarction. There is no doubt that controlling blood pressure is the key to the prevention of lacunar infarction.[23]

Diabetes mellitus is a metabolic disease characterized by insulin resistance.[29] The latest epidemiological study indicated that about 11% of adults in China were diagnosed with diabetes and 61 million people with underlying diabetes.[30,31] The total number of people with diabetes mellitus worldwide is projected to increase to 366 million by 2030 due to population growth, aging, and rising obesity rates.[32] Cardiovascular complications are the leading cause of death in patients with diabetes mellitus.[33] Adults with diabetes mellitus have increased risks of stroke due to the vicious cycle that exists between hyperglycemia and microvascular dysfunction.[34,35] One population-based study confirmed that subjects with diabetes mellitus had a two-fold higher risk of developing lacunar infarction.[36] Mohammed's study revealed that lacunar infarction was more common in diabetic patients.[37] Our study also confirmed that diabetes mellitus was an independent risk factor for early clinical deterioration in lacunar infarction patients, which was consistent with Ferrari J's study.[38] Therefore, hypertensive patients complicated with diabetes mellitus should be more worthy of the attention of clinicians, and the risk of cardiovascular and cerebrovascular accidents would be significantly increased.[39,40]

Atrial fibrillation (AF) is the most common arrhythmia in aging patients.[41] Cardiac fibrosis caused by atrial fibrillation can lead to atrial systolic dysfunction and increase the possibility of thrombosis.[42] It has been recognized as an independent factor of poor prognosis in stroke patients.[43] A 34-year follow-up study confirmed that stroke rates in patients with atrial fibrillation were nearly five times higher than in patients without atrial fibrillation.[44] In addition, the 2017 American Heart Association/American Stroke Association (AHA/ASA) statement also pointed out that risk stratification of lacunar infarction in patients with atrial fibrillation is also important for the prevention of symptomatic cerebral infarction in the future.[45] The mechanism of lacunar infarction in patients with atrial fibrillation may be related to microembolism from the left atrial appendage.[46] Lacunar infarction caused by atrial fibrillation will make patients at greater risk of cognitive impairment and disability in the future.[47,48] Additionally, in patients with atrial fibrillation, the development of new limb weakness or sensorimotor stroke should also consider the possibility of a lacunar syndrome caused by non-lacunar infarction.[49] Therefore, we need to develop appropriate preventive and therapeutic strategies to reduce the incidence of atrial fibrillation. Furthermore, anticoagulants are commonly used drugs to prevent thromboembolism in patients with atrial fibrillation, which would play an important role in reducing future lacunar infarction in patients with atrial fibrillation.[50]

In our study, low-density lipoprotein was also a risk factor for lacunar stroke in hypertensive patients. Rutten-Jacobs's study found that infarcts in the deep grey nuclei/internal capsule more often happened in lacunar infarction and were related to hyperlipidemia.[51] Tang H's study further confirmed that low-density lipoprotein level was an independent risk factor for single subcortical infarction in patients aged over 65.[52] Moreover, low-density lipoprotein can be used as an indicator of disease progression in patients with lacunar infarction. Although the use of statins brings certain benefits to lacunar infarction,[53] the range of low-density lipoprotein levels needed to be explored to prevent lacunar infarction in hypertensive patients.

However, our study has some limitations. First, the selection bias and recall bias were inevitable in this study. The diagnosis and the basic data of patients were retrospective collected based on an electronic medical record system. Second, the study was a single-center retrospective observational study, and the patients in the validation cohort were enrolled from the same local database, lacking validation with an external database from other institutes. Third, the study did not include treatment-related factors and stratify patients into different age groups, to explore their different risk factors for lacunar stroke. Undoubtedly, we need more clinical data to support our conclusions.

Conclusion

In conclusion, age, diabetes mellitus, atrial fibrillation, duration of hypertension, and low-density lipoprotein were significant predictors of lacunar infarction in hypertensive patients. The predictive model constructed based on the above five predictors demonstrated good predictive performance in predicting the probability of lacunar infarction, and this applied to both male and female patients. The nomogram has proven clinical utility and was useful for risk decision-making in patients with hypertension to prevent lacunar infarction.

Data Sharing Statement

The data and R codes are available from the corresponding author on reasonable request.

Ethical Approval

The study was approved by the Medical Ethics Committee of the Second Affiliated Hospital of Wannan Medical College and conducted in accordance with the principles of the Declaration of Helsinki (No. WYEFYLS202205).

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Disclosure

All authors declare no competing interests in the work.

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