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ORIGINAL RESEARCH

Nomogram-Based Prediction of 3-Month Unfavorable Outcome and Early Neurological Deterioration After Endovascular Thrombectomy in Acute Ischemic Stroke

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Background: Some acute ischemic stroke (AIS) patients due to large-vessel occlusion, who underwent endovascular thrombectomy (EVT), continue to experience unfavorable outcomes. Furthermore, the impact of internal carotid artery (ICA) tortuosity remains uncertain. This study aimed to determine the value of ICA tortuosity and clinical features in predicting 3-month unfavorable outcome and early neurological deterioration (END) after EVT in AIS patients through nomograms.

Methods: A total of 313 AIS patients treated with EVT at the First Affiliated Hospital of Xi'an Jiaotong University were retrospectively analyzed and randomized into two cohorts: training cohort (n=219) and validation cohort (n=94). After the selection of relevant features, nomograms for predicting the 3-month unfavorable outcome (mRS > 2) and END (an increase in NIHSS score of ≥4 within 24 hours) were established. The predictive accuracy of the nomograms was evaluated using ROC curves, calibration plots, and decision curve analysis (DCA).

Results: Among 313 patients, ICA tortuosity was observed in 19.50% (extracranial) and 21.10% (cavernous) of patients. Furthermore, 53.30% of patients experienced a 3-month unfavorable outcome, while END occurred in 15.70%. The independent predictors for the 3-month unfavorable outcome included age, NIHSS score, puncture-to-recanalization time, eTICI score, and blood glucose. The addition of two tortuosity features (extracranial and cavernous ICA tortuosity) resulted in a significant improvement in model differentiation. The nomogram that included ICA tortuosity achieved an AUC of 0.826 and 0.803 in the training and validation cohorts. ASPECT score, occlusion site, number of retriever passes, and blood glucose were identified as factors associated with END. The AUC was 0.770 and 0.772 in the training and validation cohorts. However, the incorporation of ICA tortuosity did not significantly enhance the model for predicting END.

Conclusion: ICA tortuosity characteristics significantly improve the discrimination of the nomogram model in predicting the 3-month unfavorable outcome. This can be used as guidance in clinical decision-making.

Keywords: nomogram, internal carotid artery tortuosity, endovascular thrombectomy, acute ischemic stroke, early neurological deterioration, 3-month unfavorable outcome

Introduction

The effectiveness of endovascular thrombectomy (EVT) has been validated by multiple randomized controlled trials in patients who experienced acute ischemic stroke (AIS) caused by large-vessel occlusion in the anterior circulation.[1,2] A recent meta-analysis study revealed that despite the success of second-generation thrombectomy devices, >50% of patients do not achieve favorable clinical outcomes after EVT.[3] Furthermore, some patients experience early neurologic deterioration (END), which is defined as the exacerbation of clinical symptoms that occurs shortly after EVT. Although

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the definition of END varies, its presence is frequently associated with worse clinical outcomes.[4,5] Therefore, identifying predictors for 3-month unfavorable outcome (mRS > 2) and END is crucial to determine adverse events and develop early postoperative prevention strategies, both in the short and long term. Previous studies[5,6] have identified age, NIHSS, and blood glucose as significant predictors of poor prognosis after EVT, and all of these are clinical factors. However, few studies have focused on the effect of vascular factors on the outcomes of EVT, and used this as one of the predictors. EVT is a therapeutic approach performed for blood vessels. Therefore, the influence of vascular factors, especially vascular anatomical features, deserves attention.

Vascular tortuosity is a frequently observed morphological change that affects both the arteries and veins throughout the body. Its development may be influenced by genetic predisposition, as well as vascular risk factors, including aging and hypertension.[7–9] Curved vascular anatomy is the frequent cause of thrombectomy failure. In curved vessels, the retriever stent may be stretched and folded during the procedure, reducing interaction with the thrombus.[10] Furthermore, vascular tortuosity may reduce the contact area between the guiding catheter and thrombus.[11] These factors may lead to increased number of device passes, prolonged procedure time, and greater damage to the vessel wall, which are potential risk factors for intracranial hemorrhage and unfavorable outcomes. Localized hemodynamic abnormalities, such as turbulence, may be present in curved vessels, and may likewise be a causative factor for poor postoperative outcomes. Vessels that have been damaged by challenging surgical maneuvers may lead to poor long-term prognosis under the influence of persistently abnormal hemodynamics. It has been shown that internal carotid artery (ICA) tortuosity is independently associated with decreased likelihood of first-pass effect and increased risk of intracranial hemorrhage after EVT.[11] Furthermore, it has been demonstrated that the increase in tortuosity of cavernous ICA may affect the performance of the thrombectomy and that this can be applied as a predictor of poor postoperative neurological outcomes.[10,12]

A nomogram is a graphical statistical method used to integrate multiple variables into a continuous scoring system, allowing for the precise estimation of an individual's risk for a particular clinical event. Recently, numerous nomogram models have been created to forecast clinical outcomes, including early neurological improvement, symptomatic intracranial hemorrhage, and mortality after EVT. These models often incorporate factors, such as age, National Institutes of Health Stroke Scale (NIHSS) score, and radiomic characteristics.[6,13–15] However, at present, no nomogram model has been designed to include vascular tortuosity in predicting the probability of 3-month unfavorable outcomes and END in AIS patients undergoing EVT. Therefore, it is necessary to include ICA tortuosity in the prediction model to supplement the limitations of previous models that do not consider vascular factors. This would allow for a more accurate prediction of the outcomes of patients after EVT and minimize the risk of adverse prognosis that occurs through the more stringent management of indicators such as blood pressure and blood glucose in high-risk patients, providing a reference for postoperative management strategies. The present study aims to determine the value of ICA tortuosity and clinical characteristics in predicting the 3-month unfavorable outcome and END after EVT in AIS patients by establishing and validating two nomogram models.

Methods

Study Design and Patient Selection

The present retrospective observational study was conducted at the First Affiliated Hospital of Xi'an Jiaotong University, and data were obtained from AIS patients with large-vessel occlusion, who underwent EVT between December 2018 and December 2023. The present study employed anonymized patient data, and no specific interventions outside the normal treatment process were performed. All data were collected retrospectively, so we waived informed consent. This study obtained the approval from local institutional review boards (XJTU1AF2023LSK-443) and adhered to the Declaration of Helsinki. The patients were randomly allocated to two cohorts for model development and evaluation: 70% of patients were assigned to the training cohort, and 30% of patients were assigned to the validation cohort.

The inclusion criteria were, as follows: (1) patients with confirmed diagnosis of anterior circulation AIS caused by large-vessel occlusion, which involved the ICA or M1/M2 segments of the middle cerebral artery, as verified by imaging; (2) patients who underwent EVT within 24 hours of symptom onset; (3) patients with an extended Thrombolysis in

Cerebral Infarction (eTICI) score of 2a or higher after EVT; (4) patients with a pre-stroke Modified Rankin Scale (mRS) score of ≤2. The exclusion criteria were, as follows: (1) the absence of post-EVT digital subtraction angiography images or the inability to assess ICA tortuosity through angiography; (2) the presence of malignant tumors or severe organ failure; (3) patients who were hospitalized for <24 hours.

Clinical Data Collection

The following clinical data were obtained for the analysis: patient demographics (age and gender) and baseline neurological evaluations, such as the NIHSS score, Glasgow Coma Scale (GCS) score, and Alberta Stroke Program Early CT Score (ASPECTS). Furthermore, additional cerebrovascular risk factors were recorded, which included a history of stroke, hypertension, diabetes, coronary artery disease, atrial fibrillation, and smoking status. Moreover, information on stroke etiology, initial occlusion location, and procedure-related factors were collected, which included the thrombectomy strategy, onset-to-door time (ODT), puncture-to-recanalization time (PRT), number of retriever passes, procedural modes, use of bridging thrombolysis, and postoperative eTICI score. In addition, baseline laboratory results, such as platelet count, neutrophil and lymphocyte level, blood glucose, and low-density lipoprotein (LDL) level, were recorded.

In order to facilitate the clinical interpretation of the nomogram, all continuous variables were converted into categorical variables for feature screening. The NIHSS and ASPECT scores were dichotomized using internationally recognized cut-off values: 0–4, 5–14, 15–20, and 21–42 for NIHSS, and ≤7 vs >7 for ASPECTS. ODT and PRT were dichotomized based on the 75th percentile of patients in the training cohort, with cut-off points of ≤550 minutes vs >550 minutes for ODT, and ≤144 minutes vs >144 minutes for PRT. Other continuous variables were dichotomized using median values from the training cohort, with cut-off points defined, as follows: ≤67 years old vs >67 years old for age; ≤13 vs >13 for GCS score; ≤16 umol/L vs >16 umol/L for homocysteine; ≤7 mmol/L vs >7 mmol/L for blood glucose; ≤2 mmol/L vs >2 mmol/L for LDL levels; ≤2 vs >2 for number of retriever passes.

Extracranial and Cavernous ICA Tortuosity

The assessment of ICA tortuosity was independently performed by two experienced neurointerventionalists, who had over five years of practice, and were blinded to the clinical data and patient outcomes. Following previously established classification criteria, the extracranial ICA was categorized as straight (straight alignment and at an angle of <15° relative to the common carotid artery centerline), tortuous (exhibiting S- or C-shaped elongation), coiled (marked by an exaggerated S-shape or circular configuration), or kinked (acute angulation of <90°, often associated to stenosis). Both coiled and kinked configurations were classified as indicative of tortuous extracranial ICA[11,16] (Figure 1).

Cavernous ICA tortuosity was categorized according to a previously established grading system: Type I, characterized by open configurations of the genu; Type II, presented a more acute angle at the anterior genu; Type III, displayed posterior deflection of the posterior genu, creating a buckled appearance; Type IV, exhibited the most pronounced degree of tortuosity, resembling a Simmons catheter, wherein the posterior genu was superiorly buckled in relation to the anterior genu. Types III and IV were designated as tortuous cavernous ICA[11,17] (Figure 1).

The interobserver agreement between the two physicians was assessed using the Kappa statistic. For instances where discrepancies arose between their evaluations, a third physician was consulted, and the consensus reached through a three-way discussion was used for the final analysis.

Outcomes

The NIHSS scores were documented for each patient at baseline and at postoperative 24 hours. Functional outcomes were assessed at three months after EVT through telephone interview or in-person evaluation using the mRS. The 3-month unfavorable outcome was defined as having an mRS score between 3 and 6. END was characterized by an increase of 4 or more points in the NIHSS score within 24 hours following EVT.[5]

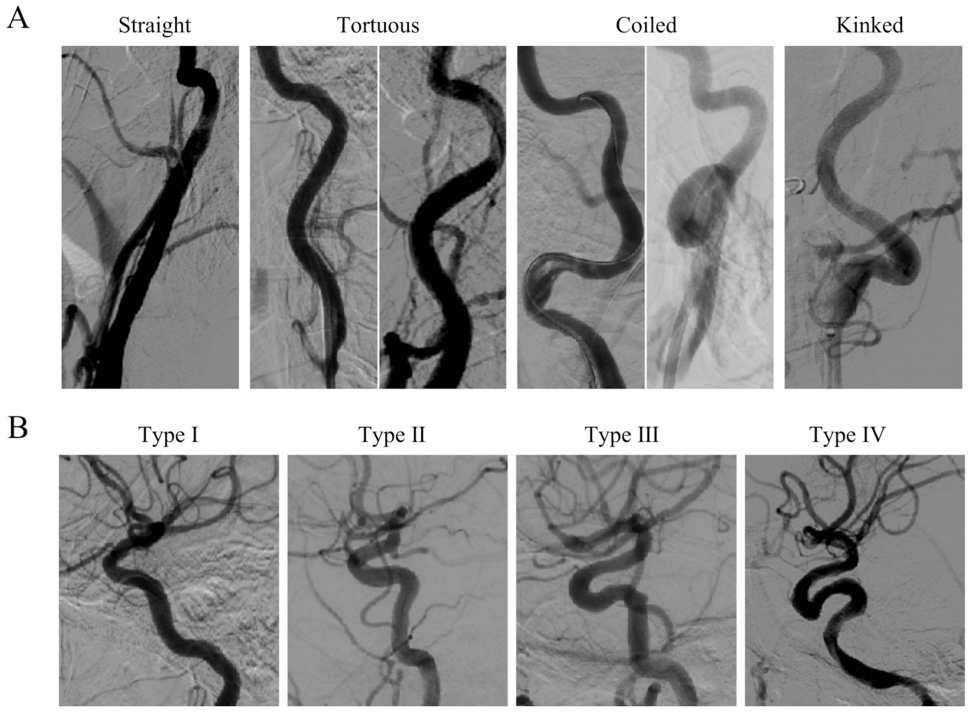

Figure 1 Classification of extracranial and cavernous internal carotid artery (ICA) tortuosity. (**A**) The extracranial ICA tortuosity was classified into four types: straight, tortuous, coiled, or kinked. Straight ICA was described as having an alignment angle of <15 degrees, when compared to the centerline of the common carotid artery. Tortuous ICA was identified by an S- or C-shaped elongation. Coiled ICA had a pronounced S-shape or a circular Bend. Kinked ICA involved a sharp angle of <90 degrees, and was often linked with stenosis. In the present study, both coiled and kinked ICAs were treated as tortuous extracranial ICA. (**B**) Cavernous ICA tortuosity was classified into four types: Type I, featured open angles in the carotid genu; Type II, had a more acute angle due to the closed configuration of the anterior genu; Type III, presented with the posterior deflection of the posterior genu, giving it a bent appearance; Type IV, the most severe, had a shape similar to a Simmons catheter, and the posterior genu was bent upwards, when compared to the anterior genu. Among these types, Type III and Type IV were considered as tortuous cavernous ICA.

Statistical Analysis

A machine learning algorithm, random forest imputation, was utilized to impute the missing data.[18] Continuous variables were presented in interquartile range (IQR), while categorical variables were presented in frequency and percentage. The comparison of baseline characteristics between the training and validation cohorts was performed using Student's *t*-test or Wilcoxon rank-sum test for continuous variables and chi-square test for categorical variables.

Univariate and multivariate logistic regression analyses were conducted to identify the potential predictors of clinical outcomes. Variables with a *p*-value of <0.1 in the univariate analysis were included in the multivariate model. Factors with a *p*-value of <0.05 in the multivariate logistic regression were deemed statistically significant.

The performance of the nomogram was evaluated via receiver operating characteristic (ROC) curve analysis, and the area under the curve (AUC) was used to reflect the predictive accuracy. Models with and without ICA tortuosity were compared based on the AUC values, in order to select the model with superior discrimination for constructing nomograms. The alignment between predicted probabilities and actual outcomes was evaluated using calibration plots. Decision curve analysis (DCA) was performed to test the clinical utility of the nomogram. All statistical analyses in the present study were performed by a neurologist, who had training in statistics and more than three years of experience in clinical statistics. These were validated by another neurologist with the same experience. All statistical analyses were conducted using StataMP17 (StataCorp LD, College Station, TX, USA). A *p*-value of <0.1 was considered statistically significant in the univariate analysis, while a *p*-value of <0.05 was considered statistically significant in the other tests.

Results

Baseline Demographic and Clinical Characteristics of Patients

A total of 313 patients, who were diagnosed with AIS caused by large-vessel occlusion in the anterior circulation, were included for the present study, after excluding 54 patients (Figure 2, flowchart). Then, these patients were assigned into two cohorts: training cohort (n=219) and validation cohort (n=94). The median age of these patients was 67 years old, and 59.70% of these patients were male. The median NIHSS score at admission was 12, and the median ASPECTS score was 9. Large-artery atherosclerosis and cardioembolism were the leading causes of stroke, accounting for 42.80% and 47.60% of cases, respectively, and the middle cerebral artery (MCA) was the most frequently affected site (55.30%). In addition, 29.70% of patients received bridging therapy, and 24.00% of patients underwent concomitant stent placement (Table 1).

There were no significant differences between the training and validation cohorts, in terms of baseline characteristics, such as age, gender, NIHSS score, or cerebrovascular disease risk factors. In terms of ICA tortuosity, the interrater agreement demonstrated good consistency, with a kappa coefficient of 0.793 for tortuosity in the extracranial ICA, and a kappa coefficient of 0.814 for tortuosity in the cavernous ICA. After discussion to resolve the differences, the finalized assessment results were, as follows: In the training cohort, 45 (20.60%) patients had extracranial ICA tortuosity, and 43

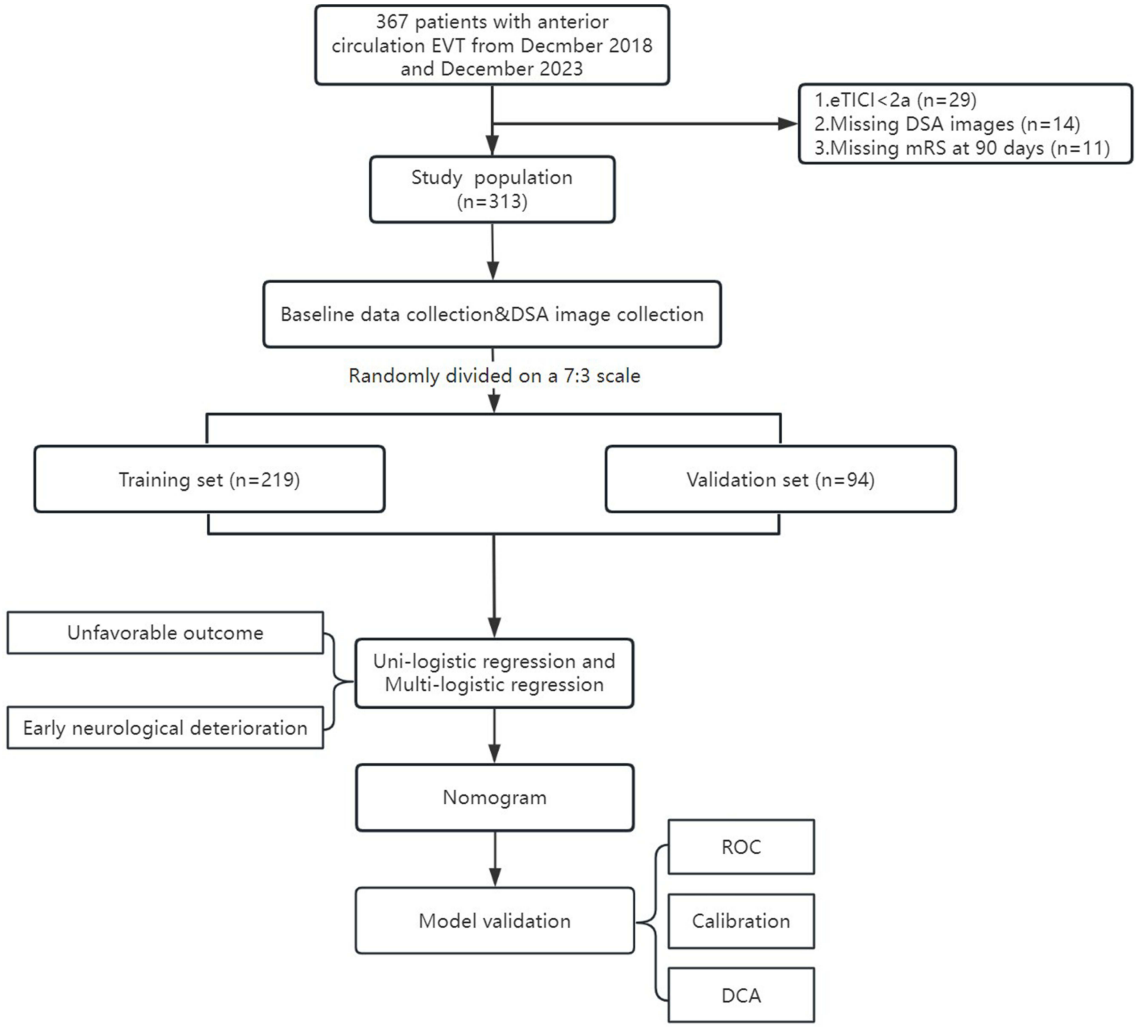

Figure 2 Study flowchart.

Abbreviations: EVT, endovascular thrombectomy; eTICI, extended Thrombolysis in Cerebral Infarction; DSA, digital subtraction angiography; mRS, modified Rankin Scale; ROC, receiver operating characteristic curve; DCA, decision curve analysis.

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Table 1 Baseline Demographics and Clinical Characteristics of All Patients

Variable	All Patients (N=313)	Training Set (n=219)	Validation Set (n=94)	*p*-Value
Age, years	67 (58–75)	67 (58–75)	67 (58–75)	0.911
Male	187 (59.70)	129 (58.90)	58 (61.70)	0.644
Baseline NIHSS score	12 (9–16)	13 (9–16)	12 (8–15)	0.357
Baseline GSC score	13 (10–15)	13 (10–15)	14 (10–15)	0.514
Baseline ASPECT score	9 (7–9)	8 (7–9)	9 (8–9)	0.499
History of antiplatelet drug use	82 (26.20)	56 (25.60)	26 (27.70)	0.700
History of anticoagulant drug use	34 (10.90)	23 (10.50)	11 (11.70)	0.755
Medical history				
Previous stroke	55 (17.60)	38 (17.40)	17 (18.10)	0.876
Hypertension	173 (55.30)	125 (57.10)	48 (51.10)	0.327
Diabetes	72 (23.00)	52 (23.70)	20 (21.30)	0.634
Ischemic heart disease	79 (25.20)	57 (26.00)	22 (23.40)	0.624
Atrial fibrillation	121 (38.70)	83 (37.90)	38 (40.40)	0.674
Current smoking	120 (38.30)	87 (39.70)	33 (35.10)	0.441
Stroke cause				0.912
LAA	134 (42.80)	93 (42.50)	41 (43.60)	
Cardioembolism	149 (47.60)	104 (47.50)	45 (47.90)	
Undetermined or others	30 (9.60)	22 (10.00)	8 (8.50)	
Initial site of occlusion				0.088
ICA	96 (30.70)	65 (29.70)	31 (33.00)	
MCA	173 (55.30)	117 (53.40)	56 (59.60)	
Combined	44 (14.10)	37 (16.90)	7 (7.50)	
First-line MT strategy				0.053
CA	97 (31.00)	64 (29.20)	33 (35.10)	
SR	112 (35.80)	73 (33.30)	39 (41.50)	
Combined CA and SR	104 (33.20)	82 (37.40)	22 (23.40)	
ODT, min	425 (323–549)	419 (322–532)	441 (325–611)	0.136
PRT, min	110 (80–144)	110 (78–150)	110 (83–133)	0.577
Passes of retriever	2 (1–3)	2 (1–3)	2 (1–2)	0.016
Balloon dilatation	89 (28.40)	61 (27.90)	28 (29.80)	0.728
Stent implantation	75 (24.00)	52 (23.70)	23 (24.50)	0.891
Intravenous thrombolysis	93 (29.70)	67 (30.60)	26 (27.70)	0.603
Final eTICI score				0.222
2a	14 (4.50)	13 (5.90)	1 (1.10)	
2b	60 (19.20)	39 (17.80)	21 (22.30)	
2c	30 (9.60)	22 (10.10)	8 (8.50)	
3	209 (66.80)	145 (66.20)	64 (68.10)	
Biochemical Indicators				
Glu, mmol/L	6.57 (5.66–8.26)	6.61 (5.65–8.29)	6.46 (5.68–8.22)	0.918
LDL, mmol/L	2.01 (1.61–2.68)	2.01 (1.63–2.73)	2.00 (1.53–2.64)	0.775
Hcy, umol/L	17.0 (12.80–24.30)	16.20 (12.80–24.00)	19.20 (13.20–24.30)	0.072
Outcome				
Unfavorable outcome (mRS>2)	173 (55.30)	125 (57.10)	48 (51.10)	0.327
END	49 (15.70)	35 (16.00)	14 (14.90)	0.808
Tortuous ICA				
Extracranial ICA tortuosity	61 (19.50)	45 (20.60)	16 (17.00)	0.369
Cavernous ICA tortuosity	66 (21.10)	43 (19.60)	23 (24.50)	0.441

Notes: The data was expressed in median (interquartile range) or number (percentage).

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale; ASPECT, Alberta Stroke Program Early Computed Tomography; LAA, large-artery atherosclerosis; ICA, internal carotid artery; MCA, middle cerebral artery; CA, contact aspiration; SR, stent retriever; ODT, onset-to-door time; PRT, puncture-to-recanalization time; eTICI, extended Thrombolysis in Cerebral Infarction; Glu, blood glucose; LDL, low density lipoprotein; Hcy, homocysteine; mRS, modified Rankin Scale; END, early neurological deterioration.

(19.60%) patients had cavernous ICA tortuosity. In the validation cohort, 16 (17.00%) patients had extracranial ICA tortuosity, and 23 (24.50%) patients had cavernous ICA tortuosity. The number of retriever passes was higher in the training cohort (p=0.016). Furthermore, the incidence for 3-month unfavorable outcomes (mRS > 2) was 57.10% in the training cohort and 51.1% in the validation cohort. END occurred in 16.00% of patients in the training cohort and 14.90% of patients in the validation cohort.

Establishment and Validation of the Nomogram for 3-Month Unfavorable Outcome

The univariate analysis identified several potential predictors of 3-month unfavorable outcome (mRS: 3–6) in the training cohort. These included the following: age (p<0.001), baseline NIHSS score (p<0.001), GCS score (p=0.007), gender (p=0.035), history of antiplatelet drug use (p=0.064), hypertension (p=0.067), atrial fibrillation (p=0.063), current smoking (p=0.007); PRT (p=0.019), number of retriever passes (p=0.022), final eTICI score (p=0.029), and blood glucose levels (p=0.002). The multivariate logistic regression analysis revealed that age (odds ratio [OR]: 2.821, 95% confidence interval [CI]: 1.374–5.793, p=0.005), baseline NIHSS score (for scores 5–14, OR: 7.900, 95% CI: 2.213–28.206, p=0.001; for scores 15–20, OR: 13.072, 95% CI: 3.186–53.628, p<0.001; for scores 21–42, OR: 18.540, 95% CI: 3.154–108.970, p=0.001), PRT (OR: 2.886, 95% CI: 1.265–6.583, p=0.012), final eTICI score of 3 (OR: 0.133, 95% CI: 0.021–0.850, p=0.033), and elevated blood glucose (OR: 2.373, 95% CI: 1.178–4.780, p=0.016) were independently associated to unfavorable outcome at three months (Table 2).

Three predictive models were developed to estimate the 3-month unfavorable outcome: Model 1, included age, baseline NIHSS score, and blood glucose, had an AUC of 0.751 (95% CI: 0.687–0.816); Model 2, the addition of PRT

Table 2 Univariate and Multivariate Logistic Regression for Factors Associated to 3-month Unfavorable Outcome

Variable	Unadjusted OR (95% CI)	*p*-Value	Adjusted OR (95% CI)	*p*-Value
Age, years	2.906 (1.665–5.072)	<0.001	2.821 (1.374–5.793)	0.005
Male	0.550 (0.316–0.959)	0.035	0.935 (0.395–2.215)	0.879
Baseline NIHSS score				
0–4	Ref	Ref	Ref	Ref
5–14	5.344 (1.715–16.654)	0.004	7.900 (2.213–28.206)	0.001
15–20	12.983 (3.796–44.409)	<0.001	13.072 (3.186–53.628)	<0.001
21–42	20.187 (4.360–93.473)	<0.001	18.540 (3.154–108.970)	0.001
Baseline GSC score	0.473 (0.274–0.815)	0.007	0.887 (0.437–1.801)	0.740
Baseline ASPECT score	0.714 (0.391–1.306)	0.275		
History of antiplatelet drug use	0.560 (0.304–1.033)	0.064	0.601 (0.285–1.265)	0.180
History of anticoagulant drug use	1.824 (0.719–4.632)	0.206		
Medical history				
Previous stroke	1.558 (0.750–3.237)	0.235		
Hypertension	1.660 (0.965–2.855)	0.067	1.553 (0.801–3.011)	0.193
Diabetes	1.033 (0.551–1.940)	0.918		
Ischemic heart disease	1.406 (0.756–2.616)	0.282		
Atrial fibrillation	1.705 (0.971–2.993)	0.063	1.296 (0.599–2.807)	0.510
Current smoking	0.471 (0.271–0.817)	0.007	0.762 (0.318–1.826)	0.542
Stroke cause				
LAA	Ref	Ref		
Cardioembolism	1.265 (0.718–2.231)	0.416		
Undetermined or others	0.824 (0.325–2.088)	0.682		
Initial site of occlusion				
ICA	Ref	Ref		
MCA	1.109 (0.603–2.040)	0.739		
Combined	1.582 (0.688–3.639)	0.280		

(*Continued*)

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Table 2 (Continued).

Variable	Unadjusted OR (95% CI)	*p*-Value	Adjusted OR (95% CI)	*p*-Value
First-line MT strategy				
CA	Ref	Ref		
SR	0.688 (0.347–1.364)	0.284		
Combined CA and SR	0.767 (0.393–1.495)	0.436		
ODT, min	0.590 (0.308–1.128)	0.111		
PRT, min	2.137 (1.114–4.027)	0.019	2.886 (1.265–6.583)	0.012
Passes of retriever	1.966 (1.101–3.510)	0.022	1.456 (0.692–3.066)	0.322
Balloon dilatation	0.642 (0.354–1.163)	0.144		
Stent implantation	0.620 (0.332–1.160)	0.135		
Intravenous thrombolysis	1.529 (0.846–2.766)	0.160		
Final eTICI score				
2a	Ref	Ref	Ref	Ref
2b	0.409 (0.078–2.136)	0.289	0.246 (0.034–1.782)	0.165
2c	0.390 (0.067–2.250)	0.292	0.239 (0.028–2.043)	0.191
3	0.179 (0.038–0.838)	0.029	0.133 (0.021–0.850)	0.033
Biochemical Indicators				
Glu, mmol/L	2.473 (1.407–4.348)	0.002	2.373 (1.178–4.780)	0.016
LDL, mmol/L	0.699 (0.408–1.197)	0.192		
Hcy, umol/L	1.049 (0.614–1.792)	0.860		

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale; ASPECT, Alberta Stroke Program Early Computed Tomography; LAA, large-artery atherosclerosis; ICA, internal carotid artery; MCA, middle cerebral artery; CA, contact aspiration; SR, stent retriever; ODT, onset-to-door time; PRT, puncture-to-recanalization time; eTICI, extended Thrombolysis in Cerebral Infarction; Glu, blood glucose; LDL, low density lipoprotein; Hcy, homocysteine.

and the eTICI score, had an improved AUC of 0.797 (95% CI: 0.738–0.856); Model 3, further incorporation of extracranial and cavernous ICA tortuosity, presented with the best performance, with a lower Akaike Information Criterion (AIC) of 246.593, and a higher AUC of 0.826 (95% CI: 0.769–0.882), when compared to Model 1 (p=0.001) or Model 2 (p=0.041) (Figure S1). The improvement in predictive accuracy from Model 1 to Model 3 was statistically significant (p<0.05). Based on Model 3, a nomogram was developed to allow for individualized risk predictions (Figure 3).

The AUC was used to evaluate the performance of the nomogram, which was 0.826 (95% CI: 0.769–0.882) for the training cohort, and 0.803 (95% CI: 0.714–0.893) for the validation cohort, indicating the good prediction ability of the model (Figure 4A for the training cohort and Figure 4B for the validation cohort). The Hosmer–Lemeshow test was performed on the training set and validation set, respectively, and the results revealed that the model fits well in the training set (x^2=8.21 p=0.609>0.1) and validation set (x^2=4.43 p=0.926>0.1). Calibration plots were drawn to validate the nomogram, in terms of the agreement between predicted and observed outcomes, in both the training and validation cohorts (Figure 5A and B). Furthermore, the nomogram revealed that the net benefit of treatment based on its prediction probability was higher, when compared to the "treat-all" or "treat-none" strategies, when the threshold probability was approximately 8% in the training cohort, and approximately 24% in the validation cohort, through the decision curve analysis (DCA) (Figure 6A and B).

Establishment and Validation of the Nomogram for END

In predicting END, the univariate analysis identified the following significant predictors: baseline NIHSS score (p=0.054), baseline ASPECT score (p=0.005), gender (p=0.015), current smoking (p=0.030), occlusion site (p=0.002), number of retriever passes (p=0.004), and blood glucose levels (p=0.008) (Table 3). In the multivariate analysis, the independent predictors for END were, as follows: baseline ASPECT score (OR: 0.362, 95% CI: 0.153–0.858, p=0.021),

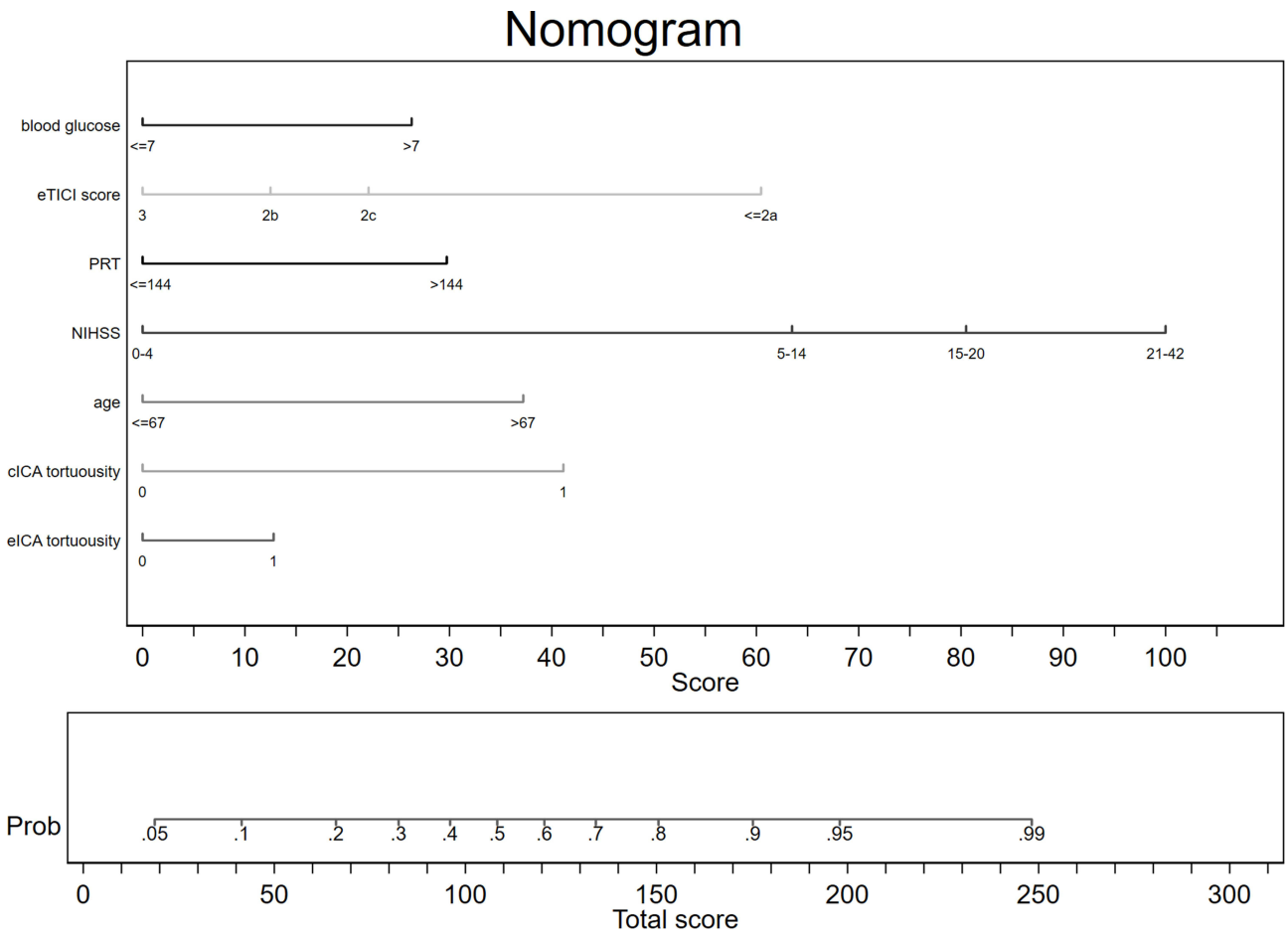

Figure 3 A nomogram designed to estimate the likelihood of unfavorable outcomes at three months (mRS >2). Numerical values were allocated to blood glucose level, the eTICI score, PRT, NIHSS, age, eICA tortuosity, and cICA tortuosity by drawing a connecting line from each specific value to the designated "score line". The aggregate score was derived as the cumulative total of individual scores obtained from the seven aforementioned variables.

Abbreviations: eTICI, extended thrombolysis in cerebral infarction; PRT, puncture-to-recanalization time; NIHSS, National Institutes of Health Stroke Scale; eICA, extracranial internal carotid artery; cICA, cavernous internal carotid artery.

occlusion at the MCA site (OR: 0.247, 95% CI: 0.097–0.627, p=0.003), number of retriever passes (OR: 2.916, 95% CI: 1.248–6.815, p=0.013), and blood glucose (OR: 2.423, 95% CI: 1.035–5.673, p=0.042).

For the prediction of END, two models were established: Model 1, the ASPECT score, occlusion site, retriever pass number, and blood glucose were combined, and an AIC of 174.076 was achieved, which was not statistically and significantly different from that in Model 2 (x^2=0.55 p=0.760); Model 2, extracranial and cavernous ICA tortuosity were included, but this did not improve the model fit (Figure S2), and the predictive performance (AUC=0.774, 95% CI: 0.689–0.860) was similar to Model 1 (AUC=0.770, 95% CI: 0.687–0.853). A nomogram was established for Model 1 (Figure 7), with an AUC of 0.770 (95% CI: 0.687–0.853) for the training cohort and an AUC of 0.772 (95% CI: 0.641–0.903) for the validation cohort (Figure 8A and B). The Hosmer–Lemeshow test was performed for the training set and validation set, respectively. The results revealed that the model fits well in the training set (x^2=5.12 p=0.823>0.1) and validation set (x^2=5.42 p=0.712>0.1). Furthermore, there was excellent agreement between the predicted and observed outcomes in both cohorts in the calibration plots (Figure 9A and B). The DCA results revealed the added clinical benefit of the nomogram when the threshold probability for END was above approximately 3% in the training cohort, and 2% in the validation cohort (Figure 10A and B).

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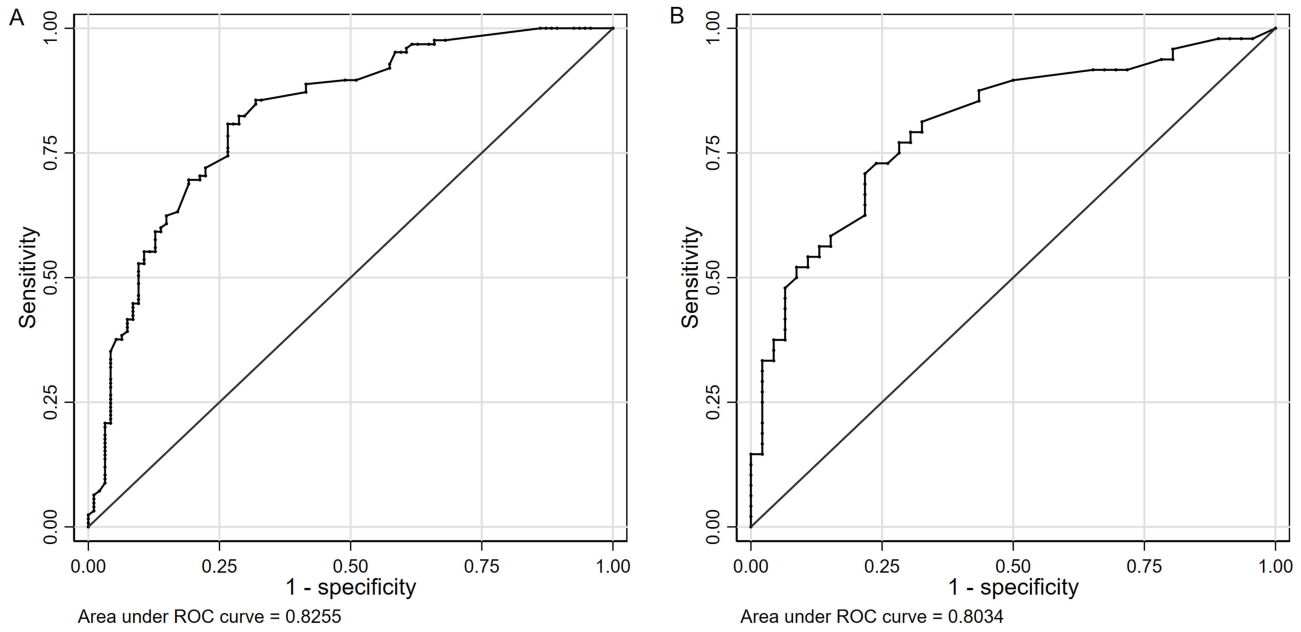

Figure 4 Receiver operating characteristic (ROC) curve for the nomogram for predicting the 3-month unfavorable outcome of patients in the training cohort (**A**) and validation cohort (**B**). AUC, area under the curve.

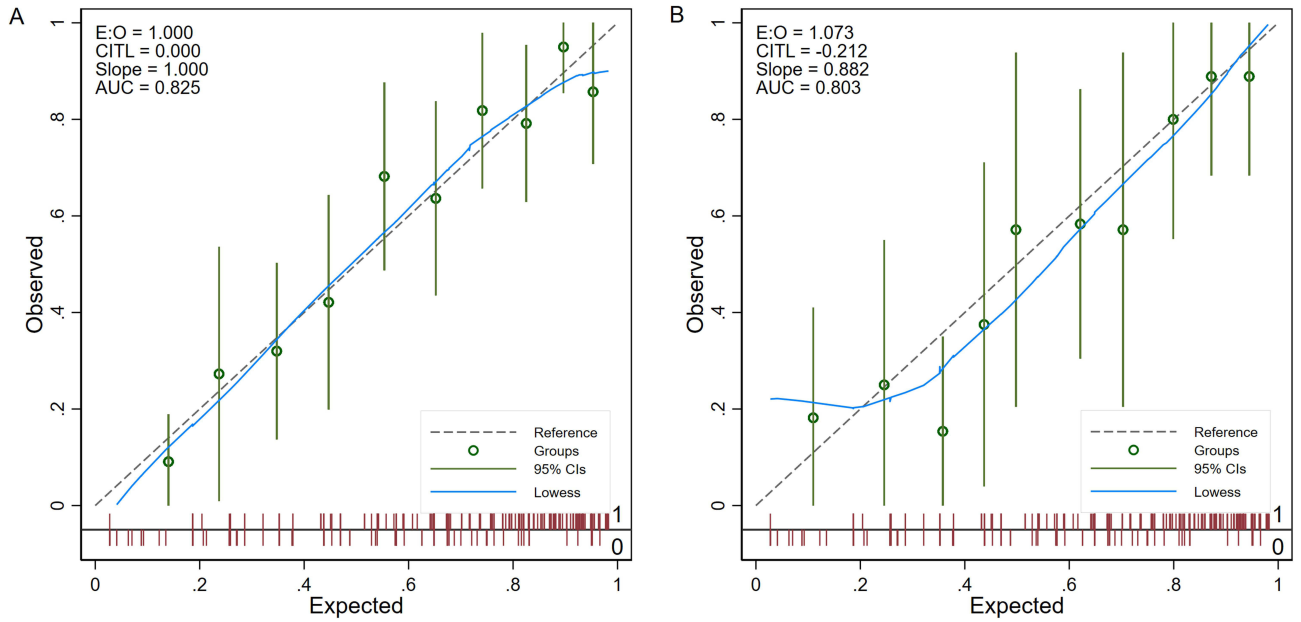

Figure 5 Calibration plot for the nomogram for predicting the 3-month unfavorable outcome of patients in the training cohort (**A**) and validation cohort (**B**). The dashed line represents the reference line where an ideal nomogram would lie.

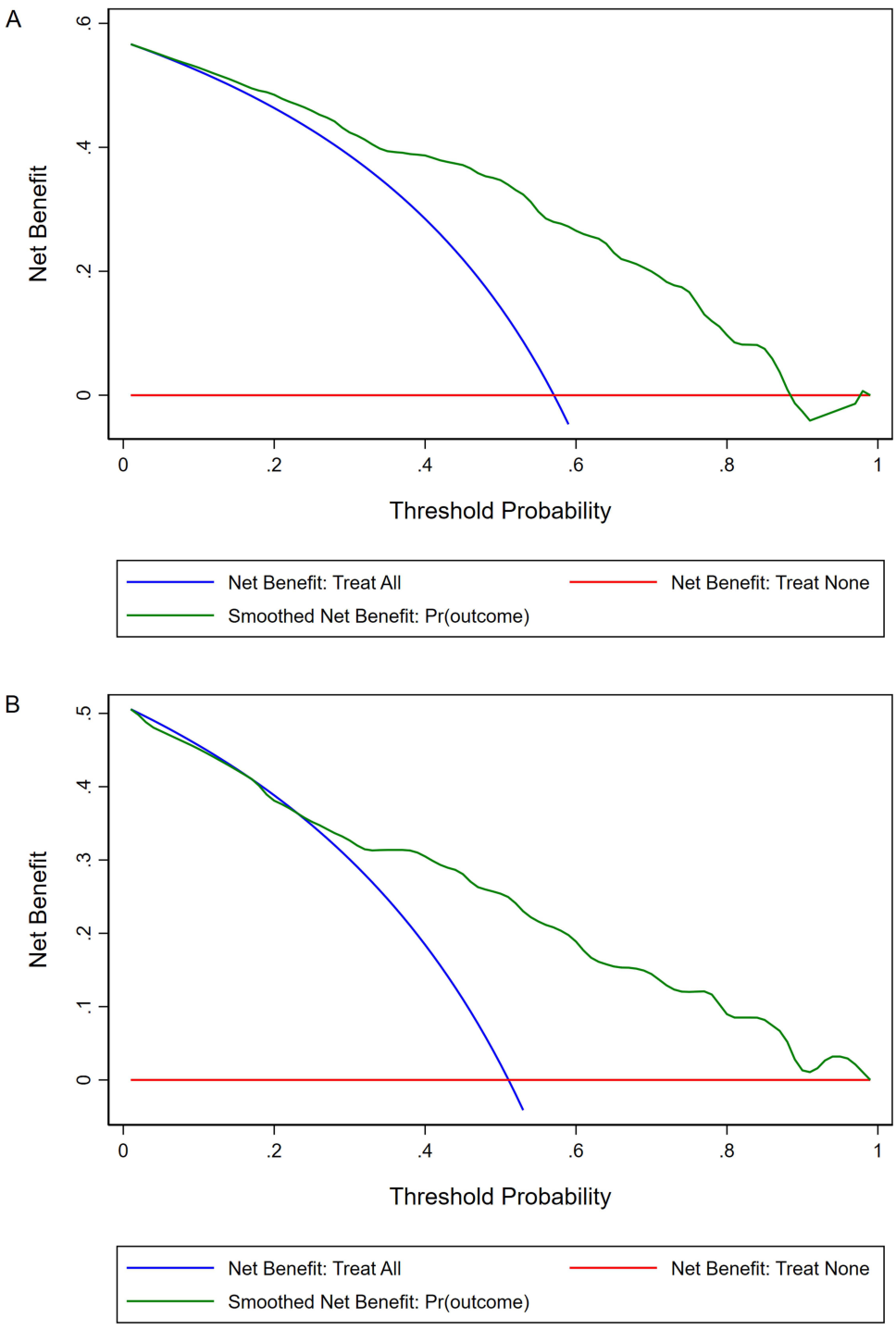

Figure 6 Decision curve analysis for the nomogram in the training cohort (**A**) and validation cohort (**B**). The blue line denotes the net benefit associated to the treatment of all patients, the red line signifies the strategy of treating no patients, and the green line represents the nomogram itself. Decision curve analysis was performed to assess the prognostic efficacy of the nomogram in forecasting the three-month adverse outcome following endovascular therapy (EVT) in patients with acute ischemic stroke (AIS). In the present study, the nomogram had a net advantage over both exhaustive treatment and no treatment strategies, when the threshold probability exceeded approximately 8% in the training cohort, and 24% in the validation cohort.

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Table 3 Univariate and Multivariate Logistic Regression for Factors Associated to Early Neurological Deterioration

Variable	Unadjusted OR (95% CI)	*p*-Value	Adjusted OR (95% CI)	*p*-Value
Age, years	0.986 (0.479–2.033)	0.970		
Male	0.400 (0.191–0.838)	0.015	0.589 (0.204–1.697)	0.327
Baseline NIHSS score				
0–4	Ref	Ref	Ref	Ref
5–14	4.444 (0.566–34.899)	0.156	4.667 (0.533–40.885)	0.164
15–20	3.667 (0.432–31.140)	0.234	2.402 (0.248–23.248)	0.449
21–42	8.800 (0.959–80.733)	0.054	5.252 (0.476–57.967)	0.176
Baseline GSC score	1.030 (0.500–2.124)	0.936		
Baseline ASPECT score	0.343 (0.163–0.721)	0.005	0.362 (0.153–0.858)	0.021
History of antiplatelet drug use	0.554 (0.217–1.415)	0.217		
History of anticoagulant drug use	1.537 (0.530–4.456)	0.429		
Medical history				
Previous stroke	1.234 (0.495–3.077)	0.652		
Hypertension	0.874 (0.423–1.807)	0.716		
Diabetes	0.943 (0.399–2.225)	0.893		
Ischemic heart disease	1.375 (0.625–3.023)	0.428		
Atrial fibrillation	0.830 (0.389–1.773)	0.631		
Current smoking	0.394 (0.170–0.913)	0.030	0.655 (0.197–2.185)	0.491
Stroke cause				
LAA	Ref	Ref		
Cardioembolism	0.758 (0.361–1.589)	0.462		
Undetermined or others	0.198 (0.025–1.574)	0.126		
Initial site of occlusion				
ICA	Ref	Ref		
MCA	0.271 (0.119–0.618)	0.002	0.247 (0.097–0.627)	0.003
Combined	0.505 (0.181–1.414)	0.194	0.420 (0.132–1.331)	0.141
First-line MT strategy				
CA	Ref	Ref		
SR	1.242 (0.466–3.308)	0.665		
Combined CA and SR	1.697 (0.676–4.260)	0.260		
ODT, min	1.102 (0.464–2.615)	0.826		
PRT, min	1.263 (0.576–2.768)	0.560		
Passes of retriever	2.971 (1.419–6.219)	0.004	2.916 (1.248–6.815)	0.013
Balloon dilatation	0.602 (0.248–1.461)	0.262		
Stent implantation	0.772 (0.316–1.888)	0.571		
Intravenous thrombolysis	0.628 (0.269–1.465)	0.282		
Final eTICI score				
2a	Ref	Ref	Ref	Ref
2b	4.714 (0.546–40.712)	0.159		
2c	1.895 (0.176–20.386)	0.598		
3	1.920 (0.237–15.584)	0.541		
Biochemical Indicators				
Glu, mmol/L	2.756 (1.305–5.820)	0.008	2.423 (1.035–5.673)	0.042
LDL, mmol/L	0.703 (0.339–1.457)	0.343		
Hcy, umol/L	1.188 (0.575–2.452)	0.642		

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale; ASPECT, Alberta Stroke Program Early Computed Tomography; LAA, large-artery atherosclerosis; ICA, internal carotid artery; MCA, middle cerebral artery; CA, contact aspiration; SR, stent retriever; ODT, onset-to-door time; PRT, puncture-to-recanalization time; eTICI, extended thrombolysis in cerebral infarction; Glu, blood glucose; LDL, low density lipoprotein; Hcy, homocysteine.

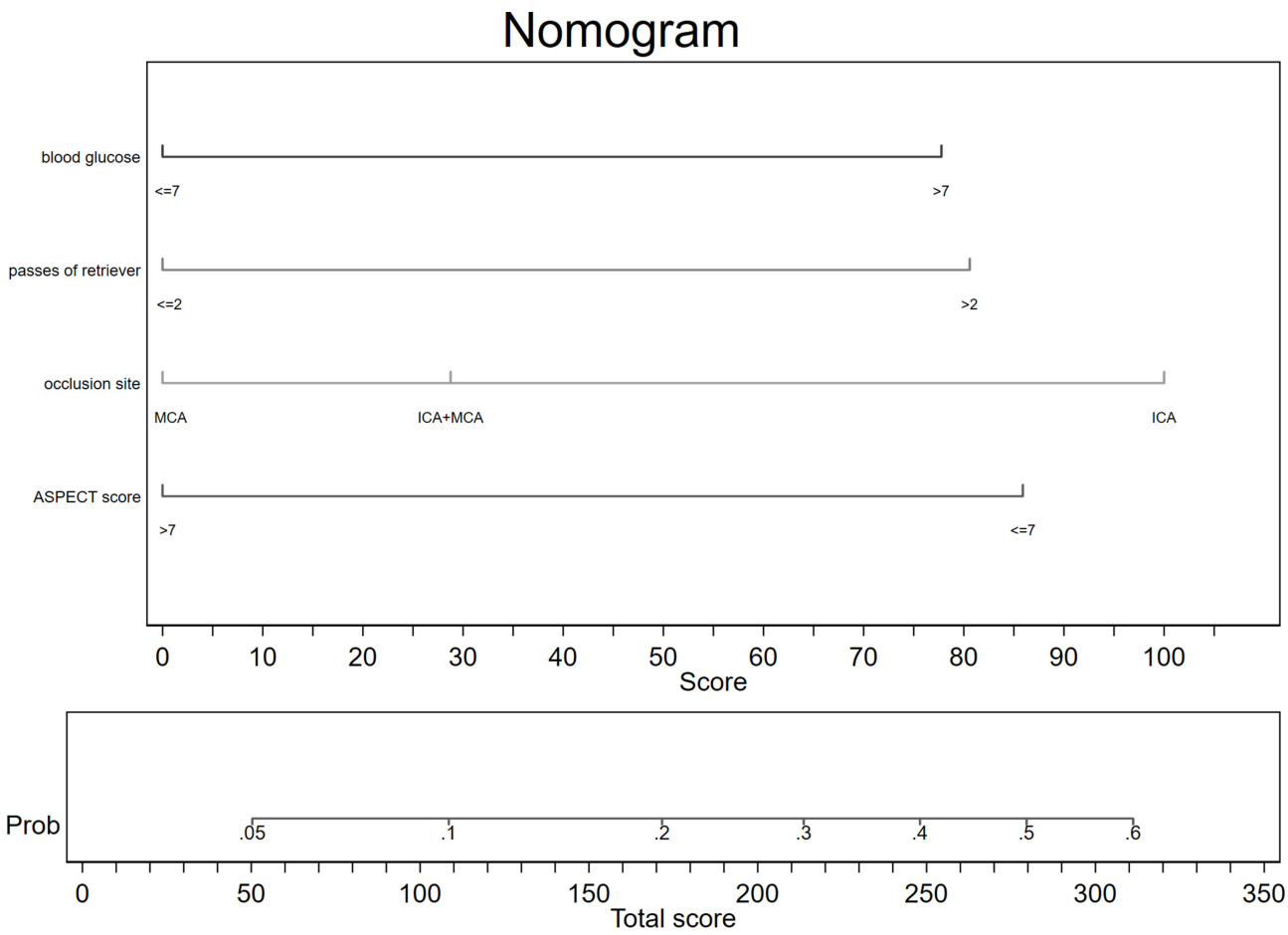

Figure 7 The nomogram designed to estimate the likelihood of early neurological deterioration. Points were allocated to the parameters, which included blood glucose levels, instances of retriever application, occlusion location, and ASPECT score, by aligning a line from each respective value to the "score line". The aggregate score was determined by summing up the individual point values derived from the four specified variables.
Abbreviation: ASPECT, Alberta Stroke Program Early Computed Tomography.

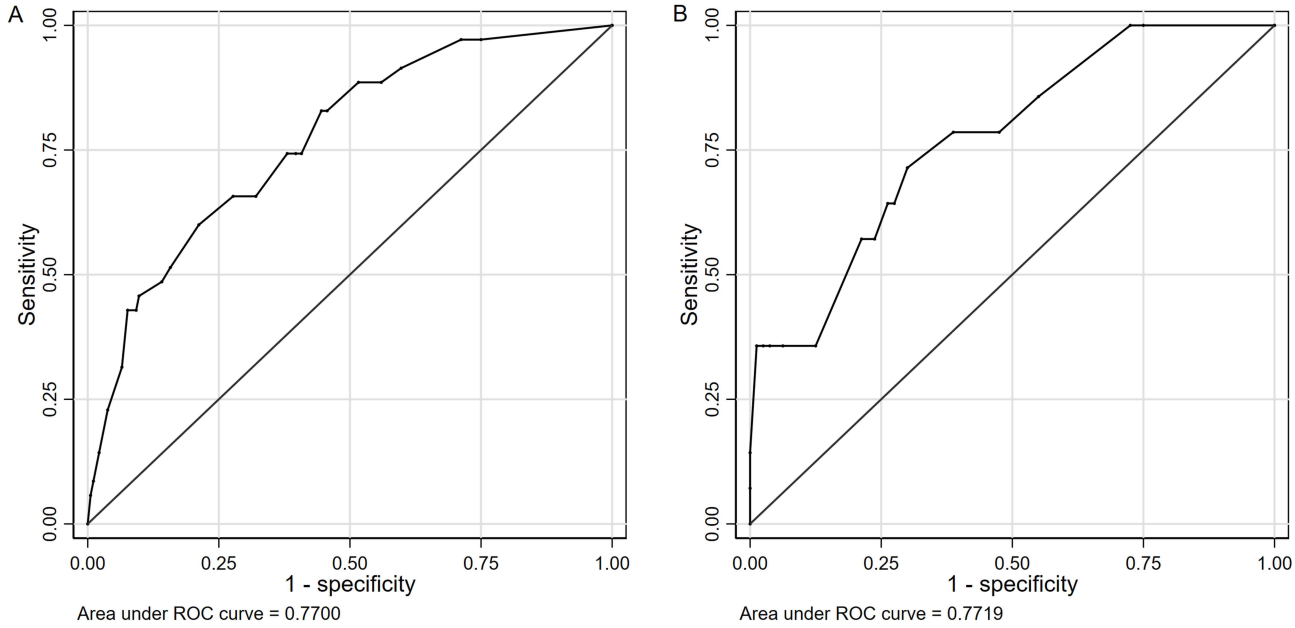

Figure 8 Receiver operating characteristic curve (ROC) for the nomogram for predicting early neurological deterioration in the training cohort (**A**) and validation cohort (**B**).
Abbreviation: AUC, area under the curve.

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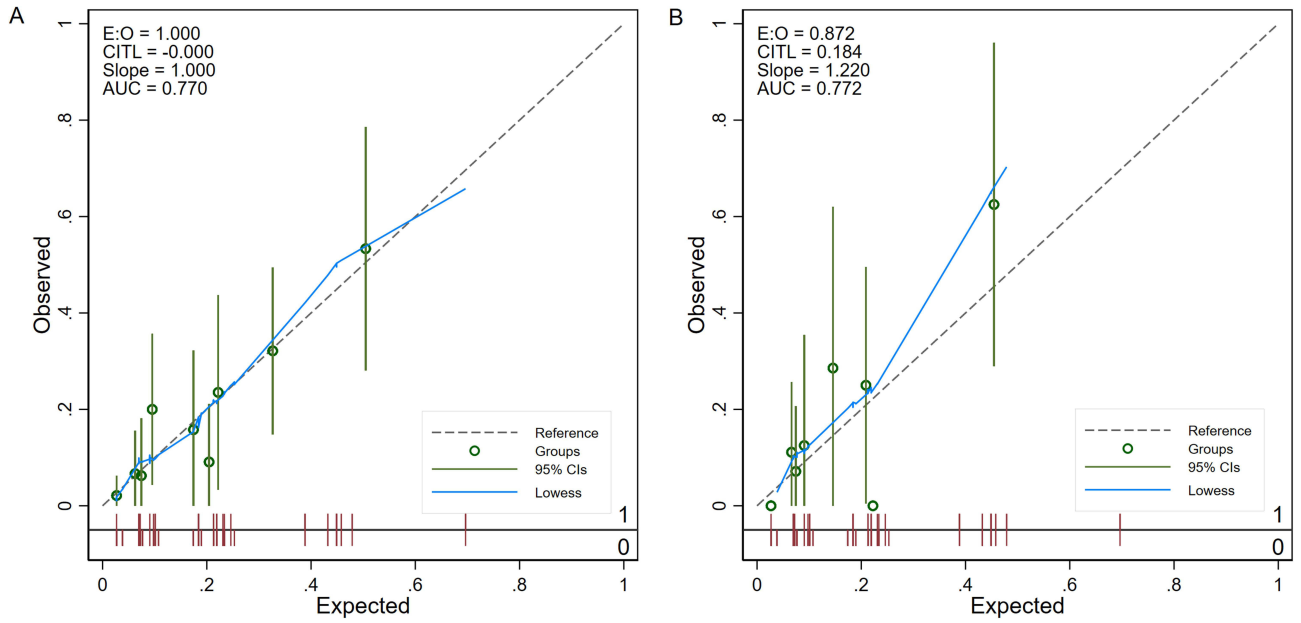

Figure 9 Calibration plot for the nomogram for predicting early neurological deterioration in the training cohort (**A**) and validation cohort (**B**). The dashed line represents the reference line where an ideal nomogram would lie.

Discussion

The present study established two nomograms to predict the probability of 3-month unfavorable outcome and END in patients with AIS, who underwent EVT for large-vessel occlusion. These models were established by incorporating both clinical and vascular geometric features, with the novel addition of ICA tortuosity as a predictive factor. The models underwent extensive evaluation and presented with strong discriminatory performance and calibration, in both the training and validation cohorts. These results underscore the potential of these nomograms in assisting in the early identification of high-risk patients, and providing timely information for clinical decision-making.

The present study introduced a key innovation, in which ICA tortuosity was incorporated as a predictive factor in the nomograms, and this has not been extensively explored in previous research. Earlier studies[6,13–15] have focused on clinical indicators, such as age, NIHSS score, and blood glucose levels. By including vascular morphology, specifically ICA tortuosity, the model demonstrated a significantly improved ability to predict the 3-month unfavorable outcome. This suggests that ICA tortuosity plays an important role in long-term outcomes following EVT. However, the inclusion of ICA tortuosity did not significantly enhance the model's performance in predicting END. This indicates that although ICA tortuosity is crucial for long-term prognosis, its impact on short-term outcomes, such as END, remains limited. The distinction between long- and short-term prognostic value highlights the need for further research into the mechanism by which ICA tortuosity influences post-thrombectomy recovery.

Several scoring systems, including the Totaled Health Risks in Vascular Events (THRIVE) score[19] and Houston Intra-Arterial Therapy 2 (HIAT2) score,[20] have been developed to predict unfavorable outcomes in patients with AIS following EVT. However, these systems do not account for the complexity of vascular morphology, including tortuosity, and its predictive power remains limited. For example, the AUC for traditional scoring systems for predicting unfavorable outcomes is generally <0.75, indicating moderate discriminative ability. In contrast, the nomogram developed in the present study incorporated both clinical factors and vascular tortuosity, increasing the AUC to 0.826. This improvement in predictive accuracy demonstrates the importance of including vascular geometric features in outcome prediction models. Furthermore, all variables in the nomogram can be easily obtained during the early post-operative period, allowing clinicians to estimate the probability of 3-month unfavorable outcome or END in individual patients. This approach is both convenient and effective, offering clinicians a valuable tool to identify high-risk patients and adjust treatment plans accordingly.

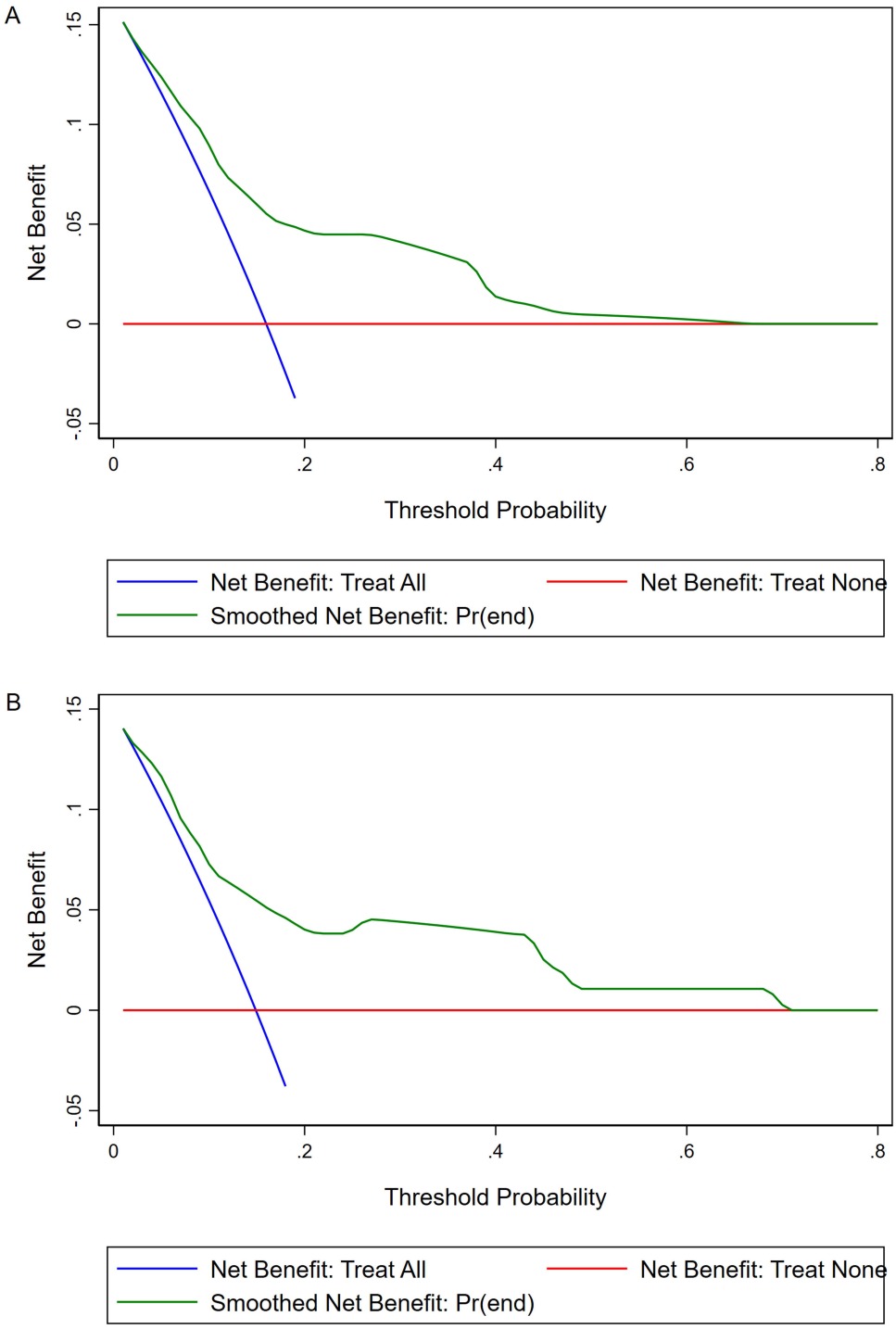

Figure 10 Decision curve analysis for the nomogram in the training cohort (**A**) and validation cohort (**B**). The blue line illustrates the net benefit associated to the treatment of all patients, the red line signifies the absence of treatment for any patient, and the green line denotes the nomogram itself. The analysis assessed the efficacy of the nomogram in forecasting early neurological deterioration in patients diagnosed with acute ischemic stroke (AIS) subsequent to endovascular therapy (EVT). The nomogram demonstrated a net benefit relative to both the all-treat and no-treat paradigms, when the threshold probability surpassed approximately 3% in the training cohort, and 2% in the validation cohort.

The mechanisms by which ICA tortuosity affects outcomes following thrombectomy remain not fully understood. Previous studies have identified hemodynamic alterations as key contributors to vascular endothelial dysfunction, and the development of atherosclerosis.[21–23] As vessel curvature increases, local turbulence and abnormal shear stress develop in tortuous arteries. These hemodynamic abnormalities may activate platelets within the vessel lumen, and contribute to

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vascular dysfunction, promoting atherosclerosis progression.[24,25] For patients who underwent mechanical thrombectomy, tortuous vessels increase the friction between the thrombectomy device and vessel wall. This added friction would exacerbate vessel wall damage and limit the operator's ability to control the device, potentially affecting procedural outcomes.[26] It can be hypothesized that ICA tortuosity contributes to mechanical damage of the vessel wall during thrombectomy, while existing hemodynamic abnormalities in the tortuous segments may further impair the vessel's elasticity, integrity and permeability. This combined damage may lead to complications, such as hemorrhagic transformation and cerebral edema, which would worsen the patient's 3-month prognosis. In addition, the complexity of navigating a tortuous artery may increase procedural difficulty, prolong operation time, and raise the risk of intraoperative complications. All of these can negatively impact patient outcomes.[27,28]

In the present study, ICA tortuosity did not have significant predictive value for END following EVT. This may be because vascular injury is generally a chronic process, with its effects being less pronounced in the early post-operative period. END is a relatively common and important complication of acute stroke.[29,30] Previous studies[31,32] have suggested that factors, such as smoking history, atrial fibrillation, and homocysteine levels, may be associated with END. Furthermore, a study suggested that the main mechanisms that contribute to END are ischemic progression, cerebral edema, and symptomatic hemorrhagic transformation.[33] Moreover, another study revealed that stress hyperglycemia may lead to the occurrence of END after surgery.[34] Vascular tortuosity increases the difficulty of surgery and may lead to the deterioration of neurologic function through these mechanisms. The ischemia and compression of brain tissues, as well as the affective effects of hyperglycemia, remains as an ongoing chronic progressive process, and its effects on neurologic function gradually worsen over time. Thus, its negative effects may not be particularly pronounced over a short period of time. Although previous studies have revealed that patients with ICA tortuosity have a higher incidence of hemorrhagic transformation and slower neurological recovery, these outcomes were typically observed within 36 hours to seven days after the procedure.[11] In contrast, the present study defined END as the neurological deterioration that occurs within postoperative 24 hours. This may have been too short a timeframe to capture the full impact of ICA tortuosity. The limited effect of ICA tortuosity on short-term outcomes contrasts with its significant predictive value for long-term outcomes. Over a 3-month period, the cumulative effects of hemodynamic abnormalities and mechanical stress on the tortuous vessel may lead to more substantial vascular damage, contributing to poorer long-term prognosis. This suggests that the mechanisms that drive short-term and long-term outcomes may differ, with ICA tortuosity having a greater influence on longer-term recovery due to its chronic impact on vascular health.

There were several limitations in the present study. First, the present study was a single-center retrospective study. The disadvantages were the limited generalizability of findings, and the sample did not fully represent broader populations. Thus, future studies using multi-center databases are required for external validation, in order to enhance the strength of the results. Furthermore, prospective studies must be undertaken to further confirm the predictive value of the nomograms. Second, advanced imaging-derived predictors were not included for the present study, although these could be of critical additional value. In the future, the insertion of such imaging biomarkers would further improve these models. Finally, continuous variables were categorized to facilitate the clinical interpretations at the time of model development. This approach may result in loss of some information. Future studies might consider more advanced models, such as machine learning, which could evaluate the full spectrum of continuous data, and potentially lead to more powerful models.

Conclusion

ICA tortuosity has significant predictive value for 3-month unfavorable outcome in AIS patients undergoing EVT. Nomograms established using various clinical factors can provide accurate predictions for both 3-month unfavorable outcome and END. The internal validation demonstrated that the model exhibits strong discriminatory power, good calibration, and clinical utility, making it a useful tool that can guide postoperative management and treatment decisions. However, further multi-center studies are needed to validate the model's reliability and effectiveness across diverse clinical settings.

Abbreviations

AUC, area under the curve; ASPECTS, Alberta Stroke Program Early CT Score; AIS, acute ischemic stroke; DCA, decision curve analysis; eTICI, extended thrombolysis in cerebral infarction; EVT, endovascular thrombectomy; GCS, Glasgow Coma Scale; HIAT2, Houston Intra-Arterial Therapy 2; ICA, internal carotid artery; LDL, low-density lipoprotein; mRS, Modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; ODT, onset-to-door time; PRT, puncture-to-recanalization time; ROC, receiver operating characteristic; THRIVE, Totaled Health Risks in Vascular Events.

Ethics Approval and Informed Consent

The need for a written informed consent was waived due to the retrospective nature of the study. The ethics approval was provided by the Medical Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University (Approval no. XJTU1AF2023LSK-443).

Disclosure

The authors declare that they have no conflicts of interest in this work.

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