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RESEARCH

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A risk prediction model for unexplained early neurological deterioration following intravenous thrombolysis

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Abstract

Background and objectives Early neurological deterioration (END) post-intravenous thrombolysis significantly impacts the long-term prognosis of stroke patients. This study aimed to establish a rapid risk prediction model for unexplained END following intravenous thrombolysis.

Methods This prospective study consecutively enrolled patients with acute ischemic stroke treated with recombinant tissue plasminogen activator intravenous thrombolysis at the Department of Neurology, Third People's Hospital of Hubei Province, and Yangluo Hospital District between June 2019 and December 2022. Unexplained END was defined as an increase of ≥ 4 points in the National Institutes of Health Stroke Scale (NIHSS) score between admission and 24 h. A nomogram was developed and assessed by calculating the area under the receiver operating characteristic curve (AUC-ROC). The calibration was assessed using the Hosmer–Lemeshow test.

Results A total of 211 patients (130 males and 110 patients aged < 65 years) were included, with 66 experiencing unexplained END. Multivariate logistic regression analysis identified large arterial disease, transient ischemic attack, high blood glucose, high neutrophil/lymphocyte ratio, important perforator disease, and low the Alberta Stroke Program Early CT scores (APSECTS) as independent risk factors for END and established the nomogram used above indicators. The nomogram showed an AUC-ROC of 0.809 (95% CI 0.7429–0.8751), with a specificity of 0.862 and sensitivity of 0.712. The positive predictive value was 0.702, and the negative predictive value was 0.868. The Hosmer–Lemeshow goodness-of-fit test ($\chi^2 = 1.069$, $P = 0.169$) indicated acceptable model calibration.

Conclusion This study successfully established a risk prediction model for END following intravenous thrombolysis and the model demonstrates good stability and predictive capacity. Further validation through a prospective, multicenter study is necessary.

Keywords Early neurological deterioration, Intravenous thrombolysis, Acute ischemic stroke, Risk prediction model, Nomogram, Prospective study

Introduction

Stroke is the second leading cause of death worldwide. Currently, intravenous thrombolysis the preferred treatment option for early ischemic stroke intravenous thrombolysis, primarily with recombinant tissue plasminogen activator (rt-PA), has revolutionized acute ischemic stroke care [1]. It works by dissolving the blood clots that cause cerebral infarction, aiming to restore blood flow and minimize brain tissue damage.

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However, this treatment is not without risks. Early neurological deterioration (END) is a concerning complication that can occur following intravenous thrombolysis in patients with acute ischemic stroke. It represents a significant worsening in the patient's neurological status, typically within the first 24 h post-treatment [2]. This phenomenon is of considerable clinical interest due to its potential to negate the benefits of thrombolytic therapy, which is otherwise a pivotal intervention in acute stroke management. Understanding END is crucial as it can dramatically impact patient outcomes, influencing both short-term recovery and long-term functional independence [3].

Several studies have sought to identify risk factors for END, with findings suggesting a multifactorial etiology [4–6]. Identified risk factors include high blood glucose levels, severe arterial occlusions, high initial stroke severity, and certain blood markers indicative of inflammation or coagulation dysfunction. These studies propose that patients exhibiting these characteristics are at a higher risk for END, leading to the hypothesis that targeted interventions in these high-risk groups could mitigate the occurrence of END. The clinical significance of this research lies in its potential to refine post-thrombolysis care strategies, improving patient outcomes by tailoring interventions to individual risk profiles. In recent years, the WORSEN early warning model has been validated for assessing the risk factors of END in ischemic stroke. This model effectively predicts END in various populations within the first week following acute ischemic stroke onset, But for the WORSEN study, patients receiving intravenous thrombolysis and mechanical thrombectomy were excluded, which is not suitable for predicting END after intravenous thrombolysis. However, the WORSEN study provided us with direction and partial basis for this research [7]. Despite this advancement, there remains a gap in risk prediction specifically for END following intravenous thrombolysis. While intracranial hemorrhage and malignant cerebral edema are known causes, several instances of END remain unexplained.

So far, we have not seen any research literature on predictive models for END after intravenous thrombolysis. Given the complex nature of END and its profound impact on patient outcomes, this study aimed to establish a comprehensive risk prediction model for END following intravenous thrombolysis. Two factors for the predictors we selected, one was a higher relevance associated with END of intravenous thrombolysis in previous studies, and the other was the predictors, could to be easily obtained in most hospitals, including high-level medical centers and primary health institutions. In this study, we will specify predictive models based on these factors and conduct internal validation to understand their predictive utility.

Methods

Study design and patients

This prospective study consecutively collected patients with acute ischemic stroke treated with rt-PA intravenous thrombolysis at the Department of Neurology, both at the headquarters of the Hubei No. 3 People's Hospital of Jianghan University and the Yangluo Hospital District, between June 2020 and December 2022. Inclusion criteria for the study are as follows: (1) patients must be over 18 years of age; (2) diagnosis should be confirmed according to the 'Chinese Guideline for Diagnosis and Treatment of Acute Ischemic Stroke (2018)' [8], with verification by cranial computed tomography (CT) or magnetic resonance imaging (MRI); (3) admission is required within 4.5 h after the onset of symptoms; (4) END after thrombolysis is defined as an increase of ≥ 4 points in the NIHSS score, recorded between admission and 24 h; (5) the occurrence of END must be unexplained, without evident causes such as malignant edema, symptomatic intracerebral hemorrhage, a recent history of stroke in the same territory, or other medical complications; (6) informed consent was obtained from either the patients or their family members. Exclusion criteria for the study included: (1) patients with serious comorbidities, such as cardiac insufficiency of grade II or higher; (2) patients with contraindications for intravenous thrombolysis, as outlined in the Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke (2018) [8]; (3) prior treatment with arterial thrombolysis or mechanical thrombectomy; (4) negative head diffusion-weighted imaging (DWI) findings, to reduce door to needle time (DNT), most patients were treated with intravenous thrombolysis after CT, then followed by magnetic resonance DWI, in fact, some patients presenting with stroke-like symptoms may be treated with intravenous thrombolytic therapy. Therefore, DWI-negative patients were excluded from this study; (5) incomplete clinical data; (6) a well-documented history of mental illness. The study was approved by the Ethics Committee of Hubei No. 3 People's Hospital of Jianghan University [2019 Ethics Section No. (43)], conducted in accordance with the Declaration of Helsinki, and written informed consent was obtained before its commencement.

Procedure

Demographic information and clinical indicators were collected through the green channel of intravenous thrombolysis post-admission. This included age, gender, and history of transient ischemic attack (TIA) prior to the current stroke, the onset time of intravenous

thrombolysis (ONT), systolic blood pressure (SBP), and presence of atrial fibrillation (AF) or valvular heart disease, identified as cardiogenic embolism. Other parameters included the Alberta Stroke Program Early CT Score (ASPECTS), neutrophil–lymphocyte ratio (Neu-Lym Ratio or NLR), important perforator disease, large arterial disease related to intravenous thrombolysis, the rt-PA dosage, bridging therapy, medical history (comprising hypertension, diabetes mellitus, AF or valvular heart disease, among other related diseases), as well as baseline and 24-h NIHSS scores, and blood glucose levels.

A CT scan was conducted prior to thrombolysis and ASPECTS was assessed. Prior to thrombolysis, a blood cell analysis was performed to obtain the neutrophil/lymphocyte ratio (Neu/Lym Ratio). This analysis was conducted using an automated hematology analyzer, which employs techniques such as electrical impedance, radio frequency conductance, spectrophotometry, and flow cytometry. The primary assessments focused on the patient's red blood cell count and hemoglobin concentration, along with white blood cell and platelet counts. Specifically, the white blood cell examination included neutrophils, lymphocytes, monocytes, eosinophils, and basophils. During intravenous thrombolysis, both MRI and CT angiography (CTA) were performed. The core infarct area was assessed using DWI, while the vascular condition was evaluated through CTA to determine whether the cerebral infarction originated from important perforator arteries or was caused by a large arterial lesion. Hemorrhagic transformation and malignant edema were assessed via a second CT scan conducted 24 h after the intravenous thrombolysis. Additionally, careful observation was maintained for other medical complications post-thrombolysis, including asphyxia, cardiac insufficiency, and pulmonary embolism.

Imaging assessments were conducted jointly by radiology imaging physicians and neurologists, all of whom hold at least an associate senior professional title. The determination of the acute cerebral infarction area was primarily based on the high signal area observed in DWI. This high signal is typically indicative of cytotoxic edema in the acute phase of cerebral infarction or the onset of vasogenic edema, leading to impaired dispersion of water molecules. Consequently, these changes are manifested as a high signal on DWI MRI.

After the intravenous injection of an iodine-containing contrast agent, a spiral CT scan was performed for post-processing and three-dimensional reconstruction. This scan assessed the bilateral internal carotid arteries, anterior cerebral arteries, middle cerebral arteries and their branches, vertebral arteries, basilar artery, posterior inferior cerebellar arteries, anterior inferior cerebellar arteries, superior cerebellar arteries, and posterior cerebral arteries. The evaluation focused on identifying large arterial occlusions, determined by the presence or absence of obstruction in anteriorly oriented blood flow. The occlusion site was correlated with the patient's medical history to identify the responsible vessel. In conjunction with the DWI-detected infarct area, the possibility of penetrating arterial infarction was assessed. The spiral CT scan also evaluated for the presence of large cerebral infarcts, characterized predominantly by low signal; cerebral hemorrhage, indicated by a persistently high signal even after the exclusion of contrast residue; and malignant cerebral edema leading to cerebral herniation.

The ASPECTS is a semi-quantitative tool used to evaluate early ischemic changes (EIC) specifically in the middle cerebral artery (MCA) donor region. This scoring system divides the MCA donor area into 10 sections across two levels. At the thalamus and basal ganglia levels, there are 7 sections (C, L, IC, I, M1, M2, M3), and at the level above the nucleus accumbens, there are 3 sections (M4, M5, M6). These levels are differentiated by the head of the caudate nucleus; sections visible at the level of the caudate nucleus's head are classified under the thalamus and basal ganglia level, while those from the next level up to the centers of the semi-ovals fall under the level above the nucleus accumbens. In ASPECTS, 1 point is deducted for each EIC observed in any of the 10 MCA donor areas. A score of 0 indicates diffuse ischemia involving the entire middle cerebral artery. A score greater than 7 is associated with a promising prognosis for independent living at 3 months post-stroke, while a score of 7 or less indicates a likelihood of dependence or high mortality risk. Notably, if the ASPECTS score is 7 or less following thrombolytic therapy, the risk of cerebral hemorrhage is 14 times higher compared to patients with a score higher than 7.

END and severe END definition

Compared with NIHSS score before intravenous thrombolysis, END was defined as an increase in two or more NIHSS points, an increment of at least one point in motor power, or description of fluctuating of clinical symptoms in medical reports during the first 48 h after intravenous thrombolysis, severe END (15) was defined as an increase of NIHSS $\geq$ 4 points. Were classified into 2 groups according to the presence or absence of END.

Statistical analysis

Continuous data following a normal distribution were presented as means ± standard deviations (SD) and analyzed using Student's *t*-test. For data not normally distributed, medians (interquartile range, IQR) were used, and analyses were conducted with the Mann–Whitney *U* test. Categorical data were expressed as *n* (%) and analyzed

using the Chi-square test or Fisher's exact test, as appropriate. In the process of nomogram construction and validation, variables demonstrating significance ($P<0.05$) in univariate logistic regression analysis were included in multivariate logistic regression analysis to identify independent risk factors for unexplained END (stepwise forward variable selection method). Based on the logistic analysis results, these independent risk factors were incorporated into the risk model prediction. The nomogram was constructed using the R programming language, with factor value ranges defined by clinical or literature analysis. The prediction model's discrimination was evaluated using the receiver operating characteristic (ROC) curve and the area under the curve (AUC). Model calibration was assessed with the Hosmer–Lemeshow test. To verify the stability of our model, we performed internal data analysis, dividing the data into training and validation groups to evaluate the model's discriminant ability. Calibration was employed to assess the consistency of the model's predictions. Additionally, we utilized decision curve analysis to determine the clinical utility of the nomogram.

All statistical analyses were conducted using SPSS Statistics version 21.0 (IBM, Armonk, NY, USA), and two-sided *P*-values of less than 0.05 were considered statistically significant.

Results

Patients disposition

A total of 279 patients were initially included. However, several exclusions were made: 24 patients were excluded due to incomplete clinical data, 24 due to definite macrovascular lesions or receipt of intravascular treatment, 11 confirmed to have large-area cerebral infarction or complications with intracranial hemorrhage, and 9 due to heart failure and myocardial infarction. Finally, a total of 211 patients were included. In terms of treatment, 90.4% of the patients received 0.9 mg/kg of rt-PA, and 9.6% received 0.6 mg/kg. Patients who have received 0.6 mg/kg of rt-PA targeted at those with high bleeding risk, mainly including patients over 85 years old, the area of cerebral infarction close to 1/3 of the middle cerebral artery, and obvious infarction was seen early on CT whose onset time were less than 3 h. Among these, a total of 66 patients experienced unexplained END (Fig. 1). Of the 211 patients, 153 cases (approximately 72%) were randomly assigned to the training group, while the remaining 58 cases (approximately 28%) formed the validation group.

Baseline characteristics

The mean age was slightly lower in the END group (62.1 ± 8.6 years) compared to the Non-END group (64.8 ± 9.2 years). SBP was comparable, with 140.7 ± 22.1 mmHg in the END group versus 139.1 ± 17.9 mmHg in the Non-END group. Blood glucose levels were higher in the END group (9.0 ± 4.1 mmol/L) than in the Non-END group (7.4 ± 3.5 mmol/L). The Neu/Lym ratio also showed a significantly increased in the END group (5.5 ± 1.4) compared to the Non-END group (4.5 ± 0.9). NIHSS scores were slightly higher in the END group (4.2 ± 2.2) than in the Non-END group (3.6 ± 1.9). The mean of ONT was marginally lower in the END group (2.8 ± 1.1 h) compared to the Non-END group (2.9 ± 0.9 h), but the comparison was not statistically significant. Lastly, ASPECTS was lower in the END group (6.8 ± 1.8) than in the Non-END group (7.7 ± 1.6) (Fig. 2).

Univariate logistic regression analysis

Univariate logistic regression analysis revealed that blood glucose >11.0 mmol/L (OR: 2.70, 95% CI 1.20–6.04, $P=0.016$), cardiogenic embolism (OR: 2.45, 95% CI 1.17–5.13, $P=0.018$), TIA (OR: 2.80, 95% CI 1.41–5.54, $P=0.003$), NIHSS scores ≥ 6 (OR: 2.04, 95% CI 1.05–3.97, $P=0.036$), large artery disease (OR: 4.00, 95% CI 2.09–7.65, $P<0.001$), important perforator (OR: 2.43, 95% CI 1.21–4.87, $P=0.012$), Neu/Lym ratio (OR: 4.17, 95% CI 2.22–7.83, $P<0.001$), and ASPECTS ≤ 6 scores (OR: 2.39, 95% CI 1.02–5.63, $P=0.045$) were associated with END after venous thrombosis (all $P<0.05$) (Table 1).

Multivariate logistic regression analysis for END after intravenous thrombolysis

Multivariate logistic regression analysis identified large artery disease (OR: 3.08, $P=0.010$, 95% CI 1.21–6.12), TIA (OR: 2.91, $P=0.012$, 95% CI 0.58–0.93, high blood glucose (OR: 1.16, $P=0.002$, 95% CI 1.05–1.27), high Neu/Lymp ratio (OR: 2.43, $P<0.0001$, 95% CI 1.73–3.34), important perforator (OR: 2.89, $P=0.025$, 95% CI 1.32–7.22, and Alberta Stroke Program Early CT Score (ASPECTS) (OR: 1.37, $P=0.011$, 95% CI 1.15–7.28) as independent risk factors for END following intravenous thrombolysis (Table 2).

Nomogram for predicting END

Based on the logistic analysis results, six independent risk factors were included in the model and developed a nomogram: large artery disease, TIA, blood glucose levels, Neu/Lym ratio, important perforator, and ASPECTS. In the nomogram, each of these 10 predictors was assigned a graphic preliminary score on a scale from 0 to 10. These scores were summed to derive a total score, which was then translated into an individual probability of experiencing END post-thrombolysis, ranging from 0 to 100% (Fig. 3). The AUC-ROC value of the nomogram

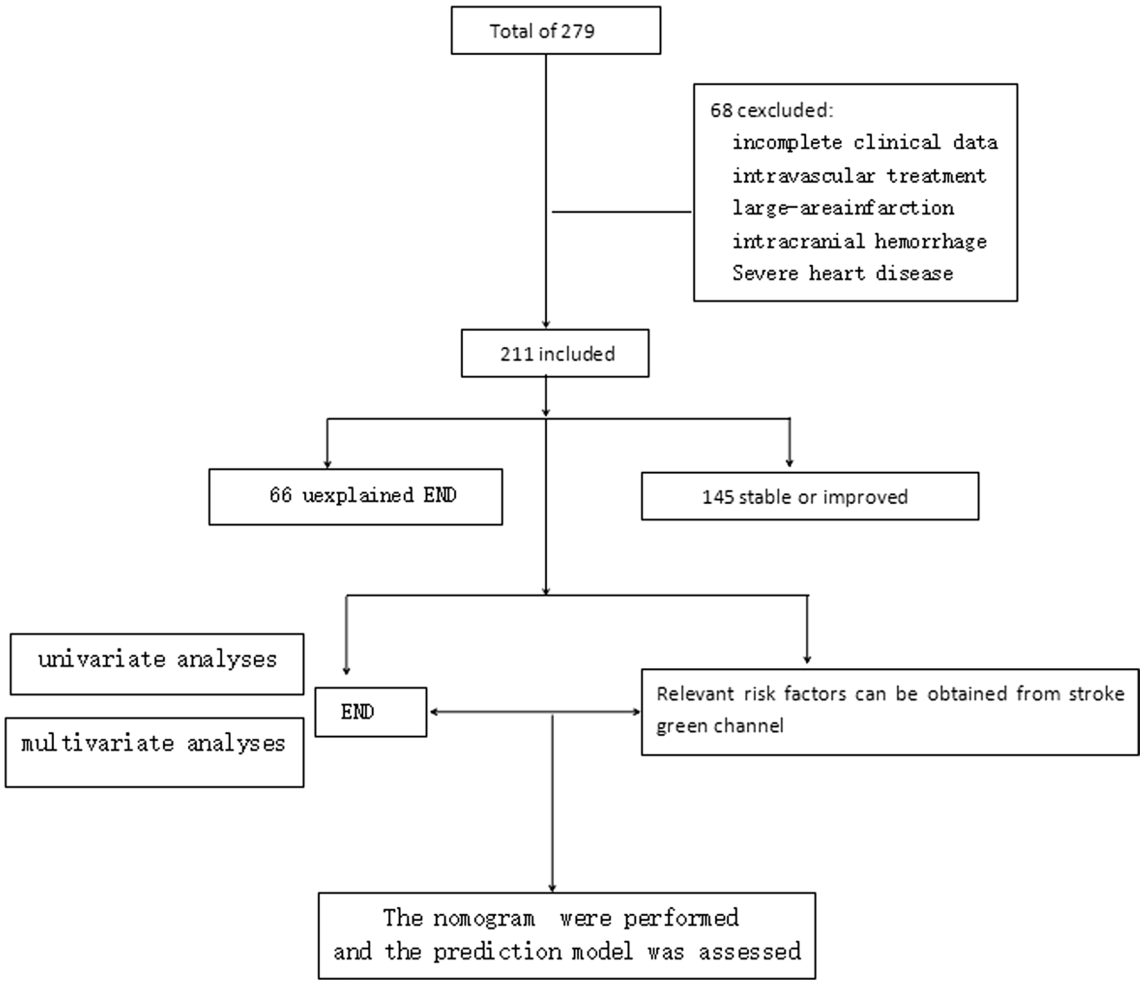

Fig. 1 Flowchart depicting patient selection and study design. *END* early neurological deterioration

was 0.809 (95% CI 0.7429–0.8751), with a specificity of 0.862 and a sensitivity of 0.712. The positive predictive value was 0.702, and the negative predictive value was 0.868. In the validation group, there were 43 cases without END, and 15 cases with END. The AUC-ROC curve for the nomogram was 0.816, with a 95% CI of 0.6783–0.9527 (Fig. 4). In the training group, the C-index was 0.846, Dxy was 0.692, the mean absolute error (MAE) was 0.027, the mean squared error (MSE) was 0.00082, and the quantity of absolute error was 0.038. In the validation group, the C-index was 0.852, Dxy was 0.705, MAE was 0.074, MSE was 0.00079, and the quantity of absolute error was 0.146. These results indicate that the actual predictive ability of the model is relatively close to the ideal, suggesting acceptable consistency between the model and the ideal model (Fig. 5). Based on the decision curve analysis, the threshold probability for the training group was set between 0.08 and 0.86, while for the validation group, it ranged from 0.11 to 0.73. These thresholds demonstrate the significant clinical relevance of using the nomogram for assessing the risk of END (Fig. 6).

Discussion

This study found that large artery disease, TIA, high blood glucose, elevated leukocyte–lymphocyte ratio, significant perforator artery cerebral infarction, and ASPECTS were independent risk factors for END following intravenous thrombolysis. A nomogram-based risk prediction model was developed and demonstrates good stability and predictive capacity. These findings may provide valuable guidance for clinical medical staff in evaluating the condition of acute ischemic stroke patients and implementing pre-treatment interventions.

The nomogram's practical application is substantial, offering a significant benefit in clinical settings. The statistical analyses of both the training and validation groups provide strong evidence of the model's stability and predictive accuracy. This model serves as a refined

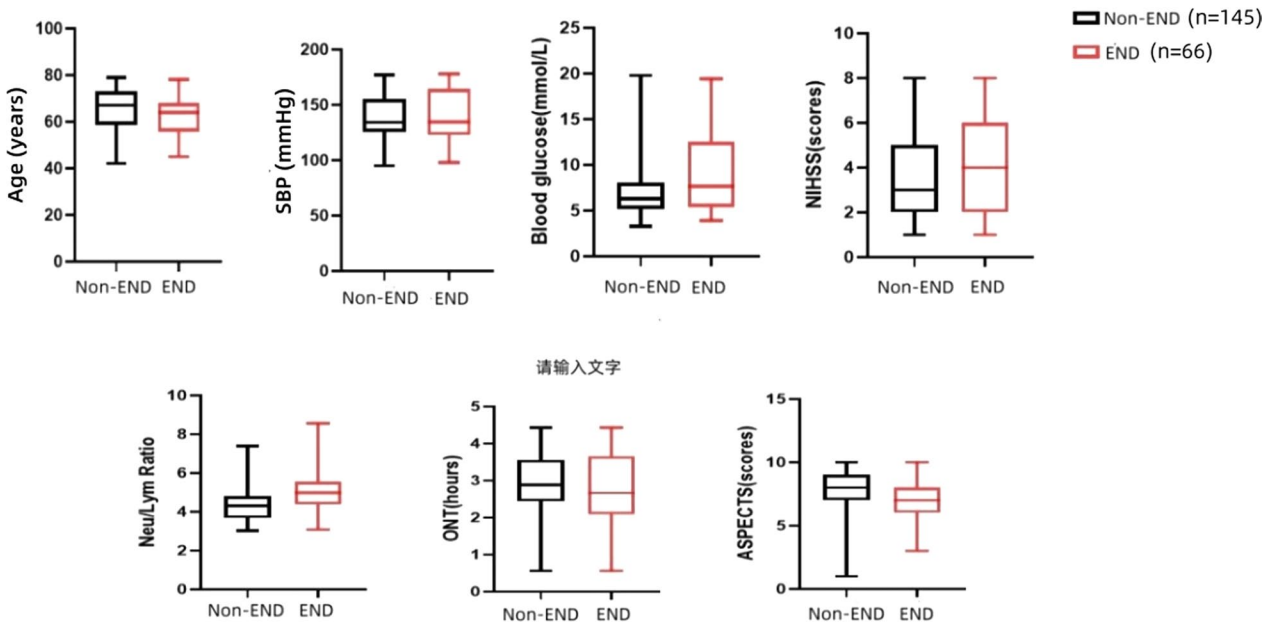

Fig. 2 Comparative analysis of baseline characteristics between Non-END and END Groups. *END* early neurological deterioration, *SBP* systolic blood pressure, *NIHSS* National Institutes of Health Stroke Scale, *ONT* onset time, *Neu/Lym ratio* neutrophil-to-lymphocyte ratio, *ASPECTS* Alberta Stroke Program Early CT Score. Data are presented as mean ± SD

tool for clinicians, enhancing the evaluation of acute ischemic stroke patients and aiding in the implementation of targeted pre-treatment interventions. The high AUC-ROC value of the model, along with its specificity and sensitivity, underlines its reliability for clinical use. Moreover, the decision curve analysis emphasizes the model's applicability in routine clinical practice by presenting a broad threshold probability range. This range is designed to accommodate a variety of clinical scenarios, thereby augmenting the model's utility for healthcare professionals who face critical decision-making in diverse patient populations.

The nomogram developed in this study for predicting unexplained END following intravenous thrombolysis in acute ischemic stroke patients marks a significant advancement, particularly when compared to existing models such as the WORSEN model, which assesses END risk factors within the first week post-stroke [7]. On the other hand, this new nomogram specifically targets the immediate post-thrombolytic phase, incorporating a diverse set of clinical and imaging parameters such as large artery disease, TIA history, and blood glucose levels. This approach not only fills a crucial gap in acute phase stroke risk assessment, but also complements existing models by providing a more nuanced tool for clinical decision-making in the critical period following thrombolysis.

Early prediction is crucial for effective doctor–patient communication and the timely implementation of preventive measures to reduce the incidence of END. Many indicators, such as aquaporin-4 levels or active N-terminal pro-brain natriuretic peptide levels, are typically obtained post-intravenous thrombolysis and are seldom measured in emergency settings [9–11]. A meta-analysis of risk factors for END occurrence, helped us identify indicators accessible in green channel facilities and primary hospitals [12]. The green channel of stroke was established in most Hospitals in China. The green channel of stroke first aid in the emergency department in the hospital with the ability of stroke treatment, makes a special, timely and rapid treatment channel within the time window. When these patients arrived at the hospital, if the onset of the disease was very short, there would be special personnel to accompany them to the clinic for examination and treatment. They would be given drugs or interventional therapy as quickly as possible in order to shorten the time delay. If there is a good green channel for stroke treatment during this process, it can make the patient to be treated as quickly as possible. Factors such as medical history (age, gender, ONT), physical examination (blood pressure, NIHSS score), imaging (including brain CT, MRI DWI, and MRA for ASPECTS score), and serum laboratory tests (blood cell analysis, blood glucose) can be utilized in emergency situations.

In many studies, it is noted that large artery disease [9, 13], coupled with a low ASPECTS [14, 15], can contribute to the occurrence of END. Large arterial lesions result in extensive ischemic tissue and potentially a

Table 1 Demographic and clinical characteristics

	All patients ($n=211$)	END ($n=66$)	Non-END ($n=145$)	*P*	OR	95% CI
Age, years, *n* (%)						
< 65	110 (52.1)	38 (57.6)	72 (49.7)		1.00	Reference
≥ 65	101 (47.9)	28 (42.4)	73 (50.3)	0.286	0.73	0.40, 1.31
Gender, *n* (%)						
Male	130 (61.6)	43 (65.2)	87 (60.0)		1.00	Reference
Female	81 (38.4)	23 (34.8)	58 (40.0)	0.476	0.80	0.44, 1.47
SBP, *n* (%)						
< 140 mmHg	123 (58.3)	38 (57.6)	85 (58.6)		1.00	Reference
< 160 mmHg	52 (24.6)	11 (16.7)	41 (28.3)	0.192	0.60	0.28, 1.29
≥ 160 mmHg	36 (17.1)	17 (25.8)	19 (13.1)	0.073	2.00	0.94, 4.27
Blood glucose, *n* (%)						
≤ 11.0 mmol/L	167 (79.1)	43 (65.2)	124 (85.5)		1.00	Reference
> 11.0 mmol/L	44 (20.9)	23 (34.8)	21 (14.5)	0.016	2.70	1.20,6.04
Cardiogenic embolism, *n* (%)						
No	176 (83.4)	49 (74.2)	127 (87.6)		1.00	Reference
Yes	35 (16.6)	17 (25.8)	18 (12.4)	0.018	2.45	1.17, 5.13
TIA, *n* (%)						
No	167 (79.1)	44 (66.7)	123 (84.8)		1.00	Reference
Yes	44 (20.9)	22 (33.3)	22 (15.2)	0.003	2.80	1.41, 5.54
NIHSS, *n* (%)						
< 6 scores	163 (77.3)	45 (68.2)	118 (81.4)		1.00	Reference
≥ 6 scores	48 (22.7)	21 (31.8)	27 (18.6)	0.036	2.04	1.05, 3.97
Large artery disease, *n* (%)						
No	156 (73.9)	36 (54.5)	120 (82.8)		1.00	Reference
Yes	55 (26.1)	30 (45.5)	25 (17.2)	< 0.001	4.00	2.09, 7.65
Important perforator, *n* (%)						
No	169 (80.1)	46 (69.7)	123 (84.8)		1.00	Reference
Yes	42 (19.9)	20 (30.3)	22 (15.2)	0.012	2.43	1.21, 4.87
ONT, *n* (%)						
< 3 h	119 (56.4)	38 (57.6)	81 (55.9)		1.00	Reference
≥ 3 h	92 (43.6)	28 (42.4)	64 (44.1)	0.816	0.93	0.52, 1.68
Neu/Lym ratio, *n* (%)						
< 4.8	110 (52.1)	19 (28.8)	91 (62.8)		1.00	Reference
≥ 4.8	101 (47.9)	47 (71.2)	54 (37.2)	< 0.001	4.17	2.22, 7.83
ASPECTS, *n* (%)						
> 6 scores	157 (74.4)	38 (57.6)	119 (82.1)		1.00	Reference
≤ 6 scores	54 (25.6)	28 (42.4)	26 (17.9)	0.045	2.39	1.02, 5.63

END early neurological deterioration, *OR* odds ratio, *95% CI* 95% confidence interval, *SBP* systolic blood pressure, *TIA* transient ischemic attack, *NIHSS* National Institutes of Health Stroke Scale, *ONT* onset time, *Neu/Lym ratio* neutrophil-to-lymphocyte ratio, *ASPECTS* Alberta Stroke Program Early CT Score

significant ischemic penumbra. Intravenous thrombolysis often has limited efficacy in such cases of large artery disease. A low ASPECTS score indicates poor collateral circulation, which can lead to ischemic progression if blood vessels cannot be adequately reconstructed. However, this study excluded patients at risk of malignant edema due to extensive cerebral infarction. Thus, hemodynamics, low perfusion, or poor collateral circulation resulting from large artery disease were the primarily considered factors. During thrombolysis, the exposure of atherosclerotic plaque surfaces, which are highly thrombogenic, can cause thrombus expansion and reformation. The dissolution of large plaques may lead to the formation of small thrombi, which can then obstruct distal branch arteries, causing ischemia and hypoxia in the corresponding brain tissue [16]. This results in secondary damage and exacerbation of clinical symptoms.

Table 2 Multivariate logistic regression analysis identifying independent risk factors for END following intravenous thrombolysis

Variables	Adjusted OR	95% CI	*P*
Blood glucose (> 11.0 mmol/L vs. ≤ 11.0 mmol/L)	1.16	1.05–1.27	0.002
Large artery disease (yes vs. no)	3.08	1.21–6.12	0.010
Important perforator (yes vs. no)	2.89	1.32–7.22	0.025
ASPECTS (≤ 6 scores vs. > 6 scores)	1.37	1.15–7.28	0.011
Neu/Lym ratio (≥ 4.8 vs. < 4.8)	2.43	1.73–3.34	< 0.0001
TIA (yes vs. no)	2.91	0.58–0.93	0.012

B regression coefficients, *SE* standard error, *WALS* weighted-average least squares, d*f* degrees of freedom, *OR* odds ratio, *CI* confidence interval

In patients with a history of early TIA, this study examined 44 patients who presented with TIA symptoms. Among them, 32 had underlying large artery lesions (either severe stenosis or unstable plaque), 9 had issues with perforating arteries, and 2 had causes that were unknown. This indicates that the main factors contributing to infarction progression in TIA patients are hypoperfusion resulting from large artery disease or the onset of new artery-to-artery embolisms.

Moreover, high glycemic levels or poorly controlled diabetes are often seen as contributing factors. Increased blood glucose levels post-stroke may impede the secondary fibrinolytic process, leading to reduced blood flow in the ischemic penumbra and an expanded cerebral infarction area [17]. In cases of infarction caused by important perforator artery occlusion, we discern the absence of large artery disease by analyzing the infarction location on DWI and CTA. This assessment aligns with the typical locations and extents of common important perforator artery infarctions. The responsible vessels may include the anterior choroidal artery, basilar artery perforators, Heubner's recurrent artery, lenticular artery,

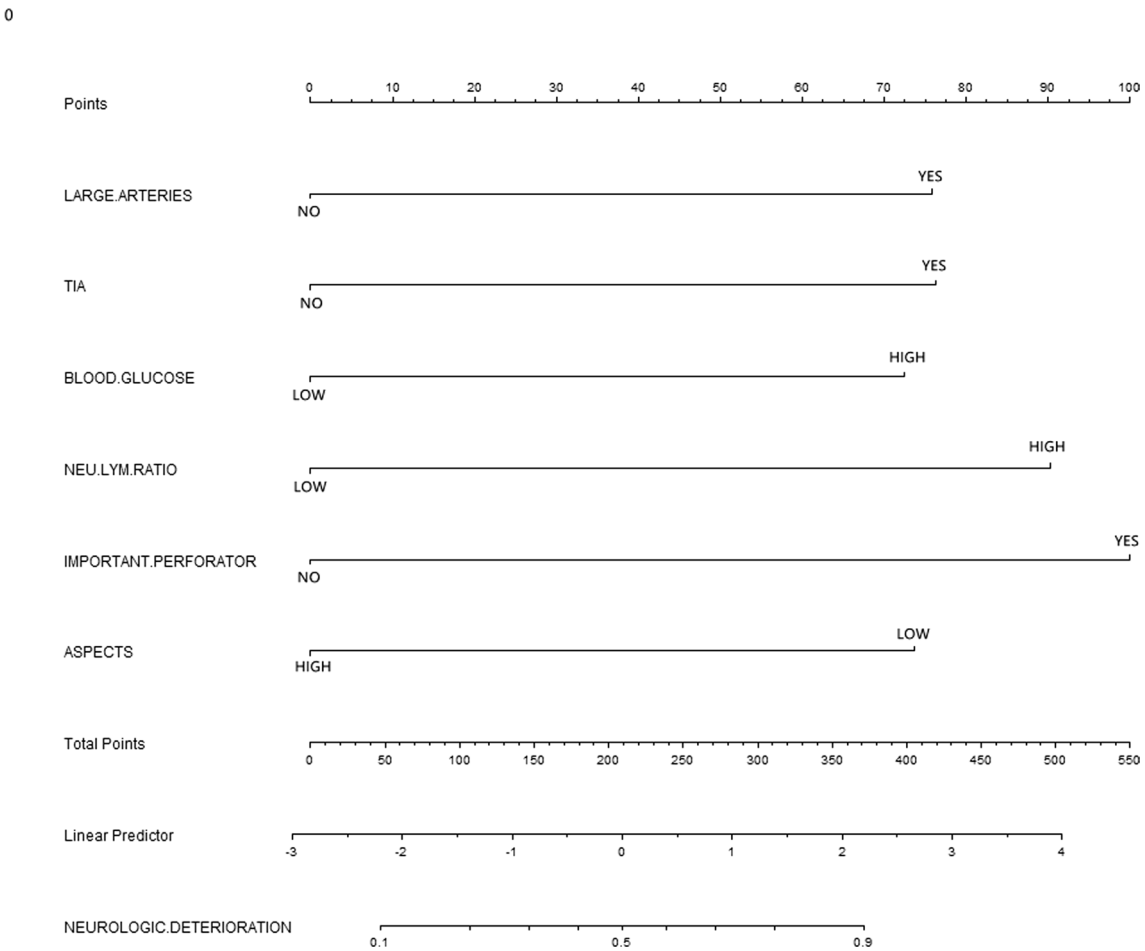

Fig. 3 Nomogram for predicting the risk of END following intravenous thrombolysis. Points assigned to each variable from the multivariate analysis are represented. The 'Total Points' is the sum of all individual scores. The lower section of the figure displays the corresponding probability of END based on the total score

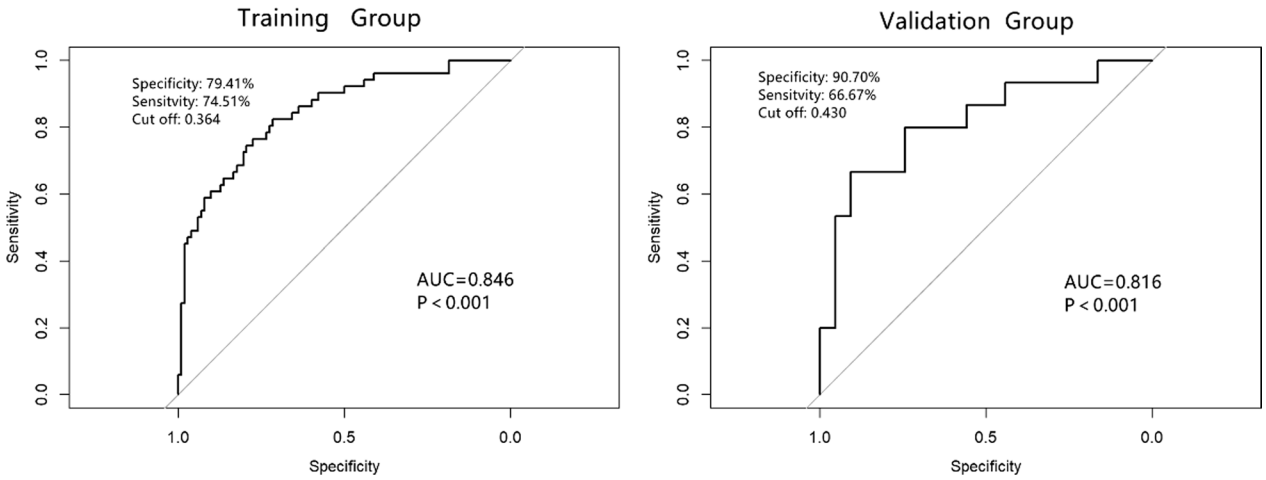

Fig. 4 The AUC-ROC of the nomogram for predicting END during the stepwise testing of the model in both the training and validation groups

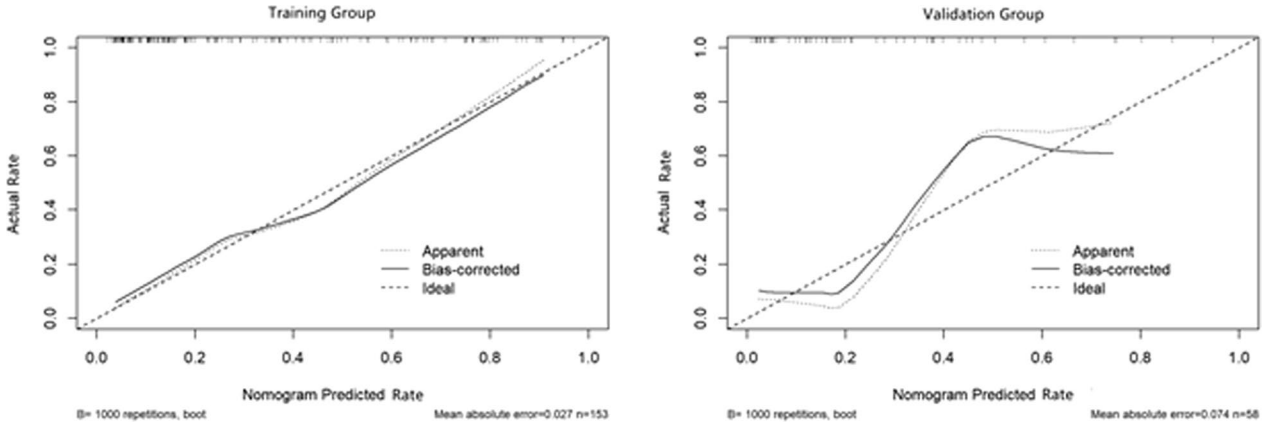

Fig. 5 Calibration curve to evaluate the consistency of the model

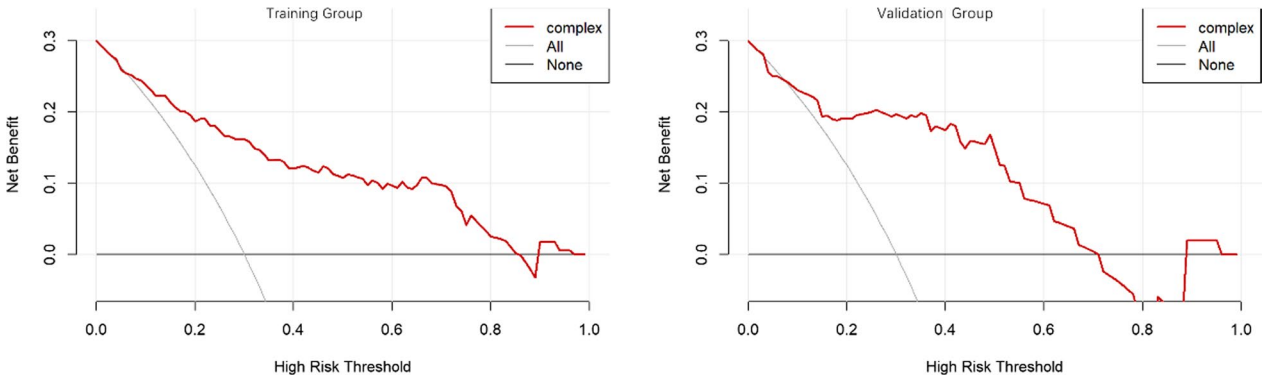

Fig. 6 The decision curve was used to evaluate the profitability of the END nomogram. The X-axis represents the threshold probability, and the Y-axis represents the net benefit. The blue solid line illustrates the nomogram of END occurrence. The gray solid line represents the assumption that all patients have END, while the red solid line represents the assumption that no patients have END (None)

and thalamic-related perforator arteries [18]. Some studies have specifically investigated the primary predictors of cerebral infarction due to small vessel disease, noting capsule warning syndrome and ventral pontine infarction as significant factors [19, 20]. Among the 33 patients studied, 23 cases showed an expansion of the ischemic area. We also recognize that most of these perforating arteries are terminal vessels, which implies a high likelihood of thrombosis extension and progression. Their compensatory capacity is relatively poor, lacking assistance from other blood vessels [21].

In the context of the Neu/Lym ratio, a study by Pengyu Gong reported that out of 1060 patients, 193 (18.2%) were diagnosed with END post-thrombolysis. The study found associations between three logistic neutrophil–lymphocyte related ratios (NLRs)—namely NLR (neutrophil–lymphocyte ratio), PLR (platelet–lymphocyte ratio), and LMR (lymphocyte–monocyte ratio)—and post-thrombolysis END, with NLR and PLR potentially serving as predictors. Specifically, NLR was identified as an independent factor for END following thrombolysis [22]. Numerous studies have corroborated the significant role of inflammatory mechanisms in the pathogenesis and progression of ischemic stroke. Peripheral blood leukocytes, triggered by inflammatory cytokines and chemokines, are released from ischemic tissues [23]. Conversely, these peripheral leukocytes can also impact ischemic tissue, with neutrophil-derived free radicals causing brain damage [24]. Lymphocyte count, on the other hand, is considered neuroprotective and contributes to neural function improvement [25]. Therefore, the leukocyte to lymphocyte ratio not only reflects the neuroinflammatory response and activity post-ischemia but also indicates the likelihood of peripheral system infection, which is associated with poor prognosis.

This study has limitations. Other factors may also affect the occurrence of END, such as hypotension during the thrombolysis period, abnormal body temperature, hypoalbuminemia, etc. The indicators selected in the design of this study were based on literature analysis, and some indicators may not have been included. For ONT for thrombolysis < 180 min compared to > 180 min, the The division time window is set based on the time window of intravenous thrombolysis with rt-PA, and further research to find a cut-off point after which END is needed to define it in the future.

While it involves a retrospective analysis of prospectively collected data, it is based on observations from a single center. It is our hope that this study will serve as an impetus for broader collaboration among hospitals. Contributions from multiple centers, particularly primary hospitals, could make the data more persuasive and valuable. Expanding the scope of collaboration can provide a more comprehensive understanding and enhance the reliability of the findings.

In conclusion, this study evaluated some risk factors that cause unexplained END and developed a nomogram-based risk prediction model for END following intravenous thrombolysis, demonstrating both stability and reliable predictive capacity. To validate these findings further, a prospective, multicenter study is warranted.

Abbreviations

rt-PA	Recombinant tissue plasminogen activator
END	Early neurological deterioration
NIHSS	National Institute of Health Stroke Scale
AUC-ROC	The area under the receiver operating characteristic curve
CT	Computed tomography
MRI	Magnetic resonance imaging
EIC	Early ischemic changes
MCA	The middle cerebral artery
NLR or Neu/Lym ratio	Neutrophil–lymphocyte ratio
PLR	Platelet–lymphocyte ratio
LMR	Lymphocyte–monocyte ratio
CTA	Computed tomography angiography
DWI	Diffusion-weighted imaging
TIA	Transient ischemic attack prior to the current stroke
ONT	The onset time of intravenous thrombolysis
SBP	Systolic blood pressure
AF	Presence of atrial fibrillation
ASPECTS	Alberta Stroke Program Early CT Score

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Author contributions
Bifeng Zhu wrote the main manuscript text, Haiwei Jiang was the main charger of these projects for the text, Jing Zuo and Dan Yan prepared manuscript drafting. Chang Gao and Yi Huang were in charge of collecting clinical research data for the text. Dan Wang was in charge of statistics for this research. All authors reviewed the manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Informed consents were obtained from the participants entering the stroke registry, and this analysis was approved by the Ethics Committee of Hubei No. 3 People's Hospital of Jianghan University.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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