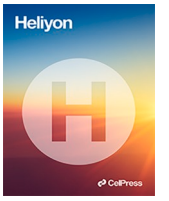
Heliyon 10 (2024) e23341

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



# A novel nomogram predicting early neurological deterioration after intravenous thrombolysis for acute ischemic stroke

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ARTICLE INFO

*Keywords:*
Early neurological deterioration
Acute ischemic stroke
Intravenous thrombolysis
Nomogram
Risk prediction

ABSTRACT

*Objectives:* Intravenous thrombolysis therapy (IVT) with recombinant tissue plasminogen activator has proven to be a beneficial treatment for acute ischemic stroke (AIS) patients when administered within 4.5 h after a stroke. This study aimed to investigate an available and inexpensive predictive tool for early neurological deterioration in AIS.
*Methods:* Patients admitted to our department with acute stroke who were given IVT with recombinant tissue plasminogen activator within 4.5 h of stroke onset were included in the study. The NIH stroke scale (NIHSS) was used to assess patients' neurological state prior to IVT and for 24 h after. Early neurological deterioration was defined as occurring if the NIHSS total score increased by $\geq$ 4 or the NIHSS individual score increased by $\geq$ 2 compared to baseline. Patients were randomly assigned to training or validation cohorts.
*Results:* Of the 266 AIS patients receiving IVT who were screened, 217 were deemed eligible for the study. Multivariate logistic regression analysis identified smoking history, NIHSS score, homocysteine level, and neutrophil to lymphocyte ratio as independent factors for predicting early neurological deterioration. ROC analysis was used to assess the quality of the resulting nomogram. The AUC for the training dataset was 0.826 (95 % CI, 0.719–0.932), and for the validation dataset was 0.887 (95 % CI, 0.763–1.000).
*Conclusion:* The robustness of this nomogram suggests that it may be a reliable tool for evaluating the progression of AIS after IVT.

## 1. Introduction

Stroke, an acute central nervous system injury, is a risk factor for death and disability in humans [1]. Acute ischemic stroke (AIS) accounts for 60–80 % of all strokes [2]. AIS occurs primarily due to atherothrombosis or thrombus in the vessels supplying blood to the brain, leading to brain tissue damage [3]. Thrombolytic or anticoagulant drugs can be used as an early treatment to restore blood perfusion [4]. Therefore, timely vascular recanalization is closely related to early neurological deterioration (END) and prognosis after AIS [5,6].

At present, intravenous thrombolysis (IVT), especially with recombinant tissue plasminogen activator (rt-PA), is the mainstay of AIS treatment. When delivered within 4.5 h of stroke onset it can significantly improve prognosis for AIS patients [7]. However, END is

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https://doi.org/10.1016/j.heliyon.2023.e23341
Received 4 July 2023; Received in revised form 17 August 2023; Accepted 1 December 2023
Available online 5 December 2023

a relatively common complication in the 24 h following IVT. The underlying mechanisms of END are not fully understood [8]. Therefore, it is essential to explore its mechanism and the related risk factors after IVT.

There is urgent clinical demand for an effective model to predict prognosis and treatment outcomes of AIS patients after IVT. Several predictive models exist [9–11] but show poor functional outcomes because they focus on a single type of risk factor. A nomogram is a visualization tool that integrates indicators from different dimensions, to provide an accurate and individualized prediction of specific outcomes [12]. Previous work has constructed a nomogram to predict AIS prognosis with relation to the neutrophil-lymphocyte ratio [13]. This study aims to explore the predictive ability of a comprehensive panel of indicators and overcome the poor predictive power of models that only consider a single risk factor. Therefore, we assessed a broad range of measures, including patients' living habits and immunological and metabolic characteristics, and verified the model's accuracy in an independent validation cohort. The resulting nomogram is useful for clinicians to explore the probability of END after IVT and identify patients at risk for poor prognosis after rt-PA treatment.

## 2. Materials and methods

### 2.1. Study design and participants

Patients were recruited by the Stroke Center of the Second Affiliated Hospital of University of South China from November 2017 to August 2022. Their clinical information was retrospectively analyzed. Patients were included if they were >18 years old, had MRI-confirmed stroke within the past 24 h, and had received IVT within 4.5 h of stroke onset. Patients were excluded if their IVT was followed by endovascular treatment, if they experienced intracranial hemorrhage (ICH) after IVT, or if they had any medical contraindications to IVT. The medical Ethics Committee at the Second Affiliated Hospital of University of South China approved the study design. No informed consent was required due to this being a retrospective study.

### 2.2. Baseline data acquisition

Demographic information, medical history, clinical information, and laboratory information were collected from all study participants. Demographic characteristics included age, sex, smoking status, and drinking history. Medical history included hypertension, diabetes mellitus, and atrial fibrillation.

Clinical information included systolic blood pressure (SBP), diastolic blood pressure (DBP), and blood glucose. Laboratory information included fibrinogen, albumin (ALB), activated partial thromboplastin time (APTT), international normalized ratio (INR), white blood cell (WBC), platelet count (PLT), neutrophil to lymphocyte ratio (NLR), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride (TG), uric acid (UA), homocysteine (HCY), total cholesterol (TC), and urea nitrogen/creatinine ratio (BUN/Cr). In addition, the NIH stroke scale (NIHSS) score was obtained.

### 2.3. Treatment methods

Once admitted to the inpatient ward, guideline-based treatments were performed on all participants immediately: eligible patients received rt-PA within 4.5 h of stroke onset [7]. The velocity of rt-PA intravenous infusion was 0.9 mg/kg (maximum dose 90 mg); 10 % was given as an intravenous bolus within 1 min, and the remaining doses were infused intravenously over an hour or so.

### 2.4. Criteria for END

NIHSS was used to assess the neurological state of AIS patients for 24 h after IVT therapy. END aggravation was defined as the NIHSS total score increasing by $\geq 4$ or the NIHSS individual score increasing by $\geq 2$ compared with baseline. The study's endpoint was END but excluded cases of END due to ICH after IVT.

### 2.5. Statistical analysis

Statistical analyses were performed using R software version 4.0.0 (http://www.R-project.org/) and SPSS software version 22.0 (IBM, New York, New York, USA). Categorical variables were expressed as frequencies (percentages, %) and continuous variables as means (standard deviation, SDs) or medians (interquartile range, IQR). Continuous variables with a Gaussian distribution were compared using *t*-test or non-parametric Mann-Whitney *U* test; categorial variables were compared using $\chi 2$ or Fisher's exact test. A two-tailed p-value $<0.05$ was deemed statistically significant.

Univariate analysis was executed first to observe the correlation between each variable and END. Variables that were significant in the univariate analysis were then selected for multivariate regression.

The 217 patients enrolled in this study were randomly assigned to either the training (n = 152) or validation (n = 65) cohort according to the theoretical ratio of 7:3. The prediction model was established, and then its discrimination, calibration, and clinical efficacy were verified in the training and validation sets. Receiver operating characteristic (ROC) curves were employed to evaluate the model's usability, and a calibration curve was plotted to contrast the predicted probability with the actual likelihood of occurrence. Decision curve analysis (DCA) was used to evaluate the feasibility of the final model in practical clinical applications by quantifying the net benefit of various threshold possibilities in the validation cohort.

## 3. Results

### 3.1. Baseline characteristics

In total, 266 AIS patients receiving VIT from November 2017 to August 2022 were screened. Forty-nine patients were excluded because of endovascular treatment (n = 28), ICH after IVT (n = 13), or missing data (n = 8). The final analysis included 217 eligible subjects (Fig. 1).

Eligible subjects were assigned to either the training (n = 152) or validation (n = 65) cohort. The median age of participants was 65.5 (55,73) years in the training cohort and 68 (57,72) in the validation cohort. There were no significant differences between cohorts in terms of smoking, drinking, or medical history (Table 1).

### 3.2. Univariate and multivariate analyses

Clinical measurements for patients who received timely IVT therapy are shown in Table 2. Univariate analysis of the training cohort showed that smoking status, NIHSS score, NLR, and HCY were significantly associated with END. Multivariate logistic regression analysis further confirmed that smoking history (OR 3.720, 95 % CI 1.513–9.148; p = 0.004), lower NIHSS score (OR 0.902, 95 % CI 0.827–0.983; p < 0.0001), HCY (OR 1.060, 95 % CI 1.015–1.108; p = 0.009) and NLR (OR 1.072, 95 % CI 1.005–1.143; p < 0.0001) were independent factors for END. These factors were therefore incorporated into the prediction models.

### 3.3. Development and validation of the prediction model

Fig. 2 shows the final nomogram for predicting END risk in AIS patients receiving IVT, constructed using the results of the logistic regression analysis. The forecast model was calculated by the prognostic effect of these variables on the scales, which can indicate the estimated likelihood of END.

ROC curves for the nomogram as applied to the two cohorts (Fig. 3, Table 3). AUC of the training dataset was 0.826 (95 % CI 0.719–0.932), and of the validation dataset was 0.887 (95 % CI 0.763–1.000). Calibration curves confirmed that the probabilistic forecasting of END aligned with the observed integration value (p > 0.05) for both the training and validation datasets. To validate the forecasting ability of the tool, DCA was used to predict the incidence of END in patients. Fig. 4A describes the excellent concordance of the predicted probability of END between the training set and the actual observations, the mean absolute deviation (MAD) was 0.056. Fig. 4B shows the testing set also can predict the probability of END properly (MAD = 0.047). As shown in Fig. 5, the threshold probability ranges of the training and validation datasets were 4.8–64.7 % and 4.5–66.2 %, respectively, indicating that the nomogram derived from this research had the strong predictive capacity and could effectively exclude false positives and false negatives.

## 4. Discussion

The present study used retrospective clinical data to construct a nomogram for use in predicting END in AIS patients receiving IVT therapy. The nomogram demonstrated good performance in terms of discrimination, calibration, and clinical efficacy. Therefore, it could be a useful tool to identify the risk to patients' neurologic status after treatment and help clinicians make the optimal clinical decisions.

Scholars have constructed other models to predict END risk in AIS patients after IVT [14,15]. However, these scoring systems are limited in their ability to predict individual risk of END. Seners et al. developed a scoring system to predict END based on occlusion site and thrombus length [16]. END was diagnosed by magnetic resonance imaging (MRI) under the compressed sensing MRI algorithm

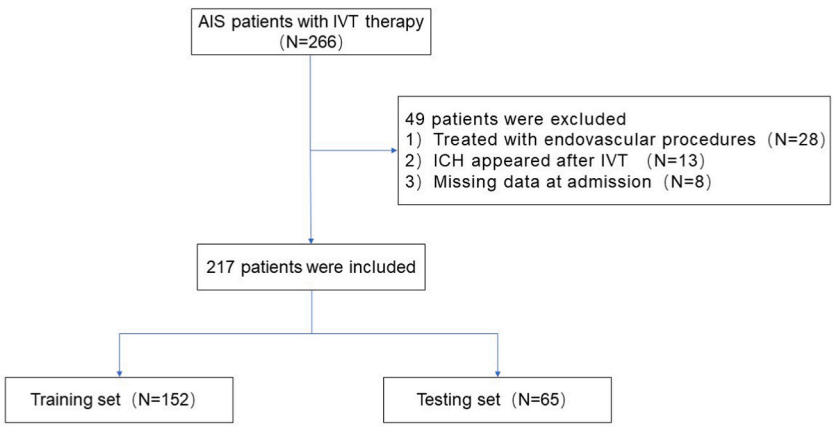


**Fig. 1.** Flowchart for screening participants.

**Table 1**
Baseline characteristics of eligible participants.

| Variables | Total sample (n = 217) | Training set (n = 152) | Testing set (n = 65) | $X^2/t/z$ | *P-value* |
|---|---|---|---|---|---|
| END, n(%) | 33(15.2) | 24(15.8) | 9(13.8) | 0.133 | 0.715 |
| Gender, n(%) | | | | 0.245 | 0.621 |
| Female | 65(30.0) | 44(28.9) | 21(32.3) | | |
| Male | 152(70.0) | 108(71.1) | 44(67.7) | | |
| Age, years | 67(56,73) | 65.5(55,73) | 68(57,72) | −0.672 | 0.502 |
| Smoking, n(%) | 73(33.6) | 49(32.2) | 24(36.9) | 0.448 | 0.503 |
| drinking, n(%) | 48(22.1) | 35(23.0) | 13(20.0) | 0.242 | 0.623 |
| NIHSS, score | 6(4,13) | 7(4,14) | 6(4,11) | −0.688 | 0.492 |
| SBP, mmHg | 151.00 ± 24.51 | 150.14 ± 24.39 | 153.00 ± 24.87 | −0.785 | 0.433 |
| DBP, mmHg | 84.70 ± 12.97 | 84.45 ± 13.16 | 85.28 ± 12.6 | −0.427 | 0.670 |
| Blood glucose, mmol/L | 6.87(5.8,9.07) | 6.86(5.7,9.2) | 7.2(6.18,8.8) | −0.726 | 0.468 |
| Hypertension, n(%) | 111(51.2) | 77(50.7) | 34(52.3) | 0.050 | 0.824 |
| Diabetes, n(%) | 41(18.9) | 28(18.4) | 13(20) | 0.074 | 0.785 |
| History_of_stroke, n(%) | 32(14.7) | 20(13.2) | 12(18.5) | 1.019 | 0.313 |
| AF, n(%) | 5(2.3) | 5(3.3) | 0(0) | 0.971 | 0.324 |
| INR | 1(0.93,1.03) | 1(0.93,1.03) | 0.99(0.92,1.02) | −1.121 | 0.262 |
| APTT, s | 35(32.7,37.8) | 34.95(32.7,38.2) | 35.1(33,37.6) | −0.535 | 0.593 |
| PLT, 10^9/L | 181(149,223) | 178(145,220) | 192(155,232) | −1.386 | 0.166 |
| Fibrinogen, g/L | 3(2.47,3.59) | 2.92(2.35,3.54) | 3.15(2.71,3.65) | −1.849 | 0.064 |
| ALB, g/L | 41.86 ± 3.93 | 41.91 ± 3.89 | 41.73 ± 4.04 | 0.316 | 0.752 |
| WBC, 10^9/L | 7.84(6.11,9.94) | 7.91(6.21,10.16) | 7.66(6.02,9.58) | −0.426 | 0.670 |
| NLR | 4.69(2.71,7.86) | 4.81(2.69,7.91) | 4.66(3,7.66) | −0.101 | 0.919 |
| HDL, mmol/L | 1.23(1.09,1.46) | 1.23(1.09,1.44) | 1.23(1.08,1.5) | −0.065 | 0.948 |
| LDL, mmol/L | 2.75 ± 0.84 | 2.72 ± 0.87 | 2.82 ± 0.78 | −0.812 | 0.417 |
| TG, mmol/L | 1.43(1,2.32) | 1.39(1,2.22) | 1.6(1.06,2.58) | −1.252 | 0.210 |
| TC, mmol/L | 4.64(3.97,5.28) | 4.57(3.93,5.27) | 4.77(4.12,5.4) | −0.944 | 0.345 |
| BUN/Cr | 75.18(58.99,93.3) | 74.41(58.08,91.21) | 78.54(65.45,97.3) | −1.315 | 0.189 |
| UA, μmol/L | 347(288,411) | 347.5(285.5415) | 344(291,391) | −0.392 | 0.695 |
| HCY, μmol/L | 13.1(9.8,17.3) | 13.5(9.9,17.6) | 11.8(9.4,16.1) | −1.191 | 0.234 |

Data are shown as mean ± SD or median (IQR) for continuous variables and as number (percentage) for categorical variables.
AIS, acute ischemic stroke; IVT, intravenous thrombolysis; END, early neurological deterioration; NHISS, National Institute Health of Stroke Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; AF, atrial fibrillation; APTT, activated partial thromboplastin time; INR, international normalized ratio; PLT, blood platelet; ALB, albumin; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; HDL, High-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; TC, total cholesterol; BUN/Cr, blood urea nitrogen-to-creatinine ratio; UA, uric acid; HCY, homocysteine.

[16]. However, its clinical diagnostic efficacy was low, with an accuracy rate of only 18.36 % [17]. Furthermore, MRI examination is expensive and time-consuming, which may negatively impact the timing of diagnosis and therapy and increase the probability of END [18]. In addition, that model failed to account for parameters before and after treatment that may be related to the occurrence of END, such as the time from the initiation of antithrombotic drugs to the initiation of treatment, blood pressure variability [19,20], non-recanalization [21], and arterial occlusion [22]. Patients who received endovascular treatment and IVT therapy were not excluded. The prediction model described in the present study rigorously excluded these potential confounds and analyzed all of the possible pre- and post-treatment factors mentioned above.

A nomogram is a risk predictive model comprised of available clinical indices. Few studies have plotted nomograms to predict END risk in AIS patients after IVT therapy. One such study reported an association between the ratio of compound inflammation before thrombolysis and early neurological outcomes; NLR and platelet-to-lymphocyte ratio were used to predict END after thrombolysis [23]. Regrettably, they only considered the influence of the immune system and ignored other information that may affect the prognosis of AIS patients. Perhaps because of this limited scope, the AUC of their prediction model was only 0.763 [23]. Another study also showed that elevated NLR could predict END after rt-PA administration [24]. Clearly, elevated NLR plays a vital role in predicting END, but those prediction models were limited by their consideration of immune indicators alone.

Changes in HCY level strongly predicted hemorrhagic transformation or clinical outcome after tPA treatment. This result is consistent with previous studies: Shi et al. reported that elevated HCY plays an essential role in AIS patients receiving rt-PA therapy and is associated with poor prognosis [25]. Increased HCY was associated with poor outcomes in AIS patients receiving thrombolytic therapy [26–28]. Mortality could be predicted by high HCY levels, especially in stroke patients with large vessel atherosclerosis subtypes [29]. It is possible that at the onset of stroke [30], impaired vessel wall integrity and disruption of cerebral vascular permeability led to endothelial dysfunction, elastic structure destruction, and basement membrane damage in cerebral arterioles and microvessels, which may lead to elevated HCY levels [31]. However, Shi et al. [25]. did not include a control group of patients who did not receive thrombolytic therapy, thus exposing them to selection bias. In addition, HCY levels are influenced by genetic factors, poor general health, malnutrition, diabetes, and other factors, and these confounding risks have not been consistently adjusted for. The AUC of the single-level prediction model was only 0.685 [25]. Matsuo et al. reported a relationship between smoking status and functional outcomes for AIS sufferers after IVT therapy. They found that poor functional outcomes occurred in 28 % of current smokers. Unfortunately, they did not assess clinical outcomes after treatment [32].

**Table 2**
Parameters of END risk in AIS patients after IVT therapy based on univariable and multivariable analyses of the training dataset.

| Variables | Univariable analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|
| | OR | 95%CI | P-value | OR | 95%CI | P-value |
| Age | 1.005 | 0.966–1.045 | 0.822 | | | |
| Gender | 0.506 | 0.206–1.247 | 0.139 | | | |
| NIHSS | 0.902 | 0.827–0.983 | 0.019 | 0.898 | 0.816–0.989 | 0.028 |
| smoking | 3.720 | 1.513–9.148 | 0.004 | 2.772 | 1.045–7.353 | 0.040 |
| drinking | 1.471 | 0.555–3.898 | 0.438 | | | |
| SBP | 1.005 | 0.987–1.023 | 0.586 | | | |
| DBP | 1.006 | 0.974–1.040 | 0.708 | | | |
| Blood glucose | 0.986 | 0.856–1.135 | 0.843 | | | |
| Hypertension | 1.774 | 0.724–4.347 | 0.210 | | | |
| Diabetes | 0.589 | 0.163–2.130 | 0.419 | | | |
| History of stroke | 1.400 | 0.424–4.623 | 0.581 | | | |
| AF | 1.348 | 0.144–12.61 | 0.794 | | | |
| INR | 0.017 | 0.000–1.995 | 0.094 | | | |
| APTT | 1.006 | 0.956–1.058 | 0.824 | | | |
| PLT | 0.998 | 0.990–1.006 | 0.618 | | | |
| Fibrinogen | 1.239 | 0.802–1.914 | 0.333 | | | |
| ALB | 1.082 | 0.960–1.218 | 0.196 | | | |
| WBC | 0.874 | 0.742–1.030 | 0.108 | | | |
| NLR | 1.072 | 1.005–1.143 | 0.034 | 1.088 | 1.016–1.166 | 0.016 |
| HDL | 2.996 | 0.738–12.156 | 0.125 | | | |
| LDL | 1.279 | 0.778–2.103 | 0.332 | | | |
| TG | 1.033 | 0.913–1.169 | 0.611 | | | |
| TC | 1.379 | 0.888–2.141 | 0.153 | | | |
| BUN/Cr | 0.997 | 0.984–1.010 | 0.626 | | | |
| UA | 1.000 | 0.996–1.005 | 0.889 | | | |
| HCY | 1.060 | 1.015–1.108 | 0.009 | 1.056 | 1.009–1.106 | 0.020 |

CI, confidence interval; OR, odds ratio; NHISS, National Institute Health of Stroke Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; AF, atrial fibrillation; APTT, activated partial thromboplastin time; INR, international normalized ratio; PLT, blood platelet; ALB, albumin; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; HDL, High-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; TC, total cholesterol; BUN/Cr, blood urea nitrogen-to-creatinine ratio; UA, uric acid; HCY, homocysteine.

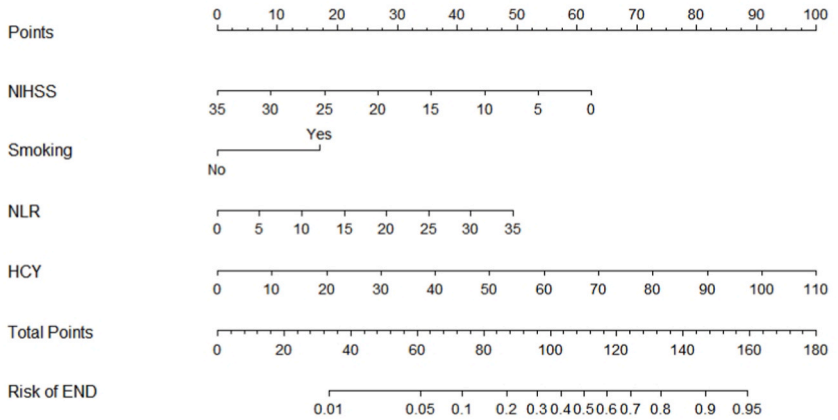


**Fig. 2.** Nomogram for predicting END risk in AIS patients with IVT therapy. Each of the four indicator scores is aligned with the "Points" line and then the four scores are added together to yield "Total Points", which can then be used to predict END risk.

Interestingly, the present study showed that a lower NIHSS score was accordant with END risk after IVT, which contrasts with several previous studies [33–35]. This may be due to differences in patient selection: other studies included patients with acute large vessel occlusive stroke, hemorrhagic infarction, parenchymal hematoma, and symptomatic intracranial hemorrhage after mechanical thrombectomy, all of which can cause a higher NIHSS score, and all of which were excluded from the present study. In addition, Vynckier et al. studied END associated with lacunar stroke patients, who had lower NIHSS scores on admission [36].

Overall, the present study found that smoking, NIHSS score, HCY, and NLR can be used as predictors of poor prognosis. These factors are largely consistent with previous studies. This multi-level model likely has greater clinical value than any of the single-level models published previously, as demonstrated by its AUC of 0.826. The nomogram described in this study considers immunity, metabolism, and patients' living habits and comprises a tool that is available even for health centers with few resources. This reliable

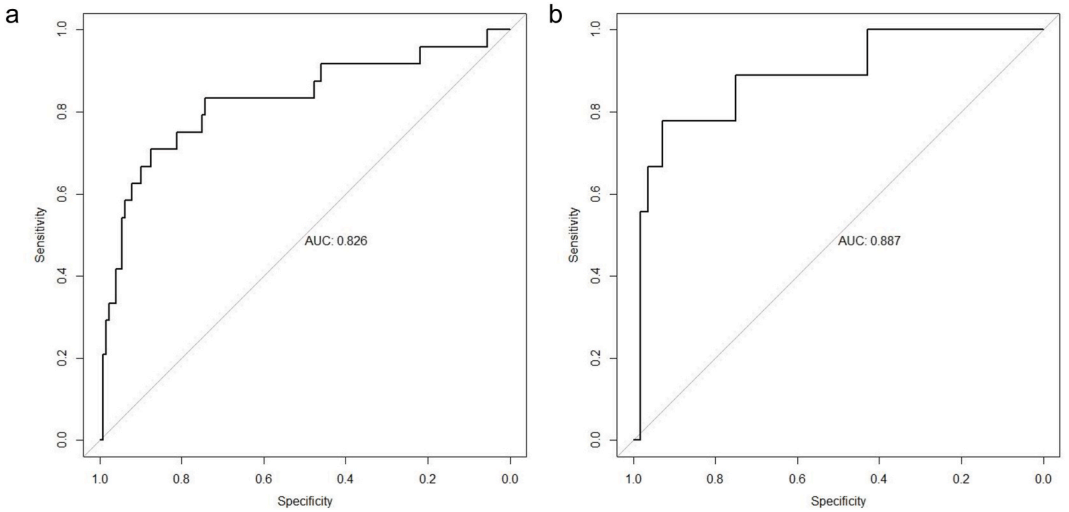


**Fig. 3.** ROC of the nomogram in the (A) training and (B) testing cohorts.

**Table 3**
ROC parameters for the nomogram for each cohort.

| | AUC | 95%CI | sensitivity (%) | specificity (%) |
|---|---|---|---|---|
| training cohort | 0.826 | 0.719–0.932 | 70.8 | 87.5 |
| validation cohort | 0.887 | 0.763–1.000 | 77.8 | 92.9 |

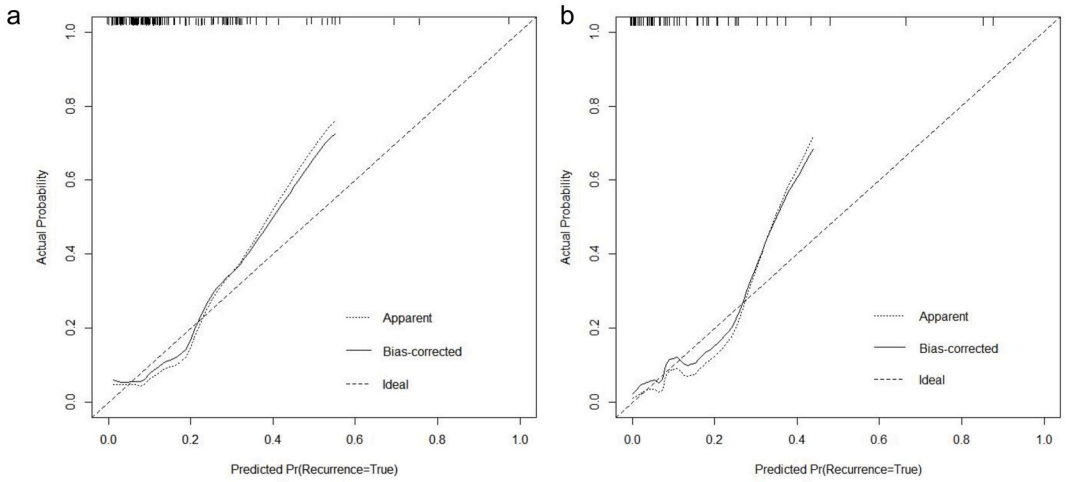


**Fig. 4.** Calibration curves for the nomogram. (A) Training cohort: MAD = 0.056, n = 152. (B) Validation cohort: MAD = 0.047, n = 65. Each cohort was repeated 1000 times.

tool is also suitable for non-neurologists to predict END risk because it does not rely on CT imaging.

This study has several drawbacks. All subjects were enrolled from the Second Affiliated Hospital of University of South China, a small research cohort, and the short follow-up time limited the statistical stringency of the results. In the future, it will be necessary to establish a prediction model with a large sample and prolonged follow-up time. Furthermore, our model has yet to be validated in an external cohort. Moreover, all features in our research were extracted from specific platforms and thresholds, which may influence the generalization of nomogram models. Prospective, multicenter studies are needed to evaluate the applicability of our nomogram to the more significant population. Finally, since this experiment was a preliminary exploratory experiment, we did not conduct further classified research on the location of stroke patients and stroke subtypes. In the subsequent study, we will conduct a more detailed evaluation of patients by combining more clinical information (MRI and CT) and then establish a multi-modal prediction model.

This novel nomogram may be a reliable tool for evaluating the progression of acute ischemic stroke after intravenous thrombolysis

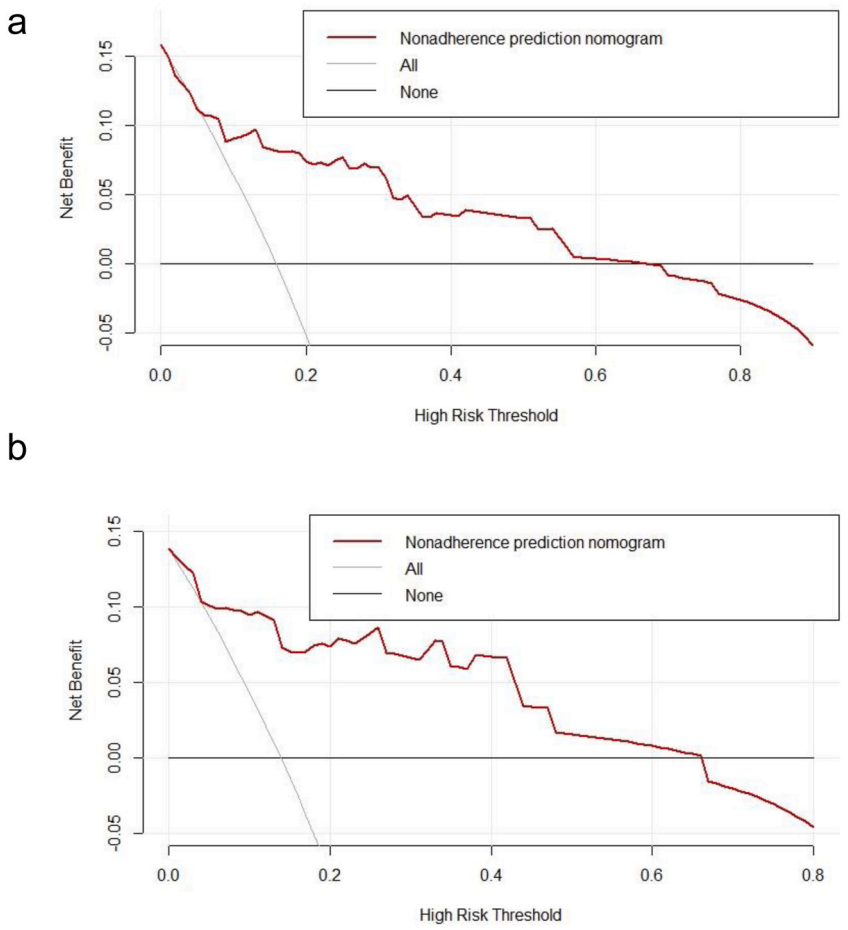


**Fig. 5.** Decision curve analysis of the nomogram. (A) The threshold probability range of the training set was 4.8–64.7 %. (B) The threshold probability range of the testing cohort was 4.5–66.2 %. The horizontal line indicates that all factors were treated with a net benefit of zero. The dashed line indicates that all candidate factors were influential, and interventions were made for all factors. The above curves were compared to the net benefit, a backslash with a negative slope.

therapy.

## Ethic approval

The medical Ethics Committee at the Second Affiliated Hospital of University of South China approved the study design [20220813k01]. No informed consent was required due to this being a retrospective study.

## Funding

This study was supported by Natural Science Foundation of Hunan Province [No.2022JJ30523]; Project of Hunan Provincial Health Commission [No.202203072849]; University of South China Clinical Research 4310 Program [No. 20224310NHYCG08]; Clinical Medical Research Center of Hunan Province [No. 2023SK4050].The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgments

We thank Department of Neurology, The Second Affiliated Hospital, Hengyang Medical School, University of South China.

## References

[1] A. Mishra, R. Malik, T. Hachiya, T. Jurgenson, S. Namba, D.C. Posner, et al., Stroke genetics informs drug discovery and risk prediction across ancestries, Nature 611 (2022) 115–123, https://doi.org/10.1038/s41586-022-05165-3.
[2] K.W. Huang, C.W. Chen, J.C. Wei, Ischemic stroke in patients with asymptomatic severe carotid stenosis without surgical intervention, JAMA 328 (2022) 1256, https://doi.org/10.1001/jama.2022.13010.
[3] J.M. Kim, J.H. Bae, K.Y. Park, W.J. Lee, J.S. Byun, S.W. Ahn, et al., Incidence and mechanism of early neurological deterioration after endovascular thrombectomy, J. Neurol. 266 (2019) 609–615, https://doi.org/10.1007/s00415-018-09173-0.
[4] Y.L. Zhu, Y.M. Lian, J.K. Wang, Z.P. Chen, R.Q. Yu, Highly sensitive and specific mass spectrometric platform for miRNA detection based on the multiple-metal-nanoparticle tagging strategy, Anal. Chem. 93 (2021) 5839–5848, https://doi.org/10.1021/acs.analchem.1c00065.
[5] K. Lin, E. Lang, In ischemic stroke upon wakening, IV thrombolysis or EVT improves functional outcome at 90 d, Ann. Intern. Med. 175 (2022) JC41, https://doi.org/10.7326/J22-0020.
[6] P. Seners, G. Turc, C. Oppenheim, J.C. Baron, Incidence, causes and predictors of neurological deterioration occurring within 24 h following acute ischaemic stroke: a systematic review with pathophysiological implications, J. Neurol. Neurosurg. Psychiatry 86 (2015) 87–94, https://doi.org/10.1136/jnnp-2014-308327.
[7] P. Khatri, Intravenous thrombolysis before thrombectomy for acute ischaemic stroke, Lancet 400 (2022) 76–78, https://doi.org/10.1016/S0140-6736(22)01286-7.
[8] M. Fisher, S.I. Savitz, Pharmacological brain cytoprotection in acute ischaemic stroke - renewed hope in the reperfusion era, Nat. Rev. Neurol. 18 (2022) 193–202, https://doi.org/10.1038/s41582-021-00605-6.
[9] N. Boulenoir, G. Turc, A. Ter Schiphorst, M.R. Heldner, D. Strambo, N. Laksiri, et al., Should patients with acute minor ischemic stroke with isolated internal carotid artery occlusion Be thrombolysed? Stroke 53 (2022) 3304–3312, https://doi.org/10.1161/STROKEAHA.122.039228.
[10] M.R. Heldner, S. Jung, C. Zubler, P. Mordasini, A. Weck, M.L. Mono, et al., Outcome of patients with occlusions of the internal carotid artery or the main stem of the middle cerebral artery with NIHSS score of less than 5: comparison between thrombolysed and non-thrombolysed patients, J. Neurol. Neurosurg. Psychiatry 86 (2015) 755–760, https://doi.org/10.1136/jnnp-2014-308401.
[11] W. Li, L. Lin, M. Zhang, Y. Wu, C. Liu, X. Li, et al., Safety and preliminary efficacy of early tirofiban treatment after alteplase in acute ischemic stroke patients, Stroke 47 (2016) 2649–2651, https://doi.org/10.1161/STROKEAHA.116.014413.
[12] D.A. Grimes, The nomogram epidemic: resurgence of a medical relic, Ann. Intern. Med. 149 (2008) 273–275, https://doi.org/10.7326/0003-4819-149-4-200808190-00010.
[13] P. Gong, Y. Xie, T. Jiang, Y. Liu, M. Wang, H. Sun, et al., Neutrophil-lymphocyte ratio predicts post-thrombolysis early neurological deterioration in acute ischemic stroke patients, Brain Behav 9 (2019), e01426, https://doi.org/10.1002/brb3.1426.
[14] J.M. Kim, J. Moon, S.W. Ahn, H.W. Shin, K.H. Jung, K.Y. Park, The etiologies of early neurological deterioration after thrombolysis and risk factors of ischemia progression, J. Stroke Cerebrovasc. Dis. 25 (2016) 383–388, https://doi.org/10.1016/j.jstrokecerebrovasdis.2015.10.010.
[15] Y. He, Q. Yang, H. Liu, L. Jiang, Q. Liu, W. Lian, et al., Effect of blood pressure on early neurological deterioration of acute ischemic stroke patients with intravenous rt-PA thrombolysis may be mediated through oxidative stress induced blood-brain barrier disruption and AQP4 upregulation, J. Stroke Cerebrovasc. Dis. 29 (2020), 104997, https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.104997.
[16] P. Seners, W. Ben Hassen, B. Lapergue, C. Arquizan, M.R. Heldner, H. Henon, et al., Prediction of early neurological deterioration in individuals with minor stroke and large vessel occlusion intended for intravenous thrombolysis alone, JAMA Neurol. 78 (2021) 321–328, https://doi.org/10.1001/jamaneurol.2020.4557.
[17] K. Tanaka, S. Matsumoto, K. Furuta, T. Yamada, S. Nagano, K.I. Takase, et al., Differences between predictive factors for early neurological deterioration due to hemorrhagic and ischemic insults following intravenous recombinant tissue plasminogen activator, J. Thromb. Thrombolysis 49 (2020) 545–550, https://doi.org/10.1007/s11239-019-02015-4.
[18] M. Wintermark, H.A. Rowley, M.H. Lev, Acute stroke triage to intravenous thrombolysis and other therapies with advanced CT or MR imaging: pro CT, Radiology 251 (2009) 619–626, https://doi.org/10.1148/radiol.2513081073.
[19] G. Nepal, G.S. Shrestha, Y.K. Shing, A. Muha, R. Bhagat, Systolic blood pressure variability following endovascular thrombectomy and clinical outcome in acute ischemic stroke: a meta-analysis, Acta Neurol. Scand. 144 (2021) 343–354, https://doi.org/10.1111/ane.13480.
[20] X. Geng, X. Liu, F. Li, J. Wang, H. Sun, A. Feng, et al., Blood pressure variability at different time periods within first 24 hours after admission and outcomes of acute ischemic stroke, J. Clin. Hypertens. 22 (2020) 194–204, https://doi.org/10.1111/jch.13785.
[21] M. Liu, L. Li, G. Li, The different clinical value of susceptibility vessel sign in acute ischemic stroke patients under different interventional therapy: a systematic review and meta-analysis, J. Clin. Neurosci. 62 (2019) 72–79, https://doi.org/10.1016/j.jocn.2019.01.002.
[22] S. Dhundass, J. Savatovsky, L. Duron, R. Fahed, S. Escalard, M. Obadia, et al., Improved detection and characterization of arterial occlusion in acute ischemic stroke using contrast enhanced MRA, J. Neuroradiol. 47 (2020) 278–283, https://doi.org/10.1016/j.neurad.2019.02.011.
[23] P. Gong, Y. Liu, Y. Gong, G. Chen, X. Zhang, S. Wang, et al., The association of neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, and lymphocyte to monocyte ratio with post-thrombolysis early neurological outcomes in patients with acute ischemic stroke, J. Neuroinflammation 18 (2021) 51, https://doi.org/10.1186/s12974-021-02090-6.
[24] Y.L. Liu, Z.Q. Wu, J.F. Qu, D.H. Qiu, G.P. Luo, H.P. Yin, et al., High neutrophil-to-lymphocyte ratio is a predictor of poor short-term outcome in patients with mild acute ischemic stroke receiving intravenous thrombolysis, Brain Behav 10 (2020), e01857, https://doi.org/10.1002/brb3.1857.
[25] Z. Shi, Y. Guan, Y.R. Huo, S. Liu, M. Zhang, H. Lu, et al., Elevated total homocysteine levels in acute ischemic stroke are associated with long-term mortality, Stroke 46 (2015) 2419–2425, https://doi.org/10.1161/STROKEAHA.115.009136.
[26] L. Li, X. Ma, L. Zeng, S. Pandey, R. Wan, R. Shen, et al., Impact of homocysteine levels on clinical outcome in patients with acute ischemic stroke receiving intravenous thrombolysis therapy, PeerJ 8 (2020) e9474, https://doi.org/10.7717/peerj.9474.
[27] L. Shen, Z. Wang, R. Wang, X. Chen, S. Cheng, Upregulation of the P2X7 receptor promotes Ca(2+) accumulation and inflammatory response in post-stroke depression, Am J Transl Res 13 (2021) 10276–10287.
[28] L. Liu, J. Teng, M. Ma, L. Guo, L. Yang, J. Gao, et al., Serum homocysteine level is an independent predictor for hemorrhagic transformation within 24 h of intravenous thrombolysis in acute ischemic stroke, J. Clin. Neurosci. 82 (2020) 13–19, https://doi.org/10.1016/j.jocn.2020.10.021.
[29] Z. Ye, Z. Zhang, H. Zhang, Y. Hao, J. Zhang, W. Liu, et al., Prognostic value of C-reactive protein and homocysteine in large-artery atherosclerotic stroke: a prospective observational study, J. Stroke Cerebrovasc. Dis. 26 (2017) 618–626, https://doi.org/10.1016/j.jstrokecerebrovasdis.2016.11.016.
[30] K.W. Nam, C.K. Kim, S. Yu, K. Oh, J.W. Chung, O.Y. Bang, et al., Plasma total homocysteine level is related to unfavorable outcomes in ischemic stroke with atrial fibrillation, J. Am. Heart Assoc. 11 (2022), e022138, https://doi.org/10.1161/JAHA.121.022138.
[31] O. Nygard, S.E. Vollset, H. Refsum, I. Stensvold, A. Tverdal, J.E. Nordrehaug, et al., Total plasma homocysteine and cardiovascular risk profile. The Hordaland Homocysteine Study, JAMA 274 (1995) 1526–1533, https://doi.org/10.1001/jama.1995.03530190040032.
[32] R. Matsuo, T. Ago, F. Kiyuna, N. Sato, K. Nakamura, J. Kuroda, et al., Smoking status and functional outcomes after acute ischemic stroke, Stroke 51 (2020) 846–852, https://doi.org/10.1161/STROKEAHA.119.027230.
[33] M.A. Font, S.M. Garcia-Sanchez, J.J. Mengual, L. Mena, C. Avellaneda, J. Serena, et al., Determinants and trends of the use of intravenous thrombolysis for minor stroke: a population-based study, 2016 to 2020, Stroke 53 (2022) 3289–3294, https://doi.org/10.1161/STROKEAHA.122.038996.

[34] T. Meinel, C. Lerch, U. Fischer, M. Beyeler, A. Mujanovic, C. Kurmann, et al., Multivariable prediction model for futile recanalization therapies in patients with acute ischemic stroke, Neurology 99 (2022) e1009–e1018, https://doi.org/10.1212/WNL.0000000000200815.

[35] K. Psychogios, L. Palaiodimou, A.H. Katsanos, G. Magoufis, A. Safouris, O. Kargiotis, et al., Real-world comparative safety and efficacy of tenecteplase versus alteplase in acute ischemic stroke patients with large vessel occlusion, Ther Adv Neurol Disord 14 (2021), 1756286420986727, https://doi.org/10.1177/1756286420986727.

[36] J. Vynckier, D.J. Seiffge, U. Fischer, Author response: early neurologic deterioration in lacunar stroke: clinical and imaging predictors and association with long-term outcome, Neurology 98 (2022) 297, https://doi.org/10.1212/WNL.0000000000013257.