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Research article

Post-thrombolysis early neurological deterioration occurs with or without hemorrhagic transformation in acute cerebral infarction: risk factors, prediction model and prognosis

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ABSTRACT

Objectives: Early neurological deterioration (END) after ischemic stroke is a severe clinical event and can be caused by hemorrhagic and ischemic injury. We studied the difference between the risk factors of END occurs with or without hemorrhagic transformation after intravenous thrombolysis.

Materials and methods: Consecutive cerebral infarction patients who underwent intravenous thrombolysis from 2017 to 2020 in our hospital were retrospectively recruited. END was defined as a ≥2 points increase on 24-h National Institutes of Health Stroke Scale (NIHSS) score after therapy compared with the best neurological status after thrombolysis and divided into two types based on the computed tomography (CT): symptomatic intracranial hemorrhage (ENDh) and non-hemorrhagic factors (ENDn). Potential risk factors of ENDh and ENDn were assessed by multiple logistic regression and applied to establish the prediction model.

Results: A total of 195 patients were included. In multivariate analysis, the previous history of cerebral infarction (odds ratio [OR],15.19; 95% confidence interval [CI],1.43–161.17; P = 0.025), previous history of atrial fibrillation (OR,8.43; 95%CI,1.09–65.44; P = 0.043), higher baseline NIHSS score (OR,1.19; 95%CI,1.03–1.39; P = 0.022) and higher alanine transferase level (OR,1.05; 95%CI, 1.01–1.10; P = 0.016) were independently associated with ENDh. While higher systolic blood pressure (OR,1.03; 95%CI,1.01–1.05; P = 0.004), higher baseline NIHSS score (OR,1.13; 95%CI,2.86–27.43; P < 0.000) and large artery occlusion (OR,8.85, 95%CI,2.86–27.43; P < 0.000) were independent risk factors of ENDn. The prediction model showed good specificity and sensitivity in predicting the risk of ENDn.

Conclusions: There are differences between the major contributors to ENDh and ENDn, while a severe stroke can increase the occurrence of both sides.

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1. Introduction

Worldwide, neurological diseases are the leading cause of disability and second leading course of death, among which stroke was the biggest contributor [1].Following the licensing of intravenous recombinant tissue type plasminogen activator (r-tPA) and construction of stroke units [2], the management of acute ischemic stroke (AIS) in hyperacute stage improved obviously. However, despite these improvements, the neurological change in the first 24 h remains largely unpredictably and a sizable proportion of patients even experienced early neurological deterioration (END), which is associated with long-term outcomes [3]. The reason of END is varied and complicated [4], and over half of ENDs still have no clear cause [5]. One study [4] classified it as reversible causes such as infectious, metabolic, hemodynamic, seizure and irreversible causes including symptomatic intracerebral hemorrhage (sICH), early recurrent ischemic stroke (ERIS), unexplained etiologies. Previous studies have identified several risk factors and prediction model of all-cause END [6] and sICH [7,8] However, risk factors of other etiology-specific END were poorly understood, and among the graver irreversible causes, sICH has contradictory treatment and different risk factors with ERIS and unexplained etiologies. It is also the greatest difficulty to balance the risk of hemorrhagic transformation and ischemic progression.

Thus, this study retrospectively reviewed the clinical records of post-thrombolysis patients, divided END into ENDh (END occurs with symptomatic intracranial hemorrhage) and ENDn (END occurs with non-hemorrhagic factors) to explore the differences between risk factors of these two types of END and establish the prediction model of ENDn.

2. Methods

2.1. Subjects

Retrospective analysis was conducted in consecutive acute cerebral infarction patients who underwent intravenous thrombolysis in Sun Yat-sen memorial hospital, Sun Yat-sen University, China between January 1st, 2017 and December 31st, 2020. Among them, those patients whose onset to needle time was more than 4.5 h or whose thrombolysis therapy was prematurely terminated due to bleeding tendency were excluded.

After intravenous alteplase (Boehringer Ingelheim, Germany) infusion, acute ischemic stroke patients were managed in a stroke unit where their neurological status was intensively followed for at least 24 h. Secondary prophylaxis with station was subsequently given if there was no contraindication, while antiplatelet therapy was not initiated within 24 h. The following information was systematically collected from medical records: age, gender, vascular risk factors (smoking or drinking history, hypertension, diabetes mellitus, hyperlipidemia), atrial fibrillation (AF), previous history of coronary heart disease (CHD) or stroke, hyperuricemia, systolic blood pressure (SBP) and diastolic blood pressure (DBP) that is closest before thrombolysis, onset to needle time (ONT) and National Institutes of Health Stroke Scale (NIHSS) scores. The stroke subtype was defined according to the Trial of Org 10172 in Acute Stroke Treatment criteria [9]. Blood test was performed on admission or on an empty stomach the next day and laboratory data was collected. Computed tomography (CT) and/or magnetic resonance (MR) were performed prior to or after the administration of alteplase for the assessment of lesions and occlusion sites. Vertebrobasilar infarcts refer to lesions in the brainstem, cerebellum or occipital lobe and the responsible vessels are the vertebral artery, basilar artery, posterior artery or its branches. Large artery occlusion (LAO) refers to severe stenosis or occlusion of internal carotid artery (ICA), proximal or distal M1 segment of middle cerebral artery (MCA), M2 segment of MCA, and basilar artery. Patients were followed up for 90-day modified Rankin Scale (mRS) scores by telephone interview, a score of 0–2 is considered a good prognosis while a score of 3–6 is thought a poor outcome.

2.2. Definition of END and subgroups

The most common definition of END so far is 4 or more NIHSS aggravations between admission and 24 h after thrombolysis. However, the development of stroke units enables closer neurological monitor after thrombolysis, and considering the recent evolution of endovascular embolectomy, this definition needs to be updated, so as to earlier detect and timely intervene possible END. Also, one recent study showed that the criteria of 2 or more NIHSS aggravations was a more accurate predictor of poor prognosis and in hospital mortality than 4 or more NIHSS worsening [10]. So, END in this study was defined as a $\geq$2 points increase on 24-h NIHSS score compared with the best neurological status after thrombolysis. Brain imaging was principally performed at the time of deterioration and/or 24 h after thrombolysis, according to the carefully review of brain imaging END was categorized into 2 groups: ENDh is END caused by symptomatic intracranial hemorrhage (sICH), ENDn refers to END caused by non-hemorrhagic factors. Besides, patients whose 24-h NIHSS score decreased, remained unchanged or deteriorated $<$2 points were classified as no-END group.

2.3. Statistical analysis

No-END group was established as the control group to explore the risk factors of ENDh and ENDn. Continuous variables subject to normally distribution are summarized as mean (standard deviation) and compared by *t*-test. And continuous variables that are not normally distributed are expressed as median (interquartile ranges) and analyzed by Wilcoxon rank sum test. Correspondingly, categorial variables are expressed as count (percentage) and compared by Chi squared test or Fisher's exact test. Then multivariate logistic regression analyses were conducted to identify independent risk factors by including variables associated with ENDh and ENDn in univariate analysis, a P value < 0.05 was considered statistically significant. After that, to build the risk prediction model, those independent risk factors of ENDn were put into the rms package, then the logistic regression analysis was used to establish the prediction

model of ENDn, and finally converted into the nomogram. Internal validation of the nomogram was performed by repeated sampling with bootstrap method for 1000 times and getting the correction curve. Besides, the area under the curve (AUC) of the prediction model was calculated to test the efficiency of the model.

The method of multivariate imputation by chained equation was used to deal with the missing values, continuous variables were replaced by means and categorial variables were interpolated by regression model coefficients. The same multivariate logistic regression analysis was carried out for each imputed dataset, and the final results were derived by combining the output of the 5 datasets. All the analysis was performed using SPSS (version 24.0) and R (version 4.0.3) statistical software.

3. Results

Among 213 eligible patients treated with intravenous thrombolysis, 18 patients were excluded because their onset to needle time was more than 4.5 h (16), or thrombolysis therapy was prematurely terminated due to bleeding tendency (2). The flowchart of patient selection is shown in Fig. 1. Finally, a total of 195 patients were included in this study, and 41 patients experienced END. The prevalence of ENDn (28, 14.36%) is more than twice that of ENDh (13,6.67%).

Univariate analyses of clinical characteristics between no-END patients and patients with ENDh or ENDn are shown in Table 1. The patients with ENDh were more likely to be older, to have previous stroke or AF history, to have severer initial neurological deficits, to have LAO or have a stroke subtype of Total anterior circulation infarction (TACI), to have lower hemoglobin, platelets, low density lipoprotein and triglyceride, or to have a higher level of neutrophilic granulocyte percentage, international normalized ratio, D-dimer and urea or alanine transaminase in comparation to patients in the group of no-END. And compared with no-END patients, hypertension, LAO, higher SBP and higher pretreatment NIHSS score were more common in patients with ENDn.

The multivariate logistic analyses revealed that previous history of cerebral infarction (OR,15.19; 95%CI,1.43–161.17; P = 0.025), previous history of AF (OR,8.43; 95%CI,1.09–65.44; P = 0.043), higher baseline NIHSS score (OR,1.19; 95%CI,1.03–1.39; P = 0.022) and higher alanine transferase (ALT) level (OR,1.05; 95%CI, 1.01–1.10; P = 0.016) were independent risk factors of ENDh (Fig.2.a). And then the nomogram of the prediction model of the ENDh was established with those risk factors (Fig.3.a). The Point of each independent predictor was the score corresponding to the upper scale, and the Total Points of each subject was the sum of the scores of each independent predictor. The Total Points corresponding to the risk axis of ENDh was the risk of ENDh. The higher the Total Points, the higher the risk of ENDh. Internal validation of the nomogram was performed by repeated sampling with Bootstrap method for 1000 times. The Calibration curve (Fig.4.a) showed an overall good coherence between the predicted and actual probability of ENDh, though the predicted probability is kind of lower than the actual probability. Besides, the ROC curve (Fig.5.a) showed good performance with an AUC of 0.934 (95%CI, 0.876,0.992). The sensitivity and specificity of the model was 0.923 and 0.900 respectively. On the other hand, higher SBP (OR,1.03; 95%CI,1.01–1.05; P = 0.004), higher baseline NIHSS score (OR,1.13; 95%CI,2.86–27.43; P < 0.000) and LAO (OR,8.85, 95%CI,2.86–27.43; P < 0.000) were independently associated with ENDn (Fig.2.b). Among the 28 ENDn patients, 19 had LAO, including ICA(n = 5), M1 segment of MCA (n = 12), M2 segment of MCA (n = 1), and BA (n = 1). Based on these results, the nomogram of the prediction model of ENDn was constructed with rms package (Fig.3.b). The Calibration curve (Fig.4.b) showed a good coherence between the predicted ENDn risk and the actual incidence of ENDn. The AUC of the ROC curve was 0.811

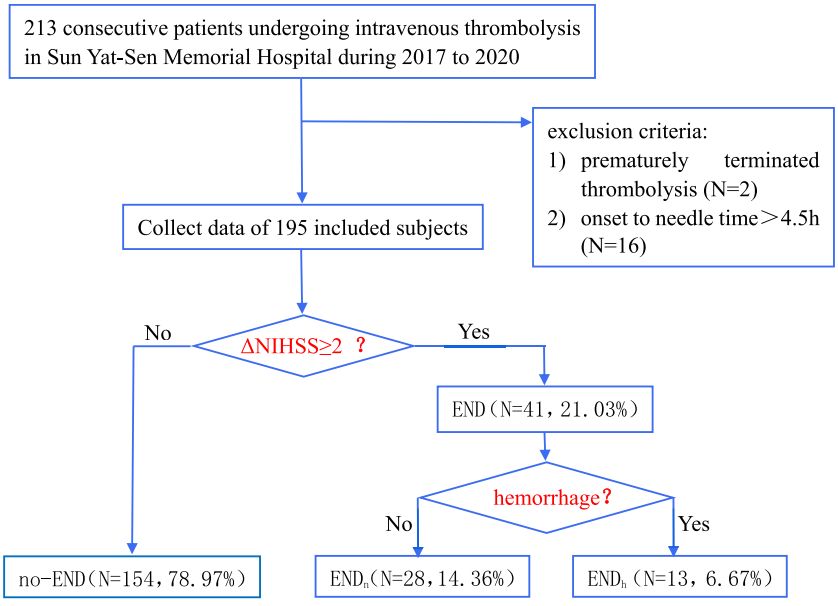

Fig. 1. Flowchart of patient selection. Abbreviations: NIHSS National Institutes of Health Scale, END Early neurological deterioration, ENDh END due to symptomatic intracranial hemorrhage, ENDn END due to non-hemorrhagic factors.

Table 1
Univariate analysis of clinical variables in acute cerebral infarction patients with early neurological deterioration due to hemorrhage and non-hemorrhagic factors.

	Total N = 195	no-END N = 154	END_h N = 13	P value (ENDh versus no-END)	ENDn N = 28	P value (ENDn versus no-END)
Age(years)	65.84 ± 13.30	64.78 ± 13.31	76.38 ± 8.46	0.002[a]	66.75 ± 13.16	0.471
Sex, male	136 (69.74%)	110 (71.43%)	8 (61.54%)	0.664	18 (64.29%)	0.447
Smoking	83 (42.56%)	70 (45.45%)	3 (23.08%)	0.118	10 (35.71%)	0.339
Drinking	48 (24.62%)	42 (27.27%)	1 (7.69%)	0.222	5 (17.86%)	0.295
Hypertension	130 (66.67%)	96 (62.34%)	10 (76.92%)	0.454	24 (85.71%)	0.016[a]
Coronary heart disease	27 (13.85%)	19 (12.34%)	4 (30.77%)	0.152	4 (14.29%)	1.000
Diabetes mellitus	56 (28.72%)	42 (27.27%)	4 (30.77%)	1.000	10 (35.71%)	0.363
Hyperlipemia	56 (28.72%)	44 (28.57%)	1 (7.69%)	0.192	11 (39.29%)	0.256
Hyperuricemia	50 (25.64%)	39 (25.32%)	4 (30.77%)	0.920	7 (25.00%)	0.971
Previous stroke	30 (15.38%)	21 (13.64%)	6 (46.15%)	0.008[b]	3 (10.71%)	0.907
Atrial fibrillation	35 (17.95%)	21 (13.64%)	8 (61.54%)	0.000[b]	6 (28.57%)	0.437
SBP(mmHg)	156.14 ± 22.58	154.25 ± 20.34	149.31 ± 19.24	0.400	169.75 ± 30.31	0.001[b]
DBP(mmHg)	87.59 ± 15.70	86.65 ± 13.78	89.85 ± 23.74	0.454	91.71 ± 20.42	0.101
Onset-to -needle time(min)	143 (100–180)	145 (103–185)	110 (72–180)	0.194	146.5 (111.5–165)	0.581
Baseline NIHSS	5 (2–9)	4.5 (2–9)	13 (9–19)	0.000[b]	9 (5–13.5)	0.001[b]
LAO	59 (30.26%)	32 (20.78%)	8 (61.54%)	0.005[a]	19 (67.86%)	0.000[b]
Stroke subtype	195	154	13	0.001[a]	28	0.084
TACI	33 (16.92%)	19 (12.34%)	7 (53.85%)		7 (25.00%)	
PACI	91 (46.67%)	70 (45.45%)	5 (38.46%)		16 (57.14%)	
POCI	28 (14.36%)	25 (9.84%)	1 (7.69%)		2 (7.14%)	
LACI	43 (22.05%)	40 (25.97%)	0 (0.00%)		3 (10.71%)	
GLU (mmol/L)	6.70 (5.55–8.90)	6.55 (5.55–8.65)	7.70 (6.20–9.70)	0.266	6.85 (5.65–10.00)	0.400
HGB (g/L)	142.00 (129.00–151.25)	142.00 (129.00–152.00)	131.00 (115.00–139.00)	0.011[a]	144.00 (134.50–154.00)	0.392
NEUT (%)	64.70 ± 13.68	63.79 ± 13.76	71.21 ± 14.89	0.072[a]	65.68 ± 12.24	0.539
PLT (10^9/L)	227.50 (187.75–278.50)	232.00 (195.00–275.00)	188.00 (158.00–214.00)	0.019[a]	229.50 (179.50–290.00)	0.530
INR (%)	0.99 ± 0.09	0.98 ± 0.09	1.06 ± 0.08	0.003[a]	0.99 ± 0.09	0.637
DD (mg/L)	0.51 (0.26–1.27)	0.40 (0.26–1.02)	1.22 (0.82–4.01)	0.000[a]	0.65 (0.20–2.78)	0.478
CREA (μmol/L)	90.00 (76.00–104.00)	89.00 (75.00–104.00)	93.00 (82.00–103.00)	0.572	91.50 (83.00–101.00)	0.743
Urea (mmol/L)	5.50 (4.38–6.70)	5.40 (4.30–6.50)	6.70 (5.50–7.50)	0.020[a]	5.30 (4.25–6.80)	0.947
ALT (U/L)	21.00 (17.00–28.00)	21.00 (17.00–26.00)	32.00 (23.00–46.00)	0.002[b]	22.50 (18.00–28.50)	0.560
LDL (mmol/L)	3.03 ± 0.98	3.03 ± 0.89	2.16 ± 1.25	0.006[a]	3.35 ± 1.21	0.109
TC (mmol/L)	4.81 (3.89–5.52)	4.77 (3.92–5.44)	3.47 (2.21–4.08)	0.016[a]	5.03 (4.72–5.55)	0.085
HCY (μmol/L)	12.45 (10.30–15.18)	12.30 (10.25–14.90)	11.80 (9.95–15.20)	0.799	13.30 (11.20–15.90)	0.312

Data are presented as mean ± standard deviation or N (%) or median (interquartile range).
Abbreviations: END Early neurological deterioration, ENDh END due to symptomatic intracranial hemorrhage, ENDn END due to non-hemorrhagic factors, SBP Systolic blood pressure, DBP Diastolic blood pressure, NIHSS National Institutes of Health Scale, LAO Large artery occlusion, TACI Total anterior circulation infarction, PACI Partial anterior circulation infarction, POCI Posterior circulation infarction, LACI Lacuna infarction, GLU Glucose, HGB Hemoglobin, NEUT Neutrophilic granulocyte percentage, PLT Platelets, INR International normalized ratio, DD D-dimer, CREA Creatinine, ALT Alanine transaminase, LDL Low density lipoprotein, TC Triglyceride, HCY Homocysteine.
[a] Variables that have the level of significance in univariate analysis.
[b] Variables that maintain the level of significance in multivariate analysis.

(95%CI, 0.710,0.912). The sensitivity and specificity were 0.821 and 0.779 respectively. So, the nomogram showed good property in predicting the risk of ENDn (Fig.5.b).

In the 3-month mRS shift analysis, a total of 184 patients were followed up. Logistic regression model was used for prognosis analysis, and the results revealed that END was closely associated with an unfavorable shift in the distribution of functional outcome (Fig. 6; OR,13.46; 95%CI,5.66–32.01; P < 0.001). The proportion of poor prognosis in END group was significantly higher than that in no-END group (80.00% versus 22.92%).

4. Discussion

According to this definition and classification to END, the present study demonstrated that more than one fifth acute ischemic stroke patients experienced END even after thrombolysis therapy. Among which the primary cause of END was non-bleeding factor, while symptomatic hemorrhagic transformation accounted for approximately one-third of all the cause of deterioration. The incidence of END in the present study was higher than that in previous reports [11–13] and this may be explained by our definition of END

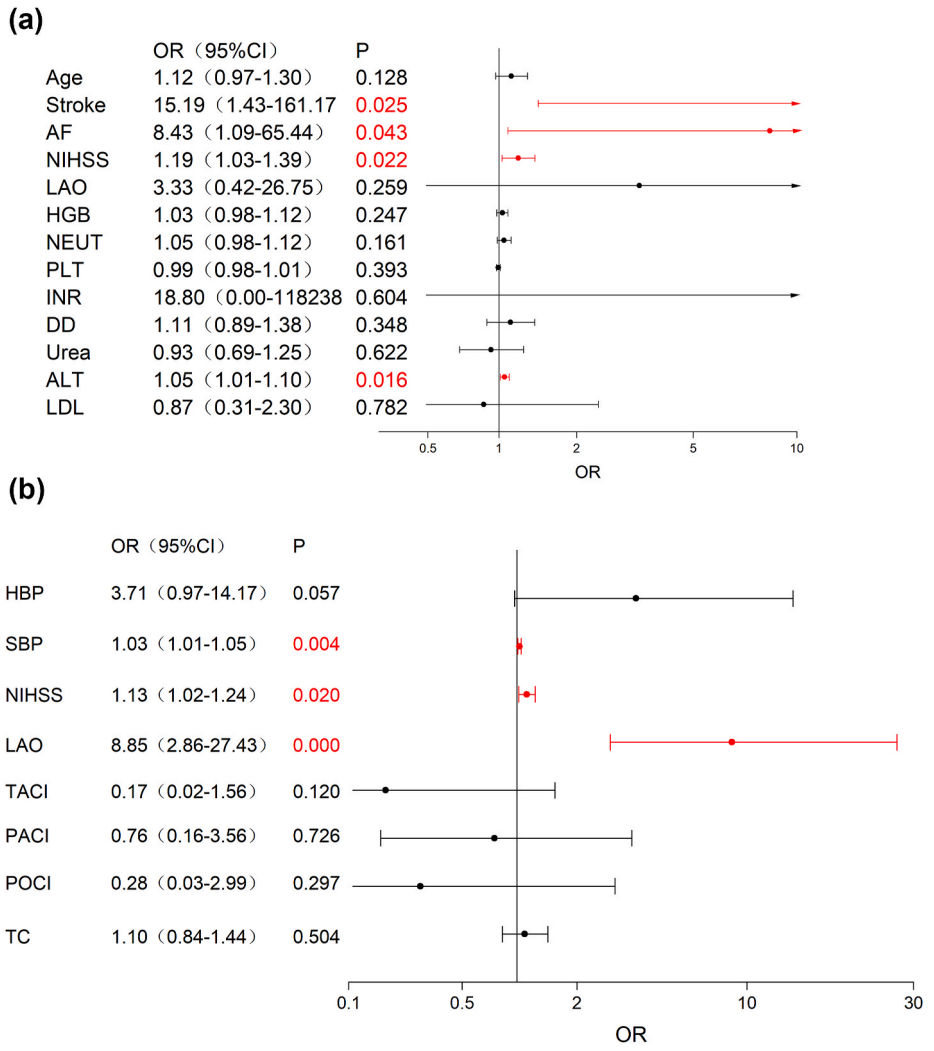

Fig. 2. a. Forest plot of the multivariate logistic analyze of the risk factors of ENDh. The previous history of cerebral infarction, previous history of AF, higher baseline NIHSS score and higher alanine transferase (ALT) level are independent risk factors of ENDh. b. Forest plot of the multivariate logistic analysis of the risk factors of ENDn. The higher SBP, higher baseline NIHSS score and LAO increased the risk of ENDn. Abbreviations: AF Atrial fibrillation, NIHSS National Institutes of Health Scale, LAO Large artery occlusion, HGB Hemoglobin, NEUT Neutrophilic granulocyte percentage, PLT Platelets, INR International normalized ratio, DD D-dimer, ALT Alanine transaminase, LDL Low density lipoprotein, HBP Hypertension, SBP Systolic blood pressure, TACI Total anterior circulation infarction, PACI Partial anterior circulation infarction, POCI Posterior circulation infarction, TC Triglyceride.

involved fewer NIHSS changes, which can predict in-hospital mortality more accurately [10]. So, in order to identify the END population and improve prognosis as much as possible, close neurological monitoring is warranted within the first 24 h after thrombolysis, and assured risk factors and prediction model can facilitate the early detection of END.

This study identified several predictive factors for ENDh, including higher baseline NIHSS score, previous history of cerebral infarction, previous history of AF, and higher ALT level. Firstly, similar to previous studies [14–16], the higher the pretreatment NIHSS score, the greater the risk of ENDh. Mazya M et al. [16] showed a 1.6-fold increased risk of sICH in patients with acute cerebral infarction who received intravenous thrombolysis with a NIHSS score of 7–12, and a 2.22-fold increased risk of sICH in patients with baseline NIHSS score $\geq$13. Secondly, in this study, previous cerebral infarction was significantly correlated with ENDh, which may be interpreted as poor cerebrovascular foundation and impaired blood-brain barrier in patients with previous stroke. The results of many studies suggest that previous history of cerebral infarction is likely to increase the risk of ENDh and worsen the prognosis [17,18]. However, in recent years, more and more evidence support the positive intravenous thrombolytic therapy in these patients. [19,20], Fuentes et al. [21] found that prior cerebral infarction, diabetes, or both do not increase the risk of ENDh. The previous history of cerebral infarction has both the negative effect of cumulative injury and the protective tolerance mechanism of promoting collateral circulation. Thirdly, consistent with the results of most previous studies [22–24], AF is an independent risk factor of ENDh. Hu et al. [25]found that intravenous thrombolysis worsen the prognosis for acute cerebral infarction patients with a history of AF, and among

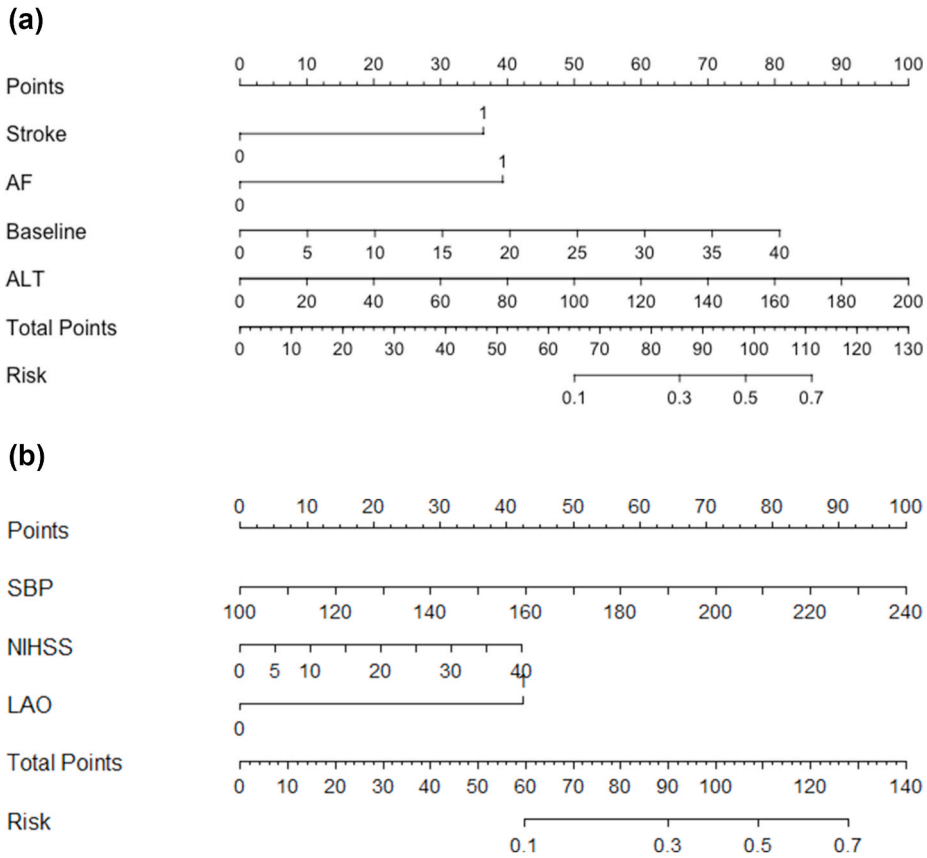

Fig. 3. a. Nomogram of the prediction model of ENDh. b.Nomogram of the prediction model of ENDn. The Point of each independent predictor was the score corresponding to the upper scale, and the Total Points of each subject was the sum of the scores of each independent predictor. The Total Points corresponding to the risk axis of END was the risk of END. Abbreviations: SBP Systolic blood pressure, NIHSS National Institutes of Health Scale, LAO Large artery occlusion.

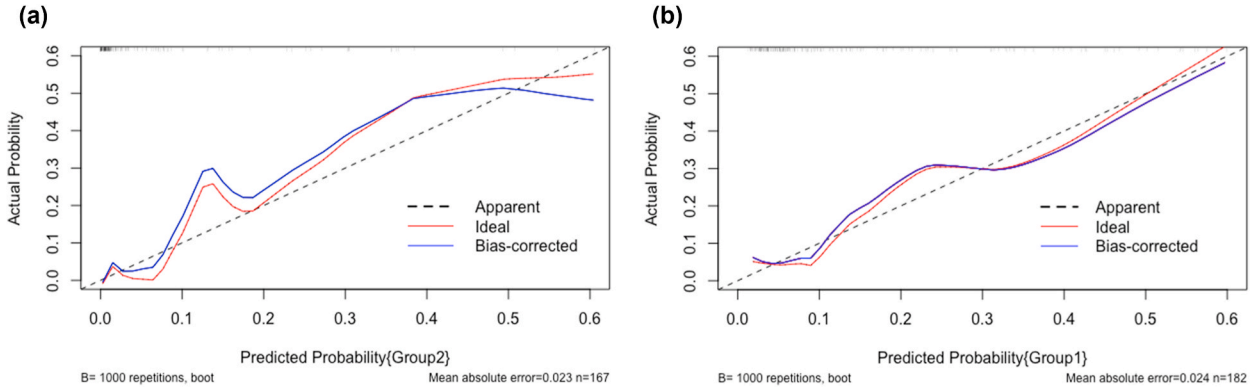

Fig. 4. a. Calibration curve of the prediction model of ENDh. b.Calibration curve of the prediction model of ENDn.

patients receiving intravenous thrombolytic therapy, those with a history of AF had an increased incidence of ENDh, poorer independent functional outcomes, and higher mortality than those without AF. One explanation is that cardiac embolus is relatively softer and have a higher recanalization rate, leading to high perfusion and reperfusion injury [26], another explanation is that cardiogenic stroke with atrial fibrillation is characterized by rapid onset, poor collateral circulation, severe symptoms, which lead to increased risk of bleeding [27]. Fourthly, this study found that the risk of ENDh increased 1.05 times for every 1U/L increase in ALT level. Since alteplase is mainly metabolized from the liver, elevated transaminase may affect the metabolism of alteplase and prolong the half-life, thus increasing the risk of bleeding. On account that the association between ALT level and ENDh has not been reported in previous

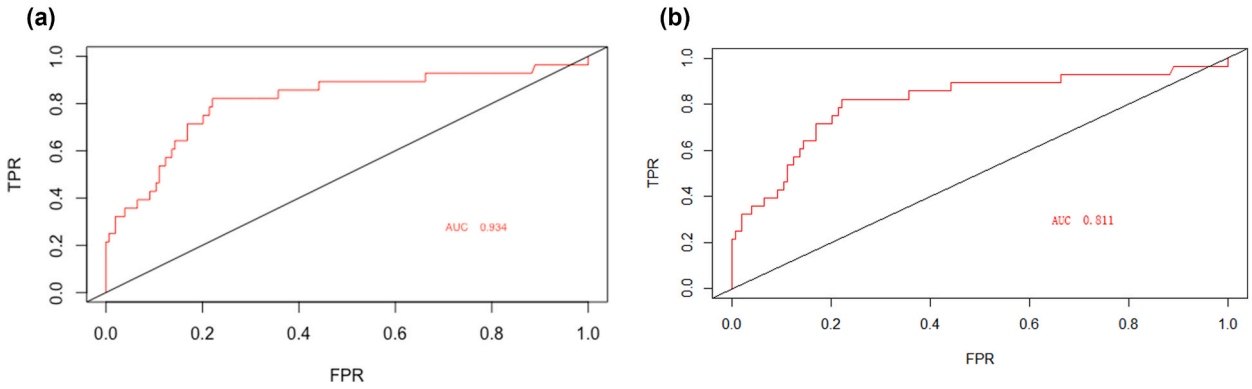

Fig. 5. a.ROC curve of the prediction model of ENDh. b.ROC curve of the prediction model of ENDn. Abbreviations: FPR False positive rate, TPR True positive rate, ROC receiver operating characteristic curve.

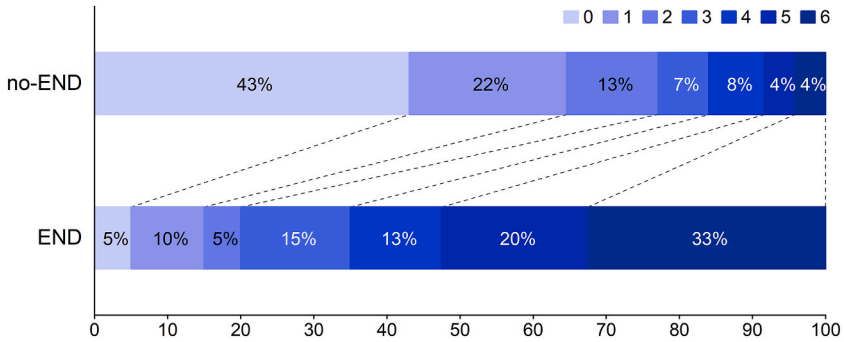

Fig. 6. Distribution of mRS score at 3 months between no-END group and END group. Abbreviations: mRS Modified Rankin scale, END Early neurological deterioration.

studies, further research is needed to verify this hypothesis.

Similarly, we found that higher pretreatment SBP, higher baseline NIHSS score and LAO are independent predictors for ENDn. Primarily, in this study, the risk of ENDn was found to increase 1.03 times for every 1 mmHg increase in SBP before intravenous thrombolysis. He Y et al. [28] got similar results, they believed that increased SBP mediated brain-blood barrier injury and AQP4 upregulation through oxidative stress response, thus leading to increased risk of ENDn. Next, consistent with previous studies, the higher the NIHSS score, the higher the ENDn risk. Miyamoto N et al. [29] found that patients with NIHSS score more than 8 at onset are the high-risk group of ENDn and took it as an indicator of WORSEN score [6], the only one relatively recognized scoring system specifically developed to detect END events based on clinical and imaging characteristics in acute ischemic stroke patients. Eventually, in this study, the proportion of ENDn in the patients with lesion of proximal M1 segment of the middle cerebral artery and internal carotid artery was significantly higher, while that proportion in the distal M1 segment and M2 segment of the middle cerebral artery was relatively low. Saarinen J et al. [30] also demonstrated that the middle M1 segment of middle cerebral artery is the cut-off point to distinguish the prognosis of patients after intravenous thrombolysis. Patients with proximal artery occlusion usually had worse outcome, even more, there was a dose-response relationship between the location of thrombus and the prognosis. With the location of thrombus moving from proximal to distal, the prognosis improved gradually and the mortality continued to decrease. This may be due to the large thrombi in the proximal artery is difficult to be completely dissolved by alteplase, and some large thrombi transformed into small thrombi after thrombolysis and embolize the distal vessels, which indirectly increased the total thrombi volume, suggesting that such patients may be more suitable for direct mechanical thrombolysis, while intravenous thrombolysis was better for cerebral infarction caused by lesions in distal M1 and M2 segments of middle cerebral artery. Further studies are needed to verify the benefits of intravenous thrombolysis and mechanical thrombectomy for different vascular segment lesions.

According to the predictors screened by the statistical analysis, a nomogram was established, and the risk prediction value of the subjects was obtained by calculating the total score of all the predictors. The risk prediction ability of the nomogram established in this study was 0.811, the consistency and clinical efficacy of the nomogram were acceptable. This prediction model has certain reference value for clinicians to intuitively analyze individual END risk of patients. Different form the WORSEN score [6] and models developed by Gong et al. [31] and Xie et al. [32], which predicted the risk of END in patients who did not receive recanalization after acute ischemic stroke, this model predicted the risk of ENDn even after thrombolytic therapy.

Several limitations exist in this study. First, this is a single-center retrospective study. The limited sample size may lead to selection

bias and statistical errors, and that the prognosis of patients was evaluated through follow-up afterwards and there may be some recall bias. Second, the collection and analysis of medication history that may affect the incidence of END is insufficient. For example, history of taking antiplatelet drugs is likely to be a protective factor for ENDn [33], while history of taking anticoagulants is likely to increase the risk of ENDh [34]. This study had not collected the premorbid usage of antiplatelet and anticoagulants drugs, and the usage of adjuvant drugs after thrombolysis therapy, which may affect the research results. Third, sixteen patients who were bridged with mechanical thrombectomy after intravenous thrombolysis were not excluded in this study, and some END may be related to thrombectomy. Finally, the constructed prediction model is only re-sampled internally and lacks external validation.

In conclusion, distinct factors were related to END subtypes. Strict neurological monitoring for patients at risk is necessary for timely detection and management. Our findings may provide information on the development of preventive measures for different subtypes of END after intravenous injection of alteplase in patients with corresponding risk factors. Further prospective studies are warranted to evaluate the efficacy of our prediction model.

Ethics approval

This study was approved by the Ethics Committee of Sun Yat-sen Memorial Hospital, Sun Yat-sen University.

Production notes

Author contribution statement

Mengzhi Jin: Conceived and designed the research programme; Performed the research; Analyzed and interpreted the data; Wrote the paper.

Qingxia Peng: Contributed materials, analysis tools or data.

Yidong Wang: Conceived and designed the research programme; Wrote and revised the paper.

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Data availability statement

Data will be made available on request.

Declaration of interest's statement

The authors declare no competing interests.

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