Am J Transl Res 2025;17(1):247-253
www.ajtr.org /ISSN:1943-8141/AJTR0160773

Original Article

Factors associated with early neurological deterioration after intravenous thrombolysis in acute cerebral infarction patients and establishment of a predictive model

Lingling Zhang, Jing Zhao, Boxin Kan, Qi Zhang

Department of Neurology, Nantong Rici Hospital Affiliated to Yangzhou University, Nantong 226000, Jiangsu, China

Received September 26, 2024; Accepted December 17, 2024; Epub January 15, 2025; Published January 30, 2025

Abstract: Objective: To analyze the factors influencing early neurological deterioration (END) after intravenous thrombolysis in patients with acute cerebral infarction (ACI) based on real-world data, and to establish a nomogram predictive model. Methods: The clinical data of 148 ACI patients who received intravenous thrombolytic therapy within 4.5 hours of onset at Nantong Rici Hospital Affiliated with Yangzhou University, from January 2020 to December 2023, were retrospectively analyzed. Patient clinical and laboratory data were collected. Patients were divided into END and non-END groups according to whether they developed END after intravenous thrombolysis. Factors influencing the emergence of END were identified by univariate and multivariate logistic regression analyses. Risk factors were included to construct a nomogram risk predictive model, which was validated for efficacy. Model discrimination was assessed using the receiver operating characteristic curve (ROC) and the area under the ROC curve (AUC). Model fitting was evaluated using a calibration curve, and consistency was assessed by Hosmer-Lemeshow (HL) analysis. Results: END occurred in 27 of 148 patients (18.24%). Multivariate analysis identified age, National Institute of Health stroke scale (NIHSS) score, fibrinogen, and the time from onset to thrombolysis as factors influencing END in ACI patients after thrombolysis. A nomogram predictive model was constructed based on the above indicators. The AUC for the model in predicting END in the training set and the test set was 0.994 (95% CI: 0.982-1.000) and 0.977 (95% CI: 0.940-1.000), respectively. HL test showed high goodness of fit (χ^2 = 1.953, P = 0.982), and the calibration curve showed good agreement between the predicted and observed values. Conclusion: Age, NIHSS score, fibrinogen, and time from onset to thrombolysis are significant factors influencing the development of END after thrombolysis in ACI patients. The predictive model based on these four variables demonstrates good discriminatory power and may assist in clinical decision-making.

Keywords: Acute cerebral infarction, intravenous thrombolysis, early neurological deterioration, influencing factors

Introduction

Acute cerebral infarction (ACI) is a common cerebrovascular disease, predominantly affecting the elderly. ACI results from insufficient blood supply to brain tissue and cerebral hypoxia-ischemia caused by occlusion of cerebral arteries [1, 2]. In China, the incidence of stroke is rising at an annual rate of 8.7%, with 30% of patients dying and the remaining 70% experiencing varying degrees of disability [3]. Therefore, timely restoration of blood flow by opening the occluded vessels is critical for the treatment of ACI. Current guidelines recommend intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) for ACI patients within 4.5 hours of onset. This therapy can rapidly re-open occluded cerebral arteries, restore blood perfusion to the ischemic area, and reduce brain tissue damage [4]. However, not all patients benefit from thrombolytic therapy, as some experience worsening neurological deficit following treatment, known as early neurological deterioration (END), which is associated with poor recovery [5]. The etiology of END is complex, and there is limited research on the etiology of END after intravenous thrombolysis. Early identification of risk factors for END and timely intervention are of great significance for its prevention and management. However, the-

https://doi.org/10.62347/GIIG7402

re are few studies investigating the risk factors associated with END after thrombolysis.

Based on this, this study aims to analyze the factors influencing END after intravenous thrombolysis in ACI patients using data and to establish a predictive model. The model will provide a scientific basis for clinicians to make a more accurate pre-thrombolysis risk assessment, helping them choose the most appropriate treatment plan that is safe and effective. This research holds significant clinical value for optimizing ACI patient management and reducing END incidence.

Data and methods

Case selection

In this retrospective study, a total of 148 patients with ACI who received intravenous thrombolysis within 4.5 hours of onset at Nantong Rici Hospital Affiliated to Yangzhou University from January 2020 to December 2023 were selected as the research subjects.

Inclusion criteria: (1) Diagnosis of ACI based in criteria outlined in the literature [6] and confirmed by head CT and/or MRI; (2) Thrombolytic therapy administered within 4.5 hours of onset; (3) Patients aged 18 years or older. Exclusion criteria: (1) Contraindications to thrombolysis; (2) Failure to complete head CT after intravenous thrombolysis; (3) Incomplete clinical data. This study was reviewed and approved by the Ethics Committee of Nantong Rici Hospital Affiliated to Yangzhou University.

Intravenous thrombolysis methods and grouping

All patients were given intravenous rt-PA (SJ-20160055, specification: 50 mg/vessel). According to the guidelines, the standard dose is 0.9 mg/kg, with a maximum dose of ≤ 90 mg. According to the patient's body weight, 10% of the dose was intravenously injected as the initial bolus, and the remaining 90% was infused within 1 hour. Patients were divided into an END group and non-END group, based on whether END occurred after intravenous thrombolysis. END was defined as an increase of ≥ 4 points in the NIHSS score within 24 hours after intravenous thrombolysis, compared with that at admission or death [7].

Data collection

The baseline and clinical data of the two groups were collected. The baseline data included age, gender, past history [hypertension, diabetes mellitus, coronary heart disease, atrial fibrillation, hyperlipidemia, ischemic stroke (cerebral infarction, transient ischemic attack)], smoking history, and alcohol consumption. Clinical data included blood pressure, blood glucose, white blood cell count, platelet count, fibrinogen, time from onset to thrombolysis, NHISS score, creatinine, high-sensitivity C-reactive protein, infarct location, homocysteine, and uric acid before thrombolysis.

Statistical method

SPSS 23.0 statistical software was used for data analysis. Measured data were expressed as mean ± standard deviation ($\bar{x} \pm s$), and intergroup comparison was performed using the independent samples t-test. Categorical data were expressed as cases and percentages [n (%)], and χ^2 test was used for comparison between groups. Logistic regression analysis was used to identify influencing factors. $P < 0.05$ was considered significant. The identified factors were introduced into RStudio software to construct a nomogram risk predictive model. The discrimination of the model was evaluated by the receiver operating characteristic curve (ROC) curve and calibration curve. Hosmer-Lemeshow analysis was used to evaluate the goodness of fit of the nomogram, with $P > 0.05$ indicating good consistency.

Results

General data comparison

Significant differences in age, fibrinogen level, NHISS score, and time from onset to thrombolysis were observed between the two groups (all $P < 0.05$). No significant differences were observed in other indicators between the two groups (all $P > 0.05$), as shown in **Table 1**.

Multivariate analysis of factors influencing END after thrombolysis in ACI patients

Variables with statistical significance by univariate analysis (age, fibrinogen, NHISS score, and time from onset to thrombolysis) were included as independent variables, with the presence or absence of END as the dependent variable (yes = 1, no = 0). The multivariate results showed

Table 1. Comparison of clinical data between the two groups [n (%), ($\bar{x}$±s)]

Factor	Non-END group (n = 121)	END group (n = 27)	χ^2/t	*P*
Age (years)	59.55±6.34	68.78±7.46	6.615	< 0.001
Gender				
-Female	43 (35.54)	9 (33.33)	0.047	0.828
-Male	78 (64.46)	18 (66.67)		
Hypertension	63 (52.07)	16 (59.26)	0.459	0.498
Diabetes	33 (27.27)	6 (22.22)	0.290	0.590
Coronary heart disease	19 (15.70)	5 (15.52)	0.005	0.944
Atrial fibrillation	16 (13.22)	6 (22.22)	0.791	0.374
Hyperlipidemia	46 (38.02)	11 (40.74)	0.069	0.793
Ischemic stroke	21 (17.36)	7 (25.93)	1.057	0.304
Smoking	56 (46.28)	12 (44.44)	0.030	0.863
Alcohol consumption	61 (50.41)	13 (48.15)	0.045	0.831
Admission systolic pressure (mmHg)	141.93±19.95	143.26±19.24	0.314	0.754
Admission diastolic pressure (mmHg)	88.48±4.36	88.89±4.96	0.430	0.668
Blood glucose (mmol/L)	9.46±2.39	8.84±2.68	1.191	0.236
White blood cell count ($\times10^9$/L)	8.64±2.12	8.96±2.36	0.697	0.487
Blood platelets ($\times10^9$/L)	206.55±21.66	201.52±20.49	1.102	0.272
Fibrinogen (g/L)	5.96±1.53	9.47±2.64	6.669	< 0.001
NIHSS score	7.26±1.98	11.63±1.62	10.666	< 0.001
Time from onset to thrombolysis (min)	205.68±20.40	221.74±20.25	3.704	< 0.001
Creatinine (μmol/L)	73.53±18.63	78.63±19.24	1.278	0.203
Hypersensitive C-reactive protein (mg/L)	14.14±3.26	15.21±4.15	1.476	0.142
Infarct site				
-Vertebrobasilar artery	55 (45.45)	12 (44.44)	0.009	0.924
-Internal carotid artery	66 (54.55)	15 (55.56)		
Homocysteine (μmol/L)	14.39±3.54	15.52±3.16	1.526	0.129
Uric acid (μmol/L)	318.14±83.60	301.63±78.75	0.937	0.350

Note: END: early neurological deterioration; NIHSS: National Institute of Health stroke scale.

Table 2. Logistic analysis of factors affecting END after thrombolysis in patients with ACI

Factor	B	SE	Wald	*P* value	OR value (95% CI)
Age	0.210	0.089	5.545	0.019	1.233 (1.036-1.468)
Fibrinogen	0.550	0.269	4.170	0.041	1.733 (1.022-2.936)
NIHSS score	1.504	0.473	10.107	0.001	4.500 (1.78-11.375)
Time from onset to thrombolysis	0.058	0.027	4.635	0.031	1.060 (1.005-1.117)

Note: END: early neurological deterioration; ACI: acute cerebral infraction; NIHSS: National Institute of Health Stroke Scale.

that advanced age, elevated fibrinogen levels, high NHISS score, and prolonged time from onset to thrombolysis were independent risk factors for END following thrombolysis therapy in ACI patients (**Table 2**).

Nomogram model building

Based on the results of multivariate analysis, the four factors affecting END after thrombolysis in ACI patients were included in the risk assessment, and a nomogram risk model was established (**Figure 1**). To further verify the predictive efficiency of the model, ROC curves for the training set and test set were generated (**Figure 2**). The model demonstrated high prediction accuracy in both sets, with an AUC of 0.994 (95% CI: 0.982-1.000) for the training set and 0.977 (95% CI: 0.940-1.000) for the test set. The Hosmer-Lemeshow test showed

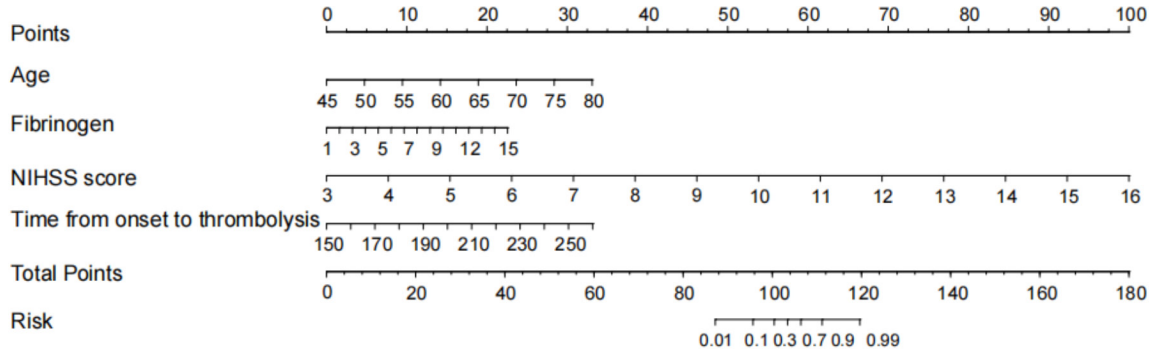

Figure 1. Nomogram predictive model. *Note*: NIHSS: National Institute of Health stroke scale.

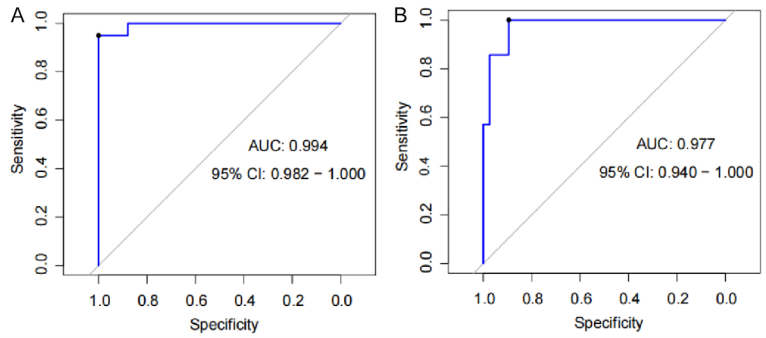

Figure 2. Receiver operating characteristic (ROC) curves for the predictive model in training (A) and test (B) sets.

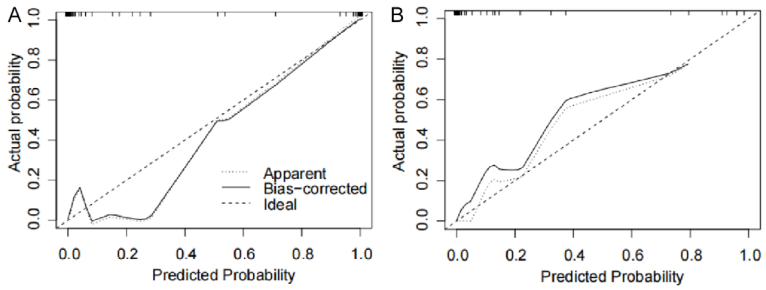

Figure 3. Calibration curves for the predictive model in training (A) and test (B) sets.

good goodness of fit (χ^2 = 1.953, P = 0.982). The calibration curve (**Figure 3**) showed strong agreement between the predicted and observed probabilities in both the training and test sets. In addition, the decision curve analysis showed a significant increase in the net benefit of the nomogram (**Figure 4**).

Discussion

Intravenous thrombolysis within an effective time window is beneficial for improving the short-term prognosis and long-term quality of life in most patients with cerebral infarction. However, many patients still experience aggravated symptoms and early neurological deterioration (END) within 24 hours after thrombolysis. END refers to the progression of the disease, characterized by neurological impairment and continuous worsening of symptoms in the early stage of ACI. At present, there is no standardized scoring system for assessing the severity or defining time window for END. Most studies have defined END within 24 hours after intravenous thrombolysis. In this study, END was defined as an increase of ≥ 4 points in NIHSS score within 24 h after intravenous thrombolysis, compared with the NIHSS score at admission or death [7]. Previous studies have reported the incidence of END after intravenous thrombolysis to be 6.7%-29.8% [8, 9]. In this study, the incidence of END was 18.24% (27/148), which is consistent with previous studies.

The results of this study showed that the factors influencing END within 24 h after intravenous thrombolysis in patients with ACI include age, NIHSS score, fibrinogen levels, and time from onset to thrombolysis. Advanced age was identified as one of the risk factors for END in ACI patients, consistent with the findings of

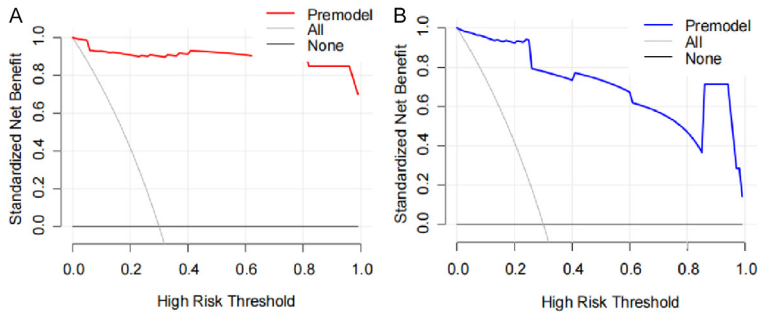

Figure 4. Decision curve analysis of the nomogram model in training (A) and test (B) sets.

Girot et al. [10]. This can be attributed to the decline in overall bodily functions with aging, including decreased organ function and reduced resistance. Additionally, the self-regulation ability of blood vessels deteriorates with age, increasing the likelihood of hemorrhagic conversion and malignant cerebral edema after thrombolysis, which may contribute to END. This study also showed that elevated fibrinogen level was a significant risk factor for END after intravenous thrombolysis in ACI patients, in line with the findings of Mehta [11] and Sun [12]. Increased fibrinogen levels can negatively affect the occurrence, development, and prognosis of ACI. Elevated fibrinogen impairs the binding ability of plasminogen to fibrin, leading to a decrease in fibrinolysis and the formation of thrombosis [13]. Foreign studies have shown a significant increase in the incidence of END following intravenous thrombolysis in patients with hyperfibrinogenemia [14].

NIHSS score is an important tool for evaluating the degree of neurological deficit after cerebral infarction, playing an important role in assessing the severity of the patient's condition and prognosis [15]. A higher NIHSS score generally indicates a larger cerebral infarction area, more severe neurological deficits, and a worse prognosis. This study indicated high NIHSS score as one of the risk factors for END after intravenous thrombolysis in ACI, which is consistent with the results of Liu [16] and Wang [17]. A higher NIHSS score suggests more severe nerve injury in ACI patients, making brain tissue more vulnerable to reperfusion injury after thrombolytic therapy, leading to the occurrence of END. Grotta et al. [18] found that intravenous thrombolysis within 3 hours of acute cerebral infarction onset was most effective. Similarly, this study showed that within the thrombolysis time window, a prolonged time from onset to thrombolysis remained an independent risk factor for END, consistent with the results of Chen et al. [19]. While intravenous thrombolysis within 4.5 h of onset is generally considered effective, a delay within this window increases the likelihood of END, as well as the risk of hemorrhage and mortality [20]. Following acute ischemic stroke, ischemia and hypoxia in local brain tissue lead to the necrosis of nerve cells in the blood supply area of the occluded vessel, forming the ischemic core. The ischemic penumbra surrounds this core, where cells are in a state of severe ischemia and hypoxia [21]. Therefore, early reperfusion to supply blood to the ischemic penumbra and improve the ischemic state is crucial for preventing further progression of the stroke. The longer the delay from onset to thrombolysis, the higher the incidence of END and the worse the prognosis. Although it is advocated to extend the time window of thrombolysis to 4.5 hours, earlier treatment remains beneficial to improve the prognosis of patients. The success of thrombolytic therapy for acute cerebral infarction depends on shortening the treatment time. Therefore, minimizing pre-hospital delays and optimizing in-hospital thrombolysis processes are essential to reducing END incidence and improving patient prognosis.

The nomogram is a tool that integrates multiple clinicopathological parameters to facilitate individualized prediction. Unlike complex formulas, it presents regression analysis results in an intuitive graphical format. In this study, a nomogram prediction model was constructed based on the influencing factors. AUC values for the test set and the validation data set were 0.994 (95% CI: 0.982-1.000) and 0.977 (95% CI: 0.982-1.000), respectively, both of which are above 0.75, indicating good discrimination of the model. These results confirm that the predictive model for END in ACI patients after thrombolysis was successfully established and underwent internal validation, demonstrating its potential to assist clinicians in decision-making.

However, this study still has some limitations. First, as a retrospective analysis with a small sample size, the conclusions may be biased. Second, due to limitations in data sources, not all potential influencing factors, such as genetic markers or imaging features, were included, which could impact the predictive accuracy of the model. Despite these limitations, the results of this study provide valuable information for future research and clinical practice. Specifically, this study identified age, NIHSS score, fibrinogen level, and time from onset to thrombolysis as independent predictors of END, findings that can be further validated in future studies and may help refine prediction tools. Additionally, the nomogram prediction model developed in this study has good discrimination and fit, making it a useful tool for clinicians in decision-making regarding thrombolytic therapy. Future studies may enhance this model by incorporating larger samples and multicenter data.

In conclusion, END is common in patients with ACI after intravenous thrombolysis. Key influencing factors include age, NIHSS score, fibrinogen level, and the time from onset to thrombolysis. It is essential to promptly assess and analyze these risk factors before thrombolysis, to identify appropriate candidates for the therapy. Patients who are unsuitable for thrombolysis should be quickly redirected to other effective treatments, thereby enhancing both the efficacy and safety of treatment.

Disclosure of conflict of interest

None.

Address correspondence to: Qi Zhang, Department of Neurology, Nantong Rici Hospital Affiliated to Yangzhou University, No. 2000 Xinghu Road, Nantong 226000, Jiangsu, China. Tel: +86-0513-85969125; E-mail: zhqixy@126.com

References

[1] Nguyen NB, Nguyen Thi HH, Thi HL, Nguyen ST and Nguyen TV. Results of acute cerebral infarction treatment with hyperbaric oxygen therapy, 2020-2022. Int Marit Health 2023; 74: 265-271.

[2] Zheng D, Li X and Fu Y. Risk factors of acute cerebral infarction in patients with primary hypertension. Ir J Med Sci 2023; 192: 2441-2445.

[3] Wang WW, Xu JP, Zhang HL and Jia JH. Influencing factors of early neurological deterioration in elderly patients with acute cerebral infarction after intravenous thrombolysis. Chin J Thrombosis and Hemostasis 2022; 28: 364-366.

[4] Wang Z and Che J. Effectiveness of alteplase intravenous thrombolysis combined with butylphthalide in patients with acute severe cerebral infarction. Folia Neuropathol 2022; 60: 421-426.

[5] Tian T, Wang L, Xu J, Jia Y, Xue K, Huang S, Shen T, Luo Y, Li S and Min L. Prediction of early neurological deterioration in acute ischemic stroke patients treated with intravenous thrombolysis. J Cereb Blood Flow Metab 2023; 43: 2049-2059.

[6] Wang G, Fang B, Yu X and Li Z. Interpretation of 2018 guidelines for the early management of patients with acute ischemic stroke. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 2018; 30: 289-295.

[7] Mori M, Naganuma M, Okada Y, Hasegawa Y, Shiokawa Y, Nakagawara J, Furui E, Kimura K, Yamagami H, Kario K, Okuda S, Koga M, Minematsu K and Toyoda K. Early neurological deterioration within 24 hours after intravenous rt-PA therapy for stroke patients: the stroke acute management with urgent risk factor assessment and improvement rt-PA registry. Cerebrovasc Dis 2012; 34: 140-6.

[8] Yu WM, Abdul-Rahim AH, Cameron AC, Kõrv J, Sevcik P, Toni D and Lees KR; SITS Scientific Committee*. The incidence and associated factors of early neurological deterioration after thrombolysis: results from SITS registry. Stroke 2020; 51: 2705-2714.

[9] Shi HX, Li C, Zhang YQ, Li X, Liu AF, Liu YE, Jiang WJ and Lv J. Predictors of early neurological deterioration occurring within 24 h in acute ischemic stroke following reperfusion therapy: a systematic review and meta-analysis. J Integr Neurosci 2023; 22: 52.

[10] Girot JB, Richard S, Gariel F, Sibon I, Labreuche J, Kyheng M, Gory B, Dargazanli C, Maier B, Consoli A, Daumas-Duport B, Lapergue B and Bourcier R; ETIS Investigators*. Predictors of unexplained early neurological deterioration after endovascular treatment for acute ischemic stroke. Stroke 2020; 51: 2943-2950.

[11] Mehta V, Sharma A, Jyoti D, Prabhakar R, Kumar R, Guria RT and Sharma CB. Fibrinogen as a predictor of early neurological deterioration in acute ischemic stroke - evidence from the Indian population. J Cent Nerv Syst Dis 2023; 15: 11795735231156349.

[12] Sun S, Cheng Y, Li L, Zhu H, Liu C and Cao Y. A high fibrinogen-to-albumin ratio on admission is associated with early neurological deteriora-

tion following intravenous thrombolysis in patients with acute ischemic stroke. J Inflamm Res 2024; 17: 4151-4161.
[13] Wolberg AS. Fibrinogen and fibrin: synthesis, structure, and function in health and disease. J Thromb Haemost 2023; 21: 3005-3015.
[14] Mehta V, Prabhakar R, Kumar R, Jyoti D and Sharma CB. Fibrinogen as a predictor of early neurological deterioration and poor outcome in acute ischemic stroke. J Assoc Physicians India 2022; 70: 11-12.
[15] You S, Wang Y, Wang X, Maeda T, Ouyang M, Han Q, Li Q, Song L, Zhao Y, Chen C, Delcourt C, Ren X, Carcel C, Zhou Z, Cao Y, Liu CF, Zheng D, Arima H, Robinson TG, Chen X, Lindley RI, Chalmers J and Anderson CS. Twenty-four-hour post-thrombolysis NIHSS score as the strongest prognostic predictor after acute ischemic stroke: ENCHANTED study. J Am Heart Assoc 2024; 13: e036109.
[16] Liu H, Liu K, Zhang K, Zong C, Yang H, Li Y, Li S, Wang X, Zhao J, Xia Z, Song B, Xu X and Gao Y. Early neurological deterioration in patients with acute ischemic stroke: a prospective multicenter cohort study. Ther Adv Neurol Disord 2023; 16: 17562864221147743.
[17] Wang M and Liu Y. Construction of a prediction model for risk of early neurological deterioration following intravenous thrombolysis in patients with acute ischemic stroke. Technol Health Care 2023; 31: 2213-2223.
[18] Grotta JC. Intravenous thrombolysis for acute ischemic stroke. Continuum (Minneap Minn) 2023; 29: 425-442.
[19] Chen GD and Liu BR. Influencing factors of early neurological deterioration in elderly acute cerebral infarction patients after intravenous thrombolysis. Chin J Geriatric Heart Brain and Vessel Diseases 2021; 23: 613-616.
[20] Singh N, Almekhlafi MA, Bala F, Ademola A, Coutts SB, Deschaintre Y, Khosravani H, Buck B, Appireddy R, Moreau F, Gubitz G, Tkach A, Catanese L, Dowlatshahi D, Medvedev G, Mandzia J, Pikula A, Shankar JJ, Ghrooda E, Poppe AY, Williams H, Field TS, Manosalva A, Siddiqui MM, Zafar A, Imoukhoude O, Hunter G, Shamy M, Demchuk AM, Claggett BL, Hill MD, Sajobi TT, Swartz RH and Menon BK. Effect of time to thrombolysis on clinical outcomes in patients with acute ischemic stroke treated with tenecteplase compared to alteplase: analysis from the AcT randomized controlled trial. Stroke 2023; 54: 2766-2775.
[21] Hurford R, Sekhar A, Hughes TAT and Muir KW. Diagnosis and management of acute ischaemic stroke. Pract Neurol 2020; 20: 304-316.