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Risks for early neurological deterioration after thrombolytic therapy in patients with acute ischemic stroke

[1]Zhilan Zhang, [2]Guoshuai Yang, [2]Yanhui Zhou, [2]Dan Hou, [2]Yujie Hu, [2]Jiangshan Zhang

[1]Department of Ultrasonic Medicine, Central South University Xiangya School of Medicine Affiliated Haikou Hospital, Haikou, Hainan Province, China; [2]Department of Neurology, Central South University Xiangya School of Medicine Affiliated Haikou Hospital, Haikou, Hainan Province, China

Abstract

Background: Early neurological deterioration (END) is a common complication following intravenous thrombolysis in acute ischemic stroke (AIS). This study aimed to identify factors associated with END to improve early risk stratification and management. *Methods:* We conducted a prospective observational study including AIS patients treated with intravenous recombinant tissue plasminogen activator (rt-PA) within 4.5 hours of symptom onset. END was defined as an increase of ≥ 4 points in the NIHSS score within 24 hours after thrombolysis. Baseline data included demographics, vascular risk factors, prior medication use, NIHSS score, onset-to-needle and onset-to-thrombectomy times, laboratory markers (including inflammatory cytokines and platelet function), and neuroimaging findings. Univariate and multivariate logistic regression analyses were performed, and model performance was evaluated using receiver operating characteristic (ROC) curves. *Results:* Among 300 enrolled patients, 66 (22.0%) developed END. Multivariate analysis identified higher NIHSS score at admission (P=0.011), longer onset-to-needle time (P=0.007), proximal large vessel occlusion (P=0.010), diabetes (P=0.018), elevated interleukin-6 (IL-6) levels (P<0.001), and increased maximum aggregation rate induced by arachidonic acid (MAR_AA) (P<0.001) as independent predictors of END. A predictive model incorporating these factors demonstrated excellent discriminative ability (AUC=0.873; 95% CI: 0.844–0.902).
Conclusion: Neurological severity, treatment delay, metabolic vulnerability, inflammation, and platelet hyperreactivity collectively contribute to END after thrombolysis. Identifying high-risk patients through clinical and biomarker profiling may help improve outcomes through early intervention.

Keywords: Acute ischemic stroke, thrombolysis, early neurological deterioration, inflammatory markers, platelet aggregation

INTRODUCTION

Acute ischemic stroke (AIS) accounts for approximately 80-85% of all stroke cases and remains a major cause of disability and death worldwide, imposing a significant economic and societal burden.[1] Timely administration of recombinant tissue plasminogen activator (rt-PA) within 4.5 hours remains the most widely accepted therapeutic approach for AIS.[2] While thrombolytic therapy has improved clinical outcomes for many patients, a considerable proportion experiences early neurological deterioration (END), which can occur despite timely and appropriate intervention.[3,4]

END is commonly characterized by a decline of 4 or more points on the National Institutes of Health Stroke Scale (NIHSS) within 24 hours after treatment, and it is closely linked to poor functional prognosis and higher mortality.[5,6] The reported incidence of END following rt-PA administration varies widely in the literature, ranging from 5% to 40%, reflecting heterogeneity in patient populations, stroke subtypes, and definitions of deterioration.[7-9] The mechanisms underlying END are complex and multifactorial.

Address correspondence to: Jiangshan Zhang, Department of Neurology, Central South University Xiangya School of Medicine Affiliated Haikou Hospital, No.43, Renmin Avenue, Meilan District, Haikou 570208, Hainan Province, China. Email: 238302062@csu.edu.cn

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While hemorrhagic transformation and malignant cerebral edema are well-recognized causes, many patients with END do not exhibit radiologically identifiable complications, suggesting that other pathophysiological pathways are involved.[8,10] Emerging evidence points to a critical role of systemic inflammation, endothelial dysfunction, blood–brain barrier disruption, and re-occlusion of previously recanalized vessels.[11,12] Furthermore, metabolic derangements are thought to exacerbate neuronal injury and oxidative stress during reperfusion, thereby promoting neurological decline.[13]

Recent advances in stroke pathophysiology have highlighted the prognostic value of inflammatory cytokines, including interleukin-6 (IL-6) and interferon-gamma (IFN-γ), which may reflect the degree of immune activation and predict secondary brain injury.[14,15] Elevated IL-6 levels, in particular, have been linked to larger infarct volumes, greater blood-brain barrier permeability, and poor recovery.[16] At the same time, platelet reactivity has gained interest as a potential risk factor for END.[17] The maximum platelet aggregation rate (MAR), particularly when induced by arachidonic acid (MAR_AA) and adenosine diphosphate (MAR_ADP), reflects platelet reactivity and is involved in thrombotic processes AIS. Recent study have shown that higher MAR_AA and MAR_ADP levels, especially at 2 hours post-thrombolysis, are independently associated with and predictive of END.[18] Despite these insights, there remains no consensus on which factors are most predictive of END in AIS patients receiving rt-PA. Most studies have been limited by retrospective designs or lack of integration across clinical, inflammatory, and hematologic domains. Furthermore, the potential protective role of prior antiplatelet therapy, such as clopidogrel, remains controversial.[19] Some studies suggest that it may reduce post-thrombolysis complications, while others report increased bleeding risk or neutral effects.[20-22]

Therefore, we conducted a prospective observational study to comprehensively investigate the clinical, temporal, laboratory, and imaging predictors of END in AIS patients treated with intravenous rt-PA. By identifying independent risk and protective factors, we aim to enhance early risk stratification, guide post-thrombolysis monitoring, and provide a foundation for individualized management strategies that may reduce the incidence and severity of END.

METHODS

This was a prospective observational study without randomization or interventional procedures, designed to investigate the associations between clinical characteristics and END in patients with AIS following thrombolytic therapy. Patients diagnosed with AIS were admitted to the Department of Neurology between November 2020 and November 2022. Those who presented within 4.5 hours of symptom onset were consecutively enrolled. All enrolled patients received intravenous thrombolysis with rt-PA in accordance with standard treatment guidelines. The study was approved by the Medical Ethics Committee (Approval No. 2020-021), and written informed consent was obtained from all participants. The study was registered at the Chinese Clinical Trial Registry (Registration No. MR-46-22-007929).

Inclusion criteria were: (1) aged ≥18 years; (2) treatment with intravenous thrombolysis using rt-PA; (3) admission within 4.5 hours after symptom onset.

Exclusion criteria were: (1) patients with newly initiated or dosage-adjusted antiplatelet or anticoagulant therapy (including aspirin, clopidogrel, ticagrelor, cilostazol, rivaroxaban, or warfarin) within 1 week before admission were excluded. Patients receiving stable long-term antiplatelet therapy were not excluded.; (2) patients with infection, fever, electrolyte disorders, mental disorders, and hemodynamic disorders at the time of admission; (3) patients with serious heart and lung diseases, liver and kidney dysfunction, or serious medical diseases, such as tumors and immune system and blood system diseases; (4) patients who had undergone endovascular therapy prior to intravenous thrombolysis; and (5) patients with hemorrhagic stroke or hemorrhagic transformation identified before intravenous thrombolysis.

Prognostic evaluation indicators and grouping

Neurological function was assessed using the NIHSS, a standardized clinical tool designed to evaluate the severity of neurological impairment in stroke patients. The NIHSS, ranging from 0 to 42, categorizes stroke severity from no symptoms (0), minor (1-4), moderate (5-15), moderate to severe (16-20), to severe stroke (21-42), with higher scores reflecting greater neurological impairment.[23] All patients underwent NIHSS evaluations three to four times before and within 24 hours after thrombolytic therapy. These

assessments were independently conducted by two experienced neurologists who had received standardized training to ensure scoring consistency. In cases of disagreement regarding neurological deficit scores, a third neurologist adjudicated to provide the final judgment. END was defined as an increase of ≥ 4 points in the NIHSS score within 24 hours following thrombolytic therapy.[24] Based on the occurrence of END, patients were categorized into either the END group or the non-END group.

Treatment

All patients included in this study received standardized intravenous thrombolytic therapy in accordance with the guidelines for the diagnosis and treatment of AIS.[25] Rt-PA (Actilyse®, Boehringer Ingelheim, Germany) was administered at a dose of 0.9 mg/kg body weight, with a maximum total dose of 90 mg. Ten percent of the total dose was given as an intravenous bolus over 1 minute, followed by continuous infusion of the remaining 90% over 60 minutes using a syringe pump. Non-contrast head computed tomography (CT) was performed routinely 24 hours after thrombolysis or earlier if neurological deterioration occurred, to assess for hemorrhagic transformation or infarct progression. In addition to thrombolytic treatment, all patients received standard supportive care, including blood pressure management, glycemic control, lipid-lowering therapy, and delayed initiation of antiplatelet therapy when appropriate.

Data collection

Baseline data were collected at the time of admission and included demographic characteristics (age, sex, body mass index (BMI)), vascular risk factors (hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, coronary artery disease, heart failure, smoking and alcohol use), and prior medication history (use of antiplatelet agents, statins, antihypertensives, hypoglycemic agents, etc.). Clinical severity was assessed using the NIHSS score at admission. Vital signs including systolic and diastolic blood pressure (BP) were recorded. Onset-to-needle time was also documented. Laboratory tests were performed within 24 hours of admission and included blood glucose, platelet count, hemoglobin, creatinine, uric acid, low-density lipoprotein (LDL) cholesterol, total cholesterol (TC), triglycerides (TG), D-dimer, white blood cell (WBC) count, C-reactive protein (CRP), fibrinogen, homocysteine, IFN-γ, tumor necrosis factor-alpha (TNF-α), and IL-6. Platelet function was evaluated by measuring the MAR_AA and MAR_ADP using light transmission aggregometry. Stroke subtype classification was based on the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria. Patients were categorized into large artery atherosclerosis (LAA), small artery occlusion (SAO), cardioembolism (CE), or other/undetermined etiologies according to clinical presentation, imaging results, and vascular evaluation. Neuroimaging findings, including lesion location (anterior vs. posterior circulation) and the presence of proximal large vessel occlusion, were assessed using head CT and/or magnetic resonance imaging (MRI), along with vascular imaging (CTA/MRA). Proximal large vessel occlusion was defined as symptomatic occlusion of major intracranial arteries, including the intracranial internal carotid artery, the M1 segment of the middle cerebral artery, the proximal M2 segment, the vertebral artery, or the basilar artery. Extracranial carotid artery disease and asymptomatic vascular occlusions were excluded.

Statistical analysis

All statistical analyses were performed using SPSS 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were tested for normality using the Kolmogorov-Smirnov test. Normally distributed variables were expressed as mean ± standard deviation (SD), while non-normally distributed variables were presented as median and interquartile range (IQR). Categorical variables were summarized as frequencies (percentages). Univariate logistic regression analysis was conducted to explore the association between each clinical factor and the occurrence of END. Variables with $P < 0.05$ in univariate analysis were included in a multivariate logistic regression model to identify independent predictors of END. To prevent model overfitting, the number of variables entered into the multivariate model was restricted according to the events-per-variable (EPV) rule, which recommends at least 10 outcome events per predictor variable. Given that 66 patients developed END in this study, the multivariate model was limited to approximately six variables. Candidate predictors were further evaluated for multicollinearity using the variance inflation

factor (VIF), with VIF > 5 indicating substantial collinearity. Variables meeting EPV and VIF criteria were included in the final multivariate logistic regression model. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the discriminatory ability of the final multivariate logistic regression model. The area under the ROC curve (AUC) and its 95% CI were calculated. A two-sided P value of < 0.05 was considered statistically significant.

RESULTS

General information of patients with AIS

A total of 321 patients diagnosed with AIS were selected to receive intravenous thrombolysis. However, 10 patients discontinued thrombolytic treatment prematurely, 6 patients had incomplete data, and 5 patients were excluded due to comorbid infections or tumors. Consequently, a final cohort of 300 patients was included in the analysis. Of these, 234 patients were categorized into the non-END group, and 66 patients were classified into the END group. Detailed information of these patients in each group were presented in Table 1.

Univariate logistic regression analysis of demographic characteristics and medical history for END

The results of univariate logistic regression analysis showed that diabetes mellitus (P = 0.003, OR = 2.296, 95% CI: 1.315–4.008), prior antiplatelet use (P = 0.002, OR = 2.761, 95% CI: 1.406–5.137), and prior clopidogrel use (P = 0.004, OR = 2.584, 95% CI: 1.356–4.925) were significantly associated with an increased risk of END (Table 1). Other factors, including age, sex, BMI, smoking, alcohol consumption, hypertension, hyperlipidemia, atrial fibrillation, heart failure, coronary artery disease, prior stroke history, prior use of statins, aspirin, antihypertensive or hypoglycemic medications, and endovascular therapy, were not significantly associated with END (P > 0.05 for all).

Univariate logistic regression analysis of clinical severity and time-related factors for END

The results indicated that higher NIHSS score at admission (P = 0.006, OR = 1.067, 95% CI: 1.018–1.117), longer onset-to-needle time (P = 0.004, OR = 1.009, 95% CI: 1.003–1.015), and presence of proximal large vessel occlusion (P = 0.014, OR = 2.066, 95% CI: 1.159–3.682) were significantly associated with increased risk of END. In contrast, variables such as systolic and diastolic blood pressure at admission, lesion location (anterior vs. posterior circulation), stroke subtype (LAA, SAO, CE, others), and hemorrhagic transformation did not show significant associations with END (P > 0.05 for all). The detailed statistical results were presented in Table 2.

Univariate logistic regression analysis of laboratory parameters and platelet function for END

The results demonstrated that several variables were significantly associated with increased risk of END, including blood glucose (P = 0.027, OR = 1.121, 95% CI: 1.013–1.241), platelet count (P = 0.020, OR = 1.005, 95% CI: 1.001–1.009), fibrinogen (P = 0.038, OR = 1.479, 95% CI: 1.021–2.144), IFN-γ (P = 0.006, OR = 1.114, 95% CI: 1.031–1.203), IL-6 (P < 0.001, OR = 1.123, 95% CI: 1.055–1.195), MAR_AA (P < 0.001, OR = 1.051, 95% CI: 1.023–1.079), and MAR_ADP (P = 0.001, OR = 1.048, 95% CI: 1.020–1.076). Other laboratory indicators, including hemoglobin, creatinine, uric acid, lipid profiles (LDL-C, TC, TG), D-dimer, WBC, CRP, homocysteine, TNF, and mean platelet volume, were not significantly associated with END (P > 0.05 for all, Table 3).

Multivariate logistic regression analysis for END

To avoid model overfitting given the limited number of END events, the final model was restricted to no more than six variables. Candidate predictors were selected based on significance in univariate analysis and then assessed for multicollinearity using VIF. MAR_ADP, IFN-γ, platelet count, blood glucose, and fibrinogen were excluded because they demonstrated VIF values > 5 when modeled alongside MAR_AA or IL-6, indicating substantial collinearity. Although prior antiplatelet use and prior clopidogrel were associated with END in univariate analyses, aspirin was not. As clopidogrel is a subset of antiplatelet therapy and these variables are subject to collinearity and confounding by indication, they were not included in the final model. After removal of these collinear variables, other predictors retained in the final model exhibited acceptable collinearity. The results of multivariate logistic regression

Table 1: Univariate logistic regression analysis of demographic characteristics and medical history for END

Variables	Non-END group (n=234)	END group (n=66)	P	OR	95% CI
Age (years)	64.59 ± 8.99	65.90 ± 8.17	0.282	1.017	0.986 – 1.050
Sex	118 (50.4%)	35 (53.0%)	0.709	1.110	0.642 – 1.918
BMI	23.77 ± 3.77	23.40 ± 3.59	0.474	0.973	0.903 – 1.048
Smoking	68 (29.1%)	23 (34.8%)	0.367	1.306	0.731 – 2.331
Alcohol consumption	44 (18.8%)	15 (22.7%)	0.479	1.270	0.655 – 2.464
Diabetes	71 (30.3%)	33 (50.0%)	**0.003**	2.296	1.315 – 4.008
Hypertension	115 (49.1%)	34 (51.5%)	0.734	1.099	0.637 – 1.899
Hyperlipidemia	58 (24.8%)	16 (24.2%)	0.928	0.971	0.514 – 1.835
Atrial fibrillation	58 (24.8%)	21 (31.8%)	0.253	1.416	0.780 – 2.572
Heart failure	15 (6.4%)	6 (9.1%)	0.453	1.460	0.543 – 3.925
Coronary artery disease	55 (23.5%)	16 (24.2%)	0.901	1.041	0.550 – 1.973
Prior stroke history	70 (29.9%)	19 (28.8%)	0.860	0.947	0.519 – 1.729
Prior statin use	58 (24.8%)	15 (22.7%)	0.731	0.892	0.467 – 1.706
Prior antihypertensive use	79 (33.8%)	20 (30.3%)	0.598	0.853	0.473 – 1.540
Prior hypoglycemic use	77 (32.9%)	21 (31.8%)	0.868	0.952	0.530 – 1.709
Prior antiplatelet use	180 (76.9%)	62 (93.9%)	**0.002**	2.761	1.406 – 5.137
Prior aspirin use	42 (17.9%)	10 (15.2%)	0.596	0.729	0.372 – 1.339
Prior clopidogrel use	138 (59.0%)	52 (78.8%)	**0.004**	2.584	1.356 – 4.925
Endovascular therapy	38 (16.2%)	14 (21.2%)	0.347	1.389	0.700 – 2.754

Notes: Male sex was coded as 1 and female as 2. Smoking history and alcohol consumption were coded as 1 for "yes" and 2 for "no." Similarly, the presence of comorbidities, including diabetes, hypertension, hyperlipidemia, atrial fibrillation, heart failure, coronary artery disease, and prior stroke history, was coded as 1, while absence was coded as 2. Prior medication use—including statins, antihypertensive agents, hypoglycemic agents, and clopidogrel—was also coded as 1 for use and 2 for non-use. Endovascular therapy was coded as 1 for patients who underwent the procedure and 2 for those who did not. OR: Odds ratio; CI: Confidence interval. Statistically significant correlations ($P < 0.05$) are highlighted by bold print.

analysis demonstrated that higher NIHSS score at admission ($P = 0.011$, OR = 1.070, 95% CI: 1.016–1.127), longer onset-to-needle time ($P = 0.007$, OR = 1.008, 95% CI: 1.002–1.014), presence of proximal large vessel occlusion ($P = 0.010$, OR = 1.529, 95% CI: 1.302–1.991) and diabetes ($P = 0.018$, OR = 1.743, 95% CI: 1.315–2.140), higher IL-6 levels ($P < 0.001$, OR = 1.153, 95% CI: 1.074–1.238), and MAR_AA ($P < 0.001$, OR = 1.064, 95% CI: 1.031–1.098) were independently associated with increased risk of END. Detailed regression coefficients and CI were shown in Table 4.

Predictive performance of the multivariable model

To assess the discriminative ability of the final predictive model, ROC curve analysis was performed. The combined model incorporating NIHSS score at admission, onset-to-needle time, proximal large vessel occlusion, diabetes, IL-6, and MAR_AA demonstrated excellent predictive performance for END, with an AUC of 0.873 (95% CI: 0.844–0.902, $P < 0.001$) (Figure 1).

DISCUSSION

Although timely administration of rt-PA is an effective strategy to restore cerebral perfusion in AIS patients, END remains a significant clinical challenge, as many still experience neurological deterioration within 24 hours, negatively impacting their prognosis.[3,4] In this prospective study, we systematically analyzed the clinical, temporal, inflammatory, and hematologic factors associated with END and identified NIHSS score at admission, onset-to-needle time, proximal

Table 2: Univariate logistic regression analysis of clinical severity and time-related factors for END

Variables	Non-END group (n=234)	END group (n=66)	P	OR	95% CI
Systolic BP at admission	145.91 ± 19.73	147.89 ± 17.90	0.463	1.005	0.991 – 1.020
Diastolic BP at admission	84.41 ± 11.36	85.10 ± 14.45	0.681	1.005	0.982 – 1.028
NIHSS score at admission	11.64 ± 5.38	13.84 ± 6.48	**0.006**	1.067	1.018 – 1.117
Onset-to-needle time	67.36 ± 7.28	77.19 ± 9.87	**0.004**	1.009	1.003 – 1.015
Lesion location	151 (64.5%)	43 (65.2%)	0.926	1.028	0.580 – 1.822
Type of stroke					
LAA	97 (41.5%)	32 (48.5%)	0.309	1.329	0.768 – 2.300
SAO	78 (33.3%)	20 (30.3)	0.643	0.933	0.694 – 1.253
CE	33 (14.1%)	11 (16.7%)	0.603	1.068	0.833 – 1.369
Others	26 (11.1%)	3 (4.5%0	0.123	0.786	0.578 – 1.068
Proximal large vessel occlusion	56 (23.9%)	26 (39.4%)	**0.014**	2.066	1.159 – 3.682
Hemorrhagic transformation	14 (6.0%)	5 (7.6%)	0.640	1.288	0.446 – 3.717

Notes: Continuous variables—including systolic and diastolic BP, NIHSS score at admission, and onset-to-needle time—were entered into the model in their original continuous form. Lesion location was categorized as anterior circulation = 1 and posterior circulation = 0, with posterior circulation used as the reference group. Stroke subtype was analyzed using dummy variables: LAA, SAO, CE, and other subtypes were coded as 1 for presence and 0 for absence. Proximal large vessel occlusion and hemorrhagic transformation were coded as binary variables (1 = presence, 0 = absence). OR: Odds ratio; CI: Confidence interval; BP: blood pressure; NIHSS: National Institutes of Health Stroke Scale; LAA: large artery atherosclerosis; SAO: small artery occlusion; CE: cardioembolism. Statistically significant correlations ($P < 0.05$) are highlighted by bold print.

large vessel occlusion, diabetes, IL-6, and MAR_AA as independent predictors. Furthermore, the multivariable model incorporating these six variables demonstrated excellent predictive performance, achieving an AUC of 0.873.

A high baseline NIHSS score was independently associated with END, consistent with previous evidence linking initial stroke severity to larger infarct cores, impaired collateral circulation, and a higher likelihood of malignant edema or reperfusion injury.[26,27] Notably, prolonged onset-to-needle time was also strong predictors of END, highlighting the critical importance of minimizing treatment delays. Time-sensitive ischemia may worsen infarct progression and increase vulnerability to reperfusion-associated complications.[28,29] These findings emphasize the need for optimized prehospital triage and in-hospital workflows.[30] In addition, diabetes was identified as an independent predictor of END. Acute hyperglycemia impairs endothelial function and collateral flow and enhances metabolic and oxidative stress, promoting microvascular no-reflow and increasing the risk of reperfusion failure despite timely thrombolysis.[31,32] Prior studies have similarly reported that diabetes increases the risk of END, hemorrhagic transformation, and poor long-term outcomes after ischemic stroke, and our findings are consistent with these reports.[33,34] Moreover, proximal large vessel occlusion was independently associated with a higher risk of END. Such occlusions typically reflect a greater thrombus burden and poorer collateral circulation, which can accelerate ischemic core progression and reduce reperfusion efficiency even after intravenous thrombolysis.[35,36] Their larger and denser clot structure may also lead to incomplete or unstable recanalization and microvascular no-reflow, thereby increasing susceptibility to reperfusion injury and END.[37]

Elevated levels of IL-6 were independently associated with deterioration, reinforcing the concept of post-ischemic immune activation as a driver of secondary brain injury.[38,39] IL-6, a key mediator of the acute-phase response, has been previously associated with infarct volume, vasogenic edema, and poor outcomes.[40] Our results are in line with those reported by Gong *et al.* linking IL-6 to infarct expansion, now provide evidence for its utility in anticipating early post-thrombolysis deterioration.[41] Another aspect of our study is the identification of platelet hyperreactivity—measured by

Table 3: Univariate Logistic Regression Analysis of Laboratory Parameters and Platelet function for END

Variables	Non-END group (n=234)	END group (n=66)	P	OR	95% CI
Blood glucose	6.27 ± 2.40	7.05 ± 2.64	**0.027**	1.121	1.013 – 1.241
Platelet count	227.56 ± 69.14	249.39 ± 54.48	**0.020**	1.005	1.001 – 1.009
Hemoglobin	140.01 (95.16, 167.61)	142.67 (102.78, 159.60)	0.685	1.003	0.990 – 1.016
Mean platelet volume	10.28 (9.65, 11.09)	10.43 (9.25, 11.13)	0.182	1.185	0.923 – 1.521
Creatinine	68.71 (49.52, 87.49)	70.44 (48.73, 86.54)	0.674	1.007	0.976 – 1.039
Uric acid	302.38 (194.91, 360.15)	304.52 (243.27, 375.24)	0.349	1.004	0.996 – 1.011
LDL cholesterol	2.89 ± 0.84	3.08 ± 0.86	0.120	1.288	0.936 – 1.773
TC	3.97 (2.32, 6.64)	4.48 (2.02, 6.49)	0.965	0.995	0.810 – 1.223
TG	1.26 (0.79, 6.88)	1.28 (1.60, 6.50)	0.691	1.051	0.821 – 1.346
D-dimer	1.20 ± 1.04	1.13 ± 1.32	0.654	0.944	0.732 – 1.216
WBC	7.93 ± 3.48	7.90 ± 3.36	0.948	0.991	0.802 – 1.212
CRP	4.48 (2.02, 12.00)	4.92 (2.14, 12.83)	0.515	1.038	0.927 – 1.162
Fibrinogen	2.80 (0.89, 3.83)	3.01 (1.00, 3.64)	**0.038**	1.479	1.021 – 2.144
Homocysteine	13.29 (4.65, 21.30)	12.68 (4.65, 20.19)	0.668	1.012	0.958 – 1.069
IFN-γ	26.00 (22.00, 31.00)	29.25 (26.00, 33.00)	**0.006**	1.114	1.031 – 1.203
TNF	9.00 (6.00, 16.00)	9.34 (7.00, 15.00)	0.575	0.975	0.894 – 1.065
IL-6	8.58 ± 4.07	10.80 ± 4.37	<0.001	1.123	1.055 – 1.195
MAR_AA	51.41 ± 11.62	57.36 ± 9.95	<0.001	1.051	1.023 – 1.079
MRA-ADP	53.78 ± 11.09	59.14 ± 9.44	0.001	1.048	1.020 – 1.076

Notes: Laboratory indicators—including blood glucose, platelet count, hemoglobin, creatinine, uric acid, LDL cholesterol, TC, TG, D-dimer, CRP, fibrinogen, and homocysteine—were entered into the logistic regression model as continuous variables. Inflammatory cytokines such as IFN, TNF, and IL-6, as well as platelet function parameters including the MAR_AA and MAR_ADP, were also analyzed in their original continuous form. LDL: Low-density lipoprotein; TC: Total cholesterol; TG: Triglycerides; CRP: C-reactive protein; WBC: white blood cell; IFN-γ: Interferon-gamma; TNF: Tumor necrosis factor; IL-6: Interleukin-6; MAR_AA: Maximum aggregation rate induced by arachidonic acid; MAR_ADP: Maximum aggregation rate induced by adenosine diphosphate; OR: Odds ratio; CI: Confidence interval. Statistically significant correlations ($P < 0.05$) are highlighted by bold print.

maximum aggregation rate (MAR_AA)—as a significant predictor of END. Elevated MAR levels may reflect a prothrombotic state prone to microthrombus formation, distal embolization, and early re-occlusion, even in patients who achieve initial recanalization.[42,43] This supports the "no-reflow" hypothesis, in which microvascular obstruction impairs tissue perfusion despite open large vessels.[44] Prior studies have rarely included platelet function testing in END prediction models. Our results suggest that such measures could improve early risk stratification and clinical decision-making.

Importantly, our multivariable model incorporating these six variables demonstrated excellent predictive performance, with an AUC of 0.873. This predictive ability is superior to many previously reported END models, which often relied primarily on clinical severity or time-to-treatment variables and typically yielded modest AUC values.[45,46] For example, models based solely on NIHSS score or onset-to-needle time capture neurological impairment and ischemic duration but do not account for inflammatory or hematologic processes that critically influence reperfusion response.[47] Other studies have incorporated inflammatory cytokines such as CRP or IL-6 to improve predictive power, but improvements remained modest due to the absence of thrombotic markers reflecting microvascular re-occlusion.[48,49] Notably, platelet function indicators such as MAR_AA have rarely been included in prior predictive frameworks.[17] Because MAR_AA reflects arachidonic acid-mediated platelet hyperreactivity and microthrombus formation,

Table 4: Multivariate logistic regression analysis for END

Variables	B	Standard Error	Wald	P	OR	95% CI
Diabetes	0.093	0.016	7.983	0.018	1.743	1.315 – 2.140
NIHSS score at admission	0.068	0.027	6.507	0.011	1.070	1.016 – 1.127
MAR_AA	0.062	0.016	14.691	0.000	1.064	1.031 – 1.098
Onset-to-needle time	0.008	0.003	7.190	0.007	1.008	1.002 – 1.014
Proximal large vessel occlusion	0.054	0.031	6.634	0.010	1.529	1.302 – 1.991
IL-6	0.143	0.036	15.416	0.000	1.153	1.074 – 1.238

Notes: All continuous variables—including onset-to-needle time, NIHSS score at admission, IL-6, and MAR_AA—were entered into the model in their original continuous form. Categorical variables were binary coded: diabetes and proximal large vessel occlusion were coded as 1 for presence and 0 for absence. NIHSS: National Institutes of Health Stroke Scale; IL-6: Interleukin-6; MAR_AA: Maximum aggregation rate induced by arachidonic acid; OR: Odds ratio; CI: Confidence interval. Statistically significant correlations ($P < 0.05$) are highlighted by bold print.

incorporating this parameter enables assessment of microcirculatory vulnerability, a key mechanism underlying END that is not captured by clinical or imaging variables alone.[50] By simultaneously integrating neurological severity (NIHSS), ischemia-reperfusion time sensitivity (onset-to-needle time), vascular lesion burden (proximal large vessel occlusion), metabolic susceptibility (diabetes), systemic inflammatory activation (IL-6), and platelet aggregation potential (MAR_AA), our model captures the multidimensional pathophysiology of END. This integrative approach likely explains its superior discriminative performance and supports its potential utility for early individualized risk stratification after thrombolysis.

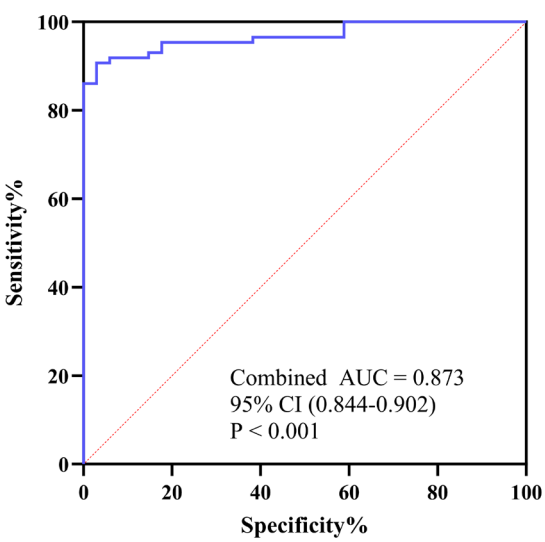

Figure 1.

Several limitations must be acknowledged. First, as the study was conducted at a single center with limited ethnic and regional diversity, its findings may have limited generalizability. Second, although we excluded patients with active infections or systemic diseases, subclinical inflammatory conditions may have influenced cytokine levels. Third, platelet function and inflammatory markers were measured only once and dynamic changes over time were not captured. Additionally, we lacked perfusion imaging data to correlate with microvascular status and END. Finally, the neutrophil-to-lymphocyte ratio (NLR) could not be evaluated because differential leukocyte data were not consistently available. Future multicenter studies should validate our findings across diverse populations and explore the temporal dynamics of inflammation and platelet reactivity, and should also include complete differential leukocyte data to enable accurate calculation of NLR, which may further refine individualized risk stratification and guide targeted preventive strategies. Interventional trials targeting IL-6 signaling or platelet inhibition in high-risk patients could help establish causality and clinical utility. Moreover, machine learning-based prediction models incorporating clinical, temporal, and molecular markers may enhance personalized stroke care.

In conclusion, in this study of AIS patients treated with intravenous thrombolysis, we identified higher NIHSS score at admission, longer onset-to-needle time, proximal large vessel occlusion, diabetes, elevated IL-6 levels, and increased MAR_AA as independent predictors of END. The multivariable predictive

model integrating these factors demonstrated excellent discriminative performance (AUC = 0.873), suggesting its potential utility for early risk stratification. These findings indicate that neurological severity, treatment delay, metabolic vulnerability, inflammatory activation, and platelet hyperreactivity collectively contribute to early neurological deterioration following thrombolysis. Early identification of high-risk patients using clinical and biological markers may facilitate individualized monitoring and prompt intervention strategies. Future multicenter studies are warranted to validate these predictors and explore targeted therapies aimed at mitigating END and improving functional recovery in this vulnerable patient population.

DISCLOSURE

Ethics: The study was approved by the Medical Ethics Committee of Central South University Xiangya School of Medicine Affiliated Haikou Hospital (Approval No. 2020-021), and written informed consent was obtained from all participants. The study was registered at the Chinese Clinical Trial Registry (Registration No. MR-46-22-007929).

Data availability: The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

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Conflict of interests: None

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