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ORIGINAL RESEARCH

Risk factors for early neurological deterioration in acute ischemic stroke: a case-control study

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Abstract

Background: Early neurological deterioration (END) represents major complication of acute ischemic stroke (AIS) and is associated with high mortality and disability. In the present study, we aimed to identify potential risk factors for early neurological deterioration in patients with AIS. **Methods**: This was a retrospective and case-control study conducted at Sun Yat-sen University's Fifth Affiliated Hospital. Between January 2021 and October 2022, 358 patients with AIS patients were examined and grouped according to whether they developed END or not. END was defined as an increase of >2 points on the National Institutes of Health Stroke Scale (NIHSS) score within the first week of admission. Baseline characteristics, vascular risk factors, laboratory findings, and neuroimaging were then compared between the END and non-END groups of patients. **Results**: END was observed in 58 of the 358 patients. The END group of patients showed a significantly higher prevalence of unstable carotid plaques (51.7% *vs.* 15.3%, $p < 0.001$) and high NIHSS scores at the time of admission (median 4.0 *vs.* 2.0, $p < 0.001$). Key biochemical markers were significantly higher in the END group, including fibrinogen, total cholesterol, low density lipoprotein cholesterin (LDL-cholesterol) and glycosylated hemoglobin A1c (HbA1c). Multivariate analysis confirmed that higher NIHSS scores at the time of admission and unstable carotid plaques were independent prognostic factors of END. **Conclusions**: Higher NIHSS scores upon admission and the presence of unstable carotid plaques were identified as significant risk factors for END in AIS patients. Identifying these factors may facilitate the early diagnosis of END and improve patient outcomes.

Keywords

Risk factors; Acute ischemic stroke; END; NIHSS; Unstable carotid plaque

1. Introduction

Stroke is a major global health problem and a major cause of death and long-term disability, and ischemic stroke is solely responsible for 87% of all cases [1]. The deterioration of neurological function in the early phase post-stroke, often referred to as early neurological deterioration (END), is observed in approximately 10–20% of stroke patients [2]. Despite the development of advanced acute therapeutic options, early neurological deterioration (END) during hospitalization remains a common problem and is associated with lethal outcomes [3]. Consequently, understanding the risk factors for END in patients with acute ischemic stroke (AIS) is essential if we are to enhance patient care and to identify efficient treatment strategies.

Various factors are known to contribute to the severity of stroke and coexisting conditions and unstable atherosclerotic plaques are known to complicate early neurological deterioration [4]. The early prediction of END will help clinicians to plan the clinical management of high-risk AIS patients to mitigate neurological degradation. Despite the clinical importance of END, research in this area faces several challenges. These include the heterogeneity in the definitions of END used in studies, the variability in the time windows considered for observing END, and the difficulties in controlling for confounding factors such as pre-existing comorbidities and variations in acute stroke treatment. In the present study, we aimed to identify prognostic factors for END in patients with AIS by analyzing a range of demographic factors, laboratory findings, and stroke-specific data.

2. Materials and methods

2.1 Study participants

Because this was a retrospective study, neither the patients nor members of the public were involved in the design or execution of this study.

2.2 Study design and criteria

In the present study, we retrospectively analyzed data acquired from patients with AIS who attended Sun Yat-sen University's Fifth Affiliated Hospital Stroke Center between January 2021 and October 2022. Patients were treated by standardized protocols that were aligned with current treatment guidelines [5].

2.2.1 Inclusion criteria

To be included in this study, patients needed to be >18 years-of-age and presented with the symptoms of AIS within 72 hours of admission. Additional inclusion criteria included AIS confirmed by computed tomography (CT) scanning or magnetic resonance imaging (MRI), a modified Rankin Score of ≤2 at admission, and the availability of a complete clinical dataset.

2.2.2 Exclusion criteria

We excluded patients with a history of psychiatric disorders, conditions that prevented NIHSS assessment, traumatic brain injury, or patients that died prior to assessment.

Patients were grouped into END or non-END groups based on whether they experienced an increase in NIHSS score of more than 2 points within the first week of admission [3].

2.3 Data collection and definitions

Demographic, clinical and laboratory data were extracted from the records of stroke patients attending our hospital. We collated a range of data for analysis, including age, sex, smoking status, medical history (hypertension, diabetes, hyperlipidemia, previous transient ischemic attack, ischemic stroke and ischemic heart disease), medication use (antithrombotic, antihypertensives, antidiabetics and statins), and various laboratory parameters (white blood cells (WBCs), platelets (PLT), fibrinogen, creatinine, uric acid, blood pressures, blood glucose, glycated hemoglobin (HbA1c), lipids and homocysteine).

Stroke was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification. We also considered the affected cerebral areas, hemorrhagic transformation, and the National Institutes of Health Stroke Scale (NIHSS) score upon admission. The impact of stroke on cerebral circulation was categorized as anterior, posterior or both. The type of stroke was classified as large-artery atherosclerosis, cardio-embolism, small-artery occlusion, stroke of another determined etiology, or stroke of undetermined etiology. We also recorded treatment options, including thrombolytic therapy, dual antiplatelet therapy (DAPT), and intensive statin therapy. Dyslipidemia was established by lipid profile (such as the levels of cholesterol or triglyceride) or by the use of medications (such as statins). Smoking was defined as consistent smoking for the duration of the last six months [6].

2.4 Neuroimaging analysis

Neuroimaging data were comprehensively assessed by a radiologist and a neurologist; findings were confirmed by mutual consensus. The recorded neuroimaging information included data relating to the affected cerebral circulation, the location of infarction, and the stroke subtype. The further impact of stroke was determined by the TOAST classification criteria [7].

2.5 Measurement of unstable carotid plaques

Unstable carotid plaques were analyzed using an ultrasound device, as follows. We utilized standard ultrasound equipment, including a high-resolution B-mode system operating in black and white modes, preferentially with linear ultrasound transducers at frequencies >7 MHz. We used an appropriate depth of focus (*e.g.*, 30–40 mm) and an optimal frame rate of 25 Hz (115 Hz) to yield optimal image quality and facilitate edge detection. We applied a log gain compensation of approximately 60 dB and gain settings were adjusted to obtain symmetrical levels of brightness on the near and far walls, or in the middle part of the field, to eliminate intraluminal artifacts.

Carotid plaque instability was established by reference to published ultrasound criteria which define a plaque as a structure intruding into the lumen by at least 0.5 mm or 50% of the intima-media thickness (IMT), or having a thickness of 1.5 mm from the media-adventitia to the intima-lumen interface [8].

2.6 Statistical analysis

All statistical analyses were performed with SPSS (version 25.0, IBM Corp., Armonk, NY, USA). Continuous data are expressed as mean ± standard deviation (SD) or median (interquartile range) while categorical data are expressed as frequencies (%) depending on their distribution. Group comparisons were performed by *t*-tests, Mann-Whitney U-tests, the chi-squared test, or Fisher's exact test, as appropriate. Factors associated with END were identified by Kendall's and Spearman's correlations and multivariable logistic regression including significant variables identified by the univariate analysis. The model provided adjusted odds ratios (ORs) with 95% confidence intervals (95% CIs). $p < 0.05$ was considered statistically significant.

3. Results

3.1 Patient characteristics

Of the 358 patients analyzed in this study (69% male, mean age: 62.09 ± 12.71 years), only 58 patients experienced END. No deaths were recorded during the study period. The END group was slightly older (64.16 ± 12.22 years) when compared to the non-END group (61.69 ± 12.77 years). There were no significant differences between the two groups in terms of baseline characteristics, demographics or medical history. However, the END group had a significantly greater frequency of unstable carotid plaques (51.724% *vs.* 15.333%, $p < 0.001$) and higher NIHSS scores at the time of admission. Significantly elevated levels of fibrinogen, total cholesterol, low-density lipoprotein cholesterol (LDL-C), and HbA1c were also detected in the END group (all $p < 0.005$). Collectively, these results indicated a greater burden of vascular disease and worse glycemic control in the END group, as shown in Table 1.

TABLE 1. A comparison of baseline clinical characteristics between the END and Non-END groups.

Clinical characteristic	Total (n = 358)	Non-END (n = 300)	END (n = 58)	$t/z/\chi^2$	*p*
Male, n (%)	247 (68.994)	209 (69.667)	38 (65.517)	0.391	0.532
Age years, median (IQR)	62 (52, 72)	62 (52, 71)	63 (55, 75)	−1.353	0.176
Smoker, n (%)	156 (43.57)	131 (43.66)	25 (43.10)	0.006	0.937
Hypertension, n (%)	225 (62.849)	185 (61.667)	40 (68.966)	1.109	0.292
Diabetes mellitus, n (%)	81 (22.626)	73 (24.333)	8 (13.793)	3.084	0.079
Hyperlipidemia, n (%)	20 (5.587)	16 (5.333)	4 (6.897)	0.225	0.635
Prior TIA or ischemic stroke, n (%)	55 (15.363)	44 (14.667)	11 (18.966)	0.691	0.406
Ischemic heart disease, n (%)	24 (6.704)	20 (6.667)	4 (6.897)	0.004	0.949
Antihypertensive medication use, n (%)	123 (34.358)	101 (33.667)	22 (37.931)	0.392	0.531
Antidiabetic medication use, n (%)	58 (16.201)	52 (17.333)	6 (10.345)	1.748	0.186
Statin use, n (%)	12 (3.352)	8 (2.667)	4 (6.897)	2.684	0.101
Anti-thrombotic medication use, n (%)	27 (7.542)	21 (7.000)	6 (10.345)	0.780	0.377
Carotid unstable plaque, n (%)	76 (21.229)	46 (15.333)	30 (51.724)	38.490	<0.001
Initial SBP mmHg, median (IQR)	153 (138, 170)	155 (68, 170)	150 (40, 168)	0.401	0.689
Initial DBP mmHg, median (IQR)	90 (81, 99)	90 (81, 100)	87 (82, 96)	0.758	0.449
NIHSS at admission, median (IQR)	3.00 (1.000, 5.00)	2.00 (1.000, 5.00)	4.00 (2.000, 8.00)	−3.889	<0.001
WBC ($\times 10^9$/L), median (IQR)	7.35 (6.180, 9.21)	7.32 (6.240, 9.01]	7.920 (6.030, 12.36]	−1.496	0.135
PLT ($\times 10^9$/L), median (IQR)	203.00 (168.00, 237.00)	206.00 (167.00, 234.00)	201.00 (172.00, 238.00)	−0.065	0.949
Fibrinogen (g/L), median (IQR)	3.03 (2.600, 3.52)	2.98 (2.570, 3.46)	3.20 (2.820, 4.02)	−3.034	0.002
Creatinine (μmol/L), median (IQR)	74.00 (64.00, 87.00)	74.000 [64.00, 87.00]	77.000 [66.00, 88.00]	−0.543	0.588
Uric acid (μmol/L), median (IQR)	354.00 (301.00, 412.00)	361.00 (305.00, 418.00)	335.00 (296.00, 404.00)	1.606	0.108
FBG (mmol/L), median (IQR)	5.50 (4.80, 6.90)	5.50 (4.80, 6.70)	5.70 (5.00, 7.40)	−1.802	0.072
TG (mmol/L), median (IQR)	1.37 (1.010, 1.92)	1.36 (1.010, 1.92)	1.44 (1.060, 1.90)	−0.099	0.922
T-CH (mmol/L), median (IQR)	4.86 (4.16, 5.73)	4.78 (4.16, 5.64)	5.33 (4.49, 6.11)	−2.275	0.023
HDL-C (mmol/L), median (IQR)	1.05 (0.90, 1.22)	1.05 (0.91, 1.21)	1.00 (0.87, 1.28)	0.602	0.547
LDL-C (mmol/L), median (IQR)	2.91 (2.34, 3.49)	2.86 (2.32, 3.42)	3.25 (2.44, 3.83)	−2.355	0.019
HbA1c (%), median (IQR)	5.70 (5.40, 6.60)	5.70 (5.40, 6.50)	6.00 (5.50, 7.50)	−2.649	0.008
Homocysteine (μmol/L), median (IQR)	11.18 (9.27, 14.54)	11.20 (9.18, 14.51)	11.03 (9.39, 14.54)	−0.206	0.837

END: Early neurological deterioration; SBP: systolic blood pressure; DBP: diastolic blood pressure; TIA: transient ischemic attack; NIHSS: National Institutes of Health Stroke Scale; WBC: white blood cell count; FBG: fasting blood glucose; HbA1c glycated hemoglobin; TG: triglyceride; T-CH: total cholesterol; HDL-C; high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; IQR: interquartile range; SD: standard deviation; PLT: platelets.

3.2 Stroke-related characteristics

In terms of stroke etiology, no significant differences were detected between the two groups in terms of cerebral circulation, hemorrhagic transformation, and thrombolysis. However, the END group had received significantly more Dual antiplatelet therapy (DAPT) (41.379% *vs.* 26.333%, $p = 0.020$). This finding showed that despite similar stroke types and severities, clinicians may have considered the END group to be at a higher risk of recurrent ischemia and therefore opted for aggressive anti-thrombotic treatment during hospitalization (Table 2).

3.3 Correlation analysis of END and clinical factors

Kendall's rank correlation and Spearman's correlation analysis was used to investigate the relationship between END and various clinical factors. Table 3 shows that unstable carotid plaques, the use of DAPT, and hemorrhagic transformation, were all positively correlated with END (Fig. 1). These results suggested that patients with more severe vascular disease, in terms of plaque stability, receiving DAPT anti-thrombotic treatment and experiencing hemorrhagic complications, were more likely to experience END. Table 4 shows that higher NIHSS scores at the time of admission, elevated fibrinogen levels, and increased levels of cholesterol and HbA1c, were positively correlated with END (Fig. 2).

3.4 Factors associated with END

When controlled for confounding variables, logistic regression analysis identified unstable carotid plaques (OR: 5.345), a high NIHSS score at the time of admission (OR: 1.137), DAPT (OR: 2.264), and increased fibrinogen levels (OR: 1.349) as independent predictors of END. These results indicate that severe initial neurological impairments, unstable vascular conditions, and a high degree of inflammation, significantly elevate the risk of neurological deterioration in a manner that is independent of other variables (Table 5 and Fig. 3).

Receiver operating characteristic (ROC) curve analysis was used to evaluate the NIHSS score at the time of admission. In this analysis, unstable carotid plaques, fibrinogen levels, and DAPT, were used to predicting END. The area under the curve (AUC) for NIHSS score (0.661) and unstable carotid plaques (0.682) indicated moderate predictive power for END. Taking the factors identified by logistic regression analysis together as a regression model resulted in an AUC of 0.802, with a sensitivity and specificity of 0.862 and 0.853, respectively (Table 6 and Fig. 4).

4. Discussion

In the present study, we investigated the prognostic value of various clinical and laboratory factors for END in patients with AIS upon admission. While no single factor provided excellent predictive value, the NIHSS score, and the assessment of carotid plaques, provided modest prognostic capabilities. The combination of factors identified by logistic regression analysis into a regression model suggested that this approach might provide a useful prognostic tool. These findings may facilitate early risk identification and the prevention of END in acute care of ischemic stroke.

Globally, stroke is a leading cause of death and disability with high incidence rates in low to middle income countries; this association may be due to socioeconomic disparities [9]. In China, the incidence of stroke incidence is greater in rural areas; this prompted the government to initiate a health campaign to mitigate risk factors and improve the care of patients with stroke [10]. The treatment of ischemic stroke primarily involves reperfusion therapies, such as intravenous

TABLE 2. Stroke-related characteristics in the END and Non-END groups.

Clinical characteristic	Total (n = 358)	Non-END (n = 300)	END (n = 58)	$t/z/\chi^2$	p
TOAST subtypes, n (%)					
LAA	179 (50.000)	137 (45.667)	42 (72.414)		
CE	22 (6.145)	17 (5.667)	5 (8.621)		
SVO	131 (36.592)	123 (41.000)	8 (13.793)	1.250	0.150
ODE	23 (6.425)	20 (6.667)	3 (5.172)		
UDE	3 (0.838)	3 (1.000)	0 (0.000)		
Cerebral circulation affected, n (%)					
Anterior circulation	206 (57.542)	173 (57.667)	33 (56.897)		
Posterior circulation	118 (32.961)	103 (34.333)	15 (25.862)	5.434	0.066
Both	34 (9.497)	24 (8.000)	10 (17.241)		
Intravenous thrombolytic therapy, n (%)	6 (1.676)	5 (1.667)	1 (1.724)	0.001	0.975
Hemorrhagic transformation, n (%)	15 (4.190)	10 (3.333)	5 (8.621)	3.385	0.066
Dual antiplatelet, n (%)	103 (28.771)	79 (26.333)	24 (41.379)	5.369	0.020
Intensive statin therapy, n (%)	157 (43.855)	125 (41.667)	32 (55.172)	3.601	0.058

LAA: large-artery atherosclerosis; CE: Cardio-embolism; SVO: Small-vessel occlusion; ODE: other determined etiology; UDE: undetermined etiology; TOAST: Trial of Org 10172 in Acute Stroke Treatment; END: Early neurological deterioration.

TABLE 3. Kendall's rank correlation analysis of END.

Variable	END	Statin use	Antithrombotic medication use	Carotid unstable plaque	Intensive statin therapy	Dual antiplatelet	Hemorrhagic transformation	Intravenous thrombolytic therapy
END	1.000*	0.087	0.047	0.328*	0.100	0.122*	0.097	0.002
Statin use	0.087	1.000*	0.593*	0.017	−0.008	0.019	−0.039	−0.024
Antithrombotic medication use	0.047	0.593*	1.000*	0.007	−0.018	−0.018	−0.060	−0.037
Carotid unstable plaque	0.328*	0.017	0.007	1.000*	0.092	0.002	0.096	−0.068
Intensive statin therapy	0.100	−0.008	−0.018	0.092	1.000*	0.309*	−0.016	−0.028
Dual antiplatelet	0.122*	0.019	−0.018	0.002	0.309*	1.000*	−0.071	−0.035
Hemorrhagic transformation	0.097	−0.039	−0.060	0.096	−0.016	−0.071	1.000*	0.299*
Intravenous thrombolytic therapy	0.002	−0.024	−0.037	−0.068	−0.028	−0.035	0.299*	1.000*

*END: Early Neurological Deterioration; *p < 0.05.*

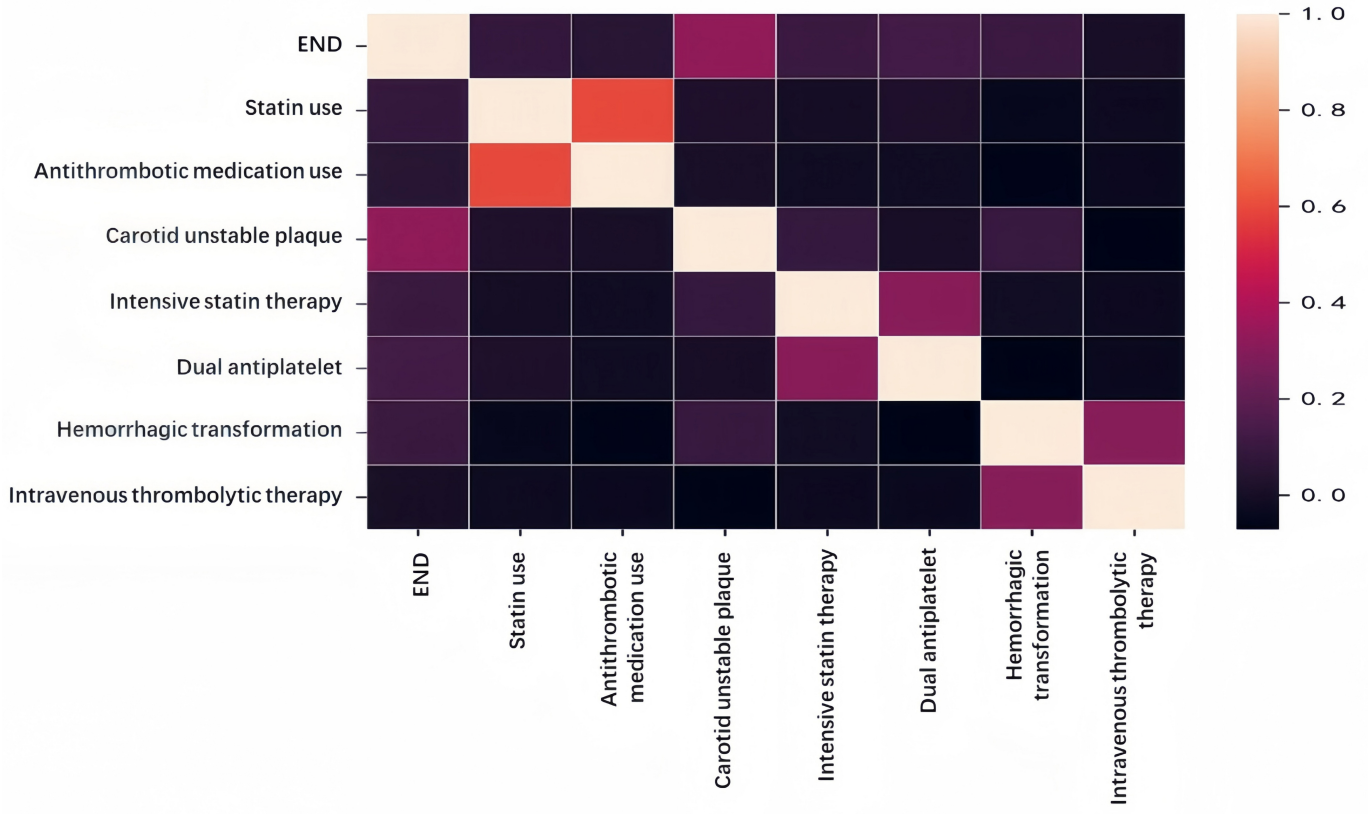

FIGURE 1. Heatmap of Kendall's rank correlation analysis of END. END: Early Neurological Deterioration.

TABLE 4. Spearman correlation analysis of END.

Variable	END	NIHSS at admission	Fibrinogen	T-CH	LDL-C	HbA1c
END	1.000*	0.208*	0.161*	0.120*	0.125*	0.140*
NIHSS at admission	0.208*	1.000*	0.015	−0.110	−0.073	−0.082
Fibrinogen	0.161*	0.015*	1.000	0.030	0.084	0.147*
T-CH	0.120*	−0.110*	0.030	1.000*	0.893*	0.127*
LDL-C	0.125*	−0.073	0.084	0.893*	1.000*	0.089
HbA1c	0.140*	−0.082	0.147*	0.127*	0.089	1.000*

*END: Early Neurological Deterioration; NIHSS: National Institutes of Health Stroke Scale; triglyceride; T-CH: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HbA1c: glycated hemoglobin; *p < 0.05.*

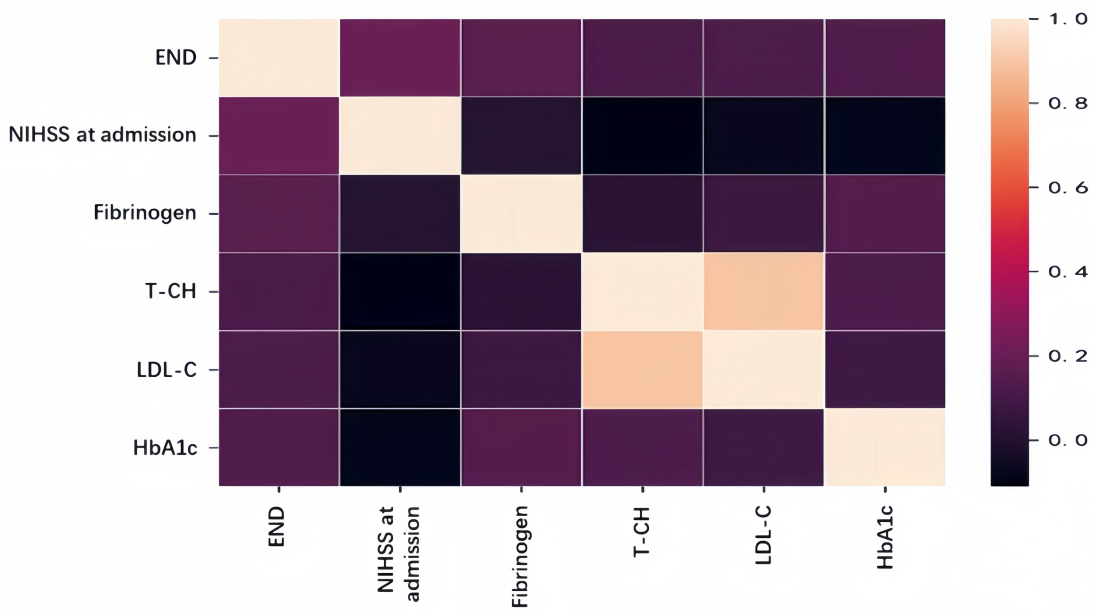

FIGURE 2. Heatmap of spearman correlation analysis of END. END: Early Neurological Deterioration; NIHSS: National Institutes of Health Stroke Scale; triglyceride; T-CH: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HbA1c: glycated hemoglobin.

TABLE 5. Multivariate logistic regression analysis of factors associated with END.

Predictor	Estimate	SE	*Z*	*p*	Odds ratio	Lower	Upper
(Intercept)	−6.422	1.036	−6.197	<0.001	0.002	<0.001	0.011
Carotid unstable plaque	1.676	0.341	4.917	<0.001	5.345	2.751	10.525
NIHSS at admission time	0.128	0.038	3.371	0.001	1.137	1.056	1.227
Dual antiplatelet	0.817	0.361	2.261	0.024	2.264	1.113	4.620
Fibrinogen	0.299	0.148	2.020	0.043	1.349	1.015	1.874
Antithrombotic medication use	0.884	0.551	1.606	0.108	2.422	0.772	6.891
LDL-C	0.580	0.383	1.513	0.130	1.786	0.851	3.861
HbA1c	0.098	0.068	1.444	0.149	1.103	0.959	1.259
Hemorrhagic transformation	0.941	0.699	1.346	0.178	2.564	0.606	9.805
Intensive statin therapy	0.333	0.351	0.950	0.342	1.395	0.702	2.790
T-CH	−0.057	0.272	−0.209	0.834	0.945	0.548	1.606
Intravenous thrombolytic therapy	0.140	1.265	0.111	0.912	1.150	0.049	10.264

NIHSS: National Institutes of Health Stroke Scale; LDL-C: low-density lipoprotein cholesterol; HbA1c: glycated hemoglobin; T-CH: total cholesterol; SE: Standard Error.

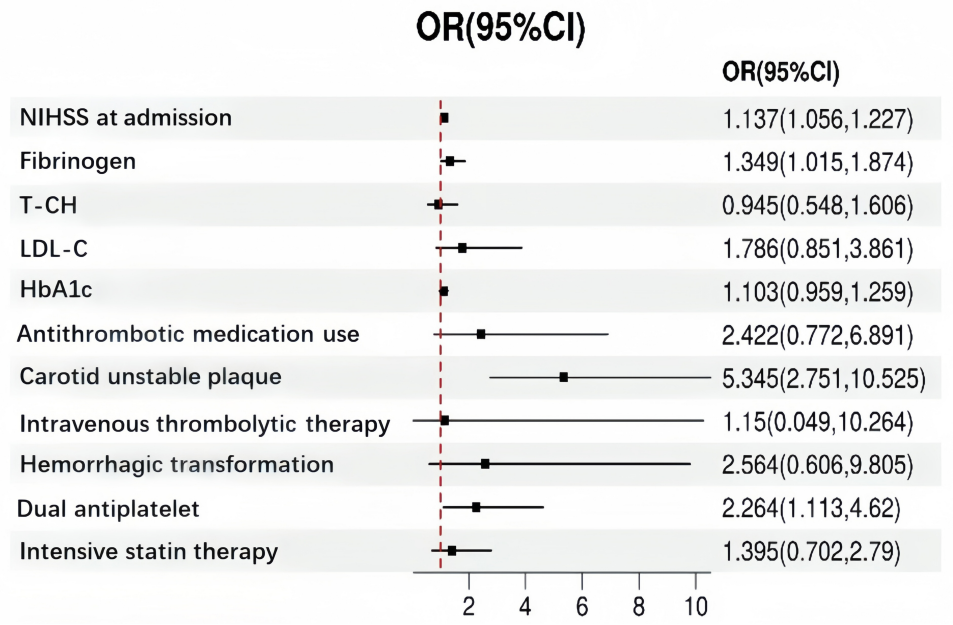

FIGURE 3. Forest plot related to END. NIHSS: National Institutes of Health Stroke Scale; LDL-C: low-density lipoprotein cholesterol; HbA1c: glycated hemoglobin; T-CH: total cholesterol; OR: odds ratio; CI: confidence interval.

TABLE 6. Receiver operating characteristic (ROC) curve analysis of factors to predict END.

Variable	AUC	Sensitivity	Specificity	Youden's index	Cutoff
NIHSS at admission time	0.661	0.621	0.630	0.251	4.000
Carotid unstable plaque	0.682	0.517	0.847	0.364	1.000
Fibrinogen	0.626	0.379	0.817	0.196	3.620
Dual antiplatelet	0.575	0.414	0.737	0.150	1.000
Regression model	0.802	0.862	0.853	0.475	0.147

AUC: area under curve; NIHSS: National Institutes of Health Stroke Scale.

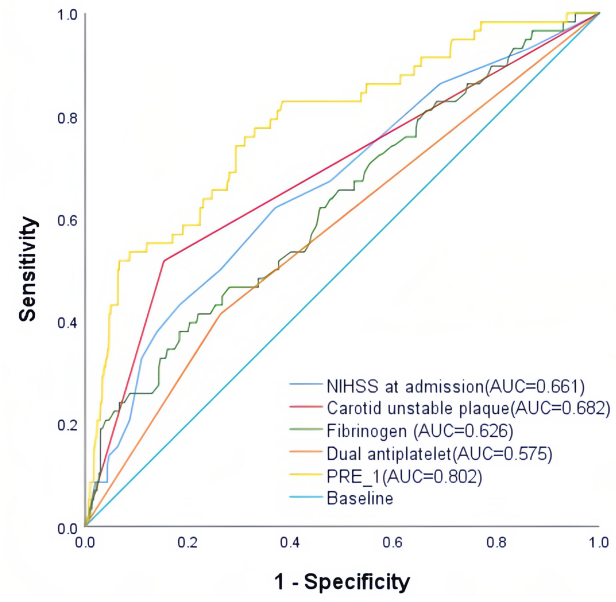

FIGURE 4. ROC curve for END. AUC: area under curve; NIHSS: National Institutes of Health Stroke Scale; PRE: Predicted Probability.

thrombolysis and mechanical thrombectomy [11]. However, the efficacy of these treatments is limited by the small therapeutic window, the risk of hemorrhagic transformation, and variations in the etiology of stroke. END represents a decline in neurological status and leads to poorer health outcomes and a higher mortality after stroke. The strategies used to prevent END include hemodynamic optimization, blood glucose control, and monitoring for signs of deterioration [12].

The pathophysiology of END is highly complex and may include infarct expansion, cerebral edema, hemorrhagic transformation and embolic occlusion. Inflammation, as demonstrated by numerous markers, including interleukin (IL)-6 and C-reactive protein (CRP), also plays a vital role in END and has been associated with lethal outcomes [13, 14]. The complexity of stroke pathology and patient variability has hindered the efficient prognosis of END and there are clear gaps in our understanding of the factors that trigger and mediate this condition [15]. In the present study, it was interesting to note that 23 patients presented with ischemic stroke of other determined etiology while only three of these patients presented with END. As hematological disorder is the most frequent etiology for acute strokes of other determined etiology [16], it is possible that in these cases, acute stroke could be the presenting manifestation of a hematological disorder.

The challenges associated with current research include the rapid identification of high-risk patients for developing preventative and mitigating strategies for END and standardizing the criteria used to identify neurological deterioration. Unstable carotid artery plaques are known to significantly enhance the risk of END due to their propensity to rupture, thus causing thromboembolism and exacerbating ischemia [17]. High-grade stenosis from unstable plaques is correlated with higher NIHSS scores and an increased risk of neurological deterioration. Systemic factors, such as high levels of fibrinogen, dyslipidemia, and poor glycemic control, can exacerbate plaque instability, thus highlighting the importance of managing these risk factors to prevent END and improve the outcomes of stroke [12]. The results of the present study indicate that patients with severe initial neurological problems, greater levels of inflammation/vascular injury, and poor lipid and glycemic control profiles, had a higher risk of early neurological deterioration.

The NIHSS score at the time of admission is a vital prognostic tool for the detection of END in patients with acute ischemic stroke; this score quantifies neurological deficits. Higher NIHSS scores indicate more severe impairment and larger infarct volumes; these scores are known to be correlated with an increased risk of END. Research has shown that END may arise from infarct expansion, cerebral edema, hemorrhagic transformation or new ischemic events. Severe initial strokes often involve larger artery occlusions, and more brain tissues are at risk, making them more susceptible to further damage due to collateral circulation failure or hemodynamic instability. High NIHSS scores also indicate a risk of complications, such as aspiration pneumonia, which can further exacerbate the poor neurological status. Early recognition of high NIHSS scores is necessary for the rapid treatment and monitoring for END as early intervention may improve long-term outcomes [18].

High levels of fibrinogen, LDL-C and HbA1c at the time of admission were also found to be associated with END. Fibrinogen plays a vital role in blood coagulation and is associated with thrombogenesis and inflammation. Elevated levels of fibrinogen can increase the risk of END, thus indicating an acute-phase reaction and increasing the risk of further thrombotic events. LDL-C (a known risk factor for atherosclerosis) plays a complex role in stroke. Paradoxically, low levels of LDL-C at the time of admission can lead to poorer outcomes. This may be due to the membrane-stabilizing and anti-inflammatory effects of cholesterol which can increase the vulnerability of neurons to ischemic damage [19]. These findings highlight the importance of management these levels in the prevention of END and improving the outcomes of patients with stroke.

HbA1c levels are linked to larger infarct sizes and poor outcomes in AIS [20]. High HbA1c levels (indicating poor glycemic control) can worsen ischemic brain damage by increasing oxidative stress, damaging the blood-brain barrier, and by promoting inflammation [21]. Thus, elevated HbA1c levels can increase the risk of END. Elevated levels of fibrinogen, abnormal LDL-C levels, and high HbA1c levels, are all associated with an elevated risk of END. These conditions can exacerbate ischemic injury, thus increasing neurological decline; these findings highlight the importance of managing these factors to prevent END and improve prognosis.

In the present study, we found that TOAST subtypes, infarct locations, alteplase thrombolysis and intensive statin therapy, may not be associated with the development of END. In contrast, previous research identified an association between TOAST subtypes and END, especially large-artery atherosclerosis and small-vessel occlusion [22]. The role of intravenous thrombolysis in reducing the risk of END is well-known, with alteplase representing the standard form of care.

The observation of higher rates of END in patients receiving DAPT questions its role in the management of acute stroke. In this study, we used the American Heart Association/American Stroke Association (AHA/ASA) guidelines for reference when treating our patients. Therefore, patients with minor non-cardioembolic ischemic stroke (NIHSS score $\leq$3) were treated with DAPT. However, even though there were similar stroke types and severities between the two patient groups, there was a difference between the two groups in terms of DAPT use. We consider this to be due to the individual judgment of clinicians who may have considered patients in the END group at a higher risk of recurrent ischemia. It is possible that the increased use of DAPT in the END group might be related to the risk of recurrent stroke or previous minor strokes or transient ischemic attacks (TIAs) [23]. However, current guidelines support the use of DAPT, and as a retrospective study, the results presented herein cannot be assumed to show any cause and effect. Previous studies have suggested that DAPT, or DAPT in combination with argatroban, are effective in preventing END [24, 25]. Therefore, the efficacy of DAPT in preventing END and other confounding factors may warrant further investigation [26].

In the present study, we confirmed that a high NIHSS score at the time of admission, and the presence of unstable carotid plaques, are independent and important risk factors for END, thus suggesting the need to develop targeted therapeutic strategies for the management of stroke. Unstable carotid plaques

are characterized by specific structures, including a thin fibrous cap and a large lipid core. These structures are susceptible to rupture, a process that can lead to cerebral ischemic events, thus increasing the risk of END. Imaging these carotid plaques by CT scanning or MRI may help to predict the risk of END and can also facilitate clinical decision making in the management of END, including aggressive interventions [27].

ROC analysis is an effective technique and demonstrated that the factors identified herein lack standalone predictive value. DAPT is often used for stroke prevention; however, this practice may not be able to predict END reliably due to patient variability and the balance between benefits and risks. Hemorrhagic transformation after ischemic stroke can lead to END but is influenced by multiple factors which can reduce its predictive ability [28]. Elevated levels of fibrinogen are linked to an increased risk of stroke although its specificity for predicting END can be reduced by a range of influencing factors [29, 30].

Dyslipidemia is characterized by high levels of total cholesterol (T-CH) and LDL-C and represents a recognized risk factor for atherosclerosis and cardiovascular diseases [31]. Despite the important role of dyslipidemia in the development of ischemic stroke, its specific influence on END is less evident. This may be because the impact of dyslipidemia on stroke is chronic rather than an immediate risk factor for END. Similarly, high HbA1c levels can lead to lethal outcomes in stroke patients but may not acutely predict END; this is because HbA1c levels do not reflect short-term glucose variations which are more relevant during the acute phase of stroke [32].

The low predictive value of these factors, as proven by our ROC analysis, suggests that they will not be effective as sole prognostic factors for END. However, their association with END indicates their potential value in a multifactorial model, as indicated by our regression model. Future research should be conducted to create comprehensive algorithms that combine clinical, laboratory and imaging data to yield a better prediction value for END in patients with ischemic stroke.

The key limitations of our study are potential selection and information biases due to its retrospective nature and single-center design. Other key limitations are a small sample size that may lack statistical power, and the use of clinical and laboratory data only from the time of admission without considering changes during hospitalization. Furthermore, we did not compare certain key factors between groups, such as the modified Rankin score. Prospective studies with larger cohorts and repeated measurements of laboratory indices are now needed to improve the prediction of END in patients with acute ischemic stroke.

5. Conclusions

Our analysis of AIS patients who developed END identified that a higher NIHSS score at the time of admission, and unstable carotid plaques, may be related to the risk of END. We used this information to construct a regression model which suggested that this data may help to predict and prevent END in patients with AIS. Our findings should be investigated further in larger scale studies. Further studies are also required to characterize the mechanisms underlying the development of END in patients with AIS and to identify ideal management strategies for patients with END.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are not publicly available because of information that could compromise the privacy of research participants, but they are available from the corresponding author.

AUTHOR CONTRIBUTIONS

LZ—Study concept and design. XDL, KKF, YMC, QF and CHL—Acquisition of data. JJL—wrote the first draft of the manuscript, statistical analysis. All authors analyze or interpret of data. All authors critically revised the manuscript for intellectual content.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Ethics Committee of the Fifth Affiliated Hospital of Sun Yat-Sen University (K157-1). The requirement for individual consent was waived by the committee owing to the retrospective nature of the study. All procedures performed in this study involving human participants were in accordance with the ethical standards of The Fifth Affiliated Hospital of Sun Yat-sen University committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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