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Research on Predictive Factors of Early Neurological Deterioration of Stroke Related to Branch Atheromatous Disease

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Abstract: ***Strokes related to acute branch atherosclerosis (BAD) account for 10% to 15% of all causes of ischemic stroke. Clinically, it is mostly manifested as early neurological deterioration (END) mainly due to the lack of motor function. It mostly occurs in 48~72h, and the clinical prognosis is poor. It is reported that the incidence of END in BAD-related stroke is as high as 17% to 75%. However, the definition of END lacks consistency in different studies: but most studies are based on the definition of clinical deterioration. In order to solve this scientific problem, we conducted a prospective cohort study at Xianyang Hospital of Yan'an University to investigate the predictive factors of early neurological deterioration in BAD-related stroke. This study is a single-center, observational prospective cohort study. This prospective study continuously included all BAD-related stroke patients in neurology of Xianyang Hospital of Yan'an University from August 2024 to August 2025. According to the criteria for the selection and exclusion of clinical research subjects, the eligible patients were divided into END group and non-END group according to whether early neurological dysfunction deterioration occurred. A total of 554 stroke patients were included in this retrospective study, of which the non-END group accounted for 429 cases and the END group accounted for 125 cases. The main purpose of the study is to explore the predictors of early neurological deterioration in BAD-related stroke.***

Keywords: Acute ischemic stroke, Branch atherosclerosis, Vascular risk factors, Early neurological deterioration**.**

1. Introduction

Acute Ischemic Stroke (AIS) poses a serious challenge in the global public health with its high incidence, high disability rate and high mortality rate [1-3]. Acute ischemic stroke is the most common type of stroke, accounting for 69.6%-72.8% of the new trokes in China [4]. Among the many etiological types of AIS, Branch Atheromatous Disease (BAD), as a special and important pathogenesis, has attracted increasing attention from the neurological community [5]. BAD specifically refers to the branch-passing artery that originates from the middle artery of the brain, the anterior cerebral artery, the basal artery and other large intracranial blood vessels [6]. Atherosclerotic plaques occur at the opening or at the proximal end, thus directly blocking a single deep branching artery, leading to infarction of its blood supply areas - such as the basal gangl region, the pons and other deep structures of the brain [7]. This kind of stroke is often manifested as a classic interstitial infarction foci in imaging, and the clinical manifestations are mostly pure motor mild hemiplegia and sensory motor stroke medium interstitial syndrome [8-10]. Stroke caused by BAD has a unique malignant clinical process that cannot be ignored [11]. Within 48 hours to 1 week after the onset of the disease, a considerable number of patients, despite receiving standardized antiplatelet, statin stabilized plaques and other basic treatments, their neurological defects still showed progressive aggravation, that is, early neurological Deteriorioration occurred (Early Neurological Deterior Ation, END) [12], which eventually leads to more serious disability, longer hospitalization time and poorer long-term functional independence, which greatly offsets the benefits of acute treatment and aggravates the social and economic burden [13].

In recent years, although research on post-AIS END predictors has been emerging, most of them focus on large blood vessel occlusion or mixed stroke, and in-depth research on the specific pathophysiological subtype of BAD is still lacking and the conclusions are inconsistent [14]. Existing exploratory studies suggest some possible predictive clues: in terms of clinical indicators, high NIHSS score at admission [15], blood pressure fluctuation pattern after admission [10], blood sugar level, inflammatory markers [16] etc. are of concern; in imaging standards In terms of Zhi, the specific infarction form presented on magnetic resonance diffuse weighted imaging (DWI) [17], large infarction volume [18], involvement of key nerve conduction bundles [14], and the plaque characteristics at the opening of the branch artery shown by high-resolution magnetic resonance vascular wall imaging [19], etc., are considered to be related to END risk. However, most of these studies are single-center, small-sample retrospective analysis [20]. The independent predictive value of each factor is not clear, and it has failed to integrate clinical, laboratory and multimodal imaging information to build a prediction model with high discrimination effectiveness. This situation makes it difficult for clinicians to carry out accurate risk stratification when facing BAD patients, so that they cannot carry out closer monitoring and more active individualized intervention for high-risk patients [21].

Therefore, it has important theoretical value and clinical urgency to systematically explore the independent predictive factors of END after BAD-related acute stroke [22]. This study aims to screen out key predictors related to END after BAD independently through a prospective cohort study design. It is expected to provide a more objective and comprehensive evaluation framework for the early clinical identification of END high-risk patients, lay the foundation for the future development of clinical prediction models, and finally promote the individualized and refined medical management

of BAD patients, improve their clinical prognosis, and reduce the burden of disease.

2. Study Design and Participants

In brief, the BAD-study was a prospective, observational cohort study between August 2024 and August 2025 at Xianyang Hospital of Yan'an University. Only patients aged 18 to 80 years with BAD-related stroke within 72 hours after onset and meeting all the following radiological criteria were enrolled: (1) diffusion-weighted imaging lesion: single (isolated) deep (subcortical) infarct; (2)the culprit vessels were LSA or PPA, and the infarct lesion on diffusion-weighted imaging conformed to one of the following characteristics (A/B): (A) LSA: comma-like infarct lesions with fan-shaped extension from bottom to top in the coronal plane or ≥3 layers on axial diffusion-weighted imaging and (B) PPA: the infarct lesion extended from the deepons to the ventral pons on the axial diffusion-weighted imaging; and (3) no ≥50% stenosis on the parent artery of the criminal vessel. The main exclusion criteria included: (1) intracranial hemorrhagic diseases, vascular malformations, aneurysms, brain abscesses, malignant space-occupying lesions, or other nonischemic intracranial lesions at baseline; (2) ≥50% stenosis of extracranial vessels with ipsilateral serial relationship; (3) cardiogenic embolism; and (4) stroke caused by other clear causes. Patients underwent brain MRI and intracranial and extracranial vascular examination to confirm radiological criteria for BAD-related stroke, especially distinguishing it from cerebral small vessel disease (Table S1). The BAD-study was approved by the Xianyang Hospital of Yan'an University.

3. Clinical Data Collection and Outcome

3.1 Assessment

Data on demographics, medical history, clinical presentation, National Institutes of Health Stroke Scale (NIHSS) scores, modified Rankin Scale (mRS) scores, laboratory parameters were prospectively collected at baseline. The acute phase indicated time from onset to 7 days of enrollment. In addition, the stenosis of intracranial and extracranial arteries was recorded.

The END was defined as follows: (1) from symptom onset to 7 days after enrollment and (2) Occurrence of deterioration of neurological deficits after initial assessment: an increase of the NIHSS score ≥4 points or NIHSS motor score ≥1 point for ischemic stroke patients.

3.2 Statistical Analysis

Use SAS 9.4 statistical software for data analysis. The counting data is expressed by frequency and percentage (%), and the χ^2 test or Fisher precision test is used for comparison between groups. The normality of the measurement data is tested first. Those who meet the normal distribution are represented by the mean ± standard deviation, and the t test is adopted; those who do not meet the normal distribution are represented by the median (quartile spacing) and the Wilcoxon rank sum test is adopted. First, select the variables with statistically significant ($P<0.05$) differences between groups through single-factor analysis, and include them in Lasso regression to further reduce the dimension and avoid multiple collinearity. The effective variables selected by Lasso regression are included in the multi-factor logistic regression model, and the independent risk factors of early neurological deterioration (END) in BAD-related stroke are analyzed step by step, and the advantage ratio (OR) and its 95% confidence interval (CI) are calculated. The difference of $P<0.05$ is statistically significant.

4. Results

4.1 Demographic and Clinical Characteristics

Of 812 patients with BAD-related stroke within 72 hours of onset, 258 were excluded based on age, MRI examination, and other criteria, resulting in a final cohort of 554 eligible patients.

For the patient's age, gender, hypertension, diabetes, coronary heart disease, smoking history, alcohol history, affected blood vessels, NIHSS score at admission, MRS score at admission, systolic pressure at admission, diastolic pressure at admission, stroke status, symptom type, blood sugar, white blood cells, monocytes, neutrophils, Lymphocytes, platelets, MPV, triglycerides, total cholesterol, LDL, uric acid, creatinine, uric acid/creatinine, HCY, prothrombin time, fibrinogen content, TAT, PIC, t-PAIC, TM, D-2 polymer, FDP, a total of 36 factors are analyzed for single-factor analysis. Research results show that gender, hypertension, diabetes, smoking history, drinking history, NIHSS score at the time of admission, MRS score at the time of admission, systolic pressure at the time of admission, rest when stroke occurs and stroke after waking up, the type of symptoms is simple exercise symptoms and other symptoms, blood sugar, white blood cells, neutrophils, The difference in the incidence of END under the grouping of total cholesterol, LDL, PIC, D-2 polymer and FDP 18 factors is statistically significant ($P<0.05$); while age, coronary heart disease, diastolic pressure at the time of admission, stroke is motor state, symptom type is simple sensory symptoms and motor sensory symptoms. , mononuclear cells, lymphocytes, platelets, MPV, triglycerides, uric acid, creatinine, uric acid/creatinine, HCY, thrombin time, fibrinogen content, TAT, t-PAIC, the difference in the incidence of END under TM grouping is not statistically significant ($P> 0.05$) (Table 1).

Table 1: Univariate analysis results of the risk of early neurological deterioration in acute BAD-related stroke

Variable	Non-END (N = 429)	END (N = 125)	Statisticst/x2	P value
Age, median	65(57-72)	64(58-73)	0.685	0.492
Gender, n (%)				
Male	305(71.1%)	83(66.4%)	4.300	0.041
Female	124(28.9%)	42(33.6%)		
Hypertension	265(61.8%)	93(74.4%)	32.128	0.000
Diabetes, n (%)	97(22.6%)	49(39.2%)	65.566	0.000
Coronary heart disease, n (%)	53(12.4%)	18(14.4%)	2.687	0.101
Smoking, n (%)	268(62.5%)	76(60.8%)	43.501	0.000
Drink alcohol	161(37.5%)	5(4.0%)	104.474	0.000
Blood vessels				
LSA, n (%)	93(21.7%)	23(18.4%)	1.264	0.261
PPA, n (%)	312(72.5%)	102(81.6%)	2.926	0.087
NHISS, (IQR)	4(2-6)	5(3-8)	2.601	0.010
MRS, (IQR)	3(2-3)	3(3-4)	3.592	0.000
Systolic pressure mmHg	151(136-167)	156(146-169)	2.32	0.021
Diastolic pressure mmHg	88(78-97)	86(78-96)	-0.599	0.550
Stroke currednce status				
Rest	352(82.1%)	105(84.0%)	10.309	0.001
Exercise	13(3.0%)	4(3.2%)	0.736	0.391
Waking up	55(12.8%)	15(12%)	12.738	0.000
Symptom type				
Pure motor symptoms	159(37.1%)	53(42.4%)	4.622	0.032
Pure sensory symptoms	21(4.9%)	3(2.4%)	1.195	0.274
Motor sensory symptoms	167(38.9%)	57(45.6%)	0.045	0.832
Other symptoms	82(19.1%)	12(9.6%)	158.957	0.000
Laboratory ndicators				
Blood glucose mmol/L	5.6(4.87-7.62)	6.93(5.55-8.93)	2.620	0.009
WBC, median	6.6(5.58-7.71)	7.00(5.87-8.42)	2.321	0.021
Monocyte, median	0.42(0.33-0.51)	0.36(0.29-0.47)	-0.894	0.372
Neutrophil, median	4.32(3.41-5.64)	4.96(3.90-5.91)	8.065	0.002
Lymphocyte, median	1.5(1.09-1.89)	1.3(1.03-1.80)	1.919	0.056
Platelet	192(159-237)	192(165-237)	-0.134	0.894
MPV, median	10.5(9.8-11.5)	10.4(9.7-11.3)	-0.653	0.514
Triglyceride, mmol/L, median	1.35(1.06-1.84)	1.57(1.04-2.03)	1.585	0.114
TC,mmol/L, median	3.98(3.35-4.73)	4.36(3.73-5.09)	2.561	0.011
LDL mmol/L	2.35(1.82-2.83)	2.56(2.08-2.98)	2.348	0.019
Uric Acid, median (IQR)	273(225-326)	281(218-346)	0.860	0.390
Creatinine, median (IQR)	70.6(63.5-84.2)	69.8(59.0-83.0)	-0.555	0.579
UA/Creatinine, (IQR)	3.74(3.17-4.5)	3.89(3.15-4.8)	1.862	0.063
HCY, median (IQR)	16.22(11.33-24.75)	17.19(11.89-24.92)	0.888	0.375
PT, median	10.9(10.4-11.4)	11(10.4-11.4)	-0.656	0.512
Fibrinogen content, median	2.59(2.23-3.09)	2.62(2.23-3.14)	-0.271	0.786
TAT, median	4.67(2.99-7.71)	5.84(4.19-9.90)	1.207	0.229
PIC, median	0.52(0.38-0.72)	0.56(0.45-0.79)	2.083	0.039
t-PAIC, median	7.55(5.57-9.78)	7.84(4.91-9.30)	-0.964	0.337
TM, median	9.2(7.66-10.54)	9.21(7.75-11.08)	0.893	0.374
D-2, median	0.33(0.19-0.50)	0.29(0.18-0.50)	2.364	0.018
FDP, median	1.92(1.30-2.50)	1.84(1.33-2.50)	2.078	0.038

LDL: Low-Density Lipoprotein; TAT: thrombin antithrombin complex; PIC: plasmin-α2-plasmininhibitor complex; t-PAIC: tissue plasminogen activator-plasminogen activator inhibitor-1 complex; TM: thrombomodulin; FDP: Fibrin Degradation Products.

4.2 Lasso Regression

Based on the classification and grouping characteristics of the research subjects as the dependent variable, a univariate analysis was first conducted. The variables with statistically significant differences after the univariate analysis were included in the multivariate Lasso regression analysis to screen for effective variables. The results showed that there were statistically significant differences in the incidence of END among the 18 groups of factors, including gender, hypertension, diabetes, smoking history, drinking history, NIHSS score at admission, MRS score at admission, systolic blood pressure at admission, stroke occurring at rest and wake-up stroke, symptom type being pure motor symptoms and other symptoms, blood glucose, white blood cells, neutrophils, total cholesterol, LDL, PIC, D-dimer, and FDP ($P < 0.05$). The results indicated that hypertension, diabetes, smoking history, MRS score at admission, systolic blood pressure at admission, blood glucose, white blood cells, neutrophils, total cholesterol, and PIC were the 10 effective

indicators obtained after Lasso regression analysis, as shown in the following figures (Figures 2 and 3).

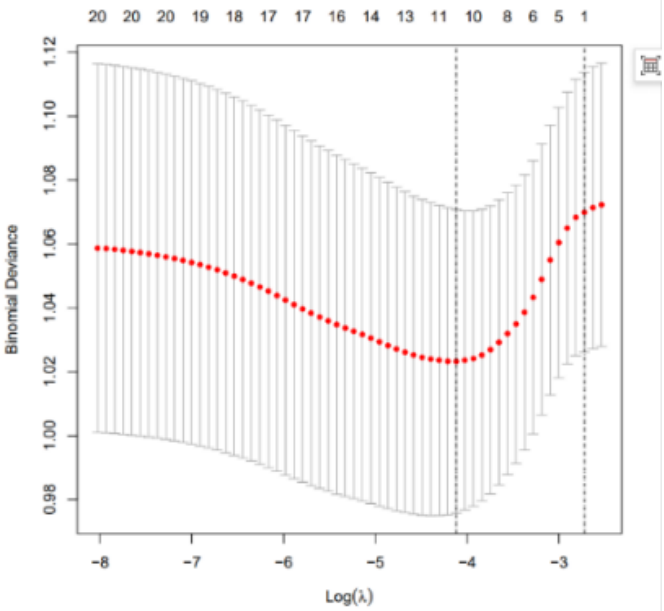

Figure 2: Lasso's coefficient roadmap

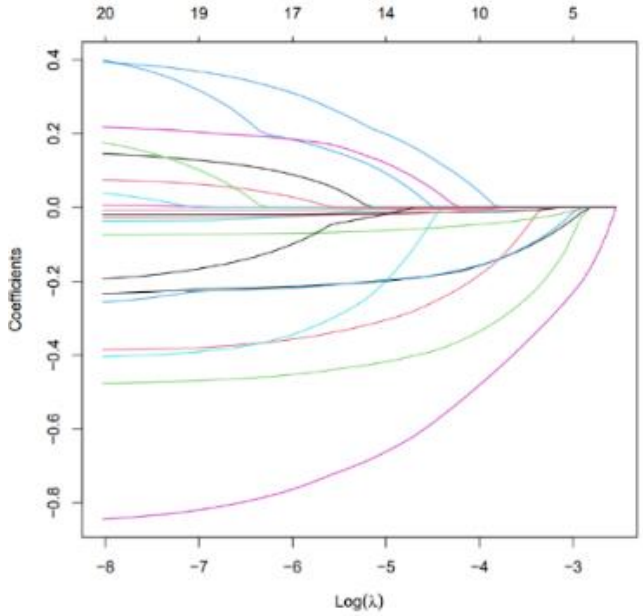

Figure 3: Cross-verification curve of Lasso

4.3 Multivariate Logistic Regression Analysis

Based on the classification and grouping characteristics of the research subjects as the dependent variable, univariate analysis was conducted first. The variables with statistical differences after univariate analysis were included in the Lasso regression analysis to obtain the effective variables and then perform multivariate Logistic regression analysis. The results showed that the MRS score at admission (OR = 1.276, 95% CI 1.029 - 1.583, P = 0.027), total cholesterol (OR = 1.256, 95% CI 1.011 - 1.559, P = 0.039), and PIC (OR = 2.309, 95% CI 1.250 - 4.265, P = 0.008) were three independent risk factors for early neurological deterioration in acute BAD-related stroke (P < 0.05) (Table 2 and Figure 3).

Table 2: Multivariate Logistic Regression Analysis of Early Neurological Deterioration Risk in Acute BAD-Related Stroke

Variable	Regression coefficient	Standard error	Wald value	P value	OR value
Hypertension	0.383	0.248	2.387	0.122	1.466
Diabetes	0.482	0.260	3.426	0.064	1.619
Smoking	0.284	0.240	1.398	0.237	1.253
MRS	0.244	0.110	4.913	0.027	1.276
Systolic pressure	0.006	0.005	1.457	0.227	1.006
Blood glucose	0.015	0.036	0.181	0.670	1.015
WBC	0.024	0.043	0.293	0.588	1.024
Neutrophil	0.075	0.039	3.640	0.056	1.078
TC	0.228	0.110	4.256	0.039	1.256
PIC	0.837	0.313	7.148	0.008	2.309

5. Discussion

Atherosclerotic disease of the perforating arteries, as a specific type of ischemic stroke, is clinically significant not only due to its high incidence rate, but also because it is prone to early neurological deterioration (END) during the course of the disease, leading to poor prognosis. This study, through a prospective cohort design, systematically analyzed the predictive factors for END in patients with BAD-related acute stroke. The results showed that the modified Rankin Scale (mRS) score at admission, total cholesterol (TC), and plasmin-α2 plasmin inhibitor complex (PIC) were independent risk factors for END in BAD-related stroke.

Compared with previous studies, previous research on END in BAD-related stroke mostly focused on clinical factors [25] and imaging features. This study also found in the univariate analysis that factors such as hypertension, diabetes, smoking, NIHSS score at admission, blood sugar, white blood cells, neutrophils, LDL, D-dimer, and FDP were related to END, but after Lasso regression and multivariate Logistic regression screening, only the mRS score, TC, and PIC remained as independent risk factors. This result suggests that traditional risk factors may have interactions or collinearity in the BAD population, and the introduction of fibrin markers provides a new dimension for END prediction. It is worth noting that in the univariate analysis of this study, smoking and drinking were shown to be "protective" factors (the proportion of smoking and drinking in the END group was lower than that in the non-END group), which may be related to selection bias, reverse causality, or confounding factors, and should be interpreted with caution. Smoking and drinking, as known vascular risk factors, theoretically should increase the risk of END. The results of this study may be related to data collection, patient self-reporting bias, or group imbalance, and need to be further verified in subsequent studies.

The innovation of this study mainly lies in the following aspects: First, focusing on BAD as a specific etiological type, avoiding the interference of confounding etiologies on END predictive factors; Second, using a prospective cohort design, with standardized data collection and unified outcome assessment criteria; Third, introducing the thrombus molecular marker PIC, which for the first time confirmed its

independent association with BAD-END; Fourth, combining Lasso regression and multivariate Logistic regression to screen out the most predictive indicators, improving the stability and interpretability of the model.

At the same time, this study also has the following limitations: 1. Single-center design: The study only included patients from one hospital, which may have selection bias and limit the generalizability of the results. Future multi-center studies are needed to verify the universality of the conclusion. 2. Imaging data not included in the analysis: This study did not systematically collect imaging indicators such as HR-MRI, DWI-ASPECTS, and collateral circulation score, and these factors may have important predictive value in BAD-END. Future research should combine imaging genomics and biomarkers to construct a multi-dimensional prediction model. 4. The timing of PIC detection was not standardized: PIC as a dynamically changing biomarker, a single detection may not fully reflect the dynamic process of thrombus formation and dissolution. Further research should explore the relationship between the dynamic changes of PIC and END.

Based on the results of this study, future research can explore the following directions in depth: Establishing a multi-dimensional prediction model: Integrating clinical indicators, thrombus molecular markers, and imaging features to construct an early warning model for BAD-END, achieving individualized risk stratification. Exploring the dynamic changes of PIC: Conducting multi-point monitoring studies to clarify the time relationship between PIC elevation and thrombus progression and END occurrence, and exploring its possibility as a therapeutic target. 3. Conduct intervention studies: For high-risk populations (such as those with high mRS score, high TC level, and high PIC level), design randomized controlled trials to evaluate the effectiveness and safety of strategies such as intensified antiplatelet therapy, intensified statin therapy, and anticoagulation in preventing END.

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