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ORIGINAL ARTICLE

Clinical prediction model for early neurological deterioration in patients with mild nondisabling ischemic stroke within 4.5 hours of onset

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ABSTRACT

Objectives: This study aimed to develop a clinical prediction model of early neurologic deterioration in patients with acute mild nondisabling ischemic stroke within 4.5 h of onset.

Patients and methods: In this prospective cohort study, patients with mild nondisabling ischemic stroke who were admitted within 4.5 h of onset between January 1, 2023, and December 31, 2024, were divided into the early neurologic deterioration group and the nonearly neurologic deterioration group based on the NIHSS (National Institutes of Health Stroke Scale) score within 72 h. The clinical data and imaging data of the patients during their emergency visits were collected. A clinical prediction model of early neurologic deterioration was established. Discrimination, calibration, and the net benefit of the model were assessed.

Results: A total of 489 patients were included, of which 422 were in the nonearly neurologic deterioration group and 67 were in the early neurologic deterioration group. Binary Logistic regression analysis showed that systolic blood pressure (odds ratio [OR] = 1.017, p = 0.012), onset-to-treatment time (OR = 1.473), the neutrophil/lymphocyte ratio (OR = 1.017), random blood glucose level (OR = 1.103), number of lesions (OR = 1.480), and vascular stenosis (OR = 1.879) were independent risk factors for early neurologic deterioration ($p < 0.05$). The area under the receiver operating characteristic curve of the model was 0.754 (95% confidence interval 0.692–0.816, $p < 0.001$). The prediction accuracy of the model was 87.3%. Hosmer-Lemeshow test yielded a chi-squared value of 4.313 (p = 0.828). The clinical decision cure of the model was higher than the two extreme lines.

Conclusion: Onset-to-treatment time, vascular stenosis, number of new lesions, random blood glucose level, systolic blood pressure, and the neutrophil-to-lymphocyte ratio were independent risk factors for early neurologic deterioration. We developed a simple model for predicting early neurologic deterioration of acute mild nondisabling ischemic stroke within 72 h.

Keywords: Acute phase, clinical prediction model, early neurological deterioration, mild nondisabling ischemic stroke.

Mild ischemic stroke (MIS) accounts for more than half of all acute ischemic strokes (AISs).[1,2] Data from the third China Stroke Registry (CNSR-III) show that patients with MIS account for approximately 51.7 to 65% of all ischemic cerebrovascular events.[3] Due to the relatively mild clinical manifestations of MIS and the low score of the National Institutes of Health Stroke Scale (NIHSS), the traditional concept often classifies MIS as a disease with quick recovery and good prognosis. In the treatment decision-making process of MIS, "whether it leads to disability" is the primary consideration factor. The majority of MIS cases (67%) are nondisabling. In the PRISMS (Rt-PA for Ischemic Stroke With Mild Symptoms trial),[4] ARAMIS (Antiplatelet *vs.* rt-PA for Acute Mild Ischemic Stroke trial),[5] and TEMPO-2 (Tenecteplase Versus Standard of Care for Minor Ischemic Stroke with Proven Occlusion)[6] studies, for patients with acute mild nondisabling ischemic stroke (MNDIS), compared with antiplatelet therapy, intravenous thrombolysis

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treatment did not significantly improve the prognosis of the patients. Current guidelines suggest that patients with mild disabling stroke should receive intravenous thrombolytic therapy within 4.5 h after the onset. According to the current guidelines, intravenous thrombolytic therapy is not recommended for patients with MNDIS.[1] However, 10 to 20% of patients with MIS experience early neurologic deterioration (END),[7] and approximately 30% of them still have varying degrees of disability after 90 days.[8] Therefore, it is of vital importance to conduct early risk stratification for MNDIS patients, accurately identify patients with END, and take timely and effective intervention measures. In view of this, there is an urgent need for more clinical data and precise screening tools to predict the patients that are more likely to develop END. However, conducting adequate disease assessments can lead to a delay in treatment time, which is contrary to the treatment principle of "time is brain." This study aimed to utilize the clinical data collected in the emergency department and develop a clinical prediction model (CPM) of END within 72 h in patients with acute MNDIS within 4.5 h of onset.

PATIENTS AND METHODS

Patients with MNDIS within 4.5 h of onset who were admitted to the Neurology Department of Tangshan Gongren Hospital between January 1, 2023, and December 31, 2024, were included in the prospective cohort study. Patients with MNDIS were required to have an NIHSS score ≤5, with each individual subitem scored ≤1 (and a consciousness score of 0), and to have none of the following conditions: complete hemiopia, severe aphasia, loss of vision or sensation, inability of limbs to resist gravity, and other functional deficits that the patient and attending physician could consider to cause disability. Other inclusion criteria were as follows: (1) patients with a previous history of ischemic stroke, but with a modified Rankin Scale score of 0–1; (2) presentation within 4.5 h of onset; (3) age ≥ 18 years old. The exclusion criteria were as follows: (1) patients who underwent intravenous thrombolysis or endovascular treatment; (2) patients with cerebrovascular malformations, arterial dissection, or tumors; (3) those currently undergoing heparin treatment or oral anticoagulant therapy; (4) those with contraindications for magnetic resonance imaging (MRI); (5) patients with heart, lung, liver, or kidney failure or abnormal coagulation function; (6) patients with hemorrhage after infarction. A written informed consent was obtained from each patient. This study was approved by the Tangshan Workers' Hospital Ethics Committee (Date: 17.06.2022, No: GRYY-LL-KJ2022-030) The study was conducted in accordance with the principles of the Declaration of Helsinki.

According to the change in the NIHSS score within 72 h of admission, the patients were divided into the non-END and the END group. Early neurological deterioration was defined as one of the following criteria: *(*1) an increase of ≥ 2 points in the NIHSS score; (2) a consciousness score of ≥ 1 point; (3) an increase in the motor score by ≥ 1 point; (4) any new neurological functional deficits that could not be measured by the NIHSS score (cognitive functional deficits, apraxia due to advanced cortical functional deficits, recognition, dysphoria or reading impairment, diplopia, and balance and gait abnormalities). The determination of END was made by two senior neurologists.

Patients' age, sex, past medical history, including hypertension, diabetes mellitus, coronary heart disease, atrial fibrillation, ischemic stroke, alcohol use, and smoking, systolic blood pressure (SBP), diastolic blood pressure, NIHSS score, and onset-to-treatment time (OTT) were recorded. Routine blood and biochemical index tests were conducted as soon as possible. White blood cell, lymphocyte, monocyte, and platelet counts, random blood glucose (RBG), creatinine, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio, and lymphocyte-to-monocyte ratio were recorded.

Imaging was performed as soon as possible for all of the patients in the emergency service with perfect cranial computed tomography and a 1.5-T MRI device, including MRI, diffusion-weighted imaging, and magnetic resonance angiography. If the patient's clinical status worsened, a follow-up cranial computed tomography was conducted.

Leukoaraiosis was evaluated according to the Blennow scale. In the study, moderate and severe leukoaraiosis were defined as leukoaraiosis. The degree of brain atrophy was evaluated as "none," "mild," "moderate," and "severe."[9] In this study, moderate and severe brain atrophy were defined as brain atrophy. Lacunar infarction was defined as a circular or oval low-density lesion with a diameter

of 3 to 20 mm in the basal ganglia region, deep white matter, cerebellum, or pons. According to the number of lacunar infarctions, < 5 lacunar infarctions were defined as 0, and ≥ 5 lacunar infarctions were defined as 1. The location and number of new infarctions were recorded on diffusion-weighted imaging.

The internal carotid artery, middle cerebral artery, anterior cerebral artery, vertebral artery, basilar artery, and posterior cerebral artery were evaluated. Diagnostic basis for vascular stenosis was as follows:[10] Grade 1, mild stenosis, signal loss of 0 to 50%; Grade 2, moderate stenosis, signal loss ranging from 50 to 69%; Grade 3, severe stenosis, signal loss of 70 to 99%; Grade 4, complete local blood flow signal loss with nonvisualization of the vessel wall. In this study, Grade ≥ 2 of the symptomatic vessel was classified as vascular stenosis. Three or more vascular stenoses were defined as multiple vascular stenoses. Imaging neurologists blinded by two senior technical titles, conducted an independent review, resolving any disagreement through consultation.

Statistical analysis

Data were analyzed using IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Continuous variables of normal distribution were expressed as mean ± standard deviation (SD), and the independent sample t-test was used for comparison between groups. Continuous variables with nonnormal distribution were expressed as the median, and the Mann-Whitney U test was used for comparison between groups. Categorical variables were expressed as composition ratios, and chi-square tests were used for comparisons between groups. Using the occurrence of END as the dependent variable and including the index $p < 0.10$ as the independent variable, a binary logistic regression analysis was used to establish the END prediction model. A p-value <0.05 was considered statistically significant. The area under the receiver operating characteristic (ROC) curve (AUC) was used to evaluate the discrimination of the model. An AUC of 0.5 indicated no discrimination, whereas an AUC of 1.0 indicated perfect discrimination. The Hosmer-Lemeshow test was used to evaluate the calibration degree of the goodness-of-fit model. Decision curve analysis (DCA) generated on the basis of the model using R software version 4.0.3 was used to evaluate the net benefit of the model.

RESULTS

A total of 489 patients with MNDIS were included in this study, among which 422 (315 males, 107 females; mean age: 61.3±11.3 years; range, 21 to 87 years) were in the non-END group. There were 67 patients (42 males, 25 females; mean age: 63.3 ± 8.7 years; range, 46 to 84 years) in the END group. When comparing the END group with the non-END group, the results showed that there were statistically significant differences between the two groups in terms of age, gender, history of diabetes, history of stroke, total protein in peripheral blood (OTT), systolic blood pressure (SBP), random blood glucose (RBG), neutrophil-to-lymphocyte ratio (NLR), number of new lesions, brain atrophy, ≥ 5 lacunar infarctions, and stenosis of the symptomatic vessel ($p < 0.10$, Table 1).

Clinical prediction model development

Considering age, sex, history of stroke, OTT, SBP, NLR, RBG, brain atrophy, ≥ 5 lacunar infarctions, number of lesions, and stenosis of symptomatic vessels ($p < 0.1$) as independent variables, binary logistic regression analysis showed that SBP (odds ratio [OR] = 1.017, 95% confidence interval [CI] 1.004–1.031, $p = 0.012$), OTT (OR = 1.473, 95% CI 1.185–1.832, $p < 0.001$), NLR (OR = 1.017, 95% CI 1.004–1.031, $p = 0.021$), RBG (OR = 1.103, 95% CI 1.020–1.193, $p = 0.015$), number of lesions (OR = 1.480, 95% CI 1.085–2.019, $p = 0.013$), and stenosis of the symptomatic vessel (OR = 1.879, 95% CI: 1.052–3.356, $p = 0.033$) were independent risk factors for END (Table 2). The multivariate logistic regression model was established as follows: Logit $p = -8.408 + 0.017 \times$ (SBP) $+ 0.387 \times$ (OTT) $+ 0.089 \times$ (NLR) $+ 0.098 \times$ (RBG) $+ 0.392 \times$ (Number of lesions) $+ 0.631 \times$ (vascular stenosis).

Assessment of the model

The prediction accuracy of the model was 87.3%, exceeding 80%. The AUC of the CPM was 0.754 (95% CI 0.692-0.816, $p < 0.001$), indicating that CPM had a good ability to distinguish between END and non-END (Figure 1a).

The chi-squared value in the Hosmer-Lemeshow chi-square test to assess the fit of the CPM was 4.313 ($p = 0.828$). Calibration scatter plots are presented in Figure 1b. These findings indicated that the predicted probability of the model fit well with the true probability and that the models had good discrimination and calibration.

The clinical practicability of the CPM was evaluated using DCA. The decision curve is

TABLE 1
Comparison of clinical data between the END group and the non-END group

	Non-END group (n = 422)		END group (n = 67)			
	n	%	n	%	χ^2/Z	*p*
Age (year)	62		65		1.792	0.073
Sex						
Male	315	74.64	42	62.69	4.195	0.041
Hypertension	274	64.93	49	73.13	1.736	0.188
Diabetes	114	27.01	29	43.28	7.396	0.007
Coronary heart disease	45	10.66	6	8.96	0.186	0.667
Stroke	43	10.19	12	17.91	3.453	0.063
Atrial fibrillation	25	5.92	2	2.99	1.112	0.292
Smoking	188	44.55	27	40.30	0.424	0.515
Alcohol use	120	28.44	17	25.37	0.269	0.604
NIHSS	2.00		2.00		1.374	0.170
OTT (h)	2.00		3.00		3.618	0.000
SBP (mmHg)	154.00		163.00		2.716	0.007
DBP (mmHg)	91.00		91.00		0.235	0.815
WBC ($\times 10^9$/L)	7.26		7.66		1.064	0.287
Neutrophil/lymphocyte ratio	2.69		3.29		2.548	0.011
Platelet/lymphocyte ratio	130.83		145.00		1.608	0.108
Lymphocyte/monocyte ratio	4.24		4.05		1.448	0.148
Random blood glucose (mmol/L)	6.68		8.20		2.672	0.008
Creatinine (mmol/L)	67.83		65.78		1.618	0.106
K^+ (mmol/L)	3.67		3.63		1.205	0.228
Na^+ (mmol/L)	140.00		140.00		0.286	0.775
Lesion locations					1.906	0.386
Anterior circulation	253	59.95	46	68.66		
Posterior circulation	156	36.97	19	28.36		
Anterior + posterior circulation	13	3.08	2	2.99		
Number of lesions					11.539	0.003
1	255	60.43	26	38.80		
2	49	11.61	14	20.90		
≥ 3	118	27.96	27	40.30		
Stenosis of symptomatic vessel	168	39.81	34	50.75	2.852	0.091
Multiple blood vessel stenosis	67	15.88	16	23.88	2.628	0.105
Leukoaraiosis	114	27.01	21	31.34	9.542	0.462
Brain atrophy	109	25.83	26	38.81	4.872	0.027
≥ 5 lacunar infarction	102	24.17	27	40.30	7.744	0.005

END: Early neurologic deterioration; NIHSS: National Institutes of Health Stroke Scale; OTT: Onset-to-treatment time; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; WBC: White blood cells. The measurement data with non-normal distribution were expressed as the median, and the Mann-Whitney U test was used for comparison between groups. Categorical variables were expressed as composition ratios, and chi-square tests were used for comparisons between groups.

presented in Figure 1c. The DCA of the CPM was higher than the two extreme lines, indicating that the CPM manifested practical clinical value.

Simplified CPM

A simple scoring method was developed, and a ROC curve analysis was applied. The cut-off

TABLE 2
Early neurological deterioration prediction model

Variables	B	SE	χ^2	*p*	OR	95% CI	
						Lower	Upper
Age	0.014	0.014	0.950	0.330	1.014	0.986	1.043
Male	–0.496	0.313	2.515	0.113	0.609	0.330	1.124
Stroke	0.113	0.401	0.079	0.778	1.119	0.510	2.457
Systolic blood pressure	0.017	0.007	6.378	0.012	1.017	1.004	1.031
Onset-to-treatment time	0.387	0.111	12.120	0.000	1.473	1.185	1.832
Neutrophil/lymphocyte ratio	0.089	0.038	5.352	0.021	1.017	1.004	1.031
Random blood glucose	0.098	0.040	5.962	0.015	1.103	1.020	1.193
Number of lesions	0.392	0.158	6.137	0.013	1.480	1.085	2.019
Stenosis of symptomatic vessel	0.631	0.296	4.538	0.033	1.879	1.052	3.356
Brain atrophy	0.355	0.401	1.286	0.257	1.427	0.772	2.636
≥ 5 lacunar infarction	0.441	0.311	2.011	0.156	1.554	0.845	2.858
Constant	-8.408	1.598	27.695	0.000	0.000	-	-

CI: Confidence interval; SE: Standard error; OR: Odds ratio. Taking whether END occurs as the dependent variable and including the index $p < 0.10$ as the independent variable, a binary logistic regression analysis was used to establish the END prediction model.

values of the maximum approximate index were determined to be 155.50 mmHg for SBP, 3.0 h for OTT, 3.24 for NLR, 7.38 mmol/L for RBG, and 1.5 for the number of new lesions. Assignment of independent risk factors in the model was as follows: SBP (> 155.5 mmHg) was assigned 1, NLR (> 3.24) as 1, RBG (> 7.38 mmol/L) as 1, OTT (> 3.0 h) as 1, the number of new lesions (≥ 2) as 1, moderate to severe stenosis or occlusion of the symptomatic vessel as 1. The total scores ranged from 0 to 6. The AUC of the simplified CPM was 0.731 (95% CI 0.679–0.800, $p < 0.001$), showing no significant difference from the CPM (0.754, 95% CI 0.692–0.816, $p > 0.05$).

This study established a simple clinical prediction model for END, with the total score ranging from 0 to 6. In the study, the CPM score of 20 patients was 0. Among these 20 patients, no END occurred.Therefore, when the score is 0, the occurrence rate of END is 0% (Figure 2).

DISCUSSION

Among patients with mild stroke, the occurrence of END significantly increases the risk of adverse functional outcomes within 90 days, and the risk is 7.5 times that of patients without END.[11] Therefore, early and rapid identification of END, particularly for patients with MNDIS, remains a major clinical challenge. In this study, we developed a simple and practical tool to predict END of patients with acute MNDIS within 72 h and accurately identified this group of high-risk patients. It indicated that for patients with MNDIS who had moderate-to-severe stenosis or occlusion of the symptomatic vessel within 3 to 4.5 h of onset, if there was more than one new lesion, RBG at the time of visit was greater than 7.38 mmol/L, SBP was greater than 155.50 mmHg, and the NLR was greater than 3.24, the risk of END within 72 h was high. These findings provide valuable guidance for clinical decision-making and early intervention in patients with MIS.

Numerous studies have demonstrated that the immune system plays a crucial role in the onset and progression of AIS. Inflammation plays a core role in secondary brain injury after stroke by promoting thrombosis and progression, aggravating microcirculation disorders, directly damaging neurons and glial cells, and damaging the blood-brain barrier (BBB).[12] This is closely related to the progression of stroke, the expansion of infarction foci, and the deterioration of neurological function. Research suggests that the aggregation and activation of various inflammatory cells, such as neutrophils, lymphocytes, and microglia, found both inside and outside the blood vessels and in the brain parenchyma of acute ischemia-reperfusion injury.[12] The NLR is a sensitive indicator reflecting the systemic inflammatory/stress state and is consistent with the severity of the disease. A high

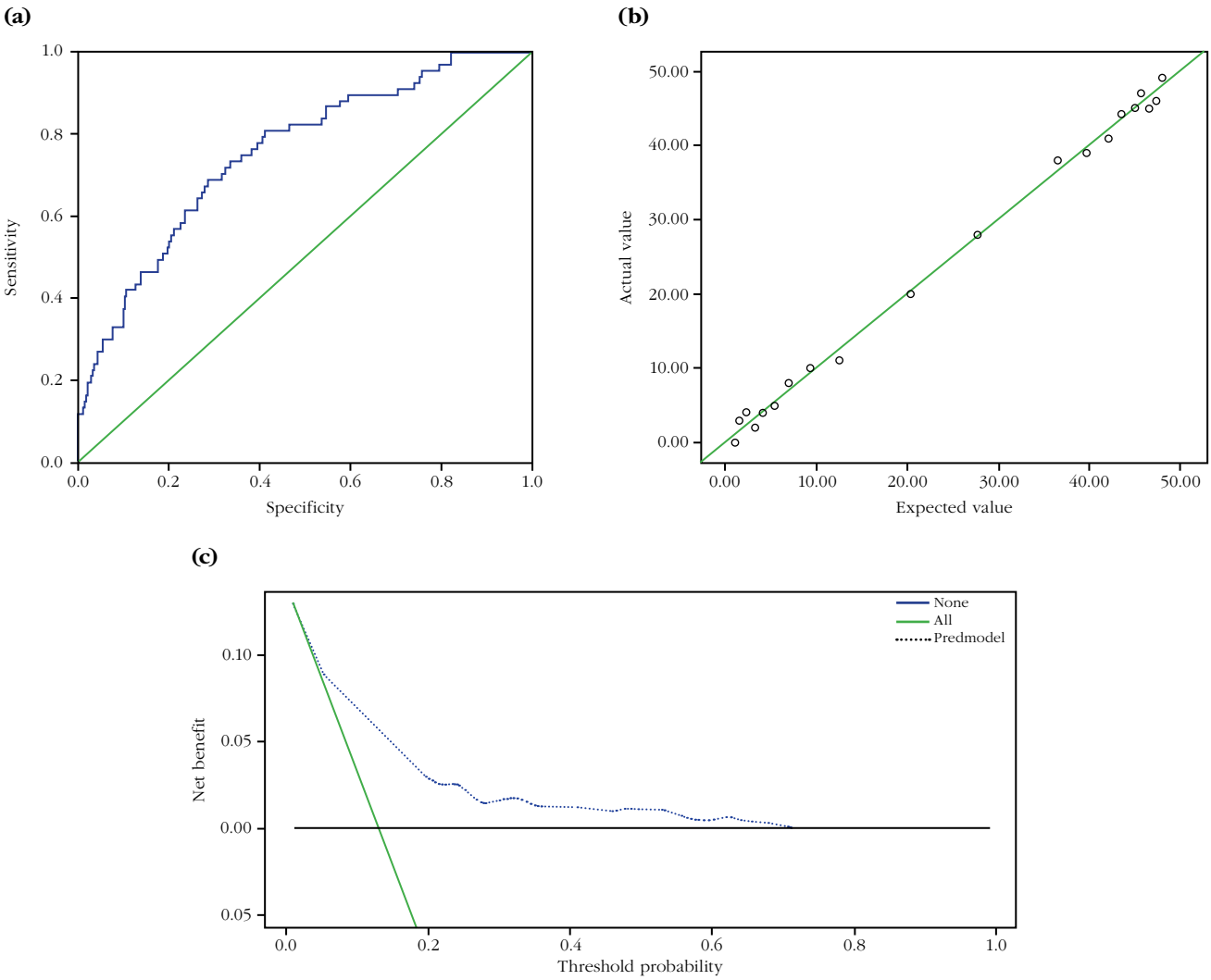

Figure 1. Discrimination, calibration, and clinical practicability of the CPM. **(a)** Receiver operating characteristic curve showing the AUC, which reflects the discrimination ability of the CPM. **(b)** Calibration scatter plot assessing the agreement between predicted and observed probabilities. **(c)** Decision curve analysis evaluating the clinical usefulness (practicability) of the CPM.

CPM: Clinical prediction model; AUC: Area under the curve.

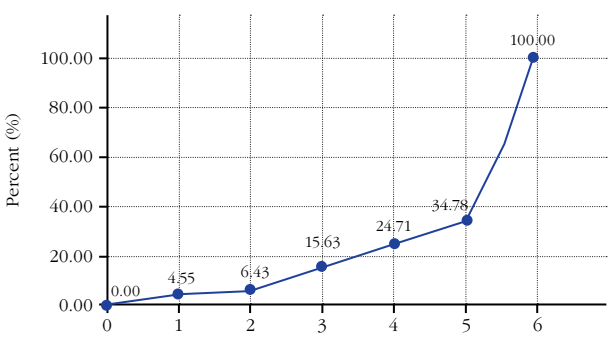

Figure 2. Incidence of END across different CPM score categories.

END: Early neurologic deterioration; CPM: Clinical prediction model.

NLR value indicates a strong pro-/anti-inflammatory imbalance state. It has now been confirmed that NLR is one of the valuable prognostic markers under various pathological conditions. A study showed that a higher NLR (5.5) was an independent predictor of three-month poor functional outcomes after mechanical thrombectomy following acute anterior circulation stroke.[13] The level of NLR in patients with AIS was associated with an increased risk of poor functional outcome at discharge. The NLR may have the ability to predict short-term functional outcomes.[14] Patients with poorer consciousness outcomes exhibited a tendency

towards elevated NLR levels.[15] However, few studies have investigated the predictive significance of NLR for END in patients with MNDIS. In the present study, NLR (OR = 1.017) was identified as an independent risk factor for END, highlighting its potential clinical value in risk stratification.

Regardless of history of diabetes, about half of the patients with AIS will experience stress-induced hyperglycemia.[16] Acute hyperglycemia is an independent risk factor for the END in patients with AIS treated with intravenous thrombolysis.[17] Studies demonstrated that blood glucose in AIS was significantly associated with increased infarction volume and poor prognosis.[18] Acute stroke can trigger neuroendocrine and inflammatory responses, leading to stress-induced hyperglycemia.[19] Hyperglycemia aggravates ischemic injury through multiple pathways: it increases lactic acid accumulation, leading to acidosis, disrupts BBB, and hyperglycemia intensifies ischemia-reperfusion injury, increasing the risk of hemorrhagic transformation. Oxidative stress and inflammation promote the generation of free radicals, aggravate endothelial dysfunction, promote thrombosis, inhibit the opening of collateral circulation, and accelerate the progression of atherosclerosis.[20-22] This cascade of reactions can create a vicious cycle, affecting the short- and long-term neurological recovery of stroke patients. This study further clarified the specific threshold (7.38 mmol/L) in a particular population, suggesting that RG > 7.38 mmol/L significantly increased the risk of END in this high-risk population. Neutrophil-to-lymphocyte ratio (> 3.24) and RBG (> 7.38 mmol/L) integrated inflammation and stress responses. These were the important biomarkers for END.

Multiple lesions increase the possibility of more vulnerable penumbra tissues around the core infarction area and also reflect more severe underlying vascular lesions or unstable states, which are prone to progression. It indicates a high embolic load or a wide range of multivascular bed involvement/poor perfusion. It also reflects the instability of emboli or insufficient compensation of collateral circulation, which is prone to lead to subsequent embolic events or the progression of *in situ* thrombosis. Multiple lesions indicate that a wider area of brain tissue is at risk of ischemia, and the possibility of progressive infarction is greater. The number of lesions is a high-risk marker in core imaging.

Blood pressure is a key indicator reflecting the elasticity of arterial vessels and hemodynamic load. Its increase usually indicates an increase in the stiffness of large arteries and a decrease in vascular compliance.[23,24] Numerous epidemiological studies have clearly pointed out that elevated SBP is an independent predictor of cardiovascular events.[25,26] Brain tissue is a hypermetabolic organ that is extremely sensitive to fluctuations in blood perfusion, and cerebral blood vessels have their unique self-regulation mechanism. In patients with chronic hypertension and arteriosclerosis, this self-regulation curve shifts to the right, causing the brain tissue to be at risk of insufficient perfusion even when the blood pressure is within the "normal" range. Excessive blood flow shock during systole can cause microcirculation disorders in the brain, damage to the BBB, and injury to endothelial function, thereby laying a potential danger for the deterioration of neurological function after stroke. After acute ischemia, the brain tissue attempts to maintain perfusion through automatic regulation, and SBP compensatorily increases. However, excessive hypertension may exceed the upper limit of the self-regulation of damaged cerebral blood vessels, leading to excessive perfusion injury (cerebral edema, hemorrhagic transformation), or promoting thrombosis extension/reformation. This study determined that in this specific population, SBP > 155.50 mmHg was an independent risk factor for END, suggesting that blood pressure management for such patients may require a stricter upper limit target, which needs to be combined with clinical research evidence and individualized assessment.

After ischemic stroke occurs, brain tissue undergoes a series of complex pathophysiological processes, the severity of which is closely related to the duration. The ischemic penumbra theory provides a core explanatory framework; after vascular occlusion, there is brain tissue with reduced blood perfusion but still alive around the ischemic core area, and the ultimate fate of this part of the tissue largely depends on the time of reperfusion. Ischemia-reperfusion injury is particularly significant when the treatment is initiated too late. At this time, BBB is disrupted, the inflammatory response is activated, and a large amount of free radicals are produced, which may lead to hemorrhagic transformation or malignant cerebral edema. The influence of treatment duration on END is particularly prominent in patients with mild stroke. In the GSR-ET study,[1] although the baseline NIHSS score of all included patients was

< 6 points, delayed treatment was still associated with a significantly higher risk of END. This study found that when the time from onset exceeded 3 h, the risk of END increased substantially. This discovery challenges the traditional notion that patients with mild stroke may have a more generous treatment time window. The extended time window for intravenous thrombolysis is 3 to 4.5 h. At this stage, the ischemic penumbra of the patient may be more fragile and prone to progression toward irreversible infarction, highlighting the critical importance of early intervention.

Studies have shown that approximately 30 to 50% of patients with acute MNDIS have significant large artery stenosis (stenosis rate ≥ 50%), particularly more common in anterior circulation stroke.[27,28] Due to the presence of well-developed collateral circulation, approximately 10 to 20% of stroke patients with large artery occlusion present with mild stroke, and up to 25 to 50% of patients develop END.[29,30] Stenosis leads to hypoperfusion of the distal brain tissue. When blood pressure fluctuates, it is prone to induce ischemia. Meanwhile, the detachment of unstable atherosclerotic plaques lead to microembolism. Although the symptoms are brief, they indicate the risk of severe stroke in the future. Large artery stenosis is an important underlying cause of MNDIS, and high-risk patients need to be identified through early vascular assessment and to take active interventions (thrombolysis or endovascular treatment) to reduce the risk of END. In clinical practice, attention should be paid to the disabling pathological basis behind nondisabling symptoms. Stenosis/occlusion of the symptomatic vessel is the core cause of persistent hypoperfusion and thrombosis progression.

These factors do not exist in isolation; there are complex interactions and synergies among them. Hyperglycemia and hypertension can further exacerbate endothelial injury and inflammatory response activation, as reflected by elevated NLR levels. Inflammation (high NLR levels) can promote thrombosis and vasospasm, aggravate the blood supply disorder of stenotic or occluded vessels, and may lead to the emergence or expansion of new lesions. Multiple lesions themselves are a sign of extensive damage, which can trigger more intense systemic inflammation and stress responses (elevations in blood glucose, blood pressure, and NLR levels). On the fragile basis of severe stenosis/occlusion of the symptomatic vessels, the superposition of the above factors greatly increases the risks of cerebral hemodynamic decompensation, thrombosis progression/reformation, and uncontrolled inflammatory cascade reactions, ultimately leading to END. These factors comprehensively reflect different pathophysiological mechanisms. The patient status was evaluated respectively from multiple key dimensions such as embolization/perfusion range (number of lesions), metabolic status (blood glucose), hemodynamics (blood pressure, vascular stenosis), and inflammation/stress (NLR). There may be interactions among these parameters (e.g., high blood glucose aggravating inflammation and high blood pressure affecting perfusion), jointly constituting a "storm" that leads to END. This combined model (imaging + biochemistry + clinical + vascular + time) provides a method for identifying patients with mild stroke at an extremely high risk of END in the ultra-early stage (at the time of visit). This is far superior to relying solely on a single factor.

This study had some limitations. The results need to be externally validated in an independent, multicenter prospective cohort to confirm their universality and predictive value. This study was a retrospective one and is susceptible to selection bias and confounding factors (e.g., previous use of antiplatelet and statin drugs, blood pressure variability, fever, and infection). Whether intervention for these factors can improve prognosis needs to be confirmed by subsequent randomized controlled trials.

In conclusion, this study focused on patients with acute mild nondisabling stroke who were admitted to the emergency department within 4.5 h of onset. A risk prediction model for END within 72 h was constructed. By integrating imaging examinations (vascular stenosis, lesion quantity), rapid detection indicators (blood glucose, routine blood tests), and vital signs (blood pressure), high-risk patients can be quickly identified. These indicators are easily obtainable and have good potential for clinical application, providing a practical risk stratification tool for clinical practice. For high-risk patients, enhanced monitoring is required and individualized early intervention strategies should be considered. Clinical trials targeting early intervention strategies for these high-risk factors (such as thrombolysis, intensified glucose-lowering treatment, individualized blood pressure reduction, and anti-inflammatory treatment) to evaluate their effects on preventing END and improving long-term prognosis.

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Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: H.M., L.L.: Designed the study and contributed to the construction and management of the database; L.L.: Performed the statistical analysis and wrote the manuscript of the manuscript; H.M.: Contributed to the revision, and provided overall oversight of the research, and acted as the guarantor who accepted full responsibility for the work and the conduct of the study. All authors read and approved the final manuscript.

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