

Development of a Clinical Prediction Model for Ultra-Early Mild Acute Ischemic Stroke with Negative CT Results

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Background: Clinical guidelines highlight the challenge of distinguishing CT-negative ultra-early mild acute ischemic stroke (AIS) from transient ischemic attack (TIA) based solely on clinical manifestations. MRI-DWI, the gold standard for differentiation, is often inaccessible in primary hospitals due to cost and time constraints, leading to widespread CT use—with a false-negative rate in mild AIS, risking delayed thrombolysis. This study aims to establish a clinical prediction model for CT-negative ultra-early mild acute ischemic stroke (AIS) by comparing the clinical data and laboratory test results of patients with CT-negative early mild ischemic stroke and transient ischemic attack (TIA), in order to promote early diagnosis and early treatment of AIS, thereby improving patient prognosis.

Methods: This study compared and analyzed the clinical data of gender, age, history of hypertension, history of diabetes, National Institutes of Health Stroke Scale (NIHSS) score, and laboratory test results such as homocysteine, neutrophil count, lymphocyte count, monocyte count, platelet count (PLT), C-reactive protein (CRP), fibrinogen (FIG), D-dimer, Random Blood glucose (GIU), total cholesterol (TCHO), triglycerides (TG), high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), neutrophil count, lymphocyte count, and platelet count to calculate the neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) in CT-negative ultra-early mild AIS and TIA patients, variables showing significant differences in difference analysis were included in a multivariate logistic regression model to identify independent predictors of AIS, and the independent predictors were used to establish a clinical prediction model for the diagnosis of early AIS with negative CT based on the statistical results.

Results: Multivariate analysis revealed that the NIHSS score, C-reactive protein (CRP), random blood glucose (GLU), total cholesterol (TCHO), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C) are independent predictors of computed tomography (CT)-negative mild acute ischemic stroke (AIS), with odds ratios (ORs) and 95% confidence intervals (CIs) as follows: NIHSS score (OR = 5.497, 95% CI: 3.599–8.395; $p < 0.001$), CRP (OR = 1.128, 95% CI: 1.005–1.295; $p = 0.038$), random blood glucose (OR = 1.103, 95% CI: 1.013–1.268; $p = 0.043$), total cholesterol (OR = 1.626, 95% CI: 1.022–2.931; $p = 0.023$), triglycerides (OR = 1.337, 95% CI: 1.025–1.721; $p = 0.031$), and LDL-C (OR = 1.542, 95% CI: 1.142–1.959; $p = 0.025$). A clinical prediction model that included these factors showed a strong ability to discriminate between outcomes, achieving area under the curve (AUC) values of 0.830 in the training set and 0.804 in the validation set. Additionally, the model demonstrated good calibration and clinical utility across various threshold probabilities, indicating its effectiveness in practical applications.

Conclusion: Our study demonstrated that The developed clinical prediction model can assist in diagnosing CT-negative ultra-early mild AIS, thereby potentially improving patient outcomes through timely intervention.

Keywords: acute ischemic stroke, AIS, transient ischemic attack, TIA, clinical prediction model, serum markers, early diagnosis

Introduction

Cerebrovascular disease, especially Acute Ischemic Stroke (AIS) caused by cerebral atherosclerosis, continues to be a major contributor to illness and death in China. AIS is marked by a localized interruption of blood flow to the brain, which results in various neurological impairments. Among various stroke subtypes, AIS is the most prevalent and is associated with high rates of disability and mortality.^{1,2} Intravenous thrombolysis administered within 6 hours of symptom onset has been demonstrated to significantly improve neurological outcomes in AIS patients.^{3–5} However, the narrow therapeutic window necessitates rapid and accurate diagnosis.⁶ Transient ischemic attack (TIA), often a precursor to ischemic stroke, shares similar pathological mechanisms and is managed with antiplatelet agents, antithrombotic therapy, and measures to enhance cerebral perfusion.⁷

Current clinical guidelines acknowledge the difficulty in distinguishing CT-negative ultra-early mild AIS from TIA based solely on clinical presentation. Magnetic resonance imaging with diffusion-weighted imaging (MRI-DWI) is the gold standard for differentiation but is frequently inaccessible in primary hospitals due to high costs and time constraints.⁸ Consequently, computed tomography (CT) is widely used for initial assessment. However, CT has limited sensitivity in detecting early ischemic changes, with false-negative rates as high as 32% in mild AIS cases,⁹ potentially leading to delays in thrombolytic therapy.

In recent years, serum biomarkers have gained attention for their roles in the pathogenesis and prognosis of ischemic stroke. Inflammation, endothelial dysfunction, and metabolic alterations play critical roles in acute cerebral ischemia.¹⁰ Markers such as high-sensitivity C-reactive protein (hs-CRP), homocysteine (HCY), and lipid profiles have been associated with stroke risk and outcomes.^{11,12} Moreover, dynamic changes in neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) may reflect the acute inflammatory state following cerebral ischemia.¹³ Although these markers show promise, their combined utility in differentiating CT-negative mild AIS from TIA in the hyperacute phase (<6 hours) remains underexplored.

Several recent studies have highlighted the potential of multi-marker models in improving early diagnostic accuracy for AIS.¹⁴ For instance, Glial Fibrillary Acidic Protein (GFAP) and S100B have been proposed as neuroglial markers indicative of astrocytic damage in AIS,¹⁵ while admission glucose and lipid levels are readily available parameters that may enhance discrimination between stroke mimics and true ischemia.^{16,17} Nevertheless, an integrated model incorporating NIHSS scores with routine serum markers has not been thoroughly validated for use in CT-negative, mild AIS within the critical 6-hour window.

This study aimed to create and validate a clinical prediction model that integrates NIHSS scores with readily available serum biomarkers to help distinguish between CT-negative mild AIS and TIA at an early stage. The goal is to offer a practical and quick diagnostic tool that can aid clinical decision-making in situations where MRI is not accessible. By doing so, the model aspires to enhance timely interventions and ultimately improve patient outcomes.

However, this paper is a single-center study with a small sample size, and the conclusions of this study may not be universal.

Materials and Methods

Study Design

This retrospective study focused on patients with CT-negative ultra-early stage mild AIS and TIA who were admitted to a comprehensive hospital in Shishi City, China, between January 2020 and December 2023. Mild AIS was defined by mild neurological deficits with specific scoring thresholds, for example, NIHSS ≤ 5 , transient ischemic attack (TIA) is typically defined as a temporary disruption of blood flow to the brain that causes symptoms lasting less than 24 hours, with minimal or no lasting neurological damage. Symptoms are generally mild in severity and may include brief episodes of weakness, numbness, speech difficulties, or visual disturbances. Unlike a stroke, which involves permanent tissue damage, a mild TIA resolves completely. The hospital is well-regarded in the region for its high-quality medical services and well-organized medical resources, making it a representative institution for diagnosing and treating patients in the area. Throughout the study period, a total of 330 patients were included, comprising 205 patients with AIS and 125 patients with TIA. The final diagnosis of Acute Ischemic Stroke (AIS) and Transient Ischemic Attack (TIA) depends on Magnetic Resonance Imaging-Diffusion-Weighted Imaging (MRI-DWI) (Figure 1).

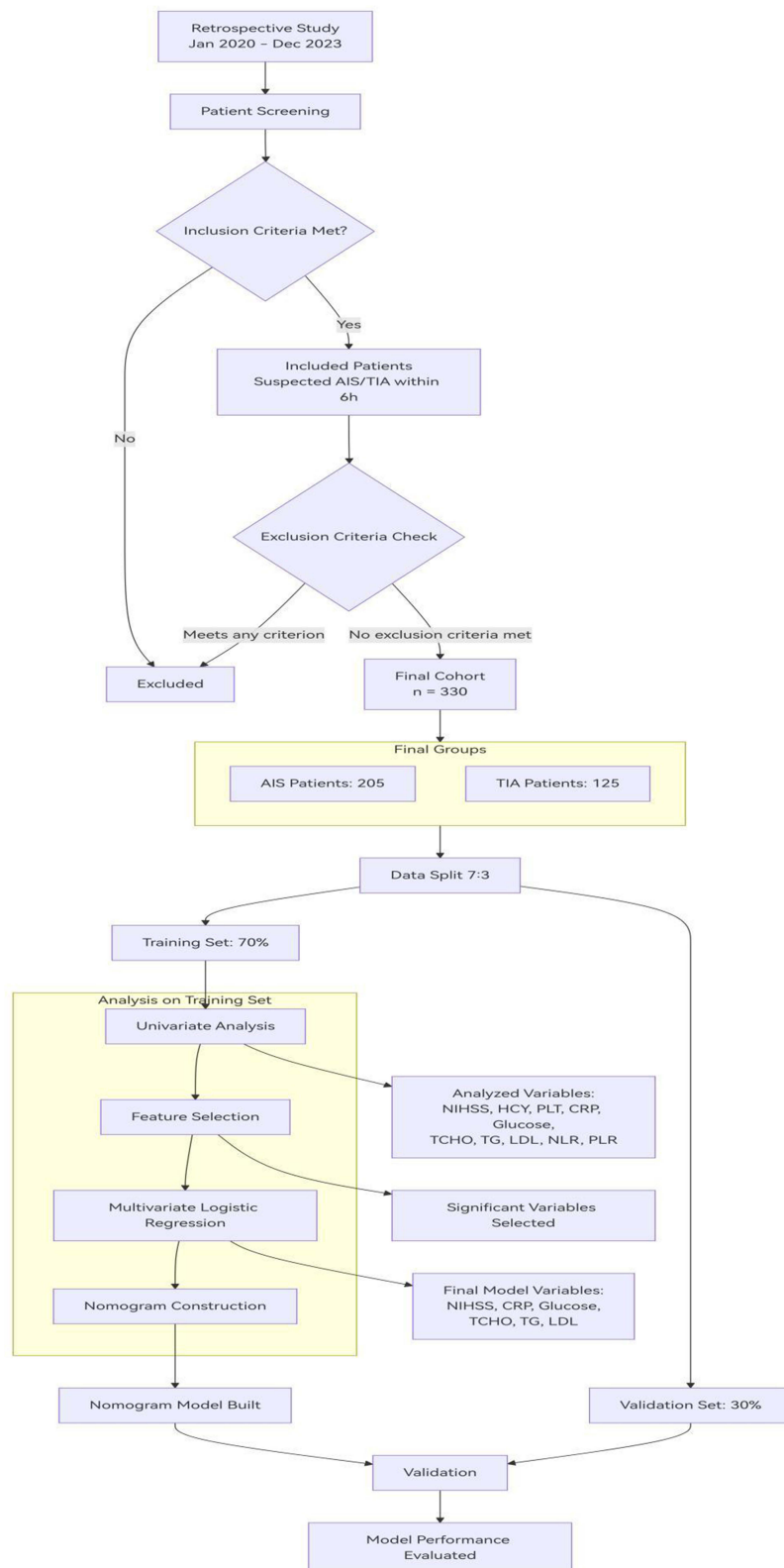


Figure 1 Study Design and Implementation Flow Chart.

Inclusion Criteria

(1) Suspected AIS or TIA patients within 6 hours of onset; (2) CT examination did not reveal responsible ischemic lesions; (3) Confirmed as AIS or TIA patients by MRI-DWI; (4) All patients had NIHSS scores of ≤ 5 points; (5) Peripheral blood was collected from all patients within 2 hours of admission for blood cell analysis and tests for D-D dimer, HCY, blood lipids, and random blood glucose.

Exclusion Criteria

(1) Incomplete information; (2) Patients with a history of infectious diseases in the past 3 weeks; (3) Patients with a history of stroke, transient ischemic attack, or craniocerebral trauma; (4) Patients with a history of craniocerebral surgery in the past 3 months; (5) Patients with hematologic diseases or other malignancies; (6) Patients who cannot cooperate for head MRI examination for some reason; (7) Patients with autoimmune diseases; (8) Patients with HIV or those taking immunosuppressants; (9) Patients with a history of arrhythmias; (10) Patients with incomplete information.

Sample Size Estimation

The study's sample size was determined using the empirical rule for multivariate regression models, based on the number of variables. Consistent with epidemiological and statistical principles for regression model sample size determination, this requires a sample size 10–20 times the number of independent variables ultimately included in the model. This ensures model fitting stability, mitigates multicollinearity, and improves statistical power. After systematic literature review, theoretical analysis, and pre-test screening, 6 independent variables were finalized for the model. Accordingly, the estimated sample size range was 60 (6×10) to 120 (6×20) cases. Ultimately, the planned sample size was set at 330 cases, meeting all statistical requirements for model development.

Laboratory Measurements

Complete blood count (CBC) was performed using a Siemens hematology analyzer (Bayer AG, Leverkusen, Germany).

C-reactive protein (CRP) was measured using a Pumen specific protein analyzer (Shenzhen Pumen Technology Co., Ltd., Guangdong, China).

D-dimer was assessed with a Sysmex CA1500 system (Sysmex Corporation, Kobe, Japan).

Lipid profiles and glucose levels were determined using a Siemens 2400 biochemical analyzer with reagents from Leadman (Siemens Healthineers, Erlangen, Germany; Leadman Biochemistry Co., Ltd., Beijing, China).

Homocysteine (HCY) was measured on a Siemens 2400 analyzer with reagents from Jiuqiang (Siemens Healthineers, Malvern, PA, USA; Beijing Jiuqiang Biotechnology Co., Ltd., Beijing, China).

The following variables were collected: gender, age, hypertension history, diabetes history, NIHSS score, HCY, neutrophil count, lymphocyte count, monocyte count, platelet count (PLT), CRP, fibrinogen (FBG), D-dimer, GLU, TG, HDL, LDL, NLR and PLR were calculated.

1. Homocysteine (HCY)

Definition: Homocysteine is an amino acid produced in the body during the metabolism of methionine. Unit: ($\mu\text{mol/L}$)

2. Platelet Count (PLT)

Definition: Platelet count refers to the number of platelets (thrombocytes) in a given volume of peripheral blood. Unit: $\times 10^9$ per liter ($\times 10^9/\text{L}$)

3. C-Reactive Protein (CRP)

Definition: C-reactive protein is an acute-phase reactant synthesized by the liver in response to inflammation, infection, tissue injury, or necrosis. Unit: milligrams per liter (mg/L)

4. Random blood glucose

Definition: Blood glucose levels reflect the balance between glucose intake, utilization, and storage. Abnormal levels indicate disorders such as diabetes mellitus or hypoglycemia.

Unit: millimoles per liter (mmol/L);

5. Total Cholesterol (TCHO)

Definition: Total cholesterol is the sum of all cholesterol fractions in the blood, including cholesterol carried by low-density lipoprotein (LDL), high-density lipoprotein (HDL), and very-low-density lipoprotein (VLDL). It is a key indicator of lipid metabolism and cardiovascular disease risk.

Unit: millimoles per liter (mmol/L)

6. Triglycerides (TG)

Definition: Triglycerides are a type of lipid (fat) synthesized by the liver and absorbed from dietary fats. They serve as a major energy storage form in the body. Unit: millimoles per liter (mmol/L)

7. Low-Density Lipoprotein Cholesterol (LDL)

Definition: Low-density lipoprotein cholesterol, often called “bad cholesterol,” is the cholesterol fraction carried by low-density lipoproteins. Unit: millimoles per liter (mmol/L)

8. Neutrophil-to-Lymphocyte Ratio (NLR)

Definition: Neutrophil-to-lymphocyte ratio is a derived inflammatory marker calculated as the ratio of absolute neutrophil count to absolute lymphocyte count. Unit: Ratio (dimensionless, no unit)

9. Platelet-to-Lymphocyte Ratio (PLR)

Definition: Platelet-to-lymphocyte ratio is another derived inflammatory and immunological marker, calculated as the ratio of platelet count to absolute lymphocyte count. Unit: Ratio (dimensionless, no unit)

10. Monocyte Count

Definition: Monocyte count refers to the number of monocytes (a type of white blood cell) in a given volume of peripheral blood.

Unit: $\times 10^9$ per liter ($\times 10^9/L$)

11. Fibrinogen (FBG)

Definition: Fibrinogen is a glycoprotein synthesized by the liver, serving as a key substrate in the coagulation cascade. When blood vessels are damaged, fibrinogen is converted to fibrin, which forms the structural framework of blood clots. Unit: grams per liter (g/L);

12. D-Dimer

Definition: D-dimer is a degradation product of cross-linked fibrin, formed when a blood clot is dissolved by the fibrinolytic system. It is a specific marker of recent thrombus formation and fibrinolysis, used to rule out deep vein thrombosis (DVT) and pulmonary embolism (PE).

Unit: milligrams per liter (mg/L)

13. High-Density Lipoprotein Cholesterol (HDL)

Definition: High-density lipoprotein cholesterol, commonly called “good cholesterol,” is the cholesterol fraction carried by high-density lipoproteins. Unit: millimoles per liter (mmol/L)

Statistical Analysis

Data were randomly split into training and validation sets at a 7:3 ratio. We performed all statistical analyses with the robust SPSS Statistics software, version 27.0 (Armonk, NY, USA), developed by IBM Corp., Armonk, NY, USA. Normality was assessed using the Kolmogorov–Smirnov test. Normally distributed data are presented as mean $\pm$ standard deviation ($\bar{x} \pm s$) and compared using the *t*-test; non-normal data are presented as median (P25, P75) and compared using the Mann–Whitney *U*-test; categorical data are presented as percentages and compared using the chi-square test.

Multivariate logistic regression identified independent risk factors. A clinical prediction model was developed using R software (v4.4.2) and evaluated for discrimination, calibration, and clinical utility. A nomogram was constructed to visualize the model. Statistical significance was set at $p < 0.05$.

Results

Baseline Characteristics

A total of 330 patients were enrolled in this study, including 205 with acute ischemic stroke (AIS) and 125 with transient ischemic attack (TIA). The cohort was randomly split into a training set ($n = 235$; 146 AIS, 89 TIA) and a validation set ($n = 95$; 59 AIS, 36 TIA) using simple random sampling (random seed = 1234) to ensure balanced group distribution. Baseline demographic, clinical, and laboratory characteristics were compared between the AIS and TIA subgroups within the training set. Continuous variables were analyzed using independent samples *t*-test (normal distribution) or Mann–Whitney *U*-test (non-normal distribution), and categorical variables were compared using chi-square test.

No significant differences were noted between the TIA and AIS subgroups in gender (male: 58.43% vs. 63.01%; $p = 0.574$), age (63.57 ± 14.05 vs. 62.18 ± 11.46 years; $p = 0.41$), smoking history (47.2% vs. 47.9%; $p = 0.893$), Alcohol drinking history (41.6% vs 41.8%; $p = 0.951$), Body weight (70.89 ± 7.12 vs. 71.23 ± 6.8 ; $p = 0.67$), History of hypertension (68.54% vs. 73.29%; $p = 0.527$), Diabetes history (26.97% vs. 29.45%; $p = 0.794$), Neutrophil count, Median (Q1, Q3) (4.3 (3.58, 5.2) vs. 4.6 (3.6, 5.8); $p = 0.184$), Lymphocyte count, Median (Q1, Q3) (1.5 (1.2, 2.1) vs. 1.6 (1.3, 2); $p = 0.631$), Monocyte count, Median (Q1, Q3) (0.4 (0.3, 0.42) vs. 0.4 (0.3, 0.5); $p = 1$), FBG, M (Q1, Q3) (2.5 (2.17, 2.95) g/L vs. 2.54 (2.27, 3.04) g/L; $p = 0.377$), D-Dimer, M (Q1, Q3) (0.38 (0.22, 0.65) mg/L vs. 0.37 (0.27, 0.76) mg/L; $p = 0.254$), HDL, M (Q1, Q3) (1.13 (0.92, 1.38) mmol/L vs. 1.08 (0.92, 1.29) mmol/L; $p = 0.491$), (all $p > 0.05$). In contrast, several variables differed significantly: the AIS subgroup had a notably higher NIHSS score (median [Q1, Q3]: 4 [3, 5] (AIS) vs 1 [0, 1] (TIA); $p < 0.001$). Additionally, HCY, M (Q1, Q3): (11.9 (9.35, 15.25) μ mol/L (AIS) vs. 10.6 (8.07, 13.43) μ mol/L (TIA); $p < 0.001$), Platelet count (PLT): 230.91 ± 58.3 (AIS) vs 215.14 ± 59.7 (TIA); $p = 0.048$), C-reactive protein (CRP) M (Q1, Q3): (0.7 (0.5, 2.18) mg/L (AIS) vs 0.5 (0.5, 1.32) mg/L (TIA); $p < 0.001$), Random blood glucose, M (Q1, Q3): (6.69 (5.68, 8.82) mmol/L (AIS) vs 5 (4.67, 6.13) mmol/L (TIA); $p < 0.001$), Total cholesterol (TCHO): 5 ± 1.12 mmol/L (AIS) vs 4.49 ± 1.14 mmol/L (TIA); $p < 0.001$, Triglycerides (TG) M (Q1, Q3): (1.4 (1.1, 1.87) mmol/L (AIS) vs 1.23 (0.9, 1.73) mmol/L (TIA); $p < 0.001$, Low-density lipoprotein cholesterol (LDL): 3.11 ± 1.06 mmol/L (AIS) vs 2.53 ± 1.06 mmol/L (TIA); $p < 0.001$, Neutrophil-to-lymphocyte ratio (NLR), M (Q1, Q3): (2.88 (2.03, 4.4) (AIS) vs 2.56 (1.88, 3.87) (TIA); $p < 0.001$), and Platelet-to-lymphocyte ratio (PLR), M (Q1, Q3): (141.67 (109.55, 174.44) (AIS) vs 123.3 (96.88, 158.21) (TIA); $p < 0.001$). (Table 1).

Table 1 Comparison of Baseline Characteristics Between AIS and TIA Groups in the Training Set (n = 235)

Variables	Total (n = 235)	TIA (n = 89)	AIS (n = 146)	P	Statistic
Sex, n (%)				0.574	0.316
Male	144 (61.28)	52 (58.43)	92 (63.01)		
Female	91 (38.72)	37 (41.57)	54 (36.99)		
Age, $\bar{x} \pm s$	62.71 $\pm$ 12.49	63.57 $\pm$ 14.05	62.18 $\pm$ 11.46	0.41	0.682
Smoking history, n (%)				0.893	$\chi^2=0.018$
NO	123 (52.3%)	47 (52.8%)	76 (52.1%)		
YES	112 (47.7%)	42 (47.2%)	70 (47.9%)		
Alcohol drinking history, n (%)				0.951	$\chi^2=0.004$
NO	137 (58.3%)	52 (58.4%)	85 (58.2%)		
YES	98 (41.7%)	37 (41.6%)	61 (41.8%)		
Body weight, (kg) $\bar{x} \pm s$	71.05 $\pm$ 7.03	70.89 $\pm$ 7.12	71.23 $\pm$ 6.85	0.67	0.426
NIHSS, M (Q1,Q3)	2 (1, 4.5)	1 (0, 1)	4 (3, 5)	< 0.001	123.916
History of hypertension, n (%)				0.527	0.401
No	67 (28.51)	28 (31.46)	39 (26.71)		
Yes	168 (71.49)	61 (68.54)	107 (73.29)		
Diabetes history, n (%)				0.794	0.068
No	168 (71.49)	65 (73.03)	103 (70.55)		
Yes	67 (28.51)	24 (26.97)	43 (29.45)		
HCY, M (Q1,Q3)	11.1 (8.6, 14.05)	10.6 (8.07, 13.43)	11.9 (9.35, 15.25)	0.043	4.101
Neutrophil count, M (Q1,Q3)	4.5 (3.6, 5.6)	4.3 (3.58, 5.2)	4.6 (3.6, 5.8)	0.184	1.762
Lymphocyte count, Median (Q1,Q3)	1.6 (1.2, 2.1)	1.5 (1.2, 2.1)	1.6 (1.3, 2)	0.631	0.231
Monocyte count, Median (Q1,Q3)	0.4 (0.3, 0.47)	0.4 (0.3, 0.42)	0.4 (0.3, 0.5)	1	0
PLT, $\bar{x} \pm s$	224.95 $\pm$ 59.18	215.14 $\pm$ 59.7	230.91 $\pm$ 58.3	0.048	3.94
CRP, M(Q1,Q3)	0.63 (0.5, 1.92)	0.5 (0.5, 1.32)	0.7 (0.5, 2.18)	0.02	5.381
FBG, M(Q1,Q3)	2.52 (2.24, 2.99)	2.5 (2.17, 2.95)	2.54 (2.27, 3.04)	0.377	0.782
D-Dimer, M (Q1,Q3)	0.38 (0.24, 0.69)	0.38 (0.22, 0.65)	0.37 (0.27, 0.76)	0.254	1.301
Random blood glucose, M(Q1,Q3)	6.05 (5.06, 7.78)	5 (4.67, 6.13)	6.69 (5.68, 8.82)	< 0.001	50.065
TCHO, $\bar{x} \pm s$	4.8 $\pm$ 1.15	4.49 $\pm$ 1.14	5 $\pm$ 1.12	< 0.001	11.26
TG, M (Q1,Q3)	1.34 (1.03, 1.86)	1.23 (0.9, 1.73)	1.4 (1.1, 1.87)	0.048	3.894
HDL, M (Q1,Q3)	1.1 (0.92, 1.34)	1.13 (0.92, 1.38)	1.08 (0.92, 1.29)	0.491	0.475
LDL, $\bar{x} \pm s$	2.91 $\pm$ 1.1	2.53 $\pm$ 1.06	3.11 $\pm$ 1.06	< 0.001	14.709
NLR, M(Q1,Q3)	2.73 (1.83, 4)	2.56 (1.88, 3.87)	2.88 (2.03, 4.4)	0.033	0.271
PLR, M(Q1,Q3)	136.96 (102.78, 177.27)	123.3 (96.88, 158.21)	141.67 (109.55, 174.44)	0.015	1.011

Multivariate Logistic Regression Analysis

Variables showing significant differences in differential analysis (all $p < 0.05$; Table 1) were included in a multivariate logistic regression model to identify independent predictors of AIS. The analysis revealed that NIHSS score (OR = 5.497, 95% CI: 3.599–8.395; $*p < 0.001$), CRP (OR = 1.128, 95% CI: 1.005–1.295; $*p = 0.038$), random blood glucose (OR = 1.103, 95% CI: 1.013–1.268; $*p = 0.043$), total cholesterol (OR = 1.626, 95% CI: 1.022–2.931; $*p = 0.023$), triglycerides (OR = 1.337, 95% CI: 1.025–1.721; $*p = 0.031$), and LDL (OR = 1.542, 95% CI: 1.142–1.959; $*p = 0.025$) were independent risk factors for CT-negative mild AIS (Table 2). In contrast, HCY, PLT, NLR, and PLR were not independently associated with AIS diagnosis in the multivariate model.

Model Development and Performance

First, meaningful variables including NIHSS, HCY, PLT, CRP, random blood glucose, TCHO, TG, LDL, NLR, and PLR were screened through difference analysis and chi-square test. Subsequently, these variables were incorporated into a multivariate regression model, and six independent risk factors for stroke were identified: NIHSS, CRP, random blood glucose, total cholesterol, triglycerides, and LDL. Finally, a nomogram was established based on these six risk factors.

Table 2 Multivariate Logistic Regression Analysis of Risk Factors for AIS

	B	S.E.	Wals	df	Sig.	Exp (B)	EXP(B) 95% C.I.	
NIHSS	1.704	0.216	62.217	1	0.000	5.497	3.599	8.395
HCY	0.023	0.034	0.459	1	0.498	1.023	0.957	1.094
PLT	0.001	0.004	0.018	1	0.895	1.001	0.992	1.009
CRP	0.120	0.070	2.910	1	0.038	1.128	1.005	1.295
GLU	0.089	0.076	1.388	1	0.043	1.103	1.013	1.268
TCHO	0.486	0.301	2.614	1	0.023	1.626	1.022	2.931
TG	0.128	0.212	0.368	1	0.031	1.337	1.025	1.721
LDL	0.041	0.322	0.016	1	0.025	1.542	1.142	1.959
NLR	0.337	0.143	5.554	1	0.108	0.997	0.987	1.854
PLR	-0.006	0.005	1.576	1	0.209	0.994	0.985	1.003
Constant	-6.850	1.440	22.633	1	0.000	0.001		

A nomogram was developed to visualize the model, allowing for the calculation of an individual’s risk of AIS based on the sum of points assigned to each predictor (Figure 2).

The model demonstrated strong discriminative ability. In the training set, the area under the receiver operating characteristic curve (AUC) was 0.830 (95% CI: 0.778–0.882), while in the validation set, the AUC was 0.804 (95% CI: 0.712–0.896) (Figures 3a and b). Calibration of the model was evaluated using the Hosmer–Lemeshow test, which yielded chi-square values of 3.8946 (*p* = 0.8665) for the training set and 6.7009 (*p* = 0.5692) for the validation set, indicating excellent agreement between predicted and observed probabilities (Figures 4a and b). Decision curve analysis further confirmed the clinical utility of the model, showing a net benefit across a wide range of threshold probabilities in both the training and validation sets (Figures 5a and b).

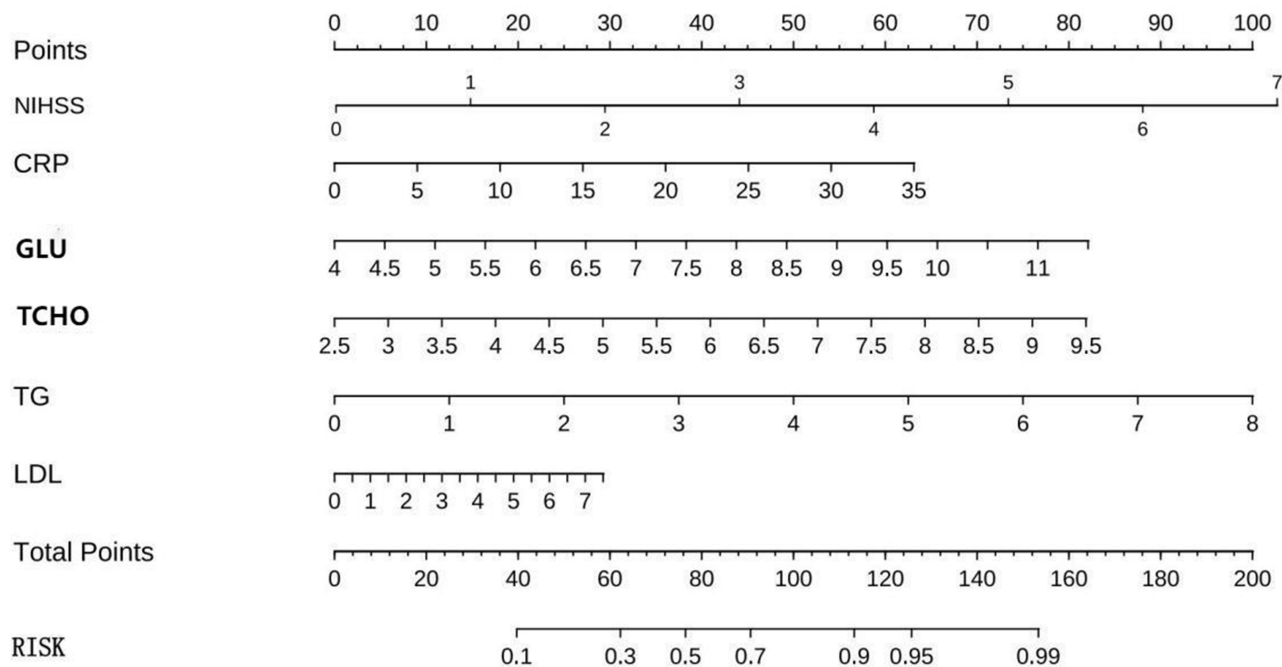


Figure 2 Nomogram for predicting the risk of CT-negative mild AIS.
Abbreviations: AIS, acute ischemic stroke; NIHSS, National Institutes of Health Stroke Scale; CRP, C-reactive protein; GLU, glucose; TCHO, total cholesterol; TG, triglycerides; LDL, low density lipoprotein cholesterol.

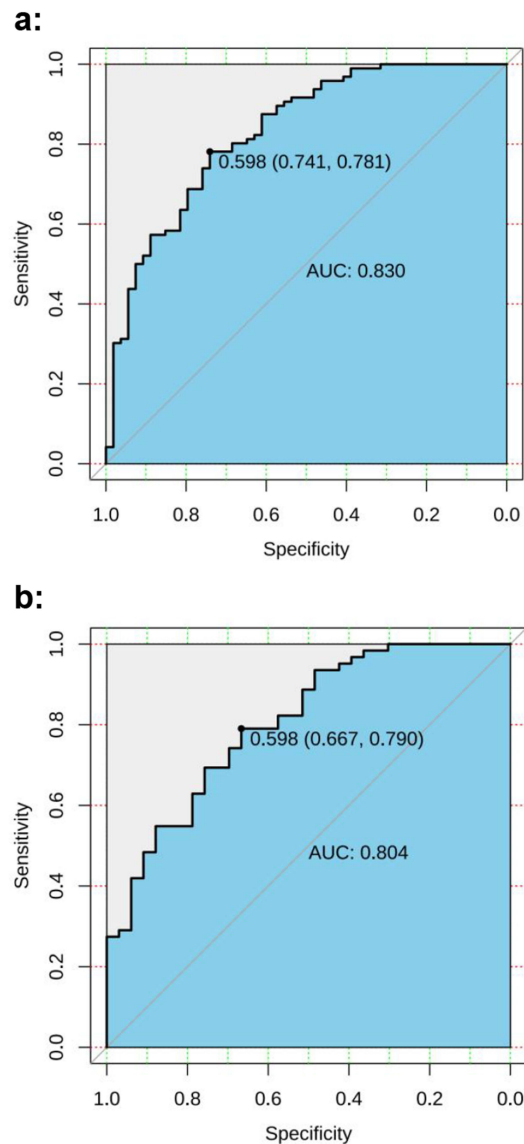


Figure 3 ROC curve of the prediction model. (a) ROC curve of the prediction model in the training set. (b) ROC curve of the prediction model in the validation set. **Abbreviations:** ROC, Receiver Operating Characteristic Curve; AUC, Area Under Curve.

Discussion

In this study, we developed and validated a clinical prediction model incorporating NIHSS score, CRP, GLU, TCHO, TG, and LDL for distinguishing CT-negative mild AIS from TIA within the critical 6-hour post-onset window. The model demonstrated robust discriminative ability, good calibration, and clinical utility across both training and validation cohorts.

Our multivariate analysis revealed that the NIHSS, CRP, glucose, total cholesterol, triglycerides, and LDL as independent predictors of mild AIS. Notably, the NIHSS score emerged as the strongest predictor (OR = 5.497), underscoring its central role in quantifying early neurological deficit and aligning with its established prognostic value in stroke outcomes.^{18,19} While the histories of hypertension and diabetes did not show significant differences between the AIS and TIA groups—likely due to these conditions being common risk factors—there was a notable association between elevated admission glucose levels and AIS. This finding supports the notion that acute hyperglycemia may reflect stress response or ischemic burden, even in the absence of diagnosed diabetes.^{20,21}

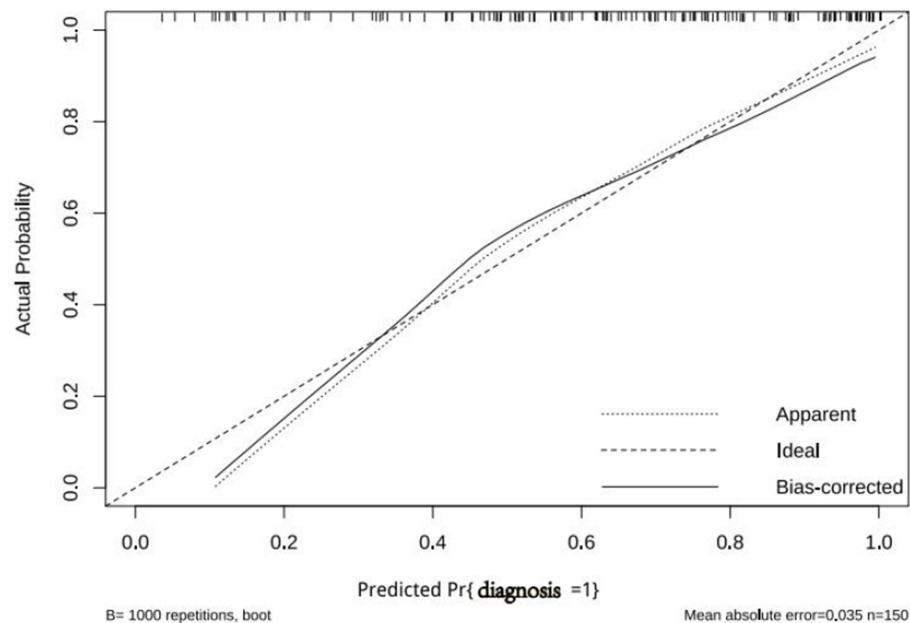
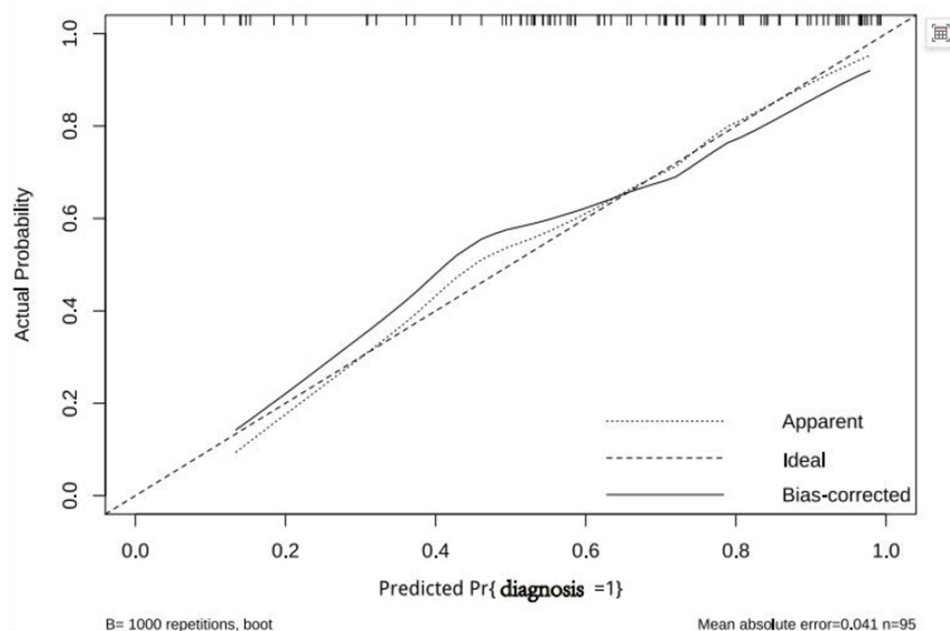
a:**b:**

Figure 4 Calibration curve. (a) Calibration curve for the training set. (b) Calibration curve for the validation set.

Abbreviation: ROC, Receiver Operating Characteristic Curve.

The inclusion of lipid parameters (total cholesterol, triglycerides, and LDL) highlights the contribution of atherogenic dyslipidemia to early ischemic injury.²² Similarly, elevated CRP, a marker of systemic inflammation, further implicates inflammatory pathways in the acute phase of AIS.²³ These findings are consistent with previous studies suggesting that both metabolic and inflammatory processes play critical roles in stroke pathogenesis.^{22–24}

Our model demonstrated strong performance with AUC values of 0.830 in the training set and 0.804 in the validation set, reflecting its satisfactory ability to distinguish between outcomes. The calibration of the model was also impressive,

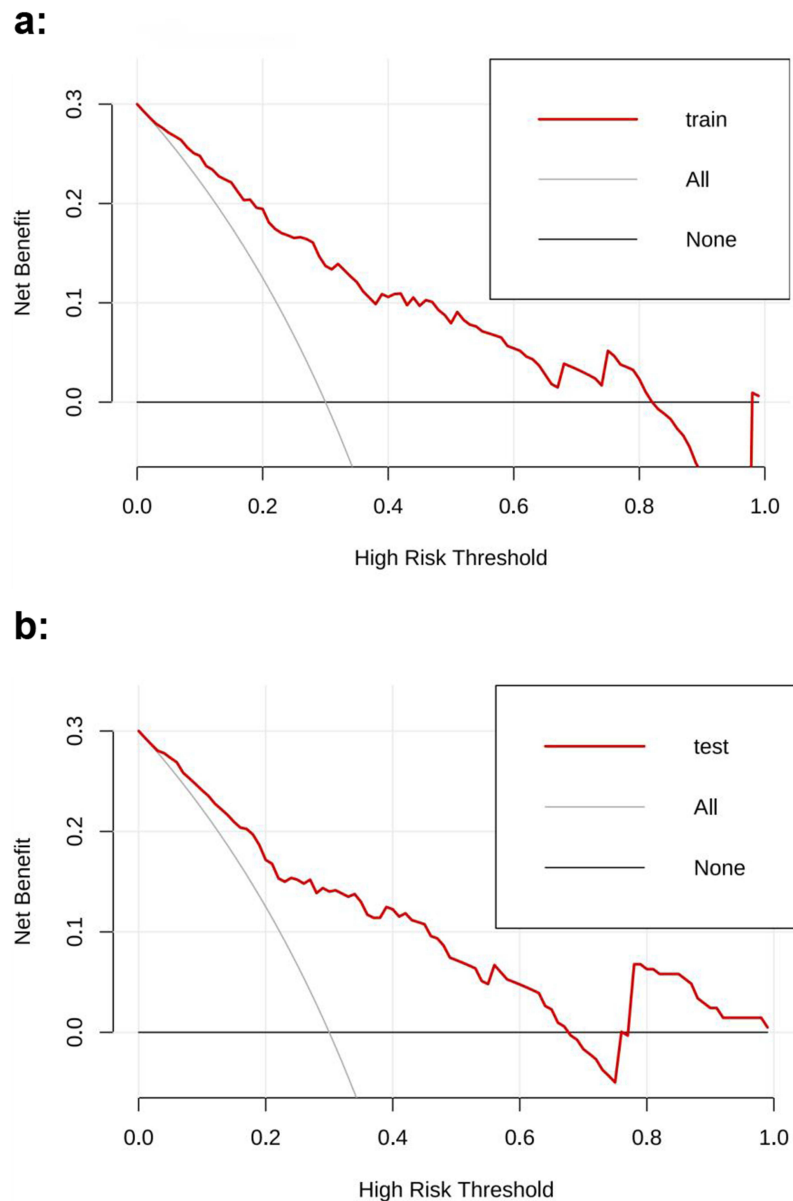


Figure 5 Decision curve. (a) Decision curve for the training set. (b) Decision curve for the validation set.
Abbreviation: ROC, Receiver Operating Characteristic Curve.

evidenced by the non-significant results from the Hosmer–Lemeshow test, which suggests that the predicted probabilities closely align with actual outcomes. Furthermore, the decision curve analysis reinforced the model's clinical relevance, showing that it maintains utility across a practical range of threshold probabilities.

A significant advantage of this model lies in its dependence on commonly available clinical and laboratory parameters, which makes it especially appropriate for resource-limited environments where MRI may not be easily accessible. By combining objective biomarkers with a validated clinical scale, specifically the NIHSS, the model enables quick risk assessment and aids in clinical decision-making during the critical thrombolytic window.

While several studies have explored biomarkers in stroke diagnosis, few have focused specifically on discriminating CT-negative mild AIS from TIA in the ultra-early phase. Our work extends the findings of Agard et al,²⁵ who emphasized the role of inflammatory ratios such as NLR and PLR, by demonstrating the additional value of lipid and metabolic markers. Moreover, unlike many previous models, ours was designed specifically for the ≤ 6 -hour timeframe, aligning with the window for intravenous thrombolysis.

Our model serves as a valuable resource for facilitating the early diagnosis of CT-negative mild AIS, especially in situations where MRI is not an option. By allowing for faster treatment decisions, this model has the potential to minimize delays in administering thrombolysis, which can lead to better functional outcomes and a decrease in disability.

Limitations and Future Directions

Several limitations should be acknowledged. First, this was a single-center, retrospective study with a modest sample size, which may limit generalizability and introduce selection bias. Second, we did not include emerging biomarkers such as GFAP or S100B, which have shown promise in stroke diagnostics.²⁶ Future prospective, multi-center studies with larger cohorts are needed to validate and refine the model. Additionally, incorporating advanced biomarkers or neuroimaging features could further improve predictive accuracy. The potential of artificial intelligence-based integration of clinical, laboratory, and imaging data also warrants exploration.

Conclusion

This prediction model provides a practical, evidence-based tool for identifying CT-negative ultra-early mild AIS in resource-limited settings. Its integration into clinical workflows may accelerate thrombolysis initiation, reduce diagnostic delays, and improve functional recovery. Future studies should validate the model in multi-center, prospective cohorts and assess its impact on real-world clinical decision-making and healthcare resource utilization.

Data Sharing Statement

The data can be obtained upon reasonable from the corresponding author.

Ethics Statement

This study was performed in line with the principles of the Declaration of Helsinki and was approved by the Ethical Committee of Shishi Municipal Hospital (the ethics approval number: 202304). As this retrospective analysis used routinely collected data informed consent was waived. This study strictly adheres to the principles of patient confidentiality. All personal information and medical data of the patients have been anonymized to ensure that no individual identities can be identified. The collection, storage, and analysis of all data during the research process comply with the relevant ethical and privacy protection standards.

Consent for Publication

All authors consent for publication.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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