British Journal of Hospital Medicine

Br. J. Hosp. Med. (Lond) **2026**; 87(9): 50688
https://doi.org/10.31083/BJHM50688

Article

Predictors of Functional Recovery in Patients With Mild Hemorrhagic Transformation Following Intravenous Thrombolysis for Acute Ischemic Stroke

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Academic Editor: John Alcolado
Submitted: 4 February 2026 Revised: 1 June 2026 Accepted: 8 July 2026 Published: 18 September 2026

Abstract

Aims/Background: Patients who develop mild hemorrhagic transformation (HT) after intravenous thrombolysis (IVT) for acute ischemic stroke (AIS) exhibit substantial heterogeneity in functional recovery. However, a systematic evaluation of predictors of functional recovery in this specific population remains lacking. This study aimed to identify the clinical and nutritional factors associated with functional recovery in these patients. **Methods:** This dual-center retrospective cohort study consecutively enrolled 204 patients with AIS who developed mild HT after IVT between March 2020 and March 2025. Based on the modified Rankin Scale (mRS) score at 3 months, patients were classified into a good functional recovery group (mRS $\leq$2, n = 153) and a poor functional recovery group (mRS $\geq$3, n = 51). Demographic, clinical, and laboratory data were collected. Nutritional status was evaluated using the Controlling Nutritional Status (CONUT) score and the Prognostic Nutritional Index (PNI). Univariate and multivariate logistic regression analyses were performed to identify independent predictors. The predictive performance of individual factors and a combined model was assessed using receiver operating characteristic (ROC) curve analysis. **Results:** Univariate analysis demonstrated that age, baseline National Institutes of Health Stroke Scale (NIHSS) score, PNI, CONUT score, arrival-to-thrombolysis time, and history of diabetes mellitus (HD) were significantly associated with poor functional recovery (all $p < 0.05$). Multivariate analysis identified HD, older age, a higher baseline NIHSS score, and a higher CONUT score as independent risk factors for poor functional recovery (all $p < 0.05$). A combined model incorporating these four variables demonstrated the highest discriminative performance, with an area under the curve (AUC) of 0.840 (95% CI: 0.783–0.897). At the optimal probability cut-off of 0.156, the model achieved a specificity of 92.2% and a sensitivity of 64.5%. **Conclusion:** In patients with AIS who develop mild HT after IVT, baseline neurological deficit severity, nutritional status, HD, and age are independent determinants of functional recovery. A model integrating these factors demonstrates superior discriminative potential and may facilitate early risk stratification and personalized management in this patient population.

Keywords: acute ischemic stroke; intravenous thrombolysis; hemorrhagic transformation; functional recovery

1. Introduction

Acute ischemic stroke (AIS) is a leading cause of mortality and long-term disability worldwide, imposing a substantial socioeconomic burden [1]. Intravenous thrombolysis (IVT) has been shown to improve early neurological outcomes in eligible patients [2]. However, clinical outcomes vary considerably even among patients who receive timely thrombolysis, with some experiencing poor functional recovery or secondary complications [3]. This heterogeneity suggests that relying solely on treatment time windows or imaging criteria is insufficient for accurately predicting functional outcomes after thrombolysis. Notably, in patients with AIS, mild neurological deficits do not necessarily indicate a favorable prognosis. A previous study have shown that a considerable proportion of patients with mild ischemic stroke may develop early neurological deterioration or experience limited functional recovery after the acute phase, especially among those who develop hemorrhagic transformation (HT) following IVT, in whom the variability in clinical outcomes is more pronounced [4]. Hemorrhagic transformation is one of the most concerning safety concerns associated with thrombolytic therapy. Its occurrence may not only offset the benefits of reperfusion but is also closely associated with poor functional outcomes and an increased risk of death [5]. Therefore, in patients with HT after thrombolysis, further identification of the key factors affecting functional recovery is of great clinical significance for optimizing individualized management and prognostic assessment.

Functional recovery after stroke is a complex process influenced by multiple factors, including the severity of neurological injury, reperfusion-related changes, inflammatory responses, metabolic disturbances, and the overall health of patients. Previous prognostic studies in AIS have primarily focused on imaging characteristics, vascular recanalization, and thrombolysis-related complications,

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while the systematic evaluation of nutritional and metabolic factors has received relatively limited attention [6,7]. Nutritional status is increasingly recognized as an important determinant of clinical outcomes in patients with acute stroke. Malnutrition is common in this population and has been associated with increased complications, delayed neurological recovery, and poorer long-term functional outcomes [8,9]. However, conventional nutritional assessments are often challenging to perform during the acute phase because of stroke severity, swallowing difficulties, or communication barriers. Consequently, objective nutritional assessment tools derived from routine laboratory tests, including serum albumin, lipid profiles, and peripheral blood cell counts, have attracted increasing attention as practical alternatives for risk stratification. These indicators are readily available and reproducible, offering new opportunities for acute-phase assessment. Nevertheless, current evidence regarding these nutritional indicators has been derived predominantly from the general stroke population, and their prognostic value in patients with HT following IVT remains insufficiently characterized.

The influence of individual patient characteristics on prognosis and functional recovery has also attracted increasing attention. For example, the roles of demographic characteristics and comorbidities in stroke recovery have gradually become a focus of investigation [10,11]. Advanced age is often accompanied by reduced physiological reserve and an increased burden of underlying diseases, both of which may influence post-stroke recovery. However, among patients who undergo intravenous thrombolysis and subsequently develop mild HT, the relationship between these factors and functional outcomes remains insufficiently investigated, and their clinical significance requires further clarification. Stroke severity is also considered an essential clinical factor that affects functional outcomes. The NIHSS score, a widely used tool for assessing neurological deficits, has been applied extensively in stroke classification and prognostic prediction [12]. However, whether a single neurological deficit score can adequately reflect the potential for functional recovery in patients with mild stroke or specific comorbidities remains controversial.

In summary, although previous studies have investigated prognostic factors in acute ischemic stroke from multiple perspectives, current evidence remains limited for the specific subgroup of patients who develop mild HT following intravenous thrombolysis, particularly regarding the integrated evaluation of nutritional status, metabolic factors, stroke severity, and demographic characteristics, which have not been systematically analyzed in this population. Consequently, reliable prediction of functional recovery in this patient population remains uncertain in routine clinical practice. Therefore, the present study aimed to systematically analyze patients with acute ischemic stroke who developed mild HT following intravenous thrombolysis and to explore the associations between clinical and laboratory factors and functional recovery outcomes to provide clinically valuable evidence to support risk stratification and individualized management in this population.

2. Methods

2.1 Study Design and Patients

This study was a dual-center retrospective cohort study. Patients with AIS who developed mild HT after intravenous thrombolysis were consecutively enrolled from the Affiliated Hospital of North Sichuan Medical College (n = 110) and Guangdong Provincial Hospital of Traditional Chinese Medicine (n = 94). The study period extended from March 2020 to March 2025. All patients fulfilled the diagnostic criteria for AIS and received intravenous thrombolysis with either recombinant tissue plasminogen activator (rt-PA) or urokinase within the recommended therapeutic time window according to standard dosing regimens.

The inclusion criteria were as follows: (1) age ≥18 years; (2) clinical and imaging diagnosis of AIS [13]; (3) treatment with intravenous rt-PA (0.9 mg/kg, maximum dose, 90 mg) within 4.5 hours of symptom onset or intravenous urokinase (1,000,000–1,500,000 IU) within 6 hours of symptom onset [14]; (4) follow-up head computed tomography (CT) or magnetic resonance imaging (MRI) performed 24–72 hours after thrombolysis demonstrating HT, classified as mild (hemorrhagic infarction type 1 or 2 according to the European Cooperative Acute Stroke Study [ECASS] criteria), without meeting the diagnostic criteria for symptomatic intracranial hemorrhage [15]; and (5) complete baseline clinical information, laboratory test results, and follow-up data.

The exclusion criteria were as follows: (1) intracranial hemorrhage or other severe intracranial space-occupying lesions before thrombolysis; (2) symptomatic intracranial hemorrhage after thrombolysis; (3) severe concomitant infection, malignant tumor, hematological disease, or autoimmune disease; (4) patients with pre-stroke severe disability (pre-stroke mRS >2) and (5) incomplete follow-up or missing key clinical data, or loss to follow-up.

2.2 Functional Outcome Assessment

Functional outcomes were evaluated using the modified Rankin Scale (mRS) at 3 months after stroke onset. The mRS is one of the most commonly used measures of functional outcome in stroke research and primarily assesses disability and independence in activities of daily living. The scale has demonstrated good reliability and validity and has been extensively applied in clinical studies and randomized controlled trials involving patients with acute ischemic stroke [16].

The mRS assessment was performed by neurologists who had received standardized training through outpatient visits or structured telephone follow-up. Outcome assessment was supplemented by a review of the patients' med-

ical records to ensure accuracy. Consistent with the common grouping method adopted in previous stroke prognostic studies, an mRS score ≤2 was defined as good functional recovery, whereas an mRS score ≥3 was defined as poor functional recovery [17]. Based on the 3-month mRS score, patients were divided into either the good functional recovery group or the poor functional recovery group. Clinical characteristics and laboratory indicators were subsequently compared between the two groups, and factors associated with functional recovery were further analyzed.

2.3 Collection of Baseline Data and Laboratory Indicators

Baseline demographic and clinical data were retrospectively extracted from the hospital's electronic medical record systems, including age, sex, body mass index (BMI), systolic blood pressure (SBP) and diastolic blood pressure (DBP) at admission, history of diabetes mellitus (HD), current smoking status, previous ischemic stroke, hypertension, hyperlipidemia, coronary artery disease, atrial fibrillation, and the type of fibrinolytic agent administered. The interval from hospital arrival to initiation of thrombolysis was recorded for each patient. Stroke subtype was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria [18]. Stroke severity at admission was assessed using the National Institutes of Health Stroke Scale (NIHSS), a standardized tool for evaluating neurological deficits in consciousness, language, motor function, and sensory function; the NIHSS score ranges from 0 to 42, with higher scores indicating more severe neurological deficits [19]. All NIHSS assessments were performed by experienced neurologists who had undergone standardized training before study initiation.

All laboratory parameters were obtained from the first venous blood sample collected after admission and before intravenous thrombolysis. All samples were analyzed in the hospital's central laboratories according to standardized operating procedures. Laboratory measurements included serum albumin, total cholesterol, peripheral blood lymphocyte count, admission blood glucose, glycated hemoglobin (HbA1c), and C-reactive protein (CRP).

Nutritional status was assessed using the Controlling Nutritional Status (CONUT) score [20] and the Prognostic Nutritional Index (PNI) [21]. The CONUT score was calculated from three laboratory parameters: serum albumin level, total cholesterol, and peripheral blood lymphocyte count, comprehensively reflecting the patient's protein reserves, lipid metabolism, and immune function. The PNI was calculated using the following formula:

PNI = Serum Albumin (g/L) + 5 × Peripheral Blood Lymphocyte Count (10^9/L).

Both nutritional indices are derived from routinely available laboratory indicators, providing objective, reproducible, and convenient measures of nutritional status, and have been widely used in prognostic studies of neurological diseases, including stroke. Since serum albumin level, total cholesterol, and peripheral blood lymphocyte count constitute the components of the CONUT score and PNI, and their information is integrated into the corresponding nutritional scores, these individual laboratory indicators were not entered separately into subsequent baseline comparisons or regression analyses to avoid redundancy and potential collinearity.

2.4 Statistical Analysis

All statistical analyses were performed using SPSS 26.0 (IBM Corp., Armonk, NY, USA) and R software (R Foundation for Statistical Computing, Vienna, Austria).

The normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Normally distributed variables were expressed as mean ± standard deviation (mean ± SD), and comparisons between groups were performed using the independent-samples *t*-tests. Non-normally distributed variables were expressed as median and interquartile range [M (Q1, Q3)] and compared using the Mann–Whitney *U* test. Categorical variables were expressed as frequencies and percentages and compared using the chi-square (χ^2) test. When the expected frequency in any cell was <5, Yates' continuity correction was applied for 2 × 2 contingency tables, whereas Fisher's exact test was used for R × C contingency tables. Functional recovery outcome was treated as the dependent variable. Univariate logistic regression analysis was initially performed to identify variables potentially associated with functional recovery. Variables with $p < 0.05$ in the univariate analysis were subsequently entered into a multivariate logistic regression model using backward stepwise selection based on the likelihood ratio method to identify independent predictors of functional recovery. Variables were retained in the model if their *p*-value was < 0.10; otherwise, they were removed stepwise. Multicollinearity among variables in the multivariate regression model was evaluated using variance inflation factors (VIFs), with VIFs >10 considered to indicate significant multicollinearity. Regression results were presented as odds ratios (ORs) with corresponding 95% confidence intervals (95% CIs).

The discriminative performance of each independent predictor and the combined model was evaluated using receiver operating characteristic (ROC) curve analysis, and the area under the curve (AUC) was calculated. The optimal cutoff values for continuous predictor variables and combined models were determined by maximizing the Youden index. The sensitivity, specificity, and corresponding optimal cutoff values for each predictor variable and combined model are reported. All statistical tests were two-tailed, and *p*-values < 0.05 were considered statistically significant.

3. Results

3.1 Baseline Demographic and Clinical Characteristics

A total of 204 patients with acute ischemic stroke who underwent intravenous thrombolysis and subsequently ex-

perienced mild HT were included in this study. Based on functional recovery outcomes at 3 months, patients were divided into a good functional recovery group (n = 153) and a poor functional recovery group (n = 51). The baseline characteristics of the two groups are detailed in Table 1.

Comparative analyses demonstrated statistically significant differences between the two groups in age, baseline NIHSS score, PNI, CONUT score, arrival-to-thrombolysis time, and history of diabetes mellitus (all $p < 0.05$). Conversely, no significant differences were observed in BMI, CRP, admission blood glucose, HbA1c, systolic or diastolic blood pressure, or other baseline characteristics, including sex, stroke subtype, smoking status, hypertension, hyperlipidemia, coronary artery disease, atrial fibrillation, history of ischemic stroke, and fibrinolytic agent type (all $p > 0.05$).

3.2 Univariate Regression Analysis

Univariate logistic regression analysis was performed using poor functional recovery as the dependent variable. The results are shown in Table 2.

History of diabetes mellitus ($p = 0.003$), age ($p = 0.007$), baseline NIHSS score ($p < 0.001$), CONUT score ($p < 0.001$), PNI ($p = 0.042$), and arrival-to-thrombolysis time ($p = 0.045$) were significantly associated with poor functional recovery. Specifically, a history of diabetes mellitus, older age, a higher baseline NIHSS score, a higher CONUT score, and a longer arrival-to-thrombolysis time were associated with an increased risk of poor functional outcomes, while a higher PNI was associated with a lower risk of poor functional recovery.

No significant associations were observed between poor functional recovery and sex, stroke subtype, smoking status, hypertension, hyperlipidemia, coronary artery disease, atrial fibrillation, previous ischemic stroke, fibrinolytic agent type, BMI, CRP, admission blood glucose, blood pressure, or HbA1c in the univariate analysis (all $p > 0.05$).

3.3 Multivariate Logistic Regression Analysis

Collinearity diagnostics demonstrated that all variance inflation factors (VIF) were below 2, indicating no significant multicollinearity among the candidate variables. PNI and arrival-to-thrombolysis time were initially included in the multivariate model but were subsequently removed during the backward stepwise selection procedure because their p-values exceeded the predefined retention criterion of 0.1. In the final multivariate logistic regression model, history of diabetes mellitus (OR = 2.640, $p = 0.014$), age (OR = 1.031, $p = 0.049$), baseline NIHSS score (OR = 1.230, $p < 0.001$), and CONUT score (OR = 1.365, $p < 0.001$) were independent influencing factors for poor functional recovery (Table 3). These findings indicate that, independent of other covariates, a history of diabetes mellitus, advanced age, higher baseline neurological deficits, and poorer nutritional status were significant predictors of an increased risk of poor functional recovery following intravenous thrombolysis in patients who developed mild HT.

3.4 Evaluation of Predictive Model Performance

The predictive performance of each independent indicator for poor functional recovery was evaluated using receiver operating characteristic (ROC) curve analysis (Fig. 1). The results showed that the combined model incorporating history of diabetes mellitus, age, baseline NIHSS score, and CONUT score achieved the highest discriminative performance, with an area under the curve (AUC) of 0.840 (95% CI: 0.783–0.897), outperforming each indicator. The optimal probability cut-off value, determined using the maximum Youden index, was 0.156, corresponding to a specificity of 92.2% and a sensitivity of 64.5%.

Among the individual indicators, the baseline NIHSS score demonstrated the greatest predictive performance (AUC = 0.761), followed by the CONUT score (AUC = 0.710), age (AUC = 0.622), and history of diabetes mellitus (AUC = 0.617). The optimal cut-off values, corresponding sensitivities, and specificities for each predictor are summarized in Table 4.

4. Discussion

Acute ischemic stroke (AIS) is one of the leading causes of mortality and long-term disability worldwide [22]. Although intravenous thrombolysis has been demonstrated to improve acute neurological function in eligible patients, hemorrhagic transformation (HT) after thrombolysis remains one of the major complications affecting functional recovery after reperfusion therapy. Compared with symptomatic intracranial hemorrhage, mild HT is more common in clinical practice and is generally characterized by less severe imaging manifestations. However, patients with mild HT exhibit considerable variability in long-term functional outcomes. This observation suggests that, in addition to the hemorrhagic event itself, multiple clinical and biological factors contribute to the regulation of post-stroke functional recovery. In the present study, patients with AIS who developed mild HT following intravenous thrombolysis were enrolled, and functional outcomes were assessed based on the modified Rankin Scale (mRS) at 3 months after stroke onset. The relationship between clinical characteristics, nutritional status, and functional recovery was systematically analyzed. The findings showed that stroke severity, nutritional status, history of diabetes mellitus, and age were independently associated with functional outcomes. These findings indicate that even among patients with relatively mild HT, these factors remain significant determinants of neurological function recovery.

Regarding stroke severity, the present study demonstrated that baseline NIHSS score was significantly associated with the 3-month functional outcome, with higher NIHSS scores predicting a greater risk of poor functional recovery. This finding suggests that the NIHSS not only

Table 1. Comparison of baseline demographic and clinical characteristics of patients between the two groups.

Variables	Good functional recovery (n = 153)	Poor functional recovery (n = 51)	Statistic	*p*-value
Age (years)	61.44 (51.75, 71.49)	66.41 (58.01, 72.98)	Z = –2.544	0.011
BMI (kg/m^2)	23.88 ± 3.08	24.50 ± 3.23	t = –1.217	0.225
Baseline NIHSS score	8.00 (5.00, 11.00)	12.00 (9.00, 15.00)	Z = –5.586	<0.001
CRP (mg/L)	12.30 (6.24, 17.31)	9.60 (5.78, 13.25)	Z = –1.665	0.096
PNI	43.38 ± 5.80	41.46 ± 5.40	t = 2.088	0.038
Arrival-to-thrombolysis time (min)	152.97 ± 14.92	158.02 ± 14.35	t = –2.108	0.036
Admission blood glucose (mg/dL)	157.69 ± 48.88	167.33 ± 53.05	t = –1.193	0.234
SBP (mmHg)	148.13 ± 19.60	153.80 ± 20.95	t = –1.758	0.080
DBP (mmHg)	87.04 ± 18.34	82.82 ± 19.09	t = 1.408	0.161
HbA1c (%)	6.27 ± 0.82	6.46 ± 1.10	t = –1.102	0.274
CONUT score	5.02 (3.04, 6.59)	7.69 (4.83, 9.12)	Z = –4.462	<0.001
Sex, n (%)			χ^2 = 0.062	0.803
Female	60 (39.22)	19 (37.25)		
Male	93 (60.78)	32 (62.75)		
Stroke subtype, n (%)			Fisher	0.676
Cardioembolism	42 (27.45)	14 (27.45)		
Large artery atherosclerosis	57 (37.25)	21 (41.18)		
Other determined etiology	6 (3.92)	0 (0.00)		
Small-artery occlusion	40 (26.14)	12 (23.53)		
Undetermined etiology	8 (5.23)	4 (7.84)		
Current smoking status, n (%)			χ^2 = 0.166	0.684
No	122 (79.74)	42 (82.35)		
Yes	31 (20.26)	9 (17.65)		
Hypertension, n (%)			χ^2 = 0.569	0.451
No	54 (35.29)	21 (41.18)		
Yes	99 (64.71)	30 (58.82)		
History of diabetes mellitus, n (%)			χ^2 = 9.529	0.002
No	111 (72.55)	25 (49.02)		
Yes	42 (27.45)	26 (50.98)		
Hyperlipidemia, n (%)			χ^2 = 3.493	0.062
No	120 (78.43)	46 (90.20)		
Yes	33 (21.57)	5 (9.80)		
Coronary artery disease, n (%)			χ^2 = 0.014	0.905
No	133 (86.93)	44 (86.27)		
Yes	20 (13.07)	7 (13.73)		
Atrial fibrillation, n (%)			χ^2 = 0.008	0.927
No	112 (73.20)	37 (72.55)		
Yes	41 (26.80)	14 (27.45)		
Previous ischemic stroke, n (%)			χ^2 = 0.015	0.902
No	134 (87.58)	45 (88.24)		
Yes	19 (12.42)	6 (11.76)		
Fibrinolytic agent, n (%)			χ^2 = 0.340	0.560
rt-PA	4 (2.61)	0 (0.00)		
Urokinase	149 (97.39)	51 (100.00)		

BMI, body mass index; NIHSS, National Institutes of Health Stroke Scale; CRP, C-reactive protein; PNI, prognostic nutritional index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; CONUT, Controlling Nutritional Status; rt-PA, recombinant tissue plasminogen activator.

reflects the severity of acute neurological deficits but also serves as a valuable tool for predicting short- and medium-term prognosis after stroke. Tang et al. [23] investigated factors associated with neurological function recovery following intravenous thrombolysis in patients with mild ischemic stroke and similarly reported that higher baseline NIHSS scores were strongly associated with unfavorable functional recovery outcomes. Our findings further sug-

Table 2. Univariate regression analysis of factors associated with poor functional recovery.

Variables	β	SE	Z	*p*-value	OR (95% CI)
Age	0.037	0.014	2.680	0.007	1.038 (1.010–1.067)
BMI	0.060	0.053	1.148	0.251	1.062 (0.958–1.178)
Sex					
Female					1.000 (Reference)
Male	0.066	0.334	0.198	0.843	1.068 (0.555–2.056)
Stroke subtype					
Cardioembolism					1.000 (Reference)
Large-artery atherosclerosis	0.100	0.401	0.250	0.803	1.105 (0.504–2.423)
Other determined etiology	–15.467	979.610	–0.016	0.987	0.000 (0.000–Inf)
Small-artery occlusion	–0.105	0.451	–0.234	0.815	0.900 (0.372–2.179)
Undetermined etiology	0.539	0.699	0.771	0.440	1.714 (0.436–6.742)
Current smoking status					
No					1.000 (Reference)
Yes	–0.179	0.419	–0.426	0.670	0.836 (0.368–1.901)
Hypertension					
No					1.000 (Reference)
Yes	–0.239	0.331	–0.723	0.470	0.787 (0.411–1.506)
History of diabetes mellitus					
No					1.000 (Reference)
Yes	1.002	0.334	3.003	0.003	2.724 (1.416–5.239)
Hyperlipidemia					
No					1.000 (Reference)
Yes	–0.897	0.511	–1.756	0.079	0.408 (0.150–1.110)
Coronary artery disease					
No					1.000 (Reference)
Yes	0.049	0.472	0.103	0.918	1.050 (0.416–2.650)
Atrial fibrillation					
No					1.000 (Reference)
Yes	0.024	0.363	0.066	0.947	1.024 (0.503–2.087)
Previous ischemic stroke					
No					1.000 (Reference)
Yes	–0.069	0.499	–0.138	0.890	0.933 (0.351–2.482)
Fibrinolytic agent					
rt-PA					1.000 (Reference)
Urokinase	15.501	1199.772	0.013	0.990	5,393,374.052 (0.000–Inf)
Baseline NIHSS score	0.215	0.043	5.016	<0.001	1.240 (1.140–1.349)
CRP	–0.041	0.024	–1.712	0.087	0.960 (0.916–1.006)
CONUT score	0.302	0.068	4.450	<0.001	1.352 (1.184–1.545)
PNI	–0.060	0.030	–2.036	0.042	0.941 (0.888–0.998)
Arrival-to-thrombolysis time	0.023	0.011	2.002	0.045	1.023 (1.001–1.046)
Admission blood glucose	0.004	0.003	1.221	0.222	1.004 (0.998–1.010)
SBP	0.014	0.008	1.667	0.095	1.014 (0.998–1.031)
DBP	–0.012	0.009	–1.330	0.184	0.988 (0.971–1.006)
HbA1c	0.223	0.182	1.226	0.220	1.250 (0.875–1.786)

Note: For the categories "other determined etiology" within stroke subtype and rt-PA within the fibrinolytic agent variable, the sample sizes were very small. Consequently, the estimated odds ratios were unstable, with values that were either extremely large or near zero, and had very wide confidence intervals; they should therefore be interpreted with caution rather than as reliable estimates of effect.

gest that in patients who develop mild HT after thrombolysis, the initial severity of neurological impairment remains a major determinant of subsequent functional recovery. This association may reflect the lasting effects on long-term outcomes by affecting neural network reconstruction and functional compensation.

Table 3. Multivariate logistic regression analysis of independent predictors of poor functional recovery.

Variables	β	SE	Z	*p*-value	VIF	OR (95% CI)
History of diabetes mellitus						
No						1.000 (Reference)
Yes	0.971	0.394	2.463	0.014	1.030	2.640 (1.219–5.717)
Age (years)	0.031	0.016	1.966	0.049	1.031	1.031 (1.001–1.064)
Baseline NIHSS score	0.207	0.046	4.499	<0.001	1.029	1.230 (1.124–1.346)
CONUT score	0.311	0.078	3.987	<0.001	1.051	1.365 (1.171–1.591)

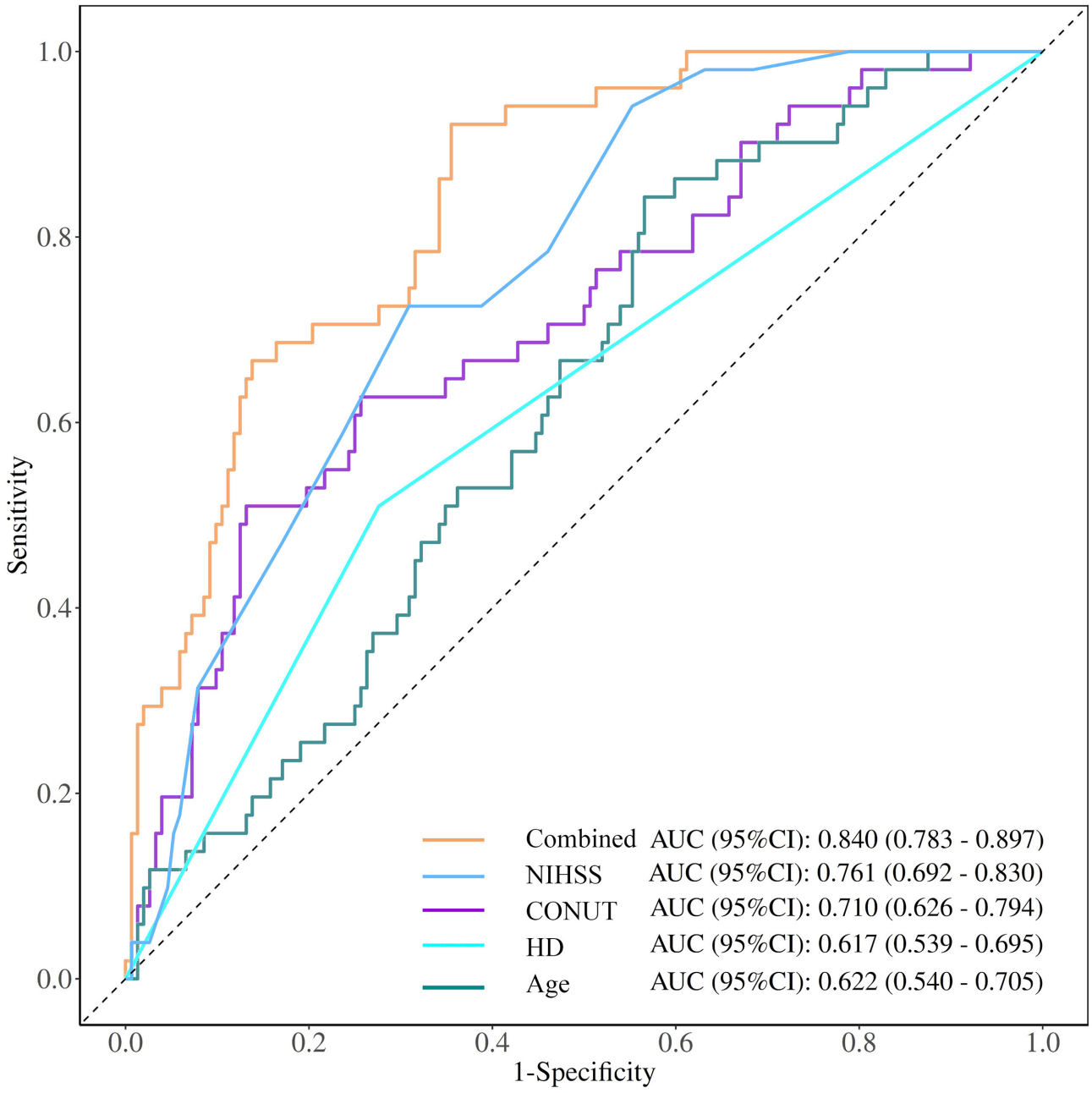

Fig. 1. Receiver operating characteristic (ROC) curve analysis of the prediction model.

Nutritional status was another important determinant of functional recovery identified in this study. Nutritional status was evaluated using both the CONUT score and PNI, and patients with poorer nutritional status exhibited a significantly higher risk of poor functional recovery. This finding is consistent with the trend in stroke research that has grad-

Table 4. Predictive performance of individual predictors and the combined model for poor functional recovery.

Variable	AUC (95% CI)	Specificity	Sensitivity	Optimal cut-off
Combined model	0.840 (0.783–0.897)	92.2%	64.5%	0.156
Baseline NIHSS score	0.761 (0.692–0.830)	69.1%	72.5%	10.500
CONUT score	0.710 (0.626–0.794)	86.8%	51.0%	7.684
Age (years)	0.622 (0.540–0.705)	43.4%	84.3%	56.736
History of diabetes mellitus	0.617 (0.539–0.695)	72.4%	51.0%	-

ually emphasized nutritional factors in recent years [24]. Previous studies have shown that malnutrition is common among patients with acute stroke and is closely associated with higher rates of infection, prolonged hospital stays, and poorer functional recovery [25,26]. Zhao et al. [27] further reported that lower PNI values and higher CONUT scores were significantly associated with unfavorable functional outcomes in patients with stroke. The present study further confirmed the prognostic value of nutritional status on functional recovery in the specific subgroup of patients with mild HT following intravenous thrombolysis. Malnutrition may affect the recovery process after stroke through multiple pathways. Poor nutritional status may weaken the immune function and reduce the capacity to regulate inflammatory responses, thereby amplifying the inflammatory response associated with ischemic stroke and HT. Additionally, insufficient protein and energy reserves may compromise neuronal repair and synaptic remodeling, which are essential for post-stroke functional recovery. In patients who have already developed mild HT, brain tissue is likely to be more susceptible to secondary injury. Consequently, malnutrition may further reduce their tolerance to ongoing pathological processes, thus hindering functional recovery.

In addition to these independent predictors, the arrival-to-thrombolysis time in our cohort was relatively long. Univariate analysis demonstrated that a longer arrival-to-thrombolysis time was associated with poorer functional recovery. However, this association did not remain statistically significant in the multivariate model after adjustment for age, baseline NIHSS score, history of diabetes mellitus, and CONUT score, suggesting that its effect on functional recovery may be partially mediated by its association with greater baseline neurological impairment or poorer nutritional status. The prolonged arrival-to-thrombolysis time observed in our cohort reflects real-world clinical practice at the participating centers during the study period, when standardized workflow optimization protocols had not yet been fully established, and urokinase was commonly administered within a wider therapeutic time window. The predominant use of urokinase (more than 97% of patients in both groups) may be attributed to several factors, including its lower cost, better accessibility in resource-limited settings, and a wider therapeutic time window (up to 6 hours) compared with rt-PA, making it a more practical treatment option in hospitals where a substantial proportion of patients present beyond the 4.5-hour window. However, efforts to minimize treatment delays should remain a clinical priority, even among patients at risk of developing mild HT.

The findings of this study further suggest that age is a valuable determinant of functional recovery in patients with AIS who develop mild HT after intravenous thrombolysis. Previous studies have consistently identified advanced age as an important predictor of unfavorable stroke prognosis [10,28,29]. Age-related reductions in neuroplasticity, increased comorbidities, and weakened overall physiological reserve may collectively limit the potential for functional recovery after stroke. The present findings indicate that, even in patients with mild HT, increasing age remains independently associated with poorer functional recovery, which is consistent with previous observations in broader populations of patients with AIS and those undergoing IVT.

This study also demonstrated that a history of diabetes mellitus was significantly associated with poor functional recovery in patients with AIS who developed mild HT after intravenous thrombolysis. Previous studies have shown that diabetes mellitus is one of the important predictors of poor prognosis in patients with ischemic stroke [30]. The present study further supports the adverse influence of diabetes mellitus on functional recovery in the specific subgroup of patients with mild HT. For patients who have already developed mild HT, these adverse factors may exert additive effects, thereby increasing the risk of poor long-term functional outcomes. Notably, the combined predictive model showed high specificity (92.2%) for distinguishing poor from good functional recovery but relatively limited sensitivity (64.5%). This performance profile suggests that the model is better suited as a preliminary screening tool for identifying patients at high risk of unfavorable functional outcomes than as a standalone prognostic instrument. Early identification of high-risk patients who develop mild HT after thrombolysis may facilitate closer clinical monitoring, timely nutritional assessment and support, and individualized rehabilitation interventions. Therefore, the combination of high specificity and moderate sensitivity provides practical clinical value for early risk stratification and post-stroke management.

This study still has several limitations. First, it was a dual-center retrospective study with a relatively small sample size, which may limit the generalizability of the findings. Therefore, multicenter studies with larger cohorts are required to validate these results. Second, nutritional status

was evaluated based on laboratory indicators obtained at admission and, therefore, could not capture dynamic changes in nutritional status during hospitalization or the potential influence of nutritional interventions on functional recovery. Third, variable selection for the multivariable analysis was based on univariable screening ($p < 0.05$), which may have excluded clinically relevant confounders, including prestroke functional status, stroke subtype, inflammatory biomarkers, detailed neuroimaging characteristics of HT, and neurological status after HT. Although major prognostic variables were incorporated into the analysis, the retrospective design of this study precluded the complete collection of these data, and residual confounding cannot be excluded. Future prospective studies with larger sample sizes and more comprehensive data collection are warranted to validate our findings.

5. Conclusion

In conclusion, among patients with AIS who develop mild HT following intravenous thrombolysis, functional recovery is determined not only by the hemorrhagic event itself but also by multiple patient-related factors, including stroke severity, nutritional status, age, and a history of diabetes mellitus. These findings corroborate previous evidence from different perspectives and underscore the importance of comprehensive clinical and nutritional assessment in this specific patient population.

Key Points

• Advanced age, history of diabetes mellitus, a higher baseline NIHSS score, and a higher CONUT score were identified as independent predictors of poor 3-month functional recovery in patients with mild hemorrhagic transformation after intravenous thrombolysis for acute ischemic stroke.

• Poor nutritional status, as reflected by a higher CONUT score, was significantly associated with unfavorable functional outcomes, underscoring the prognostic value of routine nutritional assessment in this patient population.

• A combined prediction model incorporating age, history of diabetes mellitus, baseline NIHSS scores, and CONUT scores demonstrated good discriminative performance (AUC = 0.840), supporting its potential utility for early risk stratification and individualized clinical management.

Availability of Data and Materials

The datasets generated during and analysed during the current study are available from the corresponding author on reasonable request.

Author Contributions

SXP and HFL designed the research study. SXP and ZML performed the research. QW, YRC and HFL analyzed the data. SXP and HFL drafted this article. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Medical Ethics Committee of the Affiliated Hospital of North Sichuan Medical College (Approval No. 2025ER726-1). Given that this was a retrospective cohort study, all study data were obtained from existing medical records and follow-up information. No additional interventions were performed, and all patient information was anonymized before data analysis. Accordingly, the Ethics Committee approved a waiver of the informed consent requirement.

Acknowledgment

Not applicable.

Funding

This research was supported by Scientific Research Project of Guangdong Provincial Administration of Traditional Chinese Medicine (Grant No. 20191418, Qian Wang), Clinical Research Special Fund Project of Guangdong Medical Association (Grant No. 2025MB-A1048, Hongfeng Liang), Scientific Research Project of Guangdong Provincial Administration of Traditional Chinese Medicine (Grant No. 20261315, Qian Wang).

Conflicts of Interest

The authors declare no conflicts of interest.

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