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Association of Admission Blood Urea Nitrogen With 90-Day and 1-Year Functional Outcomes After Intravenous Thrombolysis for Acute Ischemic Stroke: A Single-Center Retrospective Cohort Study

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23 **Abstract**

24 **Background** To evaluate associations of admission blood urea nitrogen with poor 90-day
25 and 1-year functional outcomes after intravenous thrombolysis for acute ischemic stroke
26 and assess multivariable model performance.

27 **Methods** This single-center retrospective cohort included 375 eligible treatment records
28 of acute ischemic stroke treated with standard-dose intravenous recombinant tissue
29 plasminogen activator from January 2018 to January 2023. Modified Rankin Scale
30 outcomes at 90 days and 1 year were classified as favorable (≤ 2) or poor (> 2). Baseline
31 variables with $< 15\%$ missingness underwent MissForest imputation. LASSO-selected
32 variables entered multivariable logistic regression models evaluated by 1000 bootstrap
33 resamples, receiver operating characteristic, calibration, and decision curves.

34 **Results** At 90 days, 207 (55.2%) had a favorable outcome and 168 (44.8%) a poor
35 outcome; at 1 year, 242 (64.5%) and 133 (35.5%) had favorable and poor outcomes,
36 respectively. In the 90-day model, age (OR = 1.04, 95% CI: 1.01–1.07, $P = 0.002$),
37 admission NIHSS score (OR = 1.12, 95% CI: 1.08–1.17, $P < 0.001$), platelet distribution
38 width (OR = 1.15, 95% CI: 1.02–1.28, $P = 0.017$), and blood urea nitrogen (OR =
39 1.42, 95% CI: 1.20–1.69, $P < 0.001$) were independently associated with poor outcome.
40 The combined model, including smoking, had an AUC of 0.840 (95% CI: 0.800–0.880),
41 versus 0.684 (95% CI: 0.630–0.738) for blood urea nitrogen alone. In the 1-year
42 model, age (OR = 1.05, 95% CI: 1.02–1.08, $P = 0.001$), admission NIHSS score (OR =
43 1.12, 95% CI: 1.08–1.16, $P < 0.001$), and blood urea nitrogen (OR = 1.15, 95% CI:
44 1.03–1.29, $P = 0.015$) were independently associated with poor outcome. The combined
45 model had an AUC of 0.818 (95% CI: 0.773–0.864), versus 0.633 (95% CI: 0.573–
46 0.693) for blood urea nitrogen alone.

47 **Conclusions** Higher admission blood urea nitrogen was associated with poor functional
48 outcomes at both time points; age and admission NIHSS score were associated with both
49 outcomes, whereas platelet distribution width was associated only with the 90-day
50 outcome. The combined models had numerically higher AUCs than blood urea nitrogen
51 alone in the study sample, but their clinical applicability requires external validation.

52 **Keywords** acute ischemic stroke; intravenous thrombolysis; blood urea nitrogen;
53 functional outcome; platelet distribution width; prognostic prediction

54 **Background**

55 Stroke remains one of the leading contributors to mortality and long-term disability
56 worldwide. Functional outcomes after acute ischemic stroke affect not only patients'
57 ability to live independently but also family caregiving and the allocation of healthcare
58 resources [1-3]. For eligible patients, intravenous thrombolysis is an important
59 component of acute reperfusion therapy. Although treatment strategies and workflows
60 have continued to improve, vascular recanalization or timely thrombolysis does not
61 necessarily ensure functional recovery, and outcomes remain markedly heterogeneous
62 among patients [4,5]. Therefore, using early admission information to identify prognostic
63 risk without delaying reperfusion therapy is of practical relevance in acute stroke
64 management.

65 Current guidelines from the United States, China, and Europe emphasize the time-
66 dependent nature of intravenous thrombolysis and require treatment decisions to
67 integrate baseline neurological deficits, imaging findings, preexisting diseases, medication
68 use, and bleeding risk [6-9]. An individual-patient-data meta-analysis of randomized
69 trials showed that age, stroke severity, and treatment delay all influence functional

70 outcomes after thrombolysis; large clinical cohorts likewise support an association
71 between shorter treatment delays and better outcomes [10,11]. These factors form the
72 basis of prognostic assessment, but patients following the same treatment pathway may
73 still have different recovery trajectories, suggesting that systemic physiological status
74 beyond the severity of focal neurological injury may also contribute to risk stratification.

75 Blood urea nitrogen is a routine biochemical marker formed when nitrogenous
76 products of protein catabolism are converted to urea in the liver and excreted by the
77 kidneys. Its level depends on the balance among urea production, glomerular filtration,
78 and tubular reabsorption and may be affected by renal function, renal perfusion,
79 effective circulating volume, protein intake, and catabolism. During the acute phase of
80 acute ischemic stroke, changes in volume status, inadequate renal perfusion, and catabolic
81 stress may all affect admission blood urea nitrogen. In the setting of intravenous
82 thrombolysis or other reperfusion therapies, this pretreatment measure may provide
83 supplementary information about systemic physiological status but cannot reflect
84 vascular recanalization itself. An association between pretreatment blood urea nitrogen
85 and poor 3-month functional outcome has been observed in a prospective cohort of
86 patients undergoing reperfusion therapy, while changes in the blood urea
87 nitrogen/creatinine ratio during hospitalization were also associated with early
88 neurological improvement [12,13]. Admission blood urea nitrogen is therefore not a

89 specific marker of any single pathological process and is better understood as an
90 integrated reflection of renal excretion and acute systemic status. This characteristic gives
91 it value in prognostic research but also requires its clinical interpretation to consider
92 creatinine, volume status, comorbidities, and the treatment context. Its appropriate role
93 in the setting of intravenous thrombolysis is to supplement early risk information, rather
94 than to serve as a thrombolysis eligibility criterion, a surrogate for treatment efficacy, or
95 an independent basis for treatment.

96 Previous multicenter cohorts and subsequent studies have reported associations
97 between admission blood urea nitrogen and short-term functional outcomes or mortality
98 after acute ischemic stroke, including a possible nonlinear association; studies of critically
99 ill patients with stroke have also suggested an association between higher blood urea
100 nitrogen and mortality [14–16]. Studies using the blood urea nitrogen/creatinine ratio
101 to characterize the related physiological state have further reported an association
102 between this ratio and 3-month outcomes [17]. However, the included patients' disease
103 severity, proportions receiving reperfusion therapy, forms of the biomarker, and outcome
104 definitions varied substantially across studies. A recent study of patients receiving
105 intravenous thrombolysis also did not support sufficient standalone discrimination of
106 functional outcomes by several biochemical or nutritional markers [18]. Observational
107 studies and a meta-analysis of platelet distribution width and stroke outcomes likewise

108 showed that results varied according to the population and assessment time point
109 [19,20].

110 Existing evidence has focused primarily on in-hospital mortality or 3-month
111 outcomes, with relatively little attention to longer-term functional outcomes among
112 patients receiving standard-dose intravenous thrombolysis. Absolute blood urea nitrogen
113 levels and their derived ratios are also not interchangeable. Accordingly, this single-
114 center retrospective cohort study separately examined the association of admission blood
115 urea nitrogen with poor functional outcomes at 90 days and 1 year after intravenous
116 thrombolysis and evaluated the discrimination, calibration, and decision-curve
117 performance of the multivariable models developed under the prespecified analysis plan.

118 **1 Methods**

119 **1.1 Study Design, Setting, and Ethics**

120 This single-center retrospective cohort study consecutively included cases of acute
121 ischemic stroke treated with intravenous thrombolysis using recombinant tissue
122 plasminogen activator at the Second Affiliated Hospital of Guangzhou Medical University
123 from January 2018 to January 2023. Clinical data were obtained from the hospital's
124 electronic medical records and information systems, including emergency department
125 records, inpatient progress notes, laboratory tests, and records of prior medication use.

126 After data collection, the records were checked by two investigators, and 10% of case
127 records were randomly selected for a second review. The study was approved by the
128 Ethics Committee of the Second Affiliated Hospital of Guangzhou Medical University
129 (2023-LCYJ-XS-24); patients or their family members provided written informed
130 consent. Study data were de-identified during analysis and reporting.

131 1.2 Study Population and Inclusion and Exclusion Criteria

132 The inclusion criteria were as follows: (1) acute ischemic stroke meeting the
133 diagnostic criteria of the Chinese Guidelines for the Diagnosis and Treatment of Acute
134 Ischemic Stroke 2018, confirmed by cranial CT or MRI with intracranial hemorrhage
135 excluded [8]; (2) age at onset ≥ 18 years; (3) stroke onset within 4.5 h; (4) eligibility for
136 intravenous thrombolysis and treatment with intravenous recombinant tissue
137 plasminogen activator; (5) written informed consent provided by the patient or a family
138 member; (6) follow-up for 12 months, with functional outcomes assessed using the
139 modified Rankin Scale; (7) receipt of the above treatment at the study hospital between
140 January 2018 and January 2023; and (8) diagnosis and treatment after admission in
141 accordance with relevant clinical standards.

142 The exclusion criteria were as follows: (1) age at onset < 18 years; (2) hemorrhagic
143 stroke, transient ischemic attack, or failure to receive intravenous thrombolysis because
144 of comorbid conditions or a contraindication to thrombolysis; (3) a severe adverse

145 reaction during intravenous thrombolysis that led to treatment termination; (4) inability
146 to take medications as prescribed during hospitalization; (5) cardioembolic stroke or
147 stroke of undetermined etiology according to the TOAST classification; (6) anticoagulant
148 use within 7 days before admission; (7) preexisting severe hepatic or renal insufficiency,
149 defined as an estimated glomerular filtration rate <30 mL/min/1.73 m² or Child-Pugh
150 class C; (8) failure to receive standard-dose intravenous recombinant tissue plasminogen
151 activator (0.9 mg/kg; maximum dose, 90 mg); and (9) $>30\%$ missingness in key clinical
152 variables for an individual patient.

153 The unit of analysis was a treatment record meeting the inclusion and exclusion
154 criteria. A small number of patients had repeated thrombectomy treatment records
155 during separate hospitalizations; in accordance with the prespecified statistical analysis
156 plan, all eligible treatment records were retained. Therefore, the 375 records analyzed
157 do not represent 375 unique patients.

158 **1.3 Clinical Data and Laboratory Measures**

159 Data collected included age, sex, smoking and alcohol use, histories of hypertension,
160 diabetes, coronary heart disease, and atrial fibrillation, and prior antiplatelet medication
161 use. Stroke subtype was recorded according to the TOAST criteria, including large-artery
162 atherosclerosis, small-artery occlusion, and stroke of other determined etiology. The
163 National Institutes of Health Stroke Scale score on admission and systolic and diastolic

164 blood pressure before thrombolysis were recorded. Variables including the NIHSS score 24
165 h after thrombolysis, the NIHSS score at discharge, and a history of statin use were not
166 included in the candidate analysis or final prediction models because their missingness
167 exceeded 15%.

168 Laboratory measures were based on the first test results obtained after admission
169 and included hemoglobin, plateletcrit, platelet distribution width, mean platelet volume,
170 platelet count, platelet-large cell ratio, non-high-density lipoprotein cholesterol,
171 apolipoprotein B, alanine aminotransferase, aspartate aminotransferase, uric acid,
172 creatinine, blood urea nitrogen, glycated hemoglobin, D-dimer, fibrinogen, prothrombin
173 time, international normalized ratio, and activated partial thromboplastin time. Blood
174 urea nitrogen was the principal laboratory measure of interest in this study; prior
175 antiplatelet pretreatment was recorded as a baseline covariate and was not used to
176 define the study groups.

177 **1.4 Functional Assessment and Study Outcomes**

178 The National Institutes of Health Stroke Scale (NIHSS) was used to assess the severity
179 of neurological deficits on admission. Scores range from 0 to 42, with higher scores
180 indicating more severe neurological deficits. The modified Rankin Scale (mRS) was used
181 to assess overall functional status after stroke. Scores range from 0 to 6, where 0
182 indicates no symptoms and 6 indicates death [21]; the individual score categories are

183 shown in Table 1. Outcome assessments were performed in a blinded manner by certified
 184 neurologists.

185 **Table 1 Modified Rankin Scale Scoring Criteria**

Score	Description
0	No symptoms at all, with no effect on daily work or activities of daily living.
1	Despite symptoms, no significant disability; able to carry out all usual duties and activities.
2	Slight disability; unable to carry out all prestroke activities but able to look after one's own affairs without assistance.
3	Moderate disability; requires some help (eg, an assistive device or assistance from another person) but able to walk independently.
4	Moderately severe disability; unable to walk independently and requires assistance with basic bodily needs (eg, eating and toileting).
5	Severe disability; bedridden and incontinent, requiring continuous nursing care and attention.
6	Death.

186 Modified Rankin Scale scores were collected at 90 days (± 7 days), 180 days (± 7
 187 days), 270 days (± 7 days), and 1 year (± 7 days) after treatment. The study endpoints
 188 were functional outcomes at 90 days and 1 year. At each time point, patients were
 189 classified into a favorable-outcome group (score ≤ 2) or a poor-outcome group (score > 2).
 190 Follow-up was conducted primarily by telephone interview and, when necessary,
 191 supplemented with outpatient follow-up records, inpatient medical records, and
 192 community health records. Follow-up results were independently entered and cross-

checked by two investigators; when discrepancies occurred, a third investigator reviewed the original records and made the final determination.

195

1.5 Statistical Analysis

Statistical analyses were performed using SPSS 27.0 and R 4.3.2. For baseline variables included in the analysis with <15% missingness, the random-forest-based MissForest method was used for imputation [22]; variables with >15% missingness were not included in the candidate analysis. Normally distributed continuous data were expressed as mean $\pm$ standard deviation and compared between groups using the independent-samples *t* test. Non-normally distributed continuous data were summarized as median (Q1, Q3) and compared between groups using a rank-sum test. Homogeneity of variance was assessed using the Levene test. Categorical data were expressed as counts and proportions and compared between groups using the χ^2 test. $P < 0.05$ was considered statistically significant.

Variables showing statistically significant between-group differences were entered into LASSO regression. The optimal λ value was selected by cross-validation, after which variables with coefficients not equal to 0 were entered into multivariable logistic regression to construct separate models for poor functional outcomes at 90 days and 1 year; the models were presented as nomograms. Internal validation was performed using

bootstrap resampling 1000 times. Discrimination was evaluated using receiver operating characteristic curves and the area under the curve, agreement between predicted probabilities and observed outcomes was evaluated using calibration curves, and net benefit across different ranges of threshold probabilities was evaluated using decision curve analysis [23].

2 Results

2.1 Patient Inclusion and Overall Characteristics

A total of 411 cases entered follow-up, 36 were lost to follow-up, and 375 eligible intravenous thrombolysis treatment records were ultimately included in the outcome analysis. Of the included records, 231 involved male patients and 144 involved female patients; the TOAST subtypes were large-artery atherosclerosis in 200, small-artery occlusion in 120, and stroke of other determined etiology in 55. Antiplatelet pretreatment was documented in 95 treatment records and was absent in 280 records. Study groups were defined by the modified Rankin Scale score at the corresponding follow-up time point. The case flow is shown in Figure 1.

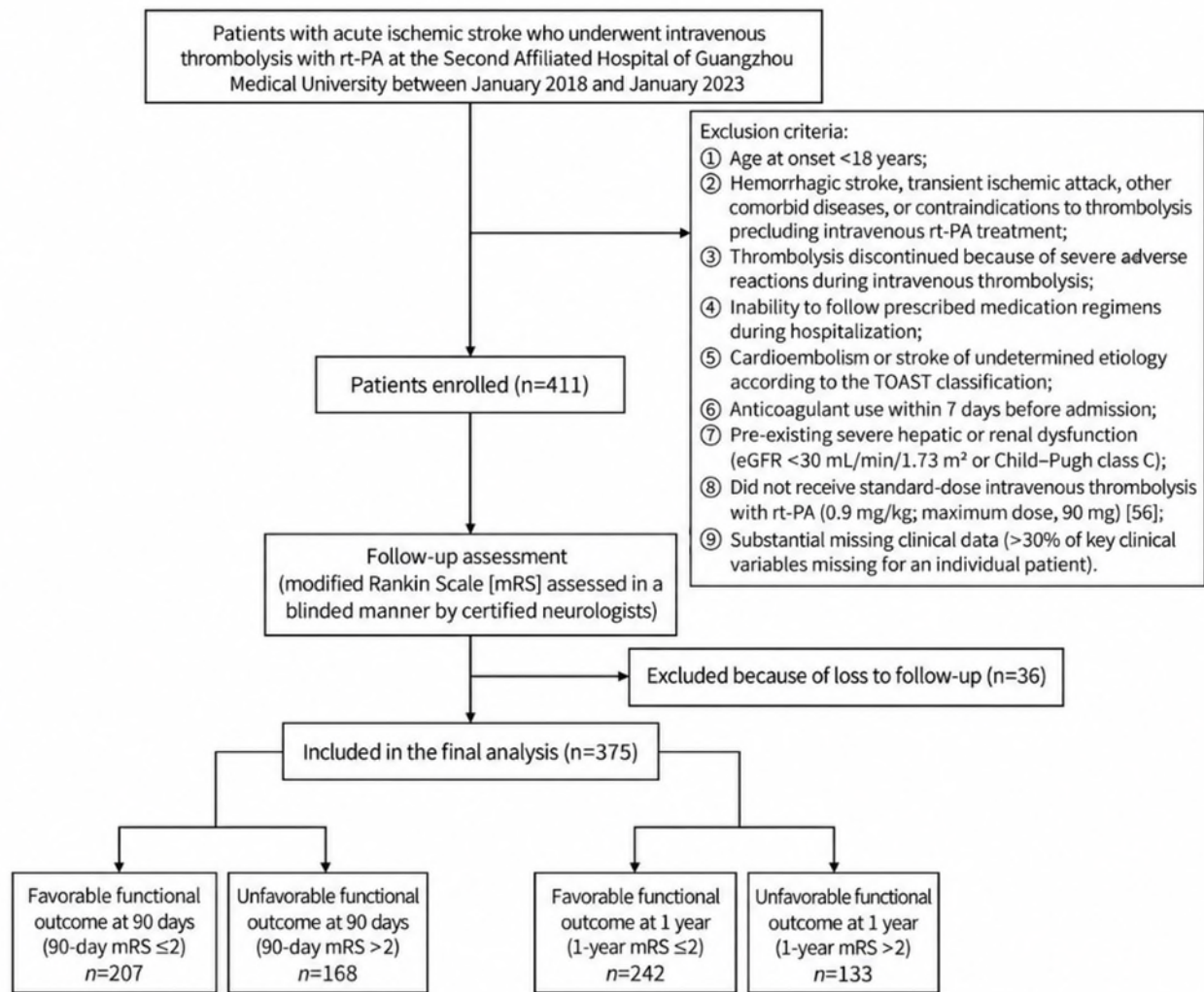


Figure 1 Flowchart of the Study Design and Case Inclusion

2.2 Functional Outcomes at 90 Days After Intravenous Thrombolysis

2.2.1 90-Day Outcome Groups and Comparison of Baseline Characteristics

Among the 375 treatment records, the 90-day outcome was favorable in 207 (55.2%) and poor in 168 (44.8%). Compared with the favorable-outcome group, the poor-outcome group was older and had higher admission NIHSS scores and admission blood urea nitrogen levels: 73 (66, 81) versus 66 (59, 71), 12.50 (7.00, 19.75) versus

236 5.00 (3.00, 8.00), and 5.40 (4.37, 7.05) versus 4.50 (3.70, 5.30), respectively (all $P <$
 237 0.001). Comparisons of the remaining baseline variables are shown in Table 2.

238 **Table 2 Comparison Between the Favorable- and Poor-Outcome Groups at 90 Days**

Variable	Favorable-outcome group	Poor-outcome group	t/z/ χ^2	P value
Age (years)	66 (59, 71)	73 (66, 81)	6.545	<0.001
Sex [n (%)]				
Male	134 (64.73)	97 (57.74)	1.919	0.166
Female	73 (35.26)	71 (42.26)		
History of diabetes [n (%)]	43 (20.77)	43 (25.60)	1.220	0.269
History of hypertension [n (%)]	114 (55.07)	115 (68.45)	6.983	0.008
History of coronary heart disease [n (%)]	24 (11.59)	36 (21.43)	6.673	0.010
History of atrial fibrillation [n (%)]	6 (2.90)	25 (14.88)	17.558	<0.001
Smoking [n (%)]	69 (33.33)	32 (19.05)	9.617	0.002
Alcohol use [n (%)]	34 (16.43)	24 (14.29)	0.325	0.569
Prior antiplatelet pretreatment [n (%)]	47 (22.71)	48 (28.57)	1.687	0.194
TOAST [n (%)]				

Variable	Favorable-outcome group	Poor-outcome group	t/z/ χ^2	P value
LAA	93 (44.93)	107 (63.69)		
SAA	91 (43.96)	29 (17.26)	30.763	<0.001
SOE	23 (11.11)	32 (19.05)		
Admission NIHSS score	5.00 (3.00, 8.00)	12.50 (7.00, 19.75)	9.698	<0.001
SBP (mmHg)	152.47±22.28	152.77±24.92	0.125	0.901
DBP (mmHg)	87.00 (77.00, 95.00)	84.00 (73.25, 93.75)	2.058	0.040
Hemoglobin (Hb, g/L)	136.00 (125.00, 145.84)	131.00 (119.00, 142.00)	2.957	0.003
Plateletcrit (PCT, %)	0.23 (0.20, 0.26)	0.23 (0.19, 0.27)	0.155	0.877
Platelet distribution width (PDW, fL)	11.30 (10.20, 12.90)	12.00 (10.60, 13.80)	2.100	0.036
Mean platelet volume (MPV, fL)	9.90 (9.50, 10.60)	10.20 (9.50, 10.70)	1.627	0.104
Platelet count (PLT, 10 ⁹ /L)	225.00 (194.00, 263.00)	219.50 (186.25, 279.75)	0.630	0.528
Platelet-large cell ratio (P- LCR, %)	24.00 (20.00, 30.00)	27.00 (21.03, 31.00)	1.866	0.062
Non-high-density lipoprotein cholesterol (mmol/L)	3.53 (2.80, 4.24)	3.03 (2.60, 3.80)	3.388	<0.001
Apolipoprotein B (ApoB, g/L)	0.98 (0.75, 1.21)	0.89 (0.73, 1.07)	2.616	0.009
Alanine aminotransferase (ALT, U/L)	14.00 (11.00, 20.00)	15.00 (11.00, 21.00)	0.544	0.587

Variable	Favorable-outcome group	Poor-outcome group	t/z/ χ^2	P value
Aspartate aminotransferase (AST, U/L)	17.00 (14.00, 21.00)	20.00 (16.00, 26.75)	3.431	<0.001
Uric acid (UA, μ mol/L)	350.00 (291.00, 415.00)	326.00 (282.25, 421.46)	0.824	0.410
Creatinine (Cr, μ mol/L)	78.00 (67.00, 91.00)	82.50 (67.00, 105.00)	2.302	0.021
Blood urea nitrogen (BUN, mmol/L)	4.50 (3.70, 5.30)	5.40 (4.37, 7.05)	6.122	<0.001
Glycated hemoglobin (%)	5.88 (5.50, 6.40)	6.00 (5.70, 6.69)	2.424	0.015
D-dimer (mg/L FEU)	0.80 (0.29, 2.04)	1.45 (0.55, 4.91)	4.910	<0.001
Fibrinogen (FIB, g/L)	2.70 (2.30, 3.10)	2.62 (2.12, 3.25)	0.093	0.926
Prothrombin time (PT, s)	11.10 (10.60, 11.60)	11.40 (10.83, 12.39)	4.039	<0.001
INR	0.96 (0.93, 1.03)	1.01 (0.95, 1.09)	3.895	<0.001
Activated partial thromboplastin time (APTT, s)	24.50 (22.30, 26.17)	24.63 (22.03, 27.40)	0.626	0.531

Note: LAA denotes large-artery atherosclerosis stroke; SAA, small-artery occlusion stroke; SOE, stroke of other determined etiology; SBP, systolic blood pressure; and DBP, diastolic blood pressure. A difference was considered statistically significant when $P < 0.05$.

2.2.2 LASSO Selection and Multivariable Logistic Regression at 90 Days

Candidate variables with statistically significant between-group differences were subjected to LASSO selection, and cross-validation identified an optimal λ value of 0.01526216. Age, admission NIHSS score, platelet distribution width, blood urea

nitrogen, and smoking were ultimately retained and entered into a multivariable logistic regression model. The LASSO variable-selection process is shown in Figure 2.

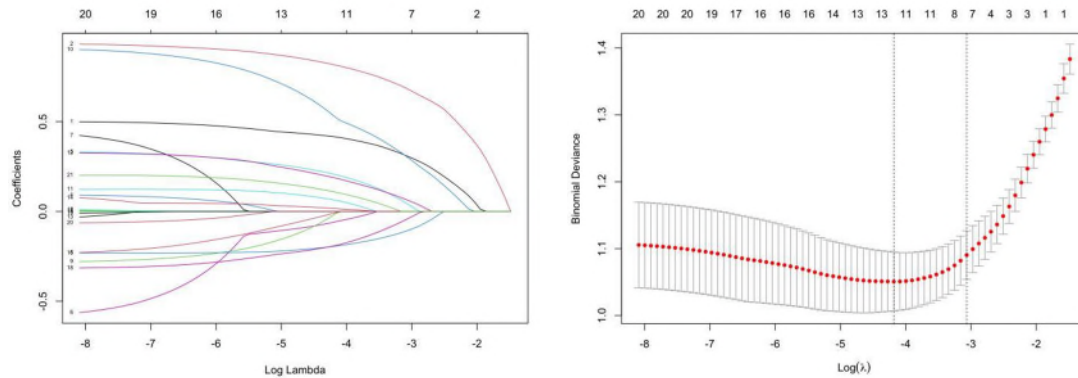


Figure 2 LASSO Variable Selection for Functional Outcome at 90 Days After Intravenous Thrombolysis

Note: Panels A and B show the coefficient paths and the cross-validation process used to select the optimal λ value, respectively.

Multivariable logistic regression showed that age (OR = 1.04, 95% CI: 1.01–1.07, $P = 0.002$), admission NIHSS score (OR = 1.12, 95% CI: 1.08–1.17, $P < 0.001$), platelet distribution width (OR = 1.15, 95% CI: 1.02–1.28, $P = 0.017$), and blood urea nitrogen (OR = 1.42, 95% CI: 1.20–1.69, $P < 0.001$) were independently associated with poor functional outcome at 90 days. The effect estimate for smoking was OR = 0.53 (95% CI: 0.17–1.64, $P = 0.050$); because the confidence interval was wide and crossed 1, this finding does not establish a clear independent protective association of smoking. The regression results are shown in Table 3.

Table 3 Multivariable Logistic Regression Analysis of Functional Outcome at 90 Days After Intravenous Thrombolysis

Variable	OR	Lower limit of 95% CI	Upper limit of 95% CI	P value
Age	1.04	1.01	1.07	0.002
Admission NIHSS score	1.12	1.08	1.17	<0.001
Platelet distribution width (PDW)	1.15	1.02	1.28	0.017
BUN	1.42	1.20	1.69	<0.001
Smoking	0.53	0.17	1.64	0.050

Note: The wide 95% CI crossed 1; therefore, the finding was not interpreted as evidence of a clear independent protective association.

A nomogram was constructed using the five model variables—age, admission NIHSS score, platelet distribution width, blood urea nitrogen, and smoking—and is shown in Figure 3.

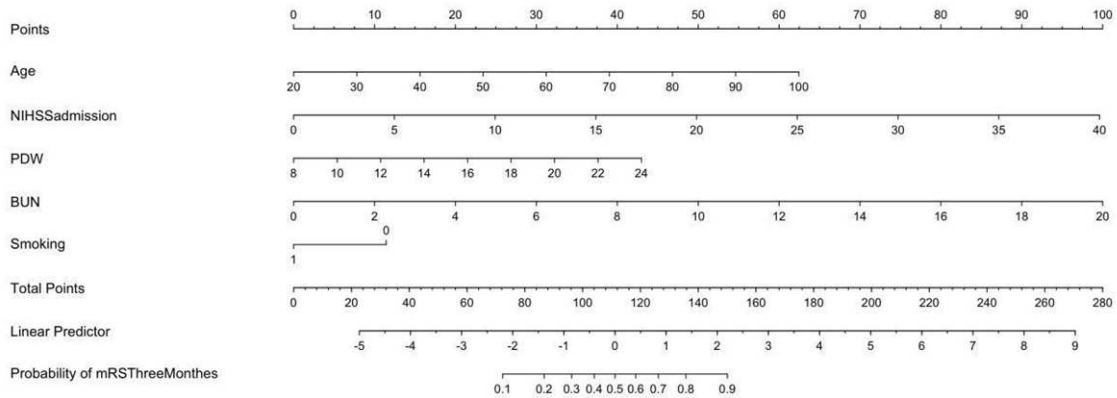
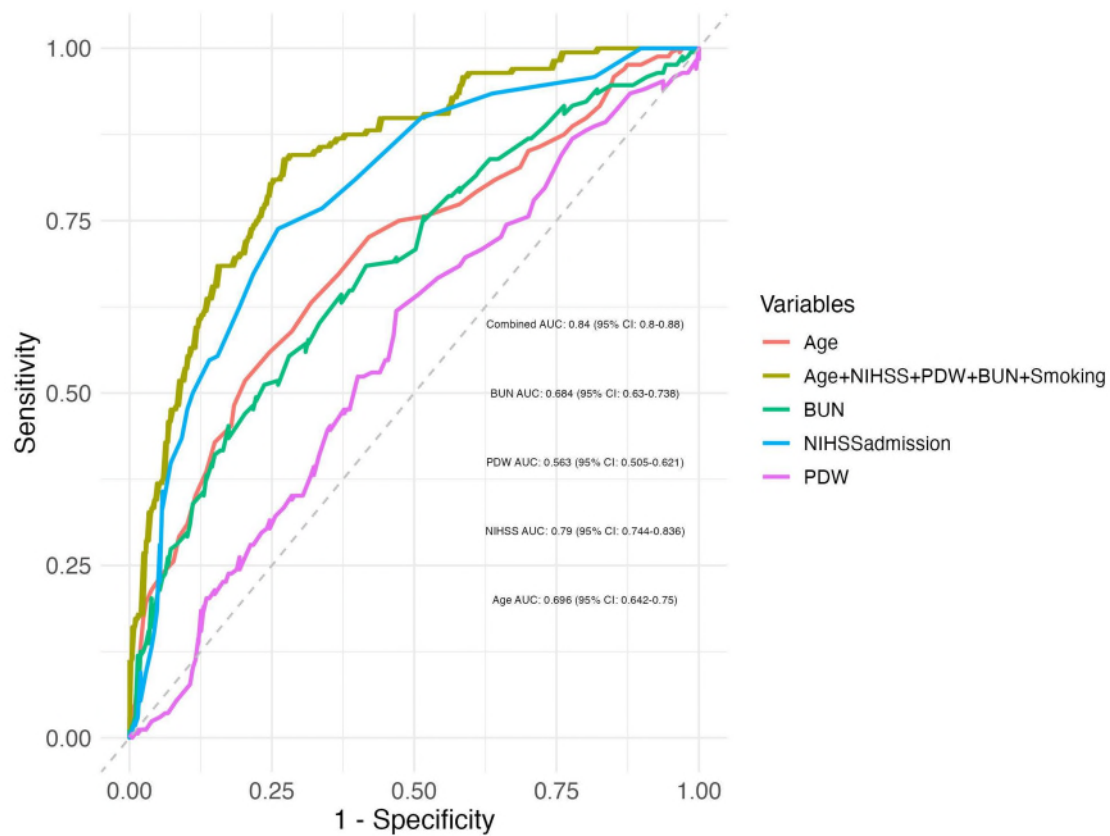


Figure 3 Nomogram of the Prediction Model for Functional Outcome at 90 Days After Intravenous Thrombolysis

2.2.3 Model Discrimination and Internal Calibration at 90 Days

The combined 90-day model had an AUC of 0.840 (95% CI: 0.800–0.880). The AUCs for admission NIHSS score, age, blood urea nitrogen, and platelet distribution width alone were 0.79 (95% CI: 0.744–0.836), 0.696 (95% CI: 0.642–0.750), 0.684 (95% CI: 0.630–0.738), and 0.563 (95% CI: 0.505–0.621), respectively (Figure 4). The combined model had a numerically higher AUC than each individual predictor; no test of AUC differences between models was performed.



277

278 **Figure 4 Receiver Operating Characteristic Curves for the Combined Model and Individual Predictors of**
 279 **90-Day Functional Outcome**

280 After bootstrap resampling 1000 times, the mean absolute error of the calibration
 281 curve for the 90-day model was 0.028 (Figure 5).

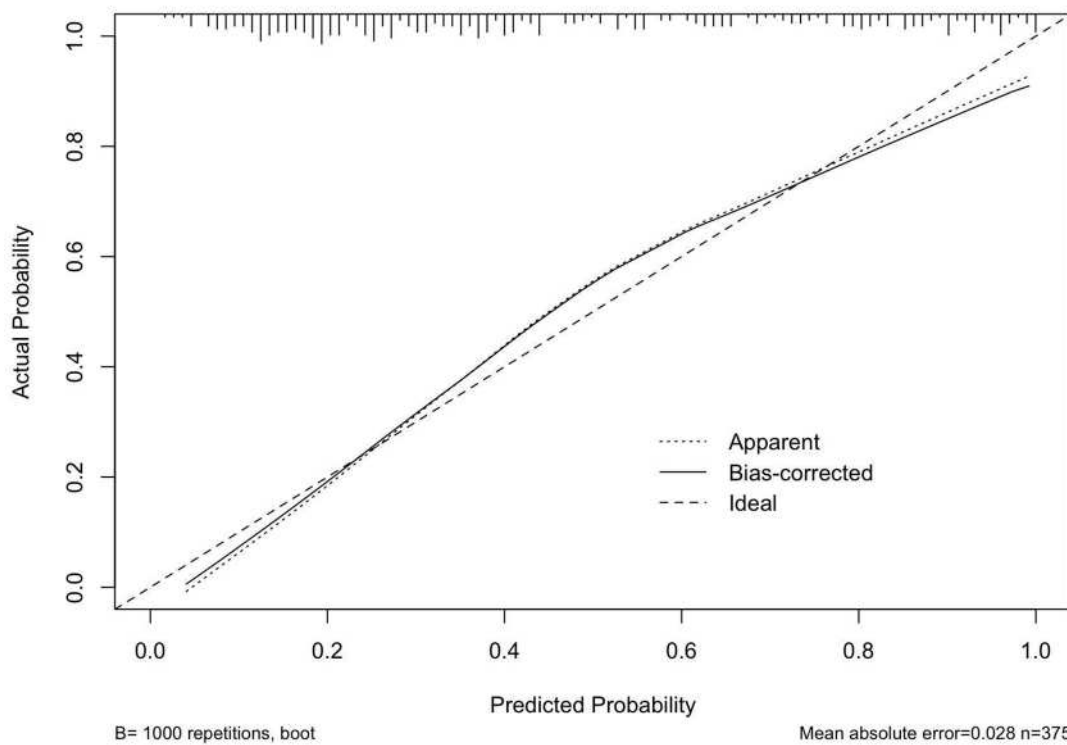


Figure 5 Calibration Curve for the Prediction Model of 90-Day Functional Outcome

2.2.4 Decision Curve Analysis of the 90-Day Models

Decision curve analysis showed that the combined model had a net benefit over the threshold probability range of 0.04–0.78; the corresponding range for the blood urea nitrogen-only model was 0.29–0.62 (Figures 6 and 7, respectively).

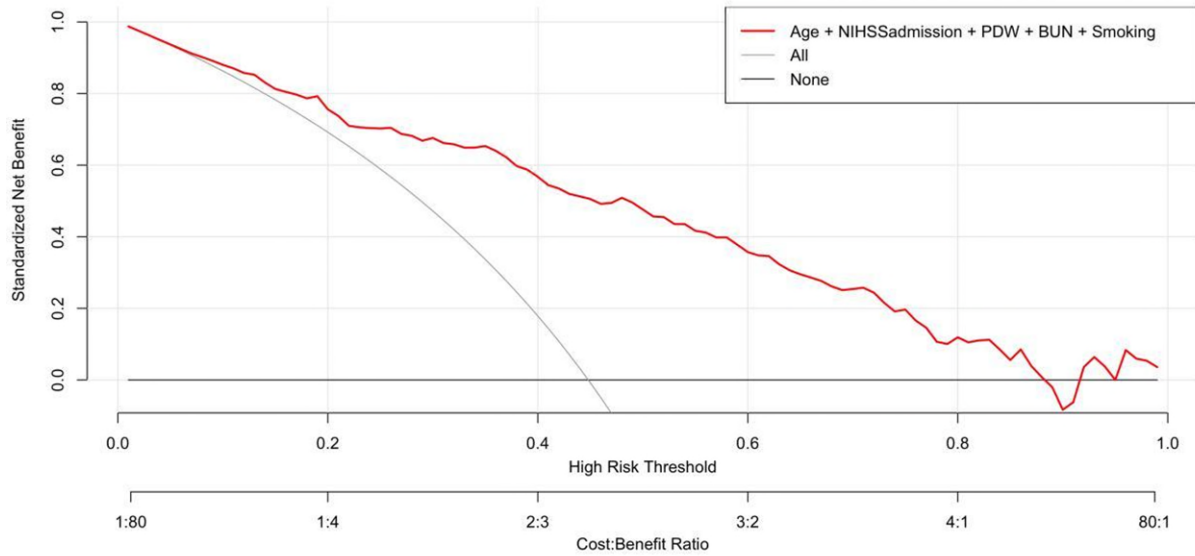


Figure 6 Decision Curve for the Combined Prediction Model of 90-Day Functional Outcome

Note: The red line represents the combined model, the black line the treat-none strategy, and the gray line the treat-all strategy.

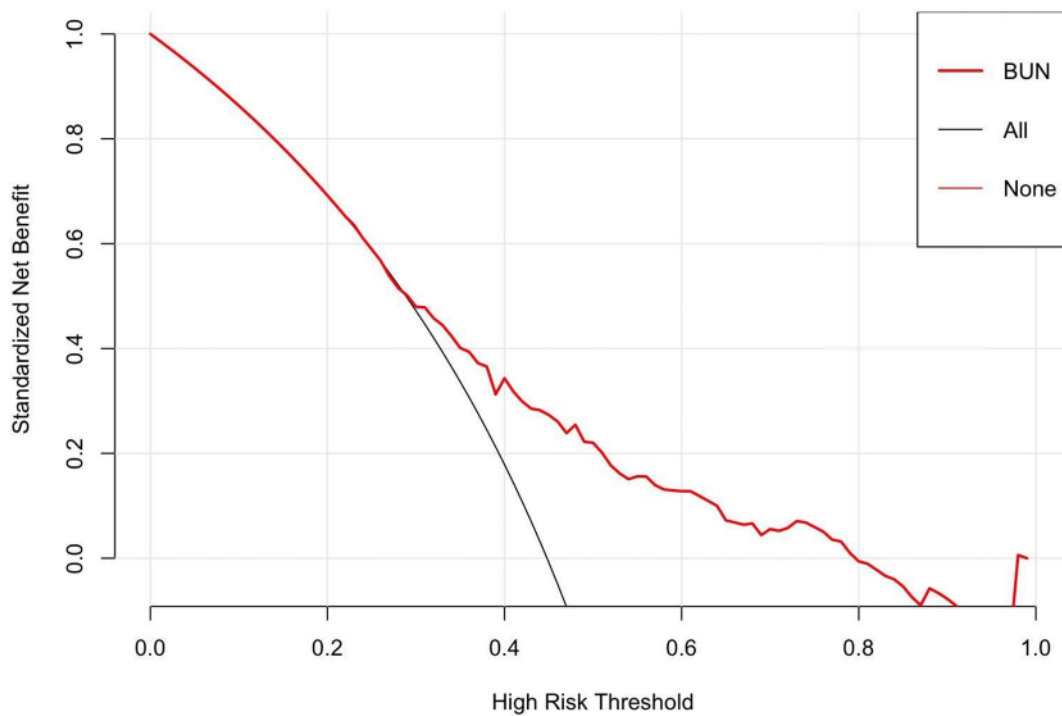


Figure 7 Decision Curve for the Blood Urea Nitrogen-Only Model of 90-Day Functional Outcome

2.3 Functional Outcomes at 1 Year After Intravenous Thrombolysis

2.3.1 1-Year Outcome Groups and Comparison of Baseline Characteristics

Among the 375 treatment records, the 1-year outcome was favorable in 242 (64.5%) and poor in 133 (35.5%). In the poor- and favorable-outcome groups, age was 74 (68.00, 82.50) and 66 (59.00, 72.00), admission NIHSS score was 14.00 (8.00, 21.00) and 5.00 (3.00, 8.25), and blood urea nitrogen was 5.23 (4.25, 6.90) and 4.60 (3.80, 5.63), respectively (all $P < 0.001$). Comparisons of the remaining baseline variables are shown in Table 4.

Table 4 Comparison Between the Favorable- and Poor-Outcome Groups at 1 Year

Variable	Favorable-outcome group	Poor-outcome group	t/z/ χ^2	P value
Age (years)	66 (59.00, 72.00)	74 (68.00, 82.50)	6.852	<0.001
Sex [n (%)]				
Male	159 (65.70)	72 (54.14)	4.855	0.028
Female	83 (34.30)	61 (45.86)		
History of diabetes [n (%)]	55 (22.72)	31 (23.31)	0.016	0.898
History of hypertension [n (%)]	138 (57.02)	91 (68.42)	4.689	0.030
History of coronary heart disease [n (%)]	28 (11.57)	32 (24.06)	9.962	0.002

Variable	Favorable-outcome group	Poor-outcome group	t/z/ χ^2	P value
History of atrial fibrillation [n (%)]	9 (3.72)	22 (16.54)	18.609	<0.001
Smoking [n (%)]	77 (31.81)	24 (18.05)	8.273	0.004
Alcohol use [n (%)]	38 (15.70)	20 (15.04)	0.029	0.865
Prior antiplatelet pretreatment [n (%)]	50 (20.66)	45 (33.83)	7.874	0.005
TOAST [n (%)]				
LAA	111 (45.87)	89 (66.92)		
SAA	100 (41.32)	20 (15.04)	27.265	<0.001
SOE	31 (12.81)	24 (18.05)		
Admission NIHSS score	5.00 (3.00, 8.25)	14.00 (8.00, 21.00)	9.732	<0.001
SBP (mmHg)	152.71±22.27	152.41±25.59	0.118	0.906
DBP (mmHg)	87.00 (77.00, 95.00)	84.00 (73.50, 92.00)	2.364	0.018
Hemoglobin (Hb, g/L)	136.00 (125.75, 145.22)	129.00 (117.00, 140.00)	3.828	<0.001
Plateletcrit (PCT, %)	0.23 (0.20, 0.26)	0.23 (0.19, 0.28)	0.027	0.979
Platelet distribution width (PDW, fL)	11.40 (10.40, 13.10)	12.00 (10.40, 14.05)	1.313	0.189
Mean platelet volume (MPV, fL)	10.00 (9.50, 10.68)	10.20 (9.60, 10.69)	0.696	0.486
Platelet count (PLT, 10 ⁹ /L)	224.50 (193.75, 263.25)	220.00 (185.50, 282.50)	0.231	0.817

Variable	Favorable-outcome group	Poor-outcome group	t/z/ χ^2	P value
Platelet-large cell ratio (P-LCR, %)	24.95 (21.00, 30.70)	27.00 (21.00, 30.50)	0.905	0.365
Non-high-density lipoprotein cholesterol (mmol/L)	3.51 (2.78, 4.20)	3.04 (2.58, 3.80)	3.318	<0.001
Apolipoprotein B (ApoB, g/L)	0.96 (0.76, 1.20)	0.88 (0.72, 1.06)	2.713	0.007
Alanine aminotransferase (ALT, U/L)	15.00 (11.00, 20.00)	15.00 (11.00, 21.00)	0.084	0.933
Aspartate aminotransferase (AST, U/L)	17.00 (14.00, 21.00)	20.00 (16.00, 27.00)	3.640	<0.001
Uric acid (UA, μ mol/L)	349.00 (287.00, 418.25)	332.00 (280.00, 414.63)	0.742	0.458
Creatinine (Cr, μ mol/L)	79.00 (67.00, 92.25)	83.00 (66.70, 105.00)	1.648	0.099
Blood urea nitrogen (BUN, mmol/L)	4.60 (3.80, 5.63)	5.23 (4.25, 6.90)	4.256	<0.001
Glycated hemoglobin (%)	5.90 (5.50, 6.43)	6.00 (5.70, 6.70)	2.185	0.029
D-dimer (mg/L FEU)	0.89 (0.32, 2.17)	1.43 (0.57, 4.93)	4.193	<0.001
Fibrinogen (FIB, g/L)	2.68 (2.26, 3.10)	2.67 (2.17, 3.37)	0.548	0.584
Prothrombin time (PT, s)	11.10 (10.60, 11.60)	11.50 (10.90, 12.51)	3.977	<0.001
INR	0.97 (0.93, 1.03)	1.01 (0.95, 1.09)	3.804	<0.001
Activated partial thromboplastin time (APTT, s)	24.50 (22.28, 26.37)	24.64 (22.10, 27.40)	0.732	0.464

Note: LAA denotes large-artery atherosclerosis stroke; SAA, small-artery occlusion stroke; SOE, stroke of other determined etiology; SBP, systolic blood pressure; and DBP, diastolic blood pressure. A difference was considered statistically significant when $P < 0.05$.

2.3.2 LASSO Selection and Multivariable Logistic Regression at 1 Year

Candidate variables associated with 1-year outcomes were subjected to LASSO selection, and cross-validation identified an optimal λ value of 0.01844922. Age, admission NIHSS score, and blood urea nitrogen were ultimately retained. The variable-selection process is shown in Figure 8.

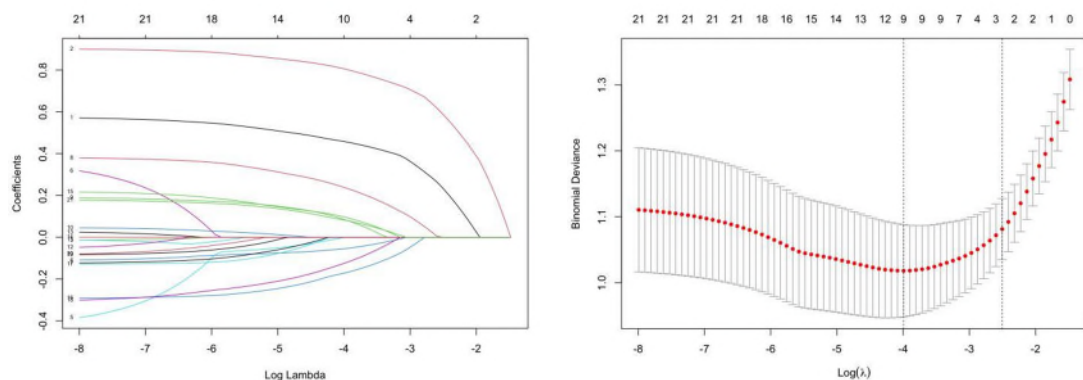


Figure 8 LASSO Variable Selection for Functional Outcome at 1 Year After Intravenous Thrombolysis

Note: Panels A and B show the coefficient paths and the cross-validation process used to select the optimal λ value, respectively.

Multivariable logistic regression showed that age (OR = 1.05, 95% CI: 1.02–1.08, $P = 0.001$), admission NIHSS score (OR = 1.12, 95% CI: 1.08–1.16, $P < 0.001$), and blood urea nitrogen (OR = 1.15, 95% CI: 1.03–1.29, $P = 0.015$) were independently associated with poor functional outcome at 1 year. The regression results are shown in Table 5, and the nomogram based on these three variables is shown in Figure 9.

Table 5 Multivariable Logistic Regression Analysis of Functional Outcome at 1 Year After

Intravenous Thrombolysis

Variable	OR	Lower limit of 95% CI	Upper limit of 95% CI	P value
Age	1.05	1.02	1.08	0.001
Admission NIHSS score	1.12	1.08	1.16	<0.001
BUN	1.15	1.03	1.29	0.015

Note: OR denotes odds ratio; CI, confidence interval.

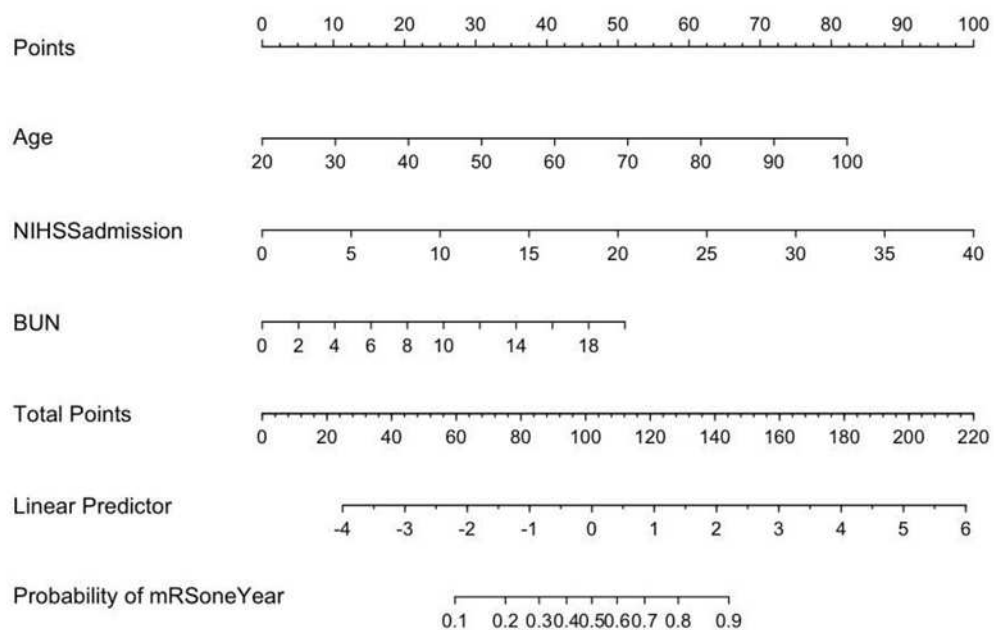


Figure 9 Nomogram of the Prediction Model for Functional Outcome at 1 Year After Intravenous

Thrombolysis

2.3.3 Model Discrimination and Internal Calibration at 1 Year

The combined 1-year model comprising age, admission NIHSS score, and blood urea nitrogen had an AUC of 0.818 (95% CI: 0.773–0.864). The AUCs for admission NIHSS score, age, and blood urea nitrogen alone were 0.803 (95% CI: 0.757–0.849), 0.714 (95% CI: 0.657–0.77), and 0.633 (95% CI: 0.573–0.693), respectively (Figure 10). The combined model had a numerically higher AUC than each individual predictor; no test of AUC differences between models was performed.

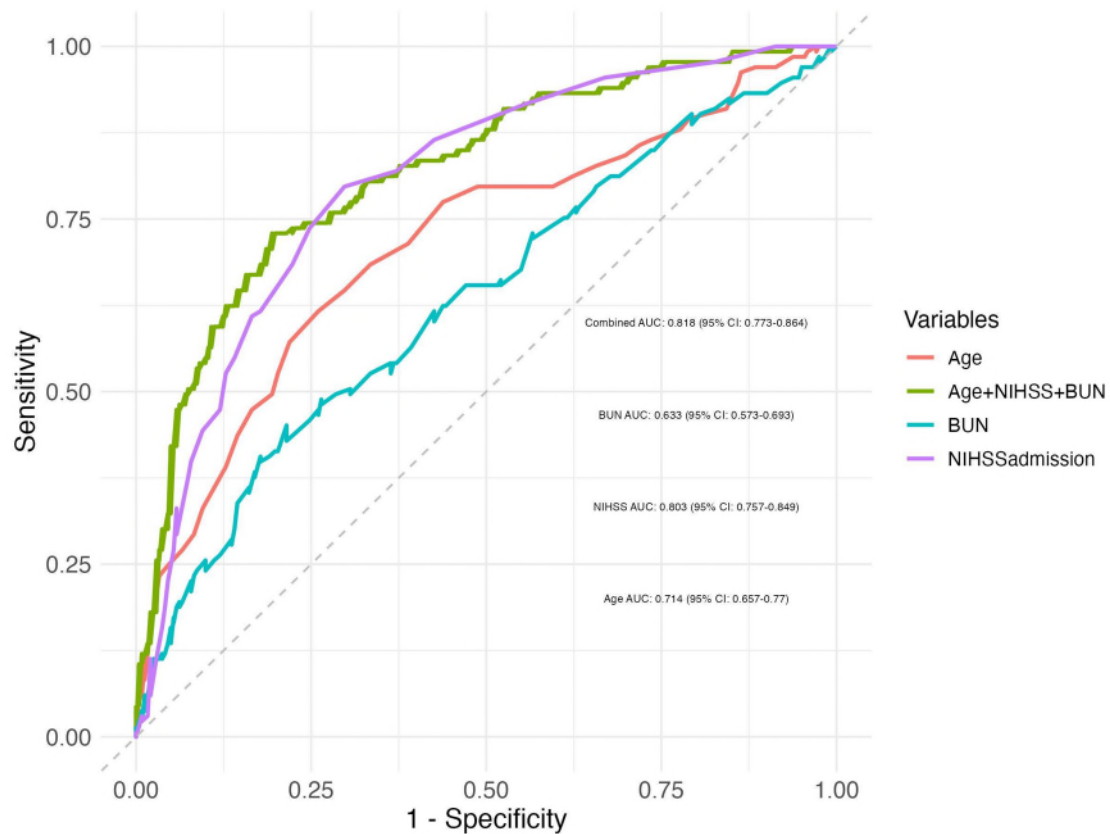
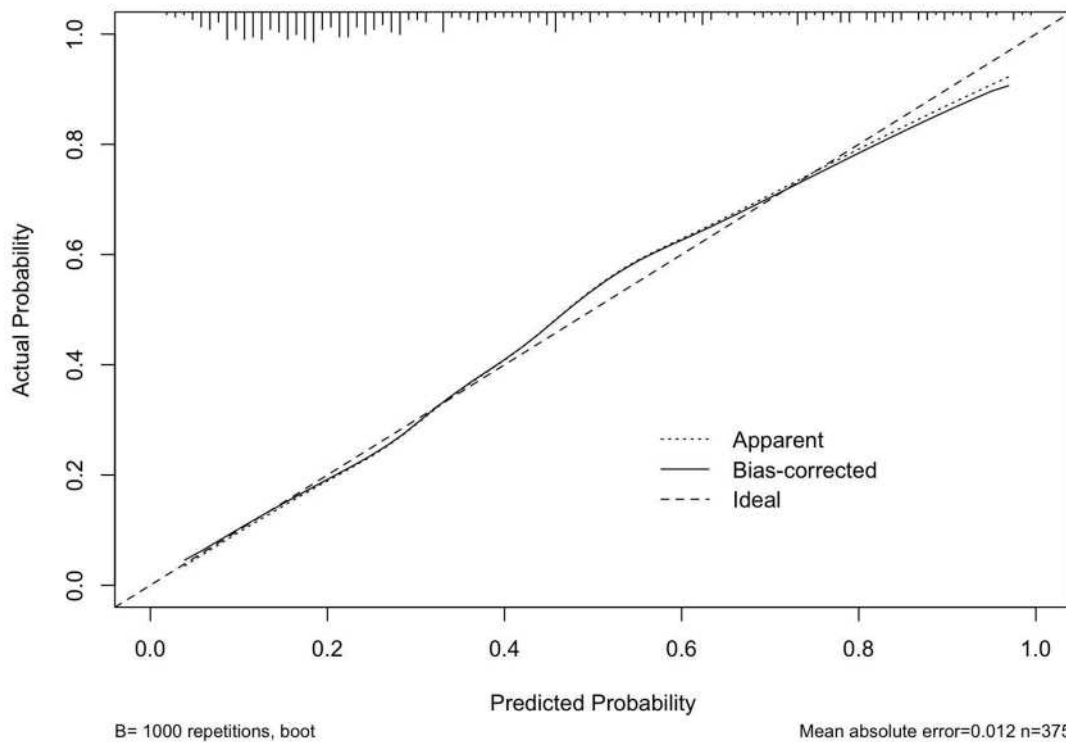


Figure 10 Receiver Operating Characteristic Curves for the Combined Model and Individual Predictors of 1-Year Functional Outcome

336 After bootstrap resampling 1000 times, the mean absolute error of the calibration
 337 curve for the 1-year model was 0.012 (Figure 11).



338
 339 **Figure 11 Calibration Curve for the Prediction Model of 1-Year Functional Outcome**

340 2.3.4 Decision Curve Analysis of the 1-Year Models

341 Decision curve analysis showed that the combined model had a net benefit over the
 342 threshold probability range of 0.03–0.69; the corresponding range for the blood urea
 343 nitrogen-only model was 0.26–0.45 (Figures 12 and 13, respectively).

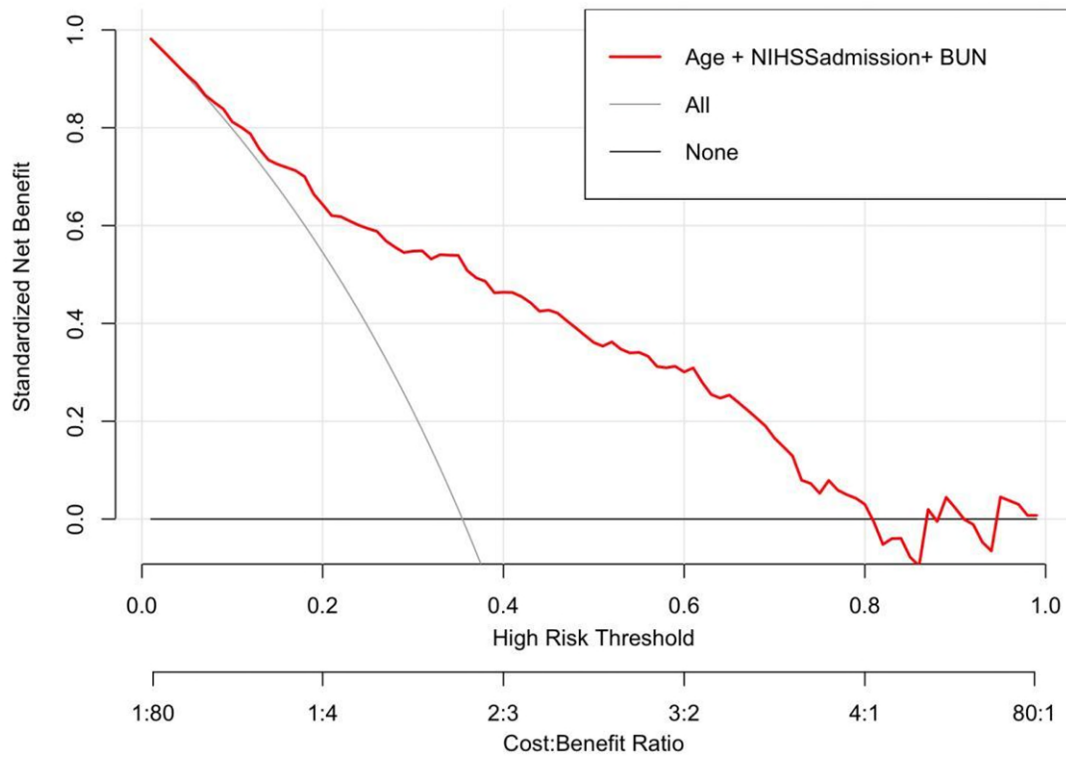


Figure 12 Decision Curve for the Combined Prediction Model of 1-Year Functional Outcome

Note: The red line represents the combined model, the black line the treat-none strategy, and the gray line the treat-all strategy.

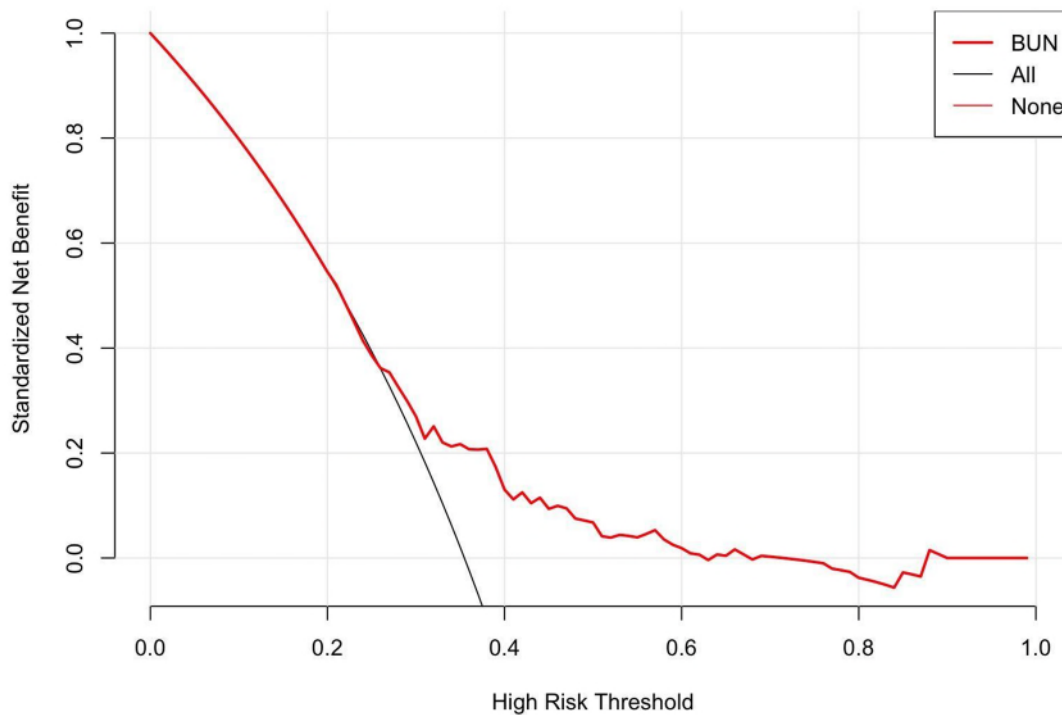


Figure 13 Decision Curve for the Blood Urea Nitrogen-Only Model of 1-Year Functional Outcome

3 Discussion

3.1 Main Findings

This study analyzed 375 eligible intravenous thrombolysis treatment records. Admission blood urea nitrogen was independently associated with poor functional outcomes in both the 90-day and 1-year multivariable models. Age and admission NIHSS score were also included in the models at both time points, whereas platelet distribution width was included only in the 90-day model. The combined models had numerically higher AUCs than blood urea nitrogen alone and showed some degree of

358 calibration and decision-curve net benefit in the study sample. These results describe
359 prognostic associations and within-sample model performance and do not support a
360 causal inference between blood urea nitrogen and functional recovery.

361 At the level of clinical interpretation, this study provides two types of related but
362 conceptually distinct information: multivariable logistic regression describes the
363 conditional association of each variable with a prespecified outcome, whereas receiver
364 operating characteristic curves, calibration curves, and decision curves describe the
365 performance of the combined models in the current sample. Blood urea nitrogen was
366 retained in the models at both time points, and each combined model had a numerically
367 higher AUC than blood urea nitrogen alone, indicating that blood urea nitrogen is more
368 appropriately considered a supplementary risk marker alongside routine information
369 such as age and admission NIHSS score rather than a stand-alone decision tool. Because
370 blood urea nitrogen is available from routine biochemical testing at admission, a higher
371 level may prompt clinicians to review renal function, urine output, volume status, and
372 nutritional and catabolic status without requiring an additional blood draw, and to
373 monitor neurological function, fluid balance, and changes in renal function during
374 subsequent observation. This study did not demonstrate that blood urea nitrogen itself
375 causes poor functional outcomes or that treatment adjustments based on this measure
376 can change outcomes.

377 The effect estimate for blood urea nitrogen was higher in the 90-day model than in
378 the 1-year model, but the two models corresponded to different outcome times and
379 included different sets of variables; this study did not test the difference between the two
380 effect estimates. This numerical difference therefore cannot be interpreted as a
381 weakening of the association with blood urea nitrogen over time or as evidence of a
382 specific effect on short-term outcomes.

383 Modified Rankin Scale scores at 90 days and 1 year reflect adjacent but distinct
384 phases of recovery. The earlier outcome is temporally closer to the initial neurological
385 injury and acute physiological state, whereas the longer-term outcome may also be
386 affected by exposure to rehabilitation, secondary prevention, recurrent events,
387 complications, and changes in chronic diseases. This study used only the first blood urea
388 nitrogen value obtained on admission and did not continuously measure these factors;
389 differences between the models at the two time points can therefore be interpreted only
390 descriptively. A more cautious conclusion is that admission blood urea nitrogen retained a
391 prognostic association at both prespecified time points in this cohort, while the specific
392 pattern of change over time requires confirmation in longitudinal studies.

393 **3.2 Blood Urea Nitrogen and Functional Outcomes**

394 Previous cohort studies have reported associations of blood urea nitrogen with short-
395 term functional outcomes or mortality after acute ischemic stroke [14-16], and the

396 blood urea nitrogen/creatinine ratio has also been associated with 3-month outcomes
397 [17]. The present study restricted the population to cases receiving intravenous
398 thrombolysis and meeting the specified criteria for stroke subtype and organ function,
399 and evaluated functional outcomes at 90 days and 1 year using the absolute blood urea
400 nitrogen level. Differences in study populations, forms of the marker, treatment settings,
401 and outcome definitions preclude direct comparison of effect estimates across studies.
402 Nevertheless, the present findings are directionally consistent with existing evidence that
403 blood urea nitrogen may reflect overall physiological reserve and acute systemic status in
404 patients with stroke.

405 The existing evidence shows both consistency and important contextual differences.
406 Earlier multicenter research included a general acute ischemic stroke population, whereas
407 subsequent studies separately examined 3-month functional outcomes, mortality among
408 critically ill patients, and the blood urea nitrogen/creatinine ratio, thereby addressing
409 different questions [14–17]. A recent intravenous thrombolysis cohort compared several
410 biochemical and nutritional measures and did not support sufficient discrimination of 3-
411 month functional outcomes by most individual markers, including blood urea nitrogen-
412 related measures [18]. This does not conflict with the finding in the present study that
413 the AUC of blood urea nitrogen alone was lower than that of the combined model: a

414 variable may retain a statistical association in a multivariable model while remaining
415 insufficient for individual prognostic assessment on its own.

416 Physiologically, blood urea nitrogen is jointly determined by protein catabolism,
417 hepatic urea synthesis, and renal clearance. Reduced glomerular filtration, inadequate
418 renal perfusion, or volume depletion may increase its level, while enhanced catabolism,
419 protein intake, gastrointestinal bleeding, and certain medications may also alter it;
420 creatinine, in contrast, is readily affected by factors such as age and muscle mass. This
421 study therefore regarded blood urea nitrogen as an integrated marker of metabolic and
422 renal status rather than a marker of renal injury alone. This interpretation is consistent
423 with the study design, but because the factors noted above were not fully measured, the
424 available data cannot determine which physiological component drove the observed
425 association.

426 Initial volume status at stroke onset is associated with outcome [24]. A prospective
427 observational study that assessed volume status using the inferior vena cava collapsibility
428 index further showed that directly assessed hypovolemia was associated with poor
429 outcome after acute ischemic stroke [25]; a study of hydration therapy based on the
430 blood urea nitrogen/creatinine ratio also observed differences in 3-month functional
431 outcomes [26]. These data provide context for blood urea nitrogen as a potential partial
432 reflection of circulating volume and renal perfusion, but neither blood urea nitrogen nor

433 its ratio is equivalent to a direct measurement of volume status. This study did not
434 record direct measures of volume status, urine output, protein intake, or dynamic
435 changes in renal function. The observed association therefore cannot be attributed to
436 dehydration, nor can the results be used to infer that hydration therapy improves
437 prognosis.

438 Recent studies have also reported associations of the blood urea nitrogen/creatinine
439 ratio and blood urea nitrogen/albumin ratio with mortality in specific stroke populations
440 [27,28]. These derived markers incorporate information reflected by creatinine or
441 albumin, respectively, and are not equivalent to the absolute blood urea nitrogen level
442 used in this study; the populations and outcomes also differed. Because this study did not
443 construct either ratio, it does not extend its conclusions to their diagnostic or prognostic
444 performance. Comparisons among different forms of the marker should be conducted in
445 the same population, using the same outcome definition and prespecified models.

446 Based on these findings, the potential clinical value of blood urea nitrogen may be
447 summarized as early signaling, comprehensive assessment, and serial reassessment. An
448 elevated admission level may be regarded as a signal for a more comprehensive
449 evaluation of systemic status and should be interpreted together with age, NIHSS score,
450 creatinine, urine output, and clinical assessment of volume status. Its changes may be
451 monitored through routine repeat testing during hospitalization, but because this study

452 did not evaluate dynamic blood urea nitrogen, it cannot define a monitoring frequency
453 or threshold. The available data also do not support changing the thrombolysis regimen,
454 hydration strategy, or renal treatment on the basis of blood urea nitrogen alone.
455 Whether blood urea nitrogen provides stable incremental value beyond routine
456 assessment requires validation in external cohorts and prospective clinical-impact studies.

457 **3.3 Other Model Variables**

458 Age and admission NIHSS score were associated with poor outcomes at both time
459 points, consistent with prior evidence regarding the relationships of age and baseline
460 stroke severity with outcomes after thrombolysis [10]. In this study, the AUC for
461 admission NIHSS score alone was higher than that for blood urea nitrogen alone,
462 indicating that baseline neurological deficits remain central to risk characterization.
463 Blood urea nitrogen may provide supplementary information in a multivariable model
464 but cannot replace standardized neurological assessment.

465 Age may reflect physiological reserve, comorbidity burden, and differences in
466 recovery capacity, whereas the admission NIHSS score directly characterizes baseline
467 neurological deficits. Both were retained in the 90-day and 1-year models, consistent
468 with the clinical understanding that stroke outcomes are jointly determined by the
469 severity of the initial injury and individual reserve. In comparison, the systemic

470 information reflected by blood urea nitrogen is less specific. It should therefore be
471 interpreted alongside age and the NIHSS score rather than as a replacement for either.

472 Platelet distribution width was associated with poor outcome at 90 days but was not
473 included in the 1-year model. Previous studies of intravenous thrombolysis and a
474 systematic review likewise observed associations between platelet distribution width and
475 stroke outcomes [19,20]. Platelets participate in thrombosis, immunity, and
476 inflammation [29], and a study of hyperacute stroke in humans showed that platelet
477 activation and chemokine release were related to local neutrophil-dominant
478 inflammation [30]. Observational cohorts of thrombolysis and mechanical thrombectomy
479 have also reported similar findings [31,32]. This study did not test a time interaction,
480 and the AUC for platelet distribution width alone was only 0.563. It can therefore be
481 interpreted only as a variable associated with the 90-day outcome, not as evidence of a
482 time-dependent mechanism or of sufficient standalone discrimination.

483 This study considered the possibility that platelet status may change during the acute
484 phase and that antiplatelet therapy may influence subsequent platelet reactivity. This
485 interpretation is biologically plausible, but the study used only the first platelet measures
486 obtained on admission and did not measure platelet function or treatment adherence
487 during follow-up. The absence of platelet distribution width from the 1-year model may
488 be related to a different outcome phase, variable selection, sample variation, or

489 unmeasured treatment factors; the current findings cannot distinguish among these
490 explanations.

491 The effect estimate for smoking in the 90-day model was $OR = 0.53$, 95% CI: 0.17–
492 1.64, and $P = 0.050$. The confidence interval was wide and crossed 1, and the available
493 findings are insufficient to support a clear independent protective association. Smoking
494 increases the risk of stroke and other cardiovascular events [33]. Observational
495 associations between smoking and outcomes in reperfusion-therapy cohorts may be
496 affected by age, stroke subtype, and other confounders, and previous results have been
497 inconsistent [34,35]. This study did not record smoking intensity, cumulative exposure,
498 or cessation status and does not interpret the direction of this effect as favorable.

499 **3.4 Model Performance and Clinical Interpretation**

500 The AUCs of the combined 90-day and 1-year models were 0.840 and 0.818,
501 respectively, whereas the AUCs for blood urea nitrogen alone were 0.684 and 0.633.
502 Although the combined models had numerically higher AUCs, this study did not test
503 between-model differences in AUC; the comparison is therefore descriptive only. Both
504 models underwent internal validation using bootstrap resampling 1000 times, with
505 mean absolute calibration errors of 0.028 and 0.012, respectively. The net-benefit
506 ranges shown by decision curve analysis likewise reflect only the current sample and the
507 specified threshold ranges.

508 Discrimination, calibration, and clinical net benefit address different questions. The
509 AUC describes a model's ability to distinguish between those who do and do not
510 experience an outcome but does not indicate whether predicted probabilities are
511 accurate. A calibration curve describes agreement between predicted probabilities and
512 observed outcomes. Decision curve analysis evaluates net benefit under assumptions about
513 a specific outcome incidence, threshold probability, and the consequences of
514 misclassification. Reporting all three helps avoid judging a model solely by its AUC, but no
515 measure of within-sample performance can replace validation in an independent
516 population.

517 The interpretation of a prediction model cannot rely on discrimination alone;
518 calibration, the target population, and the level of validation are equally important [36].
519 TRIPOD and its updated TRIPOD+AI statement emphasize transparent reporting of data
520 sources, variable handling, model development, performance assessment, and validation,
521 whether regression or machine-learning methods are used [37,38]. PROBAST and
522 PROBAST+AI assess model quality, risk of bias, and applicability across domains including
523 participants and data sources, predictors, outcomes, and analysis [39,40]. The findings
524 of this study represent model development and internal validation in a single-center
525 sample and are insufficient to support direct use of the models in clinical decision-
526 making.

527 The threshold ranges shown by decision curve analysis may describe the models'
528 potential net benefit under the current data and specified assumptions, but they cannot
529 demonstrate that model-guided intervention would improve patient outcomes.
530 Translation into a clinical tool would require a clearly defined intended clinical use,
531 prediction time point, and corresponding clinical actions; calibration, discrimination, and
532 net benefit would need to be tested in independent cohorts, together with the
533 incremental value of the models beyond routine information such as age and NIHSS
534 score.

535 3.5 Strengths and Limitations

536 This study evaluated two prespecified functional outcomes, at 90 days and 1 year, in
537 the same clinical cohort. All principal measures were obtained from routine admission
538 assessments, and model discrimination, internal calibration, and decision curve analysis
539 were fully reported according to the prespecified statistical analysis plan, providing a
540 relatively complete within-sample description of the relationship between blood urea
541 nitrogen and functional outcomes over different time scales. The study population was
542 restricted to cases that received standard-dose intravenous thrombolysis and met the
543 specified inclusion and exclusion criteria. The clear outcome definitions and assessment
544 time points reduced the influence of differences in treatment setting and endpoint
545 definitions on internal comparisons between the two models.

546 This study has important limitations. The single-center retrospective design may be
547 subject to selection bias, information bias, and residual confounding. The strict inclusion
548 and exclusion criteria, 36 cases lost to follow-up, and repeated treatment records for a
549 small number of patients also limit the generalizability of the findings and the
550 interpretation of independence among observations. The models underwent only internal
551 bootstrap validation and have not been validated in an external cohort. The study used
552 only the first laboratory results obtained on admission and did not capture dynamic
553 changes in blood urea nitrogen, renal function, or volume status. It also lacked long-term
554 follow-up information on postdischarge rehabilitation, secondary prevention, and
555 recurrent events. Accordingly, this study cannot characterize the relationship between
556 blood urea nitrogen trajectories and outcomes or exclude unmeasured confounding [39–
557 42].

558 Future studies should validate the association of blood urea nitrogen with short- and
559 long-term functional outcomes in independent multicenter cohorts with sample sizes
560 estimated in advance and should explicitly address the correlation of repeated events
561 within the same patient. Data collection could include dynamic changes in blood urea
562 nitrogen, creatinine, and estimated glomerular filtration rate, together with direct
563 measures of volume status, urine output, nutritional and catabolic markers,
564 postdischarge rehabilitation, secondary prevention, and recurrent events. Model studies

565 should prioritize testing external calibration, clinical net benefit, and incremental value
566 beyond routine assessment before determining whether model updating or prospective
567 clinical-impact studies are warranted.

568 **4 Conclusions**

569 In this single-center retrospective cohort, higher admission blood urea nitrogen levels
570 were associated with poor functional outcomes at 90 days and 1 year after intravenous
571 thrombolysis for acute ischemic stroke. Age and admission NIHSS score were associated
572 with poor outcomes at both time points, whereas platelet distribution width was
573 associated only with the 90-day outcome. The combined models had numerically higher
574 AUCs than blood urea nitrogen alone in the study sample, but their clinical applicability
575 requires external validation.

576 **List of abbreviations**

577 AI, artificial intelligence; ALT, alanine aminotransferase; ApoB, apolipoprotein B;
578 APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; AUC,
579 area under the curve; BUN, blood urea nitrogen; CI, confidence interval; Cr, creatinine;
580 CT, computed tomography; DBP, diastolic blood pressure; eGFR, estimated glomerular
581 filtration rate; FEU, fibrinogen equivalent units; FIB, fibrinogen; Hb, hemoglobin; INR,

international normalized ratio; LAA, large-artery atherosclerosis stroke; LASSO, least absolute shrinkage and selection operator; MPV, mean platelet volume; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; PCT, plateletcrit; PDW, platelet distribution width; PLT, platelet count; P-LCR, platelet-large cell ratio; PROBAST, Prediction model Risk Of Bias ASsessment Tool; PT, prothrombin time; Q1, first quartile; Q3, third quartile; rt-PA, recombinant tissue plasminogen activator; SAA, small-artery occlusion stroke; SBP, systolic blood pressure; SOE, stroke of other determined etiology; SPSS, Statistical Package for the Social Sciences; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; TRIPOD, Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis; UA, uric acid.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Second Affiliated Hospital of Guangzhou Medical University (2023-LCYJ-XS-24); patients or their family members provided written informed consent. Study data were de-identified during analysis and reporting.

599 **Consent for publication**

600 Not applicable.

601 **Availability of data and materials**

602 The datasets used and/or analysed during the current study are not publicly available
603 due to patient privacy and institutional restrictions but are available from the
604 corresponding author on reasonable request, subject to applicable institutional and ethical
605 approval.

606 **Competing interests**

607 The authors declare that they have no competing interests.

608 **Funding**

609 No funding was received for this study.

610 **Authors' contributions**

611 XL, HS, and LH contributed equally to the conception and design of the study,
612 methodology, data curation, formal analysis, visualization, and drafting and revision of
613 the manuscript. GZ, XC, JX, and QL contributed to participant follow-up, clinical data
614 collection, and data verification. YD and JZ contributed to the conception and design of

the study, supervised the project, interpreted the findings, and critically reviewed and revised the manuscript. All authors read and approved the final manuscript.

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