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Original Article

Prognostic nomogram for acute cerebral infarction based on risk factors: treatment with urinary kallidinogenase and edaravone-dexborneol

Fengqiao Ma, Dongjuan Xu, Yunyun Xu, Lianyan Wei, Hongfei Li

Department of Neurology, Dongyang People's Hospital, Wenzhou Medical University, Dongyang 322100, Zhejiang, China

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Abstract: Objective: To investigate the prognostic factors in patients with acute cerebral infarction (ACI) treated with urinary kallidinogenase combined with edaravone-dexborneol and to construct a predictive model. Methods: A total of 120 ACI patients admitted to Dongyang People's Hospital, affiliated to Wenzhou University, from January 2022 to December 2023 were retrospectively collected, of whom 101 were included after screening. An additional 105 ACI patients admitted to other hospitals during the same period were collected as an external validation cohort. Prognosis was assessed using the modified Rankin Scale (mRS), and patients were classified into the good prognosis group (mRS ≤ 2 points) and the poor prognosis group (mRS > 2 points). Clinical data of the two groups were collected for univariate and binary logistic regression analyses to construct a nomogram prediction model, and ROC curve analysis was used to validate the predictive performance. Results: Univariate analysis indicated that comorbidities, TOAST classification, infarct location, thrombolytic/anticoagulant therapy drugs, age, disease duration, National Institutes of Health Stroke Scale (NIHSS) score at admission, Glasgow Coma Scale (GCS) score at admission, and fasting blood glucose were factors associated with poor prognosis. Binary logistic regression analysis showed that brainstem infarction, clopidogrel as thrombolytic/anticoagulant therapy, and NIHSS score at admission were independent risk factors. Model Y was constructed, and the Hosmer-Lemeshow test yielded χ^2 = 9.660 and P = 0.290. A nomogram prediction model was developed, and ROC curve analysis showed that the AUC of the training set was 0.867 (95% *CI* = 0.789-0.867), the AUC of the test set was 0.769 (95% CI = 0.502-1.000), and the AUC of the validation cohort was 0.879 (95% *CI* = 0.810-0.949). Conclusion: The prognosis of ACI patients treated with urinary kallidinogenase combined with edaravone-dexborneol is influenced by multiple factors. Clinicians may construct a prognostic prediction model based on previous medical records to identify risk factors and adjust treatment strategies to improve prognosis.

Keywords: Acute cerebral infarction, Urinary Kallindinogenase, edaravone-dexborneol, prognostic evaluation, predictive model

Introduction

Acute cerebral infarction (ACI) manifests as brain tissue necrosis due to sudden interruption of cerebral blood supply, representing a prevalent clinical condition within the spectrum of strokes. It exhibits high incidence and disability rates globally. According to data from the World Stroke Organization [1], the age-standardized incidence rate (ASIR) and mortality rate (ASMR) of ACI in 2019 were 94.51/100,000 and 43.50/100,000 respectively on a global scale. In China, stroke ranks third as a cause of death. In the same year, the ASIR and ASMR of ACI in China were notably higher at 144.80/100,000 and 62.20/100,000 respectively [2], surpassing the global average. Despite a 3.3% reduction in ASMR compared to 1990, the ASIR surged by 33.5% during the same period, indicating significant room for improvement in ACI prevention and treatment in China.

There are many types of ACI. At present, the common types of ACI in clinical practice mainly include atherosclerotic cerebral infarction, sm-

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all artery occlusive cerebral infarction, cardiogenic cerebral infarction, etc. The pathogenesis of different types of ACI varies. Hence, elucidating the etiology and pathogenesis of patients, identifying the affected vessels, recognizing complications, and conducting a comprehensive analysis of the patient's condition are imperative steps in formulating a scientifically sound treatment plan for ACI in clinical practice. It is important to ensure that patients with ACI can receive effective treatment within the treatment time window, thus providing guarantee for good prognosis. Regarding the clinical treatment of ACI, thrombolytic therapy is one of the most important treatment modalities for ACI, including intravenous thrombolysis, arterial thrombolysis, combined arteriovenous thrombolysis and mechanical thrombolysis. It mainly converts plasma protein plasminogen into plasmin directly or indirectly through endogenous or exogenous plasminogen activator to promote rapid degradation of fibrin, so that the thrombus in the body is dissolved and local tissue oxygen reperfusion is restored, improving cerebral microcirculation [3]. In previous clinical practice, urokinase or alteplase (rt-PA) was often used as the first choice for thrombolytic therapy of ACI. The former is a first-generation thrombolytic drug and an endogenous plasminogen activator that can directly act on plasminogen to degrade formed fibrin clots and promote neurological recovery [4], while rt-PA is a recombinant tissue plasminogen activator. The drug can specifically bind to fibrin in thrombus to form a complex, and this activator can activate thrombolytic enzymes in the body, which then degrades fibrin into soluble products to achieve thrombolysis [5]. Numerous prior investigations have examined the efficacy and safety profiles of these two thrombolytic drugs. While the majority of both domestic and international studies assert that urokinase exhibits comparable thrombolytic efficacy to rt-PA, differing perspectives emerge regarding safety. For instance, certain studies propose that rt-PA may offer additional protection against cerebral hemorrhage in ACI patients [6], whereas contradictory findings have been reported in additional research [7]. In addition to thrombolytic therapy, some progress has also been made in the anticoagulant treatment of ACI at home and abroad [8]. Anticoagulant drugs can prevent the spread of thrombus, avoid aggravation of neurological damage, and prevent reinfarction. However, the timing of anticoagulation has an important impact on the anticoagulation effect and patient prognosis. Research indicates that anticoagulant therapy administered to patients with mild, moderate, and severe ACI often yields enhanced anticoagulation effects at 2 d, 7 d, and 11 d post-onset [9]. Consequently, the European Heart Rhythm Society and the European Association of Cardiology (EHRA-ESC) as well as the American Heart Association and Stroke Association (AHA/ASA) successively introduced the "1-3-6-12" rule [10] and the "4-14" criterion [11]. Due to the stronger operability of the former, it has become a relatively recognized timing for anticoagulation at present and is recommended by relevant guidelines in China [12].

Based on the above studies, there are many clinical treatment regimens for ACI, but no matter what treatment method or drug is adopted, the prognosis of patients may be affected by the patient's own or external environmental factors. In China, research has identified infection, hypertension, and large artery atherosclerotic type as potential contributors to secondary intracranial hemorrhage following rt-PA thrombolysis in ACI patients [13]. Furthermore, studies in the United States have suggested associations between blood glucose levels and National Institutes of Health Stroke Scale (NIHSS) scores before thrombolysis, and the risk of secondary bleeding post-rt-PA thrombolytic therapy in ACI patients [14]. Additionally, independent risk factors for vascular reocclusion after thrombolytic therapy in elderly ACI patients include a history of diabetes, systolic pressure, and the duration from onset to thrombolytic therapy [15]. Urinary kallidinogenase is a tissue kallikrein extracted from the urine of healthy adult males. Its therapeutic target is the kallikrein-kinin system (KKS), which cleaves kininogen into kinins. By binding to kinin receptors, it rapidly opens collateral microvessels during the acute phase of cerebral ischemia, improves blood perfusion in the ischemic region, and inhibits neuronal apoptosis. During the recovery phase, it promotes angiogenesis in the ischemic area and facilitates neuronal regeneration, while also exerting effects in attenuating oxidative stress and increasing the survival and migration of glial cells. Clinical studies have confirmed that urinary kallidinoge-

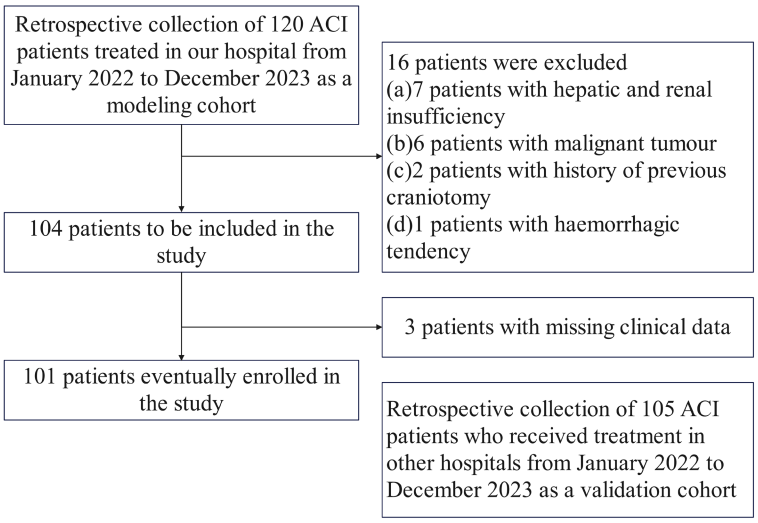

Figure 1. Flow chart of subject inclusion. Note: ACI: Acute Cerebral Infarction.

nase combined with alteplase in the treatment of ACI can increase the total effective rate to 93.33%, significantly reduce NIHSS and CSS scores, improve activities of daily living scores, and reduce levels of inflammatory factors such as CRP and IL-8, with stable efficacy observed across different TOAST subtypes of ACI patients [16]. Edaravone-dexborneol is a novel neuroprotective agent composed of edaravone and (+)-borneol at a ratio of 4:1. Edaravone efficiently scavenges oxygen free radicals and inhibits excitatory neurotoxicity, while (+)-borneol suppresses the inflammatory response, protects the integrity of the blood-brain barrier, and reduces cell apoptosis. Together, they exert synergistic and multiple neuroprotective effects [17]. Prior research has examined the clinical effectiveness of Urinary Kallindinogenase in combination with Edaravone-dexborneol for ACI treatment. However, there is a notable absence of reports addressing factors influencing prognosis in ACI patients undergoing this combined treatment. Therefore, this study endeavors to investigate and analyze the determinants impacting the prognosis of ACI patients receiving Urinary Kallindinogenase combined with Edaravone-dexborneol. Additionally, it aims to develop a predictive model for identifying patients at risk of poor prognosis. These findings aim to establish a framework for adjusting treatment strategies based on pertinent risk factors in future clinical practice for ACI patients undergoing this treatment regimen.

Data and methods

Research subjects

A total of 120 ACI patients who received treatment at Dongyang People's Hospital between January 2022 and December 2023 were retrospectively enrolled as the modeling cohort. Inclusion criteria: (a) ACI-related diagnostic criteria in the ICSI Health Care Guidelines: Diagnosis and Primary Treatment of Ischemic Stroke, 12th Edition issued by the Clinical Systems Improvement Association in 2019; (b) Patients who received treatment with Urinary Kallindinogenase combined with Edaravone-dexborneol without adverse reactions or serious side effects after medication; (c) Patients aged ≥ 18 years. Exclusion criteria: (a) Hepatic and renal insufficiency; (b) Peptic ulcer; (c) Primary tumor or brain metastasis of malignant tumor at other sites; (d) History of brain trauma; (e) History of previous craniotomy; (f) Severe coagulation disorder, or bleeding tendency in recent 1 month. Based on the above criteria and excluding cases with missing clinical data, 101 patients with ACI were finally included in the research. Based on this, 105 patients with acute cerebral infarction were collected from the MIMIC-IV database as a validation cohort using the same inclusion and exclusion criteria. **Figure 1** illustrates the subject inclusion process. This study was approved by the medical ethics committee (Approval No.: WZ-2024-K112) and complies with the Declaration of Helsinki [18].

Grouping criteria

The modified Rankin score (MRS) was utilized to evaluate patients' prognosis [19]. This scoring system categorizes ACI patients into seven grades: Grade 0 signifies complete symptom disappearance, Grade 1 indicates symptomatic but minor disability permitting the completion of daily tasks independently, Grade 2 represents mild disability hindering previous activities but not personal affairs, Grade 3 reflects moderate disability necessitating assistance for mobility, Grade 4 denotes severe disability

requiring aid for mobility and self-care, Grade 5 describes profound disability with bedridden status and full dependency, and Grade 6 indicates mortality. These grades are assigned scores ranging from 0 to 6, where higher scores indicate poorer prognosis. Previous research suggests that an MRS score ≤ 2 signifies a favorable prognosis, while an MRS score > 2 indicates an unfavorable prognosis. Patients were subsequently categorized into two groups: a good prognosis group (n = 68) and a poor prognosis group (n = 33).

Data collection

Data from patients in both groups were gathered, encompassing various parameters such as gender, comorbidities (hypertension, diabetes mellitus, cardiovascular disease, hyperlipidemia, and progressive cerebral infarction), smoking and drinking history, TOAST classification, site of cerebral infarction (basal ganglia region, frontal lobe, temporal lobe, parietal lobe, occipital lobe, brainstem, and cerebellum), thrombolytic treatment approach, and thrombolytic/anticoagulant medications (aspirin, clopidogrel, rt-PA, argatroban, and cilostazol). Additionally, factors including fever occurrence, age, disease duration, time from onset to admission, NIHSS score upon admission, GCS score upon admission, fasting blood glucose (FPG), and low-density lipoprotein cholesterol (LDL-C) were recorded.

Statistical methods

Data analysis was conducted utilizing SPSS 27.0 statistical software. The Kolmogorov-Smirnov test was employed to assess whether the measurement data adhered to a normal distribution. For normally distributed data, mean ± standard deviation (SD) was used, and an independent t-test was conducted between groups. Skewed distribution data were represented using median and quartiles [M (P_{25}, P_{75})], with between-group comparisons performed using the Mann-Whitney U test. Enumeration data were presented as number and percentage [n (%)], analyzed using the χ^2 test. Binary logistic regression analysis was employed to identify prognostic factors in ACI patients treated with Urinary Kallindinogenase and Edaravone-dexborneol. Subsequently, the "rms" and "caret" packages in Rstudio (R4.3.2) were utilized to construct a nomogram prediction model and generate a nomograph. The "pROC" package was then utilized to validate the prediction model, plotting the receiver operating characteristic curve (ROC) and calculating the area under the ROC curve (AUC). Additionally, predictive model calibration curves were generated, and the mean absolute error (MAE) and mean squared error (MSE) were computed. A significance level of $P < 0.05$ was adopted for statistical inference.

Results

Comparison of clinical data

This study included a total of 206 patients, among whom 79 had poor prognosis, resulting in a poor prognosis rate of 38.35%. There were no statistically significant differences between the two groups in terms of sex, hypertension, diabetes, cardiovascular disease, hyperlipidemia, progressive cerebral infarction, smoking history, drinking history, TOAST classification, infarct location, thrombolytic treatment regimen, thrombolytic/anticoagulant medications used, presence of fever, age, disease duration, onset-to-admission time, NIHSS score at admission, GCS score at admission, FPG, and LDL-C ($P > 0.05$), as detailed in **Table 1**.

Univariate analysis

The outcomes of univariate analysis revealed several influencing factors contributing to the poor prognosis of ACI patients treated with Urinary Kallindinogenase combined with Edaravone-dexborneol, including comorbidities (cardiovascular diseases, progressive cerebral infarction), TOAST classification, cerebral infarction site (brainstem), administration of thrombolytic/anticoagulant medications (clopidogrel), age, disease duration, NIHSS score upon admission, GCS score upon admission, and FPG levels. For detailed information, refer to **Table 2**.

Multivariate analysis

Based on the clinical data of the patients in the modeling cohort, in this study, patient prognosis was designated as the dependent variable, with comorbidities (cardiovascular diseases, progressive cerebral infarction), TOAST classification, cerebral infarction site (brainstem),

Table 1. Comparison of clinical data between the modeling and validation cohorts

Item		Modeling Cohort (n = 101)	Validation Cohort (n = 105)	$\chi^2/t/Z$	P
Prognosis	Good	68 (67.33)	59 (56.19)	2.700	0.100
	Poor	33 (32.67)	46 (43.81)		
Gender	Male	69 (68.32)	71 (67.62)	0.012	0.915
	Female	32 (31.68)	34 (32.38)		
Comorbidities	Hypertension	79 (78.22)	86 (81.90)	0.439	0.508
	Diabetes	26 (25.74)	38 (36.19)	2.624	0.105
	Cardiovascular Disease	16 (15.84)	18 (17.14)	0.063	0.801
	Hyperlipidemia	34 (33.66)	23 (21.90)	3.557	0.059
	Progressive Cerebral Infarction	13 (12.87)	10 (9.52)	0.582	0.446
Smoking History	No	59 (58.42)	60 (57.14)	0.034	0.853
	Yes	42 (41.58)	45 (42.86)		
Alcohol History	No	61 (60.40)	68 (64.76)	0.419	0.517
	Yes	40 (39.60)	37 (35.24)		
TOAST Classification	Large Artery Atherosclerosis	33 (32.67)	37 (35.24)	2.278	0.320
	Small Artery Occlusion	59 (58.42)	64 (60.95)		
	Cardioembolism	9 (8.91)	4 (3.81)		
Infarction Location	Basal Ganglia	52 (51.49)	45 (42.86)	1.538	0.215
	Frontal Lobe	25 (24.75)	30 (28.57)	0.384	0.536
	Temporal Lobe	12 (11.88)	12 (11.43)	0.010	0.919
	Parietal Lobe	16 (15.84)	22 (20.95)	0.894	0.344
	Occipital Lobe	12 (11.88)	18 (17.14)	1.145	0.284
	Brainstem	24 (23.76)	23 (21.90)	0.101	0.751
	Cerebellum	3 (2.97)	4 (3.81)	0.000	1.000
Thrombolytic Regimen	None	1 (0.99)	0 (0.00)	1.945	0.584
	Single-agent	40 (39.60)	36 (34.29)		
	Dual-agent	56 (55.45)	63 (60.00)		
	Triple-agent	4 (3.96)	6 (5.71)		
Thrombolytic/Anticoagulant Drugs	Aspirin	81 (80.20)	85 (80.95)	0.019	0.891
	Clopidogrel	67 (66.34)	73 (69.52)	0.240	0.624
	rt-PA	14 (13.86)	16 (15.24)	0.078	0.779
	Argatroban	1 (0.99)	1 (0.95)	0.000	1.000
	Cilostazol	1 (0.99)	3 (2.86)	0.217	0.641
Fever	No	100 (99.01)	99 (94.29)	2.209	0.137
	Yes	1 (0.99)	6 (5.71)		
Age (years)		65.96±10.60	65.49±10.81	0.318	0.751
Disease Duration (days)		8.00 (6.00, 9.00)	7.00 (7.00, 9.00)	-0.427	0.669
Onset-to-Admission Time (hours)		18.00 (8.00, 24.00)	16.00 (6.00, 40.50)	-0.248	0.804
NIHSS Score on Admission (Points)		3.00 (2.00, 5.00)	3.00 (1.00, 4.00)	-1.879	0.060
GCS Score on Admission (Points)		15.00 (15.00, 15.00)	15.00 (15.00, 15.00)	-1.445	0.148
FPG (mmol/L)		4.98 (4.60, 5.96)	5.37 (4.63, 6.46)	-1.213	0.225
LDL-C (mmol/L)		2.56±0.82	2.78±0.99	-1.723	0.086

Notes: NIHSS: National Institutes of Health Stroke Scale; GCS: Glasgow Coma Scale; FPG: Fasting Plasma Glucose; LDL-C: Low-Density Lipoprotein Cholesterol.

thrombolysis/anticoagulant therapy drugs (clopidogrel), age, disease duration, NIHSS score upon admission, GCS score upon admission, and FPG serving as independent variables for binary logistic regression analysis (variable assignment depicted in **Table 3**). The findings revealed that the location of cerebral infarction in the brainstem, administration of thrombolytic/anticoagulant therapy drug clopidogrel, and NIHSS score upon admission emerged as independent risk factors influencing the prognosis of ACI patients treated with Urinary Kallindinogenase combined with Edaravone-dexborneol. Further details are presented in **Table 4**.

Logistic regression model construction

Utilizing the outcomes of binary logistic regression analysis and the associated formula (b), a

Table 2. Univariate analysis of prognosis in patients with ACI treated with Urinary Kallindinogenase and Edaravone-dexborneol

Item		Good prognosis group (n = 68)	Poor prognosis group (n = 33)	$\chi^2/t/Z$	*P*
Sex	Male	48 (70.59)	21 (63.64)	0.496	0.481
	Female	20 (29.41)	12 (36.36)		
Comorbidities	Hypertension	53 (77.94)	26 (78.79)	0.009	0.923
	Diabetes	16 (23.53)	10 (30.30)	0.533	0.465
	Cardiovascular disease	5 (7.35)	11 (33.33)	11.249	0.001
	Hyperlipidemia	24 (35.29)	10 (30.30)	0.248	0.619
	Progressive cerebral infarction	5 (7.35)	8 (24.24)	4.246	0.039
Smoking history	N/A	38 (55.88)	21 (63.64)	0.550	0.458
	Yes	30 (44.12)	12 (36.36)		
Drinking history	N/A	44 (64.71)	17 (51.52)	1.616	0.204
	Yes	24 (35.29)	16 (48.48)		
TOAST typing	Large artery atherosclerosis	17 (25.00)	16 (48.48)	9.973	0.007
	Arteriole occlusion	47 (69.12)	12 (36.36)		
	Cardiac embolism	4 (5.88)	5 (15.15)		
Cerebral infarction site	Basal ganglia region	38 (55.88)	14 (42.42)	1.611	0.204
	Frontal lobe	18 (26.47)	7 (21.21)	0.330	0.566
	Temporal lobe	8 (11.76)	4 (12.12)	0.000	1.000
	Parietal lobe	11 (16.18)	5 (15.15)	0.018	0.895
	Occipital lobe	10 (14.71)	2 (6.06)	0.868	0.352
	Brainstem	11 (16.18)	13 (39.39)	6.611	0.010
	Cerebellum	0 (0.00)	3 (9.09)	3.607	0.058
Thrombolytic regimen	N/A	0 (0.00)	1 (3.03)	5.422	0.143
	Monotherapy	23 (33.82)	17 (51.52)		
	Double drug combination	42 (61.76)	14 (42.42)		
	Triple drug combination	3 (4.41)	1 (3.03)		
Thrombolytic/anticoagulant drugs	Aspirin	56 (82.35)	25 (75.76)	0.609	0.435
	Clopidogrel	51 (75.00)	16 (48.48)	6.995	0.008
	rt-PA	9 (13.24)	5 (15.15)	0.000	1.000
	Argatroban	0 (0.00)	1 (3.03)	0.138	0.710
	Cilostazol	0 (0.00)	1 (3.03)	0.138	0.710
Heating or not	No	68 (100.00)	32 (96.97)	0.138	0.710
	YES	0 (0.00)	1 (3.03)		
Age (years)		64.32±10.19	69.33±10.79	-2.274	0.025
Course of disease (d)		7.00 (6.00, 8.00)	9.00 (7.00, 11.00)	-3.568	< 0.001
Time from onset to admission (h)		17.50 (8.50, 24.00)	18.00 (7.00, 24.00)	-0.709	0.478
NIHSS score on admission (points)		2.50 (1.00, 3.00)	5.00 (4.00, 9.25)	-5.402	< 0.001
GCS score at admission (points)		15.00 (15.00, 15.00)	15.00 (15.00, 15.00)	-2.040	0.041
FPG (mmol/L)		4.92 (4.53, 5.59)	5.41 (4.70, 6.46)	-1.966	0.049
LDL-C (mmol/L)		2.60±0.81	2.47±0.85	0.730	0.470

Note: NIHSS stands for the United States National Institutes of Health Stroke Scale, GCS refers to the Glasgow Coma Scale. Additionally, FPG represents fasting plasma glucose, and LDL-C denotes low-density lipoprotein cholesterol.

binary logistic regression model (c) was formulated. The model's coefficient underwent an Omnibus test, yielding $\chi^2 = 58.713$, $P < 0.001$. Further examination revealed Model-2 log-likelihood of 68.919, Cox & Snell R2 of 0.441, and Nagelkerke R2 of 0.615, indicating substantial explanatory power. The Hosmer-Lemeshow test yielded $\chi^2 = 9.660$, $P = 0.290$, suggesting satisfactory model fit.

$$Y = \beta_0 + \beta_1 x_1 + \quad + \beta_n x_n \qquad (b)$$

$$Y = 1.413 \times \textit{Brainstem} - 1.517 \times \textit{Clopidogrel} + 0.477 \times \textit{NIHSS}\ (\textit{admission}) \qquad (c)$$

Construction of nomogram model

Utilizing the findings from binary logistic regression analysis, a nomogram prediction model

Table 3. Variable assignment

Variable		Assignment method
Dependent variable	Prognosis	Good Prognosis = 0; Poor Prognosis = 1
	Comorbidities-cardiovascular disease	no = 0; yes = 1
	Comorbidity-progressive cerebral infarction	no = 0; yes = 1
	Cerebral infarction site-brainstem	no = 0; yes = 1
	Thrombolytic/Anticoagulant Therapy Agents-Clopidogrel	no = 0; yes = 1
Independent variable	Age	Original value input
	Course of disease	Original value input
	NIHSS score on admission	Original value input
	GCS score at admission	Original value input
	PBG	Original value input

Note: NIHSS stands for the United States National Institutes of Health Stroke Scale, GCS refers to the Glasgow Coma Scale, FBG Fasting Blood Glucose.

Table 4. Prognosis assessment via binary logistic regression in ACI patients treated with urinary Kallindinogenase and Edaravone-dexborneol

Independent variables	*B*	*S.E.*	*Wald* χ^2	*P*	*OR*	95% *CI*	
						Lower limit	Upper limit
Comorbidities-Cardiovascular (Yes)	1.450	0.856	2.866	0.090	4.261	0.796	22.824
Comorbidity-progressive cerebral infarction (Yes)	1.062	0.862	1.518	0.218	2.893	0.534	15.680
Cerebral infarction site-brainstem (yes)	1.413	0.694	4.140	0.042	4.108	1.053	16.026
Thrombolytic/anticoagulant therapy agent - clopidogrel (yes)	-1.517	0.669	5.139	0.023	0.219	0.059	0.814
Age	0.035	0.032	1.222	0.269	1.035	0.973	1.101
Course of disease	0.284	0.159	3.202	0.074	1.328	0.973	1.812
NIHSS score on admission	0.477	0.152	9.924	0.002	1.612	1.198	2.169
GCS score at admission	-1.455	3197.029	0.000	1.000	0.234	0.000	-
PBG	-0.123	0.124	0.990	0.320	0.884	0.693	1.127
Constant	15.246	47955.439	0.000	1.000	-	-	-

Note: NIHSS: the United States National Institutes of Health Stroke Scale, GCS: Glasgow Coma Scale, FBG: Fasting Blood Glucose.

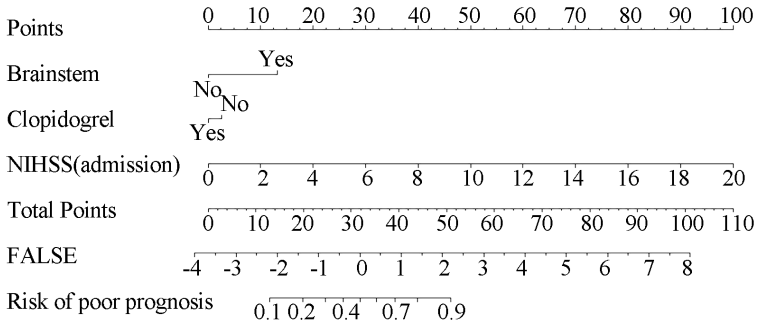

Figure 2. Nomogram predictive model of prognosis in patients with ACI treated with Urinary Kallindinogenase and Edaravone-dexborneol. Note: NIHSS: the United States National Institutes of Health Stroke Scale.

was developed employing the "rms" and "caret" packages within Rstudio (R4.3.2), depicted in **Figure 2**. The total score of the model increased by 13 points by combining the cerebral infarction site-brainstem. No thrombolytic/anticoagulant therapy-clopidogrel treatment increased the total score of the model by 3 points. In the nomogram model, the NIHSS score upon admission carried the most significant weight, with a 2-point increase resulting in a 10-point rise in the total model score. The total score ranges from 0 to 110 points, with higher scores indicating a heightened risk of poor prognosis for patients. For instance, with a total model score of 10 points, the likelihood of poor prognosis stands at 10%; however, with a total score of 51 points, this probability escalates to 90%.

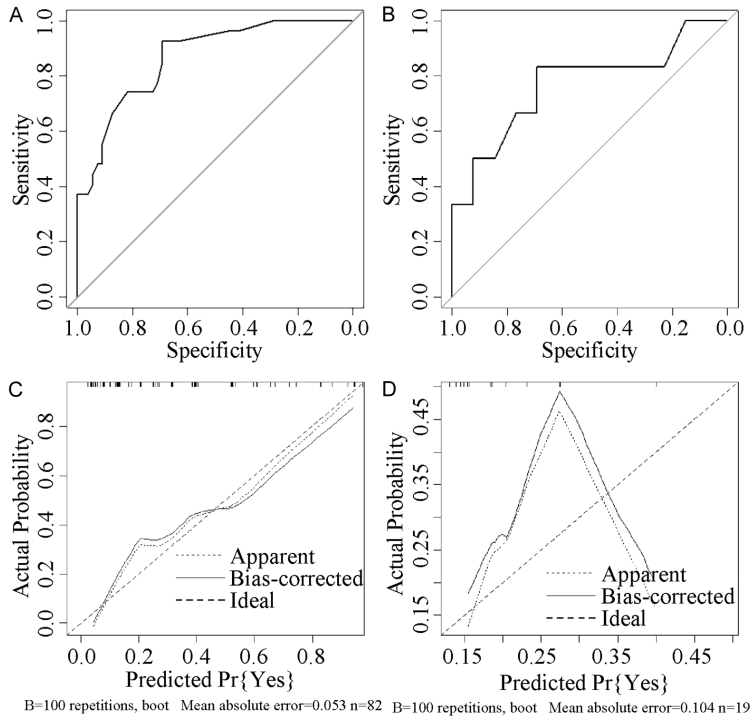

Figure 3. ROC curve and calibration curve of the prognostic nomogram model in patients with ACI treated with Urinary Kallindinogenase and Edaravone-dexborneol x-bamphenol. Note: (A) ROC curve of training set; (B) ROC curve of test set; (C) Calibration curve of training set; (D) Calibration curve of test set.

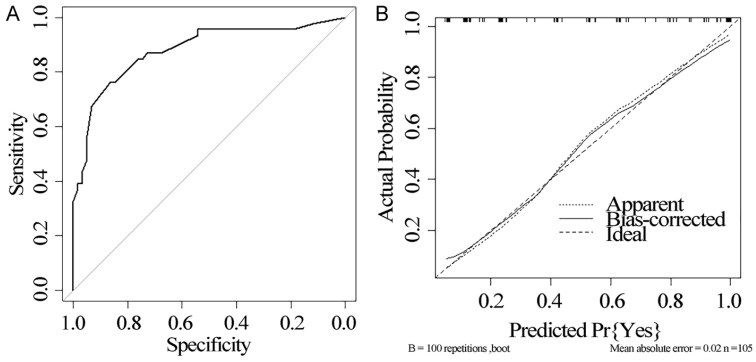

Figure 4. External validation of the nomogram model for predicting prognosis in ACI patients treated with uriculin combined with Edaravone-dexborneol. Note: (A) ROC curve; (B) Calibration curve.

Internal validation of the model

To assess the predictive capability of the nomogram model, the "pROC" package was employed. Among the 101 patients in the modeling cohort, 82 were allocated to the training set and 19 to the test set, maintaining a 4:1 ratio. The ROC curve analysis indicated an AUC of 0.867 (95% CI = 0.789-0.867) for the training set and 0.769 (95% CI = 0.502-1.000) for the test set, underscoring the model's strong discriminatory capacity. Calibration curve analysis revealed minimal errors, with MAE = 0.061 and MSE = 0.0048 for the training set, and MAE = 0.130 and MSE = 0.0219 for the test set. These findings suggest close alignment between predicted and actual outcomes. As depicted in **Figure 3**.

External validation of the model

External validation was performed using clinical data from 105 patients in the validation cohort. The ROC curve analysis revealed an AUC of 0.879 (95% CI: 0.810-0.949), indicating strong discriminatory power. The calibration curve analysis demonstrated a mean absolute error (MAE) of 0.020 and a mean squared error (MSE) of 0.0006, suggesting excellent agreement between predicted and observed outcomes. Detailed results are shown in **Figure 4**.

Discussion

There are several hypotheses about the mechanism of Urinary Kallindinogenase in treating acute cerebral infarction. Han et al. highlighted Urinary Kallindinogenase's role in augmenting angiogenesis within the subventricular zone and increasing capillary density in the peri-infarct region, thereby enhancing collateral circulation [20]. Additionally, Song et al. observed that Urinary Kallindinogenase improves neurological symptoms by enhancing cortical motor area function remodeling in ACI patients [21]. In their study, Zhang et al. discovered that Edaravone-dexborneol could alleviate neuro-

logical deficit symptoms in the CA1 region of rats' hippocampi. They observed a reduction in apoptosis and neuronal damage, attributing these effects to Edaravone-dexborneol's inhibition of mitogen-activated protein kinase (MARK) and activation of nuclear factor erythrocyte lineage-2 related factor 2 (Nrf2) by upregulating MKP-1 levels, thus mitigating cerebral ischemia-induced injury [22]. Both domestically and internationally, Urinary Kallindinogenase and Edaravone-dexborneol have undergone extensive investigation for treating various neurological injury-related diseases, including ACI. It is believed that the combined use of these drugs positively influences the improvement of NIHSS and MRS scores in patients. However, due to the poor physical condition of patients with ACI, often accompanied by a variety of complications and external factors, their prognosis may be adversely affected.

This study conducted factor analysis on ACI patients' prognosis under dual drug treatment. The findings revealed that cerebral infarction occurring in the brainstem, administration of clopidogrel for thrombolytic/anticoagulant therapy, and NIHSS score at admission independently influenced the prognosis of ACI patients receiving Urinary Kallindinogenase combined with Edaravone-dexborneol. The brain stem is an important brain tissue connecting the brain and spinal cord. It participates in maintaining the physiological functions of the body such as respiration, circulation, and digestion, and also controls the motor and sensory functions of the human body. Pontine infarction is the most common brainstem infarction. Compared with other parts, there are more pontine nuclei and greater blood supply demand [23]. Although Urinary Kallindinogenase and Edaravone-dexborneol have strong neuroprotective functions, patients are still more likely to have a poor prognosis due to the relatively high sensitivity of pons to ischemia and more severe symptoms than patients with infarction at other sites. Clopidogrel functions as a platelet aggregation inhibitor by selectively obstructing the binding of ADP to platelet receptors. Within this study, the occurrence of adverse prognosis was 32.86% (46/140) among patients receiving clopidogrel treatment, contrasting with 50.00% (33/66) among those not undergoing clopidogrel treatment. This discrepancy might stem from clopidogrel's synergistic interaction with Urinary Kallindinogenase and Edaravone-dexborneol in ACI treatment, amplifying the efficacy of the other two medications. Studies in China have also confirmed that the combination of clopidogrel and Urinary Kallindinogenase can further improve the neurological function and prognosis of patients, with an effect better than that of Urinary Kallindinogenase alone [24], while the application of clopidogrel combined with Edaravone-dexborneol in ACI has not been reported at present. The NIHSS score is a quantitative tool used clinically to assess the degree of ACI nerve defect, and the median NIHSS score at admission in patients with poor prognosis in this study was twice that in patients with good prognosis. Shah's study found that bleeding after thrombolysis in patients with ACI was closely associated with NIHSS score at admission [25]. Wang's study on patients aged 80 years and older with ACI revealed that those with a baseline NIHSS score $\geq$ 15 points (OR = 1.414, 95% CI = 1.150-1.740) exhibited a higher likelihood of poor prognosis, mirroring the findings of this investigation [26]. However, the NIHSS scores upon admission in our study were comparatively lower, potentially due to the participants' younger age and fewer comorbidities.

Leveraging the independent risk factors influencing the prognosis of ACI patients treated with Urinary Kallindinogenase combined with Edaravone-dexborneol, this study developed a nomogram prediction model. Validation confirmed the model's fitting and discriminatory abilities. The nomogram illustrates that with a total score of 10 points, the incidence of poor prognosis stands at 10%; while with a total score of 51 points, it escalates to 90%. In addition, it can be found from this model that The NIHSS score has the greatest weight on admission. Therefore, in the future clinical treatment of ACI, special attention should be paid to patients with higher NIHSS scores on admission. It is not only necessary to strengthen prognostic evaluation, but also to consider more comprehensively when formulating treatment regimens to improve the prognosis of patients as much as possible.

This study still has certain limitations: (a) although samples from two hospitals were included, regional factors may still have intro-

duced bias into the results; (b) as a retrospective study, the possibility of missing data may have prevented some potential variables from being included in the analysis, thereby reducing the reliability of the study findings.

Conclusion

This study identified brainstem infarction, clopidogrel use, and elevated NIHSS scores at admission as independent risk factors affecting the prognosis of acute brain injury (ACI) treated with urokinase combined with Edaravone-dexborneol. Based on these findings, a nomogram prediction model was constructed, which can provide a good reference for clinical prognostic assessment. Future research should increase the sample size and conduct multicenter studies to further clarify the risk factors for patient prognosis.

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Disclosure of conflict of interest

None.

Address correspondence to: Fengqiao Ma, Department of Neurology, Dongyang People's Hospital, Wenzhou Medical University, Dongyang 322100, Zhejiang, China. Tel: +86-15157905195; E-mail: mafengqiao2024@163.com

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