

Construction of a prediction model of adverse prognosis risk of urokinase intravenous thrombolysis in ACI patients and the prediction value of serum PPAR- γ and leptin levels

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Abstract: Objective To explore the risk factors influencing the poor prognosis of urokinase intravenous thrombolysis in patients with acute cerebral infarction (ACI), analyze the predictive value of serum PPAR- γ and leptin levels, and construct an effective predictive model. Methods One hundred patients with ACI who received urokinase intravenous thrombolysis in our hospital from November 2020 to December 2021 were selected as the research subjects, and the clinical data were collected and retrospectively analyzed. All patients were followed up for three months, and the prognosis of the patients was evaluated according to the modified Rankin scale (mRS) score, and those with mRS score ≥ 4 were included in the poor prognosis group ($n=28$). Those with an mRS score less than 4 points were included in the good prognosis group ($n=72$). The risk factors influencing the poor prognosis of patients with ACI were screened using 2-test and t-test, and the high risk factors were identified through the logistic regression model, and a prediction model was constructed. The risk factors and the prediction efficiency of the prediction model on the poor prognosis of patients were analyzed through the ROC. Results The incidence of poor prognosis in ACI patients treated with thrombolytic therapy with urokinase was 28.00%, and the proportion of patients in the poor prognosis group who were accompanied with atrial fibrillation, the time from onset to intravenous thrombolysis $> 4.5h$, and NIHSS score > 10 before thrombolysis was significantly higher than that in the control group ($P < 0.05$). The serum the levels of PPAR- γ and Leptin in the poor prognosis group were higher than those in the good prognosis group (both $P < 0.05$). Logistic regression analysis showed that combined atrial fibrillation, NIHSS score > 10 before thrombolysis, time from onset to intravenous thrombolysis $> 4.5h$, and high serum PPAR- γ and Leptin levels were all independent risk factors for poor prognosis of urokinase intravenous thrombolysis in patients with ACI ($P < 0.05$). ROC curve research results showed that: The AUC for predicting adverse prognosis in patients with ACI based on the combination of atrial fibrillation, time from onset to intravenous thrombolysis ($> 4.5h$), NIHSS score before thrombolysis (> 10 points), high serum PPAR- γ level and Leptin level was 0.666 (95%CI: 0.540-0.792), 0.614 (95%CI: 0.482-0.746), respectively. 0.781 (95%CI: 0.676-

0.887), 0.694(95%CI: 0.572-0.816), 0.712 (95%CI: 0.592-0.832); The specificity were 62.53%, 60.04%, 78.15%, 75.08% and 46.92%, respectively. The specificity was 67.51%, 61.73%, respectively. 67.59%, 60.03% and 87.55%, The ROC AUC of the predictive model for predicting adverse outcomes in patients with ACI was 0.879 (95%) CI: 0.802-0.956), with a sensitivity of 84.43%, specificity of 77.56%, and Jordan Index of 0.619. Conclusion There are many risk factors affecting the poor prognosis of patients with ACI after intravenous thrombolysis with urokinase, among which the NIHSS score, serum PPAR- γ level and Leptin level have better prediction efficiency before thrombolysis. The predictive model constructed in this study has high predictive value for poor prognosis of patients with ACI, which is worthy of clinical reference.

Keywords: patients with ACI; Intravenous thrombolysis with urokinase; Risk prediction model; Serum PPAR- γ level; Serum PPAR- γ level; Prognostic value

Acute cerebral infarction (ACI) is a kind of acute ischemic cerebrovascular disease that is difficult to treat and easy to repeat. In severe cases, ACI can even lead to adverse consequences^[1] such as disability and death. At present, it is generally believed that early treatment is the key to improve the prognosis quality of ACI patients. Thrombolytic therapy has become the first choice for the clinical treatment of such patients. Urokinase is the first generation of thrombolytic drugs, which mainly promotes the recovery of ischemic penumbra blood supply by activating endogenous thrombin, and then plays a role^[2-3] in improving cerebral nerve injury. A large number of clinical data have confirmed^[4] that intravenous thrombolytic therapy with urokinase can significantly improve the vast majority of patients with ACI, but there are still some patients with poor prognosis, but the specific influencing factors are still unclear. Peroxisome proliferator-activated receptor- γ (PPAR- γ) is a nuclear transcription factor^[5] that^[6] inhibits inflammatory responses. PPAR- γ has some potential value in the treatment of some neurological diseases, such as neuropathic pain, but the specific mechanism of its action in nerve injury diseases is still unclear. In addition, some scholars have found^[7] that the serum level of Leptin in ACI patients is significantly higher than that in normal people, but there are few reports on the predictive value of Leptin in the clinical prognosis of ACI patients. Based on the above background, the clinical data of 100 ACI patients treated with intravenous thrombolysis with urokinase in our hospital from November 2020 to December 2021 were retrospectively analyzed, and a prediction model was constructed, in order to provide new ideas for improving the clinical prognosis of ACI patients.

1. Data and Methods

1.1 General data 100 ACI patients treated with intravenous thrombolysis with urokinase in our hospital from November, 2020 to December, 2021 were selected as the research objects. Their clinical data were collected and retro-

spectively analyzed. The prognosis of the patients was evaluated according to the modified Rankin scale (mRS) score. The patients with mRS Score > 2 were included in the poor prognosis group ($n=28$), and those with mRS Score ≤ 2 were included in the good prognosis group ($n=72$). In the poor prognosis group, there were 16 males and 12 females, aged 49-75 years. In the good prognosis group, there were 34 males and 38 females, with age ranging from 50 to 76 years. There was no significant difference in the history of diabetes, hypertension, and other general data between the two groups ($P > 0.05$). The trial was approved by the ethics committee of the hospital.

1.2 Inclusion and exclusion Criteria

Inclusion criteria: (1) The first episode of acute cerebral infarction (ACI) was clearly diagnosed, and the diagnostic criteria were according to “Chinese Expert Consensus on Emergency Treatment of Acute Stroke 2018”^[8]; (2) no contraindications to thrombolytic therapy, can tolerate urokinase thrombolytic therapy; (3) Both sexes, onset time less than 6 hours; (4) Complete clinical data and good compliance; (5) All patients had informed consent.

Exclusion criteria: (1) patients with recent history of anticoagulant therapy; (2) patients with blood system diseases; (3) patients with acute or chronic infections; (4) patients with recent history of surgery or trauma; (5) previous history of hemorrhagic stroke.

1.3 Intervention methods

1.3.1 Data collection Clinical information of patients was collected through the hospital electronic medical record system by the responsible physician in this study and verified by another physician. The clinical data collected included the patient’s age, sex, date of visit, time of first onset, past medical history, alcohol and smoking history, antiplatelet therapy, vital signs at the time of visit, previous history of hemorrhagic stroke, and the National Institutes of Health stroke scale before thrombolysis The National Institutes of Health Stroke Scale (NIHSS) score and other clinical data were collected.

1.3.2 The patients were followed up by telephone at 3 months after discharge. The modified Rankin scale (mRS) was used to evaluate the prognosis of the patients, which was divided into 7 grades as follows: 0 was asymptomatic; 1 (mild symptoms); 2 is mild disability; 3 is moderate disability; 4 for severe disability; 5 is severely disabled; Patients with mRS Score ≥ 4 were included in the poor prognosis group, and those with Mrs Score otherwise were included in the good prognosis group. After collecting relevant information, the related factors affecting the prognosis of patients were analyzed to screen out the risk factors. loglist regression analysis was used to analyze the correlation between statistically significant risk factors and disease prognosis. Finally, the Area Under the receiver operating characteristic curve (ROC) was used to analyze the predictive value of each risk factor for the prognosis of the disease.

1.4 Observation indicators

1.4.1 Serum Peroxisome proliferator-activated receptor γ (PPAR- γ) and Leptin levels were measured at 3 months after thrombolytic therapy. 15ml of fasting elbow venous blood was collected from the patients and placed in an anticoagulant tube. The serum levels of PPAR- γ and Leptin in the upper layer were detected by Enzyme linked immunosorbent assay (ELISA). The kits were purchased from Abcam company, UK, and the detection operation was in accordance with the instructions.

1.4.2 The area under the receiver operating characteristic (ROC) curve (AUC) was used to evaluate the predictive value. AUC less than 0.5 was regarded as no predictive value, AUC between 0.5 and 0.7 was regarded as good predictive accuracy, and ≥ 0.7 was regarded as high predictive accuracy.

1.5 Statistical methods spss19.0 software was used for statistical analysis of the experimental data, [n(%)] was used to represent the count data, test, c^2 and ($\bar{x} \pm s$) was used to represent the measurement data. The independent sample 't' test was used to compare the two groups, and logistic regression was used to analyze the risk factors affecting the prognosis of the disease. Logistic regression analysis was used to analyze the risk factors affecting the prognosis of the disease. The predictive efficacy was evaluated by the receiver operating characteristic (ROC) curve, and $P < 0.05$ indicated that the difference was statistically significant.

2. Results

All patients were followed up for 3 months, and no patient was lost to follow-up or dropped out.

2.1 Univariate analysis of factors related to poor prognosis of urokinase intravenous thrombolysis in ACI patients. Among 100 ACI patients treated with urokinase thrombolysis, 28 patients had poor prognosis, and the incidence of poor prognosis was 28.00%. The proportion of patients with atrial fibrillation, time from onset to intravenous thrombolysis > 4.5 h and NIHSS score > 10 before thrombolysis in the poor prognosis group was significantly higher than that in the control group, and the difference was statistically significant ($P < 0.05$). There was no significant difference in gender, age, history of drinking and smoking, systolic blood pressure, diastolic blood pressure, history of diabetes, history of hypertension, history of hyperlipidemia, coronary atherosclerosis, antiplatelet therapy, and blood glucose > 7 mmol/L before thrombolysis between the two groups ($P > 0.05$). **Table 1** shows the data.

Table 1. Univariate analysis of factors associated with poor prognosis of urokinase intravenous thrombolysis in ACI patients

Grouping	Poor prognosis group (n=28)	Good prognosis (n=72)	T / χ	P
Gender			0.794	0.373
male	16 (57.14)	34 (47.22)		
female	12 (42.86)	38 (52.78)		
Age	66.29±17.76	65.28±17.33	0.260	0.796
Smoking history			0.631	0.427
is	18 (64.29)	40 (55.56)		
no	10 (35.71)	32 (44.44)		
History of drinking			2.677	0.102
is	13 (46.43)	21 (29.17)		
no	15 (53.57)	51 (70.83)		
Systolic blood pressure (mmHg)	141.31±17.34	142.73±19.01	0.343	0.732
Diastolic Blood Pressure (mmHg)	81.68±10.39	83.14 ± 10.37	0.632	0.529
hypertension			0.012	0.914
is	12 (42.86)	30 (41.67)		
no	16 (57.14)	42 (58.33)		
diabetes			0.009	0.926
is	10 (35.71)	25 (34.72)		
no	18 (64.29)	47 (65.28)		
Hyperlipidemias			0.100	0.752
is	5 (17.86)	11 (15.28)		
no	23 (82.14)	61 (84.72)		
Atrial fibrillation			36.763	0.000
is	16 (57.14)	3 (4.17)		
no	12 (42.86)	69 (95.83)		
Hardening of the coronary arteries			2.381	0.123
is	10 (35.71)	15 (20.83)		
no	18 (64.29)	57 (79.17)		
Time from onset to intravenous thrombolysis (h)			5.534	0.019
> 4.5h	19 (67.86)	30 (41.67)		
4.5 h or less	9 (32.14)	42 (58.33)		
NIHSS score before thrombolysis (score)			7.545	0.006
> 10	16 (57.14)	20 (27.78)		
≤10	12 (42.86)	52 (72.22)		
Antiplatelet therapy (n/%)			3.172	0.075
is	13 (46.43)	20 (27.78)		
no	15 (42.86)	52 (72.22)		
Blood glucose before thrombolysis (mmol/L)			2.317	0.128
> 7	16 (57.14)	29 (40.28)		
≤7	12 (42.86)	43 (59.7)		

2.2 The serum levels of PPAR- γ and Leptin in patients with different prognosis outcomes were higher in the poor prognosis group than in the good prognosis group (all $P < 0.05$). See **Table 2**.

Table 2. The comparison of serum PPAR- γ and Leptin levels between two groups ($\bar{x} \pm s$)`

Groups	Number of cases	PPAR- γ (pg/mL)	Leptin (ug/L)
Poor prognosis group	28	36.41 $\pm$ 7.03	8.59 $\pm$ 1.46
Good prognosis group	72	25.59 $\pm$ 6.27	5.37 $\pm$ 1.81
t		7.488	9.243
P		0.000	0.000

2.3 logistic regression analysis of clinical factors affecting the prognosis of ACI patients after intravenous thrombolysis with urokinase. The relevant factors with statistically significant differences in univariate analysis were substituted into the logistic model for analysis. The independent variables included atrial fibrillation, NIHSS score before thrombolysis, time from onset to intravenous thrombolysis, serum PPAR- γ level and Leptin level. logistic regression analysis showed that poor prognosis of ACI patients (defined as “no” =0, “yes” =1) was the dependent variable. The results of logistic regression analysis showed that atrial fibrillation, NIHSS score > 10 before thrombolysis, time from onset to intravenous thrombolysis > 4.5h, and high serum PPAR- γ and Leptin levels were all independent risk factors affecting the poor prognosis of intravenous thrombolysis with urokinase in ACI patients ($P < 0.05$). **Table 3** and **Table 4** are shown.

Table 3. Variable assignment table

Related factors	Variable names	Variable assignment
Atrial fibrillation	X1	1= yes, 0= no
Time from onset to intravenous thrombolysis	X2	1 > 4.5h, 0 $\leq$ 4.5h
NIHSS score before thrombolysis	X3	1 > 10 points, 0 $\leq$ 10 points
ppar-gamma	X4	Actual value
Leptin	X5	Actual value

Table 4. Multivariate analysis of influencing poor prognosis of urokinase intravenous thrombolysis in ACI patients

Projects	β values	SE	Wald values	P-value	OR value (95%CI)
Combined atrial fibrillation	1.915	0.518	13.667	0.000	6.787 (2.459-18.733)
Time from onset to intravenous thrombolysis (> 4.5h)	1.073	0.314	11.677	0.001	2.924 (1.580-5.411)
NIHSS score before thrombolysis (> 10)	0.736	0.327	5.066	0.024	2.088 (1.100-3.963)
ppar-gamma	0.671	0.239	7.882	0.005	1.956 (1.225-3.125)
Leptin	0.614	0.411	4.997	0.025	0.892 (0.807-0.986)

2.4 The predictive value of various risk factors for the poor prognosis of ACI patients after urokinase thrombolytic therapy The AUC of atrial fibrillation, time from onset to intravenous thrombolysis (> 4.5h), NIHSS score before thrombolysis (> 10 points), high serum PPAR- γ level and Leptin level in pre-

dicting poor prognosis of ACI patients were 0.666 (95%CI: 0.540-0.792) and 0.614(95%CI: 0.540-0.792), respectively. 0.482-0.746), 0.781 (95%CI: 0.676-0.887), 0.694(95%CI: 0.572-0.816), 0.712 (95%CI: 0.592-0.832); The sensitivity were 62.53%, 60.04%, 78.15%, 75.08% and 46.92, respectively. The specificity were 67.51%, 61.73%, 67.59%, 60.03% and 87.55%, respectively. See **Table 5** for details.

Table 5. Predictive efficacy of various risk factors on poor prognosis of patients with ACI

Variables	AUC	Sensitivity (%)	Specificity (%)	Youden index	95%CI
Combined atrial fibrillation	0.666	62.53	67.51	0.300	0.540 ~ 0.792
Time from onset to intravenous thrombolysis (> 4.5h)	0.614	60.04	61.73	0.283	0.482 ~ 0.746
NIHSS score before thrombolysis (> 10)	0.781	78.15	67.59	0.456	0.676 ~ 0.887
ppar-gamma	0.694	75.08	60.03	0.350	0.572 ~ 0.816
Leptin	0.712	46.92	87.55	0.344	0.592 ~ 0.832

Due to the limited sample size, this study did not divide the training set and the test set according to the proportion. The ten-fold cross validation method was used to construct the prediction model. That is, the data were randomly divided into 10 points each time, one of which was used as the test set, and the remaining 9 were used as the training set, and the prediction model was repeated 10 times to avoid the “over-fitting” phenomenon. The independent predictors of poor prognosis in ACI patients treated with urokinase thrombolytic therapy were obtained by Logistic regression analysis, and a logistic regression prediction model was constructed. The data of the prediction model were calculated by Medcalc software, and the predictive efficiency was analyzed by ROC curve. The results showed that the ROC area under the curve (AUC) of the prediction model for predicting the poor prognosis of ACI patients was 0.879 (95%CI: 0.802-0.956), the sensitivity was 84.43%, the specificity was 77.56%, and the Youden index was 0.619.

3 Discussion

The formation of ACI is related to the stenosis and occlusion of the cerebral blood supply artery caused by various reasons. The occurrence of cerebral ischemia and hypoxia will seriously affect the normal metabolic activity of the brain tissue, resulting in the sudden decrease of blood perfusion of the brain or cervical artery, and eventually lead to the apoptosis[9-10] of brain tissue cells due to lack of nutrition. Intravenous thrombolytic therapy within 4.5 hours of onset is a common method for the treatment of patients with ACI. This treatment method can improve the occlusion state of cerebral vessels in the shortest time, restore brain blood supply as soon as possible, and reconstruct cerebral blood perfusion^[11]. Intravenous thrombolysis with urokinase is a widely used thrombolytic agent in clinical application at present, which can effectively dissolve thrombo-

sis, open occluded arteries and reduce infarct area. However, some scholars have found[12-13] that the symptoms of neurological deficits in some patients with ACI worsen after intravenous thrombolysis with urokinase. It can be seen that actively exploring the related factors affecting the short-term prognosis of urokinase intravenous thrombolysis in patients with ACI is beneficial to guide the clinical development of reasonable intervention programs as soon as possible, which is of great significance to improve the clinical prognosis of such patients.

A total of 100 patients with ACI were included in this study, of which 28 patients had poor prognosis, and the incidence of poor prognosis was 28.00%, which was lower than the 42.7% reported by Wu Qiaoling^[14] et al. This may be due to the small sample size included in this study and may also be related to individual differences in patients. Studies have found^[15] that PPAR- γ is a ligand-activated transcription regulator, which can promote the increase of adipose tissue and enhance the insulin sensitivity of liver and skeletal muscle. At the same time, PPAR- γ is also related to the occurrence of inflammatory response. Studies have found^[16] that PPAR- γ is contained in brain tissue and has a certain protective effect on neurological function in patients with neurodegenerative diseases with significant inflammatory response. The expression level of PPAR- γ increased during brain ischemia, and reached the peak at 24h after ischemic injury and continued to increase for 14 days. In addition, PPAR- γ can enter the blood circulation through the blood-brain barrier, so the expression of PPAR- γ can also be detected in the serum of ACI patients. The results of this study showed that the serum PPAR- γ level in the poor prognosis group was higher than that in the good prognosis group, suggesting that the change of serum PPAR- γ level may have a certain predictive value for the poor prognosis of ACI patients. Further Logistic regression analysis showed that elevated serum PPAR- γ level was an independent risk factor for poor prognosis of ACI patients after intravenous thrombolysis with urokinase. ROC curve analysis showed that the AUC of high serum PPAR- γ level in predicting poor prognosis of ACI patients was 0.694(95%CI: The sensitivity and specificity were 75.08% and 60.03%, respectively, suggesting that monitoring the changes of serum PPAR- γ levels in ACI patients can assist clinical better evaluation of their prognosis. This is basically consistent with the conclusions of scholar Su Lihua^[17] et al.

Leptin is a non-glycosidic peptide hormone that regulates glucose, fat and energy metabolism. It also promotes platelet aggregation, the release of inflammatory mediators and insulin resistance, and is associated^[18] with the occurrence of cardiovascular and cerebrovascular diseases. Zheng Jingjing^[19] et al. found that serum Leptin was an independent risk factor affecting the poor prognosis of ACI patients treated with intravenous thrombolysis with urokinase, but the predictive value of Leptin for the prognosis of ACI patients was not further clarified. The results of this study showed that the serum level of Leptin in the poor prognosis group was higher than that in the good prognosis group, and the proportion of patients with NIHSS score > 10 was also significantly higher than that in the good

prognosis group, suggesting that the patients in the poor prognosis group still had severe neurological impairment after intravenous thrombolysis with urokinase. The results of Logistic regression analysis showed that serum Leptin level was an independent risk factor for poor prognosis in ACI patients, which was consistent with the conclusions of previous studies. The reason is that the increase of Leptin level can accelerate the release of inflammatory factors, further aggravate vascular endothelial injury, and increase the risk of cerebral thrombosis. In addition, urokinase plays a role in thrombolysis mainly by promoting fibrinolysis, while Leptin can inhibit fibrinolysis by increasing the secretion of inflammatory factors such as TNF- α , leading to poor^[20] prognosis of patients. ROC curve analysis showed that the AUC of high Leptin level in predicting poor prognosis of ACI patients was 0.712 (95%CI: 0.592-0.832), and the specificity and sensitivity were 87.55% and 46.92%, respectively. In conclusion, serum Leptin level has a high predictive value for poor prognosis in patients with AIC, but its sensitivity needs to be improved.

Therefore, this study aimed to further improve the identification efficiency of poor prognosis of ACI patients by constructing a logistic regression model. Due to the small sample size included in this study, a ten-fold cross validation method was used to construct a prediction model, and the ROC curve was used to analyze its prediction efficiency. The results showed that the ROC area under the curve (AUC) of the prediction model for predicting the poor prognosis of ACI patients was 0.879 (95%CI: 0.802-0.956), the sensitivity was 84.43%, the specificity was 77.56%, and the Youden index was 0.619. It can be seen that the prediction model constructed in this study can significantly improve the accuracy of predicting the poor prognosis of ACI patients, and can effectively guide clinicians to early identify high-risk groups with poor prognosis after urokinase thrombolysis, and formulate effective intervention measures in time.

In conclusion, serum PPAR- γ and leptin levels can be used as non-invasive predictors for the prognosis of ACI patients, and the prediction efficiency can be further improved by constructing a prediction model. Limitations of the study: (1) The sample size was small and originated from our hospital, so the generalization was not strong; (2) The follow-up time is short, so it is necessary to further extend the follow-up time and expand the sample size to verify the accuracy of the conclusions.

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