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Assessment and prognostic value of serum uric acid and neuron-specific enolase on the efficacy of intravenous thrombolytic therapy in cerebral infarction

Yanjing Zang[1]*, Hongwei Zheng[2], Shuli Liu[1], Suyu Wang[1] and Yan Shi[1]
[1]Geriatrics Department, The NO. 2 Hospital of Baoding, Dongfeng West Road, Baoding, Hebei, China
[2]Department of Medical Imaging, Baoding First Central Hospital, Baoding, Hebei, China

Abstract: Assessment and prognostic value of serum uric acid (SUA) and neuron-specific enolase (NSE) on the efficacy of intravenous thrombolytic therapy in cerebral infarction. A retrospective analysis was performed on clinical data of 159 patients with acute cerebral infarction who received rt-PA intravenous thrombolytic therapy from 2015 to 2020 and patients with an mRS>2 points were assigned to the poor prognosis group and with mRS≤2 to the good prognosis group. The receiver operating characteristic curve (ROC) was used to examine the prognostic value of SUA and NSE in intravenous thrombolytic therapy for acute cerebral infarction, and logistic regression analysis was utilized to elucidate the predictive features. SUA levels were adversely correlated with prognosis, whereas NSE was positively correlated with prognosis (r=0.465 and -0.501, *P*=0.000 and 0.000). The ROC curve showed that the predictive accuracy of SUA was 77.4% and of NSE was 71%. SUA≤337.5 mmol/l and NSE≥24.50 ng/ml are considered viable criteria to predict the curative effect and prognostic value of intravenous thrombolytic therapy for acute cerebral infarction. SUA and NSE demonstrate great potential to accurately predict the therapeutic effect and prognosis of intravenous thrombolytic therapy for acute cerebral infarction.

Keywords: Cerebral infarction, intravenous thrombolysis, serum uric acid, neuron-specific enolase, National Institutes of Health Stroke Scale.

INTRODUCTION

Acute cerebral infarction (ACI), also known as cerebral ischemic stroke (CIS), shows the highest prevalence in China, and exhibits an increase in its incidence with age, with a global prevalence of 68%. ACI is characterized by high mortality, high disability and high morbidity, which constitutes a major public health issue (Gunda *et al*., 2022). Studies have shown that the standardized prevalence of ACI in China is 2.32% in residents aged between 40 and 75 years, and the recurrence rate within 1 year after discharge from the hospital can be as high as 14.7% after recovery from the first episode (regardless of whether neurological deficits remain). Nearly 50% to 70% of surviving patients exhibit varying degrees of neurological deficits such as hemiparesis, hemiplegia, limb numbness, hemianopia, and aphasia. The etiology of ACI includes genetics, gender, age, heart disease, hypertension, smoking, hyperlipidemia, congenital stenosis of cerebral vessels, and lack of exercise Qiu *et al*., 2020; Yang *et al*., 2022).

Aspirin plus atorvastatin is often used clinically for ACI management, in which aspirin exerts an antithrombotic effect by inhibiting platelet aggregation, thereby relieving the patient's symptoms. In addition, recombinant Tissue Plasminogen Activator (rt-PA) (Zheng *et al*., 2021; Lu *et al*., 2020; Lu *et al*., 2020; Guan *et al*., 2020; Frans *et al*., 2020) i.e., intravenous thrombolytic therapy with alteplase, is currently the most effective treatment for acute ischemic stroke. However, it is associated with suboptimal efficacy and poor prognosis (Gopal *et al*., 2021; Müller *et al*., 2021)..

Hyperuricemia is an independent risk factor for acute cerebrovascular diseases, while it has also been reported that serum uric acid (SUA) protects cerebral blood vessels (Chen *et al*., 2020; Wang *et al*., 2020; Sun *et al*., 2020; Liu *et al*., 2021).. Neuron-specific enolase (NSE) is related to hypoxic-ischemic brain injury. In cerebral infarction, serum levels of cellular factors such as Hcy, NSE, UA, hs-CRP and inflammatory factors such as IL-6, IL-8 and TNF-α are significantly increased in patients with progressive lesions. Clinically, serum Hcy levels are usually measured in hypertensive patients to clarify hypertension typing and renal function indicators such as UA and NSE are determined to assess renal target organ damage (Müller *et al*., 2021; Lissner *et al*., 2021; Topuzova *et al*., 2019). Nonetheless, few trials have reported the predictive value of SUA and NSE in the treatment and prognosis of patients with acute cerebral infarction receiving rt-PA. Therefore, the intent of this study was to clarify the predictive value of SUA and NSE on the efficacy of rt-PA.

**Corresponding author:* e-mail: yanjueqiaoduixlzla@163.com

MATERIALS AND METHODS

Subjects

A total of 159 patients with acute cerebral infarction who underwent rt-PA intravenous thrombolytic therapy between January 2015 and January 2020 in the Stroke Screening Center of our hospital were included.

Inclusion criteria: (1) patients who met the criteria of *Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke 2010* (Lee *et al*., 2021); (2) aged > 18 years old; (3) first-episode of cerebral infarction confirmed by MRT/CT detection; (4) SUA and NSE used as clinical assessment indices; (5) rt-PA routine intravenous thrombolytic therapy was administered within 6 hours of onset.

Exclusion criteria: (1) severe multifunctional organ disease, failure, tumor; (2) blood tumors; (3) immune system diseases; (4) craniocerebral injury, cerebral hemorrhage, subarachnoid hemorrhage, etc.; (5) pregnant women; (6) severe trauma or surgery; (7) who had not signed the informed consent.

According to the 90-day follow-up results, the eligible patients were divided into a good prognosis group (108 cases) and a poor prognosis group (51 cases).

The original sample size calculation estimated that 80 patients in each group would be needed to detect a 3-point difference between groups in a 2-sided significance test with a power of 0.8 and an alpha error level of 0.05.

Informed consent was obtained from patients and signed prior to enrollment in this study. The study protocol was approved by the hospital ethics committee. Ethics number: JI-KI20200506. All processes were in accordance with the Declaration of Helsinki ethical guidelines for clinical research.

Data collection

The demographic characteristics of the participants and laboratory and subjective measurement indicators were retrospectively collected. On the day of admission, the demographic variables such as age, gender, diabetes, infarct location, hypertension, smoking, alcohol consumption and clinical subjective measurements such as atrial fibrillation, thrombolysis time and National Institutes of Health Stroke Scale (NIHSS) score were collected. The blood biochemical indices included SUA, NSE, total cholesterol, triglycerides, low-density lipoprotein and blood creatinine. Fasting blood was collected the following morning and sent for examination. The mRS results were collected during telephone follow-up or follow-up visits 90 days after rt-PA treatment.

STATISTICAL ANALYSIS

SPSS 20.0 statistical software was used for data analysis. The measurement data were expressed as mean ± standard deviation (x±s) and analyzed using the t-test. The count data were expressed as a rate (%) and subject to the variance test. The logistics regression analysis was used to identify independence predictors and the Pearson correlation coefficient was used to assess the correlation of risk predictors. The AUC of the receiver operating characteristic curve (ROC) was employed to determine the optimal predictive value of SUA and NSE. The difference was defined as statistically significant with P<0.05 (Chen *et al*., 2020; Lissner *et al*., 2021; Ryczek *et al*., 2021; Elnady *et al*., 2021; Wang *et al*., 2020; Ndrepepa *et al*., 2018; Copur *et al*., 2022).

RESULTS

General information

There was no statistically significant difference in age, gender, diabetes, infarct location, hypertension, smoking, alcohol consumption, total cholesterol, triglycerides, low-density lipoprotein, and serum creatinine between the two groups of patients (P>0.05); however, notable differences were reported in atrial fibrillation, thrombolysis time, NIHSS score, SUA and NSE (*P*<0.05, table 1).

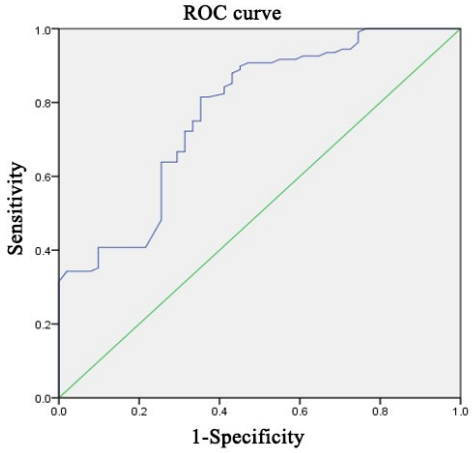

Fig. 1: ROC curve of serum uric acid

Logistics multiple regression analysis

Atrial fibrillation, thrombolysis time and NIHSS score showed predictive values for evaluating the effectiveness and prognosis of intravenous thrombolytic therapy for acute cerebral infarction (*P*<0.05) (table 2).

ROC curve prediction accuracy

The ROC curve was used to assess the predictive usefulness of SUA and NSE in rt-PA intravenous thrombolytic treatment for acute cerebral infarction. The findings revealed that the area under the curve was 0.774 and 0.710, respectively. SUA≤337.5 mmol/l and NSE≥

24.50ng/ml are considered viable criteria to predict the curative effect and prognostic value of intravenous thrombolytic therapy for acute cerebral infarction. (*P*=0.000, figs. 1, 2). The area under the curve for thrombolysis time, NIHSS score and atrial fibrillation was 0.906, 0.751 and 0.667, respectively (*P*=0.000) see fig. 3 for details.

Correlation analysis

Univariate linear analysis revealed that SUA, NSE, NIHSS score, atrial fibrillation and thrombolysis time were all associated with prognosis (r=0.456, -0.501, -0.488, 0.313 and -0.582) (table 3).

DISCUSSION

Acute cerebral infarction is characterized by high incidence, high mortality and high morbidity. The pathological basis of cerebral infarction is atherosclerosis. Atherosclerosis in the brain of patients triggers stenosis of the arterial lumen and even blockage in severe cases, which causes ischemia and hypoxia in the tissue cells of the brain, resulting in a series of clinical symptoms such as coma, vomiting and cognitive impairment (Müller *et al*., 2021; Chen *et al*., 2020). Therefore, clinical treatment of cerebral infarction mainly emphasizes stabilization of plaque, inhibition of platelet aggregation, improvement of vascular endothelial function, anti-inflammation, anticoagulation and antioxidation. It has been reported that timely rt-PA intravenous thrombolytic therapy provides substantial treatment benefits for acute cerebral infarction. However, the therapeutic outcome is inconsistent among patients with similar baseline characteristics. It was found that prognostic risk predictors may allow certain anticipations of the therapeutic effect of rt-PA intravenous thrombolysis (Ryczek *et al*., 2021).

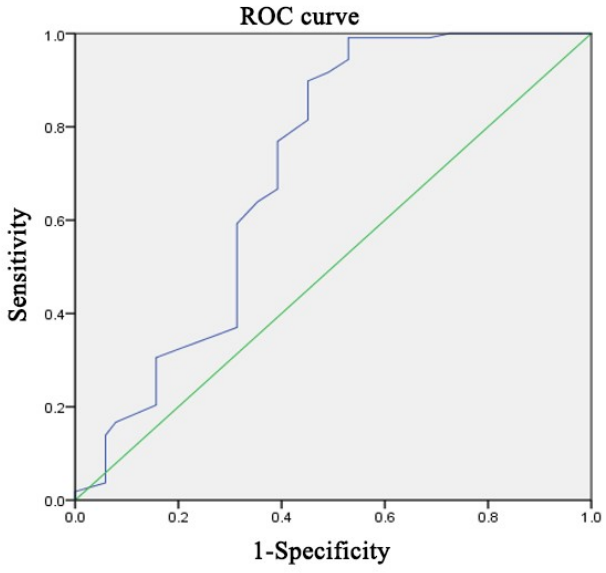

Fig. 2: ROC curve of neuron specific enolase.

NSE is functionally enolase active and plays an important role as a protease in the aerobic oxidation and anaerobic enzymes of sugar. It catalyzes the cleavage of α-phosphoglycerol to generate phosphoenolpyruvate, which enables the smooth progress of glucose metabolism in vivo and generates ATP, providing nutritional protection to neuronal cells (Elnady *et al*., 2021). Serum NSE is normally undetectable in healthy individuals. Sustained ischemia and hypoxia lead to the impairment of brain cell function, disruption of cell membrane permeability and entry of NSE from the cells into the cerebrospinal fluid and then into the human circulation through the blood-brain barrier, resulting in high concentrations of NSE in the serum. This provides a scientific rationale for the existence of a correlation between alterations in serum NSE levels and acute cerebral infarction. Research has revealed that the serum concentration of SUA and NSE provides insights into the therapeutic outcomes of rt-PA. However, the mechanism of their predictive value remains elusive (Wang *et al*., 2020).

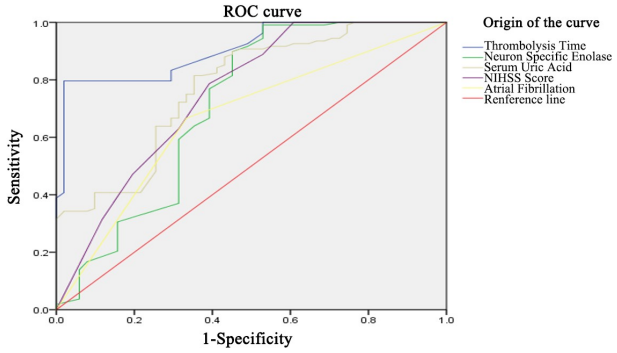

Fig. 3: ROC curve of independent risk factors

In the present study, after rt-PA intravenous thrombolytic therapy, the poor prognosis group had a lower SUA level and a higher NSE level, suggesting significant differences in the serum concentration of SUA and NSE between patients with different prognostic outcomes of rt-PA intravenous thrombolytic therapy. SUA has a two-pronged effect on the body. Crystal SUA accelerates inflammation, while soluble SUA yields an anti-inflammatory effect. Also, SUA contributes to stabilizing blood pressure, removing free radicals, improving immunity and preventing aging. In the current study, an increase in SUA indicates a better prognostic result of thrombolysis but a poor prognosis. An increasing body of research indicates that SUA has an influence on the predictive effect of rt-PA intravenous thrombolytic treatment and can protect the neurological system of patients with acute cerebral infarction during the thrombolysis process. However, controversies exist in the positive and negative protection mechanisms of SUA. To be sure, patients with thrombolysis showed a higher correlation of SUA than patients without thrombolysis. Serum UA levels have been reported to be associated with cerebral infarction and

Table 1: Baseline analysis

Factors		mRS≤2	mRS>2		
		n=108	n=51	Statistic tests	*P*
Gender (n)	Male	53	24	x2=0.321	>0.05
	Female	55	25		
Age (years)		56.6±7.9	56.7±5.8	t=-1.38	>0.05
Infarct Site	Basal Ganglia	80	40	x2=0.001	>0.05
	Non-Basal Ganglia	28	11		
Diabetes (n)		23	11	x2=0.001	>0.05
Hypertension (n)		67	40	x2=0.002	>0.05
Smoking (n)		87	42	x2=0.003	<0.05
Drinking (n)		78	34	x2=0.004	>0.05
Atrial Fibrillation (n)		36	34	x2=0.005	<0.05
Total Cholesterol (Mmol/l)		4.35±0.89	4.98±1.05	t=2.56	>0.05
Triglyceride (Mmol/l)		2.15±0.77	2.65±0.68	t=1.34	>0.05
Low Density Lipoprotein (Mmol/l)		2.87±0.98	3.12±0.77	t=2.76	>0.05
Serum Creatinine (Umol/l)		67.5±1.3	68.9±1.03	t=1.28	>0.05
Thrombolysis Time (Min)		74.5±42.88	153.25±66.87	t=8.960	<0.05
Nihss Score (Points)		6.809±2.03	9.941±3.59	t=6.999	<0.05
Serum Uric Acid (Mmol/l)		405.47±47.38	352.37±46.49	t=6.658	<0.05
Neuron Specific Enolase (Ng/Ml)		17.29±2.65	26.36±11.52	t=7.246	<0.05

Table 2: Multivariate logistics regression analysis

Prognostic factor regression analysis		regression coefficient	standard error	wald x^2	P	OR	95% CI	
							Lower limit	Upper limit
Good prognosis	Intercept	-15.304	5.536	7.641	0.006			
	Serum Uric Acid	-0.071	0.019	13.94	0	1.074	1.035	1.115
	Neuron Specific Enolase	0.225	0.105	4.617	0.032	1.252	1.02	1.537
	Nihss Score	0.706	0.196	12.966	0	2.027	1.38	2.977
	Atrial Fibrillation	3.405	1.208	7.94	0.005	30.117	2.82	321.681
	Thrombolysis Time	0.039	0.011	12.093	0.001	1.04	1.017	1.063

Table 3: Correlation analysis

	1	2	3	4	5	6
1. Prognosis	1					
2. Serum Uric Acid	0.465	1				
3. Neuron Specific Enolase	-0.501	-0.258	1			
4. NIHSS Score	-0.488	-0.013	0.238	1		
5. Atrial Fibrillation	0.313	0.158	0.111	0.111	1	
6. Thrombolysis Time	-0.582	-0.064	0.387	0.398	0.262	1

demonstrate good potential as a diagnostic indicator of atherosclerotic cerebral infarction. UA induces the development and progression of cerebral infarction by promoting the oxidation of LDL, stimulating the production of free radicals causing massive platelet aggregation and thrombosis, causing an inflammatory response and damage to blood vessels. Additionally, it has (Ndrepepa *et al*., 2018; Copur *et al*., 2022; Rahimi-Sakak *et al*., 2022; Zhao *et al*., 2022) also been reported that patients with hyperuricemia after thrombolytic therapy had better NIHSS scores and mRS scores than those with normal SUA. Thus, the increase of SUA may exert a protective role in the neurological mechanism, which is in agreement with the results of the present study.

NSE mainly exists in brain neurons and neuroendocrine cells. When the brain cells are damaged by long-term ischemia and hypoxia (Wang *et al*., 2023), NSE leaks from damaged neurons and enters systemic circulation through the blood-brain barrier. Therefore, early detection of serum NSE provides a sensitive indication of the extent and scope of early neuronal injury. It is concluded from

the current study that the NSE level of the good prognosis group is lower than that of the poor prognosis group. Studies have suggested (Mu *et al*., 2023) that the increase in serum NSE level is positively correlated with the severity of brain damage after ischemia and hypoxia, which consolidates the results of the present study. The reason may be that elevated NSE levels indicate more severe neuronal damage. It can be speculated that NSE levels may serve as an independent risk factor for assessing short-term prognosis and the higher the serum NSE test value, the more severe the irreversible damage to brain tissue cells; the more serious the secondary neuronal damage due to intracranial hypertension and ischemic reperfusion injury of brain tissue, the poorer the prognosis (Dubey *et al*., 2023).

SUA and NSE can evaluate the treatment outcome of thrombolysis and the degree of protection on the cerebrovascular system (Ricke *et al*., 2023). Nevertheless, there is no trial currently targeting the predictive value of SUA and NSE on prognosis, and the current study observed that SUA and NSE are correlated with prognosis, and both areas of the curve are higher than 70%. It is assumed that both show good potential as predictors of rt-PA intravenous thrombolytic therapy.

The limitations of this study are that it is a single-center retrospective study and has a small sample size, which may compromise the reliability and usefulness of this study to some extent. In addition, individual differences in the study population (e.g., alcohol consumption, smoking, physical activity and individual fitness) and other factors resulted in unavoidable between-study heterogeneity in the current study.

CONCLUSION

To sum up, SUA and NSE demonstrate great potential to accurately predict the therapeutic effect and prognosis of intravenous thrombolytic therapy for acute cerebral infarction.

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