

Effect of glycated hemoglobin index and mean arterial pressure on acute ischemic stroke prognosis after intravenous thrombolysis with recombinant tissue plasminogen activator

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Abstract

To determine whether glycated hemoglobin and mean arterial pressure (MAP) during thrombolysis are prognostic factors of intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) for acute ischemic stroke (AIS).

A total of 125 AIS patients, who received rt-PA intravenous thrombolysis in our hospital, were included into the present study, and divided into good prognosis group and poor prognosis group. Univariate and multivariate logistic regression analyses were used to determine the prognostic factors of AIS treated by rt-PA thrombolysis, Spearman correlation analysis was used to analyze the correlation of the accumulated cigarette consumption in the smoking subgroup and glycated hemoglobin in the diabetic subgroup with the prognosis after intravenous thrombolysis and the symptomatic intracranial hemorrhage (sICH).

Univariate analysis revealed that the interval from onset to thrombolysis, baseline National Institutes of Health Stroke Scale (NIHSS) score, MAP during thrombolysis and DRAGON score were prognostic factors. Multivariate logistic regression analysis revealed that baseline NIHSS score and MAP during thrombolysis were independent prognostic factors for rt-PA thrombolysis. Furthermore, the glycated hemoglobin index was positively correlated with the incidence of sICH.

The NIHSS score before thrombolysis and MAP during thrombolysis were independent factors for the prognosis of AIS treated by thrombolysis. The higher the glycated hemoglobin index of diabetic patients, the more likely they are to develop sICH, the glycated hemoglobin index was negatively correlated with the prognosis after intravenous thrombolysis. The accumulated cigarette consumption was negatively correlated with the prognosis after intravenous thrombolysis.

Abbreviations: AIS = acute ischemic stroke, APTT = activated partial thromboplastin time, CT = computed tomography, ECASS-II = European Cooperative Acute Stroke Study, MAP = mean arterial pressure, MRI = magnetic resonance imaging, mRS = modified Rankin scale, NIHSS = National Institutes of Health Stroke Scale, rt-PA = recombinant tissue plasminogen activator, sICH = symptomatic intracranial hemorrhage.

Keywords: acute ischemic stroke, glycated hemoglobin index, intravenous thrombolysis, mean arterial pressure, prognosis, recombinant tissue plasminogen activator

1. Introduction

Acute ischemic stroke (AIS) is a common clinical disease, has high morbidity and mortality, is an important cause for the disability of patients, and is the first major cause of death in China.^[1] Due

to the restrictions of thrombolytic indications and time window, at present, the thrombolytic rate is relatively low in China,^[1] and not every patient is able to benefit from thrombolysis. In particular, the proportion of AIS patients reaching the hospital within the “time window” in Nanchang District of Jiangxi province is very low, and the proportion of patients receiving thrombolysis is also low, which seriously affects the treatment of AIS. To date, the factors that affect the prognosis of thrombolysis for AIS remain unclear. Known factors that affect the prognosis of AIS treated with rt-PA intravenous thrombolysis include National Institutes of Health Stroke Scale (NIHSS) score during thrombolysis,^[2–7] blood glucose during thrombolysis,^[8,9] and DRAGON score.^[10–15] Therefore, the aim of the present study was to investigate the effects of the glycated hemoglobin index, mean arterial pressure (MAP), DRAGON score, and baseline NIHSS score on the prognosis of AIS treated with rt-PA intravenous thrombolysis in China.

2. Materials and methods

2.1. Clinical subjects

A total of 125 AIS patients, who were treated by rt-PA thrombolytic therapy at the Department of Neurology or Emergency Department of Jiangxi Provincial People's Hospital

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from July 2012 to December 2017, were included into the present study. Among these patients, 63 patients were men and 62 patients were women. Computed tomography (CT) revealed no bleeding and fresh infarcts. The clinical and imaging findings definitely indicated AIS. All patients were approved by the Ethics Committee of our hospital to participate in the present study. All participants provided a written consent. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Based on the 2010 guidelines for the diagnosis and treatment of AIS,^[16] and the 2014 guidelines for the diagnosis and treatment of AIS in China,^[17] the inclusion criteria were as follows: patients who were within 18 to 80 years old; patients who reached the hospital within 4.5 hours after onset of AIS; patients with signs of brain function damage that lasted for >1 hour; patients whose intracranial hemorrhage was excluded by cranial CT, and patients who had no imaging changes of early large area cerebral infarction; patients or their family members who provided an informed consent. The exclusion criteria were as follows: patients with a history of intracranial hemorrhage, including suspected subarachnoid hemorrhage; patients with a history of craniocerebral trauma in the last 3 months; patients who had gastrointestinal or urinary tract bleeding in the last 3 weeks; patients who received major surgical operations in the last 2 weeks; patients who received arterial biopsy at sites that were not easy to stop the bleeding by compression in the last 1 week; patients with a history of cerebral infarction or myocardial infarction in the last 3 months, excluding obsolete lacuna cerebral infarction without signs of neurological deficit; patients with severe heart, liver, and kidney dysfunction or severe diabetes mellitus; patients who presented with evidence of active bleeding or trauma (such as fracture) during the physical examination; patients who orally received anticoagulant warfarin, had a prothrombin time international normalized ratio (INR) of >1.5, received heparin treatment within 48 hours, and presented with an activated partial thromboplastin time (APTT) that exceeded the normal range; patients with a platelet count of $<100 \times 10^9/L$ and a blood glucose level of $<2.7 \text{ mmol/L}$; patients with a systolic blood pressure of $>180 \text{ mmHg}$ ($1 \text{ mmHg}=0.133 \text{ kPa}$), or a diastolic blood pressure of $>100 \text{ mmHg}$; pregnant patients; patients who did not cooperate.

2.2. Thrombolytic method

If patients were admitted within 4.5 hours after the onset of AIS, they were treated with rt-PA at a total dose was 0.9 mg/kg (the maximum dose was $<90 \text{ mg}$),^[16,17] in which 10% of rt-PA was administered by intravenous bolus injection for a duration of 1 minute, and the remaining 90% was dissolved in 100 mL of 0.9% sodium chloride and administered by intravenous drip for a duration of 1 hour. At 24 hours after thrombolysis, the coagulation index was examined and CT or magnetic resonance imaging (MRI) was performed. If intracranial hemorrhage was excluded, 200 mg of aspirin (*qd*) was given. After 2 weeks, the dose was altered to 100 mg, *qd*.

2.3. Observation indexes and efficacy assessment

The NIHSS score was calculated before thrombolysis, and the modified Rankin scale (mRS) score was calculated at 90 days after thrombolysis to assess the prognosis. A mRS score of 0 to 1 at 90 days after thrombolysis indicates a good prognosis, while a mRS score of 2 to 5 indicates a poor prognosis.^[18] The condition of an increase in NIHSS score by >4 points and parenchymal

hematoma type-2 was defined as symptomatic intracerebral hemorrhage (sICH).^[18,19]

2.4. Related factors affecting efficacy and prognosis

Factors that may affect the prognosis include age, sex, smoking, the accumulated cigarette consumption, alcoholism, alcohol consumption (annual gram), hypertension, diabetes, atrial fibrillation, myocardial infarction, hyperlipidemia, stroke history, interval between onset and thrombolysis, baseline NIHSS score, anterior circulation infarction, post circulation infarction, MAP during thrombolysis, blood glucose during thrombolysis, muscle enzyme, blood creatinine/blood uric acid, glycated hemoglobin index, and DRAGON score. A total of 22 factors were selected. The accumulated cigarette consumption = the number of smoking years \times the number of cigarettes smoked per day.^[20] The accumulated cigarette consumption of >100 cigarette year was defined as smoking addiction. The amount of alcohol consumed (g year) = the number of drinking years \times the gram of alcohol consumed per day,^[21] and alcohol consumption reaching 60 g year was defined as alcoholism. Glycated hemoglobin index = glycated hemoglobin level \times the number of years that a patient suffered from diabetes $\times 100$. The DRAGON score was determined according to the cerebral arterial high density shadow revealed by head CT at admission or signs of early infarction, a mRS score >1 before stroke, age, blood glucose before thrombolysis (at admission), the interval between onset and treatment, and the NIHSS score before thrombolysis (at admission).

2.5. Statistical analysis

Data were analyzed using SPSS 19.0; Armonk, NY statistical software. In the univariate analysis, measurement data were compared using *t* test, and count data were compared using Chi-square test. $P < .05$ was considered statistically significant. Variables that were statistically significant in the univariate analysis were selected as independent variables, and subjected to multivariate unconditional stepwise logistic regression analysis. Spearman correlation analysis was used to analyze the correlation of the accumulated cigarette consumption in the smoking subgroup and glycated hemoglobin index in the diabetic subgroup with the prognosis after intravenous thrombolysis and the sICH.

3. Results

3.1. General information

From January 2013 to December 2016, 125 AIS patients received rt-PA intravenous thrombolysis. Among these patients, 63 patients were men and 62 patients were women, and the age of these patients ranged within 35 to 79 years old, with an average age of 65.44 ± 8.21 years old. Before the thrombolysis, the NIHSS score was within 5 to 38 points, and the average score was 14.23 ± 6.02 points. The interval from onset to thrombolysis was within 110 to 270 minutes, with an average of 213.76 ± 39.21 minutes. The NIHSS and mRS scores were calculated at 90 days after thrombolysis, in which 49 patients (39.20%) were assigned in the good prognosis group and 76 patients (60.80%) were assigned in the poor prognosis group. Ten patients (8%) died, while 8 patients (6.40%) developed sICH. Among these 8 patients, 1 patient had posterior circulation infarction, and 7 patients had anterior circulation infarction.

Table 1**Comparison of the clinical data between the good prognosis group and poor prognosis group.**

General information	All patients n = 125	Good prognosis n = 49	Poor prognosis n = 76
Age	65.44 ± 8.21	62.44 ± 5.21	66.82 ± 7.23
Gender			
Male (%)	63 (50.40%)	22 (44.90%)	41 (53.95%)
Female (%)	62 (49.60%)	27 (55.10%)	35 (46.05%)
Smoker (%)	64 (51.20%)	22 (44.90%)	42 (55.26%)
The number of cigarettes smoked per year, (smoker)	417.50 ± 219.76	271.30 ± 140.93	487.62 ± 222.23 [#]
Alcoholism (%)	63 (50.40%)	18 (36.73%)	45 (59.21%)
Alcohol consumption (annual gram) (alcoholism)	1201.50 ± 305.10	1108.60 ± 288.00	1286.20 ± 325.80
Hypertension (%)	70 (56.00%)	20 (40.82%)	50 (65.79%)
Diabetes (%)	72 (57.60%)	22 (44.90%)	47 (61.84%)
Glycated hemoglobin index (diabetes)	56.70 ± 25.28	31.76 ± 5.93	67.79 ± 22.49 [#]
Atrial fibrillation (%)	28 (22.40%)	8 (16.33%)	20 (26.32%)
Myocardial infarction (%)	12 (9.60%)	2 (4.08%)	10 (13.16%)
Hyperlipidemia (%)	40 (32.00%)	20 (40.82%)	20 (26.32%)
Stroke history (%)	20 (16.00%)	6 (12.24%)	13 (17.11%)
Interval between onset and thrombolysis, min	213.76 ± 39.21	190.10 ± 39.76	227.25 ± 31.20 [#]
Baseline NIHSS score	14.23 ± 6.02	10.39 ± 5.27	16.71 ± 5.13 [#]
Anterior circulation infarction (%)	111 (88.80%)	45 (91.84%)	66 (86.84%)
Post circulation infarction (%)	14 (11.20%)	4 (8.16%)	10 (13.16%)
Mean arterial pressure during thrombolysis	106.46 ± 8.01	100.88 ± 7.82	110.07 ± 5.79 [#]
Blood glucose during thrombolysis	8.30 ± 2.95	7.11 ± 2.75	9.55 ± 3.15
muscle enzyme	158.32 ± 87.57	140.45 ± 59.35	178.80 ± 80.55
Blood creatinine/blood uric acid	0.31 ± 0.11	0.21 ± 0.18	0.41 ± 0.21
DRAGON score	3.61 ± 1.52	2.10 ± 0.77	4.58 ± 1.01 [#]

Comparison between good prognosis group and poor prognosis group.

[#] $P < .01$.

3.2. Univariate analysis

Multivariate analysis revealed the following: the difference in the interval from onset to thrombolysis, baseline NIHSS score, MAP during thrombolysis and DRAGON score between the good prognosis group and poor prognosis group were statistically significant ($P < .05$); in the diabetic subgroup and smoking subgroup, the differences in glycated hemoglobin index and accumulated cigarette consumption between the good prognosis group and poor prognosis group were statistically significant ($P < .05$); the differences in the remaining factors were not statistically significant ($P > .05$) (Table 1).

3.3. Multivariate regression analysis

With the 4 statistically significant factors screened by univariate analysis (the interval from onset to thrombolysis, baseline NIHSS score, MAP during thrombolysis, and DRAGON score) as independent variables, a non-conditional stepwise logistic

regression analysis was carried out. The results revealed that the differences in baseline NIHSS score and MAP during thrombolysis between the good prognosis group and poor prognosis group were statistically significant ($P < .05$). This suggests that the baseline NIHSS score and MAP during thrombolysis are prognostic factors for AIS treated by intravenous thrombolysis (Table 2).

3.4. Correlation analysis of subgroups

Spearman correlation analysis was performed in the smoking subgroup and diabetic subgroup. The results revealed that the accumulated cigarette consumption and the glycated hemoglobin index were negatively correlated with the prognosis after intravenous thrombolysis. Furthermore, the glycated hemoglobin index was positively correlated with the incidence of sICH, and the accumulated cigarette consumption was not correlated to the incidence of sICH (Table 3).

4. Discussion

A total of 125 AIS patients who received rt-PA intravenous thrombolysis in our hospital were included into the present study.

Table 2**Results of the multivariate logistic regression analysis.**

	B	S.E.	Wals	P	OR
The interval from onset to thrombolysis	0.029	0.017	3.142	.076	1.030
Baseline NIHSS score	0.248	0.110	5.134	.023 [*]	1.282
Mean arterial pressure during thrombolysis	4.188	1.232	11.556	.001 [#]	65.870
DRAGON score	0.139	0.073	3.648	.056	1.149
Constant	-45.505	15.721	8.379	.004	0.000

^{*} $P < .05$.[#] $P < .01$.**Table 3****Results of the Spearman correlation analysis.**

	sICH	Good prognosis
Glycated hemoglobin index	0.370 [#]	-0.745 [#]
Number of cigarettes smoked per year	0.004	-0.468 [#]

sICH = symptomatic intracranial hemorrhage.

[#] $P < .01$.

Among these patients, 49 patients (39.20%) had good prognosis at 90 days after thrombolysis.

Univariate analysis revealed that age, sex, smoking, alcoholism, hypertension, diabetes, atrial fibrillation, myocardial infarction, hyperlipidemia, history of cerebral stroke, anterior and posterior circulation infarction, blood glucose during thrombolysis, creatine kinase, and blood creatinine/blood uric acid ratio were not significantly correlated with the prognosis of AIS treated by rt-PA thrombolysis. Furthermore, the interval from onset to thrombolysis, baseline NIHSS score, MAP during thrombolysis and DRAGON score were influence factors for the prognosis of AIS patients treated with rt-PA intravenous thrombolysis. However, there were interactions between these factors, and these factors were not independent predictive factors. Multivariate logistic analysis revealed that only differences in baseline NIHSS score and MAP during thrombolysis were statistically significant. These 2 were independent predictive factors for the prognosis of AIS after thrombolysis. Dharmasaroja et al^[2] observed 203 patients who received thrombolytic therapy, and their results revealed that the NIHSS score during thrombolysis was an independent predictive factor for the prognosis of AIS treated with thrombolysis, and the median was 8 points in patients with good outcomes and 15 points in patients with poor outcomes. The present study also revealed that baseline NIHSS score during thrombolysis was an independent predictive factor for the prognosis of AIS after thrombolysis, and the median NIHSS score was 9 points in patients with good prognosis and 16 points in patients with poor prognosis. These were consistent with the conclusions reported by a number of studies^[3–5]: the baseline NIHSS score was an independent predictive factor for the prognosis of AIS after thrombolysis, and the lower the NIHSS score was, the better the prognosis became. The results of the present study suggest that MAP is an independent predictor of prognosis after rt-PA intravenous thrombolysis. This is the same with the conclusion in the study conducted by Albers et al,^[6] in which the lower the baseline MAP was, the better the prognosis of AIS patients <85 years old, who were treated with rt-PA intravenous thrombolysis. Furthermore, the National Institute of Neurological Disorders and Stroke rt-PA Stroke (NINDS) study also observed that MAP was an important prognostic factor.^[7] Therefore, the present study has proven that the lower the baseline arterial pressure is, the better the prognosis of Chinese AIS patients treated with rt-PA intravenous thrombolysis.

In the diabetic subgroup and smoking subgroup, differences in the glycated hemoglobin index and the accumulated cigarette consumption between patients with good prognosis and poor prognosis were statistically significant ($P < .05$). The correlation analysis revealed that the accumulated cigarette consumption of smoking patients and the glycated hemoglobin index of diabetic patients were negatively correlated with good prognosis ($r = -0.468$, $P < .01$; $r = -0.745$, $P < .01$; respectively). Furthermore, the glycated hemoglobin index of diabetic patients was positively correlated with the incidence of sICH ($r = 0.370$, $P < .001$). This suggests that the higher the glycated hemoglobin levels of diabetic patients, the higher the incidence of sICH after intravenous thrombolysis in AIS patients. In the present study, in the smoking subgroup, the accumulated cigarette consumption was negatively correlated with the prognosis after intravenous thrombolysis ($r = -0.468$, $P < .001$). However, there was no significant correlation between the accumulated cigarette consumption and sICH ($P > .05$, Table 3). Barua et al^[22] observed in an in vitro experiment that acute smoke exposure could enhance thrombosis and fibrinolytic resistance, but no enhancement in the lysis of the

vein clot could be seen in smokers when exposed to rt-PA. Smoking can affect the lysis effect of rt-PA on thrombus, thereby influencing the effect and prognosis of intravenous thrombolysis for AIS. However, the results of a small-sample study conducted by German researcher Kufner et al^[5] revealed that rt-PA intravenous thrombolysis did not increase the incidence of sICH in smokers. Swiss researchers Wahlgren et al^[23] observed that the incidence of sICH was lower in smokers treated with rt-PA intravenous thrombolysis. Therefore, the effect of smoking on the prognosis of rt-PA intravenous thrombolysis and sICH in the Chinese population needs to be elucidated through large sample-size prospective clinical studies. In the analysis of diabetic subgroup, the glycated hemoglobin index was positively correlated with the incidence of sICH ($r = 0.370$, $P < .001$), and the higher the glycated hemoglobin level was, the higher the incidence of sICH became after intravenous thrombolysis for AIS. In 2010, Lees et al^[3] revealed in a study that diabetes could make patients benefit less from intravenous thrombolysis. The European Cooperative Acute Stroke Study (ECASS) published in 2012 revealed that sICH more easily occurred in patients with a blood glucose level of 166 mg/dL than in patients with a blood glucose level of 127 mg/dL during thrombolysis.^[8] In 2017, Chinese scholars Liu et al^[24] analyzed the independent risk factors of sICH, including a serum glucose of >90 mmol/L at admission, in 1128 AIS patients treated with rt-PA intravenous thrombolysis. The result revealed that the abnormal increase in or poor control of glucose could increase sICH risk during intravenous thrombolysis in AIS patients. The second European Cooperative Acute Stroke Study (ECASS-II) revealed that^[9] continuous hyperglycemia affected the prognosis of thrombolysis and the incidence of sICH. The possible mechanisms may be as follows: damage to microvessels and great vessels, which increases the risk of intracranial hemorrhage in patients^[25]; long-term diabetes or persistent hyperglycemia can increase blood condensation, and has a resistance to antithrombotic therapy.^[26] On the basis that most of the sICH cases occurred in the diabetic subgroup in the present study, the correlation between glycated hemoglobin level and the prognosis of rt-PA intravenous thrombolysis and sICH was analyzed. The results suggested that the higher the glycated hemoglobin level of diabetic patients, the higher the incidence of sICH after intravenous thrombolysis for AIS, and the poorer the prognosis.

In the present study, among the 125 patients, 27 patients were treated with rt-PA thrombolysis at 0 to 3 hours after the onset, and the prognosis was good in 18 patients (66.67%), while 98 patients were treated with rt-PA thrombolysis at 3.0 to 4.5 hours after the onset, and the prognosis was good in 31 patients (31.63%). These results reveal that it is effective for Chinese patients to receive rt-PA intravenous thrombolysis within the time window of 3.0 to 4.5 hours. In the univariate analysis of the present study, both the interval from onset to thrombolysis and DRAGON score significantly affected the prognosis. However, in the logistic regression analysis, after excluding for confounding factors, the influence of the interval between onset to thrombolysis and DRAGON score was not significant in predicting the prognosis of intravenous thrombolysis. Since our hospital performs intravenous thrombolysis mostly within 3.0 to 4.5 hours, intravenous thrombolytic therapy with rt-PA within the time window of 3.0 to 4.5 hours had a positive effect, making it an effective and safe method for AIS patients. This was similar to the results reported by many studies at home and abroad.^[18,27–29] In the present study, sICH occurred in 8 patients (6.40%). This was similar to the conclusion that there was no

significant increase in the incidence of sICH when the intravenous thrombolysis time window was extended from 3 to 4.5 hours, as reported by Asaithambi et al^[29] in 2014. Only 21.6% (27 cases) of the 125 patients treated with intravenous thrombolysis in this study were within 3.0 hours after the onset, reflecting the residents of Nanchang, lack of awareness of AIS, fail to seek early medical treatment, and have longer time to visit our hospital for intravenous thrombolysis. In addition, there is a need to strengthen health education in pre-hospital management for residents in our province, in order to shorten the time from the onset of the disease to the visit to the hospital, and strengthen the management of the green channel for stroke patients in our hospital, in order to shorten the interval between their visit of hospital and thrombolytic treatment.

There are still some deficiencies in our study design. In the AIS imaging evaluation, the role of different imaging examinations in AIS patients and their influence on prognosis were not further discussed.^[30–38]

The present study has eventually proven that the baseline NIHSS score was an independent predictive factor for the prognosis of AIS treated with intravenous thrombolysis. This is consistent with the results of large-scale intravenous thrombolysis studies conducted at home and abroad. The severity of early neurological deficits affects the thrombolytic effect of patients. Therefore, in the ECASS III study, patients with a baseline NIHSS score of >25 did not receive thrombolytic therapy.^[39] In the present study, 2 patients with posterior circulation infarction and a baseline NIHSS score of >25 had good prognosis after thrombolytic therapy, while 6 patients with infarction and a baseline NIHSS score of >25 had poor prognosis after thrombolytic therapy. Among these 6 patients, 5 patients had anterior circulation cerebral infarction, and 1 patient had posterior circulation infarction. These results confirm that patients with posterior circulation infarction and a baseline NIHSS score of >25 can benefit from intravenous thrombolytic therapy.

In summary, rt-PA intravenous thrombolysis is presently well-recognized as an effective treatment for AIS, and the baseline NIHSS score and MAP during thrombolysis influence the prognosis of AIS treated by intravenous thrombolysis. In the smoking subgroup, the accumulated cigarette consumption was negatively correlated with the prognosis of intravenous thrombolysis. In the diabetic subgroup, the glycosylated hemoglobin index was positively correlated with the incidence of sICH, but negatively correlated with the prognosis after intravenous thrombolysis.

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