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Expression of p53, bax and bcl-2 and predictive value of fibrinogen, D-Dimer, and mean platelet volume in patients with acute cerebral infarction after intravenous thrombolysis

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ABSTRACT

This was to study the application value of fibrinogen (FIB), D-dimer (D-D), and mean platelet volume (MPV) in the prediction of vascular re-occlusion (VRO) after intravenous thrombolysis (IVT) in patients with acute cerebral infarction (ACI). 114 patients with ACI were retrospectively included as the research objects and then were divided into the improvement group (66 cases) and the progressive group (48 cases). A multivariate Logistic regression model was applied to analyze the independent risk factors of VRO after IVT. The receiver operator characteristic (ROC) curve was also adopted to assess the predictive value of relevant factors for VRO after IVT. In addition, the expression of p53, bax and bcl-2 genes was investigated in patients with acute cerebral infarction and healthy people by real-time PCR. As a result, MPV, FIB, and D-D levels of venous blood in the improvement group were remarkably lower than those in the progressive group (P<0.05). The regression coefficients between MPV, FIB, D-D at admission and VRO after IVT were 0.411, 0.362, and 0.391, respectively, so there was a significant positive correlation (P<0.05). The combined prediction model of MPV, FIB, and D-D had greater sensitivity, specificity, and area under the curve (AUC) in predicting the risk of VRO after IVT than single MPV, FIB, or D-D, showing differences of statistical significance (P<0.05). In conclusion, MPV, FIB, and D-D in venous blood at admission were independent risk factors for the VRO after IVT. The combined model of MPV, FIB, and D-D had an excellent predictive performance on the risk of VRO after IVT. The expression level of genes p53 and bax was 4.5 and 3 times higher in patients than in controls, respectively. The expression of gene bcl-2 decreased (0.75 times) in patients (P<0.001).

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Introduction

Cerebral infarction is also known as ischemic stroke, as it is called stroke in traditional Chinese medicine. It is a blood supply disorder in the local brain tissue area caused by various reasons, leading to ischemic and hypoxic necrosis of brain tissue, and then resulting in corresponding neurological deficits clinically (1-3). Cerebral infarction is classified into cerebral thrombosis, cerebral embolism, and lacunar cerebral infarction according to the different pathogeneses. Cerebral thrombosis is the most common type of cerebral infarction, accounting for about 60% of all cerebral infarctions. Cerebral infarction is more likely to occur in people over 50-60 years old, often with atherosclerosis, hypertension, rheumatic heart disease, coronary heart disease, or diabetes, as well as smoking, drinking, and other bad habits (4,5). About 25% of patients had a history of transient ischemic attack. Before the onset of the disease, there are many prodromal symptoms, including headache, dizziness, vertigo, transient limb numbness, and weakness. The onset is generally fast, and most patients have the onset during resting and sleeping (6). In most patients, symptoms peak within a few hours or even 1-3 days. After the onset of cerebral infarction, most patients are conscious, but a few may have different degrees of disturbance of consciousness, and the general vital signs have no significant changes. A large area of infarction in the cerebral hemisphere complicated with severe cerebral edema will impair the function of the diencephalon and brain stem. At the same time, consciousness disorder, even brain hernia and death may occur soon after the onset of the disease (7–9). If the first symptom is unconsciousness, it may result in posterior circulation cerebral infarction.

The principle of clinical treatment of acute cerebral infarction (ACI) is to improve the blood circulation in the ischemic area of the brain as soon as possible and promote the recovery of neurological function. Thrombolytic therapy can be first given, that is, when there are indications within 3-6 hours after the onset, thrombolysis can be administered intravenously as soon as possible. Arterial thrombolysis is also an alternative, followed by general treatment (10,11). Intravenous thrombolysis (IVT) is currently the most important drug therapy to restore blood flow. Cerebral arterial thrombosis is mainly composed of platelets, a small amount of red blood cells and cross-linked fibrins. Thrombolytic drugs can dissolve blood clots by activating plasminogen to form plasmin and destroying the cross-linking among fibrin molecules. Thrombolytic drugs include recombinant tissue plasminogen activator (rt-PA), urokinase, and tenecteplase (12-14). The major thrombolytic

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drugs currently used in China are rt-PA and urokinase, and the effective thrombolytic time window is limited. The effective time window for saving penumbra tissue is within 4.5 or 6 hours. In addition to the well-known hemorrhagic transformation, the common complications of IVT therapy for ACI include systemic hemorrhage, vascular re-occlusion (VRO), vasogenic edema, allergy, and cerebral edema (15,16). VRO is a common complication of endovascular treatment of ACI, which is associated with worsening clinical symptoms; early VRO also predicts poor long-term prognosis. It may be related to the activated aggregation of exposed platelets in the lipid core after thrombolysis or vascular endothelial injury, insufficient use of perioperative antiplatelet drugs, or resistance to antiplatelet drugs (17).

From the above, how to diagnose and prevent VRO after IVT in ACI is a clinical issue that needs to be solved. Therefore, 114 patients with ACI who visited the Department of Neurology of Changzhou Wujin Hospital Affiliated with Jiangsu University (Wujin Clinical College of Xuzhou Medical University) Hospital from January 2015 to July 2022 were retrospectively included as the research objects. These patients were divided into an improvement group (66 cases) and a progressive group (48 cases) according to their National Institute of Health stroke scale (NIHSS) score. A multivariate Logistic regression model was adopted for analyzing the independent risk factors of VRO after IVT. The receiver operator characteristic (ROC) curve was also used to evaluate the predictive value of related factors for VRO after IVT.

Materials and Methods

Research objects

114 patients with ACI were retrospectively included as the research objects, as they visited the Department of Neurology of Changzhou Wujin Hospital Affiliated with Jiangsu University (Wujin Clinical College of Xuzhou Medical University) Hospital from January 2015 to July 2022. With 62 males and 52 females, these objects were aged 23-79 years old. This project had been approved by the ethics committee of the hospital. All the patients participated voluntarily and signed an informed consent form before the implementation of this project.

Inclusion criteria: (1) These patients were over 20 years old. (2) These patients were treated with human rt-PA. (3) They didn't have cognitive impairment and able to communicate normally. (4) Their baseline data was complete.

Exclusion criteria: (1) Malnourished patients. (2) Patients complicated with severe liver and kidney dysfunction. (3) Patients have recently supplemented with vitamin B12, folic acid, etc. (4) Patients had an acute myocardial infarction, congenital heart disease, and other heart diseases. (5) Patients had a complication of hyperthyroidism. (6) Patients had poor compliance.

Intravenous rt-PA therapy

Patients were treated with intravenous rt-PA by a professional neurologist. According to the patient's weight, an alteplase injection was administered intravenously at a dose of 0.9 mg/kg. 10% of the dose was injected within 1 minute, and the remaining 90% was administered to the patient by a micropump.

Criteria for grouping

According to NIHSS score, included patients were divided into the improvement group (66 cases) and the progressive group(48 cases). In the improvement group, the NIHSS score decreased by 2 or more points 3 days after treatment compared with pre-treatment, or patients were completely cured. In the progressive group, the NIHSS score increased by 2 points or more within 3 days after treatment compared with pre-treatment.

Collection of baseline data

Demographics of patients (gender, age, height, weight) and vascular risk factors (smoking, alcohol drinking, hypertension, hyperlipidemia, diabetes, coronary heart disease, and atrial fibrillation) were included. Imaging findings (infarction site, atherosclerotic plaque or not in the blood vessel of the neck) and clinical data (NIHSS score at admission, taking antiplatelet aggregation drugs or not, thrombolysis time) were also collected.

Diagnostic criteria of past medical history were stated as follows. (i) For smoking history, patients had continuous smoking for 5 years or more, and they smoked more than 10 cigarettes per day; or they quit smoking for less than 5 years. (ii) For drinking history, patients had continuous drinking for more than 5 years, among which males drank 40 g or more of ethanol per day, while females drank 20 g or more per day. Otherwise, they drank alcohol frequently within 2 weeks, reaching 80 g or more of ethanol. (iii) For the history of atrial fibrillation, patients were found to have typical atrial fibrillation waveform through electrocardiography. (iv) For the history of coronary heart disease, patients had coronary heart disease in the past, with typical heart-related precordial pain; or had myocardial infarction previously but had been cured. (v) For the history of diabetes, the random blood glucose content (or blood glucose at any time) reached 11.1 mol/L or above, with typical symptoms of diabetes including polydipsia, polyuria, polyphagia, and weight loss. (vi) For the history of hypertension, the systolic blood pressure of patients measured at different times was above 140 mmHg, and the diastolic blood pressure was above 90 mmHg.

Observation indicators

(1) Before treatment, venous blood samples were drawn from patients. Coagulation function, D-dimer (D-D), and routine blood tests were performed. The values of mean platelet volume (MPV), D-D, and fibrinogen (FIB) were recorded, respectively.

(2) NIHSS assessment was performed on patients by a number of senior physicians, combined with clinical symptoms. The NIHSS scores before and after thrombolytic therapy were recorded.

Real-time RT RCR

The gene expression of p53, bax and bcl-2 as well as the internal control gene glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was evaluated. mRNA was isolated from Human peripheral blood mononuclear cells (PBMCs) and converted to cDNA using commercially available kits (Sigma) according to the kit instructions. cDNA production was performed according to the instructions of the kit (USA Invitrogen, California) using oligo-dT primers. MMPs mRNA expression was tested by real time-RT RCR using Taqman q-PCR expression assay (Invitrogen). Ran-

Gene name	Primer	Primer sequence
GAPDH	Forward	5'-GAAGGTGAAGGTCGGAGTC-3'
	Reverse	5'-GAAGATGGTGATGGGATTTC-3'
	Probe	5'-CCGACTCTTGCCCTTCGAAC-3'
P53	Forward	5'-TAACAGTTCCTGCATGGGCGGC-3'
	Reverse	5'-AGGACAGGCACAAACACGCACC-3'
	Probe	5'-CGGAGGCCCATCCTCACCATCATCA--3'
bax	Forward	5'-TGGAGCTGCAGAGGATGATTG-3'
	Reverse	5'-GAAGTTGCCGTCAGAAAACATG-3'
	Probe	5'-ACATACTAAATTGGAGCACTCTGTGTG-3'
bcl2	Forward	5'-TTGGCCCCCGTTGCTT-3'
	Reverse	5'-CGGTTATCGTACCCCGTTCTC-3'
	Probe	5'-AGCGTGCGCCATCTTTCCCAG-3'

dom primers were used according to the manufacturer's instructions. The sequences of primers and probes for p53, bax and bcl-2 are listed in Table 1.

RT-PCR conditions for p53 were as follows: 30 min at 60 °C, 10 min at 95 °C, and then 45 cycles of amplification for 15 s at 95 °C and 1 h at 55 °C followed by end extension for 10 min at 72 °C. PCR for bcl-2 and bax was performed as follows: 95°C for 10 minutes; 50 cycles of 95 °C for 15 minutes; 60 °C for 1 hour. All samples were compared with GAPDH.

Each sample was replicated in triplicate and PCR reaction was performed with sufficient negative controls. The specificity of PCR was evaluated by melting curve evaluation and subsequently by agarose gel electrophoresis.

Statistical methods

Data processing in this work was performed with SPSS 19.0, and the Shapiro-Wilk test was utilized to judge the normality of measurement data. The measurement data were represented in mean ± standard deviation (x(_);x±*s*), while the enumeration data were expressed in percentage (%). The t-test was adopted to compare the normally distributed measurement data between groups, while the Wilcoxon rank-sum test was used to compare the measurement data in a skewed distribution. Under the multivariate logistic regression model, the independent risk factors of VRO after IVT were analyzed. With receiver operating characteristic (ROC) curves, the predictive value of related factors for VRO after IVT was evaluated. A difference was counted to have statistical significance at $P<0.05$.

Results

Comparison of baseline data of two groups of patients

As shown in Table 1 below, the gender ratio and age of patients in the improvement group were significantly different from those in the progressive group($P<0.05$). There was no significant difference in height, weight, and histories of smoking, drinking, coronary heart disease, hypertension, hyperlipidemia, and diabetes ($P>0.05$).

Table 1. Comparison of baseline data of patients.

Indicators		Improvement group	Progressive group	*P*
Gender/n	Male	40 (60.61%)	20 (41.67%)	<0.05
	Female	26 (39.39%)	28 (58.33%)	
Height/cm		162.58±10.76	160.77±11.15	>0.05
Body weight/kg		62.51±5.93	61.28±8.13	>0.05
Age/years old		57.23±6.15	69.36±8.41	<0.05
Smoking history	Yes	10 (15.15%)	7 (14.58%)	>0.05
	No	56 (84.85%)	41 (85.42%)	
Drinking history	Yes	6 (9.09%)	4 (8.33)	>0.05
	No	60 (90.91%)	44 (91.67%)	
History of atrial fibrillation	Yes	5 (7.58%)	3 (6.25%)	>0.05
	No	61 (92.42%)	45 (93.75%)	
History of coronary heart disease	Yes	11 (16.67%)	7 (14.58%)	>0.05
	No	55 (83.33%)	41 (85.42%)	
History of hypertension	Yes	35 (53.03%)	27 (56.25%)	>0.05
	No	31 (46.97%)	21 (43.75%)	
History of hyperlipidemia	Yes	15 (22.73%)	10 (20.83%)	>0.05
	No	51 (77.27%)	38 (79.17%)	
History of diabetes	Yes	13 (19.7%)	9 (18.75%)	>0.05
	No	53 (80.3%)	39 (81.25%)	

Comparison of venous blood test results between groups

As could be known from Figure 1, the MPV of venous blood of the improvement group was 8.73±1.26 fL, the FIB level was 2.74±0.68 g/L, and the D-D level was 0.76±0.18 g/L. In the progressive group, MPV, FIB, and D-D turned out to be 10.48±2.24 fL, 3.52 ±0.82 g/L, and 1.59±0.35 g/L, respectively. The MPV, FIB, and D-D levels of venous blood in the improvement group were notably lower than those in the progressive group, showing differences of statistical significance (P<0.05).

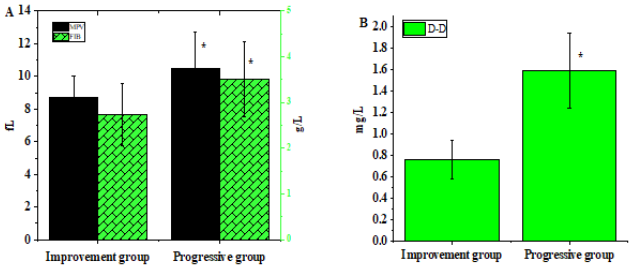

Figure 1. Comparison of venous blood test results between groups. (A: MPV; B: FIB; C: D-D). Note: * indicated that the difference between the improvement group and the progressive group was statistically significant (P<0.05).

Regression analysis of related factors of VRO after IVT

The patients' gender, age, MPV, FIB, and D-D in venous blood at admission were taken as independent variables, and VRO after IVT was adopted as the dependent variable for logistic univariate regression analysis. The results were displayed in Table 2 below. The regression coefficients of gender, age, MPV, FIB, and D-D with RVO after IVT were 0.563, 0.522, 0.308, 0.455, and 0.432, respectively. Thus, there was a significant positive correlation (P<0.05). The regression coefficient of MPV in venous blood and VRO after IVT was 0.308, so the positive correlation was extremely significant (P<0.05).

Further multivariate logistic regression analysis was made and shown in Table 3. The regression coefficients of venous blood MPV, FIB, and D-D at admission with VRO after IVT were 0.411, 0.362, and 0.391, respectively, showing significant positive correlations (P<0.05). The regression coefficients of gender and age with VRO after IVT were 0.186 and 0.231, respectively, without a significant positive correlation (P>0.05).

Figure 2 was the array chart for predicting the risks of VRO after IVT, including three indicators of venous MPV, FIB, and D-D. According to the value of each independent variable, the specific position in the chart was found, and then the corresponding score was obtained. These scores were added to get the total score, and the corresponding predicted percentage was worked out with the total score. The percentage represented the probability of VRO after IVT.

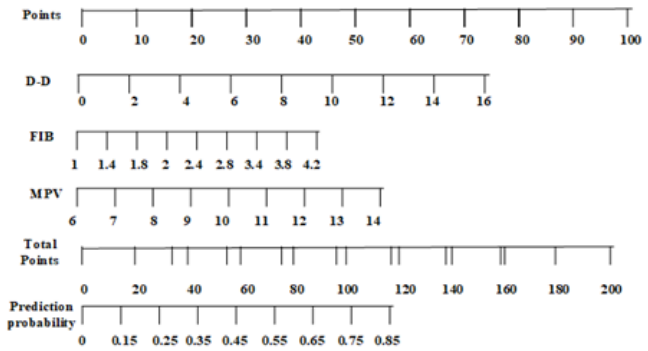

Figure 2. Array chart for predicting the risk of VRO after IVT.

Comparison of diagnostic performance between ultrasound system and routine ultrasound

The gene expression of p53, bax and bcl-2

The results showed that the expression level of genes p53 and bax was 4.5 and 3 times higher in patients than in controls, respectively. The expression of gene bcl-2 decreased (0.75 times) in patients (P<0.001) (Figure ?).

Discussion

Currently, IVT drugs are one of the most effective for ACI. Through the intravenous infusion of thrombolytic drugs, the fibrinolysis in the thrombus can be dissolved, so that the blocked blood vessels can be recanalized. This method of treatment is called IVT therapy (18-20). After

Table 2. Univariate regression analysis of related factors of VRO after IVT.

Variables	Regression coefficient	t	*P*
Gender	0.563	4.051	0.027
Age	0.522	4.865	0.009
MPV	0.308	5.334	0.000
FIB	0.455	4.368	0.011
D-D	0.432	6.121	0.003

Table 3. Multivariate regression analysis of related factors of VRO after IVT.

Variables	Regression coefficient	t	*P*
Gender	0.186	1.355	0.062
Age	0.231	1.237	0.059
MPV	0.411	3.684	0.005
FIB	0.362	4.078	0.038
D-D	0.391	4.833	0.004

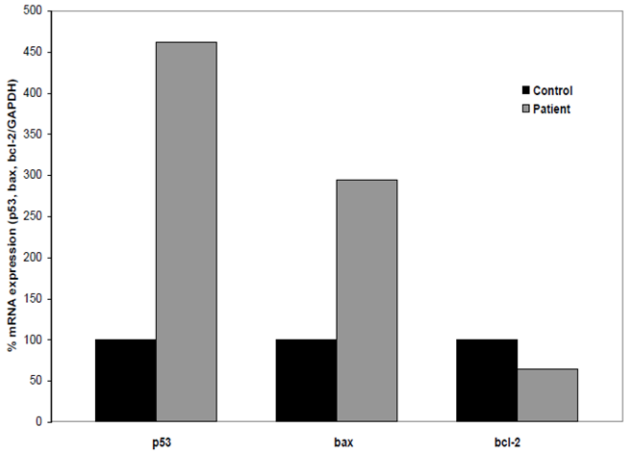

Figure 3. The expression level of genes p53, bax and bcl-2 in patients suffering from acute cerebral infarction and controls.

a stroke occurs, IVT is administered to patients within 4.5 hours, which can save some of the brain tissue that has not yet been necrotic. 1 minute of later treatment, 1.9 million brain cells will die. However, IVT has certain hidden dangers, for example, VRO after the treatment needs early prediction and prevention (21,22). This work retrospectively included 114 patients with ACI as research objects, who visited the Department of Neurology of Changzhou Wujin Hospital Affiliated with Jiangsu University (Wujin Clinical College of Xuzhou Medical University) Hospital from January 2015 to July 2022. These objects were divided into the improvement group (66 cases) and the progressive group(48 cases). A multivariate Logistic regression model was used to analyze the independent risk factors of VRO after IVT, and the ROC curve was adopted to evaluate the predictive value of related factors for VRO after IVT. From the baseline data, the gender ratio and age of patients in the improvement group were greatly different from those in the progressive group(P<0.05). There was no significant difference between groups in height, weight, history of smoking, history of drinking, history of coronary heart disease, history of hypertension, history of hyperlipidemia, and history of diabetes (P>0.05). Such results were consistent with clinical cognition. For cases of ACI, men were more than women; the number of male cases was generally 2-6 times that of females. The higher the age, the greater the probability of ACI (23).

FIB is a glycoprotein synthesized and secreted by hepatocytes, which can appear in the acute phase of the inflammatory response, and also has a coagulation function. It has a certain correlation with platelet aggregation rate and plasma viscosity. It is the most abundant coagulation factor in plasma (24). D-D is the product of the simplest fibrinolysis process, with high stability and specificity. When the body's blood is in a highly coagulable state or is affected by other diseases and then fibrin cleavage is active, its content in plasma will rise. MPV is an indicator of the mean size of platelets and is often used for judging bleeding, changes in bone marrow hematopoietic function, and the therapeutic effect of certain diseases. In coagulation-related indicators, MPV, FIB, and D-D of venous blood in the improvement group were remarkably lower than those in the progressive group, with differences of statistical significance (P<0.05). This suggested that MPV, FIB, and D-D might be related to VRO after IVT. Multivariate logistic regression analysis showed that the regression coefficients of MPV, FIB, and D-D in venous blood at admission were 0.411, 0.362, and 0.391, respectively with VRO after IVT; suggesting the significant positive correlations (P<0.05). It was illustrated that venous MPV, FIB, and D-D at admission had a high correlation with VRO after IVT, and were independent risk factors for this event (25-29). The ROC curve was adopted for analyzing the prediction performance of the prediction model as well as the single MPV, FIB, and D-D on the risk of VRO after IVT. The predictive sensitivity, specificity, and AUC of the prediction model for predicting the risk of VRO after IVT were all greater than those of single MPV, FIB, and D-D, showing differences of statistical significance (P<0.05). This demonstrated that the combined model of MPV, FIB, and D-D had an excellent predictive performance on the risk of VRO after IVT.

The bcl2 gene family is a complex network regulating apoptosis that some of its genes can inhibit apoptosis and others can induce it (30,31). Apoptosis is initiated by various stimuli and inhibited by increasing bcl-2 gene expression (32). Increasing the expression and activity of P53 increases bax transcription and inhibits bcl-2 gene activity. P53 regulates the bax in transcription level (33,34). In this study, increasing bax expression and inhibition of bcl-2 transcription showed that the expression and activation of p53 can increase transcription.

114 ACI patients were retrospectively included as research objects, who visited the Department of Neurology of Changzhou Wujin Hospital Affiliated with Jiangsu University (Wujin Clinical College of Xuzhou Medical University) Hospital from January 2015 to July 2022. These objects were grouped into an improvement group (66 cases) and a progressive group (48 cases). The independent risk factors of VRO after IVT were analyzed under a multivariate Logistic regression model, and the predictive value of related factors for VRO after IVT was evaluated through ROC curves. MPV, FIB, and D-D levels in venous blood at admission were proved as independent risk factors for VRO after IVT. The combined model of MPV, FIB, and D-D showed a splendid prediction performance on the risk of VRO after IVT. However, due to the limitation of time and energy, the number of patients included was relatively small, and they all came from the same hospital. These perhaps had some impact on the results. Besides, only 3 coagulation-related indicators MPV, FIB, and D-D were included. In the following research, a large number of patients with ACI treated with IVT would be re-selected. The data of coagulation-related indicators would also be re-collected to explore the clinical application value of coagulation indicators in a more in-depth and comprehensive manner. In conclusion, the results of this work gave a reference value for the prediction and prevention of VRO after IVT in patients with ACI.

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