Study on the Risk Factors of Bleeding Transformation and Poor Prognosis in Acute Cerebral Infarction Patients after Emergency Thrombolysis

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To explore the risk factors of bleeding transformation and poor 90 d prognosis in acute cerebral infarction patients after emergency thrombolysis. A total of 576 acute cerebral infarction patients treated with thrombolytic therapy in emergency department from July 2018 to February 2021 were analyzed retrospectively. They were divided into groups according to the bleeding transformation and 90 d prognosis after treatment, including 92 patients with bleeding transformation and 244 patients with poor 90 d prognosis. The general data, treatment-related indicators and laboratory indicators of patients in each group were compared and logistic regression model was used to evaluate the independent risk factors of bleeding transformation and poor 90 d prognosis. The incidence of bleeding transformation after thrombolytic therapy in emergency department was 15.97 % (92/576). In the hemorrhagic transformation group, the proportion of patients with moderate to severe leukoaraiosis, D-dimer level and urine specific gravity level were significantly higher than those in the non-hemorrhagic transformation group ($p<0.05$). The incidence of poor 90 d prognosis after thrombolytic therapy in emergency department was 42.36 % (244/576). The age, baseline national institutes of health stroke scale score, bleeding conversion ratio, baseline random blood glucose level, international normalized ratio, proportion of large artery occlusion, D-dimer level, fibrinogen level, prothrombin time and urine glucose ratio in poor prognosis group were significantly higher than those in good prognosis group ($p<0.05$). Multivariate analysis showed that moderate to severe leukoaraiosis and high D-dimer level were independent risk factors for hemorrhagic transformation in acute cerebral infarction patients after emergency thrombolysis ($p<0.05$). High baseline national institutes of health stroke scale score and high white blood cell count level were independent influencing factors of poor 90 d prognosis of acute cerebral infarction patients after emergency thrombolysis ($p<0.05$). Hemorrhagic transformation in acute cerebral infarction patients undergoing emergency thrombolytic therapy is closely related to moderate to severe leukoaraiosis and D-dimer level. While, patients with high baseline national institutes of health stroke scale score and white blood cell count have poor 90 d prognosis.

Key words: Acute cerebral infarction, thrombolysis, hemorrhage, prognosis, infection

In recent years, intravenous thrombolysis has been widely used in the emergency treatment of Acute Cerebral Infarction (ACI) patients. The short-term and long-term prognosis of patients can be significantly improved by quickly opening the responsible vessels and restoring the blood perfusion in the focus area, but it has been reported that the subsequent bleeding transformation events are also increasing[1,2]. It has been reported that intravenous thrombolysis may increase the risk of symptomatic hemorrhage transformation in ACI patients[3] and even lead to deterioration of neurological function and death in severe cases. At the same time, there are controversies among the relevant research conclusions about the potential risk factors of poor 90 d prognosis of ACI patients and there is no definite conclusion yet[4]. Based on the above evidence, this study retrospectively analyzed 576 ACI patients treated with emergency thrombolytic therapy in our hospital from July 2018 to February 2021 and divided them into groups according to the bleeding transformation and 90 d prognosis after treatment, in order to explore the risk factors of bleeding transformation and poor 90 d prognosis of ACI patients after emergency thrombolysis, which are reported as follows. A total of 576 ACI patients treated with emergency thrombolytic therapy in our hospital from July 2018 to February 2021 were included in the study. They were divided into groups according to the bleeding transformation and 90 d prognosis after treatment, including 92 patients with bleeding transformation and 244 patients with poor 90 d prognosis. Inclusion criteria includes patients with clinically diagnosed ACI; successful completion of emergency thrombolytic therapy; head Computed Tomography (CT) examination was completed 24 h before and after thrombolysis.

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Baseline National Institutes of Health Stroke Scale (NIHSS) score was 4-30 points; complete clinical data. Exclusion criteria includes contraindication of intravenous thrombolysis; baseline modified Rankin Scale (mRS) score >2 points; organ dysfunction; severe diabetes; systemic infection cannot be controlled; malignant tumor; connective tissue disease and autoimmune system diseases. The design of this study meets the requirements of Helsinki declaration and has obtained the informed consent of patients and their families. The patient's gender, age, blood pressure, complicated brain diseases, complicated basic diseases, clinical treatment (recombinant tissue-Plasminogen Activator (rt-PA) dose), Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification, imaging examination data and laboratory examination data were recorded. Judging the degree of leukoaraiosis with reference to the results of skull CT examination (Volatile Suspended Solids (VSS) method); continuously scan the front and back areas of the central sulcus, take three cut-off planes to score and score >2 points to judge moderate to severe[5]. Diagnostic criteria of hemorrhagic transformation, there is slice high-density shadow in skull CT within 24 h after emergency thrombolysis[5]. Criterion of poor prognosis, mRS score >2 in follow-up after 90 d[6]. Choose Statistical Package for the Social Sciences (SPSS) 18.0 software to analyze the data. Kolmogorov-Smirnov test was used to evaluate the normality of data and T test was used to compare the measurement data conforming to normal distribution, which was expressed as ($\bar{x}\pm s$). Chi-square (χ^2) test was used to compare the counting data, which was expressed as percentage (%). Logistic regression model was used to complete multivariate analysis. $p<0.05$ was statistically significant. The incidence of bleeding transformation after thrombolytic therapy in emergency department was 15.97 % (92/576). In the hemorrhagic transformation group, the proportion of patients with moderate to severe leukoaraiosis, D-dimer (D-D) level and urine specific gravity level were significantly higher than those in the non-hemorrhagic transformation group ($p<0.05$) as shown in Table 1. The incidence of poor 90 d prognosis after thrombolytic therapy in emergency department was 42.36 % (244/576). The age, baseline NIHSS score, bleeding conversion ratio, baseline random blood glucose level, International Normalized Ratio (INR), proportion of large artery occlusion, D-D level, Fibrinogen (FIB) level, Prothrombin Time (PT) and urine glucose ratio in poor prognosis group were significantly higher than those in good prognosis group ($p<0.05$) as shown in Table 2. Multivariate analysis showed that moderate to severe leukoaraiosis and high D-D level were independent risk factors for haemorrhagic transformation in ACI patients after emergency thrombolysis ($p<0.05$). High baseline NIHSS score and high White Blood Cell (WBC) count level were independent influencing factors of poor 90 d prognosis of ACI patients after emergency thrombolysis ($p<0.05$) as shown in Table 3. Leukoaraiosis is one of the common pathological types of cerebral small vessels in the elderly, but its influence on the prognosis of patients after thrombolysis in emergency is still controversial[7]. The results of this study confirmed that moderate to severe leukoaraiosis is an independent risk factor for hemorrhagic transformation in ACI patients after emergency thrombolysis ($p<0.05$), which may be because intravenous thrombolytic therapy can cooperate with leukoaraiosis to lead to cytotoxicity, thus aggravating endothelial cell function and blood-brain barrier damage and finally stimulating the occurrence of hemorrhagic transformation[8,9]. Studies have confirmed that patients with severe leukoaraiosis have an increased risk of symptomatic intracranial hemorrhage by 105 %-20 % after emergency thrombolysis[10] and the increased incidence of distant cerebral hemorrhage is also related to severe leukoaraiosis. However, other studies have evaluated patients with hemorrhagic transformation and white matter lesion scale (based on Magnetic Resonance Imaging (MRI) examination). The results showed that leukoaraiosis is not directly related to hemorrhagic transformation of ACI patients after emergency thrombolysis and the differences in the above studies may be related to the different races involved[11]. Although multivariate analysis confirmed that leukoaraiosis is related to hemorrhage transformation after thrombolysis in ACI patients, this study did not confirm the independent influence of this lesion on the 90 d prognosis of patients, which is consistent with the previously reported results[12]. Leukoaraiosis has certain predictive value in the improvement of short-term cognitive function in ACI patients, but it cannot accurately evaluate the improvement effect of motor function[13]. However, the basic experimental study shows that[14], the neurological damage caused by leukoaraiosis is related to abnormal oxidative stress, excitatory amino acid toxicity, abnormal inflammatory reaction and inhibition of cerebrovascular regulation function. The low cerebral perfusion level caused by leukoaraiosis often takes a long time to influence the prognosis, so it is difficult to

predict the poor 90 d prognosis of patients. D-D is one of the biochemical indexes commonly used in clinic, which is mainly used to reflect the hypercoagulable state of blood and secondary hyperfibrinolysis. Some studies believe that its level can reflect the risk of bleeding transformation, which may be due to the continuous activation of inflammatory injury in the body under high D-D state and the aggravation of coagulation disorder, which eventually leads to the formation and expansion of hematoma[15]. The results of this study also confirmed that there was an independent correlation between D-D level and bleeding transformation of ACI patients after emergency thrombolysis. The results of this study confirmed that high baseline NIHSS score and high WBC count were independent influencing factors of poor prognosis of ACI patients after emergency thrombolysis ($p<0.05$). NIHSS score is an important index for evaluating the degree of neurological deficit in stroke patients, which can directly reflect the severity of the disease and the prognosis after thrombolysis[16]. The WBC count is closely related to the inflammatory reaction of the body and the hyper inflammatory reaction is an important factor to promote the progression of ACI patients. Studies have confirmed that WBC count can be used to predict the risk of early deterioration of neurological function in stroke patients[17]. There are some shortcomings in this study, it is a single-center retrospective study which cannot completely eliminate the influence of confounding factors due to the lack of MRI data, the evaluation of leukoaraiosis was changed to VSS based on CT examination of the skull, which may reduce the accuracy of the overall evaluation, so it needs further confirmation in the follow-up study. To sum up, for ACI patients undergoing emergency thrombolytic therapy, the occurrence of hemorrhagic transformation is closely related to moderate to severe leukoaraiosis and D-D level. However, those with higher baseline NIHSS score and WBC count had poor 90 d prognosis.

TABLE 1: COMPARISON OF CLINICAL DATA BETWEEN PATIENTS WITH AND WITHOUT HEMORRHAGIC TRANSFORMATION

Indicators	No hemorrhagic transformation (n=484)	Hemorrhagic transformation (n=92)	p
Age (years)	68.23±12.07	70.63±12.74	0.31
Male	280	64	0.5
Complicated with moderate and severe leukoaraiosis	104	48	0.02
Lacunar cerebral infarction	278	64	0.48
Alteplase	0.72±0.14	0.75±0.15	0.92
Combined with basic diseases			
Hypertension	291	68	0.31
Type 2 Diabetes Mellitus (T2DM) (case)	67	13	0.88
Coronary heart disease	48	19	0.36
Atrial fibrillation	85	20	0.82
Past history of cerebral infarction	65	26	0.24
Baseline NIHSS score (points)	10.69±1.37	11.13±1.59	0.11
Intravenous drops of drugs to reduce Blood pressure	98	33	0.39
Time from onset to admission (h)	183.72±50.47	190.03±52.21	0.95
Lesion location			0.33
Anterior circulation	388	60	
Posterior circulation	56	20	
Have both	40	12	
TOAST typing			0.45
Atherosclerosis of aorta	160	32	
Occlusion of arterioles	178	28	
Cardiogenic embolic	96	16	

Systolic blood pressure (mm Hg)	152.30±24.66	154.74±22.90	0.85
Diastolic pressure (mm H)	88.16±12.47	89.59±13.20	0.68
WBC count (×10^9/l)	7.41±1.20	7.27±1.15	0.5
PLT count (×10^9/l)	191.58±57.43	185.90±54.27	0.11
Baseline random blood glucose (mmol/l)	6.99±1.12	7.06±1.15	0.52
HbA1c (%)	6.31±0.86	6.48±0.92	0.27
INR	1.04±0.04	1.06±0.05	0.53
D-D (mg/l)	0.81±0.15	1.27±0.25	0.03
FIB (g/l)	2.85±0.60	2.81±0.57	0.78
PT (s)	12.25±1.54	12.33±1.66	0.55
APTT (s)	27.07±4.12	26.55±3.90	0.17
Specific gravity	1.01±0.05	1.06±0.07	0.04
Urine sugar (+)	62	24	0.18
Serum creatinine (μmol/l)	72.50±18.09	73.72±19.30	0.81

TABLE 2: COMPARISON OF CLINICAL DATA BETWEEN GOOD AND POOR 90 D PROGNOSIS GROUPS

Indicators	Good 90 d prognosis groups (n=332)	Poor 90 d prognosis groups (n=244)	p
Age (years)	67.89±6.58	69.14±7.37	0.02
Male	194	140	0.88
Complicated with moderate and severe Leukoaraiosis	71	83	0.3
Lacunar cerebral infarction	183	167	0.27
Combined with basic diseases			
Hypertension	228	127	0.19
T2DM	42	41	0.62
Coronary heart disease	30	42	0.33
Atrial fibrillation	53	57	0.3
Past history of cerebral infarction	45	41	0.67
Baseline NIHSS score (points)	6.41±1.26	15.90±3.74	0
Rt-Pa (Alteplase)	0.74±0.14	0.77±0.16	0.9
Intravenous drops of drugs to reduce Blood pressure	61	73	0.19
Time from onset to admission (h)	180.36±57.44	175.94±53.19	0.32
Hemorrhage transformation	28	64	0.02
Lesion location			
Anterior circulation	260	192	0.25
Posterior circulation	48	16	
Have both	24	36	
TOAST typing			0
Atherosclerosis of aorta	88	104	
Occlusion of arterioles	156	56	
Cardiogenic embolic	24	34	
Systolic blood pressure (mm Hg)	152.69±27.82	154.28±27.43	0.6

Diastolic pressure (mm H)	88.12±12.70	89.42±13.17	0.78
WBC count (×10^9/l)	7.25±1.63	8.01±1.98	0.03
PLT count (×10^9/l)	192.06±37.57	189.32±35.79	0.48
Baseline random blood glucose (mmol/l)	6.44±1.50	6.58±1.60	0.1
HbA1c (%)	6.31±0.72	6.70±0.86	0.27
INR	1.06±0.12	1.09±0.14	0.01
D-D (mg/l)	0.59±0.16	0.87±0.23	0
FIB (g/l)	2.71±0.54	3.10±0.70	0
PT (s)	12.07±3.40	12.89±4.22	0
APTT (s)	5.91±1.83	6.03±1.95	0.89
Specific gravity	1.02±0.02	1.04±0.03	0.48
Urine sugar (+)	24	60	0.02
Serum creatinine (μmol/l)	72.45±16.10	74.20±0.11	0.15

TABLE 3: MULTIVARIATE ANALYSIS OF RISK FACTORS FOR BLEEDING TRANSFORMATION AND POOR 90 D PROGNOSES

Indicators	B	SE	OR	95 % CI	p
Hemorrhage transformation					
Complicated with moderate and severe leukoaraiosis	-1.127	0.72	0.49	0.20-0.79	0.03
D-D	0.58	0.39	1.95	1.14-5.33	0.01
Poor 90 d prognosis					
Baseline NIHSS score	0.44	0.1	1.54	1.20-5.09	0
WBC count	0.69	0.23	1.33	1.10-3.48	0.02

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Fei Li and Weilian Wang have contributed equally to this work.

Conflict of interests:

The authors declared no conflict of interests.

REFERENCES

1. McHutchison CA, Chappell FM, Makin S, Shuler K, Wardlaw JM, Cvoro V. Stability of estimated premorbid cognitive ability over time after minor stroke and its relationship with post-stroke cognitive ability. Brain Sci 2019;9(5):117-22.
2. Wardlaw JM, Benveniste H, Nedergaard M, Zlokovic BV, Mestre H, Lee H, *et al.* Perivascular spaces in the brain: Anatomy, physiology and pathology. Nat Rev Neurol 2020;16(3):137-53.
3. Chodnicki KD, Pulido JS, Hodge DO, Klaas JP, Chen JJ. Stroke risk before and after central retinal artery occlusion in a US cohort. Mayo Clinic Proc 2019;94(2):236-41.
4. Khan M, Heiser H, Bernicchi N, Packard L, Parker JL, Edwardson MA, *et al.* Leukoaraiosis predicts short-term cognitive but not motor recovery in ischemic stroke patients during rehabilitation. J Stroke Cerebrovasc Dis 2019;28(6):1597-603.
5. Nakada T, Kwee IL. Fluid dynamics inside the brain barrier: Current concept of interstitial flow, glymphatic flow and cerebrospinal fluid circulation in the brain. Neuroscientist 2019;25(2):155-66.
6. Georgakis MK, Duering M, Wardlaw JM, Dichgans M. WMH and long-term outcomes in ischemic stroke: A systematic review and meta-analysis. Neurology 2019;92(12):e1298-308.
7. Nagaraja N, Tasneem N, Shaban A, Dandapat S, Ahmed U, Policeni B, *et al.* Cerebral microbleeds are an independent predictor of hemorrhagic transformation following intravenous alteplase administration in acute ischemic stroke. J Stroke Cerebrovasc Dis 2018;27(5):1403-11.
8. Javierre-Petit C, Schneider JA, Kapasi A, Makkinejad N, Tamhane AA, Leurgans SE, *et al.* Neuropathologic and cognitive correlates of enlarged perivascular spaces in a community-based cohort of older adults. Stroke 2020;51(9):2825-33.
9. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, *et al.* 2018 guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2018;49(3):e46-110.
10. Wardlaw JM, Smith C, Dichgans M. Small vessel disease: Mechanisms and clinical implications. Lancet Neurol 2019;18(7):684-96.

11. Liu Y, Zhang M, Chen Y, Gao P, Yun W, Zhou X. The degree of leukoaraiosis predicts clinical outcomes and prognosis in patients with middle cerebral artery occlusion after intravenous thrombolysis. Brain Res 2018;1681:28-33.
12. Levine DA, Galecki A, Kabeto M, Nallamothu BK, Zahuranec DB, Morgenstern LB, *et al.* Mild cognitive impairment and receipt of procedures for acute ischemic stroke in older adults. J Stroke Cerebrovasc Dis 2020;29(10):105083.
13. Chen Y, Yan S, Xu M, Zhong G, Liebeskind DS, Lou M. More extensive white matter hyperintensity is linked with higher risk of remote intracerebral hemorrhage after intravenous thrombolysis. Eur J Neurol 2018;25(2):380-e15.
14. McGrory S, Ballerini L, Doubal FN, Staals J, Allerhand M, Valdes-Hernandez MD, *et al.* Retinal microvasculature and cerebral small vessel disease in the Lothian Birth Cohort 1936 and mild stroke study. Sci Rep 2019;9(1):6320.
15. Mikati AG, Mandelbaum M, Sapnar S, Puri AS, Silver B, Goddeau RP, *et al.* Impact of leukoaraiosis severity on the association of time to successful reperfusion with 90-day functional outcome after large vessel occlusion stroke. Transl Stroke Res 2020;11(1):39-49.
16. Li Y, Li M, Yang L, Qin W, Yang S, Yuan J, *et al.* The relationship between blood–brain barrier permeability and enlarged perivascular spaces: A cross-sectional study. Clin Interv Aging 2019;14:871-8.
17. Yang CM, Hung CL, Su HC, Lin HJ, Chen CH, Lin CC, *et al.* Leukoaraiosis and risk of intracranial hemorrhage and outcome after stroke thrombolysis. PLoS One 2018;13(5):e0196505.

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