

# Risk factors and secondary prevention interventions for recurrence of acute cerebral infarction within half a year after rhTNK-tPA treatment

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## Abstract

**Objective:** To investigate the risk factors for the recurrence of acute cerebral infarction (ACI) within half a year after treatment with recombinant human TNK tissue-type plasminogen activator (rhTNK-tPA) and secondary prevention. **Methods:** A total of 84 patients with ACI treated with rhTNK-tPA in our hospital from March 2023 to April 2024 were selected for the study. The patients were divided into a recurrence group and a non-recurrence group according to whether they recurred within half a year after treatment. The clinical data of the two groups of patients were compared, and the risk factors of recurrent cerebral infarction were analyzed. The risk prediction model of the nomogram was constructed by incorporating the risk factors and its effectiveness was verified. Model discrimination was assessed by using the receiver operating characteristic curve (ROC). Model fit was evaluated with calibration curves. Hosmer-Lemeshow (HL) analysis was applied to assess model consistency. At the same time, the effect of secondary prevention on the recurrence rate was explored. **Results:** There were 20 patients with a recurrence of ACI, and the recurrence rate was 23.81%. Multivariate Logistic regression analysis showed that the risk factors of recurrence in patients with ACI included age  $\geq 70$  years, smoking, hypertension, diabetes, irregular or never using antiplatelet drugs ( $P < 0.05$ ). The prediction model of the nomogram was constructed according to the above indexes. The area under the curve (AUC) of the model's training and test sets for predicting recurrence within six months in patients with acute cerebral infarction was 0.918 (95%CI: 0.848-0.988) and 0.850 (95%CI: 0.703-0.997). At the same time, the HL test showed good goodness of fit ( $\chi^2 = 1.684$ ,  $P = 0.989$ ). The calibration curves indicated good agreement between the predicted values of the nomograms and the actual observed values. The recurrence rate of ACI patients who took secondary prevention measures was lower than that of patients who did not take corresponding measures ( $P < 0.05$ ).

**Conclusions:** Patients with ACI have a high recurrence rate within half a year. Age  $\geq 70$  years, smoking, hypertension, diabetes, irregular or never use of antiplatelet drugs are risk factors for recurrence. The prediction model of nomogram combined with 5 indicators can be used as an accurate and rapid clinical evaluation tool. The recurrence rate can be reduced by taking corresponding secondary prevention interventions for patients.

**Keywords:** Acute cerebral infarction, rhTNK-tPA, recurrence, high risk factors, secondary prevention

## INTRODUCTION

Acute cerebral infarction (ACI) accounts for about 69.6%-70.8% of stroke in China. The 1-year mortality of patients with ACI is 14.4%-15.4%, and the disability rate is about 33.0%.<sup>1</sup> In recent years, with the aging trend of the population and the changes in people's lifestyles, the incidence of ACI has increased year by year. Currently, ultra-early thrombolytic therapy is a common treatment option for ACI, which can reverse the vascular

occlusion and re-establish blood circulation to the brain. RhTNK-TPA is a new thrombolytic drug, which is commonly used in ACI within 4.5 h of the onset of disease and has a good thrombolytic effect.<sup>2,3</sup> However, after clinical treatment, despite taking related drugs, there is still a risk of recurrence, with the recurrence rate being highest within 5 years. The morbidity and mortality rate of recurrence is high.<sup>4,5</sup> Secondary prevention is an important measure for the prevention of ACI

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recurrence. However, most of the existing studies mostly focus on the drug treatment of ACI and lack the exploration of the recurrence risk factors and secondary prevention measures. Therefore, this study aimed to investigate the risk factors of recurrence within 6 months, in the patients taking rhTNK-tPA in the treatment of ACI, and to formulate secondary prevention measures to reduce the recurrence of stroke in these patients.

## METHODS

Eighty-four patients with ACI who received rhTNK-tPA treatment in our hospital from March 2023 to April 2024 were selected for the study. Inclusion criteria were: (1) Meet the clinical diagnostic criteria of ACI<sup>6</sup> and confirmed by cranial CT, magnetic resonance (MRI), and other examinations. (2) The patient had a first ACI and was treated with rhTNK-tPA within 4.5 hours of onset. (3) Patients' clinical data were complete and patients or family members agreed with the research. Exclusion criteria were: (1) The patient has abnormal functioning of important organs. (2) The patient has a past history of mental illness. (3) The patient has sensory, motor, and central nervous system dysfunction due to other diseases. (4) Patients withdrew from the study due to death or other reasons during the study period. The research was approved by the hospital's ethical review board.

### *Treatment method*

All patients received routine symptomatic and comprehensive treatment after admission, such as controlling intracranial pressure, antiplatelet aggregation, nutritional support, and correcting water and electrolyte imbalance. On this basis, all patients were treated with rhTNK-tPA [Manufacturer: Shiyao Group Mingfu Pharmaceutical (Guangzhou) Co., LTD.; approval number: Sinophasic Approval word S20150001; specification: 16 mg/ dose]. According to the patient's body weight, 0.25 mg/kg, the maximum dose  $\leq$  25 mg. rhTNK-tPA (16 mg/ branch) was added to 3 mL sterile water for injection and gently shaken until completely dissolved. The drug solution with a concentration of about 5.33 mg/mL was prepared, and the drug was given by a single intravenous injection for 5-10s.

### *Recurrence criteria and grouping*

Patients were followed up at least once a month by telephone or on-site follow-up for 6 months,

starting from the first day after treatment. If the patient had a recurrence, the specific time, cause, and nature of the disease were informed in time. Recurrence was determined based on the following criteria: ① The symptoms and signs of the patients were improved after discharge, but new symptoms and signs of neurological deficit occurred again on the ipsilateral or contralateral side. ② The patient was found to have a new lesion on cranial CT or MRI. During the follow-up, 84 enrolled patients were classified into recurrence and non-recurrence groups based on whether the patients had recurrence.

### *Data collection*

Clinical data of the patients in both groups were collected, including gender, age, education level, smoking, drinking, family history of stroke, history of hypertension, history of diabetes, history of hyperlipidemia, and use of antiplatelet drugs.

### *Effect of secondary prevention interventions on recurrence rates*

The effects of secondary prevention (smoking cessation, secondary prevention of antiplatelet drugs, use of blood pressure-lowering drugs/salt restriction in hypertensive patients, use of hypoglycemic drugs in diabetic patients, and use of lipid-lowering drugs in hyperlipidemia patients) on the recurrence rate of patients were analyzed. Smoking cessation was defined as ever smoking ( $\geq$ 1 cigarette/day) but having quit smoking for  $\geq$ 3 months. Specific secondary prevention nursing measures were: (1) Secondary prevention drug measures: adhere to long-term, stable medication; secondary preventive drugs are mainly antiplatelet aggregation, such as aspirin and statins. The role of aspirin was to improve blood circulation, reduce the viscosity of the blood, and prevent vascular blockage. While statins were lipid-lowering, while the stable plaque formed, the role of statin was to slow down the arteriosclerosis plaque, preventing the plaque from tearing and causing obstruction. For patients with hypertension, antihypertensive drugs such as amlodipine and nimodipine were given to lower the blood pressure. For diabetic patients, it is necessary to closely monitor and pay attention to blood glucose changes, and at the same time, metformin or acarbose and other hypoglycemic drugs should be given for treatment. (2) Scientific education: Patients were organised to participate in lectures on the subject of ACI. Information on ACI is distributed to enhance patients' self-awareness of cardiovascular disease

prevention. (3) Active exercise: Patients should mainly rest in bed during the recovery period; when the recovery period is over, they should carry out necessary exercise. Before exercising, cardiac function should be evaluated, and appropriate aerobic exercise such as walking and playing Tai Chi can be chosen according to the evaluation. (4) Lifestyle control: obese patients should be guided to lose weight, control body fat within a reasonable range, and reduce the cardiovascular risk caused by obesity. Patients were instructed to give up their alcohol and tobacco habits and maintain daily emotional stability. (5) Dietary care intervention: the dietary principle is less oil, less salt, less fat, salt daily control within 6 g, food should be light, salt, or salt-free, eat more potassium-rich foods, diet intake must be light, by eating more nuts, appropriate fish, and shrimp to maintain balanced nutrition.

### *Statistical analysis*

Data were analyzed using SPSS 23.0 statistical software. Measurement data were expressed as mean  $\pm$  standard deviation ( $\bar{x}\pm s$ ), and inter-group comparison was performed using the T-test of two independent samples. Count data were expressed as the number of cases and percentage[n(%)], and were compared between groups using the  $\chi^2$  test or Fisher exact probability method. Logistic regression analysis was employed to analyze the influencing factors. Differences were considered statistically significant at  $P < 0.05$ . The influencing factors were introduced into RStudio software, which was employed to construct a risk prediction model for the nomogram. Model discrimination was assessed by ROC curves and calibration curves. The consistency of the predictive models of the nomograms was assessed using Hosmer-Lemeshow analysis, with  $P > 0.05$  representing good consistency.

## **RESULTS**

### *Comparison of general information*

According to whether the patients had a recurrence, a total of 20 patients (23.81%) were obtained in the recurrence group, and 64 patients were in the non-recurrence group. Univariate analysis showed that the related factors of recurrence in patients with ACI were age, drinking, smoking, hypertension, diabetes, hyperlipidemia, and use of antiplatelet drugs ( $P < 0.05$ ), as shown in Table 1.

### *Multivariate logistic regression analysis of recurrence in patients with ACI*

In this study, the dependent variable was whether the patients with ACI had recurrence after six months (recurrence = 1, no-recurrence = 0). Variables with significance in the univariate analysis were incorporated as independent variables in the logistic regression analyses, and the independent variable assignments are shown in Table 2. The results indicated that the risk factors for recurrence in patients with ACI were age  $\geq 70$  years, smoking, hypertension, diabetes, irregular or never using antiplatelet drugs ( $P < 0.05$ ), as shown in Table 3.

### *Construction of nomogram risk prediction model*

Based on the results of multivariate analysis, the above-mentioned factors affecting the recurrence of ACI patients were included in the risk assessment, and a nomogram risk model was established (Figure 1). To further validate the predictive efficacy of the model, the ROC curves are plotted for the training and test sets, respectively (Figure 2). The model had high prediction accuracy in both the training and test set, with AUC of 0.918 (95%CI: 0.848-0.988) and 0.850 (95%CI: 0.703-0.997), respectively. The HL test revealed good agreement ( $\chi^2 = 1.684$ ,  $P = 0.989$ ). The calibration curves (Figure 3) indicate that the predicted probabilities of the nomograms are in good agreement in both the training and test sets.

### *Effect of secondary prevention on recurrence rate of ACI*

The recurrence rate within six months of ACI patients who took secondary prevention after rhTNK-tPA treatment was lower than that of patients who did not take corresponding secondary prevention, and the difference was statistically significant ( $P < 0.05$ ), as shown in Table 4.

## **DISCUSSION**

Cerebral infarction is a common disease threatening human health. In recent years, with the accelerated aging of China's population and unhealthy lifestyles<sup>7-9</sup>, the incidence of ACI has increased and has a high recurrence rate.<sup>10-12</sup> Most patients with recurrent ACI have a poor prognosis, leading to adverse outcomes such as severe disability, and causing a huge burden on the patient's family and society.<sup>13-15</sup> Akagi *et al.*<sup>16</sup> found that the risk of cerebral infarction

**Table 1: Univariate analysis of relapse related factors [n(%)]**

Influencing factor	Non-recurrence group (n=64)	Recurrent group (n=20)	$\chi^2$ value	P value
Gender				
female	30(46.87)	8(40.00)	0.291	0.590
male	34(53.13)	12(60.00)		
Age (yrs)				
<70	45(70.31)	9(45.00)	4.253	0.039
≥70	19(29.69)	11(55.00)		
Cultural level				
Primary school	19(29.69)	8(40.00)	1.216	0.545
Junior and senior high schools	24(37.50)	5(25.00)		
College or above	21(32.81)	7(35.00)		
Smoking history				
no	47(73.44)	9(45.00)	5.545	0.019
yes	17(26.56)	11(55.00)		
Family history of stroke				
no	34(53.13)	10(50.00)	0.060	0.807
yes	30(46.87)	10(50.00)		
Drinking history				
no	44(68.75)	8(40.00)	5.341	0.021
yes	20(31.25)	12(60.00)		
Hypertension				
no	45(70.31)	8(40.00)	6.013	0.014
yes	19(29.69)	12(60.00)		
Hyperlipemia				
no	46(71.87)	8(40.00)	6.743	0.009
yes	18(28.13)	12(60.00)		
Diabetes				
no	45(70.31)	7(35.00)	8.057	0.005
yes	19(29.69)	13(65.00)		
Use of antiplatelet drugs				
Regular use	50(78.13)	7(35.00)	12.993	<0.001
Irregular or never used	14(21.87)	13(65.00)		

**Table 2: Assignment of argument variables**

Factors	Assign
Age	<70= 0; ≥70= 1
Smoking history	No = 0; Yes = 1
Drinking history	No = 0; Yes = 1
Hypertension	No = 0; Yes = 1
Hyperlipemia	No = 0; Yes = 1
Diabetes	No = 0; Yes = 1
Use of antiplatelet drugs	Regular use = 0; Irregular or never used = 1

in patients with low adherence (adherence rate <80%) was 9.69 times (95%CI: 3.86-24.3) higher than that in patients with good adherence (compliance rate 81%-100%). It is suggested that improving patients' adherence to secondary prevention medications may reduce the risk of adverse prognosis. Therefore, it is important to improve the management of ACI, explore its high-risk factors for recurrence, and actively adopt secondary prevention.<sup>17-19</sup>

In terms of risk factors for recurrence in patients with ACI, this study identified age ≥70

**Table 3: Multivariate logistic regression analysis of relapse after treatment**

Factors	B	SE	Wald	P value	OR value (95%CI)
Age	2.106	0.835	6.362	0.012	8.212(1.599-42.176)
Smoking history	1.814	0.841	4.654	0.031	6.136(1.181-31.892)
Drinking history	0.901	0.750	1.443	0.230	2.461(0.566-10.698)
Hypertension	1.779	0.782	5.176	0.023	5.925(1.279-27.440)
Hyperlipemia	1.036	0.725	2.041	0.153	2.817(0.680-11.664)
Diabetes	1.884	0.788	5.707	0.017	6.577(1.403-30.843)
Use of antiplatelet drugs	1.925	0.769	6.261	0.012	6.857(1.518-30.982)
Constant	-6.340	1.449	19.132	<0.001	

years, smoking, comorbid hypertension, diabetes mellitus, and irregular or never use of antiplatelet agents were risk factors for recurrence within six months in patients with ACI treated with rhTNK-tPA. Age is an uncontrollable factor. Studies<sup>20</sup> point out that after the age of 50, the incidence of cardiovascular and cerebrovascular diseases can more than double with every 10 years of increase. A study by Liu<sup>21</sup> indicated that the recurrence rate of ACI in patients aged >65 years was 1.175 times higher than in patients aged <65 years. The present investigation found that smoking was a high-risk factor for recurrence in patients with ACI. A retrospective cohort study<sup>22</sup> in Korea also found that smoking was a predictor of cerebral infarction in men. Cigarettes contain nicotine and other substances that can cause excitation of the vasomotor center after entering the human body, a significant increase in peripheral vascular resistance and an increase in blood viscosity, leading to an increased risk of recurrence of ACI. In addition, smoking leads to an increase in carbon monoxide levels in the patient's body,

leading to damage to their vascular endothelial cells and facilitating platelet aggregation<sup>23</sup>, which ultimately increases the risk of recurrence of cerebral infarction. This study also found that hypertension was an independent risk factor for recurrence in patients with ACI. Long-term high blood pressure can cause cerebral small artery spasms, a continuous increase in intravascular pressure accompanied by internal damage and lipid accumulation, cause atherosclerosis, and promote the recurrence of cerebral infarction. Del *et al.*<sup>24</sup> studies also identified uncontrolled systolic blood pressure as a risk factor for new cerebral infarctions in the stenotic vascular region weeks after the cerebral infarction event. Comorbid diabetes is also an independent risk factor for recurrence in patients with ACI. Studies have shown that the adhesion ability of red blood cells in diabetic patients is enhanced due to changes in the body's hemorheology. At the same time, the platelet aggregation ability of patients was significantly increased, and the anticoagulation mechanism of the body was

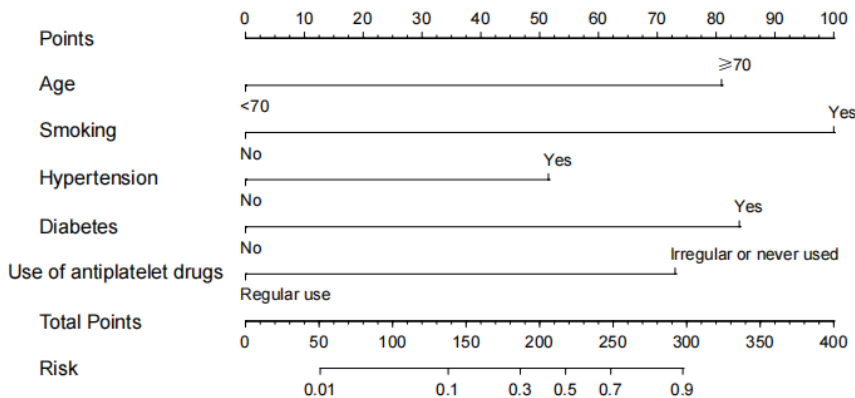


Figure 1. Nomogram prediction model

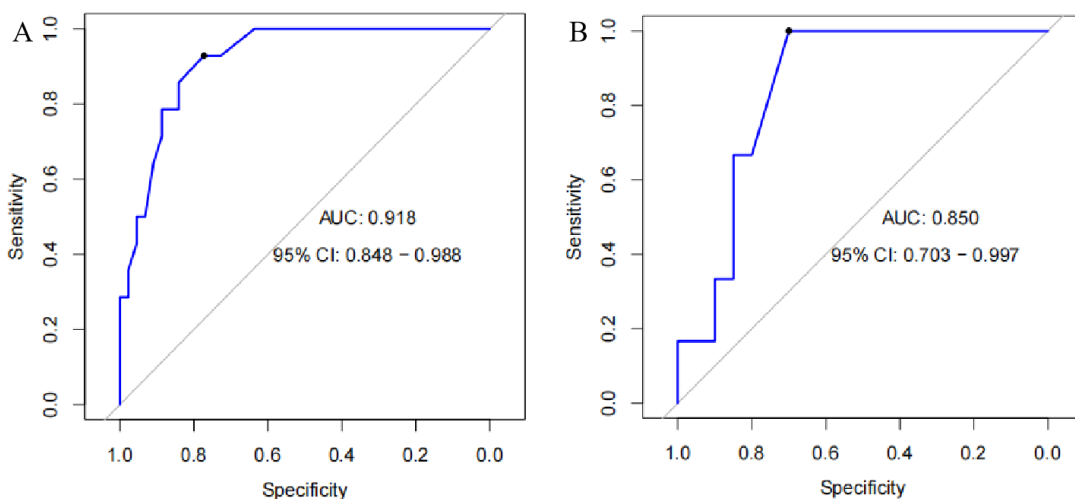


Figure 2. ROC curve of the nomogram for predicting recurrence of acute cerebral infarction  
 A: ROC curve of the training set; B: ROC curve of the test set

significantly weakened. The patient’s blood is in a hypercoagulable state, which can significantly increase the recurrence rate of cerebral infarction.<sup>25</sup> Irregular or never use of antiplatelet agents is likewise an independent risk factor for recurrence in ACI patients. Antiplatelet drugs are important drugs to prevent the recurrence of ACI in clinical practice. Common antiplatelet drugs include aspirin and alprostadi. One study<sup>26</sup> noted that intervention with antiplatelet agents is effective in reducing the recurrence rate in patients with ACI, but irregular or never use of antiplatelet agents reduces the effectiveness of secondary prevention and leads to an increased risk of ACI recurrence. In addition, this study constructed a nomogram risk prediction model based on risk

factors and plotted ROC curves to evaluate model discrimination. The nomogram was composed of age, smoking, hypertension, diabetes, irregular or never use of antiplatelet drugs, and the results confirmed its high reliability and clinical utility.

This study revealed that the recurrence rate of ACI patients who took secondary prevention within half a year was lower than those who did not take secondary prevention, which was consistent with the study of Yu *et al.*<sup>27</sup> The results suggest that secondary prevention are beneficial to reduce the risk of recurrence in patients with ACI. It is suggested that by intervening in these risk factors, guiding patients to take preventive drugs, improving their living habits, and increasing their rehabilitation exercises, the recurrence of ACI can

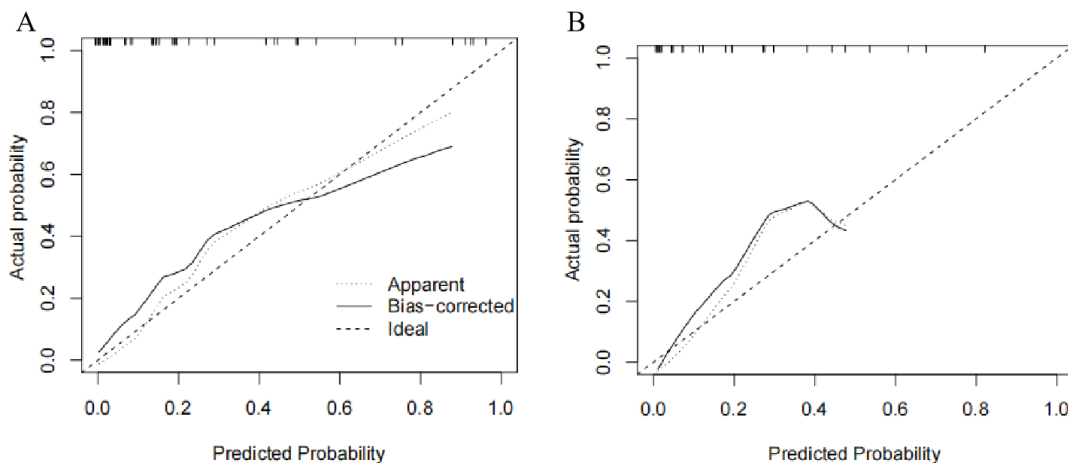


Figure 3. Calibration curves for the predictive effect of the nomogram model  
 A: Training set calibration curve; B: Test set calibration curve

**Table 4: Effects of secondary prevention interventions on recurrence rates in patients with ACI**

Secondary precaution	n	Whether to implement	n	Number of recurrences (n)	Recurrence rate (%)	P value
Smoking cessation	28	yes	7	0	00.00	0.023
		no	21	11	52.38	
Use of antiplatelet drugs	84	yes	52	7	13.46	0.005
		no	32	13	40.63	
Salt restriction in hypertensive patients	31	yes	11	1	9.09	0.020
		no	20	11	55.00	
Hypertensive patients take antihypertensive drugs	31	yes	10	1	10.00	0.046
		no	21	11	52.38	
Diabetics take hypoglycemic drugs	32	yes	13	2	15.38	0.012
		no	19	12	63.16	
Patients with hyperlipidemia take lipid-lowering drugs	30	yes	9	1	11.11	0.049
		no	21	11	52.38	

be reduced to a certain extent, as well as lowering blood viscosity. Previous studies<sup>28</sup> have confirmed that age, history of coronary artery disease, and smoking history were risk factors for recurrence in patients with ACI after application of secondary prevention with antiplatelet agents. Among them, antiplatelet aggregation drugs can better improve the hemorheological state of the body, promote continuous blood perfusion in the brain region, and reduce the risk of recurrence. Therefore, long-term, regular administration of antiplatelet drugs is important to reduce the risk of ACI recurrence. Clinical nursing staff can implement “data bombardment” education to patients through paper charts, electronic charts, and other forms to strengthen their cognizance of the current situation of ACI recurrence. At the same time, the “relapse-promoting factors” and their mechanisms of action were summarized for the patients with ACI. If the patient has a previous history of smoking and alcohol consumption, he or she should be advised to abstain from smoking and alcohol after the first ACI. Patients with a previous history of hypertension should have their blood pressure controlled after the first acute cerebral infarction and adhere to the use of antiplatelet agents at regular intervals. For older patients with coronary heart disease and low education levels, a frequent follow-up mechanism should be established, and patients should be regularly assessed and given secondary prevention education to reduce the risk of ACI recurrence. In addition, patients with

cerebral infarction should not only pay attention to physical function rehabilitation training, but also carry out psychological intervention at an early date. By strengthening the patients’ and their families’ knowledge about the importance of secondary stroke prevention medication and the efficacy of the medication, and by making regular telephone follow-up visits, we can improve the patients’ compliance.

To conclusion, rhTNK-tPA treated ACI patients still have the risk of recurrence. Clinicians should strengthen the identification of risk factors, and take secondary preventive nursing countermeasures to reduce the recurrence rate of patients.

## DISCLOSURE

Data availability: The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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