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Analysis of the Risk Factors for the Recurrence of Ischemic Stroke with Diabetes Mellitus and Establishment of Cox's Regression Model and the Personal Prognosis Index in Two Years of Follow-Up

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Abstract

Background: Ischemic stroke is a major cause of disability and mortality in patients with type 2 diabetes mellitus (T2DM), and diabetic stroke has a high recurrence rate.
Objectives: This prospective cohort study aimed at investigating the risk factors and establishing Cox's regression model and personal prognosis index for the recurrence of ischemic stroke at a two-year follow-up in T2DM patients.
Methods: T2DM patients with ischemic stroke, who were consecutively admitted to the Neurology Department of North China University of Science and Technology Affiliated Hospital between January 1, 2015, and December 31, 2015, were retrospectively reviewed. These cases were followed up since the onset of ischemic stroke for 2 years. Univariate and multivariate Cox's proportional hazard regression model was used to analyze risk factors associated with the recurrence rate. Thus, a recurrence model and personal prognosis index were set up.
Results: During the follow-up period, 44 cases relapsed. Furthermore, the 1-year recurrence rate was 16.48%, while the 2-year recurrence rate was 24.18%. The univariate and multivariate Cox proportional hazard regression model revealed that the independent risk factors associated with recurrence were TOAST criteria (X_1) (RR = 1.663; 95% CI = 1.015 - 2.760, P = 0.032), hypertension grade (X_2) (RR = 1.897; 95% CI = 1.097 - 3.280, P = 0.022), duration of diabetes mellitus (X_3) (RR = 1.151; 95% CI = 1.009 - 1.991, P = 0.039), total cholesterol (X_4) (RR = 1.13; 95% CI = 1.006 - 1.876, P = 0.035), and Essen stroke risk score (ESRS) (X_5) (RR = 2.055; 95% CI = 1.357 - 3.134, P = 0.001). The personal prognosis index of the recurrence model was as follows: $PI = 0.504\ X_1 + 0.640\ X_2 + 0.345\ X_3 + 0.759\ X_4 + 0.823\ X_5$.
Conclusions: TOAST criteria, hypertension grade, duration of diabetes mellitus, total cholesterol, and ESRS were the independent risk factors associated with the recurrence of ischemic stroke with diabetes mellitus. The recurrence model and personal prognosis index equation were successfully established.

Keywords: Ischemic Stroke, Recurrence Rate, Risk Factors, Type 2 Diabetes Mellitus, Cox Proportional Hazard Regression Model

1. Background

Diabetic ischemic stroke is a new concept proposed based on the etiology of stroke in recent years, which refers to ischemic cerebrovascular disease complicated by diabetes, and is mostly induced by microvascular and small vessel infarction (1). The disease has mild recurrent and progressive clinical symptoms (2). Diabetic ischemic stroke is the main cause of disability and mortality in diabetic patients (3). The recurrence rate of diabetic stroke is very high (4). Previous epidemiological studies have revealed that many risk factors are correlated to the recurrence of diabetic ischemic stroke (5-8). However, most of these studies are retrospective studies with small sample sizes and low efficiency, which are not effective in the prediction of recurrent stroke in diabetic patients. Therefore, the present cohort study of 201 patients with newly diagnosed diabetic ischemic stroke was carried out through two years. The risk factors for the prognosis of recurrence were identified, and a short-term recurrence prediction model was established. Our results may provide a scientific basis for the screening of high-risk populations and the development of individualized, standardized, and preventive therapies.

2. Methods

2.1. Subjects

The sample size was calculated based on the conventional sample size formula for the cohort study and the estimated prevalence of this disease. A test power of 90% at a significance level of 0.05 was chosen for sample size calculation. In this prospective cohort study, data were collected from 210 patients with primary diabetic ischemic stroke, who were diagnosed in the Department of Neurology in the Affiliated Hospital of North China University of Science and Technology and treated in 5 inpatient centers of our hospital in Tangshan city, Hebei Province, China from January 1, 2015, to December 31, 2015. The inclusion criteria were as follows: (1) patients who met the diagnostic criteria for ischemic stroke formulated in the "Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke, China 2014" and confirmed by the head computed tomography (CT) or magnetic resonance imaging (MRI); (2) patients who met the diagnostic criteria of diabetes mellitus developed by the World Health Organization (WHO); (3) patients who were $\geq$ 18 years old; (4) patients who visited a doctor within three days after onset. The exclusion criteria were as follows: (1) patients with the transient ischemic attack, hemorrhagic stroke, mixed stroke, and brain tumor-associated hemorrhage (n = 6); (2) patients with malignancy, hematopathy, and collagenopathy (n = 1); (3) patients with serious heart, liver, lung, and kidney diseases (n = 2); (4) patients with drug abuse and seizure (n = 0). Thus, a total of 201 patients who were eligible for this study were included. All subjects provided informed consent prior to enrollment into the present study. The present study was approved by the Ethics Committee of the Affiliated Hospital of North China University of Science and Technology (ID: 20141211, December 11, 2014).

2.2. Questionnaire Design

A unified questionnaire was compiled using the EpiData 3.1 software. To avoid too many missing values in the study, the variables in the questionnaire were chosen according to domestic and foreign studies on risk factors for the recurrence of ischemic stroke and revised based on the actual practice experience of our hospital (9). The main contents included the following items: (1) basic personal data: gender, age, height, body mass, marital status, culture and education, and occupation; (2) previous history of disease: history of hypertension, diabetes, heart disease, transient ischemic attack, and peripheral arterial disease; (3) family history, smoking history, and drinking history; (4) laboratory data, imaging data, diagnosis, and treatment during hospitalization; (5) clinical characteristics, National Institutes of Health Stroke Scale (NIHSS) score on admission, Essen Stroke Risk Scale (ESRS) score and modified Rankin scale (MRS) score at discharge.

2.3. Follow-Up Data

Recurrence criteria of diabetic ischemic stroke were as follows: (1) At one week after stroke, symptoms, and signs were stabilized or improved, the signs of new neurological damage occurred or original signs were aggravated; (2) the appearance of new ischemic lesions and space-occupying lesions without edema or bleeding, which was confirmed by CT (256CT, Philips, Netherlands) or MRI (Ingenia 3.0T, Philips, Netherlands) examinations. The CT scanner and MRI equipment were calibrated before each examination, and the results were reviewed by an experienced radiologist. At the onset of symptoms as the starting point and the time of recurrence or loss to visit the patients as the endpoint, the follow-up was performed once a month and terminated on January 1, 2017. A follow-up form was separately designed, and the forms of telephone follow-up and face-to-face inquiries were adopted. The follow-up contents included basic physical examination items and post-discharge treatment (including drug use, blood pressure, blood glucose, and blood lipid control). The blood glucose and lipid profile were detected using a biochemistry analyzer (Beckman Coulter, Shanghai, China). If the patient relapsed, the specific time and cause were considered. According to the purpose of the study, the outcome event was defined as the recurrence of diabetic ischemic stroke.

2.4. Statistical Analysis

Data were statistically analyzed using SPSS 16.0 software. Categorical variables were presented as numbers (percentages). Continuous variables at baseline in both groups were normally distributed and expressed as mean $\pm$ standard deviation. Mann-Whitney U test and chi-squared test were used to identify baseline differences in clinical variables between patients with or without recurrent stroke. The recurrence rate was analyzed using the Kaplan-Meier method. The regression model included clinical predictors of recurrence with a univariate P value $<$ 0.05 as independent variables. The risk of subsequent stroke to each variable was determined by multivariable Cox regression analysis. $P < 0.05$ was considered statistically significant. Then, the prognostic index equation was established and the receiver operating characteristic (ROC) was drawn.

3. Results

3.1. General Information of the Patients

The data of 201 eligible patients were collected. Among these patients, five patients had incomplete data, and

three patients died during hospitalization (since these patients died of initial ischemic stroke or other causes, they were not included in the analysis). Finally, a total of 193 patients were studied in the present study, of whom 99 patients were male (51.3%). The patients' age range was 30-81 years, with the average age of 60.2 $\pm$ 10.1 years. The variables at baseline in both groups were normally distributed.

3.2. Follow-Up Conditions

At the end of the follow-up period, 11 patients (5.7%) lost the follow-up (Figure 1). The mean duration of the follow-up was 254.78 $\pm$ 17.8 days. The investigators conducted a balanced test on the basic characteristics of the follow-up group, and the group lost the follow-up. The results revealed that the differences in gender, age, marital status, educational level, history of hypertension, history of diabetes, history of heart disease, family history of stroking and trial of org 10 172 in acute stroke treatment (TOAST) classification between these two groups were not statistically significant ($P > 0.05$). Therefore, the investigators considered that loss to follow-up had not a considerable impact on the study results. A total of 182 patients completed the follow-up, and 44 patients recurred during this period. Furthermore, the 1-year recurrence rate was 16.48% and the 2-year recurrence rate was 24.18%. These patients were divided into two groups, according to recurrence: recurrent group (n = 44) and non-recurrence group (n = 138).

3.3. Univariate Analysis of Risk Factors for the Recurrence of Diabetic Ischemic Stroke

The distribution of the main risk factors in these two groups was compared. The result revealed that the differences in these 11 factors, such as hypertension grade, history of diabetes, history of coronary heart disease, TOAST classification, aspirin use on admission, duration of diabetes, red blood cell (RBC) count, hemoglobin, low-density lipoprotein (LDL), total cholesterol (TC), and ESRS score were statistically significant between these two groups ($P < 0.05$, Table 1).

3.4. Multivariate Stepwise Cox's Regression Analysis of the Risk Factors for the Recurrence of Diabetic Ischemic Stroke

According to the effects of the factors with statistical significance difference in the univariate analysis, the forward LR method in Cox's proportional hazard model was used for the multivariate analysis. Factors that were finally included in the main effect equation were as follows: TOAST classification, hypertension grade, duration of diabetes, TC and ESRS score and according to the results, they were independent risk factors for the recurrence of diabetic ischemic stroke (Table 2). The fitted recurrence model of diabetic ischemic stroke was as follows: $h(t) = h_0(t) \exp(0.504 X_1 + 0.640 X_2 + 0.345 X_3 + 0.759 X_4 + 0.823 X_5)$ (h(t): risk function; $h_0(t)$: benchmark risk function; X_1: TOAST classification; X_2: hypertension grade; X_3: diabetes duration; X_4: TC; X_5: ESRS score). Based on Cox's proportional hazard regression model, the prognosis index (PI) of the exponential equation was established through the standardized transformation of the observed variables: $PI = 0.504 X_1 + 0.640 X_2 + 0.345 X_3 + 0.759 X_4 + 0.823 X_5$. The risk of relapse could be predicted by introducing the observed variables (risk factors). The smaller PI could cause the lower the risk of recurrence, whereas the greater PI could cause the higher the risk of recurrence.

3.5. The ROC Curve Analysis

Using the individual PI as the test variable and the actual follow-up results as state variables, the ROC curve was drawn (Figure 2). The results revealed that the area under the curve (AUC) was 0.796 (95% CI = 0.661 - 0.873, P = 0.002), the Youden's index was 0.474, and the corresponding PI was 1.237. Therefore, 1.237 was determined as the cut-off point. That is when the PI is $\geq$ 1.237, the probability of recurrence is high. Also, the negative and positive predictive values were 0.731 and 0.785, respectively. The negative and positive likelihood ratios were 0.629 and 0.702, respectively.

4. Discussion

The high recurrence rate of diabetic ischemic stroke has been reported. The risk of recurrence of diabetic ischemic stroke was 12 times more than non-diabetic ischemic stroke (10, 11). A cohort study conducted by Putaala et al. revealed that (12) the cumulative recurrence rate of diabetic ischemic stroke was 29.7%. Consistently, in the present study, the 1-year recurrence rate was 16.48%, while the 2-year recurrence rate was 24.18%.

Although the TOAST classification was used in patients with diabetic ischemic stroke, cohort studies on TOAST classification and prognosis (including relapse) have been rarely conducted. The study conducted by Putaala et al. also revealed that the type of cerebral infarction in diabetic patients was different from that of non-diabetic stroke patients, and atherosclerotic thrombotic cerebral infarction and multiple cerebral infarctions were more common (12). The reason may be related to the metabolic abnormalities in proteins, lipids, and glucose in diabetics. The lesions on large vessels in the brain, multiple branches, and multiple segments of brain micrangium lead to the dystrophy, degeneration, and necrosis of the wall, as well as the fibrinolytic system dysfunction of distal small vessels (13). Another study revealed that the sites and types of diabetic

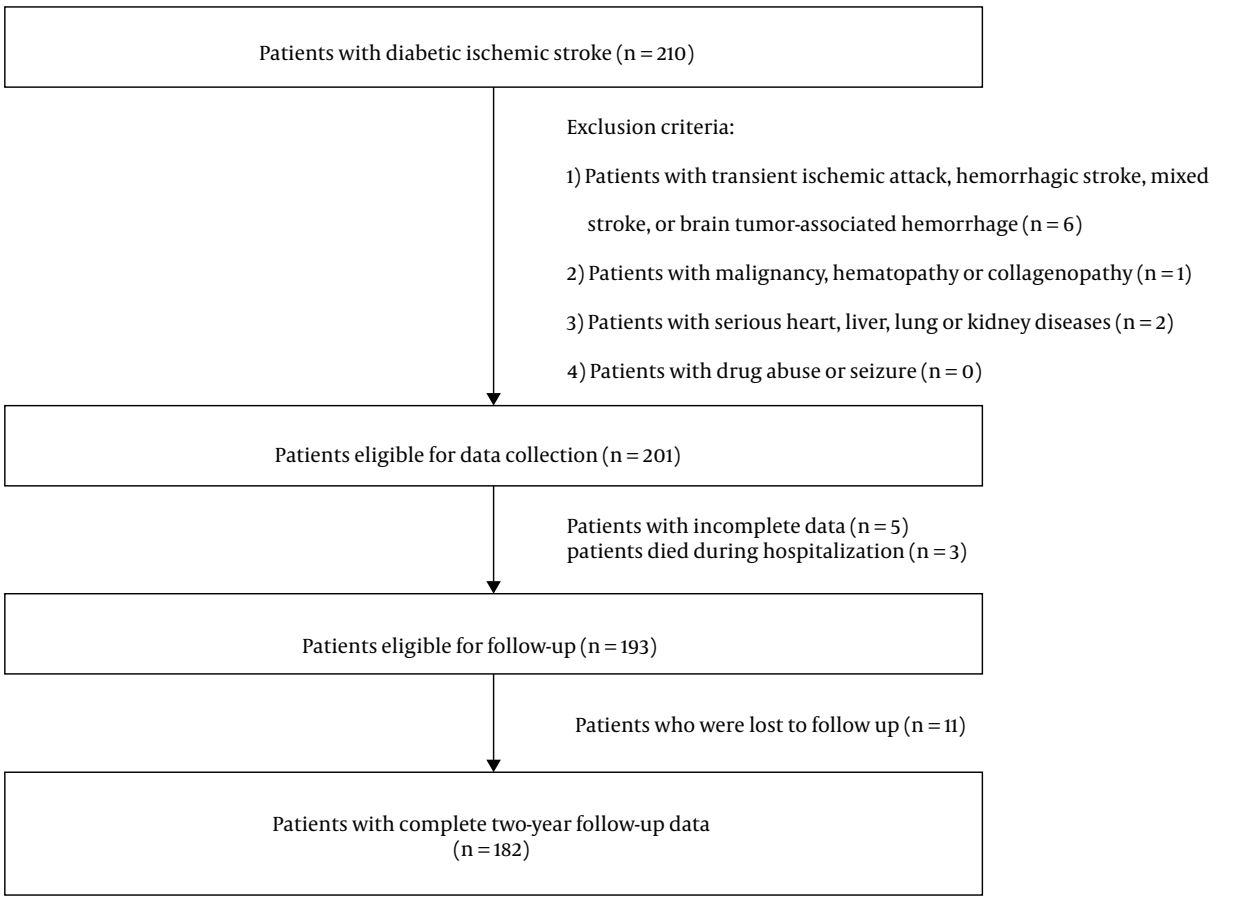

Figure 1. Flow chart of the patient recruitment

cerebral infarction were different from non-diabetic cerebral infarction. The former mostly is manifested as posterior circulation and lacunar cerebral infarction, while the latter is mostly manifested as complete or partial anterior circulation infarction (14, 15). Our results revealed that the type of diabetic ischemic stroke mainly caused large-artery atherosclerosis and arteriole occlusion. In the non-recurrence group, large-artery atherosclerosis was observed in 65.2% and arteriole occlusion in 29.7% of the cases. In the recurrence group, large-artery atherosclerosis was observed in 40.9% and arteriole occlusion in 47.7% of the cases. The univariate and multivariate Cox's regression analysis revealed that the TOAST classification was correlated with the recurrence of diabetic ischemic stroke and was an independent risk factor for recurrence.

Hypertension and diabetes have been considered to have a synergistic effect on the recurrence of ischemic stroke (16-18). In patients with diabetic ischemic stroke, insulin resistance may play a decisive role in the pathogenesis of hypertension (19). First, the sensitivity to insulin in the peripheral organs of diabetic patients is reduced, but the islet cells still preserve insulin secretion resulting in compensatory hyperinsulinemia and promoting hypertension (20). Second, hyperglycemia also promotes the reabsorption of sugar in the proximal renal tubules, leading to an increase in the effective osmotic pressure of blood circulation (21). Also, hyperglycemia can promote the proliferation of vascular smooth muscle cells, resulting in the coexistence of hypertension and hyperglycemia (22). The synergistic relationship between hypertension and diabetes with the recurrence of ischemic stroke has been rarely reported. The results of the present cohort study revealed that both hypertension grade (RR = 1.897, 95% CI = 1.097 - 3.280) and diabetes duration (RR = 1.151, 95% CI = 1.009 - 1.991) were independent risk factors for the recurrence of diabetic ischemic stroke. This suggests that their combined action leads to the recurrence of stroke.

This observation is similar to that in diabetes patients, who are easily complicated with hypertension. Furthermore, the incidence of hyperlipidemia in diabetic patients

Table 1. Univariate Analysis of the Risk Factors for Recurrent Ischemic Stroke with Diabetes Mellitus (N = 182)

Variables	Recurrence (N = 44)	Non-Recurrence (N = 138)	χ^2/t	P
Gender			3.607	0.058
Male	17 (59.1)	76 (41.3)		
Female	27 (40.9)	62 (58.7)		
Marriage			0.101	0.751
Married	42 (95.5)	130 (94.2)		
Unmarried, divorced, widowed	2 (4.5)	8 (5.8)		
BMI, kg/m^2			0.486	0.784
< 24.0	12 (27.3)	37 (26.8)		
24.0 ~ 27.9	22 (50.0)	76 (55.1)		
≥ 28.0	10 (22.7)	25 (18.1)		
History of hypertension			0.202	0.653
No	12 (27.3)	33 (23.9)		
Yes	32 (72.7)	105 (76.1)		
Hypertension grade			4.458	0.035
Levels 1 and 2	4 (12.5)	28 (26.7)		
Level 3	28 (87.5)	77 (73.3)		
Duration of hypertension (year)	6.86 ± 8.005	4.76 ± 6.082	1.842	0.067
Mean arterial pressure (mmHg)	111.41 ± 11.685	111.53 ± 14.245	0.046	0.964
History of TIA			0.736	0.391
No	43 (97.7)	137 (99.3)		
Yes	1 (2.3)	1 (0.7)		
Family stroke history			2.887	0.089
No	6 (13.6)	8 (5.8)		
Yes	38 (86.4)	130 (94.2)		
Progress			0.885	0.347
No	35 (79.5)	118 (85.5)		
Yes	9 (20.5)	20 (14.5)		
Diagnostic history of diabetes			6.795	0.009
Newly diagnosed diabetes	4 (9.1)	39 (28.3)		
Diabetes on admission	40 (90.9)	99 (71.7)		
Duration of diabetes (year)	6.70 ± 5.857	3.88 ± 4.588	3.310	0.001
History of coronary heart disease			5.440	0.020
No	33 (75.0)	123 (89.1)		
Yes	11 (25.0)	15 (10.9)		
TOAST classification				
Aortic atherosclerosis	18 (40.9)	90 (65.2)	8.656	0.034
Cardioembolism	4 (9.1)	5 (3.6)		
Small artery occlusion	21 (47.7)	41 (29.7)		
Other etiological types	1 (2.3)	2 (1.4)		
LDL (mmol/L)	3.58 ± 1.101	3.11 ± 0.909	8.892	0.001
TC (mmol/L)	5.69 ± 1.301	5.10 ± 1.008	5.087	0.003
NIHSS score on admission	4.55 ± 3.487	3.93 ± 4.055	0.907	0.366
MRS score at discharge	2.02 ± 1.263	1.68 ± 1.254	1.569	0.119
ESRS score	2.67 ± 1.229	1.68 ± 1.254	2.272	0.024

Abbreviations: BMI, body mass index; ESRS, essen stroke risk score; LDL, low-density lipoprotein; MRS, modified rankin scale; NIHSS, national institutes of health stroke scale; TC, total cholesterol; TIA, transient ischemic attack; TOAST, trial of org 10 172 in acute stroke treatment.
[a] Data are shown as No. (%) or mean ± SD.

is also high, and lipid metabolism disorders accelerate vascular injury (23-26). The collaborative atorvastatin diabetes study (CARDS) also revealed that high TC level was correlated with ischemic stroke recurrence, and taking

Table 2. Multivariable Cox Regression Analysis of the Risk Factors for Recurrent Ischemic Stroke with Diabetes Mellitus

Variables	HR (95% CI)	Regression Coefficient	SE	P
TOAST classification	1.663 (1.015 ~ 2.760)	0.504	0.244	0.032
Hypertension grade	1.897 (1.097 ~ 3.280)	0.640	0.279	0.022
Duration of diabetes	1.151 (1.009 ~ 1.991)	0.345	0.142	0.039
Total cholesterol	1.130 (1.006 ~ 1.876)	0.265	0.125	0.035
ESRS Score	2.055 (1.357 ~ 3.134)	0.823	0.211	0.001

Abbreviations: ESRS, essen stroke risk score; TOAST, trial of org 10 172 in acute stroke treatment.

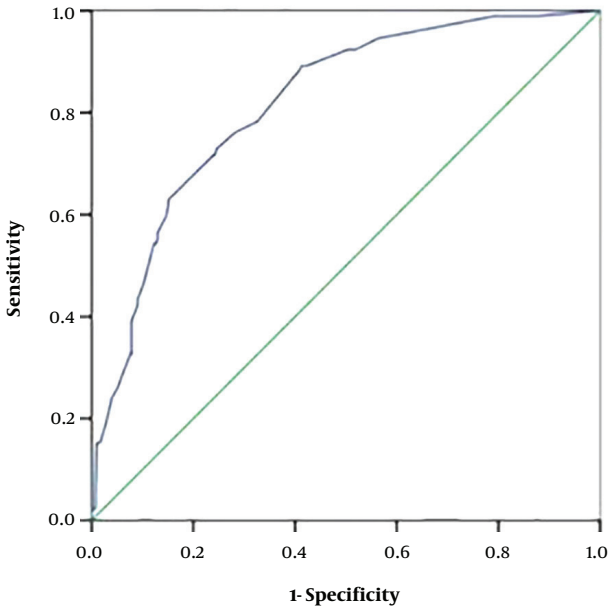

Figure 2. Receiver operating characteristic (ROC) curve analysis of the recurrent ischemic stroke with diabetes mellitus prediction model

statins to regulate blood lipids can reduce the recurrence of stroke. Another study revealed that taking statins reduced the risk of stroke by approximately 21% in diabetic patients, and by only 16% in non-diabetic patients. It is evident that patients with diabetes benefit more from statins therapy, which makes lipid-lowering therapy more important in diabetes patients (27-30). In the present study, according to the univariate analysis, the differences in TC and LDL were statistically significant, but the multivariate analysis revealed that LDL was eliminated, while TC was included. Furthermore, the risk of recurrence of diabetic ischemic stroke in the group with high TC was 13% higher than that in the group with normal TC (RR = 1.130, 95% CI = 1.006 - 1.876).

The strong point of this study was using the standardized method to evaluate patients' characteristics, including TOAST criteria, hypertension grade, duration of diabetes mellitus, TC level, and ESRS, and the establishment of a Cox's regression model for the prognosis of stroke recurrence in diabetic patients. There were some limitations to this study. First, the patients were recruited from five inpatient centers of the Tangshan city, and the sample size was relatively small. Also, the unequal sample size between the recurrent and non-recurrent groups may lead to bias in the estimation of sensitivity and specificity. Further studies with a larger sample size covering a wider geographic area in China are needed to confirm the results of the current study.

In conclusion, ESRS is a commonly used tool for predicting the recurrence risk of stroke. ESRS is mainly used to predict the recurrence risk of cardiovascular and cerebrovascular events in patients with ischemic stroke and transient ischemic attack. Studies on the prediction of the recurrence risk of diabetic ischemic stroke using ESRS have rarely been conducted. In the present study, ESRS was selected in both the univariate and multivariate Cox's proportional hazard models, which was found as an independent risk factor for the recurrence of ischemic stroke (RR = 2.055, 95% CI = 1.357 - 3.134). The higher the score is, the greater the risk of recurrence becomes.

Footnotes

Authors' Contribution: AYC and WYX conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. JYR, LYZ, FJY, FJY, SSX, and CJJ designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript. AYC coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conflict of Interests: All authors have contributed significantly to the manuscript and declare that the work is original and has not been submitted or published elsewhere. None of the authors have any financial disclosure or conflict of interest.

Ethical Approval: This study was conducted in accordance with the declaration of Helsinki. This study was ap-

proved by the Ethics Committee of North China University of Science and Technology Affiliated Hospital.

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Informed Consent: Written informed consent was obtained from all participants

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