Risk Factors Associated with Recurrence within 90 Days of Ischemic Stroke Onset in Chinese Medicine Hospital: A National Cross-Sectional Study in China

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Abstract

Objective: The short- and long-term risk factors for stroke recurrence may be different. This study is aimed to determine the risk factors for recurrence within 90 days in patients with ischemic stroke in China. Method: This was a cross-sectional registry-based study in Chinese medicine hospitals from eight provinces and ten cities in China between November 3, 2016 and May 28, 2018. Two thousand one hundred and twenty patients with ischemic stroke aged between 35 and 80 years. Stroke recurrence was defined as an outcome indicator. Computed tomography/magnetic resonance imaging was used as a diagnostic tool for stroke recurrence. Patients’ age, sex, height, weight, body mass index (BMI), education level, medical history, family history, smoking, and drinking were recorded. Routine laboratory examinations were performed. Associated factors were investigated by calculating the odds ratio (OR) using logistic regression modeling. Results: In all, 2120 patients were included in the study, 712 (33.6%) of whom were women and 1408 (66.4%) were men, with a mean age of 62.84 ± 9.35 years. Eighty-two patients experienced stroke recurrence within 90 days, and the accumulative recurrence rates of stroke were 3.9% (95% confidence interval [CI], 3.0%–4.7%). The binary logistic analysis showed that previous history of one (OR = 8.113; 95% CI, 3.040–21.071), two (OR = 2.842; 95% CI, 1.000–8.075) were independently associated with stroke recurrence within 90 days. Conclusions: The accumulative recurrence rate of ischemic stroke was 3.9% within 90 days. Number of previous history of ischemic stroke and BMI <18.5 kg/m² were independent risk factors for stroke recurrence. Medical history and solar terms of ischemic stroke were not found to be associated with stroke recurrence within 90 days. Effective secondary prevention for patients with a previous history of ischemic stroke is urgently needed to address this stroke recurrence burden.

Keywords: Chinese Medicine Hospital, ischemic stroke, recurrence, risk factors

Introduction

Stroke is the world’s second-most common cause of death, accounting for a combined 15 million deaths in 2015. It has remained one of the leading causes of death globally over the past 15 years. It has significant morbidity, high mortality, high disability, and high rates of recurrence. In China, there are an estimated 2.5 million new stroke cases each year and 7.5 million stroke survivors. The World Health Organization estimated that in 2014, the incidence of stroke in China ranked first in the world, with an annual growth rate of 8.7%.

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It has become the second-leading cause of death in those aged ≥60 years and the fifth-leading cause of death in people aged 15–59 years old. Ischemic stroke is the predominant type of stroke. It accounts for 66.4% of strokes in China. Stroke recurrence is the main reason for patients’ long-term disability and increasing mortality, which affects patients’ survival time and quality of life. In 2013, a Chinese study showed that the recurrence rates of stroke within 3 months ranged 7.4%–12.9%. A secondary prevention strategy was taken in China, focusing on when the early recurrence rates of stroke are still very high. Patients in an earlier phase after stroke were more likely to have a higher risk of stroke recurrence and poor functional outcomes at 3 months after stroke onset. A significant minority of patients with a stroke become disabled or die due to recurrent strokes or neurological deterioration. The associated risk factors for stroke recurrence in the short-term prognosis of ischemic stroke are unknown in the Chinese population. We conducted a study of the prognosis of the stroke to assess risk factors for recurrence within 90 days in ischemic stroke patients in China.

The aim of this study was to determine the recurrence rates of stroke within 90 days and associated risk factors in patients with ischemic stroke.

**METHODS**

**Study design**

This is a cross-sectional registry-based study. The present analysis is part of a larger study, which aimed to study the risk assessment model for ischemic stroke endpoint events from November 3, 2016 to April 1, 2019 in China.

**Setting**

This study was sponsored by the Institute of Basic Research in Clinical Medicine of the China Academy of Chinese Medical Sciences. Chinese medicine hospitals from 10 cities in eight provinces covering a wide range of geographic areas in China took part in the study: Dimension Hospital Beijing University of Chinese Medicine (Beijing, northern China), Iguanodon Provincial Hospital of Chinese Medicine (Iguanodon, southern China), The Affiliated Hospital to Changchun University of Chinese Medicine (Jilin, Northeastern China), The First Affiliated Hospital of Henan University of Chinese Medicine (Henan, mid-China), The First Affiliated Hospital of Henan University of CM, Dong Hospital (Henan, mid-China), Dongfang Hospital Beijing University of Chinese Medicine (Beijing, northern China), Taiyuan Hospital of Traditional Chinese Medicine (Taiyuan, northern China), Shijiazhuang Hospital of Traditional Chinese Medicine (Shijiazhuang, Hebei, northern China), Beijing Wuhan Hospital of Traditional Chinese Medicine (Beijing, northern China), Shanghai CM-integrated Hospital (Shanghai, eastern China), Weeeing Hospital of Traditional Chinese Medicine (Shannon, eastern China), The Second Affiliated Hospital of Shanghai University of Chinese Medicine (Shanghai, eastern China), and Shanghai Provincial Hospital of Chinese Medicine (Shanghai, eastern China).

**Participants**

We recruited participants with ischemic stroke were recruited from November 3, 2016 to May 28, 2018, from Chinese medicine hospitals from 10 cities in eight provinces in China. All patients underwent routine medical evaluation by a doctor at baseline; patients with first-ever ischemic stroke received a 90-day follow-up. Patients’ age; sex; height; weight; body mass index (BMI); education level; medical history including history of ischemic stroke, hypertension, diabetes mellitus, coronary heart disease, and dyslipidemia; and family history of stroke were recorded by the doctor, and routine blood lipid examination was performed at baseline.

Participants were eligible if they had ischemic stroke and were aged 35–80 years old; met the TOAST (The Trial of Org 10172 in acute stroke treatment) criteria for large-artery atherosclerosis and small-vessel occlusion (lacune) according to their medical history and computed tomography/magnetic resonance imaging findings; willing to respond truthfully and timely to researcher queries after recruitment; and able to cooperate with data collection. Patients were excluded if they had any of the following: diagnosis of transient ischemic attack (TIA) hemorrhagic stroke or mixed stroke; met the TOAST criteria for cardioembolism or other determined or undetermined etiological sub-type of ischemic stroke; or unable to participate in data collection for any reason.

**Variables and assessment criteria**

The medical diagnostic criteria for ischemic stroke were based on Acute Ischemic Stroke Diagnosis and Treatment Guidelines of China (version 2014) (The Chinese Society of Neurology, Chinese Medical Association, Beijing, China) as promulgated by the Chinese Society of Neurology, Chinese Medical Association.

Survey respondents with a history of ischemic stroke were asked to provide investigators with their article or electronic medical records (inpatient or outpatient records), which contained their patient medical history, physical examination findings, and neurological imaging information.

The primary outcome was stroke recurrence within 90 day, including ischemic stroke and hemorrhagic stroke, according to the definition of ischemic stroke recurrence events given by the CHANCE study.

Dependent variables we analyzed comprised stroke recurrence within 90 days (yes, no).

Independent variables included sex (male, female), age (in years and divided into 35–50, 50–65, 65–80), BMI (in kg/m² and divided into <18.5, 18.5–23.9, ≥24), educational level (primary school and below, junior middle school, senior middle school, and college and above), medical history (ischemic stroke, hypertension, diabetes mellitus, coronary heart disease, and dyslipidemia), family history (stroke), smoking, drinking, and total cholesterol (TC)/high-density lipoprotein cholesterol (HDL-C) ratio.

**Data source and measurement**

This study is based on a multicenter clinical registry study in
Chinese medicine hospitals in ten cities from eight provinces in China between November 3, 2016, and May 28, 2018. We conducted a national cross-sectional study of patients using the ischemic stroke registration database. We identified stroke recurrence events within 90 days of onset of ischemic stroke. If patients presented with first-ever ischemic stroke, they were followed up to assess whether a new stroke event occurred in the next 90 days. If the patient had a previous history of ischemic stroke, they were asked whether they had had a stroke in the last 90 days. The associated risk factors were assessed during the baseline period.

Over 15 variables were considered, including patients’ demographic characteristics (e.g., sex, age, education level), physical examination findings (height, weight), ischemic stroke-related behavioral factors (e.g., smoking, drinking), history of previous ischemic stroke (e.g., none, one, two, three or more), personal and family medical history of stroke and chronic diseases adopting standardized disease coding from the International Classification of Diseases, Tenth Revision (e.g., ischemic or hemorrhagic stroke, hypertension, diabetes mellitus, coronary heart disease, dyslipidemia), and laboratory test results (e.g., TC, HDL-C).

Eight variables were included in the final logistic regression analysis. They were defined as follows.

Sex and age, according to the patient’s ID card.

The patient’s education level was reported by the patient themselves or a family member.

The self-reporting of personal medical history (e.g., ischemic stroke, hypertension, diabetes mellitus, coronary heart disease, and dyslipidemia) and family history of stroke were verified by field investigation. The survey respondents with a history of stroke were asked to provide investigators with their article or electronic medical records (inpatient or outpatient records), which contained the patient history, physical examination findings, and neurological imaging information. A family history of stroke was restricted to lineal relative members.

Diabetes mellitus was defined as the use of insulin and/or oral hypoglycemic medications, a self-reported history of diabetes, or fasting plasma glucose ≥7.0 mmol/L in the field survey.

Height and weight were measured according to a standardized protocol and technique, with participants wearing no shoes. BMI was calculated as weight (kg) divided by height squared (m²); BMI <18.5 kg/m² was defined as underweight, 18.5–23.9 kg/m² as normal weight, and ≥24 kg/m² as overweight/obese.

Blood samples were drawn from participants’ antecubital veins to measure TC and HDL-C in the field survey. Blood samples were collected from subjects in the morning after an overnight fast (at least 8 h) and were tested in the laboratory section of the patient’s participating hospital.

Data were collected in face-to-face interviews and recorded initially on preprinted standardized data collection forms. After collection, data were entered into a well-protected database using a specific online electronic data capture (EDC) system. The online EDC system and operation rules of data entry, auditing, and locking were constructed by the data administrators from the Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences. All data were double entered by two people. All data then underwent subsequent re-entry to check for input errors. If any discrepancy between the first and second entry was found, the entry was confirmed by consulting the original documents.

Study size
The sample size was calculated based on an estimated mean recurrence rate of stroke within 90 days of 10.15%, with a 95% confidence interval (CI) and an allowable error of 1.5%. To compensate for inevitable attrition, we added 20% to this number. This gave us a sample size of 2029 patients with ischemic stroke. The sample size calculations were performed using the Power Analysis and Sample Size V.11.0 (PASS) (NCSS Statistical Software Inc., Kaysville, USA).

Statistical methods
Normally distributed continuous data were analyzed using the independent t-test, while the rank-sum test was used for nonnormally distributed data. The Chi-square test was used to analyze categorical data. Binary logistic regression was used to analyze risk factors and evaluate odds ratios (ORs) and 95% CI for risk factors for stroke recurrence.

Variables that were considered clinically relevant or that were statistically significant at $P < 0.10$ in the univariate analysis were entered into the binary logistic regression analysis to examine the variables independently associated with stroke recurrence. Variables for inclusion were carefully chosen, given the number of events available, to ensure the parsimony of the final models. We used binary logistic regression models to estimate the adjusted effects of stroke recurrence within 90 days. In the logistic regression analysis, the continuous variables included TC/HDL-C ratio, and categorical variables included sex, age, educational level, medical history, and family history.

The Box-Tidwell method was used to test whether there was a linear relationship between independent variables and logit conversion values of dependent variables. The tolerance or variance expansion factor (VIF) can be used to diagnose multicollinearity between independent variables. The tolerance or VIF was obtained using a linear regression model. A tolerance >0.1 or VIF is <10 and is considered collinear.

The ENTER method was used to filter methods for arguments. The Omnibus Tests of Model Coefficients and the Hosmer and Lemeshow test was conducted to evaluate the significance of the model and degree of fit. Percentage accuracy in classification determines the predictive power of the model. Categorical variables are presented as a percentage or frequency and continuous variables as the mean ± standard
deviation (SD). The OR with 95% CI is reported as the result of the logistic regression model. P values are two-tailed. P < 0.05 was considered statistically significant. The mean imputation method was used to fill missing data.

The date that the studentized residual error was >2.5 times the SD was not excluded in the final analysis. It was not identified as an outlier after rechecking the data.

All analyses were performed using the Statistical Package for the Social Science V.22.0 (SPSS Inc., Chicago, Illinois, USA).

**Results**

**Study flow**

A total of 2148 patients with ischemic stroke were registered in the registration database from November 15, 2016, to May 28, 2018. Seventeen (0.8%) patients were excluded (three patients with TIA, two patients with mixed stroke, seven patients aged >80 years, and five patients aged <35 years); 1442 (67.5%) patients were registered following their first-ever ischemic stroke, and 1431 patients received a 90-day follow-up (one patient died, 10 patients were lost to follow-up because patients refused follow-up or the researcher could not contact with patients via the provided phone number); 689 (32.5%) patients had at least two ischemic strokes. Finally, 2120 patients completed data collation. Eighty-two patients had a stroke event within 90 days; 2120 patients were included in the final analysis. Figure 1 shows a flow chart of the study.

**Characteristics of the study population**

In total, 2120 participants (mean age 62.84 ± 9.35 years), comprising 1408 men and 712 women, were included in the final analysis. Of those, 1431 (68.2%) patients had their first-ever ischemic stroke and just 16 patients had a stroke event during the 90-day follow-up; 689 (32.5%) patients had a history of previous ischemic stroke and 66 patients had a stroke event in the last 90 days. Finally, 82 participants, people were identified as having a stroke events within 90 days. The overall 90-day cumulative recurrence rate for stroke was 3.9% (95% CI, 3.0%–4.7%). History of previous ischemic stroke, BMI, education level, 24 solar terms of onset, medical history of diabetes mellitus, family history of stroke, and TC/HDL-C ratio in the recurrence group was significantly different from those in the nonrecurrence group (all P < 0.1). The laboratory features of the participants are listed in Table 1.

**Binary logistic analysis of the risk of recurrence among patients with ischemic stroke**

The binary logistic regression model indicated that multiple characteristics were independently associated with stroke recurrence, including the previous history of stroke and BMI. Table 2 shows that the adjusted ORs for the previous history of ischemic stroke (vs. none previous history of ischemic stroke group) were 8.113 (95% CI, 4.497–14.637), 8.848 (95% CI, 4.025–9.449), and 24.599 (95% CI, 9.307–65.018). It increased significantly with the number of previous ischemic strokes (P < 0.001). The OR for BMI <18.5 kg/m² (vs. BMI, 18.5–23.9 kg/m² group) was 2.842 (95% CI, 1.000–8.075) (P = 0.050). However, there was no significant difference between participants with different age, sex, educational level, medical history of diabetes mellitus, family history of stroke, or TC/HDL-C ratio.

**Discussion**

The short-term prognosis of ischemic stroke (especially stroke recurrence and its risk factors) has not been well-explored previously. The short- and long-term risk factors for stroke recurrence may be different. This study aimed to determine the risk factors for recurrence within 90 days in a Chinese ischemic stroke population using a cross-sectional study of 2120 individuals from a clinical registration database. Just 16 (0.8%) patients had a stroke event during a 90-day follow-up among patients with first-ever ischemic stroke and 66 (3.1%) patients had a stroke event in the previous 90 days among patients with a previous history of ischemic stroke. The recurrence rates of stroke for patients with first-ever ischemic stroke is lower than that for patients with a previous history of ischemic stroke in this study.

In the present study, the accumulative recurrence rate of stroke was 3.9% within 90 days of onset of ischemic stroke, which is significantly lower than that reported by Moroney et al. and Wang et al. We identified the risk factors for short-term recurrence of ischemic stroke. A previous history of ischemic stroke and BMI <18.5 kg/m² were independently associated with stroke recurrence. Our study found that a previous history of ischemic stroke was related to stroke recurrence. When the patient had a previous history of three or more ischemic strokes, the risk of recurrence was greatly increased. No correlation between the number of previous ischemic strokes and stroke recurrence has been reported in previous studies. Similar studies support our conclusion. Suzuki’s study confirmed that the annual rate of recurrent ischemic stroke was significantly
higher in patients who had an ischemic stroke at least twice than in patients who had first-ever ischemic stroke.[23] Ling et al.’s study showed that the 1-year recurrence rates of stroke were just 4.8% in patients with first-ever ischemic stroke,[24] and recurrence frequency increases if the first recurrence happened.[25] Moreover, BMI <18.5 kg/m² was shown to be significantly related to an increased risk of short-term stroke recurrence, which was reported by a previous study.[21]

Although some studies indicated that age, sex, and educational level were an independent risk factor for stroke recurrence,[26-28] the results of this study did not reveal any association between age, sex, educational level, and stroke recurrence within 90 days. Similarly, Li et al.’s[29] study found no association between age and stroke recurrence in patients with ischemic stroke aged 18–45 years. In 2013, a Chinese study[14] suggested that sex and educational level had no statistically significant effect on stroke recurrence rates at 3 months. In addition, the present study also suggested that histories of hypertension, diabetes mellitus, coronary heart disease, dyslipidemia, and family history of ischemic stroke were not independently associated with stroke recurrence within 90 days. This may be related to the treatment and control of basic diseases; however, it seems to contradict previous studies.[27,30] Toyoda et al.’s[31] study showed that diabetes mellitus was not independently predictive of early recurrence. In addition, some studies have indicated that TC, HDL-C, and TC/HDL-C ratio were risk factors for the long-term stroke recurrence of ischemic stroke.[12,34] However, blood lipid test (TC and HDL-C) data come from different clinical laboratories in this study. Therefore, our study only included the TC/HDL-C ratio in the final analysis. No statistically significant association between TC/HDL-C ratio and stroke recurrence within 90 days was found.

Therefore, there may be different risk factors for stroke recurrence in the short and long term. This study considered the effect of multidimensional risk factors (including demographic, personal and family medical history, physical examination

### Table 1: Characteristics of the study population

| Characteristic | All (n=2120), n (%) | Nonrecurrence (n=2038), n (%) | Recurrence (n=82), n (%) | P |
|----------------|---------------------|-------------------------------|--------------------------|---|
| Age (years), mean±SD | 62.84±9.35 | 62.79±9.34 | 64.13±9.75 | 0.202* |
| Sex | | | | |
| Men | 1408 (66.4) | 1348 (66.1) | 60 (73.2) | 0.186† |
| Women | 712 (33.6) | 690 (33.9) | 22 (26.8) | 0.202* |
| BMI (kg/m²), mean±SD | 24.26±3.04 | 24.29±3.04 | 23.64±3.01 | 0.059* |
| Education level | | | | |
| Primary school and below | 651 (30.7) | 636 (31.2) | 15 (18.3) | 0.012‡ |
| Junior middle school | 645 (30.4) | 617 (30.3) | 28 (34.1) | 0.218 |
| Senior middle school | 569 (26.8) | 545 (26.7) | 24 (29.3) | 0.058 |
| College and above | 255 (12.0) | 240 (11.8) | 15 (18.3) | 0.096 |
| Twenty-four solar terms of onset | | | | |
| Winter solstice-awakening from hibernation | 647 (30.5) | 622 (30.5) | 25 (30.5) | 0.054† |
| Vernal equinox-grain in ear | 504 (23.8) | 485 (22.9) | 19 (23.2) | 0.054* |
| Summer solstice-white dew | 400 (18.9) | 383 (18.1) | 17 (20.7) | 0.054* |
| Autumnal equinox-heavy snow | 569 (26.8) | 548 (25.8) | 21 (25.6) | 0.054* |
| History of previous ischemic stroke | | | | |
| None | 1431 (67.5) | 1415 (69.4) | 16 (19.5) | <0.001‡ |
| 1 times | 534 (25.2) | 488 (23.9) | 46 (56.1) | 0.058 |
| 2 times | 123 (5.8) | 111 (5.4) | 12 (14.6) | 0.058 |
| ≥3 times | 32 (1.5) | 24 (1.2) | 8 (9.8) | 0.058 |
| Medical history | | | | |
| Hypertension | 1391 (65.6) | 1332 (65.4) | 59 (72.0) | 0.218‡ |
| Diabetes mellitus | 603 (28.4) | 573 (28.1) | 30 (36.6) | 0.096† |
| Coronary heart disease | 333 (15.7) | 316 (15.5) | 17 (20.7) | 0.020† |
| Dyslipidemia | 293 (13.8) | 281 (13.8) | 12 (20.7) | 0.828‡ |
| Family history of stroke | 207 (9.8) | 194 (9.5) | 13 (15.9) | 0.058† |
| Smoking | 819 (38.6) | 784 (38.5) | 35 (42.7) | 0.442† |
| Drinking | 512 (24.2) | 493 (24.2) | 19 (23.2) | 0.832‡ |
| TG (mmol/L), mean±SD | | | | |
| TC | 4.61±1.22 | 4.63±1.22 | 4.24±1.21 | 0.050* |
| HDL-C | 1.16±0.32 | 1.16±0.32 | 1.13±0.31 | 0.437* |
| TC/HDL-C ratio | 4.18±1.36 | 4.19±1.36 | 3.90±1.25 | 0.054* |

*Two independent t-test (two-sided), †Pearson χ² (two-sided), ‡Mann-Whitney U-test (two-sided). BMI: Body mass index, SD: Standard deviation, TC: Total cholesterol, HDL-C: High-density lipoprotein cholesterol, TG: Triglyceride
findings, personal history and behavioral factors, solar terms, and laboratory testing) on stroke recurrence. Further studies are necessary to elucidate the relationship between risk factors and stroke recurrence in the short-term prognosis of ischemic stroke. In precision medicine today, individualized treatment is garnering increasing attention. Secondary prevention may not be better in patients with a previous history of ischemic stroke. A more suitable secondary prevention strategy should be developed for patients with a previous history of ischemic stroke.

This study is a part of a larger multicenter population-based prospective ischemic stroke registry study. The compiled data with 1-year follow-up have enabled us to investigate risk factors for stroke recurrence in patients with ischemic stroke. However, some limitations of this study should be noted. First, there was a recall bias due to the use of self-reported questionnaires because the information regarding the personal and family medical history of stroke and chronic diseases were obtained based on the recall of the patient or their family members. Second, there was a possible selection bias because continuous inclusion was disrupted (e.g., recruited individuals did not agree to participate in the study, researcher-related travel issues). Finally, there may be a competition risk of stroke recurrence because patients died or were lost to follow-up within 90 days.

**Conclusions**

We found that the accumulative recurrence rates of stroke within 90 days were 3.9% among patients with ischemic stroke in the study population from a registration database. The number of previous ischemic strokes and BMI were independent risk factors for stroke recurrence within 90 days. Underweight patients are at increased risk of stroke recurrence, whereas obese patients have a similar risk to their normal-weight counterparts. Optimal weight management should be promoted as part of secondary prevention. Effective secondary prevention for patients with a previous history of ischemic stroke is necessary to address this stroke recurrence burden.
Trial registration
URL: https://clinicaltrials.gov/ct2/show/NCT03174535. ClinicalTrials.gov number: NCT03174535.

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Conflicts of interest
There are no conflicts of interest.

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