Journal of Neurological Disorders

J Neurol Disord
Volume 11:4 2023

Research Article Open Access

The Long-Term Incidence of Recurrent Stroke and Risk Factors Associated with Transient Ischemic Attack Patients

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Abstract

Background: The incidence of recurrent stroke and mortality ratio of patients with a transient ischemic attack (TIA) and minor ischemic stroke (MIS) is a challenging issue, especially the long-term recurrence ratio.

Aims: This study aimed to estimate the long-term incidence of ischemic stroke recurrence and identify the risk factors associated with recurrent stroke in the Xuzhou region of China.

Settings and design: This was a cross-sectional study conducted on a group of patients with TIA or MIS between the ages of 20 and 80 years.

Methods and material: A total of 297 individuals participated. Medical records were one of the data sources. The data of patients who meet the selection criteria gathered from the Neurology department, affiliated hospital of Xuzhou medical university

Statistical analysis used: Statistical package for Social Science (SPSS) version 23 was used for statistical analysis.

Results: In this study, 297 patients were included for analysis; 30 (9.17%) patients were lost to follow-up at 5 years. Post onset of the TIA and MIS analysis reveals that the cumulative incidences of recurrent stroke at 3,6,12, 36, and 60 months were 6.73% (20/297), 10.77% (32/297), 18.86% (56/297), 25.25% (75/297), and 33.33% (99/297), respectively. Multivariate regression analysis demonstrated that age, current smoking, poorly controlled hypertension, diabetes, vascular stenosis, and plaque vulnerability as independent risk factors for ischemic stroke recurrence. Further analysis based on different vascular stratification of carotid atherosclerosis showed that 5-year cumulative survival was 10% lower in patients with severe stenosis than in patients with plaque vulnerability.

Conclusion: This study aimed to estimate the long-term incidence of ischemic stroke recurrence and identify the risk factors associated with recurrent stroke in the Xuzhou region of China.

Keywords: Minor ischemic stroke • Transient ischemic attack • Stroke recurrence • Risk factors • Secondary prevention

Introduction

A transient ischemic attack (TIA), a mini-stroke, is a temporary episode of neurological dysfunction caused by a temporary blood supply disruption to a specific brain area. TIAs are similar to ischemic strokes, but the symptoms typically resolve within 24 hours, often lasting only a few minutes. However, TIAs should not be ignored, as they are warning signs of an increased risk of a future stroke. Stroke was recognized as the principal cause of death and disability-adjusted life-years (DALYs) at the national level in China in 2017 [1]. The incidence of stroke recurrence among patients with a TIA or minor ischemic stroke can vary depending on several factors, including the duration of follow-up, the specific population studied, and the management of risk factors. However, stroke recurrence rates may have changed with recent advances in secondary prevention management [1]. The rate of stroke recurrence reduced until the mid-2000s, though it has remained unchanged over the last decade [2]. Studies have shown that the risk of stroke recurrence is highest in the immediate period following a TIA or minor ischemic stroke. Within 30 days after the initial event, the risk of recurrent stroke can range from 4% to 10%. Moreover, the study determines the different stroke recurrence ratios, ranging from 7%-20% at 1 year to 16%-35% at 5 years [3]. This may be related to the lifestyle and risk factors associated with TIA, and MIS differs from country to country. Besides these, the incidence of stroke recurrence in developing countries remains insufficiently explored.

The primary goal of secondary prevention strategies after TIA or ischemic stroke is to reduce the risk of recurrent stroke [4]. It's important to note that these figures are general estimates and may vary among different patient populations and healthcare settings. Additionally, effective management of risk factors, such as hypertension, diabetes, and atrial fibrillation, can help reduce the risk of stroke recurrence. This study investigated the cumulative incidence of recurrent TIA or MIS in China and the risk factors associated with recurrence.

Subjects and Methods

Study population

This prospective cohort study included 327 TIA or MIS patients aged 18-80 treated in the Affiliated Hospital of Xuzhou Medical University from January to December 2016. A total of 30 patients were lost during follow-up, and the remaining 297 patients were followed until December 31, 2021.

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Received: 12-July-2023, Manuscript No. jnd-23-105604; **Editor assigned:** 14-July-2023, PreQC No. P-105604 (PQ); **Reviewed:** 28-July-2023; QC No. Q-105604; **Revised:** 02-August-2023; Manuscript No. R-105604 (R); **Published:** 09-August-2023, **DOI:** 10.4172/2329-6895.11.4.562

Inclusion and exclusion criteria

The following inclusion and exclusion criteria were used to include the patient in the study; age: 45-80, Stroke was defined as an episode of neurologic deficit lasting >24 hours or clinical symptoms where Magnetic Resonance Imaging (MRI) or Computed Tomography (CT) showed infarctions related to the clinical findings and caused by extracranial or intracranial atherosclerosis [5, 6]. MIS was defined as an NIHSS score ≤ 5 at admission [7]. TIA was described as a clinical diagnosis of transient focal cerebral dysfunction lasting <24 hours with no objective evidence of brain infarction on brain imaging. Clinical symptoms were classified with the Oxfordshire Community Stroke Project Classification (OCSP) [8]. Only ischemic and hemorrhagic strokes were recurrent 30 days after the initial event or earlier and different vascular regions were documented. Carotid atherosclerosis examines by duplex ultrasound and divided into two different vascular strata: Degree of stenosis and plaque vulnerability. All the patients were classified as having mild stenosis (<50% diameter reduction) and severe stenosis (≥ 50% diameter reduction). The consensus criteria were used to define the <50% stenosis when the peak systolic velocity (PSV) is <125 cm/second and a plaque of the internal carotid artery (ICA) [9].

Patients diagnosed with TIA or MIS due to non-vascular causes (primary and metastatic neoplasms, paralysis after a seizure, traumatic brain injury, etc.) resulting in brain dysfunction or intracerebral hemorrhage and incomplete 5 years of follow-up data after onset were excluded from the study.

Data collection

Baseline data were collected in this study within 24 h after admission, including demographic information, past medical history, admission evaluation, and laboratory data. The NIHSS score was used to assess the severity of neurological impairment within 24 h of admission. The patients were followed up 3, 6, 12, 36, and 60 months after TIA or MIS onset. All enrolled patients were interviewed face-to-face or contacted over the telephone by trained research coordinators. The interviewers were trained centrally with a standardized interview protocol [10]. All-cause Mortality was defined as death from any cause during follow-up. The Ethics Committee approved the study of the Affiliated Hospital of Xuzhou Medical University, and all patients or their legally authorized representatives have written informed consent.

Statistical analysis

Continuous variables that conformed to a normal distribution were expressed as mean ± standard deviation, and did not conform to a normal distribution were expressed as median (interquartile range). Categorical variables are reported as the frequency (%). The chi-squared test (or Fisher's exact test, where appropriate) was used to compare groups and one-way analysis of variance (or Kruskal-Wallis test) for continuous variables. The Kaplan-Meier estimates were used to determine the cumulative risk of recurrence and the combined outcome of recurrence or death at 3, 6, 12, 36, and 60 months. Univariate Cox regression analysis was used to identify baseline differences in clinical variables of patients with vs. without stroke recurrence and all-cause mortality. After adjusting for covariates, multivariate Cox regression was used to analyze the factors associated with the 5-year prognosis of TIA or MIS. A two-tailed probability (p) value of <0.05 was considered statistically significant. We analyzed the data using Statistical Product Service Solutions (SPSS) 22.0.

Results

Patient's recruitment

A total of 424 patients were enrolled in this study. Among that 97 were excluded due to non-acute ischemic stroke or an NIHSS score >3 at admission. The remaining 327 patients had experienced TIA or MIS, and 30 (10.1%, 30/327) patients were lost to follow-up. Finally, 297 patients with TIA or MIS were included for analysis, as shown in (Figure 1).

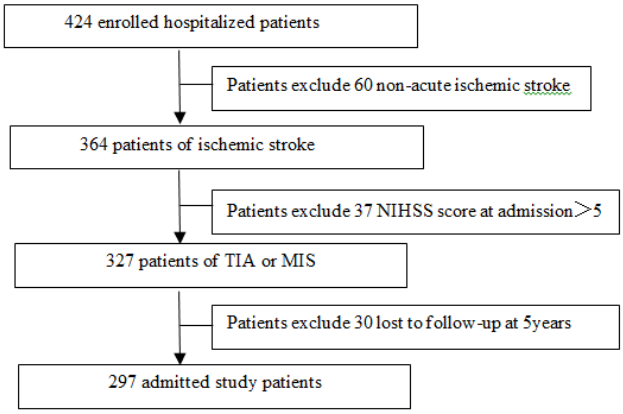

Figure 1. Flow chart showing the patient selection

Incidence of stroke recurrence and all-cause mortality

At 5 years of follow-up, (33.33%, 99/297) of patients experienced recurrent strokes, and the mortality rate was (13.13%, 39/297). The prevalence of stroke recurrence and rate of mortality at 3, 6, 12, 36, and 60 months was 6.73% (20/297), 10.77% (32/297), 18.86% (56/297), 25.25% (75/297) and 33.33% (99/297), respectively (Figure 2).

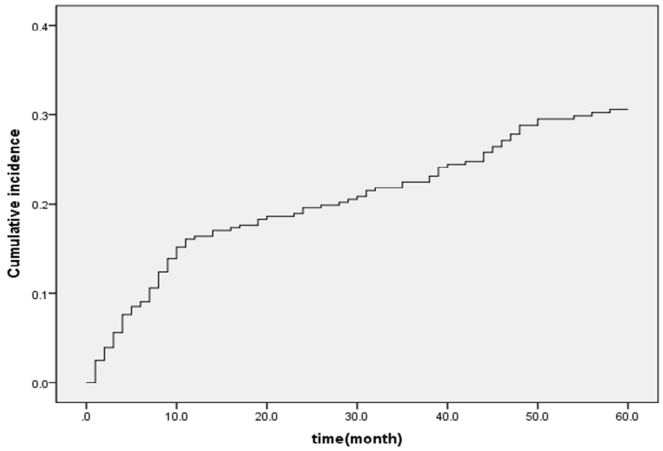

Figure 2. Cumulative incidence of stroke recurrence

Risk factors of stroke recurrence

The univariate analysis showed that patients with stroke recurrence were associated with age, gender, smokers, hypertensive and diabetes mellitus, poor compliance with secondary prevention medication, degree of stenosis, and vulnerable plaque after 5 years of follow-up. There were no statistically significant differences in alcohol consumption, fasting blood glucose, total cholesterol, triglyceride, low-density lipoprotein cholesterol, lipoprotein A, hypersensitive C-reactive protein, neutrophil to lymphocyte ratio, uric acid, and other indicators between patients with recurrent stroke and those without recurrent stroke (Table 1).

Furthermore, multivariate regression analysis was used to identify independent risk factors for stroke recurrence with TIA or MIS after 5 years. The results showed that age (odds ratio [OR]=1.046; 95% confidence interval [CI]=1.021-1.070; p=0.000), current smoking (OR=0.564; 95% CI=0.359-0.885; p=0.013), and poor control of hypertension (OR=2.355; 95% CI=1.412-3.929; p=0.001), poor control of diabetes mellitus (OR=3.255; 95% CI=1.112-3.429; p=0.001), poor compliance with antiplatelet drug (OR=1.234; 95% CI=0.582-1.215; p=0.025) and poor compliance with

statins therapy (OR=1.342; 95% CI=0.852-2.115; p=0.025), degree of stenosis (OR=0.391; 95% CI=0.256-0.597; p=0.000) and vulnerable plaque (OR=2.187; 95% CI=1.407-3.400; p=0.001) were independent risk factors for stroke recurrence with TIA or MIS after 5 years of onset (Table 2).

Table 1. Clinical data analysis of patients with or without stroke recurrence at 5 years after TIA or MIS

Variables	Recurrence (n=99)	No recurrence (n=198)	Z/T/χ^2	P
Age (year)	73 (64, 79)	65 (59, 72)	-4.792	0
Sex (n, %)			7.923	0.005
Male	74 (74.75%)	115 (58.09%)		
Female	25 (25.25%)	83 (41.91%)		
Smoking (n, %)			129.53	0
Current	29 (29.29%)	31 (15.66%)		
Never or cessation	70 (70.71%)	167 (84.34%)		
Alcohol use (n, %)			1.656	0.437
Moderate or heavy	19 (19.19%)	33 (16.67%)		
Mid or never	80 (80.81%)	169 (85.35%)		
Hypertension (n, %)			9.4	0.009
Never	34 (34.34%)	82 (41.41%)		
Poor control	17 (17.17%)	12 (6.06%)		
Better control	48 (48.48%)	104 (52.53%)		
Diabetes mellitus (n, %)			7.266	0.026
Never	64 (64.65%)	150 (75.76%)		
Poor control	19 (19.19%)	17 (8.59%)		
Better control	16 (16.16%)	31 (15.65%)		
Antiplatelet agent (n, %)			8.104	0.004
Poor compliance	51 (51.52%)	68 (34.34%)		
Better compliance	48 (48.48%)	130 (65.66%)		
Statins drugs (n, %)			8.345	0.004
Poor compliance	48 (48.48%)	62 (31.31%)		
Better compliance	51 (51.52%)	136 (68.69%)		
Degree of carotid stenosis (n, %)			19.583	0
Mild stenosis	60 (60.61%)	166 (83.84%)		
Severe stenosis	39 (39.39%)	32 (16.16%)		
Characteristics of carotid plaque (n, %)			18.942	0
Vulnerable plaque	69 (69.70%)	85 (42.93%)		
Stable plaque	30 (30.30%)	113 (57.07%)		
Fasting plasma glucose (mmol/L)	5.940 (5.060,7.810)	5.570 (5.005,7.260)	-1.86	0.063
Total cholesterol (mmol/L)	5.190 (4.240,5.850)	4.910 (4.135,6.085)	-0.439	0.66
Triglycerides (mmol/L)	1.310 (1.040,1.780)	1.280 (0.980,1.960)	-0.219	0.826
Low-density lipoprotein cholesterol (mmol/L)	3.705 ± 1.224	3.535 ± 1.037	1.252	0.581
Lipoprotein a (mmol/L)	200 (105,288)	204 (106,322)	-0.452	0.651
Hypersensitive C-reactive protein (mmol/L)	3.000 (1.600,4.300)	2.700 (1.400,4.300)	-0.697	0.486
Neutrophil (*109/L)	4.080 (3.240,5.290)	4.110 (3.260,5.040)	-0.18	0.857
lymphocyte (*109/L)	1.700 (1.300,2.000)	1.800 (1.350,2.200)	-1.822	0.069
neutrophil to lymphocyte ratio	2.389 (1.791,3.350)	2.260 (1.716,3.209)	-1.268	0.205
uric acid (mmol/L)	289 (234,332)	282 (239,323)	-0.586	0.558
Homocysteine (mmol/L)	15.700 (13.390,18.970)	14.600 (12.360,18.500)	-1.624	0.104
Fibrinogen (mg/L)	3.090 (2.550,3.570)	2.840 (2.410,3.370)	-2.206	0.027

Table 2. Multivariate regression analysis of risk factors of stroke recurrence

Variables	β	SE.	Wald	df	OR	95%CI	P
Age	0.045	0.012	14.029	1	1.046	1.021-1.070	0.000
Sex	0.451	0.242	3.480	1	1.571	0.977-2.524	0.062
Current smoking or not	-0.573	0.230	6.193	1	0.564	0.359-0.885	0.013
Poor control of hypertension	0.857	0.261	10.760	1	2.355	1.412-3.929	0.001
Poor control of diabetes mellitus	0.587	0.621	7.160	1	3.255	1.112-3.429	0.001
Poor compliance with the Antiplatelet agent	0.429	0.322	1.960	1	1.234	0.582-1.215	0.025
Poor compliance with statins drugs	0.294	0.232	1.609	1	1.342	0.852-2.115	0.025
Degree of carotid stenosis	-0.939	0.216	18.911	1	0.391	0.256-0.597	0.000
Characteristics of carotid plaque	0.783	0.225	12.077	1	2.187	1.407-3.400	0.001
Fibrinogen	0.181	0.102	3.168	1	1.199	0.982-1.463	0.075

Vascular stratification of the carotid artery is associated with recurrentstroke

In the study, we further evaluated the different vascular stratification of carotid artery atherosclerosis. The analysis reveals that 5-year cumulative incidence was higher in patients with severe stenosis than in patients with plaque vulnerability, about 10% higher (Figures 3 and 4).

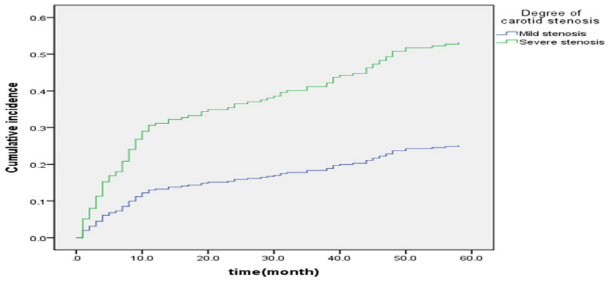

Figure 3. Cumulative incidence of stroke recurrence for carotid severe stenosis

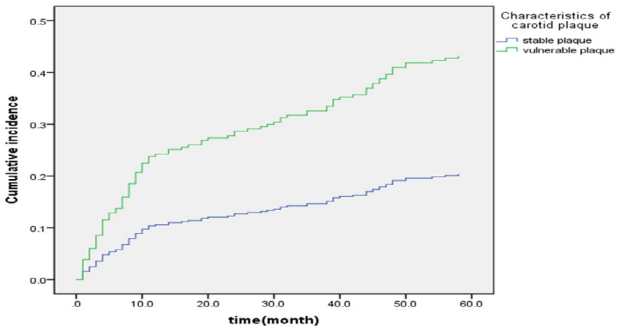

Figure 4. Cumulative incidence of stroke recurrence for carotid vulnerable plaque

Discussion

In this prospective cohort study, the cumulative incidence of recurrent stroke and mortality was 18.86% at 1 year and 33.33% at 5 years during the 5-year follow-up period. Nevertheless, these results were higher than the prevalence of 9.8% at 3 months and 13.2% at 1 year, as reported by the China National Stroke Registry (CNSR) study [10, 11]. However, another study in the United Kingdom reported stroke due to large artery atherosclerosis was 12.9% 3 months, 22.6% at 1 year, 45.8% at 5 years, which was higher than our study [12]. These studies suggested that clinical outcomes of patients with TIA or MIS may differ among countries and regions. In addition, in parallel with previous studies, age was identified as an independent risk factor for stroke recurrence and mortality with TIA or MIS after 5 years because of multiple diseases and more severe large artery atherosclerosis [13].

Similar to previous studies, smoking was an independent risk factor associated with TIA or MIS after 5 years [14, 15]. Persistent smoking increases the risk of stroke recurrence because it promotes thrombosis and reduces cerebral blood flow *via* arterial vasoconstriction [16]. Although, our study suggests that alcohol consumption was not a risk factor for recurrent stroke after 5 years of TIA or MIS and probably because of a dose-response relationship between drinking quantity and the risk of stroke recurrence [17]. Therefore, it is essential to control smoking among MIS patients.

Similarly, our study found that poor control of hypertension and diabetes mellitus was identified as an independent risk factor for recurrent stroke and mortality TIA or MIS after 5 years. Hence, the 2021 AHA/ASA guideline points out that managing vascular risk factors in secondary stroke prevention is essential, including diabetes, smoking cessation, lipids, and especially hypertension. They proposed that the best way to achieve the goals of therapy tailored by establishing multidisciplinary teams [18]. Parallel to previous reports, our study also showed that poor compliance with antiplatelet and statin therapy is considered an independent risk factor for recurrent stroke and mortality [19, 20].

Furthermore, our study identified that vascular stratification, including the degree of carotid stenosis and vulnerable plaque, were associated risk factors with recurrent stroke and mortality after 5 years of TIA or MIS onset. Moreover, the results showed that incidence was 10% higher in patients with severe stenosis than in patients with plaque vulnerability. Like previous studies, carotid stenosis ≥ 50% has a higher incidence of recurrent stroke among patients [21]. The study further elaborated that carotid artery plaque ipsilateral to acute ischemic anterior circulation stroke was associated with an increased risk of recurrent stroke.

Conclusion

In conclusion, the results of this study suggested that age, current smoking, poor control of hypertension and diabetes mellitus, poor compliance with antiplatelet and statins therapy, severe carotid stenosis, and vulnerable plaque were significantly associated with recurrent stroke. Our study findings might have implications for therapeutic trials designed to prevent stroke. Future studies of multiple centers base are required to recruit more clinical cases and incorporate more risk factors associated with recurrent stroke to predict the incidence of recurrent stroke comprehensively. Hence, older patients should be closely monitored for various indicators, early detection, and treatment.

Acknowledgement

None.

Conflict of Interest

The authors declared no conflict of interest.

Authors Contribution

Hongmei Ding, Bilal Muhammad, and Deqin Geng conceived and designed experiments; Hongmei Ding and Bilal Muhammad collected data; Xiaolong Wang, Shu Kan, Ruiguo Dong, Weiwei Chen, and Yingfeng Mou analyzed the data; Hongmei Ding and Bilal Muhammad drafted the manuscript. All the authors reviewed and approved the publication of the final manuscript.

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How to cite this article: Ding, H, Muhammad B, Wang X and Kan S, et al. "The long-Term Incidence of Recurrent Stroke and Risk Factors Associated with Transient Ischemic Attack Patients." *J Neurol Disord*. 11 (2023):562.