Predictors of recurrent ischemic stroke: A retrospective cohort study

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Abstract

**Background:** Cerebrovascular events are one of the most common causes of disability and the third leading cause of death in developed countries. Herein, we aimed to investigate the potential underlying causes of recurrent ischemic stroke.

**Methods:** This study was a retrospective cohort study which conducted in Razi Hospital, Tabriz, Iran between March 2018 and September 2020. Patients with the diagnosis of recurrent ischemic stroke during the study period were eligible to be included. Baseline characteristics and data on the recurrence were collected using chart reviews. Binary logistic regression was used to examine the factors related with recurrence.

**Results:** One hundred participants with a mean age of 68.88 years were included in the study among them 59% were male. Hypertension, diabetes, heart disease, smoking and hyperlipidemia identified in 79%, 42%, 24%, 15%, and 15%, respectively. The average recurrence time of stroke was about 2.52 years. There was only a significant relationship between history of heart diseases and ischemic stroke recurrence (risk ratio: 0.10; 95% confidence interval: 0.03-0.33).

**Conclusions:** We found no significant association between ischemic stroke recurrence and underlying diseases except for heart diseases. Further large-scale observational studies and meta-analysis are recommended to evaluate the association.

Introduction

Cerebrovascular diseases are one of the most common neurological conditions which are associated with high mortality and long-term morbidities (1). Patients who recover from the first stroke events are at high risks of recurrence, especially within the first two years (2). Moreover, some other comorbidities like hypertension, diabetes mellitus, atrial fibrillation, and transient ischemic attack are risk factors for recurrent stroke (3). Approximately 80–85% of patients who experienced the first cerebrovascular accident survived the second attacks, however, about 15–30% of patients in different communities with a history of recent stroke within the past two years had recurrent stroke (4, 5).

Compared to the first stroke attacks, neurological disorders caused by a relapse is more serious, more difficult to treat and has a higher mortality which leads to hospital readmission and long-term disability (6). Additionally, the cumulative effects of previous stroke complications should be taken into consideration (7). Therefore, secondary prevention is of importance for these individuals.

Previous studies have evaluated the incidence and predictors of stroke in some populations (8, 9). Furthermore, some systematic review and meta-analyses have evaluated the cumulative risk and risk factors for recurrent stroke (6, 7, 10). Nevertheless, to our best of knowledge, no previous recent study has assessed the predictors of recurrent stroke in Iranian population. So, we aimed to investigate the predictors of recurrent stroke and their presentation in a tertiary center in Northwest of Iran.
Methods

Study design and subjects

This study is a retrospective cohort study. We used cluster sampling and 100 individuals with recurrent ischemic stroke from March 2018 to September 2020 which re-admitted to Razi Medical Training Center, Tabriz University of Medical Sciences, Tabriz, Iran were enrolled to the study.

The patients with the diagnosis of recurrent ischemic stroke during the study period were eligible to be included in the study. The participants should have complete baseline information and agree to participate in the study. The exclusion criteria included lack of history of ischemic stroke or different final diagnosis other than ischemic stroke.

Data collection

For included participants with recurrent ischemic stroke, we completed the questionnaire for each patient. The data included identification characteristics, hospitalization date, age, gender, underlying diseases (e.g., diabetes mellitus, hypertension, hyperlipidemia, and heart diseases), smoking, family history of cardiovascular or cerebrovascular diseases, age when the first stroke attack occurred, final diagnosis, complications, and treatment method used for previous stroke. The time interval of ischemic stroke recurrence was calculated in terms of years and it was classified along with age, sex and other variables and the impact of each variable on the recurrence of ischemic stroke was investigated.

Outcomes

The primary outcome was to determine the predictors of recurrent ischemic stroke. The secondary outcomes were to provide the characteristic of patients with recurrent ischemic stroke by age, sex, underlying disease, and time interval of ischemic stroke recurrence.

Statistical analysis

The analysis was conducted using the Statistical Package for the Social Sciences (SPSS) version 24 (SPSS Inc., Chicago, IL, USA). To evaluate the normal distribution of variables, the Smirnov-Kolmogorov test was performed. By using descriptive statistical techniques, demographic characteristics were examined and provided with percentages, frequencies, means, and standard deviations (SD). The independent sample T-test or Mann-Whitney U test was used to analyze quantitative variables. Also, we used binary logistic regression to explore the relationship between underlying risk factors affecting on stroke recurrence. Statistical significance was given to p-values under 0.05.

Ethical considerations

Written informed consent was obtained from all of the participants at the beginning of the study. The study protocol was approved by the ethics committee of Tabriz University of Medical Sciences, Tabriz, Iran. All methods were performed in accordance with the national guidelines and regulations.
Results

Of the 100 patients enrolled in the study, among them 59% were men and the mean age was 68.88 years (SD: 10.51) (Table 1). The histogram of the age of study population also indicates that the majority of patients were in the age range of 65 to 75 years (Figure 1). The frequency of the hypertension, diabetes mellitus, heart diseases, smoking, and hyperlipidemia were respectively 79%, 42%, 24%, 15%, and 15%, respectively (Table 1). Among the 100 participants, the interval between the two strokes was reported for 79 of them, which the average time interval of stroke recurrence was 3±2 years, and the time of stroke recurrence was one year or less in 42 cases (Table 1 and Figure 2). Twelve patients had more than one recurrent ischemic stroke attack.

Table 1. Baseline characteristics of participants

<table>
<thead>
<tr>
<th>Variables</th>
<th>Number, mean</th>
<th>Percent, standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline characteristic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>59</td>
<td>59%</td>
</tr>
<tr>
<td>Age, year (mean)</td>
<td>68.88</td>
<td>10.51</td>
</tr>
<tr>
<td><strong>Underlying conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>79</td>
<td>79%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>42</td>
<td>42%</td>
</tr>
<tr>
<td>Smoking</td>
<td>15</td>
<td>15%</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>15</td>
<td>15%</td>
</tr>
<tr>
<td>Heart diseases</td>
<td>24</td>
<td>24%</td>
</tr>
<tr>
<td><strong>Time interval of ischemic stroke recurrence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time interval, year (mean)</td>
<td>2.52</td>
<td>3.34</td>
</tr>
</tbody>
</table>

The regression model showed 90% lower risk of recurrent ischemic events in patients without history of heart diseases (risk ratio (RR): 0.10; 95% confidence interval (CI): 0.03-0.33). Hypertension, diabetes mellitus, hyperlipidemia, smoking, and age did not have a significant effect on the stroke recurrence (Table 2).

Table 2. Binary logistic regression analysis for prediction factors of recurrent ischemic events.
<table>
<thead>
<tr>
<th></th>
<th>Risk ratio</th>
<th>Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>0.76</td>
<td>0.17-3.45</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.45</td>
<td>0.14-1.48</td>
</tr>
<tr>
<td>Heart diseases</td>
<td>0.10</td>
<td>0.03-0.33</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.13</td>
<td>0.24-5.47</td>
</tr>
<tr>
<td>Age</td>
<td>1.01</td>
<td>0.95-1.06</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1.41</td>
<td>0.32-6.29</td>
</tr>
</tbody>
</table>

**Discussion**

In the present cohort study of 100 participants, we assessed clinical phenotype and potential etiologies of stroke recurrence. Our findings showed no significant association between underlying diseases, smoking, and age with recurrence of ischemic stroke except for history of heart diseases.

The risk of recurrent stroke might depend on the type of initial stroke, known mechanisms such as carotid stenosis, atherosclerosis, atrial fibrillation and other causes, mostly are modifiable and determination and management of above-mentioned factors help to prevent stroke recurrence (11). The importance of these diagnostic measures is to eliminate the etiology of the recurrent stroke and cerebrovascular diseases. Diagnostic studies are the primary diagnostic measures in the first step, because most of the etiologic sources could easily be identified (12). Evidence show that the rate of stroke recurrence in patients with intracranial or carotid atherosclerosis is higher than other causes (6). In addition to these factors, there are other reasons responsible for stroke recurrence which must be identified and managed promptly (6).

In the first 12 months after the initial stroke, the risk of a second stroke is 8–12% and within five years, the risk of recurrent stroke reaches to 16.6% (11). Mortality rate after second stroke is higher than initial stroke (9). The findings of a retrospective study indicated that the statistics about the risk of recurrent stroke is different in various countries, which can be due to differences in patient treatment and management methods, study methodology, and follow-up duration, which means that the mentioned differences lead to the different findings of the risk factors of recurrent stroke (13).

Irie and colleagues included 368 patients with stroke with a history of hypertension in the initial stroke hospitalization and second stroke attack during follow-up period. In this study, a J-type relationship was identified between post-stroke diastolic blood pressure and stroke recurrence. Patients who had a diastolic blood pressure between 80 and 84 mmHg after stroke had a risk of recurrent stroke by 3.8%, which was significantly lower than other groups which had lower (p < 0.05) and higher (p < 0.01) diastolic blood pressures (14). In other population-based studies, blood pressure has been shown as an independent risk factor for ischemic stroke recurrence (15). In this regard, a recent systematic review and meta-analysis on risk factors of ischemic stroke recurrence showed that hypertension increased the risk of stroke recurrence by 1.67 time (odds ratio (OR): 1.67, 95% CI: 1.45, 1.92, P < 0.00001) (6). In the same
way with the above-mentioned studies, the present study also showed that hypertension significantly increased the risk of ischemic stroke. However, our results showed no significant association between hypertension and recurrent ischemic stroke (RR: 0.76; 95% CI: 0.17–3.45). Additionally, in systolic blood pressure of 130 to 160 mmHg, for every 10 mmHg increase in blood pressure, the probability of stroke recurrence increases by 28% (16). Therefore, reducing blood pressure greatly reduces the risk of cardiovascular diseases and treatment by antihypertensive agents should be considered as one of the most important measures to prevent primary and recurrent strokes. As a result, treatment of blood pressure in patients with a history of stroke should be done more aggressively to keep it at a lower level and even in some guidelines, more emphasis has been placed on the treatment of blood pressure than diabetes (11).

In some studies, other unrelated factors have also been introduced as the cause of stroke recurrence, such as alcohol consumption, hyperlipidemia, and atrial fibrillation (17). The results showed that the history of heart diseases and arterial narrowing of large cerebral vessels is significantly related to the occurrence of recurrent stroke or transient ischemic attack one year after the initial stroke (11). Findings of the article by Lai and colleagues showed that age, gender, history of hypertension, diabetes, and previous strokes were not related to ischemic stroke recurrence (18). According to University of Massachusetts Framingham studies, heart diseases were more likely to cause strokes in the population with this disease. Stroke occurs on average about ten years after cardiovascular events such as myocardial infarction in the population that had not regular visits and follow-up (19). In addition, an observational study in Turkey showed that transient ischemic attack (OR: 2.98; 95% CI: 1.54–5.76), hypertension (OR: 1.96; 95% CI: 1.11–2.64), and atrial fibrillation (OR: 1.74; 95% CI 1.44–2.66) were significantly associated with recurrent ischemic stroke (20). Moreover, atrial fibrillation (OR: 1.88; 95% CI: 1.56, 2.25, P < 0.00001) and coronary heart disease (OR: 1.77, 95% CI: 1.31, 2.39, P = 0.0002) were significantly associated with ischemic stroke recurrence (6). Findings of our study showed a significant 90% lower risk of recurrent ischemic stroke in those without history of heart diseases (RR: 0.10; 95% CI: 0.03–0.33). It can be as a result of small sample size that was included in the present study and can be evaluated in the future meta-analysis or large-scale cohort studies.

Regarding the effects of age on ischemic stroke recurrence, a meta-regression showed that age does not have a significant role in the heterogeneity between the studies (7). Moreover, a population-based study on 2874 patients with stroke over 1995–2004 in the United Kingdom showed that older age was associated with significant increased risk of recurrent stroke at ten years (p = 0.04), while it did not have significant results at one and five years follow-up (21). In addition, our logistic regression analysis showed no significant association between ischemic stroke recurrence and age (RR: 1.01; 95% CI: 0.95–1.06).

We also found no significant association between diabetes mellitus (RR: 0.45; 95% CI: 0.14–1.48) and smoking (RR: 1.13; 95% CI: 0.24–5.47) and ischemic stroke recurrence which was mostly due to the small sample size of our study. Results of a meta-analysis of 11 studies including 14455 of patients with initial stroke and 1545 patients with recurrent stroke showed that diabetes mellitus significantly increased the
risk of recurrent stroke (OR: 1.50; 95% CI: 1.30–1.72, P < 0.00001), while smoking did not have a significant relationship with recurrent stroke (OR: 0.96; 95% CI: 0.80–1.15, P = 0.62) (6). A study conducted in Northern Sweden over 1995–2008 on 6700 patients with the aim to determine the predictors of stroke recurrence showed that diabetes mellitus was one of the significant predictors of stroke recurrence (HR: 1.34; 95% CI: 1.15–1.57) (22). Furthermore, a population-based study conducted in Australia showed that diabetes mellitus as a prognostic factor for stroke recurrence (HR: 2.10; 95% CI: 0.95, 4.40) (23).

In a study in northern Manhattan, the history of hypercholesterolemia in people with atherosclerotic ischemic stroke was detected more than in other people with other types of ischemic stroke, and it predicts the possibility of intracranial atherosclerosis (24). Moreover, the results of the meta-analysis by Zheng et al. revealed that dyslipidemia was not significantly associated with recurrent stroke (OR: 0.92; 95% CI: 0.67–1.27, P = 0.62) (6). Similarly, we found no significant association between hyperlipidemia and ischemic stroke recurrence (RR: 1.41; 95% CI: 0.32–6.29). The differences between the studies could be as a result of using different definitions for hyperlipidemia and using various kits for measurement of lipid profile in studies. Therefore, further large-scale studies are needed to determine the relationship between stroke and hyperlipidemia.

The study has several limitations which should be considered in the interpretation of the results. First, we only included patients with ischemic stroke while other types and subtypes of the disease was not included. Moreover, the study was conducted in a small specific population in Iran. Therefore, the findings cannot be generalized to other populations or to other types of strokes. Second, because this study was observational in nature, we were unable to determine a cause-effect relationship. Third, retrospective method of the research has limitations in terms of data collection, participant enrollment, and control group availability. Fourth, we only collected data regarding heart disease overall, while different types of cardiovascular diseases were not reported in the present study. Fifth, we only included 100 participants, so we could not find a statistically significant association.

**Conclusions**

We only found a reduced risk of stroke in patients without history of heart diseases. Nevertheless, clinical evaluations and proper management of comorbidities in patients with stroke should be considered to reduce the risk of recurrent ischemic stroke. Future studies should evaluate the effects of controversial factors on ischemic stroke recurrence, using large-scale observational studies and systematic reviews.

**Declarations**

**Ethics approval and consent to participate**

Written informed consent was obtained from all of the participants at the beginning of the study. The study protocol was approved by the ethics committee of Tabriz University of Medical Sciences, Tabriz,
Iran. All methods were performed in accordance with the national guidelines and regulations.

**Consent for publication**

Not applicable.

**Availability of data and materials**

The datasets generated and/or analyzed during the current study are not publicly available due for they are personal data but are available from the corresponding author on reasonable request.

**Competing interests**

The authors declare that they have no conflicts of interests.

**Funding**

None.

**Authors’ contributions**

S.S., Y.S.: designed the study. S.S., Y.S., F.M.: patient data acquisition, statistical analysis, and interpretation of data. S.A.N., Y.S.: preparation and critically revision of the manuscript. All the authors have read and approved the final version of the manuscript.

**Acknowledgments**

None.

**References**


Figures

![Age histogram of patients with recurrent ischemic stroke included in the study.](image)

**Figure 1**

Age histogram of patients with recurrent ischemic stroke included in the study.
Figure 2

Time interval of ischemic stroke recurrence in patients with ischemic stroke.