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Five-Year Recurrence Rate and the Predictors Following Stroke in the Mashhad Stroke Incidence Study: A Population-Based Cohort Study of Stroke in the Middle East

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Keywords
Stroke · Recurrence rate · Iran · Middle East

Abstract
Background: Little is known about the risk of recurrent stroke in low- and middle-income countries. This study was designed to identify the long-term risk of stroke recurrence and its associated factors. ***Methods:*** From November 21, 2006 for a period of 1 year, 624 patients with first-ever stroke (FES) were registered from the residents of 3 neighborhoods in Mashhad, Iran. Patients were followed up for the next 5 years after the index event for any stroke recurrence or death. We used competing risk analysis and cause-specific Cox proportional hazard models to estimate the cumulative incidence of stroke recurrence and its associated variables. ***Results:*** The cumulative incidence of stroke recurrence was 14.5% by the end of 5 years, with the largest rate during the first year after FES (5.6%). Only advanced age (adjusted hazard ratio [HR] 1.02; 95% CI 1.01–1.04) and severe stroke (National Institutes of Health Stroke Scale score >20; HR 2.23; 95% CI 1.05–4.74) were independently associated with an increased risk of 5-year recurrence. Case fatality at 30 days after first recurrent stroke was 43.2%, which was significantly greater than the case fatality at 30 days after FES of 24.7% ($p = 0.001$). ***Conclusion:*** A substantial number of our patients

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either died or had stroke recurrences during the study period. Advanced age and the severity of the index stroke significantly increased the risk of recurrence. This is an important finding for health policy makers and for designing preventive strategies in people surviving their stroke.

Introduction

Stroke recurrence rates vary widely between countries with less information in low- to middle-income countries [1]. Although some international efforts, such as Global Burden of Disease study, provide worldwide data regarding burden of stroke [2], there is still a high level of uncertainty regarding stroke estimates, particularly in low- to middle-income countries without national-based health surveillance systems. Cohorts or repeated cross-sectional epidemiological studies from such countries are instrumental in providing these estimates. In addition, the relationship between stroke types and long-term recurrence has not been thoroughly investigated [3].

In a population-based study of stroke, the Mashhad Stroke Incidence Study (MSIS), we have previously shown an excessive rate of stroke in Iran as compared to many western countries [4]. In this study, we sought to determine the 5-year risk of stroke recurrence and the associated risk factors in the MSIS.

Methods

Study Population

MSIS is a prospective population-based stroke cohort [4]. From November 21, 2006 to November 20, 2007, all cases with stroke were recruited from 3 different neighborhoods (total population 450,229; online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000485509). The study was approved by the Ethics Committee of the Mashhad University of Medical Sciences, Iran.

Definitions

Stroke was defined according to the World Health Organization criteria [5]. Recurrent stroke was defined as stroke-like symptoms that occurred at least 24 h after the index event, and were not attributable to edema, mass effect, brain shift syndrome, or hemorrhagic transformation [6, 7].

Follow-Up

Patients or their proxies were telephoned at 28 days, 1 and 5 years after their index stroke, and were asked to participate in an outpatient face-to-face follow-up visit. Severely disabled patients, who could not visit the outpatient department, were mostly assessed in their homes, but in a few cases, only telephone interviews were conducted. From March 10, 2013 to January 21, 2014, 3 investigators (A.A., P.H., and Abbas Heshmati) and community health volunteers visited the patient's most recent addresses and checked with patients or neighbors for any change in contact numbers or address [8].

Statistical Analysis

We used competing risk analysis to determine the cumulative incidence of recurrent stroke, with death considered a competing event for recurrence. Kaplan-Meier analysis was used to determine cumulative risk of death during the 5-year period of follow-up. To control for the effect of previous strokes, first-ever stroke (FES) was considered the denominator in the data analyses. We assessed the role of all prognostic variables on stroke recurrence using univariable and multivariable cause-specific Cox proportional hazard regression (backward stepwise model) analyses. R statistical software was used to run competing risk analysis and cause-specific Cox proportional hazard regression with 95% CIs. SPSS statistical software version 16 (SPSS Inc., Chicago, IL, USA) was used for all other analyses.

Results

Cohort Characteristics

In total, 684 patients with acute stroke were registered in the MSIS, of whom 624 had FES (online suppl. Fig. 1). Among those with FES, there were 512 (82.1%) ischemic strokes, 80 (12.8%) intracerebral hemorrhages, 14 (2.2%) subarachnoid hemorrhages, and 18 (2.9%) undefined strokes. Despite all attempts, 69 patients were lost to follow-up due to change of address or loss of contact; 3 immediately after discharge from hospital, 5 during the first year, and 61 patients after 1 year (online suppl. Table 1).

Recurrence Risk

During the 5-year follow-up period, among 624 FES, 330 patients died and 81 patients had at least one recurrent stroke. The majority of recurrent events following FES were reported within the first year after the index stroke, with 7 (1.1%) occurring within the first 30 days and 29 (4.6%) occurring between the first month and the first year. Competing risk analysis accounting for death demonstrated that the cumulative incidence of recurrent stroke over 5 years was 14.5%, with the greatest incidence of first recurrence during the first year (5.6%; Fig. 1; online suppl. Table 2).

Case Fatality

Among those with FES who experienced recurrence, 64.2% (52/81) died within 5 years after the index stroke. Case fatality at 30 days after first recurrent stroke was 43.2%, which was significantly greater than the case fatality at 30 days after FES of 24.7% ($p = 0.001$). However, at 5 years after stroke, there was no detectable difference

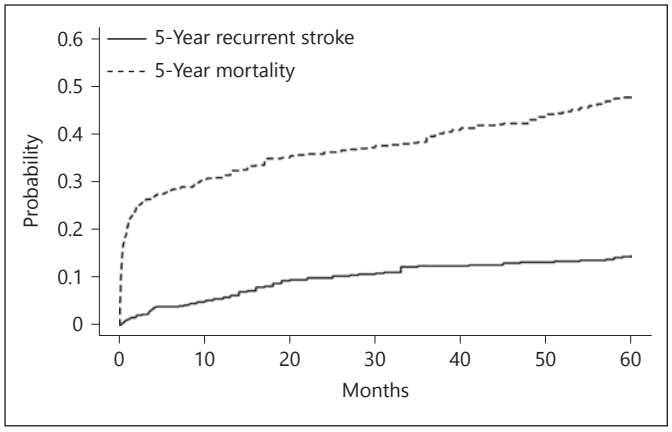

Fig. 1. The cumulative incidence of recurrent stroke accounting for competing risk of death after the index first-ever stroke during the 5-year study period.

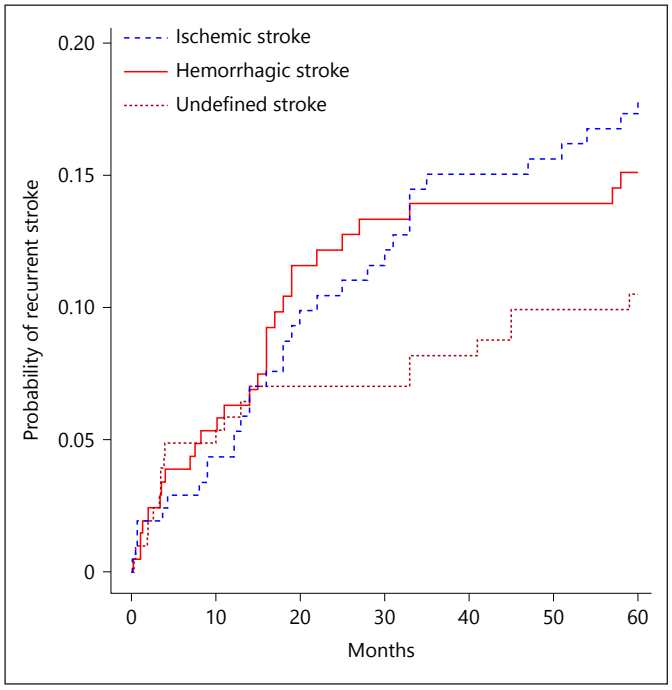

Fig. 2. The cumulative incidence of recurrent stroke during the 5-year study period: a competing risk analysis of death according to the index first-ever index stroke types.

between these groups (68.1% among those with any recurrent event and 55.2% among those without a further event, $p = 0.7$). Although stroke, by itself, was the most common reason for death among all patients, after recurrence the rate of death due to stroke increased significantly (69.2% in patient with recurrence, 36% in those without recurrence; $p < 0.001$).

Association between Index Stroke Subtype and Risk of Recurrence

At the 5-year follow-up, patients with ischemic stroke (17.9%) had the largest cumulative incidence rate of recurrent stroke, followed by hemorrhagic stroke (15.1%) and undefined stroke (10.5%). However, these differences were not statistically significant ($p = 0.1$; Fig. 2; online suppl. Table 2).

Factors Associated with Recurrence

In univariable cause-specific Cox proportional hazard regression analysis, increasing age and history of atrial fibrillation were associated with an increased 5-year risk of recurrent stroke (online suppl. Table 3). In multivariable analysis, the only factors independently associated with an increased risk of stroke recurrence at 5 years were older age (hazard ratio [HR] 1.02; 95% CI 1.01–1.04) and severe stroke, as based on the NIHSS score (HR 2.23; 95% CI 1.05–4.74).

Color version available online

Discussion

Our study has major clinical and public health implications. First and foremost, to the best of our knowledge, the MSIS is the only population-based study of stroke in the Middle East, and so provide unique data on recurrences and deaths in this region. A substantial number of our patients with FES either died (330/624) or had a recurrent stroke (81/624). After controlling the competitive effect of death, 5-year recurrence was 14.5%. The largest rate of recurrence was observed during the first year after the index events. Stroke severity at the time of the index stroke and advanced age were associated with an increased risk of stroke recurrence. In addition, 30-day case-fatality was greater in those with a recurrent stroke than those without.

Recurrence following an initial stroke has not been thoroughly investigated, particularly in low- to middle-income countries. In our study, one out of 6 patients with FES had at least one recurrent event within 5 years of their stroke. In a recent meta-analysis, 5-year stroke recurrences varied from 16 to 32% [1]. However, none of these studies were conducted in the Middle East. Although the proportion of our subjects having recurrences is less than in some of these prior studies, the majority of these studies were performed between 10 and 30 years ago [9–12] (Fig. 3). Likewise, stroke case fatality in our study was similar to those reported in high-income countries 2–3 decades ago [13–15]. Such a high rate of death may affect

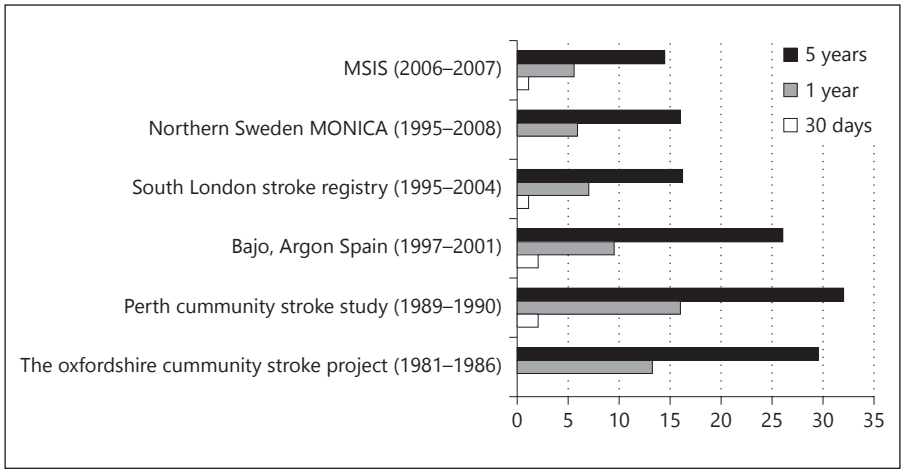

Fig. 3. The 30-day, 1- and 5-year cumulative risk of the recurrent stroke among patients with first-ever strokes: a comparison between population-based studies of stroke from the 1980s to 2008.

the rate of recurrence but, in competing risk analysis, death did not affect the recurrence rate. Similar to a previous study [10], we showed that recurrent stroke is more likely to be fatal than initial stroke. Furthermore, significantly larger proportions of patients with a history of recurrence died due to stroke itself, emphasizing the importance of secondary prevention. Similar to previous studies [16, 17], we found that advanced age was associated with more frequent recurrences. A relatively younger age of our patients at time of index strokes [4] might also affect the rate of stroke recurrence.

Despite having an estimated HR above 2 in univariable analysis, AF did not appear to be independently associated with stroke recurrence. It is possible that the prevalence of AF is underestimated in our sample, partly because only patients who were hospitalized had long-term cardiac monitoring.

Our study has some limitations. We were unable to identify the underlying pathophysiology of recurrent stroke in the majority of cases, as many patients died or became disabled after recurrence. We cannot also comment on the effects of treatment on recurrence figures, as we have limited information about the long-term compliance of our patients (online suppl. Table 4). Although recurrences after stroke may have changed since this study was completed, our data are relatively contemporaneous with case ascertainment being completed in 2007 and follow-up completed in December 2012. Strengths of this study include the use of several overlapping sources to find cases of stroke, including revisiting all cases. Furthermore, our study provides unique data, being the first population-based study of stroke in the Middle East with long-term outcome after stroke. A large sample size of patients with stroke and recurrences provides adequate statistical power for the outcomes assessed. Thus, we provide novel information about the long-term outcome of stroke in Iran and, potentially, many similar with similar risk factors and health care systems.

Conclusion

The rate of stroke recurrence in our study is comparable with stroke recurrence in high-income countries between 1 and 3 decades ago. A considerable number of our patients died or had recurrent events. Case-fatality was poorer in those having a first stroke recurrence than in those with a first-ever stroke. Further studies, from both low- to middle-income and high-income countries are necessary to implement worldwide preventive measures against stroke recurrence.

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Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

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