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Abstract:

Background: Population-based data regarding stroke among women are scarce in developing countries. This study was designed to determine whether sex differences exist in stroke incidence, mortality, and recurrence.

Methods: The Mashhad Stroke Incidence Study (MSIS) is a population-based cohort study in Iran. For a period of one year, all patients with stroke in three geographical regions in Mashhad were recruited and then followed up for 5 years. Age- and sex-specific crude incidence rates were standardized to the WHO New World Population. Male/female incidence rate ratios were assessed for all age groups and all subtypes of first ever stroke (FES).

Results: The annual crude incidence rate of FES (per 100000 population) was similar in men (144; 95% CI: 129-160) and women (133; 95% CI: 119-149). Standardized FES annual incidence rates were 239 (95% CI: 213-267) for men and 225 (95% CI 200-253) for women, both greater than in most western countries. There were no significant differences in stroke recurrence or case-fatality between women and men during early and long-term follow up

Conclusion: The similar incidence of stroke between men and women highlights the importance of equally prioritizing adequate preventive strategies for both sexes. The greater relative incidence of stroke in women in Mashhad compared with other countries warrants improvement of primary and secondary stroke prevention.

Introduction:

The underlying ethology, incidence, mortality and outcomes of stroke vary substantially between men and women (1). Although age-specific stroke rates are greater in men, women have more absolute numbers of stroke and poorer outcomes than men due to longer life expectancy and higher incidence rates at age >85 years (1,2). Stroke may also be more severe in women (3), and with a greater 30-day case fatality (4).

Valid data regarding women stroke are scarce, particularly in the low/middle-income countries. The current study is designed to investigate sex-specific differences in stroke incidence, mortality and recurrence during five-year follow up in Mashhad, Iran.

Methods and patients:

Population:

The present study is part of the Mashhad Stroke Incidence Study (MSIS). The methods of the MSIS have been previously described (5, 6). Using multiple overlapping sources all individuals with an acute stroke including ischemic stroke (IS), intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), and undefined stroke (US) and were recruited and followed for 5 years for any changes in health condition (5) (Figure-1; online supplemental data). The study was approved by the Ethics Committee of the Mashhad University of Medical Sciences.

Baseline assessment

We collected details of clinical history, neurological examinations, neuroimaging information, vascular risk factors and socioeconomic status (education, occupation, household income) for all patients. Specific questions regarding menstruation, pregnancies, use of oral contraceptive pills

and menopause were also obtained.

Statistical analysis:

The male/female (M/F) age-adjusted incidence rate ratios were assessed for all age groups and all subtypes of initial stroke. Using the direct method (7) age and sex-specific crude incidence rates were standardized to the WHO New World Population (WHO 2000-2025) standard population. Kaplan-Meier curves were used to compare the cumulative risk of death. Competing risk analysis was used to determine the cumulative incidence of recurrent stroke, with death considered as a competing event for recurrence. Prognostic variables associated with death were assessed using Cox proportional hazard, backward stepwise regression analysis. $P \leq 0.05$ (two sided) was considered to be statistically significant. 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., Illinois, and USA) was used for the rest of the statistical analyses. Patients who were not completely followed were included in the competing risk and Kaplan-Meier analyses until they were followed.

Results:

During the study period, a total of 327 (52.4%) men and 297 (47.6%) women with first-ever stroke (FES) were identified. The mean age of stroke was similar between men (65.0 ± 14.6) and women (64.1 ± 15.0; p=0.6). Women were more likely than men to have a history of hypertension (p<0.001), to be single, divorced or widowed (p<0.001), to be unemployed or a home-maker (p<0.001) and have an educational level of less than 12 years (p-value<0.001). Men more often had a history of coronary artery disease, including myocardial infarction ≤ 27 days (p=0.04) and ≥ 28 days before stroke (p=0.01) than women (Table-1). Despite all attempts, 69 patients were not

accessible 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 first year (Table-1: online supplemental data).

Incidence:

The age-specific crude annual incidence rates of stroke are shown in the table 2. The incidence of FES increased similarly in both sexes with each decade of life, with a significant rise after the age 45. There were no differences in overall standardized FES incidence rates between men (239, 95% CI: 213-267) and women (225, 95% CI: 200-253) either. Similarly, no sex differences were found for any age group. The total M/F incidence ratio was 1.06 (95% CI: 0.9-1).

Stroke Subtypes

The total male/female incidence rate ratios were similar across all types of stroke (Table-3). Age-adjusted incidence rate of ICH among women <45 years were almost 3.5 fold higher than men in same age group (F/M ratio: 3.5; 95% CI: 1-11). No significant differences were observed across all subtypes of IS (Table-2; online supplemental data).

Stroke Recurrence

Women and men had similar rate of recurrent stroke either at one year (women: 5.4% vs men: 5.5%, Log rank P= 0.7) and five years after index stroke (men: 13.2% vs women: 13%, Log rank P= 0.7) (Figure-1). Multivariate cox proportional hazard model revealed that only the National Institutes of Health Stroke Scale (NIHSS; HR: 1.05, 95% CI: 1.01-1.09) and age (HR: 1.03, 95% CI: 1.01-1.04) were significantly associated with five-year recurrence rate for men.

Case fatality

Case fatality was similar in women and men at 30 days (women: 20.4% vs men: 21.2%), one year (women: 31.3% vs men: 35.5%) and five years (women: 53.8% vs men: 60.5%) with no statistically significant differences (Log-rank P: 0.1) (Figure-2). Stroke itself was the most common reason for death in both women (43.2%) and men (39.7%; p= 0.9).

In univariable Cox proportional hazard regression, increasing age, NIHSS at admission, history of atrial fibrillation and having less than 12 years of education were associated with an increased 5-year risk of death for both sexes (Table-4). Furthermore, other sex-specific factors increasing risk of five-year death among men and women are also shown in table 4.

The multivariable Cox proportional hazard model evidenced that advanced age (men: HR: 1.03, 95% CI: 1.02-1.04; women: HR: 1.03, 95% CI: 1.02-1.05) and NIHSS (men: HR: 1.11, 95% CI: 1.09-1.12; women: HR: 1.12, 95% CI: 1.1-1.14) were significantly increased the risk of death during five-year after FES in both men and women. Furthermore, a history of hypertension (HR: 1.5, 95% CI: 1.1-2.1) was also significantly associated with increased five-year case fatality for men. Among women, a history of atrial fibrillation (HR: 2.04, 95% CI: 1.3-3.2), current smoking (HR: 1.8, 95% CI: 1.1-3) and having less than 12 years of education (HR: 7.3, 95% CI: 1.7-30.9) were significant predictors of five-year case fatality.

Discussion

Our study has important implications regarding sex-specific differences in stroke epidemiology. In contrast to many studies, the annual incidence rate of FES, the mean age at stroke onset and long-term risk of recurrent stroke and mortality were similar in our male and female subjects. In addition, the level of education had a significant effect on the mortality rate among women.

Stroke incidence and mortality vary significantly between men and women. As compared to some high-income countries (8–10), we observed higher age-adjusted incidence rates of FES for both sexes in the MSIS. This finding can be probably due to a relatively younger age distribution in Mashhad (5). In many studies, stroke reported more frequently in men (about 33%) than women (4). Such differences can be partially explained by an overall longer life expectancy among women (11). In our study, although the annual incidence rate of FES among men was 6% higher than women, this figure did not reach a significant value. This is an important finding, highlighting a greater burden of stroke among women in the MSIS. In addition, the age of stroke also varied in men and women. In a systematic review, the mean age of stroke among women and men were 72.9 years and 68.6 years, respectively (4). We found that a relatively younger age for stroke occurrence, with a similar mean age at stroke onset among women and men (at ~65 years). Having added this finding to a relatively higher rate of stroke in women in our population indicates a dramatically higher burden of women stroke, emphasizing a target oriented plan to control stroke in women.

To assess the possible reasons of the higher incidence rate of women strokes, we reviewed vascular and demographic risk factor, stratifying subjects according to their age and menopausal status. In total, hypertension was more frequently observed in women than men. In addition, socioeconomic status was also different, with a higher rate of unemployment and low educational level (<12 years) in women. These findings may partially explain our significant difference with many studies which needs long-term public plans to fight against stroke in women.

Studies regarding stroke etiology according to sex are also scarce. Some studies showed higher incidence rates of ICH and IS among men than those in women (3, 4, 9). Such differences might be explained by the difference in the frequency of vascular risk factors (i.e. smoking, addiction

and alcohol overuse among men) (3). In contrast, despite the presence of different vascular risk factors, our women and men had similar incidence rates across all subtypes of stroke. However, among patients with ICH, women <45 had significantly a higher incidence of stroke (3.5 fold) compared to men at similar age groups. Inconsistent with previous reports (4, 12), SAH was more common among men in Mashhad; however, due to relatively low sample size in SAH, this finding should be taken into account with cautions.

We did not find a significant difference in the overall mortality and recurrence rates of stroke among men and women. A systematic review showed that the 30-day case fatality of stroke was 1.25 fold greater in women than men (4) which could be attributable to higher mean age of women than men at time of first stroke. The lack of difference in case fatality in our study, might be due to the age distribution of stroke in men and women in our population. In the MSIS, education less than 12 years was also an independent predictor of five-year death in women. In the Framingham study, the highest stroke case fatality for men and women was attributed to SAH and ICH (13). A similar pattern was observed in our study with the highest 30-day cumulative rate of death in SAH (for men) and ICH (for women). Women had a higher incidence of ICH at younger ages and died more commonly than men due to ICH within 30-day after the index stroke. This might be explained by a larger prevalence of hypertension in our women than men.

There are some limitation which may affect our results. We were not able to completely follow up eleven percent of patients during five-year period of study. Among these patients, both male and female were significantly younger and had lesser severity of stroke than those who were followed up. So their inclusion may have somewhat modified the risk factors independently associated with the risk of recurrence and death for men and women if any of these people had a recurrent event or died.

To control any source of bias in data collection at baseline and follow up period for men and women, we reviewed the frequency of patients admitted in hospitals versus those who solely managed in the community and also any differences in basic characteristic among those with and without complete follow up time. Hospital admission rates were similar between both sexes (62.4% of men and 64.6% women). Therefore, we believe that we were able to capture all men and women with stroke accurately. Finally, an almost door- to -door survey with the help of about 1000 volunteers provided a detailed information about any possible stroke in the study area. Dropout rates during follow up period were similar between men and women. In addition, the list of missing variables, those who lost to follow and those without imaging (undefined strokes) were not significantly different between both sexes.

In summary, a relatively high incidence of stroke among women with a higher rate of death in less educated patients warrant a thorough prevention methods not only to control risk factors but also to improve public health general knowledge. Furthermore, as women tend to live longer, according to the higher life expectancy in Iran (male/female: 74/77), the fact that there is no difference in the age of onset of stroke, is another disadvantage for women which will live longer with their disability.

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Table 1. Characteristics of the Mashhad stroke incidence Study cohort by sex.

Variable	Male N (%)	Female N (%)	P value
Age (mean ± SD)	64.99 ±14.6	64.11 ± 15.03	
Hypertension	165 (50.9)	208 (70.3)	<0.001
History of Transient Ischemic Attack	26 (8)	23 (7.7)	
Diabetes	98 (30.2)	89 (30)	
Hyperlipidemia	70 (21.7)	78 (26.6)	
Atrial fibrillation	24 (7.6)	28 (9.7)	
History of acute myocardial infarction ≤27 days before stroke	9 (2.8)	2 (0.7)	0.04
History of acute myocardial infarction ≥28 days before stroke	39 (11.9)	18 (6.1)	0.01
History of Dementia	14 (4.3)	9 (3)	
Current smoker	61 (18.7)	37 (12.5)	0.03
Ex-smoker	66	32	0.001
Addiction	54 (16.5)	24 (8.1)	0.001
Alcohol (daily drinker)	18 (5.6)	0	<0.001
Family history of stroke	54 (16.5)	58 (19.5)	
Married	284 (87.7)	180 (61.2)	<0.001
Household income			
Low	165 (50.5)	171 (57.6)	
Medium	132 (40.4)	106 (35.7)	
High	30 (9.2)	20 (6.7)	
Patient`s occupation			
Work pre stroke	178 (58.4)	14 (4.8)	
Retired	86 (26.5)	5 (1.7)	<0.001
Disabled	7 (2.2)	2 (0.7)	
Unemployed or home maker	54 (16.6)	270 (92.8)	
Education			
≤ 12 years	233 (71.7)	261 (90)	<0.001
≥ 13 years	92 (28.3)	29 (10)	
NIHSS at admission	10.9 ± 10.34	10.7 ± 10.2	

*Abbreviation (in alphabetic order): National institutes of health stroke scale (NIHSS)

Table 2. The age and sex specific and WHO age-adjusted incidence rates of first-ever stroke in Mashhad, Iran.

Age group (years)	Men			Women			Male/Female ratio (95% CI)*
	Population	Number	Incidence (95% CI))	Population	Number	Incidence (95% CI))	
<45	186087	26	14 (9-20)	183256	32	17 (12-24)	0.8 (0.5-1)
45-54	20681	51	247 (186-321)	19915	42	211 (154-282)	1.17 (0.8-2)
55-64	10146	69	680 (533-855)	9950	66	663 (517-838)	1.03 (0.7-1)
65-74	6820	83	1217 (976-1500)	6283	73	1162 (917-1452)	1.05 (0.8-1)
75-84	3109	77	2477 (1969-3077)	2835	63	2222 (1723-2823)	1.1 (0.8-1.5)
>85	556	21	3777 (2407-5664)	591	21	3553 (2265-5329)	1.06 (0.6-2)
Total	227399	327	144 (129-160)	222830	297	133 (119-149)	
WHO age-adjusted			239 (213-267)			225 (200-253)	1.06(0.9-1)

*Male/Female age-adjusted incidence rate ratio; CI, Confidence Interval; WHO, World Health Organization; Incidence is per 100,000 population per year.

Table 3. The age and sex specific incidence rates per 100000 along with the male-female incidence ratio for all subtypes of first ever stroke.

Age groups	Ischemic Stroke					Intracerebral Hemorrhage				
	Male		Female		Male/Female ratio (95% CI)*	Male		Female		Male/Female ratio (95% CI)*
	Number	Incidence rate	Number	Incidence rate		Number	Incidence rate	Number	Incidence rate	
<45	19	10	22	12	0.9 (0.5-2)	2	1.1	7	3.8	0.3(0.06-2)
≥45	245	593	226	571	1.03 (0.9-1)	43	104	28	70.7	1.5(1.02-2)
Total	264	116.1	248	111.3		45	19.7	35	15.7	
WHO age-adjusted	172 (152-195)		168 (147-190)		1.02 (0.9-1)	30 (22-40)		22 (15-31)		1.3 (0.9-2)

Table 3 continued:

Age groups	Subarachnoid Hemorrhage					Undefined Stroke				
	Male		Female		Male/Female ratio (95% CI)*	Male		Female		Male/Female ratio (95% CI)*
	Number	Incidence rate	Number	Incidence rate		Number	Incidence rate	Number	Incidence rate	
<45	3	1.6	2	1.1	1.5(0.4-7)	2	1.1	1	0.5	2 (0.5-13)
≥45	5	12.1	4	10.1	1.2(0.5-3)	8	19.4	7	17.7	1.1(0.5-3)
Total	8	3.5	6	2.7		10	4.4	8	3.6	
WHO age-adjusted	4.5 (2-9)		4 (1-8)		1.3 (0.5-3)	6 (3-11)		5 (2-11)		1.2 (0.6-3)

Table 4: Univariable analysis of risk factors for mortality during five years after first ever stroke using Cox proportional hazards regression.

Variable	Male			Female		
	Five-year death		Hazard ratio (95% CI)	Five-year death		Hazard ratio (95% CI)
	Yes N (%)	No N (%)		Yes N (%)	No N (%)	
Age (mean±SD)	69+13.3	59.8+14.7	1.03 (1.01-1.04)	70.4+13.7	57.8+13.7	1.04 (1.03-1.06)
NIHSS at admission (mean±SD)	14.3+11.4	4.7+5.1	1.09 (1.07-1.1)	14.9+11.5	5.2+5.6	1.1 (1.08-1.1)
History of TIA before index stroke	17 (9.2)	9 (6.3)	1.4 (0.8-2.3)	12 (8.2)	11 (7.4)	1.2 (0.7-2.2)
Diabetes mellitus	60 (32.6)	37 (26.1)	1.07 (0.8-1.4)	39 (26.7)	48 (32.2)	0.8 (0.6-1.2)
Hypertension	111 (60.3)	53 (37.3)	1.7 (1.3-2.3)	103 (70.5)	104 (69.8)	1.03 (0.7-1.5)
Atrial fibrillation	20 (10.9)	4 (2.8)	2.3 (1.4-3.6)	21 (14.4)	7 (4.7)	2.4 (1.5-3.7)
Hyperlipidemia	44 (23.9)	26 (18.3)	1.1 (0.8-1.6)	33 (22.6)	45 (30.2)	0.7 (0.5-1.1)
Current smoker	26 (14.1)	35 (24.6)	1.7 (1.1-2.6)	18 (12.3)	18 (12.1)	0.9 (0.6-1.6)
Current alcohol drinker	6 (33.)	12 (8.5)	0.5 (0.2-1.01)	0	0	
Persian ethnicity	152 (82.6)	126 (88.7)	0.7 (0.5-1.04)	122 (83.6)	118 (79.2)	1.2 (0.8-1.9)
Index stroke						
Intracerebral hemorrhage	29 (15.8)	16 (11.3)	1.3 (0.5-3.1)	20 (13.7)	15 (10.1)	1.9 (0.6-6.5)
Ischemic stroke	145 (78.8)	118 (83.1)	0.8 (0.3-1.7)	123 (84.2)	123 (82.6)	1.4 (0.5-4.5)
Subarachnoid hemorrhage	4 (2.2)	4 (2.8)	0.8 (0.2-2.7)	0	6 (4)	

Income						
Low annual income (< $US 2580)	98 (53.3)	66 (46.5)	1.1 (0.7-1.7)	99 (67.8)	70 (47)	3 (1.2-7.5)
Middle annual income ($US 2580 -5160)	67 (36.4)	65 (45.8)	0.9 (0.5-1.4)	42 (28.8)	64 (43)	1.7 (0.7-4.3)
Employment status						
Retired	52 (28.3)	33 (23.2)	1.3 (0.9-1.9)	1 (0.7)	4 (2.7)	0.5 (0.1-4)
Disabled	4 (2.2)	3 (2.1)	1.5 (0.5-4)	2 (1.4)	0	4.1 (0.9-20)
Unemployed	40 (21.7)	14 (9.9)	1.8 (1.2-2.6)	136 (93.2)	132 (88.6)	1.7 (0.8-3.5)
Educated <=12 years	34 (18.5)	60 (42.3)	2 (1.4-2.9)	10 (6.8)	26 (17.4)	2.2 (1.1-4.2)
Family history of stroke	33 (17.9)	21 (14.8)	1.2 (0.8-1.7)	28 (19.2)	29 (19.5)	1.1 (0.7-1.6)

Figure 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 among men and women.

Figure 2. Kaplan-Meier curve showing the five-year probability of death among men and women in MSIS.