European Journal of Internal Medicine 24 (2013) 167–171

Contents lists available at SciVerse ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original article

Sex differences in clinical presentation, severity and outcome of stroke: Results from a hospital-based registry

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ARTICLE INFO

Article history:
Received 8 August 2012
Received in revised form 16 October 2012
Accepted 17 October 2012
Available online 17 November 2012

Keywords:
Acute stroke
Sex difference
Stroke outcome

ABSTRACT

Background and purpose: Sex related differences in cardiovascular disease and stroke are issues of increasing interest. The aim of this study was to evaluate for sex differences in clinical presentation, severity of stroke and outcome in a population of patients admitted to 4 public and 1 private hospitals in three different regions of Italy.

Methods: All hospital admissions for ischemic and haemorrhagic stroke (ICD-IX code 434 and 431 respectively) between January 1st and December 31st, 2011 at five different hospitals located in three different regions of Italy: Milan (North), Rome and Perugia (Center), and Palermo (South) have been recorded and sex-differences have been evaluated.

Results: A total of 1272 stroke patients were included in the analysis: 1152 ischemic and 120 haemorrhagic strokes, 567 women and 705 men. Compared to men, women were significantly older (mean age 75.2 SD 13.7 vs 71.5 SD 12.5 years, $P<0.001$) and their stroke severities at onset, measured by NIHSS, were also compared to men (10 SD 8 vs 8 SD 7, $P<0.001$).

Female sex was associated with a worse functional prognosis measured *by modified Rankin Scale score* (mRS$\geq$3), as well as in-hospital mortality, without reaching statistical significance.

There were no observed significant differences between sexes regarding the number of patients treated with thrombolytic therapy. Analysis of the distribution of risk factors between sexes showed a prevalence of atrial fibrillation in women (29% vs 21%, $P=0.003$).

Conclusions: Both stroke severity and functional outcome were worse in women.

1. Introduction

Stroke in women is a recognized public health issue worldwide because of its influence on post-stroke disability [1]. Since women have longer life expectancies, there is a higher stroke prevalence in women [2,3], and this sex difference in the number of stroke events is expected to increase further over the next few decades [4,5]. Moreover, women have a worse functional outcome after stroke than men [6,7], and a higher mortality especially in the oldest age groups [8]. In fact, at onset, women tend to be 4 to 5 years older, on average, than men and present more comorbidities [9,10], both these variables affect the severity of stroke at presentation and impact the timelines of acute stroke care.

The aim of this study was to evaluate for sex-differences in clinical presentation, severity of stroke and outcome in patients admitted to five hospitals in three different regions of Italy.

2. Subjects and methods

Consecutive stroke patients admitted to five Italian hospitals, 4 public (Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan; Santa Maria della Misericordia Hospital, Perugia; San Camillo Forlanini Hospital, Rome; and Civico Hospital, Palermo) and 1 private

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0953-6205/$ – see front matter
http://dx.doi.org/10.1016/j.ejim.2012.10.004

(San Raffaele Hospital, Milan) from Northern, Central and Southern Italy, discharged with the codes for ischemic and haemorrhagic stroke according to the International Classification of Diseases (ICD-IX codes 434 and 431 respectively) between January 1st and December 31st 2011, were recorded in the Stroke Units databases.

Each database was analyzed for data on sex differences regarding stroke severity at clinical presentation assessed by *National Institute of Health Stroke Scale* (*NIHSS*) [11], functional outcome assessed by *modified Rankin Scale score* (*mRS*) [12] at discharge and in-hospital mortality were recorded.

Each hospital followed Human Research rules and this observational study was approved by the local hospital boards.

All patients were managed in sub-intensive stroke units and standard stroke care guidelines [13,14] were followed.

Patients admitted within 3 h from stroke onset meeting SITS-MOST criteria and according to physicians discretion were treated with thrombolysis [15]. Information concerning inclusion/exclusion criteria for thrombolysis were not collected.

Stroke was classified as large-artery atherosclerotic, cardioembolic, lacunar or cryptogenic according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria [16].

Variables included in study analysis were: (1) baseline demographic characteristics (age and sex); (2) risk factors for stroke (3) clinical stroke severity at admission and at discharge assessed by NIHSS; (4) functional outcome, at discharge and at 3-months follow-up, measured by mRS score; and (5) any difference in thrombolytic treatment and prognosis at the 5 participating hospitals.

Functional outcome was measured according to the mRS: 0, 1, 2 = no- to slight disability; 3,4, 5 = moderate- to severe disability; 6 = death. For the purpose of this study, clinical outcomes (mortality and disability) were assessed at three months, the functional outcomes were assessed by outpatient visits or by structured telephone interviews using mRS. Time of occurrence and cause of death were also recorded. The causes of death were divided into: neurological (stroke recurrence, status epilepticus, edema or herniation), cardiovascular (myocardial infarction, heart failure, sudden death or other cardiovascular diseases and pulmonary embolus), and other causes (pneumonia, cancer, and other causes).

3. Statistical analysis

Pearson's chi-square or Fisher's Exact Test were used to compare categorized proportions.

A comparison of discrete variables was conducted using a non-parametric test (Mann–Whitney).

Multivariate logistic regression was performed in order to define risk factors for dichotomic outcomes.

Multivariate linear regression was carried out with the aim of evaluating independent variables for NIHSS values at entry. An alpha level of 0.05 was used for each statistical test.

No imputation was done for missing data.

4. Results

Over the 12-month study period, 1272 consecutive patients with acute stroke were included in the databases of the 5 participating hospitals: 567 patients were women (45%) and 705 men (55%); 1152 ischemic (521 women vs 631 men) and 120 haemorrhagic strokes (46 women vs 74 men), not statistically significant differences were observed between sexes.

Women were significantly older than men, (mean age 75.2 SD 13.7 vs 71.5 SD 12.5 years, $P<0.001$); date of birth was available for all patients except for 1 woman and 2 men. The length of hospital stay was longer for women (11 SD 8 vs 10 SD 8 days, $p=0.001$), (Table 1).

Table 1
Age, hospital stay and NIHSS at onset and discharge by sex in the whole population.

	Sex	N	Mean	SD	*P* value
Age	Female	566	75.2	13.7	<0.001
	Male	703	71.5	12.5	
Hospital stay	Female	396	10.8	7.8	0.001
	Male	520	9.5	7.5	
NIHSS at onset	Female	550	9.9	7.8	<0.001
	Male	689	7.9	7.0	
NIHSS at discharge	Female	357	6.7	7.5	0.002
	Male	462	4.9	6.2	

Stroke severity at admission assessed by NIHSS score was significantly worse in women than men (NIHSS 10, SD 8; median 7, interquartile range 13 vs NIHSS 8, SD 7; 5 , interquartile range 9, $P<0.001$). Similarly, women resulted significantly more severely neurologically impaired at discharge than men (NIHSS score 7, SD 8; median 3, interquartile range 10 vs NIHSS 5, SD 6; 2 interquartile range 5 $P=0.002$), (Table 1) and multivariate linear regression revealed that female sex and age were significantly associated with greater stroke severity at hospital's admission, (Table 3a).

There was no observed significant difference between sexes in terms of receiving thrombolysis treatment even if there was a slight tendency for men to be treated more frequently (10% vs 12%), (Table 2).

The in-hospital mortality was similar for both sexes (women 5% vs male 4%) (Table 2), and the multivariate logistic model suggested that that the following were independent predictors of in-hospital death: age, stroke severity at onset, and length of hospital stay (Table 3b).

Regarding functional outcome assessed by mRS score, either at discharge (44% vs 37% $P=0.030$) or at 90-day follow-up (51% vs 40%, $P=0.022$), both resulted worse (mRS ≥ 3) for women compared to men (Table 2); 3-months follow-up data were not available for all patients.

Table 4 lists the distributions of risk factors for both sexes: women were less likely to be smokers and alcohol consumers; whereas, history of hypertension, diabetes and dyslipidemia had similar distributions between the sexes. Obesity [17] was more frequent in women without reaching statistical significance, while atrial fibrillation (AF) was statistically significant in women compared to men (29% vs 21%, $P=0.003$).

Table 2
Thrombolytic treatment, in-hospital death and functional outcome by sex.

			F	M	Total	P value
Thrombolytic treatment	No	n	369	465	834	0.392
		%	90.0	88.2	89.0	
	Yes	n	41	62	103	
		%	10.0	11.8	11.0	
	Total	n	410	527	937	
		%	100	100	100	
In-hospital death	No	n	425	560	985	0.499
		%	94.7	95.6	95.2	
	Yes	n	24	26	50	
		%	5.3	4.4	4.8	
	Total	n	449	586	1035	
		%	100	100	100	
mRS score at discharge	<=2	n	252	368	620	0.030
		%	56.1	62.8	59.9	
	3+	n	197	218	415	
		%	43.9	37.2	40.1	
	Total	n	449	586	1035	
		%	100	100	100	
3 months-mRS	<=2	n	89	146	235	0.022
		%	48.9	60.1	55.3	
	3+	n	93	97	190	
		%	51.1	39.9	44.7	
	Total	n	182	243	425	
		%	100	100	100	

Table 3a
Multivariate linear regression analysis for NIHSS at hospital admission.

		beta	*P* value
Sex	F vs M	1.71	<0.001
Age		0.09	<0.001

Patients receiving thrombolysis treatment were fewer in the South compared to the Center and North 9%, 11% and 13%, respectively. A greater proportion of patients in the South were discharged with a worse functional outcome compared to those in the Center and North 54%, 43%, and 33% respectively, $P<0.001$. In-hospital mortalities were similar among the three regions (Table 5).

5. Discussion

In this study, women were older than men at stroke onset with the greatest discrepancies between 75–85 and ≥86 years. These findings are consistent with those reported by other population studies and registries [4,9]. Moreover, data from a European Multicenter Multinational Hospital-Based Registry examining a population of about 4,500 patients found that women were significantly older compared to men at stroke onset [7], as did the "Get with the Guidelines-Stroke (GWTG-Stroke) Program," where more stroke events were reported to be in women >80 years [4], as well as data from a systematic review on sex differences in stroke epidemiology [18].

In this study population, women presented with more severe strokes at onset than men measured by the NIHSS, but no specific symptom profiles for any possible sex-related differences were evaluated. Currently, literature on differences in stroke severity between the sexes is conflicting [19]. In fact, limited evidence suggests that women with stroke present different symptoms than men, as it is known for acute coronary syndrome [20]. Specifically, women are reported to experience more aphasic disorders, visual field disturbances and dysphagia than men; while there have been no reported differences in either motor or sensory deficits [21,22].

Furthermore, stroke in women is more frequently associated with anterior circulation ischemia, while men are more likely to have cerebellar and brainstem symptoms and higher incidences of posterior circulation syndromes than women [23].

Two studies measuring the stroke severity with the Canadian Neurological Scale reported different results. In one, women had greater severity on presentation [19], whereas, the second study reported no sex differences [9]. Two other studies measuring stroke severity with NIHSS reported little or no sex differences [24,25], while a Danish study measuring stroke severity with the Scandinavian Stroke Scale reported more severe stroke in women [26].

Other studies have reported impaired levels of consciousness in women more frequently than men, which could contribute to greater stroke severity [5,27].

In our cohort of patients, the severity of stroke at onset was greater in women regardless of age, that might be also related to their higher pre-stroke morbidity. In this study, greater stroke severity in women led to longer hospital stays. This finding has been confirmed by other studies. Elderly women tend to have longer hospital stays also due to the fact that they more often live alone, are more socially isolated and more severely ill at baseline [6].

Table 3b
Multivariate logistic model for in-hospital death.

	OR	95% CI
Age	1.05	(1.01–1.09)
NIHSS at onset	1.23	(1.17–1.29)
Lenght of stay	0.89	(0.84–0.94)

Table 4
Risk factor distribution by sex.

			F	M	Total	*P* value
Hx of hypertension	No	n	110	157	267	0.319
		%	26.8	29.8	28.5	
	Yes	n	300	370	670	
		%	73.2	70.2	71.5	
	Total	n	410	527	937	
		%	100.0	100.0	100.0	
Diabetes	No	n	286	373	659	0.545
		%	79.4	77.7	78.5	
	Yes	n	74	107	181	
		%	20.6	22.3	21.5	
	Total	n	360	480	840	
		%	100.0	100.0	100.0	
Smoking habit	No	n	395	455	850	0.001
		%	83.9	75.8	79.4	
	Yes	n	76	145	221	
		%	16.1	24.2	20.6	
	Total	n	471	600	1071	
		%	100.0	100.0	100.0	
Alchool consumption	No	n	296	395	691	0.010
		%	99.7	97.1	98.2	
	Yes	n	1	12	13	
		%	0.3	2.9	1.8	
	Total	n	297	407	704	
		%	100.0	100.0	100.0	
Dyslipidemia	No	n	217	294	511	0.905
		%	72.8	72.4	72.6	
	Yes	n	81	112	193	
		%	27.2	27.6	27.4	
	Total	n	298	406	704	
		%	100.0	100.0	100.0	
Obesity	No	n	269	376	645	0.320
		%	90.3	92.4	91.5	
	Yes	n	29	31	60	
		%	9.7	7.6	8.5	
	Total	n	298	407	705	
		%	100.0	100.0	100.0	
TIA	No	n	227	307	534	0.971
		%	95.0	95.0	95.0	
	Yes	n	12	16	28	
		%	5.0	5.0	5.0	
	Total	n	239	323	562	
		%	100.0	100.0	100.0	
AF	No	n	248	350	598	0.01
		%	70.9	78.8	75.3	
	Yes	n	102	94	196	
		%	29.1	21.2	24.7	
	Total	n	350	444	794	
		%	100.0	100.0	100.0	

Table 5
Thrombolytic treatment, functional outcome at discharge and in-hospital death by geographical areas.

			North	Center	South	Total	*P* value
Thrombolytic treatment	No	n	247	457	130	834	0.475
		%	87.3	89.4	90.9	89.0	
	Yes	n	36	54	13	103	
		%	12.7	10.6	9.1	11.0	
	Total	n	283	511	143	937	
		%	100.0	100.0	100.0	100.0	
mRS at discharge	<=2	n	237	317	66	620	<0.001
		%	56.8	66.7	46.2	59.9	
	3+	n	180	158	77	415	
		%	43.2	33.3	53.8	40.1	
	Total	n	417	475	143	1035	
		%	100.0	100.0	100.0	100.0	
In-hospital death	No	n	399	451	135	985	0.469
		%	95.7	94.9	94.4	95.2	
	Yes	n	18	24	8	50	
		%	4.3	5.1	5.6	4.8	
	Total	n	417	475	143	1035	
		%	100.0	100.0	100.0	100.0	

Regarding functional outcome, women tend to have poorer outcomes compared to men. In this study, in fact, women were more disabled, leading to a lower quality of life after stroke compared to men.

To date, only few studies have been conducted with the aim of assessing sex-differences in functional outcome after stroke [6,8,28]. Data from these studies have shown that women have less favourable outcomes, more physical impairments and limitations in activities of daily living (ADL) measured by the Barthel Index compared to men [8,9,23,29,30].

In this study, there was a higher prevalence of AF in women compared to men, and this was probably due to their older age at the time of stroke [31]. Several studies have shown that women are generally at higher risk than men for cardioembolic stroke due to AF [18,32,33], whereas others studies have failed to show this [34]. Given that AF is more prevalent in the elderly [35], and women with AF are less treated than men with anticoagulant therapy in primary prevention [36], due to the facts they are less recruited in RCTs [37], and have a higher risk of thromboembolic complications from AF compared to men.

As cardioembolic stroke is more severe than other stroke subtypes [38], the higher prevalence of AF is more than likely to explain the increased stroke severity in women.

Women have been reported to have a higher stroke case-fatality rate [18] while in our study population, this was not statistically significant. The high rates of loss to follow up at 90 days could explain this result.

In our study, thrombolysis was administered with a slight prevalence in favour of men. This was probably highly influenced by the fact that in Italy there is the age limit of 80 years for thrombolysis treatment (EMEA). This means women ≥80 years of age, which is a significant stroke age group, are excluded a priori from thrombolysis treatment. Recently published data from the IST 3-trial will induce the decision to raise the EMEA thrombolysis age limit of 80 years [39].

Limitations of this study included the following: data were not homogeneous and came from different databases, there was a high percentage of loss to follow up and links between specific neurological symptoms and severity were not evaluated for.

6. Conclusions

This study suggests, as in other studies, that sex-differences in stroke patients do in fact exist, that women are older at stroke onset with higher severity and have worse functional outcome compared to men. Elderly women have been neglected for years by stroke researchers. The only way to face this growing health emergency and to limit health care costs is to better prevent cerebrovascular disease in women. Based upon our observations, we believe that research on sex differences in stroke should be encouraged to better address acute stroke care also by sex.

Learning Points

- To understand potential sex-related differences in stroke manifestations.
- To be aware of the different burden of cerebrovascular disease in women and men.
- To emphasize the importance of including women in randomized clinical trials.

Financial disclosures

Paola Santalucia: has served on the speaker's bureau of Boehringer-Ingelheim and Sanofi-Aventis.

Francesca Romana Pezzella: has received grant from Boehringer-Ingelheim.

Maria Sessa: no disclosure.

Serena Monaco: no disclosure.

Giuseppe Torgano: no disclosure.

Sabrina Anticoli: no disclosure.

Elisa Zanoli: no disclosure.

Mario Maimone Baronello: no disclosure.

Maurizio Paciaroni: has served on the speakers' bureaus of Sanofi Aventis, Guidotti and Boehringer Ingelheim.

Valeria Caso: has served on the speakers' bureaus of Sanofi Aventis and Boehringer Ingelheim.

Acknowledgment

The study was supported by an independent grant from Boehringer-Inghelheim to the Women Stroke Association (WSA).

We thank Dr. Orietta Picconi* for the statistical analysis.

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