Sex similarity of in-hospital stroke fatality in La Rioja (Spain)

Similitudes de género en la letalidad intrahospitalaria por ictus en La Rioja (España)

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Abstract: **Stroke fatality depends on several factors. Some of them (hypertension, diabetes, aging or atrial fibrillation) are well known but the influence of others, such as the sex, is still unclear. The aim of this work was to determine if sex has influence on in-hospital fatality after a first-ever stroke. Patients registered in a discharge hospital database due to a first-ever stroke in 2010 were analyzed. Unadjusted and adjusted analyses of the effect of risk factors in the in-hospital stroke fatality, the sex being the main independent variable, were carried out. All gender differences were statistically evaluated. In the discharge hospital database, 570 patients were registered due to a first-ever stroke (49.1 % were men and 50.9 %, women). Stroke cause the death of 52 patients (13.2 % of men and 20.3 % of women). Results from the bivariate analysis revealed the following significant differences between men and women: age, fatality, and presence of hypertension, coronary heart disease and peripheral artery disease. However, after adjusting for baseline characteristics fatality was similar in women than in men. Even if stroke fatality in women seems to be higher than in men, when adjusting analyses for other risk factors gender differences disappear.**

Key words: **Stroke, Case-fatality, Gender Differences, Equity, Social Epidemiology**

Resumen: **La letalidad por ictus depende de varios factores. Algunos de ellos (la hipertensión, la diabetes, el envejecimiento o la fibrilación auricular) son bien conocidos, pero la influencia de otros, tales como el sexo, todavía no está clara. El objetivo de este trabajo fue determinar si el sexo influye en la letalidad hospitalaria después de un primer episodio de ictus. Se analizaron los pacientes registrados por ictus en una base de datos de altas hospitalarias en 2010. Se analizó, mediante análisis ajustados y no ajustados, el efecto de diferentes factores de riesgo (siendo el sexo la variable principal) en la letalidad hospitalaria por ictus. Se evaluaron estadísticamente todas las diferencias por género. En la base de datos de altas hospitalarias había 570 pacientes registrados por un primer episodio de ictus (49,1 % hombres y 50,9 % mujeres). El ictus causó la muerte de 52 pacientes (13,2 % de los hombres y 20,3 % de las mujeres). Los resultados del análisis bivariante**

mostraron las siguientes diferencias significativas entre hombres y mujeres: la edad, la letalidad y la presencia de hipertensión, enfermedad coronaria y enfermedad arterial periférica. Sin embargo, tras ajustar por las características basales, la letalidad fue similar en mujeres que en hombres. Aunque la letalidad por ictus parece mayor en mujeres, al ajustar los análisis por otros factores de riesgo las diferencias de género desaparecen.

Palabras clave: Ictus, Letalidad, Diferencias Género, Equidad, Epidemiología Social.

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1. INTRODUCTION

Stroke constitute a frequent cause of acute hospitalization and severe morbidity (Bejot et al., 2007), and represent 9.7 % world mortality, approximately (Strong et al., 2007). In Spain, stroke is the second cause of death, producing between 8 and 14% in-hospital mortality (Alvarez Sabín, 2008). Nevertheless, in the last years a decrease in stroke mortality has been observed. It has been related to an increase of survival after a stroke event, due to the stability of incidence and prevalence data (Zhang et al., 2012).

The influence of numerous factors in stroke mortality has been extensively assessed. Atrial fibrillation, diabetes, hypertension or aging are well known risk factors and their effect on stroke mortality is accepted (Mukherjee & Patil, 2011; Roger et al., 2011). However, the role of other factors, such as the sex, is still unclear. Although the fact that incidence is higher in males, except upper than 85 years old, and prevalence is higher in females because of their higher life expectancy is accepted (Appelros et al., 2009; Turtzo &

McCullough, 2008), major doubts are related to sex influence in stroke mortality and shot-term (before 30 days) and in-hospital fatality. Some studies have shown a higher mortality in males, others in females and others that differences are non-existent (Denti et al., 2013; Hoffmeister et al., 2013; Sheikh & Bullock, 2007). Regarding short-term fatality, the MONICA study reported variations, depending on countries, from 15 % to 49 % in males and from 18 % to 57 % in females (Thorvaldsen et al., 1995). Nevertheless, results from different studies have shown little soundness since then, obtaining higher fatality rates either in males or in females (DeVries et al., 2013).

Considering in-hospital fatality, some authors indicate that it do not seem to have differences between sexes when adjusting mortality by covariates such as age, stroke type, cardiovascular risk factors and severity (K.K. Andersen et al., 2011; Maeda et al., 2013; Park et al., 2013). However, some studies have reported that there is no equity in the assistance or treatment given to males and females. Females have also been suggested to receive hospital assistance later than males (Gargano et al., 2009), what would cause higher fatality. Even the fact that females receive less diagnosis tests and are treated with tissue plasminogen activator less frequently than males has been pointed out, although that could be due to the presence of other confounding variables, such as age or live alone (Reid et al., 2008).

The aim of this work was to determine if sex has influence on in-hospital fatality after a first-ever stroke.

2. MATERIAL AND METHODS

2.1. Study population and source of data

This retrospective cohort study (Doll, 2001) included all patients registered in the Minimum Basic Data Set (MBDS) of the two hospital of La Rioja (Spain), a discharge hospital administrative database, presenting as main diagnosis any of the 430.xx to 434.xx ICD-9-CM codes in 2010. For patients with several stroke events in 2010, only the first event (first-ever) was included in the study (DeVries et al., 2013). Patients who were hospitalized in precedent years

(1996-2009), being detected by the presence of any 430.xx to 438.xx ICD-9-CM codes in any diagnosis, were also excluded of this study.

2.2. Study variables

The dependent variable assessed was the in-hospital fatality and the main independent variable was the sex. The study covariates were age at the hospital discharge; presence of: diabetes (ICD-9-CM codes: 250) (Johansen et al., 2006), hypertension (ICD-9-CM codes: 401-405, 642.0, 642.1, 642.2 and 642.7) (Towfighi et al., 2011), atrial fibrillation (ICD-9-CM codes: 427.3) (Towfighi et al., 2011), coronary heart disease (ICD-9-CM codes: 410-414 and 429.2) (Hirsch et al., 2012) or peripheral artery disease (ICD-9-CM codes: 440.20-440.24, 440.30-440.32, 440.4, 440.9, 443.9 and 445.02) (Hirsch et al., 2012); stroke type (isquemic: 433 and 434 ICD-9-CM codes; and haemorrhagic 430-432 ICD-9-CM codes), thrombolytic therapy (99.10 ICD-9-CM procedure codes) (Abilleira et al., 2011) and length of the hospitalization.

2.3. Statistical analyses

Means and standard deviations (SD) were calculated for quantitative variables and frequencies for qualitative findings. Means were compared by Student-Fisher t-test. Differences between proportions were assessed by chi-square test for contingency tables. Fisher's test was used when appropriate.

Logistic regression models were applied to calculate an age-adjusted estimation of the odds ratio between sex and other possible risk factors, each coded as binary variables. Gender was forced into the multivariate models regardless of statistical significance. Age was used as a continuous variable. Adjusted models were developed using backward elimination technique ($p<0.3$ to enter, $p<0.1$ to stay) (Gargano et al., 2009). Results are presented in odds ratios (OR) and 95 % confidence intervals (CI 95). The OR show the effect of each category of the independent variable on the dependent variable in relation to the reference category, adjusted for the rest of the variables

included in the model. All p values are two-sided. Statistical analyses were performed with the SPSS 15.0 software package.

3. RESULTS

The MBDS contained 570 patients who suffered a first-ever stroke which caused their hospitalization in 2010 in La Rioja. Among them, there were 280 (49.1 %) men and 290 (50.9 %) women. The global median age was 76.7 years old; men's median age was 72.9 and women's, 80.4. Stroke caused the death of 52 patients (16.8 %), 13.2 % of all men and 20.3 % of all women.

Several sex differences among patients included in our study were observed. Women were older and presented higher hypertension and atrial fibrillation but lesser coronary heart disease and peripheral artery disease than men (Table 1).

Table 1. Study population characteristics and bivariate analysis data

	Total	Males	Females	p
Sex, n (%)	570 (100)	280 (49.1)	290 (50.9)	
Age, X (SD) (years)	76.74 (12.1)	72.93 (12.5)	80.41 (10.4)	<0.001
Length of stay, Md (Pc25-75) (days)	6 (3-9)	6 (4-9)	6 (3-9)	0.711
Comorbidity, n (%)				
Diabetes	27 (4.7)	53 (18.9)	71 (24.5)	0.108
Hypertension	379 (66.5)	168 (60.0)	211 (72.8)	0.001
Atrial fibrilation	45 (7.9)	60 (21.4)	86 (29.7)	0.024
Coronary heart disease	56 (9.8)	36 (12.9)	20 (6.9)	0.016
Peripheral artery disease	69 (12.1)	45 (16.1)	24 (8.3)	0.004
Stroke type, n (%)				
Haemorrhagic	120 (21.1)	59 (21.1)	61 (21.0)	0.927
Isquemic	450 (78.9)	221 (78.9)	229 (79.0)	0.927
Thrombolytic therapy, n (%)[a]	21 (4.7)	14 (6.3)	7 (3.1)	0.097
Fatality, n (%)	96 (16.8)	37 (13.2)	59 (20.3)	0.022

[a] Percentage of patients treated with thrombolytic therapy among those who suffered an isquemic stroke.
X: mean, SD: standard deviation; Md: median, Pc.percentil
Source: Elaboration by authors.

The unadjusted analyse gave a significant higher fatality in women than in men: OR 1.68 (CI 95 1.07-2.63) (Table 2). In this analyse, age and stroke type also showed significant differences in their influence in stroke fatality.

Regarding our results, ageing and having a haemorrhagic stroke increases the risk of in-hospital fatality. None of the other factors analysed showed significant influence on fatality due to stroke, although peripheral artery disease, thrombolytic therapy and length of the hospitalization gave significance values close to 0.05.

Table 2. Unadjusted and adjusted female to male odds ratio for in-hospital fatality by risk factors

	Deaths	ORc (CI 95)	ORa (CI 95)
Sex			
Females	59 (20.3)	1.68 (1.07-2.63)	1.36 (0.83-2.22)
Males	37 (13.2)		
Age		1.04 (1.02-1.07)	1.04 (1.02-1.07)
Diabetes			
Yes	18 (14.5)	0.80 (0.46-1.40)	
No*	78 (17.5)		
Hypertension			
Yes	64 (16.9)	1.01 (0.63-1.61)	
No*	32 (16.8)		
Atrial fibrilation			
Yes	24 (16.4)	0.96 (0.58-1.60)	
No*	72 (17.0)		
Coronary heart disease			
Yes	7 (12.5)	0.68 (0.30-1.56)	
No*	89 (17.3)		
Peripheral artery disease			
Yes	1 (5.6)	0.28 (0.04-2.15)	
No*	95 (17.2)		
Stroke type			
Haemorrhagic	39 (32.5)	0.30 (0.19-0.48)	4.01 (2.44-6.60)
Isquemic	57 (12.7)		
Thrombolytic therapy			
Si	5 (23.8)	2.27 (0.80-6.44)	2.78 (0.95-8.11)
No*	52 (12.1)		
Length of stay		1.02 (0.99-1.05)	

ORc: crude odds ratio; ORa: adjusted odds ratio; CI 95: confidence interval 95%
* Reference category
Source: Elaboration by authors.

Nevertheless, in the multivariate study we obtained a slightly higher but non significant fatality in women (1.36, CI 95: 0.83-2.22) after adjusting by age, stroke type and thrombolytic therapy (Table 2). Regarding the effect of other risk factors, we obtained that both ageing and suffering a haemorrhagic stroke increases the risk of fatality. However, surprisingly, it seems that not receiving thrombolytic therapy decreases the risk of fatality.

4. DISCUSSION

This study analyzed the influence of sex in the in-hospital fatality caused by an acute stroke. Incident patients who were hospitalized due to a first-ever of acute stroke in the hospitals of La Rioja were analyzed in this study. Proportion of men and women in the study population was very similar and both sexes suffer isquemic and haemorrhagic strokes in the same proportion. However some differences among them were observed when a bivariate analysis of main characteristics and risk factors was performed. Remarkably, results from that study revealed that women were older and presented higher fatality than men, data which is in agreement with other studies (Park et al., 2013). With regard to significant sex differences in studied risk factors, hypertension and atrial fibrillation rates were higher in women but coronary heart disease and peripheral artery disease were lesser than in men. This results are similar to other studies, even if in some cases the differences were not statistical significant (Förster et al., 2009; Lai et al., 2005; Park et al., 2013). Another disparity observed between women and men was the administration of thrombolytic therapy. As previously suggested (Reeves et al., 2008; Reid et al., 2008), we observed that women receive significantly less thrombolytic treatment than men, although the reason why that occurs is still unclear (Reid et al., 2008).

Unadjusted analysis of the effect of risk factors in the in-hospital stroke fatality disclosed that sex, age and stroke type had a significant impact. In particular, consistent with other literature, case fatality was higher in women than in men, in older patients and in patients affected of a haemorrhagic stroke than in those who had an isquemic stroke (DeVries et al., 2013; Park et al., 2013; Reker et al., 2002). Fatality was also higher in patients who received thrombolytic therapy. This effect was previously observed by other authors who explained that differences observed in patients treated with thrombolytic agents almost certainly result from baseline differences in their clinical status (Bateman et al., 2006; Wahlgren et al., 2008).

Adjusting for baseline characteristics, the disparity in fatality rates observed in the unadjusted analysis disappeared. When fatality was adjusted by age, stroke type and thrombolytic therapy, fatality was similar in women than in men. This data are in agreement with some previous authors who also reported an apparently higher fatality in women which disappear after adjustment by confounding covariates (Arboix et al., 2010; Lavados et al., 2005; Maeda et al., 2013; Park et al., 2013). The cause of the higher fatality observed in women before adjustment seems to be the confounding effect of the age, since data reflected that women were older than men. Nevertheless, some studies have found sex differences in mortality (Zhang et al., 2012) and even a time-dependent effect has been suggested (M. N. Andersen et al., 2005; Olsen et al., 2007).

Our study was subject to some limitations. First, this study is based on an administrative database, what prevented us from analysing some factors that are usually accepted as risk factors, such as tobacco and alcohol consumption or neurological status and stroke severity at the time of admission. Second, the fact that only first-ever stroke have been analysed in order to avoid some biases due to post-stroke effects or treatments, may introduce other kind of biases.

Despite of those biases, results from this study allow us to enunciate that even if stroke fatality in women seems to be higher than in men, when adjusting analyses for other risk factors gender differences disappear.

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