Sex-Related Time-Dependent Variations in Post-Stroke Survival – Evidence of a Female Stroke Survival Advantage

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Key Words

Ischaemic stroke • Intracerebral haemorrhage • Mortality, sex-related

Abstract

Background: Women live longer than men, yet most studies show that gender has no influence on survival after stroke.

Methods: A registry was started in 2001, with the aim of registering all hospitalized stroke patients in Denmark, and it now holds 39,484 patients of which 48% are female. We studied the influence of gender on post-stroke mortality, from the time of admission through the subsequent years until death or censoring (mean follow-up time: 538 days). All patients underwent an evaluation including stroke severity, computed tomography and cardiovascular risk factors. Independent predictors of death were identified by means of a survival model based on 22,222 individuals with a complete data set. **Results:** Females were older and had severer stroke. Interestingly, the risk of death between genders was time dependent. The female/male stroke mortality rate favoured women from the first day of stroke and remained so during the first month suggesting a female survival advantage. Throughout the second month the rate reversed in favour of men suggesting that women in that period are paying a 'toll' for their initial survival advantage. Hereafter, the

rate steadily decreased, and after 4 months women continued to have the same low risk as in the first week. **Conclusions:** Our study suggests a female superiority in stroke survival competence.

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Introduction

Women live longer than men, and being male is now the single largest demographic risk factor for early mortality in developed countries [1, 2]. Nevertheless, most recent studies report no difference in survival rates after stroke between men and women, neither in immediate post-stroke mortality nor in long-term mortality [3–20]. In only a minority of studies, survival rates were better in men [21–24] or in women [25–30].

In regard to stroke, women and men differ in several ways. Female stroke sufferers are older [4, 7, 18, 30] and have severer strokes than men [4, 30]. Men are more often smokers and consume more alcohol than women [4, 7, 30]. Furthermore, known risk factors for stroke prevail at an earlier age in men compared to women [31].

Since stroke severity is related to both gender and survival, it is potentially an important confounder that should be included in the analysis in order to reduce bias

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[30]. Moreover, studies have shown that the importance of including the severity when modelling stroke is essential with respect to short-term survival [30, 32, 33]. However, in the majority of larger studies on gender and stroke survival, there is no information on stroke severity [3, 5, 6, 10, 15, 16, 23].

An ongoing nationwide Danish stroke registry was established in March 2001, with the aim of registering all patients hospitalized with acute stroke. In February 2007, the registry included 39,484 patients. In these patients stroke severity was measured on the day of admission using a validated stroke scale, a cardiovascular risk factor profile was established, stroke subtype was determined on the basis of computed tomography (CT)/magnetic resonance (MR) scanning and survival was followed up to 5 years from the stroke.

Males appear to be more vulnerable to infections, injury and stress [2, 34, 35] and mortality rates from cerebrovascular diseases are generally higher in men [1, 2]. In order to test our hypothesis that women not only live longer after a stroke, but that they are also better stroke survivors, we aimed to investigate the independent influence of gender on post-stroke mortality from the very first day of admission and during the subsequent 5-year follow-up.

Methods

The study is based on data collected in the Danish National Indicator Project (NIP) [33]. The NIP is expected to include information from all stroke admissions in Denmark. Coverage is now about 75% of all stroke admissions. All Danish hospitals have committed themselves to report a predefined set of data on all patients admitted to hospital with acute stroke, which includes age, gender, stroke severity on admission – measured by the Scandinavian Stroke Scale (SSS) [36, 37] – and a predefined cardiovascular profile. The SSS is a validated neurological stroke scale that evaluates the patient's level of consciousness, eye movement, power in arms, hands, and legs, orientation, aphasia, facial paresis, and gait – giving a total score from 0 to 58 in which lower scores indicate severer strokes. The cardiovascular profile includes information on: alcohol consumption ($\leq 14/21$ drinks per week for women and men, respectively, being within limit), smoking habits (daily smoker, ex-smoker, never smoked), previous stroke, and the following conditions (whether they were known before the onset of stroke or newly diagnosed during hospitalization): diabetes mellitus (DM), atrial fibrillation (chronic or paroxysmic), arterial hypertension, myocardial infarction and intermittent arterial claudication. Diagnoses of DM, atrial fibrillation, arterial hypertension, myocardial infarction, previous stroke and intermittent arterial claudication were made according to current Danish standards [38]. The distinction between ischaemic stroke and primary intracerebral haematomas is determined following

CT/MR scans. Stroke is defined according to the WHO criteria [39]. Patients with subarachnoid haemorrhage are excluded from the study as were patients with transient ischaemic attacks. For patients with multiple records (events) only the first event is included in the analysis. Hence patients are only registered once and patients of less than 40 years of age are not included. Patients in whom CT/MR scans were not performed (0.4%) or unavailable (0.7%) were excluded from the study. An explanation of the cause of missing CT/MR scan information is not available in the NIP registry.

In Denmark, patients with acute stroke are exclusively treated and rehabilitated in public hospitals, which have a commitment to report all stroke admissions to the NIP registry. Almost 90% of the patients registered in the NIP database are treated in a stroke unit within 2 days of arrival at hospital [40].

Survival of the patients included in the NIP database was registered and followed through the Danish Registry of Persons. We studied all-cause mortality only. Inclusion of patients in the NIP started on 1 March 2001, and the end of study follow-up (censoring date) was 15 February 2007. Less than 0.2% of the patients were lost to follow-up, mainly due to emigration, and these patients were taken out of the analysis. The study was approved by the board of NIP and by the Danish Data Protection Agency.

Statistical Analyses

Firstly, differences between the genders with respect to age, SSS score and risk factor profile were analysed using a multiple logistic regression model. Age and SSS scores were modelled using a smooth non-linear function to test for linearity.

Secondly, independent predictors of death were identified by means of survival analysis. We applied a generalized additive model to the data in a time-split format assuming the response to follow a Poisson distribution [41]. The cardiovascular risk factors were included as factor variables. Age and SSS score were included as continuous variables, possibly non-linearly using smoothing splines. Since the difference between genders was of primary interest, all relevant interactions pertaining to gender were included. Finally, gender was included as a time-varying variable in order to study if the effect of gender was constant over time, i.e. whether the hazard was proportional. In all the statistical analyses, significance of model terms were tested based on a likelihood ratio test at a significance level of 5%.

We carried out an analysis of informative missingness in the data. In identifying the final model only complete cases were included in the analysis. All 39,384 patients had information on age, gender and survival time; from these, 22,222 cases were complete, with information on all risk factors. We did not find any relation between gender and the probability of missing risk factors, and thus decided to use complete cases in the analysis, as this theoretically should lead to valid (if inefficient) inference. Regarding the risk factors the missingness is not random, so the effect of risk factors on survival may be biased. Especially, the SSS of patients among the complete cases (mean SSS 41.4) used in the analysis is lower than patients with missing one or more risk factors (mean SSS 45.0).

The statistical software R [42] was used for the statistical analyses.

Results

Of the 39,484 patients included in the study 18,947 (48.0%) were women and 20,537 (52.0%) were men. Women were older than men (75.3 vs. 70.3 years; $p < 0.001$) and had severer strokes expressed by the mean SSS score (39.5 vs. 43.3, $p < 0.001$). The time from symptoms to hospitalization was 1 day (median); 63% were admitted within 1 day after the onset of symptoms, 97% within 7 days after the onset of symptoms and 99% within 30 days after the onset of symptoms. Patients admitted within 1 day were slightly older (71.3 vs. 70.0, $p < 0.001$) and had severer strokes (SSS 43.9 vs. 50.3, $p < 0.001$) compared to those admitted 1 day or later after the first symptoms. We found a tendency for men to be admitted more often within 1 day when compared to women (83.5 vs. 82.3%, $p = 0.0345$).

We studied all-cause mortality only and did not consider multiple strokes as an event. However, patients having multiple strokes were more often male in univariate analysis (54.8 vs. 52.0%, $p < 0.001$), slightly younger (72.1 vs. 72.7 years, $p < 0.001$) and had severer first strokes (SSS 39.0 vs. 41.4, $p < 0.001$) compared to the study population.

Descriptive statistics for gender, related to stroke subtype and cardiovascular risk factor profile, can be seen in table 1. After adjusting for age, stroke severity, stroke subtype and cardiovascular risk factors, women were less often alcohol consumers, less often smokers; they less often suffered from DM, myocardial infarction and previous strokes, and they had a lower incidence of intracerebral haemorrhage.

The partial effect of age and SSS score on the probability of being female, as opposed to being male, can be seen in figure 1. The curve regarding age appears to be U shaped, with the probability of being female lowest in the late fifties, after which it increases steadily ($p < 0.001$ for significance of the U shape). The partial effect of the SSS score on the probability of being female compared to male can be seen to increase almost linearly with increasing stroke severity ($p = 0.01$ for reduction to linear relationship).

Survival

Of the 18,947 women, 5,847 (30.9%) died (from all causes) during the follow-up. In comparison, out of the 20,537 men, 5,339 (26.0%) died (from all causes) during the follow-up. Seven, 30 and 90 days unadjusted case-fatality rates in women and men were: 6.6 versus 5.1%, 12.1 versus 9.1%, and 18.9 versus 15.1%, respectively. The dif-

Fig. 1. Fitted relationship between gender and age (solid line), and gender and stroke severity (dotted line).

ference in the unadjusted survival was significant ($p < 0.001$ in a log-rank test), indicating better survival for men. This conclusion would be reversed when including all possible confounders.

Intracerebral haemorrhage occurred in 7.6% of the patients. The risk of death from all causes was significantly higher (hazard ratio, HR, 1.619, $p < 0.001$) for patients suffering intracerebral haemorrhage. We did not find any interaction between gender and stroke subtype ($p = 0.513$). The same pattern in the time-varying HR for gender was seen for both stroke subtypes.

In the multivariate survival analysis, adjusting for stroke severity, age, stroke subtype and cardiovascular risk factors, we found that females had an overall (i.e. proportional) lower risk of all cause death compared to males (HR 0.832; confidence interval, CI, 0.782–0.886, $p < 0.001$). Other determinants of death were: increasing stroke severity, alcohol consumption over the limit, DM, intermittent arterial claudication, previous strokes and atrial fibrillation. We then proceeded to analyse the proportional hazard assumption of the model. Most interestingly, we found the risk between genders was time dependent, i.e. the proportional hazard assumption was rejected. Figure 2 shows the time-dependent HR for gender. Striking changes in risk were observed within the first

Table 1. Estimated odds ratios for females in multiple logistic regression (first level is reference) and HR estimated from a Poisson regression model with time-varying HRs for gender

Risk factor	Females				Males				Odds ratio ¹	Hazard ratio
	n	%	died	%	n	%	died	%		
Gender										
Female	18,947	100.0	5,847	30.9	–	–	–	–	–	0.748 ² (<0.001)
Male	–	–	–	–	20,537	100.0	5,339	26.0	–	[0.782, 0.886]
Alcohol consumption										
Over limit	532	19.6	111	20.9	2,182	80.4	442	20.3	2.660 (<0.001)	1.220 (0.001)
Under limit	14,453	48.6	3,724	25.8	15,306	51.4	3,507	22.9	[2.350, 3.012]	[1.801, 1.378]
Smoking status										
Yes	7,693	37.4	1,706	22.2	12,898	62.6	2,856	22.1	2.046 (<0.001)	1.191 (<0.001)
No	6,841	60.6	1,882	27.5	4,443	39.4	1,003	22.6	[1.928, 2.170]	[1.117, 1.270]
Diabetes mellitus										
Yes	2,207	42.3	800	36.2	3,010	57.7	883	29.3	1.275 (<0.001)	1.294 (<0.001)
No	15,425	48.6	4,388	28.4	16,343	51.4	3,973	24.3	[1.170, 1.391]	[1.189, 1.408]
Myocardial infarction										
Yes	1,271	34.7	526	41.4	2,390	65.3	827	34.6	2.013 (<0.001)	1.280 (<0.001)
No	15,936	48.9	4,428	27.8	16,648	51.1	3,868	23.2	[1.814, 2.233]	[1.172, 1.399]
Arterial hypertension										
Yes	8,688	49.6	2,428	27.9	8,827	50.4	2,171	24.6	0.804 (<0.001)	0.931 (0.020)
No	8,516	45.9	2,564	30.1	10,038	54.1	2,471	24.6	[0.760, 0.852]	[0.877, 0.989]
Intermittent arterial claudication										
Yes	569	38.9	184	32.3	895	61.1	294	32.8	1.015 (0.834)	1.324 (<0.001)
No	15,062	47.4	4,049	26.9	16,733	52.6	3,761	22.5	[0.884, 1.165]	[1.170, 1.499]
Previous stroke										
Yes	3,847	45.1	1,497	38.9	4,692	54.9	1,560	33.2	1.231 (<0.001)	1.149 (<0.001)
No	13,673	48.3	3,643	26.6	14,607	51.7	3,270	22.4	[1.147, 1.321]	[1.074, 1.229]
Atrial fibrillation										
Yes	3,442	54.6	1,673	48.6	2,858	45.4	1,147	40.1	1.032 (0.458)	1.285 (<0.001)
No	14,098	46.4	3,507	24.9	16,283	53.6	3,630	22.3	[0.949, 1.122]	[1.197, 1.380]
Type of stroke										
Intracerebral haemorrhage	1,469	48.9	807	54.9	1,536	51.1	714	46.5	1.141 (0.028)	1.619 (<0.001)
Infarct	17,478	47.9	5,040	28.8	19,001	52.1	4,625	24.3	[1.014, 1.284]	[1.466, 1.788]
SSS	–	–	–	–	–	–	–	–	– ³	0.466 ⁴ (<0.001)
Age	–	–	–	–	–	–	–	–	– ⁵	2.868 ⁶ (<0.001)

n = Numbers of patients with information on the risk factor; died = patients with information on the risk factor who died.

Results in parenthesis are p values, those in square brackets are 95% CI.

The alcohol consumption limit was 14/21 drinks per week for women and men, respectively.

¹ From multiple logistic regression.

² Assuming proportional hazard in Cox model, see figure 2 for time-varying hazard ratio.

³ Relationship between gender and SSS is shown in figure 1.

⁴ Hazard ratio is given for a change in SSS from 40 to 55, corresponding to the interquartile range.

⁵ Relationship between gender and age is shown in figure 1.

⁶ Hazard ratio is given for a change in age from 62 to 80 corresponding to the interquartile range.

150 days since the stroke, hereafter the risk seems to be decreasing constantly with time, implying that the risk of death decreases for women in comparison to men. It can be seen that women survive better than men within the first 30 days following stroke, but this conclusion reverts between 30 and 60 days following stroke. In this time period women have a 15% increase in risk compared to men. After 60 days, the risk is constantly lower for women than

men and continually decreasing. Variations of the HR with time were independent of stroke severity (SSS). Considering the first 150 days as a whole, we found the HR of women compared to men to be 0.9164 (95% CI 0.8495–0.9886), indicating an overall better survival rate during these first 150 days following stroke. The HRs of risk factors in the final model are also given in table 1. In this model about 30% of the cases were excluded due to miss-

Fig. 2. Changes in the HR between genders as a function of time (solid line). A strongly time-varying HR is seen in the period between 0 and 150 days following stroke. After this period the HR decreases constantly with time, implying that the likelihood of death decreases for women compared to men. As a comparison, the time-invariant HR from the Cox proportional hazard model is shown (dashed line). The dotted line indicates no gender difference, i.e. a HR of 1. Figures for cases with a complete data set: $n = 22,222$, mean age = 72.7 years, mean SSS = 41.4, percentage of women = 46.8%.

ing one or more covariates. Our analysis leads us to believe that the nature of the missing data is not informative missing, as the results were unaffected in stratified analysis. Similarly, the conclusions of the study were essentially the same when our analyses were based only on patients admitted within 1 day after onset of symptoms ($p = 0.681$), indicating that the time to admission did not influence the results.

Discussion

The overall result of our study is that women survive stroke better than men and live longer. As women who survive strokes, from which men die, are vulnerable – a large proportion of them subsequently die within the following months; hence, partly (but not completely) outweighing their initial advantage. In addition to their superior survival competence, women also live longer after having survived stroke.

Weaknesses and Strengths

Our study's strengths are firstly the large sample size allowing for sufficient statistical power. Secondly, we included patients without limitations upon age, gender or stroke severity, and stroke severity was measured in all patients using a well-validated neurological scale. This measure is of paramount importance in comparative evaluations of stroke prognosis because gender, besides age, was also strongly related to stroke severity, i.e. women had severer strokes. Finally, we had survival data on nearly all patients, with less than 0.2% lost to the follow-up.

Although the NIP was designed as a nationwide register of all patients admitted with acute stroke, coverage is not yet complete (presently about 75%) and because of the large number of people involved in nationwide registration, missing data are unavoidable. When identifying our final model only complete cases were included in the analysis. The percentage of missing data in each item was about 15%, leading to exclusion of about 40% of the cases due to missing one or more covariates. Still, our survival model was based on 22,222 individuals with a complete data set and our analysis led us to believe that the nature of the missing data was not informative missing. Analysis of the omitted data for patients with a recorded age, SSS score, smoking status, alcohol consumption and type of stroke ($n = 3,578$) gave the same time variation pattern for gender ($p = 0.145$).

We excluded patients younger than 40 years from the analysis. They comprised only 1.6% of the entire population. Compared to the age distribution of the population studied, the leverage of these observations (especially from children) is high from a statistical viewpoint and could introduce bias.

We cannot account for patients who died before hospitalization and patients treated at home. Hence, we have no information regarding the balance of age and gender in patients who died before getting to hospital. However, patients with stroke are hospitalized in Scandinavian countries, and the stroke admittance rate is close to the incidence reported in the population-based series [43]. Moreover, we consider bias in this respect to be of no major importance as we were able to adjust for stroke severity, stroke type and cardiovascular risk factors in all patients included in our final model.

The Female Stroke Survival Advantage

The female/male stroke mortality rate was in favour of women from the very first day after the stroke. We interpret this finding as a suggestion of a female superiority in

survival competence. As the majority of patients were admitted on the very first day of stroke and as we were able to adjust for differences in age, initial stroke severity, stroke subtype and the cardiovascular risk factor profile, we do not consider differences in stroke severity between the two genders to constitute a likely bias. Moreover, due to the sizeable number of patients in our study and a high number of events (deaths) registered already within the first days of stroke, we consider our observation statistically well validated.

We found no study to date, aimed at studying gender differences in stroke survival. Survival advantage for females has, however, been reported for infectious and parasitic diseases as well as for malignancies [34, 44] and has been explained as a result of a lower male resistance to infection, injury and stress [2, 34]. Hence, female rodents sustain more favourable outcomes than males after ischaemic brain injury [35, 45, 46]. It is noteworthy in this context that female mortality is lower for all causes of death over the lifespan including cerebrovascular diseases [1, 2].

'Toll of Survival Advantage'

The initially lower mortality of females remains lower than that of men during the first month after stroke onset. The gap between men and women then, however, steadily narrows, and after the first month the mortality rate of women starts to exceed that of men and stays higher during the second month following stroke. Thereafter, the mortality rate of women again becomes lower than that of men, and after 4 months women reach the same low HR seen in the first week.

In our interpretation this finding reflects the fact that women are paying a 'toll' for their survival advantage. Those who survive strokes from which men die succumb at a later stage because the severity of their stroke is incompatible with life or they become victims of complications. Although the 'toll of survival advantage' partly outweighs the initial survival advantage, there is still a net benefit of the female survival advantage as the HR of women to men was 0.916 (first 150 days following stroke). To the best of our knowledge, our observation of a 'toll of survival advantage' for females in stroke is new.

Studies on gender-specific differences in mortality within the first 3 months have revealed diverging results: in the WHO-MONICA populations the age-adjusted 28-day case fatality is higher among women [23]. Stroke severity and other prognostic confounders were, however, not recorded in these studies. In several studies the level of consciousness, or degree of paresis, was used as a mark-

er of stroke severity, and no difference in 1- to 3-month survival between genders was observed when adjusting for these and other confounding variables [6, 7, 11]. In a study using the NIH Stroke Scale as marker of stroke severity there was no gender-specific difference in 3-month survival [8] when adjusting for this and other relevant confounders, as also done in our study. In the Rochester population, stroke severity was determined retrospectively from hospital records and no gender-specific difference in 3-month survival was found [17]. On the other hand, in a Dutch study using the Glasgow Coma Scale as marker of stroke severity, women had a better 6-month survival rate [26], while in a Polish study, using the level of consciousness as marker of stroke severity, 2-week survival was poorer in women [22].

The 'toll of survival advantage' phenomenon in females observed in our study implies that survival after stroke should be handled separately in men and women, as the longer survival period of women does not necessarily reflect a less severe stroke or a more favourable effect of a given treatment. Also, gender differences in case-fatality rates should be handled cautiously. Female stroke victims are older, they have severer strokes and their cardiovascular-risk-factor profile differs significantly from that of males as shown in this study. Therefore, case-fatality rates of men and women are not directly comparable. Accordingly, the female case-fatality rate was significantly higher in our study, despite the markedly better survival competence of women, in agreement with results from a large Swedish national stroke register [7].

Among stroke survivors there is some evidence of women having a worse functional outcome [7, 47, 48]. A female survival advantage leading to severer strokes among female survivors may at least in part explain this finding.

The Longer Life Expectancy of Female Stroke Survivors

Except for the period between 30 and 60 days after stroke where women are paying the 'toll of survival advantage', mortality is markedly lower in female stroke survivors and the gap between men and women continues to increase. In this respect also, our study diverges from most other studies. Two larger studies with 1- [9] and 10-year [16] follow-ups did not find any gender-specific differences in stroke mortality, but, except for age, these studies did not adjust for stroke severity or other confounders of importance for stroke survival. Three studies [13, 18, 19] used validated stroke severity scores: in one study [13] (1-year follow-up) there was no gender-

specific difference in mortality, in another [18] (3-year follow-up) the mortality of females was marginally, yet insignificantly lower, and in a third study [30] (10-year follow-up) mortality was significantly lower in women when adjusting for stroke severity and other relevant confounders. In other studies, stroke severity was estimated on the basis of consciousness levels or various neurological deficits: in the IST study [25] women were less likely to be dead within 6 months, while in other studies 1-year [11, 12, 14] and 3-year survival [19, 20] did not differ between genders. In the Rochester population [10, 17],

gender did not influence 5-year stroke survival, while in the Framingham population [28] 5-year survival was better among females.

Generally, women experience myocardial infarction and stroke several years later than men [31]. We believe this is also reflected in the low long-term female/male mortality rate of our study; also female stroke survivors experience myocardial infarction and recurrent stroke later than men. Our study also suggests that a female survival advantage plays a role.

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