Sex and gender differences in acute stroke care: metrics, access to treatment and outcome. A territorial analysis of the Stroke Code System of Catalonia

Yolanda Silva, Laura Sánchez-Cirera, Mikel Terceño, Laura Dorado, Adrián Valls, Marina Martínez, Sònia Abilleira, Marta Rubiera, Helena Quesada, Laura Llull, Ana Rodríguez-Campello, Joan Martí-Fàbregas, Laia Seró, Francisco Purroy, Iago Payo, Sònia García, David Cánovas, Jurek Krupinski, Natalia Mas, Ernest Palomeras, Dolores Cocho, Maria Àngels Font, Esther Catena, Elsa Puiggròs, Claudia Pedroza, Gemma Marín, Dolors Carrión, Xavier Costa, Mari Cruz Almendros, Ivan Torres, Carla Colom, John Alejandro Velasquez, Gloria Diaz, Xavier Jiménez, Teresa Subirats, Anna Deulofeu, Verónica Hidalgo, Mercè Salvat-Plana, and Natalia Pérez de la Ossa, Catalan Stroke Code and Reperfusion Consortium (Cat-SCR)

Abstract

Introduction:

Previous studies have reported differences in the management and outcome of women stroke patients in comparison with men. We aim to analyze sex and gender differences in the medical assistance, access to treatment and outcome of acute stroke patients in Catalonia.

Patients and methods:

Data were obtained from a prospective population-based registry of stroke code activations in Catalonia (CICAT) from January/2016 to December/2019. The registry includes demographic data, stroke severity, stroke subtype, reperfusion therapy, and time workflow. Centralized clinical outcome at 90 days was assessed in patients receiving reperfusion therapy.

Results:

A total of 23,371 stroke code activations were registered (54% men, 46% women). No differences in prehospital time metrics were observed. Women more frequently had a final diagnosis of stroke mimic, were older and had a previous worse functional situation. Among ischemic stroke patients, women had higher stroke severity and more frequently presented proximal large vessel occlusion. Women received more frequently reperfusion therapy (48.2% vs 43.1%, $p < 0.001$). Women tended to present a worse outcome at 90 days, especially for the group receiving only IVT (good outcome 56.7% vs 63.8%; $p < 0.001$), but not for the group of patients treated with IVT + MT or MT alone, although sex was not independently associated with clinical outcome in logistic regression analysis (OR 1.07; 95% CI, 0.94–1.23; $p = 0.27$) nor in the analysis after matching using the propensity score (OR 1.09; 95% CI, 0.97–1.22).

Discussion and conclusion:

We found some differences by sex in that acute stroke was more frequent in older women and the stroke severity was higher. We found no differences in medical assistance times, access to reperfusion treatment and early complications. Worse clinical outcome at 90 days in women was conditioned by stroke severity and older age, but not by sex itself.

Keywords: Acute stroke, sex, gender, outcome

Introduction

Stroke is one of the leading causes of death and functional dependency, especially in women mainly due to the progressive increase in life expectancy.[1,2] Sex and gender differences in the clinical presentation of stroke, outcome and access to treatment have been reported in observational and randomized controlled trials.[2–5]

Several studies have shown an increased prevalence of non-traditional stroke symptoms and signs in women compared with men, which may lead to the disease being misrecognized, impacting the outcome since the most appropriate treatment may not be given.[6,7] Several studies have in fact revealed that women present higher mortality, dependency, and post-stroke depression rates than men.[8–10]

Moreover, some studies have shown that women were less likely than men to receive recanalization therapy.[11,12] Clinical and social characteristics that are more common in women with stroke, such as older age, living alone, and increased prestroke disability, could potentially reduce the use of reperfusion treatment in women. It should be noted that most of the previous studies agree that despite greater age and higher stroke severity, outcomes after endovascular thrombectomy in females are comparable with males.[13–17]

A better knowledge of all these conditioning factors is essential to improve management and treatment protocols and, especially, to tailor the resources in the acute and chronic phase after a stroke. The aim of this study was to analyze sex and gender differences in the care process, outcome and access to reperfusion treatment of ischemic stroke patients in our region.

Patients and methods

This observational study is based on the *Codi Ictus Catalunya* (CICAT) registry, a government-mandated, prospective, hospital-based dataset that includes all stroke codes in Catalonia, Spain. The territory of Catalonia includes a total population of 7.5 million inhabitants distributed in an area of 32,000 km^2. The Catalan Stroke network currently consists of 6 comprehensive stroke centers, 8 primary stroke centers, and 15 tele-stroke centers. The Stroke Code protocol was implemented in Catalonia in 2006, and the activation criteria are non-disabled or with minor disability patients with suspicion of acute stroke of less than 8 h from onset or unknown time of onset. The Emergency Medical Services (EMS), with single centralized coordination, is the Stroke Code's primary activator, but the stroke code protocol can also be activated from emergency departments in all stroke and non-stroke centers of the region of Catalonia, as well as for patients suffering an acute stroke while admitted at any hospital for other diseases. The patient transport system guarantees the urgent and priority transfer of patients with suspected acute stroke to the nearest stroke center, including a phone-call pre-notification to the receptor center.

For this study, we used data from consecutive patients in whom the stroke code was activated from January 2016 to December 2019. The following variables were collected by the stroke centers in the CICAT registry: demographic information, pre-stroke functional status (modified Rankin Scale (mRS)), source of the stroke activation (EMS with and without pre-notification to the stroke center, emergency room of a non-stroke center or a stroke center for patients arriving on their own, in-hospital stroke, or primary health care center), National Institutes of Health Stroke Scale (NIHSS) at admission, stroke subtype (ischemic stroke, transient ischemic attack, intracerebral hemorrhage, or stroke mimic), the presence of large vessel occlusion and site of occlusion, revascularization treatment (none, intravenous thrombolysis alone (IVT), mechanical thrombectomy (MT) with or without thrombolysis), time metrics including: time of symptom onset or last time seen well, stroke code alert, stroke center arrival, neuroimaging, initiation of intravenous thrombolysis and groin

puncture. Symptomatic intracerebral hemorrhage (sICH) after revascularization treatment was defined according to the European Cooperative Acute Stroke Study II (ECASS II) criteria.[18] Successful recanalization following MT was defined as a grade 2b or 3 according to the modified thrombolysis in cerebral ischemia (TICI) scale.[18] Functional outcome was centrally evaluated at 90 days (±15 days) in patients receiving reperfusion therapy through a structured telephone-based interview by certified assessors using the modified Rankin scale (mRS).

First, outcomes related to the stroke care process at a pre-hospital level were analyzed: source of stroke code activation, time from onset to hospital arrival and final diagnosis. Second, outcomes related to in-hospital process and reperfusion therapies were explored. Due to the potential impact of the previous functional situation of patients in the management and treatment decision, we excluded from the analysis patients with a previous mRS > 2, who theoretically had no criteria for stroke code activation according to our regional protocol. We analyzed the proportion of patients receiving revascularization treatment and in-hospital times (door-to-needle and door-to-groin puncture), as well as performance and complications after reperfusion treatment: rate of SICH after reperfusion therapy, rate of complete recanalization after MT, mortality and clinical outcome at 90 days. Good functional outcome was defined as a mRS score of ⩽2 at 90 days.

This is a real-world evidence analysis using the population-based CICAT registry, which satisfies all legal requirements mandated by the local law of personal data protection. The dataset was processed and analyzed according to local and European laws: Regulation (EU) 2016/679 of the European Parliament and of the Council of April 27, 2016, on Data Protection and Spanish Organic Law 3/2018, of December 5, on Protection of Personal Data and Guarantee of Digital Rights. In accordance with the legal procedure dictated by the Stroke Plan of the Catalan Health Department, the Ethical Committee of the Josep Trueta University Hospital approved the study (registry code SEX-ICTUS 172_19). Informed consent was waived due to the retrospective nature of the study.

Statistical analysis

Continuous and ordinal variables were described by the mean and standard deviation (SD) or median and interquartile range (IQR) as appropriate. Categorical variables were described as counts and percentages. For all comparisons between groups by biological sex, the χ^2 test, or the Fisher exact test whenever necessary, was applied for categorical variables. Continuous variables were tested for normality with the Kolmogorov–Smirnov test, and then compared between groups using a t-test, Mann–Whitney test, or ANOVA. All tests were performed as two-sided and p-values <0.05 were considered significant. The analysis of good functional result at 90 days focused on the population that received reperfusion treatment, and we performed a binary logistic regression analysis to adjust for possible confounding variables. Variables with a p-value <0.1 in the univariate analysis were introduced in the model. We used an automated enter regression method for the selection of the final models. We did not apply any imputation method to replace missing data.

In addition, propensity score matching was employed to identify a cohort of patients with comparable baseline characteristics to estimate the average effect of being a woman in neurological outcomes. Propensity scores were calculated for all patients with logistic regression using age, baseline NIHSS, previous mRS, and the presence of large vessel occlusion to predict the probability of being a woman according to these variables. Patients for whom the mRS score was missing at 90 days and those who did not received reperfusion therapies were excluded for the propensity score estimation. Missing data on propensity score covariates were handled with multiple imputation, assuming that values were missing at random. Multiple imputation employed 10 iterations using all variables. All datasets were matched with a 1:1 nearest-neighbor matching

algorithm with a caliper width equal to 0.1 of the standard deviation of the logit of the propensity score. Balance was evaluated before and after matching based on the mean standardized mean difference for all covariates across matched datasets, using a threshold of 0.1 or below to consider a covariate as well balanced. We estimated the effect of being a woman on functional independence at 90 days by binary logistic regression, without adjustment for covariates, using a cluster-robust standard error. Model estimates were pooled according to the Rubin rule.

Data analysis was performed using the IBM SPSS Statistics package, version 24 and R version 4.1 (R Foundation for Statistical Computing) with the mice, MatchThem, and survey packages.

Results

A total of 23,371 stroke code activations were registered during the study period; of these, 10,798 (46.2%) were women and 12,573 (53.8%) were men. Table 1 shows the characteristics of stroke code activations by biological sex. Women were older, had more frequently previous functional dependence and more severe stroke symptoms. The distribution of the source of stroke activation did not show relevant clinical differences between the two sexes. The activation of the stroke code by the EMS with prior notification, which accounted for 60.4% of patients, was related to the severity of the stroke (OR for EMS activation: NIHSS 1.06 (95% CI, 1.05–1.07)), and no interaction was observed between sex and stroke severity (p for interaction = 0.12) (Figure 1).The time from symptom onset to hospital arrival between groups and the percentage of wake-up strokes were similar. The final diagnosis of patients is shown in Table 1, with a more frequent diagnostic of stroke mimic in women (19.0% vs 14.2%, $p < 0.001$). Alternative diagnoses in patients with stroke mimic were different between sexes, with seizures (26.1%), functional disorder (14.4%) and migraine (9.9%) being more frequent in women, and seizures (37.2%) and metabolic disorders (9.8%) in men. In both men and women, the severity of the stroke was distributed equally in all age groups, except in patients over 75 years of age, in whom cases with severe stroke predominated, especially in women representing 32% of cases compared to 18% in men ($p < 0.001$) (Figure 2).

Table 1.

Characteristics of stroke code activation by sex: source of stroke activation, prehospital metrics, and final diagnosis.

	Women n = 10,798	Men n = 12,573	p-Value
Age, years (mean ± standard deviation)	73.6 ± 15.2	69.8 ± 13.9	<0.001
mRS pre-stroke 0–2 (n, %)	8683 (80.4%)	11,264 (89.6%)	<0.001
Source of stroke code activation (n, %)			0.001
EMS with pre-notification	6577 (60.9%)	7548 (60.0%)	
EMS without pre-notification	1256 (11.6%)	1310 (10.4%)	
Emergency room of a non-stroke code hospital	1198 (11.1%)	1454 (11.6%)	
Emergency room of a stroke code hospital	1272 (11.8%)	1632 (13.0%)	

	Women *n* = 10,798	Men *n* = 12,573	*p*-Value
In-hospital (admitted for other disease)	495 (4.6%)	629 (5.0%)	
Wake-up stroke (*n*, %)	2893 (26.8%)	3288 (26.2%)	0.268
Stroke subtype (*n*, %)			<0.001
Ischemic stroke	6945 (64.3%)	8237 (65.5%)	
Transient ischemic attack	596 (5.5%)	841 (6.7%)	
Intracerebral hemorrhage	1077 (10.0%)	1610 (12.8%)	
Subarachnoid hemorrhage	127 (1.2%)	95 (0.8%)	
Stroke mimic	2053 (19.0%)	1790 (14.2%)	
NIHSS at admission (median (IQR))	9 (4, 18)	7 (3, 16)	<0.001
Etiology of stroke mimic (*n*, %)			<0.001
Migraine	133 (9.9%)	48 (3.9%)	
Psychiatric disorders	194 (14.4%)	54 (4.4%)	
Seizures	352 (26.1%)	458 (37.2%)	
Metabolic disorders	107 (7.9%)	121 (9.8%)	
Tumor	65 (4.8%)	70 (5.7%)	
Confusional syndrome	59 (4.4%)	61 (5%)	
Syncope	77 (5.7%)	89 (7.2%)	
Nervous system infection	35 (2.6%)	30 (2.4%)	
Time metrics, min (median (IQR))			
Onset–hospital arrival	117 (65, 265)	118 (64, 267)	0.986
Hospital arrival-image	22 (15, 35)	22 (14, 34)	0.020
Hospital arrival-tPA	37 (27, 53)	35 (26, 51)	0.036
Hospital arrival-groin	72 (50, 98)	72 (49, 98)	0.563
Groin-recanalization	48 (28, 75)	48 (29, 75)	0.543

mRS: modified Rankin score; IQR: interquartile range; tPA: alteplase; EMS: Emergency Medical Services; NIHSS: National Institutes of Health Stroke Scale.
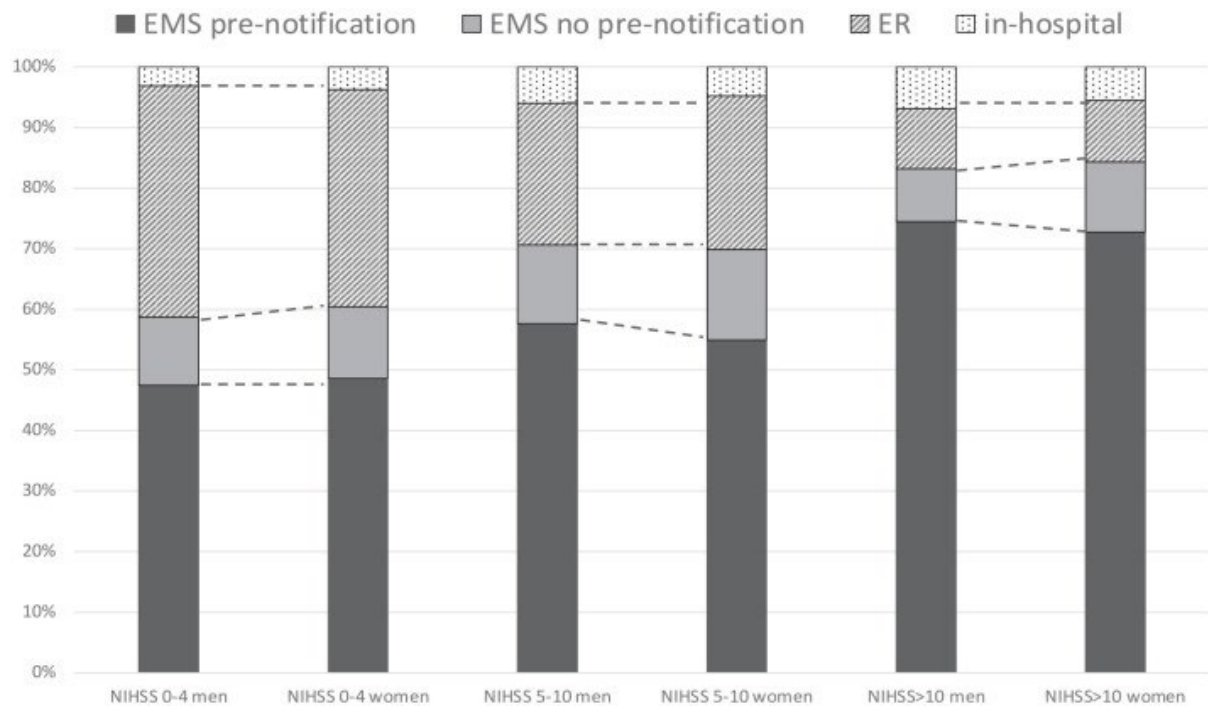

Figure 1.

Source of stroke code activation by sex and stroke severity.

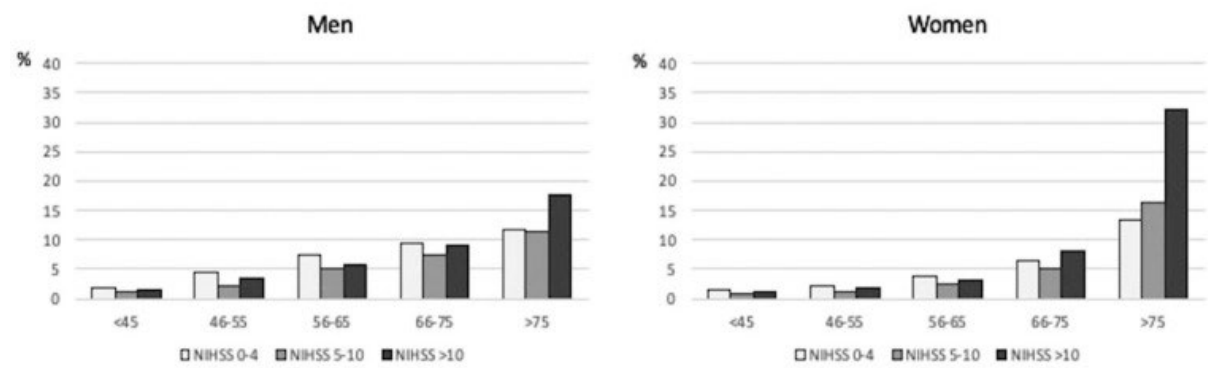EMS: Emergency Medical Services; ER: Emergency room.

Figure 2.

Proportion of cases by age and stroke severity among men and women (excluding stroke mimic).

Due to the imbalance regarding previous functional dependence between women and men, we analyzed clinical characteristics, outcome and access to treatment only in patients with ischemic stroke and previous mRS < 3 (12,904 patients). In this subgroup of patients, we observed that women were significantly older (74 vs 69 years, $p < 0.001$) and had higher stroke severity at admission (baseline NIHSS 8 (3–17) vs 6 (3–13), $p < 0.001$). Women had a higher percentage of large vessel

occlusions (35.8% vs 31.1%, $p < 0.001$), which were more frequently proximal intracranial occlusions and less frequently extracranial carotid occlusions compared to men. Women more frequently received reperfusion therapy (48.2% vs 43.1%, $p < 0.001$) and there were no differences on pre- and in-hospital time metrics ([Table 2]).

Table 2.

Clinical characteristics, metrics, and outcome of patients with ischemic stroke and prior mRS < 3.

	Women *n* = 5485	Men *n* = 7419	*p*-Value
Age, years (mean ± standard deviation)	73.8 ± 13.6	69.4 ± 13.2	<0.001
NIHSS at admission (median (IQR))	8 (3–17)	6 (3–13)	<0.001
Wake-up stroke (*n*, %)	1584 (28.9%)	2067 (27.9%)	0.204
Large vessel occlusion (*n*, %)	1909 (35.8%)	2245 (31.1%)	<0.001
Site occlusion (*n*, %)			<0.001
Extracranial ICA	202 (3.7%)	462 (6.2%)	
TICA	238 (4.3%)	228 (3.1%)	
MCA M1	959 (17.5%)	998 (13.5%)	
MCA M2	439 (8.0%)	494 (6.7%)	
ACA	46 (0.8%)	45 (0.6%)	
PCA	62 (1.1%)	127 (1.7%)	
BA/VA	128 (2.4%)	196 (2.7%)	
Revascularization treatment (*n*, %)	2645 (48.2%)	3199 (43.1%)	<0.001
IVT	1548 (28.2%)	1983 (26.7%)	
MT	701 (12.8%)	729 (9.8%)	
IVT + MT	396 (7.2%)	487 (6.6%)	
No treatment	2840 (51.8%)	4220 (56.9%)	
Time metrics, min (median (IQR))			
Onset-stroke code activation	122 (60–306)	127 (58–312)	0.750
Onset-hospital arrival	122 (65–290)	124 (65–303)	0.979

	Women n = 5485	Men n = 7419	p-Value
Hospital arrival-image	22 (15–34)	22 (15–35)	0.579
Hospital arrival-tPA	36 (26–52)	35 (26–50)	0.158
Hospital arrival-groin	72 (49–97)	71 (49–97)	0.429
Groin-recanalization	48 (28–75)	49 (29–75)	0.669

IVT: intravenous thrombolysis; MT: mechanical thrombectomy; mRS: modified Rankin score; IQR: interquartile range; tPA: alteplase; NIHSS: National Institutes of Health Stroke Scale; IQR: interquartile range.

Among patients receiving endovascular therapy, again women were significantly older (73 vs 68 years; $p < 0.001$), but clinical and radiological stroke severity were similar between the two sexes. Occlusion at the proximal MCA (47.6% vs 36.3%) and the terminal ICA (14.5% vs 10.0%) were more frequent in women while extra ICA (4.3% vs 7.1%), tandem (4.3% vs 14.1%), and basilar occlusion (5.9% vs 7.7%) were more frequent in men. Concomitant intravenous alteplase was less frequently administered in women (36.1% vs 40.0%, $p = 0.05$) mainly due to prior anticoagulant treatment (Table S1). With regard to the procedure, men were more frequently treated under general anesthesia (7.4% vs 11.0%, $p < 0.001$) and with acute carotid stenting (3.0% vs 9.5%, $p < 0.001$). The number of passes of thrombectomy, complete final recanalization and complication rate were similar in both sexes (Table S1).

Table 3 shows the clinical outcome of women and men treated with different modalities of reperfusion therapy. The rate of sICH was similar in both sexes for all reperfusion modalities. Although we observed higher mortality at 90 days in men, women tended to present a worse outcome at 90 days with a lower percentage of functional independency, especially for the group receiving only IVT (good outcome 56.7% vs 63.8%; $p < 0.001$), but not for the group of patients treated with IVT + MT (50.4% vs 54.5%, $p = 0.30$) or MT alone (34.5% vs 39.3%; $p = 0.10$). However, in the multivariate analysis, sex was not independently associated with clinical outcome in all patients treated with reperfusion therapy (OR 1.07; 95% CI, 0.92–1.23) nor in patients treated with endovascular therapy (OR 1.028; 95% CI, 0.83–1.26) (Table 4).

Table 3.

Clinical outcome of patients treated with different modalities of reperfusion therapy by sex.

	Women	Men	p-Value
IVT [a]	n = 1548	n = 1983	
sICH (n, %)	27/881 (3.1%)	45/1098 (4.1%)	0.222
Mortality 90 days (n, %)	147/1194 (12.3%)	173/1502 (11.5%)	0.527
Good outcome 90 days (n, %)	677/1194 (56.7%)	959/1502 (63.8%)	<0.001
IVT + MT [b]	n = 396	n = 487	

	Women	Men	*p*-Value
sICH (*n*, %)	9/311 (2.9%)	9/366 (2.5%)	0.726
Mortality 90 days (*n*, %)	41/284 (14.4%)	64/334 (19.2%)	0.119
Good outcome 90 days (*n*, %)	143/284 (50.4%)	182/334 (54.5%)	0.304
MT [c]	*n* = 701	*n* = 729	
sICH (*n*, %)	16/531 (3%)	21/540 (3.9%)	0.433
Mortality 90 days (*n*, %)	108/525 (20.6%)	157/565 (27.8%)	0.006
Good outcome 90 days (*n*, %)	181/525 (34.5%)	222/565 (39.3%)	0.100

IVT: intravenous thrombolysis; MT: mechanical thrombectomy; sICH: symptomatic intracerebral hemorrhage.

[a]Missing data for SICH 1552/3531 (44%), missing data for mortality and mRS at 90 days 835/3531 (23%).

[b]Missing data for SICH 206/883 (23%), missing data for mortality and mRS at 90 days 265/883 (30%).

[c]Missing data for SICH 359/1430 (25%), missing data for mortality and mRS at 90 days 340/1430 (24%).

Table 4.

Multivariate analysis: factors related to poor outcome (mRS > 2) at 90 days in patients treated with any reperfusion therapy and patients with MT.

	OR	Lower limit of 95% CI	Upper limit of 95% CI	*p*-Value
Patients treated with any reperfusion therapy (intravenous and/or endovascular)				
Sex (women)	1.071	0.927	1.238	0.275
Age	1.043	1.037	1.049	<0.001
NIHSS at admission	1.101	1.088	1.114	<0.001
Large Vessel Occlusion	1.428	1.211	1.685	<0.001
Patients treated with MT				
Sex (women)	1.028	0.837	1.264	0.791
Age	1.037	1.029	1.045	<0.001
NIHSS at admission	1.077	1.060	1.093	<0.001

	OR	Lower limit of 95% CI	Upper limit of 95% CI	p-Value
Previous iv-tPA	0.487	0.395	0.600	<0.001
General anesthesia	2.227	1.392	3.562	0.001

NIHSS: National Institutes of Health Stroke Scale; tPA: alteplase; MT: mechanical thrombectomy.

After the propensity score, 2039 women were matched with 2039 men. Mean standard differences across imputed datasets were less than 10% after matching, indicating that both cohorts were balanced (Figure S1). After matching, no difference was found in functional independence at 90 days between the two sexes (OR 1.09; 95% CI, 0.97–1.22).

Discussion

In our study, no differences in medical assistance times, access to reperfusion treatment or early complications after reperfusion therapy by biological sex were observed in patients with acute ischemic stroke. However, women presented worse prognoses, which could mainly be attributed to differences such as older age and more severe stroke compared to men.

Several studies have assessed sex and gender differences in the use of medical emergency services in patients with acute ischemic stroke with conflicting results.[3,19–23] Our study, focused on patients activated in our stroke code protocol that includes all subtypes of stroke, TIA, and stroke mimics, did not detect relevant differences in the quality of the activation of the stroke code between sexes. The EMS sensitivity and time of response was similar in women and men, whether in mild, moderate, or severe stroke, suggesting that misrecognition of symptom presentation was not a factor in our system.

Among all stroke codes, we found a higher percentage of stroke mimics in women as has been reported in the literature.[3,7,24] Moreover, differences in the etiology of stroke mimics have been observed, with a greater percentage of migraine and psychiatric disorders in women. Given that the diagnosis of stroke mimic was made in the evaluation in the emergency room and not all patients underwent MRI, a more exhaustive study of these patients would be interesting since the treatment decisions may have an impact on the prognosis.

Regarding the stroke characteristics and etiology, and in accordance with previous studies, we observed that women were older, had more severe stroke and more frequent large major occlusion and less extracranial carotid occlusion. Although we have not recorded the incidence of atrial fibrillation, these results are consistent with other studies showing more severe strokes with a higher percentage of cardioembolic origin due to atrial fibrillation in women.[9,25–29] Accordingly, in our cohort we observe a significant peak of female patients over 75 years of age with severe stroke, demonstrating that this is a population group that is particularly exposed and sensitive to the consequences of stroke. This fact should be considered in a personalized approach concerning atrial fibrillation recognition and anticoagulation therapy in primary health care especially in old women in order to avoid catastrophic outcomes. On the other hand, men had higher extracranial carotid occlusion that is more frequently attributed to other vascular risk factors. Caso et al.[27] observed that men presented a statistically higher frequency of smoking, alcohol abuse, and symptomatic peripheral artery disease.

In our study, women more frequently received revascularization therapies (48.2% vs 43.1%, p < 0.001), in contrast to other published studies. Foerch et al.[29] showed that women had a

13% lower chance of being admitted within the first 3 h in comparison with men and this delay may have an impact on the administration rate of thrombolysis. A meta-analysis including 18 observational studies with acute ischemic stroke, indicated that women had 30% lower odds of receiving thrombolysis than men, although a significant heterogeneity of results between the different centers was observed. [8] Another study suggested that delay on arrival was explained by a higher prevalence of women living alone. [30] In our series we did not find differences in hospital arrival times, and although there was a slight delay in time from arrival to image and to treatment administration in women, this finding was not observed in a sensitivity analysis focused on patients with ischemic stroke and mRS < 3, suggesting that this delay is probably related to a higher percentage of female patients with a previous situation of disability that may lead to greater uncertainty in the treatment decision. Due to the retrospective nature of our study, we did not collect the signs and symptoms of patients, nor the presence of cardiovascular risk factors, so we cannot attribute the finding to lack of recognition of the symptoms in the emergency room nor to the comorbidity or fragility of patients.

We did not observe differences in short term efficacy nor complication rates due to reperfusion therapies, with similar rates of recanalization, complications, and early neurological assessment in both sexes. The outcome at 90 days tended to be worse in women, but this observation was related to older age and greater stroke severity as we showed in the logistic regression and the propensity score matched analysis. Based on our results, we suggest that the worse prognosis in women is due, above all, to their older age and stroke severity, but not to the sexual condition itself. These findings are consistent with much of the previous literature, suggesting that certain bio-psycho-social factors that affect the subacute phase have an important influence on functional recovery. [31–33] It is possible that older age in women with stroke, emotional impact, greater depression, the degree of social and family support, or even access to rehabilitation therapies, may explain these differences in long-term evolution. These aspects need to be thoroughly investigated to plan interventions aimed at minimizing gender differences in stroke recovery. [2,34]

Our study has some limitations: our population registry does not record details on alarm symptoms, sociocultural data, and medical history, which prevents us from understanding the influence of these factors and from separating the impact of biological sex and gender on the results. On the other hand, clinical outcome was only assessed in patients who received reperfusion therapy, which does not allow us to know the differences in the impact of general care between the two sexes. We also do not have data on the resources for admission to stroke units or rehabilitation programs, which may have a significant impact on the clinical recovery. As strengths, our study is based on a large and mandatory population registry, with a centralized evaluation of the outcome, which ensures an unbiased reflection of the general population in our setting.

Conclusions

In our setting, we conclude that the identification of stroke patients, early care and treatment, access to reperfusion therapies and immediate response to treatment did not differ between men and women. Long-term prognosis is mainly conditioned by age and the severity of the stroke rather than by sex itself.

Acknowledgments

None

Footnotes

References

1. Girijala RL, Sohrabji F, Bush RL. Sex differences in stroke: review of current knowledge and evidence. *Vasc Med* 2017; 22: 135–145.

2. Rexrode KM, Madsen TE, Yu AYX, et al. The impact of sex and gender on stroke. *Circ Res* 2022; 130: 512–528.

3. Bushnell C, Howard VJ, Lisabeth L, et al. Sex differences in the evaluation and treatment of acute ischaemic stroke. *Lancet Neurol* 2018; 17: 641–650.

4. Towfighi A, Markovic D, Ovbiagele B. Sex differences in revascularization interventions after acute ischemic stroke. *J Stroke Cerebrovasc Dis* 2013; 22: e347–e353.

5. Carcel C, Wang X, Sandset EC, et al. Sex differences in treatment and outcome after stroke: pooled analysis including 19,000 participants. *Neurology* 2019; 93: e2170–e2180.

6. Gall SL, Donnan G, Dewey HM, et al. Sex differences in presentation, severity, and management of stroke in a population-based study. *Neurology* 2010; 74: 975–981.

7. Merino JG, Luby M, Benson RT, et al. Predictors of acute stroke mimics in 8187 patients referred to a stroke service. *J Stroke Cerebrovasc Dis* 2015; 24: 48–52.

8. Pezzella FR, Santalucia P, Vadalà R, et al. Women Stroke Association statement on stroke. *Int J Stroke* 2014; 9: 20–27.

9. Ihle-Hansen H, Sandset EC, Ihle-Hansen H, et al. Sex differences in the Norwegian Tenecteplase Trial (NOR-TEST). *Eur J Neurol* 2022; 29: 609–614.

10. Bushnell CD, Reeves MJ, Zhao X, et al. Sex differences in quality of life after ischemic stroke. *Neurology* 2014; 82: 922–931.

11. Strong B, Lisabeth LD, Reeves M. Sex differences in IV thrombolysis treatment for acute ischemic stroke: a systematic review and meta-analysis. *Neurology* 2020; 95: e11–e22.

12. Eriksson M, Åsberg S, Sunnerhagen KS, et al. Sex differences in stroke care and outcome 2005-2018: observations from the Swedish Stroke Register. *Stroke* 2021; 52: 3233–3242.

13. Sheth SA, Lee S, Warach SJ, et al. Sex differences in outcome after endovascular stroke therapy for acute ischemic stroke. *Stroke* 2019; 50: 2420–2427.

14. Bala F, Casetta I, Nannoni S, et al. Sex-related differences in outcomes after endovascular treatment of patients with late-window stroke. *Stroke* 2022; 53: 311–318. [

15. Casetta I, Fainardi E, Pracucci G, et al. Sex differences in outcome after thrombectomy for acute ischemic stroke. A propensity score-matched study. *Eur Stroke J* 2022; 7: 151–157.

16. Deb-Chatterji M, Schlemm E, Flottmann F, et al. Sex differences in outcome after thrombectomy for acute ischemic stroke are explained by confounding factors. *Clin Neuroradiol* 2021; 31: 1101–1109.

17. Chalos V, de Ridder IR, Lingsma HF, et al. Does sex modify the effect of endovascular treatment for ischemic stroke? A subgroup analysis of 7 randomized trials. *Stroke* 2019; 50: 2413–2419.

18. Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). *Lancet* 1998; 352: 1245–1251.

19. Park SJ, Shin SD, Ro YS, et al. Gender differences in emergency stroke care and hospital outcome in acute ischemic stroke: a multicenter observational study. *Am J Emerg Med* 2013; 31: 178–184.

20. Gattringer T, Ferrari J, Knoflach M, et al. Sex-related differences of acute stroke unit care: results from the Austrian stroke unit. *Stroke* 2014; 45: 1632–1638.

21. Park HA, Ahn KO, Shin SD, et al. The effect of emergency medical service use and inter-hospital transfer on prehospital delay among ischemic stroke patients: a multicenter observational study. *J Korean Med Sci* 2016; 31: 139–146.

22. Reeves MJ, Fonarow GC, Zhao X, et al. Quality of care in women with ischemic stroke in the GWTG program. *Stroke* 2009; 40: 1127–1133.

23. Kelly AG, Hellkamp AS, Olson D, et al. Predictors of rapid brain imaging in acute stroke: analysis of the get with the guidelines-stroke program. *Stroke* 2012; 43: 1279–1284.

24. Al Khathaami AM, Alsaif SA, Al Bdah BA, et al. Stroke mimics: clinical characteristics and outcome. *Neurosciences (Riyadh)* 2020; 25: 38–42.

25. Meirhaeghe A, Cottel D, Cousin B, et al. Sex differences in stroke attack, incidence and mortality rates in northern France. *J Stroke Cerebrovasc Dis* 2018; 27: 1368–1374.

26. Bushnell CD, Chaturvedi S, Gage KR, et al. Sex differences in stroke: challenges and opportunities. *J Cereb Blood Flow Metab* 2018; 38: 2179–2191.

27. Caso V, Paciaroni M, Agnelli G, et al. Gender differences in patients with acute ischemic stroke. *Womens Health* 2010; 6: 51–57.

28. Dahl S, Hjalmarsson C, Andersson B. Sex differences in risk factors, treatment, and prognosis in acute stroke. *Womens Health* 2020; 16: 1745506520952039.

29. Foerch C, Misselwitz B, Humpich M, et al. Sex disparity in the access of elderly patients to acute stroke care. *Stroke* 2007; 38: 2123–2126.

30. Reeves MJ, Prager M, Fang J, et al. Impact of living alone on the care and outcomes of patients with acute stroke. *Stroke* 2014; 45: 3083–3085.

31. Lisabeth LD, Baek J, Morgenstern LB, et al. Sex differences in the impact of acute stroke treatment in a population-based study: a sex-specific propensity score approach. *Ann Epidemiol* 2017; 27: 493–498.e2.

32. Carcel C, Woodward M, Wang X, et al. Sex matters in stroke: a review of recent evidence on the differences between women and men. *Front Neuroendocrinol* 2020; 59: 100870

33. Sohrabji F, Park MJ, Mahnke AH. Sex differences in stroke therapies. *J Neurosci Res* 2017; 95: 681–691.

34. Ahnstedt H, McCullough LD, Cipolla MJ. The importance of considering sex differences in translational stroke research. *Transl Stroke Res* 2016; 7: 261–273.