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ORIGINAL RESEARCH

Sex Differences in Profile and In-Hospital Death for Acute Stroke in Chile: Data From a Nationwide Hospital Registry

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BACKGROUND: Knowledge of local contextual sex differences in the profile and outcome for stroke can improve service delivery. We aimed to determine sex differences in the profile of patients with acute stroke and their associations with in-hospital death in the national hospital database of Chile.

METHODS AND RESULTS: We present a retrospective cohort based on the analysis of the 2019 Chilean database of Diagnosis-Related Groups, which represents 70% of the operational expenditure of the public health system. Random-effects multiple logistic regression models were used to determine independent associations of acute stroke (defined by main diagnosis *International Classification of Diseases, Tenth Revision* [*ICD-10*] codes) and in-hospital death, and reported with odds ratios (ORs) and 95% CIs. Of 1 048 575 hospital discharges, 15 535 were for patients with acute stroke (7074 [45.5%] in women), and 2438 (15.6%) of them died during hospitalization. Differences by sex in sociodemographic and clinical characteristics were identified for stroke and main subtypes. After fully adjusted model, women with ischemic stroke had lower in-hospital death (OR, 0.79 [95% CI, 0.69–0.91]) compared with men; other independent predictors included age per year increase (OR, 1.03 [95% CI, 1.03–1.04]), chronic kidney disease (OR, 1.47 [95% CI, 1.20–1.80]), atrial fibrillation (OR, 1.50 [95% CI, 1.26–1.80]), and other risk factors. Conversely, for intracerebral hemorrhage, women had a higher in-hospital mortality rate than men (OR, 1.19 [95% CI, 1.02–1.40]); other independent predictors included age per year increase (OR, 1.009 [95% CI, 1.003–1.01]), chronic kidney disease (OR, 1.55 [95% CI, 1.23–1.97]), oral anticoagulant use (OR, 1.88 [95% CI, 1.37–2.58]), and other risk factors.

CONCLUSIONS: Sex differences in characteristics and in-hospital death of hospitalized patients exist for acute stroke in Chile. In-hospital death is higher for acute ischemic stroke in men and higher for intracerebral hemorrhage in women. Future research is needed to better identify contributing factors.

Key Words: Chile ■ death ■ hospitalization ■ risk factors ■ sex ■ stroke

Despite advances in knowledge and interventions, stroke remains the second-leading cause of death worldwide.[1] Further research is needed to better define determinants and risk factors to improve public health policies and a focus toward personalized medicine. Awareness of sex differences in stroke is growing, with studies consistently showing that women are older at presentation and have more atrial fibrillation and hypertension and poorer functional outcomes.[2–4] There are divergent results in regard to sex differences in case fatality,[5–8] where most studies have been undertaken in developed countries, leaving a knowledge gap in relation to low- and middle-income countries where the influence of specific socioeconomic factors

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CLINICAL PERSPECTIVE

What Is New?

- Using national data for annual hospital discharges in Chile, we have detected sex differences in the characteristics, management, and early in-hospital death for patients with acute stroke.
- Of relevance, in-hospital death is higher for acute ischemic stroke in men and higher for intracerebral hemorrhage in women.

What Are the Clinical Implications?

- The impact of sex on in-hospital death across the subtypes of stroke may stem from differences in the social determinants of health and unconscious bias in the delivery of care.
- Further research is required to provide better granularity over factors contributing to sex differences in early stroke death.

Nonstandard Abbreviation and Acronym

ICH	intracerebral hemorrhage
IR-DRG	International Refined Diagnosis-Related Groups Database
IS	ischemic stroke

is likely to be important. Thus, our aim was to determine sex differences in characteristics and determinants of in-hospital death for patients with acute stroke, using the nationwide hospital database of Chile.

METHODS

Design

A retrospective cohort study undertaken according to Strengthening the Reporting of Observational Studies in Epidemiology criteria (see Table S1)[9] using the Chilean International Refined Diagnosis-Related Groups (IR-DRG) database of hospital discharges for the public health insurance scheme of Chile.[10] IR-DRG classification is an international standardized method of data collection from clinical discharges that categorizes patients into homogeneous groups on the basis of similar characteristics and according to disease complexity, hospital workload, quality of service, and associated costs.[11,12] Hospitals aiming for inclusion in the Chilean IR-DRG database are required to have certified codifiers to ensure that the integrity of the data meets high-quality standards.[13] For this secondary data analysis, institutional review board approval was waived and informed consent was not required.

In Chile, there are 95 hospitals with high and medium complexity levels.[14] Our analysis pertains to hospital discharges from 65 hospitals (68% [65/95]) nationwide from this complexity level during 2019, which represent 70% of the operating expenditure of the public health system in Chile.[14,15] All patients (aged ≥18 years) with a main diagnosis of stroke who were discharged from the hospital between January 1 and December 31, 2019, and registered in the Chilean IR-DRG, were considered. In cases with multiple discharges, the second and subsequent events were included as readmission events, except for admissions that occurred within 24 hours of last discharge, which were considered as a continuous hospitalization of the first event. Patients without information on sex, date of birth, admission and discharge date, and status at discharge were excluded.

Measures

Stroke diagnosis was defined as any of the following *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes in the main patient diagnosis: subarachnoid hemorrhage (SAH) (I60), intracerebral hemorrhage (ICH) (I61–I62), ischemic stroke (IS) (I63) and undetermined stroke (I64).[16] Low socioeconomic status (SES) was obtained through the national health insurance assigned group, which categorizes individuals on the basis of their income into 4 main types; low SES is assigned to those without income or with an income lower than the minimum country wage.[17] Presence of a stroke unit was correlated with the hospitals reported by the Ministry of Health of Chile that defined a stroke care unit as a geographically delimited place within a hospital establishment, where an interdisciplinary team specialized in the area follows a treatment protocol.[18] Most variables were analyzed at patient level, except for the presence of a stroke unit and high rurality percentage, which was analyzed at a hospital level and a municipal level, respectively. The percentage of rurality was designated according to the patient's municipality of residence.[19] High rurality percentage was defined as the population in the highest interquartile range (quartile 3–quartile 4), that is, rurality percentage >14.2%. Risk factors and comorbidities were identified in secondary diagnoses by *ICD-10* and in-hospital procedures by *International Classification of Diseases*, *Ninth Revision* (*ICD-9*) codes (Table S2).

The main outcomes were the sex differences in hospitalized patient characteristics, care, and in-hospital death adjusted for age (continuous), low SES, high percentage of rurality,[19] risk factors, stroke subtype, and clinical characteristics. In-hospital death was defined as death during hospitalization that was due to stroke as the main diagnosis in all patients discharged in 2019.

Statistical Analysis

For bivariate analysis, categorical variables were analyzed using the χ^2 independence test or Fisher's test. Quantitative variables were analyzed using Student's *t* test for normal distribution and Mann–Whitney *U* test for a nonnormal distribution. To evaluate the association between sex and in-hospital death and hospital variables, we performed a logistic regression model with random effects, using the unique hospital identifier as the random effect to account for heterogeneity across hospitals. The final model was adjusted by age (continuous) and then for variables of clinical relevance, such as SES, high percentage of rurality, and risk factors with significant association in the bivariate analysis. Absence of a stroke care unit at a hospital level was not included due to collinearity with the model. Results are reported as odds ratios (ORs) with 95% CIs. Significance level was defined as $P<0.05$. All statistical analyses were performed using STATA version 18.0 (StataCorp, College Station, TX). The data that support the findings of this study are available from the corresponding author upon reasonable request.

RESULTS

Of 1 048 575 IR-DRG hospital discharges in Chile during 2019, there were 15 535 patients with a main diagnosis of stroke (Figure 1). Of these, 366 had an undetermined primary diagnosis of stroke (Table 1). Patients with incomplete data that were excluded from the analysis accounted for only 0.68% (n=107) of the total.

Women accounted for 45.54% (7074/15535) of stroke and they were older than men (70.4±14.8 years versus 67.0±13.5 years; P<0.001). Table 1 and Table S3 outlines the other patient characteristics, stroke care unit, and outcomes. After adjustment for age, women belonged to a lower SES (OR, 1.92 [95% CI, 1.77–2.08]), had more hypertension (OR, 1.10 [95% CI, 1.01–1.18]), obesity (OR, 1.64 [95% CI, 1.45–1.86]), and valvular heart diseases than men (OR, 1.28 [95% CI, 1.05–1.55]) (Table S3). Conversely, women had lower odds of residing in areas with a high percentage of rurality (OR, 0.85 [95% CI, 0.79–0.91]), were less likely to be smokers (OR, 0.64 [95% CI, 0.57–0.71]), had less history of ischemic heart disease (OR, 0.53 [95% CI, 0.46–0.60]), and received fewer magnetic resonance imaging studies (OR, 0.85 [95% CI, 0.76–0.94]). In-hospital complications by sex showed lower pneumonia (OR, 0.75 [95% CI, 0.68–0.83]) and acute kidney injury (OR, 0.71 [95% CI, 0.61–0.83]) for women than men. Overall, 2438 (15.69%) patients died during hospitalization.

Table 1. Baseline Characteristics of Patients With Overall Acute Stroke by Sex

Baseline characteristics, n (%)	Women n=7074; 45.54%	Men n=8461; 54.46%	*P* value
Sociodemographic characteristics			
Age, y, mean±SD	70.36±14.76	67.00±13.45	<0.001[¶]
Low socioeconomic status[*]	5783 (81.75)	5801 (68.56)	<0.001[¶]
High percentage of rurality[†]	1649 (23.31)	2227 (26.32)	<0.001[¶]
Risk factors and medical history, n (%)			
Hypertension	5477 (77.42)	6241 (73.76)	<0.001[¶]
Diabetes	2506 (35.43)	2860 (33.80)	0.034[¶]
Dyslipidemia	863 (12.20)	995 (11.76)	0.400
Current smoking	653 (9.23)	1248 (14.75)	<0.001[¶]
Chronic kidney disease	615 (8.69)	749 (8.85)	0.728
Obesity	617 (8.72)	512 (6.05)	<0.001[¶]
Heart diseases	1818 (25.70)	2051 (24.24)	0.036[¶]
Ischemic heart diseases	347 (4.91)	711 (8.40)	<0.001[¶]
Valvular heart disease	228 (3.22)	201 (2.38)	0.001[¶]
Atrial fibrillation	1153 (16.30)	1086 (12.84)	<0.001[¶]
Others	721 (10.19)	735 (8.69)	0.001[¶]
OACs	534 (7.55)	509 (6.02)	<0.001[¶]
Multimorbidity[‡]	5021 (70.98)	5805 (68.61)	0.001[¶]
Stroke by subtype, n (%)			
Ischemic stroke	4659 (65.86)	5781 (68.33)	0.001[¶]
Intracerebral hemorrhage	1568 (22.17)	2112 (24.96)	
Subarachnoid hemorrhage	675 (9.54)	374 (4.42)	
Undetermined	172 (2.43)	194 (2.29)	
Hospitalization			
Hospitalization days, median (IQR)	8 (5–15)	8 (5–15)	0.463
Stroke care unit,[§] n (%)	2822 (39.89)	3347 (39.56)	0.671
Mechanical ventilation, n (%)	686 (9.70)	747 (8.83)	0.062
Readmission, n (%)	224 (3.17)	298 (3.52)	0.221
Diagnostic test, n (%)			
Brain CT	6513 (92.07)	7820 (92.42)	0.410
Brain MRI	824 (11.65)	1229 (14.53)	<0.001[¶]
In-hospital complications,[‖] n (%)	1873 (26.48)	2201 (26.01)	0.513
Dysphagia	634 (8.96)	699 (8.26)	0.120
Pneumonia	825 (11.66)	1151 (13.60)	<0.001[¶]
Pressure ulcers	288 (4.07)	271 (3.20)	0.004[¶]

(Continued)

Table 1. Continued

Baseline characteristics, n (%)	Women n=7074; 45.54%	Men n=8461; 54.46%	*P* value
ARDS	164 (2.32)	215 (2.54)	0.370
Urinary tract infection	34 (0.48)	23 (0.27)	0.032[¶]
Acute kidney injury	286 (4.04)	436 (5.15)	0.001[¶]
In-hospital mortality, n (%)	1172 (16.57)	1266 (14.96)	0.006[¶]

ARDS indicates acute respiratory distress syndrome; CT, computed tomography; IQR, interquartile range; MRI, magnetic resonance imaging; and OAC oral anticoagulants.
*Among those with National Healthcare insurance.
†Based on municipality of residence.
‡Two or more comorbidities.
§Measured at hospital level.
‖At least 1 in-hospital complication.
¶Denotes statistically significant results.

Ischemic Stroke

Among 10 440 patients with IS, 5781 were men (55.37%) who tended to be younger than women (67.85±12.56 years versus 71.57±14.20 years; *P*<0.001); Table 2 and Table S4 define other characteristics and unadjusted results. After adjustment for age (Figure 2), women had lower SES (OR, 2.01 [95% CI, 1.81–2.22]); lower odds of residing in areas with a high percentage of rurality (OR, 0.80 [95% CI, 0.73–0.87]); and more risk factors such as hypertension (OR, 1.16 [95% CI, 1.05–1.28]), diabetes (OR, 1.09 [95% CI, 1.01–1.18]), obesity (OR, 1.74 [95% CI, 1.49–2.02]), valvular heart diseases (OR, 1.39 [95% CI, 1.12–1.71]), and oral anticoagulant use (OR, 1.18 [95% CI, 1.009–1.38]). However, women had less ischemic heart disease (OR, 0.56 [95% CI, 0.48–0.65]) and current smoking (OR, 0.55 [95% CI, 0.49–0.63]) than men. There were no significant sex differences in the duration of hospitalization (*P*=0.12), the availability of a stroke unit (*P*=0.57), craniectomy (*P*=0.31) or the use of reperfusion treatment, whether intravenous thrombolysis (*P*=0.53) or thrombectomy (*P*=0.81). Regarding imaging, although there was no sex difference in the use of computed tomography (CT) (*P*=0.97), women had less magnetic resonance imaging (OR, 0.87 [95% CI, 0.77–0.98]) than men. Regarding in-hospital complications, women had less pneumonia (OR, 0.66 [95% CI, 0.58–0.75]) but more urinary tract infections (OR, 2.31 [95% CI, 1.14–4.69]) compared with men (Figure 2).

In-Hospital Death in IS

There were 1017 (9.74%) patients who died in the hospital, but there were no significant differences in the crude in-hospital death in IS between the sexes (women, 9.74% versus men, 9.74%; *P*=0.99) (Table S5). However, after adjustment for age, women had a lower

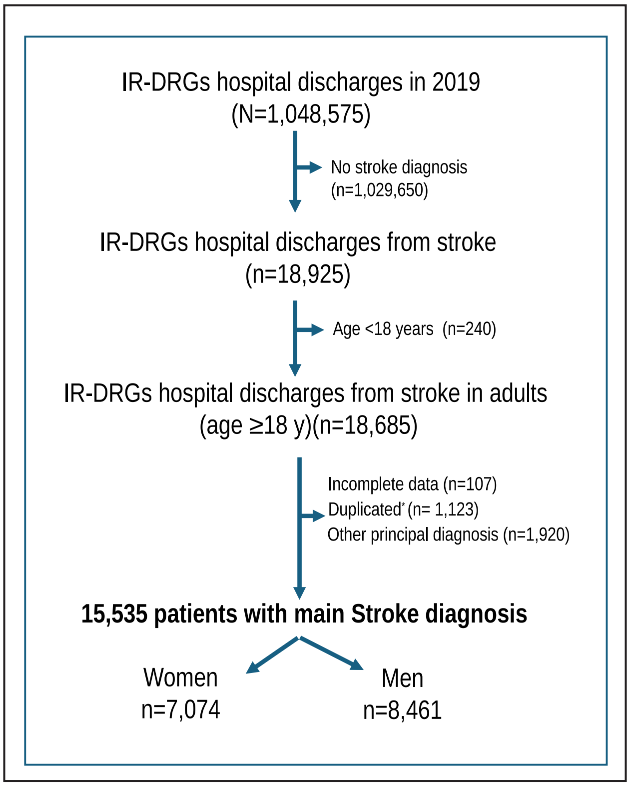

Figure 1. Study setup flowchart.
*Duplicated data due to multiple hospital discharges by the same patient were reentered as a readmission event. DRGs indicates database of Diagnosis-Related Groups.

in-hospital death in IS than men (OR, 0.83 [95% CI, 0.72–0.95]) (Figure 2), and this result remained significant in the fully adjusted model (OR, 0.79 [95% CI, 0.69–0.91]) (Table S6). Other variables independently associated with in-hospital death in IS were age (OR, 1.03 [95% CI, 1.03–1.04]), chronic kidney disease (OR, 1.47 [95% CI, 1.20–1.80]), atrial fibrillation (OR, 1.50 [95% CI, 1.26–1.80]), dyslipidemia (OR, 0.40 [95% CI, 0.30–0.52]), current smoking (OR, 0.66 [95% CI, 0.51–0.85]), and the presence of valvular heart disease (OR, 0.51 [95% CI, 0.33–0.80]) (Figure 3). Sex disaggregated predictors of in-hospital death in IS are outlined in Table S6.

Women had a lower risk of dying only between the ages of 75 and 84 years in the fully adjusted analysis when compared with men (OR, 0.68 [95% CI, 0.54–0.87]) (Figure 3, Table S7).

Intracerebral Hemorrhage

Of 3680 patients with ICH, 2112 were men (57.39%) who were younger than women (66.2±14.56 years versus 71.20±14.30 years; *P*<0.001) (Table 2). Adjustment for age showed that women had lower SES (OR, 2.03 [95% CI, 1.71–2.43]), lower odds of residing in areas with a high percentage of rurality (OR, 0.84 [95% CI,

Table 2. Characteristics and Outcome of Patients With Acute Stroke According to Stroke Subtype by Sex

Baseline characteristics, n (%)	Ischemic stroke			Intracerebral hemorrhage			Subarachnoid hemorrhage		
	Women	Men	*P* value	Women	Men	*P* value	Women	Men	*P* value
	n=4659; 44.63%	n=5781; 55.37%		n=1568; 42.61%	n=2112; 57.39%		n=675; 64.35%	n=374; 35.65%	
Sociodemographic characteristics									
Age, y, mean±SD	71.57±14.20	67.85±12.56	<0.001[#]	71.20±14.30	66.17±14.56	<0.001[#]	59.68±15.43	58.02±16.16	0.101
Low socioeconomic status[*]	3854 (84.22)	3963 (71.00)	<0.001[#]	1309 (83.48)	1465 (69.37)	<0.001[#]	476 (70.52)	240 (64.17)	0.035[#]
High rurality[†]	979 (21.01)	1434 (24.81)	<0.001[#]	422 (26.91)	628 (29.73)	0.061	179 (26.52)	91 (24.33)	0.438
Risk factors and medical history, n (%)									
Hypertension	3718 (79.80)	4349 (75.23)	<0.001[#]	1218 (77.68)	1568 (74.24)	0.016[#]	414 (61.33)	194 (51.87)	0.003[#]
Diabetes	1824 (39.15)	2138 (36.98)	0.023[#]	498 (31.76)	585 (27.70)	0.008[#]	117 (17.33)	74 (19.79)	0.324
Dyslipidemia	604 (12.96)	798 (13.80)	0.211	177 (11.29)	158 (7.48)	<0.001[#]	60 (8.89)	19 (5.08)	0.025[#]
Current smoking	441 (9.47)	990 (17.13)	<0.001[#]	93 (5.93)	190 (9.00)	0.001[#]	109 (16.15)	55 (14.71)	0.538
Chronic kidney disease	422 (9.06)	487 (8.42)	0.254	145 (9.25)	231 (10.94)	0.094	26 (3.85)	17 (4.55)	0.587
Obesity	417 (8.95)	346 (5.99)	<0.001[#]	117 (7.46)	135 (6.39)	0.204	69 (10.22)	23 (6.15)	0.026[#]
Heart diseases	1416 (30.39)	1601 (27.69)	0.002[#]	303 (19.32)	370 (17.52)	0.161	48 (7.11)	43 (11.50)	0.016[#]
Ischemic heart diseases	275 (5.90)	558 (9.65)	<0.001[#]	59 (3.76)	121 (5.73)	0.006[#]	9 (1.33)	15 (4.01)	0.005[#]
Valvular heart disease	200 (4.29)	170 (2.94)	<0.001[#]	16 (1.02)	28 (1.33)	0.399	6 (0.89)	2 (0.53)	0.528
Atrial fibrillation	886 (19.02)	833 (14.41)	<0.001[#]	208 (13.27)	219 (10.37)	0.007[#]	26 (3.85)	15 (4.01)	0.899
Others	563 (12.08)	582 (10.07)	0.001[#]	116 (7.40)	123 (5.82)	0.055	18 (2.67)	20 (5.35)	0.026[#]
OACs	359 (7.71)	340 (5.88)	<0.001[#]	149 (9.50)	139 (6.58)	0.001[#]	18 (2.67)	19 (5.08)	0.042[#]
Multimorbidity[‡]	3523 (75.62)	4198 (72.62)	0.001[#]	1022 (65.18)	1309 (61.98)	0.046[#]	358 (53.04)	184 (49.20)	0.233
Hospitalization									
Hospitalization days, median (IQR)	8 (5–14)	8 (5–14)	0.689	8 (4–16)	8 (4–17)	0.151	8 (4–16)	8 (4–17)	0.488
Stroke care unit,[§] n (%)	1845 (39.60)	2286 (39.54)	0.952	561 (35.78)	820 (38.83)	0.059	365 (54.07)	198 (52.94)	0.725
Readmission, n (%)	140 (3.00)	202 (3.49)	0.163	52 (3.32)	66 (3.12)	0.745	27 (4.00)	21 (5.61)	0.231
Diagnostic test, n (%)									
Brain MRI	647 (13.89)	1038 (17.96)	<0.001[#]	108 (6.89)	141 (6.68)	0.800	53 (7.85)	33 (8.82)	0.583
Brain CT	4350 (93.37)	5392 (93.27)	0.844	1438 (91.71)	1940 (91.86)	0.872	586 (86.81)	334 (89.30)	0.240
Angiography	931 (19.98)	1416 (24.49)	<0.001[#]	180 (11.48)	232 (10.98)	0.638	320 (47.41)	144 (38.50)	0.005[#]
Treatment, n (%)									
Thrombolysis	320 (6.87)	397 (6.87)	0.998	…..	…..	…..	…..	…..	…..
Thrombectomy	58 (1.24)	75 (1.30)	0.812	…..	…..	…..	…..	…..	…..
Craniectomy	16 (0.34)	29 (0.50)	0.220	76 (4.85)	138 (6.53)	0.031[#]	…..	…..	…..
Aneurysm repair	…..	…..	…..	…..	…..	…..	297 (44.00)	135 (36.10)	0.013[#]
Mechanical ventilation,[‖] n (%)	131 (2.81)	209 (3.62)	0.021[#]	279 (17.79)	401 (18.99)	0.356	274 (40.59)	130 (34.76)	0.063
<96 h	57 (1.22)	99 (1.71)	0.041[#]	150 (9.57)	203 (9.61)	0.963	135 (20.00)	76 (20.32)	0.901
≥96 h	73 (1.57)	110 (1.90)	0.194	126 (8.04)	199 (9.42)	0.143	137 (20.30)	54 (14.44)	0.019[#]
In-hospital complication,[¶] n (%)	1100 (23.61)	1342 (23.21)	0.634	525 (33.48)	708 (33.52)	0.979	221 (32.74)	120 (32.09)	0.828
Dysphagia	457 (9.81)	503 (8.70)	0.051	140 (8.93)	175 (8.29)	0.491	30 (4.44)	18 (4.81)	0.784
Pneumonia	470 (10.09)	700 (12.11)	0.001[#]	24 (15.56)	376 (17.80)	0.072	100 (14.81)	61 (16.31)	0.520
Pressure ulcers	181 (3.88)	177 (3.06)	0.022[#]	78 (4.97)	77 (3.65)	0.047[#]	23 (3.41)	14 (3.74)	0.778
ARDS	90 (1.93)	122 (2.11)	0.520	48 (3.06)	77 (3.65)	0.333	26 (3.85)	11 (2.94)	0.444
Urinary tract infections	24 (0.52)	12 (0.21)	0.008[#]	7 (0.45)	10 (0.47)	0.905	2 (0.30)	1 (0.27)	0.933

(*Continued*)

Table 2. Continued

Baseline characteristics, n (%)	Ischemic stroke			Intracerebral hemorrhage			Subarachnoid hemorrhage		
	Women	Men		Women	Men		Women	Men	
	n=4659; 44.63%	n=5781; 55.37%	*P* value	n=1568; 42.61%	n=2112; 57.39%	*P* value	n=675; 64.35%	n=374; 35.65%	*P* value
Acute kidney injury	185 (3.97)	266 (4.60)	0.115	79 (5.04)	153 (7.24)	0.006[#]	15 (2.22)	10 (2.67)	0.646
In-hospital death	454 (9.74)	563 (9.74)	0.992	504 (32.14)	580 (27.46)	0.002[#]	190 (28.15)	100 (26.74)	0.625

ARDS indicates acute respiratory distress syndrome; CT, computed tomography; IQR, interquartile range; MRI, magnetic resonance imaging; and OAC oral anticoagulants.

*Among those with National Healthcare insurance.

[†]Based on municipality of residence.

[‡]Two or more comorbidities.

[§]Measured at hospital level.

[‖]Numbers may not add to 100% due to patients without hours of ventilation registered.

[¶]At least 1 in-hospital complication.

[#]Denotes statistically significant results.

0.72–0.98]), and more dyslipidemia (OR, 1.46 [95% CI, 1.16–1.84]) but less current smoking (OR, 0.74 [95% CI, 0.57–0.96]) and history of ischemic heart disease (OR, 0.58 [95% CI, 0.41–0.80]). Women also had less acute kidney injury compared with men (OR, 0.71 [95% CI, 0.53–0.95]) (Figure 2) and underwent fewer craniectomies (OR, 0.72 [95% CI, 0.53–0.98]). There were no significant sex differences in the duration of hospitalization (*P*=0.06), the availability of a stroke care unit (*P*=0.15), or the use of computed tomography scans (*P*=0.83).

In-Hospital Death in ICH

There were 1084 (29.46%) patients with ICH who had an in-hospital death. Women had higher in-hospital death with ICH than men (32.1% versus 27.5%; age-adjusted OR, 1.18 [95% CI, 1.02–1.37]; and fully adjusted OR, 1.19 [95% CI, 1.02–1.40]) (Figure 4). Other independent predictors of in-hospital death with ICH were age (OR, 1.009 [95% CI, 1.003–1.01]), chronic kidney disease (OR, 1.55 [95% CI, 1.23–1.97]), oral anticoagulant use (OR, 1.88 [95% CI, 1.37–2.58]), hypertension (OR, 0.70 [95% CI, 0.59–0.84]), current smoking (OR, 0.58 [95% CI, 0.42–0.81]) and dyslipidemia (OR, 0.54 [95% CI, 0.39–0.73]) (Figure 4). Unlike women, chronic kidney disease was associated with in-hospital death with ICH in men (OR, 2.00 [95% CI, 1.47–2.70]). Other sex-disaggregated predictors of in-hospital death with ICH are outlined in Table S8.

Women with ICH between the ages of 55 and 64 and 65 and 74 years had significantly higher in-hospital death with ICH than men (Figure 4, Table S7). In the fully adjusted model, the 55 to 74 years age range remained significant (OR, 1.23 [95% CI, 1.02–1.48]).

Subarachnoid Hemorrhage

Of 1049 patients hospitalized for SAH, 675 were women (64.35%); there was no age difference by sex (women, 59.68±15.43 years versus men, 58.02±16.16 years; *P*=0.10) (Table 2). After adjustment for age, women had more hypertension (OR, 1.43 [95% CI, 1.09–1.87]), dyslipidemia (OR, 1.76 [95% CI, 1.03–3.01]), and obesity (OR, 1.77 [95% CI, 1.08–2.89]) but less ischemic heart disease (OR, 0.30 [95% CI, 0.13–0.70]) and oral anticoagulant use (OR, 0.46 [95% CI, 0.23–0.91]) than men (Figure 2). Women had more angiography (OR, 1.51 [95% CI, 1.11–2.05]) and more aneurysm repair procedures than men (OR, 1.64 [95% CI, 1.16–2.31]). There were no significant sex differences in rural residence (*P*=0.48), duration of hospitalization (*P*=0.70), availability of a stroke care unit (*P*=0.60), and use of computed tomography scans (*P*=0.22).

In-Hospital Death in SAH

There were 290 (27.65%) patients who died of an SAH. For in-hospital death with SAH, there was no difference by sex (women, 28.15% versus men, 26.74%; age-adjusted OR, 1.05 [95% CI, 0.78–1.40]) (Figure 2). The only independent predictor of in-hospital death with SAH was age (OR, 1.01 [95% CI, 1.004–1.02]) (Figure S1). Interestingly, age was associated with in-hospital death in SAH in men (OR, 1.02 [95% CI, 1.007–1.04]) but not in women (*P*=0.153) (Table S9). Other sex-disaggregated predictors of in-hospital death in SAH can be found in Table S9 and Figure S1.

DISCUSSION

In this study, which used national data for annual hospital discharges for stroke, we outline sex-disaggregated data for sociodemographic, clinical characteristics, and hospital outcomes. We show that sex influences in-hospital death by stroke subtype, which is higher in men with IS and in women with ICH.

The characteristics of our patients with acute stroke are consistent with other populations, in that women tend to be older and of lower SES, and have greater comorbidities of hypertension, atrial fibrillation, and obesity but less ischemic heart disease and smoking, than

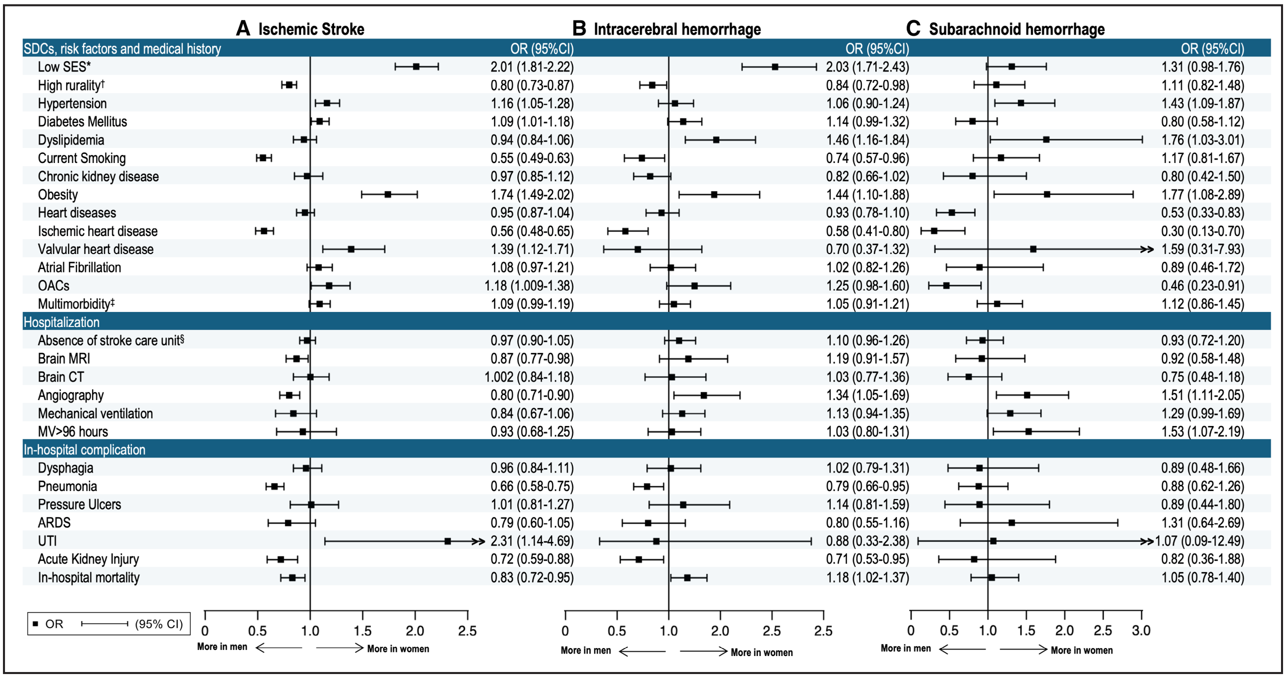

Figure 2. Age-adjusted differences in baseline characteristics in women compared with men, by stroke subtype.
*Among those with National Healthcare insurance. †Based on municipality of residence. ‡Two or more comorbidities. §Measured at hospital level. ARDS indicates acute respiratory distress syndrome; CT, computed tomography; MRI, magnetic resonance imaging; MV, mechanical ventilation; OACs, oral anticoagulants; OR, odds ratio; SDCs, sociodemographic characteristics; SES, socioeconomic status; and UTI, urinary tract infection.

men.[2,6,20–23] Although we were unable to account for baseline severity in our analysis, our observations align with other studies in showing a greater survival in women after IS.[5,20,24–27] The reasons for this remain unexplained, but raise issues of sexual dimorphism in neuroanatomy or biology,[25] unequal interaction of predictor variables,[27]

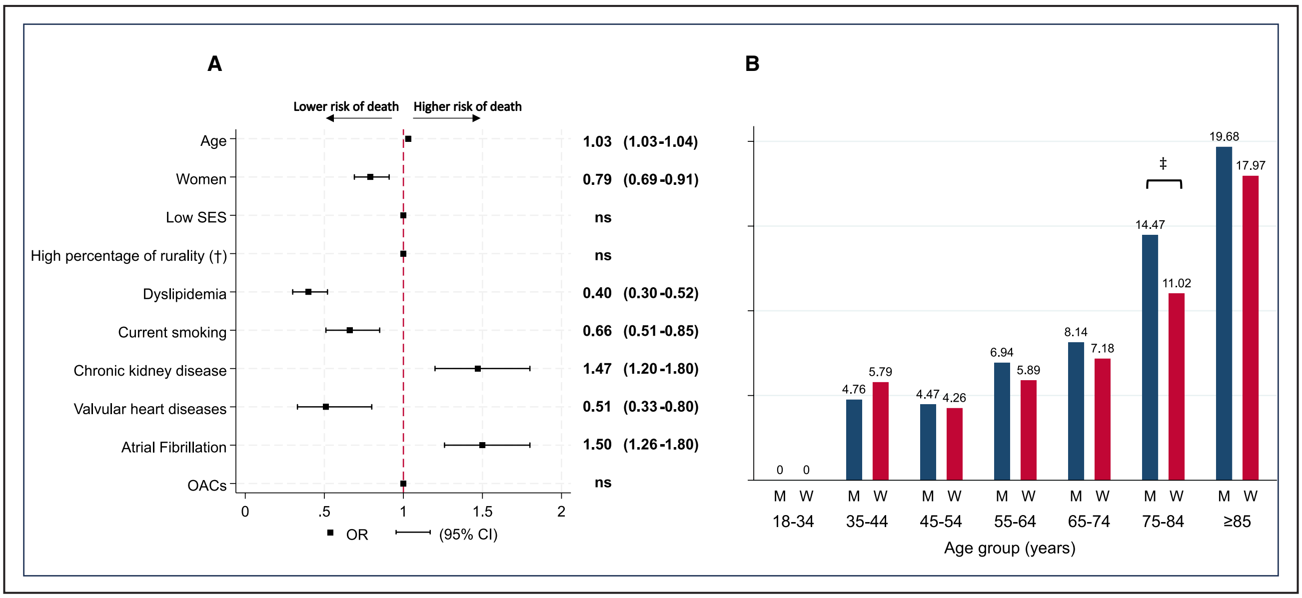

Figure 3. Predictors of in-hospital death in ischemic stroke, by sex and age group.
A, Independent predictors of in-hospital death in ischemic stroke. Adjusted for age, sex, low socioeconomic status, higher percentage of rurality, dyslipidemia, current smoking, chronic kidney disease, valvular heart diseases, atrial fibrillation, and oral anticoagulants. **B**, In-hospital death in ischemic stroke disaggregated by sex and age group. *Logistic regression model with random effects. †Based on municipality of residence. ‡Statistically significant results (*P*<0.05). M indicates men; ns, nonsignificance; OACs, oral anticoagulants; OR, odds ratio; SES, socioeconomic status; and W, women.

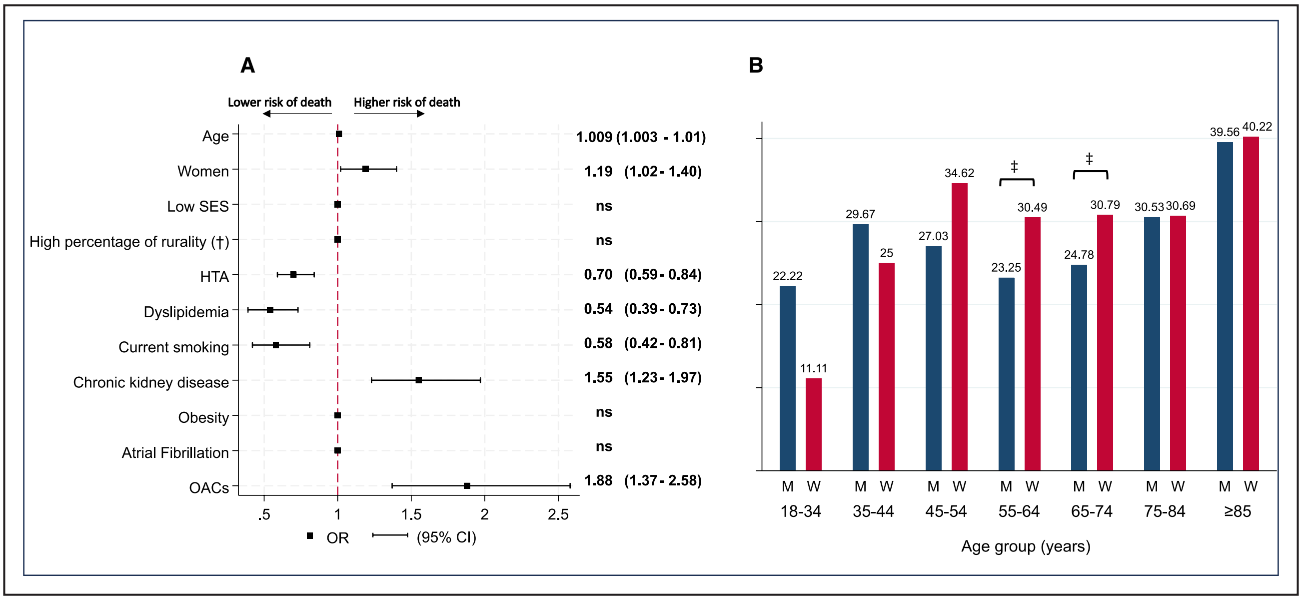

Figure 4. Predictors of in-hospital death for intracerebral hemorrhage, by sex and age group.
A, Independent predictors of in-hospital death of intracerebral hemorrhage. adjusted for age, sex, low socioeconomic status, high percentage of rurality, hypertension, dyslipidemia, current smoking, chronic kidney disease, obesity, atrial fibrillation, and oral anticoagulants. **B,** In-hospital death of intracerebral hemorrhage disaggregated by sex and age group. *Logistic regression model with random effects. †Based on municipality of residence. ‡Statistically significant results (P<0.05). M, men; ns, nonsignificance; OACs, oral anticoagulants; OR, odds ratio; SES, socioeconomic status; and W, women.

and a survival advantage in relation to poststroke infections.[28] A Japanese Stroke Registry of 19956 patients with IS showed that women had a lower case fatality rate among those who developed a poststroke infection.[28] Further research is needed to understand the underlying factors of sex differences on survival after IS.

For ICH, women were 19% more likely to die in the hospital than men, and this could not be explained by age or baseline risk factors. Significantly, this distinction was noted during a productive phase of life, especially among individuals aged ≥55 years. While conflicting results shown elsewhere[6–8,21,29] may stem from differences in methodologies, there may also be sociocultural explanations.[29,30] Women in our study were twice as likely to belong to a lower SES than men, and although this was controlled in the multivariable analysis, it is important to note that disadvantaged women are more susceptible to social isolation, sex-based violence, poor social support, and insufficient education than men.[31–34] At the 479054 participants of the UK Biobank, social isolation but not loneliness was associated with higher risk of all-cause death.[35] A national health survey of 4473 people in Chile showed poorer health-related quality of life reported in women than men.[36] Thus, the social context of Chilean women may contribute to a higher probability of a severe presentation and worse outcome in stroke.

Furthermore, early death is inherently connected with quality of hospital care,[37–39] but the influence of sex-based bias in care is underreported. In cardiovascular studies, men are often perceived as being physically stronger, leading health care providers to be more inclined to recommend and perform medical procedures for them than for women.[40] There are few reports specifically in relation to the management of patients with acute ICH where a performance focus is on do not resuscitate orders: Results suggest higher use of do not resuscitate orders in women than men,[41] although such differences could relate to incomplete adjustment for confounding variables.[42] Patients with ICH with severe illness are unable to make critical end-of-life decisions. While we did not have access to the severity of the initial illness or data on various quality metrics, given the strong connection between in-hospital death and quality of care, it is plausible that the greater severity of ICH in women and the perception of their being more fragile might have influenced decisions. Unconscious sex-related biases may also have influenced the findings of fewer medical interventions in women, which potentially limited diagnostic and therapeutic efforts; such is the case of the lower likelihood of craniectomies performed in women compared with men. Further investigation into sex disparities in the intensity of care after acute ICH is clearly warranted.

Our study has several limitations. In particular, we lacked data on the time from the onset of symptoms to presentation and severity of the neurological deficit. In the database used, we were also unable to access information regarding early withdrawal of life-sustaining treatment and other management that are associated with outcomes. There might have been miscoding errors and missing data that influenced the results. However, the large sample size, national representation,[15] and nondifferential bias in the data still provide a reliable overview of sex differences in the early outcome from acute stroke in Chile.

In summary, we have defined sex differences in the characteristics, management and early in-hospital death for patients with acute stroke in Chile. The impact of sex on in-hospital death across the subtypes of stroke may stem from differences in the social determinants of health and unconscious bias in the delivery of care. Further research is required to provide better granularity over factors contributing to sex differences in early stroke death.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S9
Figure S1

REFERENCES

1. Feigin VL, Stark BA, Johnson CO, Roth GA, Bisignano C, Abady GG, Abbasifard M, Abbasi-Kangevari M, Abd-Allah F, Abedi V, et al. Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the global burden of disease study 2019. *Lancet Neurol*. 2021;20:795–820. doi: 10.1016/S1474-4422(21)00252-0
2. Peters SAE, Carcel C, Millett ERC, Woodward M. Sex differences in the association between major risk factors and the risk of stroke in the UK biobank cohort study. *Neurology*. 2020;95:e2715–e2726. doi: 10.1212/WNL.0000000000010982
3. Guo X, Xiong Y, Huang X, Pan Z, Kang X, Chen C, Zhou J, Zheng H, Chen Y, Hu W, et al. Sex-based differences in long-term outcomes after stroke: a meta-analysis. *PLoS One*. 2023;18:e0283204. doi: 10.1371/journal.pone.0283204
4. Rexrode KM, Madsen TE, Yu AYX, Carcel C, Lichtman JH, Miller EC. The impact of sex and gender on stroke. *Circ Res*. 2022;130:512–528. doi: 10.1161/CIRCRESAHA.121.319915
5. Bonkhoff AK, Karch A, Weber R, Wellmann J, Berger K. Female stroke: sex differences in acute treatment and early outcomes of acute ischemic stroke. *Stroke*. 2021;52:406–415. doi: 10.1161/STROKEAHA.120.032850
6. James ML, Cox M, Xian Y, Smith EE, Bhatt DL, Schulte PJ, Hernandez A, Fonarow GC, Schwamm LH. Sex and age interactions and differences in outcomes after intracerebral hemorrhage. *J Women's Health*. 2017;26:380–388. doi: 10.1089/jwh.2016.5849
7. Ganti L, Jain A, Yerragondu N, Jain M, Bellolio MF, Gilmore RM, Rabinstein A. Female gender remains an independent risk factor for poor outcome after acute nontraumatic intracerebral hemorrhage. *Neurol Res Int*. 2013;2013:1–7. doi: 10.1155/2013/219097
8. Lu P, Cao Z, Gu H, Li Z, Wang Y, Cui L, Wang Y, Zhao X. Association of sex and age with in-hospital mortality and complications of patients with intracerebral hemorrhage: a study from the Chinese stroke center Alliance. *Brain Behav*. 2023;13:e2846. doi: 10.1002/brb3.2846
9. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007;370:1453–1457. doi: 10.1016/S0140-6736(07)61602-X
10. Ministerio de Salud Chile Fondo Nacional de Salud. Base de datos Grupos Relacionados por Diganóstico (GRD) 2019. 2020. Accessed October 31, 2023. https://www.fonasa.cl/sites/fonasa/datos-abiertos/bases-grd.
11. Zapata M. Importance of the GRD system to achieve hospital efficiency. *Rev Médica Clínica Las Condes*. 2018;29:347–352. doi: 10.1016/j.rmclc.2018.04.010
12. Águila RA, Muñoz DMA, Sepúlveda SV. Experiencia en el desarrollo e implementación de la metodología de grupos relacionados por diagnóstico en un hospital universitario chileno. Evaluación a diez años de funcionamiento. *Rev Médica Chile*. 2019;147:1518–1526. doi: 10.4067/S0034-98872019001201518
13. Ministerio de Salud Chile Fondo Nacional de Salud. Bases administrativas licitación pública para compra de servicios de salud de resolución de patologías agudas o reagudizadas, a través de mecanismo de pago por grupos relacionados por el diagnóstico (GRD), para el Fondo Nacional de Salud. 2023 Accessed January 5, 2024. https://www.mercadopublico.cl/Procurement/Modules/RFB/DetailsAcquisition.aspx?qs=/b4qKxBRxvK+YJCz2AXWlw==.
14. Subsecretaría de Redes Asistenciales. Ley de presupuestos del Sector Público N°21.516 de 2023. 2023 Accessed April 16, 2023. https://www.minsal.cl/wp-content/uploads/2021/05/Glosa-01-d-Ano-2023.pdf.
15. Ministerio de Salud Chile Fondo Nacional de Salud. Balance de Gestión Integral 2020. Accessed October 31, 2023. https://www.dipres.gob.cl/597/articles-266871_doc_pdf
16. World Health Organization, ed. *Clasificación estadística internacional de enfermedades y problemas relacionados con la salud, Décima revisión*. 10a rev. ed. OPS, Oficina Sanitaria Panamericana, Oficina Regional de la Organización Mundial de la Salud; 1995:1–3.
17. Superintendencia de Salud Ministerio de Salud Chile. ¿Cómo se clasifican los beneficiarios de Fonasa según su tramo? 2022 Accessed October 31, 2023. https://www.supersalud.gob.cl/consultas/667/w3-article-6304.html.
18. Novoa J, Candia O, San Martin M, Santos I, Parra C, Mendez N. Modelo de *Gestión de la Red Neurológica en la atención de las personas con ataque cerebrovascular (ACV)*. Ministerio de Salud Chile. 2020. Accessed February 13, 2024. https://www.minsal.cl/wp-content/uploads/2021/03/Modelo-de-Gesti%C3%B3n-de-la-Red-Neurol%C3%B3gica-en-la-atenci%C3%B3n-de-las-personas-con-ACV.pdf.
19. Población por zona Urbana-Rural, Censos 1992, 2002 y 2017. Accessed February 13, 2024. https://www.bcn.cl/siit/estadisticasterritoriales//resultados-consulta?id=294859.
20. Renoux C, Coulombe J, Li L, Ganesh A, Silver L, Rothwell PM. Confounding by pre-morbid functional status in studies of apparent sex differences in severity and outcome of stroke. *Stroke*. 2017;48:2731–2738. doi: 10.1161/STROKEAHA.117.018187
21. Abdel-Fattah A-R, Pana TA, Tiamkao S, Sawanyawisuth K, Kasemsap N, Mamas MA, Myint PK. Différences sexuelles dans la mortalité par accident vasculaire cérébral en Thaïlande : une étude de cohorte nationale. *Ann Cardiol Angeiol*. 2023;72:1–7. doi: 10.1016/j.ancard.2022.11.003

22. Yu AYX, Austin PC, Rashid M, Fang J, Porter J, Vyas MV, Smith EE, Joundi RA, Edwards JD, Reeves MJ, et al. Sex differences in intensity of care and outcomes after acute ischemic stroke across the age continuum. *Neurology*. 2023;100:e163–e171. doi: 10.1212/WNL.0000000000201372
23. Arauz A, Serrano F, Ameriso SF, Pujol-Lereis V, Flores A, Bayona H, Fernández H, Castillo A, Ecos R, Vazquez J, et al. Sex differences among participants in the Latin American stroke registry. *J Am Heart Assoc*. 2020;9:e013903. doi: 10.1161/JAHA.119.013903
24. Xu M, Amarilla Vallejo A, Cantalapiedra Calvete C, Rudd A, Wolfe C, O'Connell MDL, Douiri A. Stroke outcomes in women: a population-based cohort study. *Stroke*. 2022;53:3072–3081. doi: 10.1161/STROKEAHA.121.037829
25. Dehlendorff C, Andersen KK, Olsen TS. Sex disparities in stroke: women have more severe strokes but better survival than men. *J Am Heart Assoc*. 2015;4:e001967. doi: 10.1161/JAHA.115.001967
26. Carcel C, Wang X, Sandset EC, Delcourt C, Arima H, Lindley R, Hackett ML, Lavados P, Robinson TG, Muñoz Venturelli P, et al. Sex differences in treatment and outcome after stroke: pooled analysis including 19,000 participants. *Neurology*. 2019;93:e2170–e2180. doi: 10.1212/WNL.0000000000008615
27. Vaartjes I, Reitsma JB, Berger-van Sijl M, Bots ML. Gender differences in mortality after hospital admission for stroke. *Cerebrovasc Dis*. 2009;28:564–571. doi: 10.1159/000247600
28. Irie F, Matsuo R, Nakamura K, Wakisaka Y, Ago T, Kamouchi M, Kitazono T. Fukuoka stroke registry investigators. Sex differences in the risk of 30-day death after acute ischemic stroke. *Neurol Clin Pract*. 2021;11:e809–e816. doi: 10.1212/CPJ.0000000000001087
29. Craen A, Mangal R, Stead TG, Ganti L. Gender differences in outcomes after non-traumatic intracerebral hemorrhage. *Cureus*. 2019;11:e5818. doi: 10.7759/cureus.5818
30. Fukuda-Doi M, Yamamoto H, Koga M, Palesch YY, Durkalski-Mauldin VL, Qureshi AI, Yoshimura S, Okazaki S, Miwa K, Okada Y, et al. Sex differences in blood pressure–lowering therapy and outcomes following intracerebral hemorrhage: results from ATACH-2. *Stroke*. 2020;51:2282–2286. doi: 10.1161/STROKEAHA.120.029770
31. OECD. *Education at a Glance 2021: OECD Indicators*. Vol 2021. OECD Publishing; 2021. doi: 10.1787/b35a14e5-en
32. Naito R, Leong DP, Bangdiwala SI, McKee M, Subramanian SV, Rangarajan S, Islam S, Avezum A, Yeates KE, Lear SA, et al. Impact of social isolation on mortality and morbidity in 20 high-income, middle-income and low-income countries in five continents. *BMJ Glob Health*. 2021;6:e004124. doi: 10.1136/bmjgh-2020-004124
33. Perera C, Bakrania S, Ipince A, Nesbitt-Ahmed Z, Obasola O, Richardson D, Van De Scheur J, Yu R. Impact of social protection on gender equality in low- and middle-income countries: a systematic review of reviews. *Campbell Syst Rev*. 2022;18:e1240. doi: 10.1002/cl2.1240
34. Kim H, Grogan-Kaylor A, Han Y, Maurizi L, Delva J. The Association of Neighborhood Characteristics and Domestic Violence in Santiago, Chile. *J Urban Health*. 2013;90:41–55. doi: 10.1007/s11524-012-9706-6
35. Valtorta NK, Kanaan M, Gilbody S, Ronzi S, Hanratty B. Loneliness and social isolation as risk factors for coronary heart disease and stroke: systematic review and meta-analysis of longitudinal observational studies. *Heart*. 2016;102:1009–1016. doi: 10.1136/heartjnl-2015-308790
36. Matute I, Burgos S, Alfaro T. Socioeconomic status and perceived health-related quality of life in Chile. *MEDICC Rev*. 2017;19:51. doi: 10.37757/MR2017.V19.N2-3.9
37. Weimer JM, Nowacki AS, Frontera JA. Withdrawal of life-sustaining therapy in patients with intracranial hemorrhage: self-fulfilling prophecy or accurate prediction of outcome?*. *Crit Care Med*. 2016;44:1161–1172. doi: 10.1097/CCM.0000000000001570
38. Martinez J, Mouzinho M, Teles J, Guilherme P, Nogueira J, Félix C, Ferreira F, Marreiros A, Nzwalo H. Poor intensive stroke care is associated with short-term death after spontaneous intracerebral hemorrhage. *Clin Neurol Neurosurg*. 2020;191:105696. doi: 10.1016/j.clineuro.2020.105696
39. Zurasky JA, Aiyagari V, Zazulia AR, Shackelford A, Diringer MN. Early mortality following spontaneous intracerebral hemorrhage. *Neurology*. 2005;64:725–727. doi: 10.1212/01.WNL.0000152045.56837.58
40. Daugherty SL, Blair IV, Havranek EP, Furniss A, Dickinson LM, Karimkhani E, Main DS, Masoudi FA. Implicit gender bias and the use of cardiovascular tests among cardiologists. *J Am Heart Assoc*. 2017;6:e006872. doi: 10.1161/JAHA.117.006872
41. Nakagawa K, Vento MA, Seto TB, Koenig MA, Asai SM, Chang CWJ, Hemphill JC. Sex differences in the use of early do-not-resuscitate orders after intracerebral hemorrhage. *Stroke*. 2013;44:3229–3231. doi: 10.1161/STROKEAHA.113.002814
42. Guha R, Boehme A, Demel SL, Li JJ, Cai X, James ML, Koch S, Langefeld CD, Moomaw CJ, Osborne J, et al. Aggressiveness of care following intracerebral hemorrhage in women and men. *Neurology*. 2017;89:349–354. doi: 10.1212/WNL.0000000000004143