ORIGINAL RESEARCH

Sex Differences Among Participants in the Latin American Stroke Registry

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***Background*—**Reports on sex differences in stroke outcome and risk factors are scarce in Latin America. Our objective was to analyze clinical and prognostic differences according to sex among participants in the LASE (Latin American Stroke Registry).

***Methods and Results*—**Nineteen centers across Central and South America compiled data on demographics, vascular risk factors, clinical stroke description, ancillary tests, and functional outcomes at short-term follow-up of patients included from January 2012 to January 2017. For the present study, all these variables were analyzed according to sex at hospital discharge. We included 4788 patients with a median in-hospital stay of 8 days (interquartile range, 5–8); 2677 were male (median age, 66 years) and 2111 female (median age, 60 years). Ischemic stroke occurred in 4293: 3686 as cerebral infarction (77%) and 607 as transient ischemic attack cases (12.7%); 495 patients (10.3%) corresponded to intracerebral hemorrhage. Poor functional outcome (modified Rankin scale, 3–6) was present in 1662 (34.7%) patients and 38.2% of women (P<0.001). Mortality was present in 6.8% of the registry, with 7.8% in women compared with 6.0% in men (P=0.01). Death and poor functional outcome for all-type stroke showed a higher risk in female patients (hazard ratio, 1.3, P=0.03; and hazard ratio, 1.1, P=0.001, respectively).

***Conclusions*—**A worse functional outcome and higher mortality rates occurred in women compared with men in the LASE, confirming sex differences issues at short-term follow-up. **(*J Am Heart Assoc*. 2020;9:e013903. DOI: 10.1161/JAHA.119.013903.)**

Key Words: Latin America • sex • stroke outcome • stroke registry • vascular risk factors

Stroke is the second leading cause of death worldwide, with nearly 5.5 million deaths related to this condition in 2016.[1] In the Global Burden of Disease study, stroke subanalysis showed that men and women had similar age-specific incidences at ages up to 55 years, with higher rates in men at 55 to 75 years and a subsequent decrease in patients older than 75 years.[2] The overall global sex prevalence in 2016 was 41.1 million women and 39.0 million men.[1,2]

Sex differences have been reported in stroke registries worldwide[3–6] based on risk factors, prevalence, incidence,

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Accompanying Tables S1 and S2 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013903

*A complete list of the Latin American Stroke Registry members can be found in the appendix at the end of the article.

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Clinical Perspective

What Is New?

- This is the first report addressing sex disparities in post-stroke functional outcomes in Latin America. We documented worse functional outcomes and higher mortality in women.

What Are the Clinical Implications?

- Stroke networks in Latin America should emphasize quality of care in stroke patients, improving in not only scientific knowledge and technology, but also in access to acute stroke care and post-stroke services geared toward reducing the noted sex-based stroke disparities.

and socioeconomic status, with worse clinical outcomes in women compared with men.[7,8] Although age-specific incidence of stroke and overall mortality is higher in men, the life expectancy of women worldwide is higher, and the risk of stroke increases with age.[7] On the other hand, the estimates of lifetime risk of stroke have also been analyzed by sex, with the risk among men at 24.7% and the risk among women at 25.1%, from the age of 25 years onward.[9]

In Latin America, stroke incidence varies from 90 to 120/100 000 people in Central Latin America to 121 to 150/100 000 people in Andean Latin America.[2] Despite similarities in language and socioeconomic characteristics, the region differs in genetic and ethnic characteristics. To our knowledge, there is no information available regarding sex differences and functional status after a first-ever stroke from an unselected population-based sample in this region.

The LASE (Latin American Stroke Registry) is an initiative that explores several topics related to functional status in patients following stroke via a multicenter, population-based sample from tertiary hospitals in the region using robust data compilation and methodology. The aim of this study was to analyze the influence of sex on underlying patient characteristics, stroke subtypes, and functional outcome, among participants in the LASE.

Methods

The data sets generated during and/or analyzed during the current study are not publicly available because of each institutional policy but are available from the corresponding author on reasonable request.

The LASE is a multicenter initiative from tertiary referral hospitals with ongoing stroke registries that could fulfill inclusion criteria (described later) from across Central and Andean Latin America. Participating centers were recruited through formal invitation because of their known work in stroke care in their respective country/region. The corresponding Institutional Ethics Committee approved all the stroke data sets according to international and local research regulations. Because of the lack of treatment influence, the registry was exempt from informed consent. However, patients or family members (if the patient was neurologically impaired) verbally agreed to participate in the project.

A total of 18 centers (see Figure 1) worked together for the LASE initiative, integrating countries from the Central and Andean region of Latin America, including Mexico (9 centers from the cities of Mexico City, Durango, Morelia, and Guadalajara), Colombia (2 centers from Bogotá and 1 from Cali), Perú (2 centers from Lima), Argentina (1 center from Buenos Aires), Costa Rica (1 center from San José), Paraguay (1 center from Asuncion), and Ecuador (1 center from Quito). Most of the participating centers provide neurologic medical assistance to low- and middle-income populations referred from hospitals all around the country and contribute as university hospitals together with medical attention for social and mixed insurance medical programs. Although all participating centers had an institutional stroke program for acute care (inpatient) and subsequent follow-up (outpatient) and staffing by qualified medical professionals trained in stroke care, only 4 hospitals (Paraguay, Costa Rica, Argentina, and 1 in Colombia) have a stroke unit, and none have the primary stroke center certification. The availability of imaging studies varies in each center and in each country. Intravenous thrombolysis is available in all hospitals, but only a few can offer thrombectomy, and all hospitals offer similar levels of treatment based on stroke treatment guidelines.

The analysis was performed by three investigators (FS, MAB, and AA) in a single database that was compiled from the data sets provided by all the participating centers. The data set used was provided to all centers at the start of the project and contained a standardized set of clinical variables. Data recollection was maintained up to the time of the final analysis for this study.

Setting and Population

The data sets were prospectively collected from consecutive patients admitted to participating hospitals (study period from January 2012 to January 2017). The inclusion criterion to recruit patients for the present analysis from the data sets was patients with a first stroke as demonstrated by imaging studies. All ischemic strokes (IS), primary intracerebral hemorrhages (ICH), and transient ischemic attack were included, whereas subarachnoid hemorrhage cases were excluded (as the analysis of this condition is done in a separate department in most of the hospitals). Only patients older than 18 years of age were included in the present

Figure 1. Participating centers and number of cases per center.

analysis, as most of the hospitals only attend adult cases. We also excluded cases with incomplete in-hospital information that could not be corroborated via medical files. Cerebral venous thrombosis cases were also excluded from the current analysis, as this condition will be analyzed in a separate study.

IS subtype classification was based on the modified Trial of Org 10172 of the Acute Stroke Treatment classification using a consensus approach, and if necessary, modified by the findings of subsequent ancillary diagnostic tests. For the purpose of the present study, the analysis of data was performed on the basis of the acute case; therefore, only in-hospital information was analyzed. Information was collected from the original data sets, but for those missing data we attempted to review all relevant medical records to collect all available information.

Risk Factors Recorded

The data set of each center was compiled in a single database by 2 of the authors (FS and MAB). *Baseline characteristics*: age, sex and place of living (rural or urban). *Vascular risk factors and comorbid conditions*: hypertension (defined as previous known,

current treatment, or values ≥140/90 mm Hg in at least 2 subsequent measurements), atrial fibrillation (history of chronic atrial fibrillation, supported by past ECG and positive ECG during hospitalization or past medical history with positive ECG), previous myocardial infarction (previous diagnosis based on a documented transient elevation of biochemical markers of myocardial necrosis with typical ECG signs), transient ischemic attack (defined as an acute neurological deficit of vascular origin lasting <1 hour, with no parenchymal lesions on brain imaging), diabetes mellitus (DM; defined as previous known, concurrent treatment with insulin or oral hypoglycemic medications, or fasting plasma glucose level ≥140 mg/dL), smoking (current or former practice [subject had stopped smoking for at least 2 years preceding the stroke event]), and family history of stroke or acute myocardial infarction.

Paraclinical Assessment

In addition to cerebral computed tomography and/or magnetic resonance imaging, most of the patients received a standardized workup to rule out definite causes of stroke.

The workup consisted of routine blood tests and a coagulation study (tests for protein S, protein C, antithrombin III, and antiphospholipid antibodies were performed only in young patients with no other vascular risk factors), 12-lead ECG and echocardiography, and at least 1 of the following vascular studies: digital subtraction angiography, magnetic resonance angiography, computed tomography angiography, and cervical and transcranial Doppler, according to availability at each medical center.

The following disorders were considered to be definite causes of IS: large-artery atherosclerosis (defined by a stenosis of at least 50% or occlusion of the corresponding vessel); lacunar stroke (defined by a small, deep infarct <15 mm in diameter in a patient with hypertension); cardioembolic causes, including atrial fibrillation, recent (within 4 months before the stroke) myocardial infarction, dilated cardiomyopathy, rheumatic mitral stenosis, mitral or aortic vegetations or prostheses, left atrial or left ventricular thrombus or tumor, akinetic left ventricular segment, spontaneous echo contrast of the left atrium, and complex atheroma of the aortic arch; and other determined etiologies of stroke, such as nonatherosclerotic arteriopathies (eg, dissection), coagulopathies, and hematologic or systemic disorders (eg, antiphospholipid-antibody syndrome). Cryptogenic stroke was recorded in patients with no likely etiology despite an extensive evaluation. In cases where the cause of a stroke could not be determined with confidence because of insufficient ancillary diagnostic tests, unidentified etiology with incomplete evaluation was recorded; on the other hand, cases with ≥2 possible etiologies or those with disagreement among raters were reviewed by the expert from the stroke clinic at each hospital to determine the most suitable etiology based on all evidence.

Outcome Measures

For the purposes of this analysis, only in-hospital evolution and discharge information was taken into account. Clinical outcome was systematically recorded as measured by the modified Rankin scale at discharge. Poor clinical outcome was defined as a modified Rankin scale 3 to 6, whereas the total mortality in this period of time was analyzed in spite of the death considered or not related to the index stroke.

Statistical Analysis

We compared female and male patients (as the dependent variable) using chi-squared test or Fisher's exact test for dichotomous data (vascular risk factors, demographics, type of stroke, functional outcome, and age groups), and the Mann–Whitney U or Student *t* test for continuous data, according to normality tests on continuous variables (age or length of in hospital stay). Mean and SD for normally distributed variables, as median and interquartile range for not normally distributed variables are also provided.

Potential predictor factors (vascular risk factors, age groups, severity of the infarction [according to National Institutes of Health stroke scale] and acute therapy intervention [intravenous thrombolysis, thrombectomy, and stroke unit admission]) of death and poor functional outcome (modified Rankin scale, 3–6) by sex were selected on the basis of clinical plausibility, and separate univariate analysis for each risk factor; those with $P<0.1$ were entered in a stepwise forward regression model, adjusting for age. Stratified analysis for sex in terms of death and poor functional outcome was performed. The Hosmer–Lemeshow goodness-of-fit test was used in logistic regression models when analyzing covariate influence.

Multivariate Cox regression analysis was performed to compare sex by functional outcome and death (adjusted for age groups, vascular risk factors, type and severity of stroke [National Institutes of Health stroke scale score grouped into mild, moderate, or severe]). Kaplan–Meier survival curves were used to assess the absolute risk of recurrent cerebrovascular events in the acute period (in-hospital). Significance was defined as $P<0.05$. Odds ratios (ORs), hazard ratios (HRs), and 95% CIs were calculated. All statistical analyses were performed using the SPSS 22.0 package (SPSS Statistics for Windows, IBM Corp., Armonk, NY).

Results

Patients and Demographics

We recruited and registered data from 5336 patients: 275 (5.1%) of these patients were excluded because of the absence

of complete information in their medical records and were not reachable, 40 (0.7%) subjects were excluded because of lack of initial neuroimaging, 48 (1%) patients were not included in the present study because of a diagnosis of cerebral venous thrombosis, and 185 (3.4%) were excluded because of incomplete data regarding stroke subtype etiology. Accordingly, only 4788 patients with an imaging-confirmed first stroke and with complete inpatient clinical information were included in the analysis. Patients had a median in-hospital stay of 8 days (interquartile range, 5–8), which was similar in men and women. Detailed information according to each country and center, can be found in Tables S1 and S2.

There were 2677 males (median age, 66 years; interquartile range, 56–77) and 2111 females (median age, 69 years; interquartile range, 56–80). IS occurred in 4293 patients: 3686 as cerebral infarction (77%) and 607 as a transient ischemic attack cases (12.7%); 495 patients (10.3%) corresponded to ICH; see Table 1.

Table 1. General Features and Vascular Risk Factors

	Men n=2677 (%)	Women n=2111 (%)	Total N=4788 (%)	*P* Value
Age, y*	66 (56–77)	69 (56–80)	67 (55–78)	0.06†
Hospital stay, d*	7 (3–8)	7 (4–8)	8 (5–8)	0.15†
Risk factors				
Hypertension	1618 (60.4)	1286 (60.9)	2904 (60.7)	0.93
Diabetes mellitus	662 (24.7)	530 (25.1)	1192 (24.9)	0.88
Current smoking	492 (18.4)	252 (11.9)	744 (15.5)	<0.001
Coronary disease	256 (9.6)	135 (6.4)	391 (8.2)	<0.001
Hypercholesterolemia	697 (26.0)	496 (23.5)	1193 (24.9)	0.02
Known atrial fibrillation	247 (9.2)	168 (8.0)	415 (8.7)	0.1
Type of stroke				
Ischemic	2068 (77.3)	1618 (76.6)	3686 (77)	0.23
Intracerebral hemorrhage	285 (10.6)	210 (9.9)	495 (10.3)	0.35
Transient ischemic attack	324 (12.1)	283 (13.4)	607 (12.7)	0.23
National Institutes of Health stroke scale (admission)*	7 (3–15)	8 (4–16)	8 (4–15)	0.01†
Acute management (ischemic stroke)				
Intravenous thrombolysis	197 (7.4)	192 (9.1)	389 (8.1)	0.03
Thrombectomy	19 (0.7)	17 (0.8)	36 (0.8)	0.70
Stroke unit	1710 (63.9)	1293 (61.3)	3003 (62.7)	0.06
Etiology of ischemic stroke (Trial of Org 10172 of the Acute Stroke Treatment)				0.24
Atherosclerotic	524 (25.4)	376 (23.3)	900 (24.4)	
Cardioembolic	464 (22.4)	380 (23.5)	844 (22.9)	
Small-vessel disease	193 (9.3)	157 (9.7)	350 (9.5)	
Other etiologies	135 (6.5)	120 (7.4)	255 (6.9)	
Cryptogenic	214 (10.4)	178 (11.0)	396 (11.0)	
Incomplete evaluation	526 (25.4)	404 (25.0)	930 (25.5)	
Functional outcome (discharge)				
Poor functional outcome (modified Rankin scale 3–6)	859 (31.9)	811 (37.8)	1670 (34.5)	<0.001
Death	161 (6.0)	165 (7.7)	326 (6.7)	0.02

*Median (interquartile range).
†*P* value by Mann–Whitney U Wilcoxon test.

Vascular Risk Factors by Sex

No significant differences were found among men and women on the frequency of hypertension (OR, 0.9; 95% CI, 0.8–1.1; *P*=0.93) and DM (OR, 1.0; 95% CI, 0.8–1.1; *P*=0.88), which was 60.7% and 24.9%, respectively, in the entire data set. Current smoking (OR, 1.3; 95% CI, 0.5–0.7; *P*<0.001), hypercholesterolemia (OR, 1.1; 95% CI, 1.0–1.2; *P*=0.02), and coronary disease (OR, 1.4; 95% CI, 0.5–0.9; *P*<0.001) were significantly more frequent in men. In terms of transient ischemic attack, no significant differences were found for vascular risk factors among men and women.

Stroke Etiology by Sex

IS cases according to the Trial of Org 10172 of the Acute Stroke Treatment classification were as follows: atherothrombotic, 24.4%; cardioembolic, 22.9%; small-vessel disease, 9.5%; other determined etiology, 6.9%; cryptogenic, 11%; and unidentified etiology with incomplete evaluation, 25.5%. No differences were found among men and women by IS subtype (see Table 1).

In terms of ICH, the most common location was the basal ganglia. Of all cases, 75.4% were associated with hypertension, 5.9% with arteriovenous malformations, 4% were related to nonaneurysmal subarachnoid hemorrhage, 3.8% to amyloid angiopathy, 2.8% to drugs (antiplatelet/anticoagulants), and 7.7% were undetermined because of incomplete studies. No differences were detected among men and women according to ICH etiology. Hypertensive ICH presented with 202 (40.8%) patients who were taking antihypertensive medication irregularly or had suspended their usage; 76 (15.4%) patients did not know they had hypertension.

In-Hospital Functional Outcome by Sex

Overall, poor functional outcome was present in 1662 (34.7%) patients, with 38.2% of women having this condition (OR, 1.3; 95% CI, 1.2–1.5; *P*<0.001) and 31.9% in male patients (OR, 1.1; 95% CI, 1.0–1.2; *P*<0.001). Mortality was present in 6.8% of the registry, with 7.8% in women compared with 6.0% in men (OR, 1.3; 95% CI, 1.0–1.6; *P*=0.02).

Acute management did not influence poor functional outcome by sex, according to those admitted to a stroke unit (male, 47% versus female, 48.7%; *P*=0,49), received intravenous thrombolysis (male, 12.5% versus female, 12.5%; *P*=0.9), or acute thrombectomy (male, 1.9% versus female, 1.2%; *P*=0.30); findings were the same in terms of mortality by sex for male versus female for stroke unit (*P*=0.9), intravenous thrombolysis (*P*=0.17), and acute thrombectomy (*P*=0.49). When the composite of "any acute reperfusion therapy" was analyzed by sex for each country, no significant difference was found.

By stroke subtype, the worst functional prognosis, including the highest mortality, corresponded to ICH patients: 43.2% with modified Rankin scale 3 to 6 (214 ICH patients: female cases, 50% versus 38.5% in male patients; *P*=0.009), of which 62 (12.5%) patients died (female cases, 13.3% versus 11.9% in male patients; *P*=0.64). Table 2 depicts the OR for major risk factors and subtype of stroke by functional outcome. Overall, female IS presented with the highest poor clinical outcome (OR, 2.9, 95% CI, 1.9–3.1; *P*<0.001) compared with male cases (OR, 2.4; 95% CI, 1.9–3.1; *P*<0.001). On the other hand, the highest risk of death was seen in male ICH patients (OR, 2.4; 95% CI, 1.6–3.6; *P*<0.001) versus female cases (OR, 2.0; 95% CI, 1.3–3.1; *P*=0.001).

Unadjusted and adjusted Cox proportional hazard models (adjusted for age groups, risk factors, and type of stroke)

Table 2. Unadjusted Odds Ratio for Major Risk Factors and Subtype of Stroke by Outcome (Poor Functional Outcome and Death)

	Modified Rankin Scale 3–6				Death			
	Women		Men		Women		Men	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Risk factors								
Hypertension	2.2 (1.8–2.6)	<0.001	1.5 (1.3–1.8)	<0.001	1.6 (1.1–2.2)	0.009	1.6 (1.1–2.2)	0.008
Diabetes mellitus	1.7 (1.4–2.1)	<0.001	1.4 (1.1–1.6)	<0.001	1.2 (0.8–1.7)	2.53	1.1 (0.8–1.6)	0.40
Current smoking	1.1 (0.8–1.5)	0.28	1.8 (1.5–2.3)	<0.001	1.2 (0.7–1.9)	0.36	1.4 (0.9–2.0)	0.08
Dyslipidemia	0.8 (0.7–1.1)	0.17	0.6 (0.5–0.8)	<0.001	0.9 (0.6–1.3)	0.92	0.6 (0.4–0.9)	0.02
Stroke subtype								
Ischemic	2.9 (2.3–3.7)	<0.001	2.4 (1.9–3.1)	<0.001	1.6 (1.0–2.4)	0.03	1.1 (0.7–1.6)	0.66
Intracerebral hemorrhage	1.7 (1.3–2.3)	<0.001	1.3 (1.1–1.7)	0.01	2.0 (1.3–3.1)	0.001	2.4 (1.6–3.6)	<0.001

OR indicates odds ratio.

Table 3. Cox Proportional Hazard Ratios Analysis for Clinical Outcome at Discharge According to Sex

Outcome	Men (%)	Women (%)	Unadjusted		Adjusted*	
			HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
All-type stroke						
Death	161 (6.0)	165 (7.7)	1.3 (1.0–1.6)	0.02	1.3 (1.1–1.6)	0.03
Modified Rankin scale 3–6	859 (31.9)	811 (37.8)	1.2 (1.1–1.3)	<0.001	1.1 (1.0–1.3)	0.001
Ischemic stroke						
Death	126 (6.1)	136 (8.4)	1.3 (1.0–1.7)	0.01	1.3 (1.0–1.6)	0.02
mRs 3–6	744 (36.0)	702 (43.4)	1.2 (1.0–1.3)	0.002	1.2 (1.0–1.3)	0.002
Intracerebral hemorrhage						
Death	34 (11.9)	28 (13.3)	1.1 (0.7–1.9)	0.58	…	…
Modified Rankin scale 3–6	109 (38.2)	105 (50.0)	1.3 (1.0–1.7)	0.03	1.3 (1.0–1.8)	0.02

HR indicates hazard ratios.
*Adjusted for age, vascular risk factors, National Institutes of Health stroke scale score (dichotomized), etiology (for ischemic stroke), and acute management (reperfusion therapy for ischemic stroke).

for death and poor functional outcome on all-type stroke showed an association for greater risk in female patients (HR, 1.3; *P*=0.03; and HR, 1.1; *P*=0.001, respectively). This finding was also observed in IS and ICH (see Table 3). Kaplan–Meier survival curves of the entire sample and for the 3 types of stroke related to mortality showed a significant difference between men and women (Figure 2) in terms of all-type stroke, IS, and ICH.

When analyzing for age groups, female patients had a higher risk of poor functional outcome in the 61- to 70-year-old and 71- to 80-year-old group (HR, 1.2 and 1.3, respectively). For mortality, this association was found only in the 50- to 60-year-old group (HR, 2.2); see Table 4.

Discussion

In this study, we found worse functional outcome and higher mortality among women. In addition, our study shows major findings on the initial severity and outcome, where women had higher initial National Institutes of Health stroke scale, tended to be younger, and presented with a poorer outcome at discharge. This is concordant with data from other, similar reports.[10–13] In many countries, the total burden of disease attributed to stroke is greater in women than in men.[12] Women have been reported to have worse outcome, including greater mortality, worse functional outcome, and poorer health-related quality of life versus men.[13] A meta-analysis of population-based studies[5] found that stroke tended to be

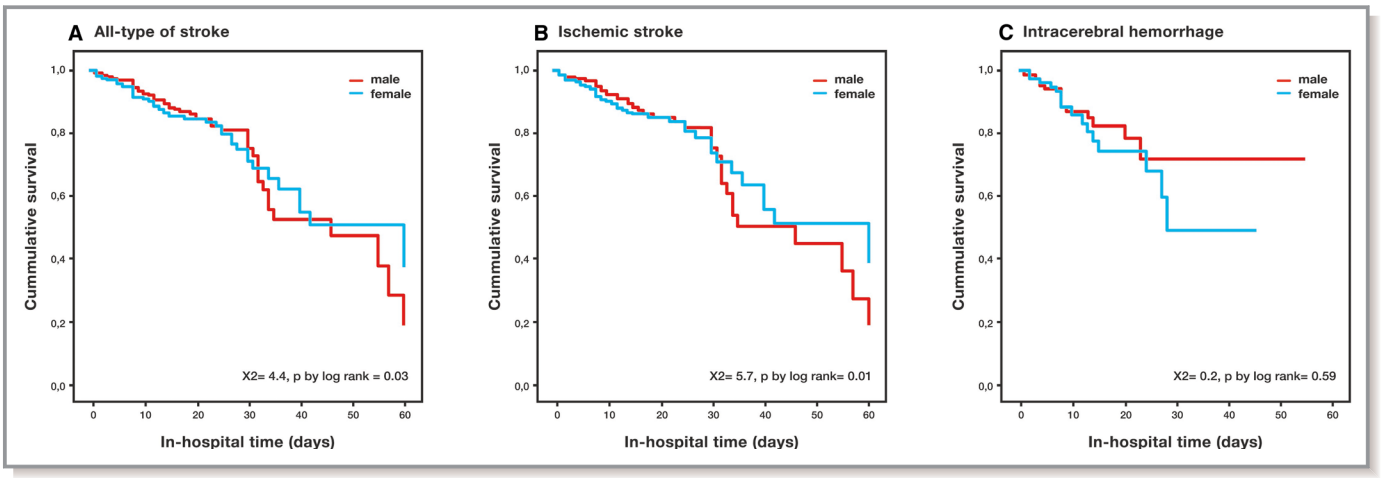

Figure 2. Kaplan–Meier survival curves for mortality according to sex in: (**A**) all-type stroke, (**B**) ischemic stroke, and (**C**) intracerebral hemorrhage.

Table 4. Cox Proportional Hazard Ratios Analysis for Clinical Outcome at Discharge According to Age Groups*

Functional Outcome	<50 years (N=800)		50–60 years (N=831)		61–70 years (N=1245)		71–80 years (N=1049)		>80 years (N=911)	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Modified Rankin scale 3–6	n=229		n=273		n=387		n=358		n=423	
Sex	1.0 (0.8–1.4)	0.66	1.2 (0.9–1.6)	0.08	1.2 (1.0–1.5)	0.06	1.3 (1.1–1.6)	0.004	0.9 (0.8–1.2)	0.85
Hypertension	1.2 (0.8–1.5)	0.23	1.0 (0.7–1.3)	0.90	1.7 (1.3–2.1)	<0.001	1.7 (1.3–2.3)	<0.001	1.5 (1.2–1.9)	0.001
Diabetes mellitus	1.5 (1.0–2.1)	0.04	1.2 (0.9–1.6)	0.18	1.3 (1.0–1.6)	0.01	1.1 (0.8–1.4)	0.33	1.3 (1.0–1.6)	0.02
Smoking	1.4 (1.0–1.9)	0.08	1.1 (0.8–1.5)	0.39	1.3 (1.0–1.7)	0.03	1.1 (0.8–1.4)	0.47	0.8 (0.6–1.0)	0.11
Hypercholesterolemia	0.7 (0.4–1.2)	0.09	0.9 (0.7–1.2)	0.73	0.7 (0.6–0.9)	0.009	0.7 (0.5–0.9)	0.05	0.9 (0.7–1.2)	0.74
Death	n=38		n=42		n=83		n=61		n=102	
Sex	0.8 (0.5–1.7)	0.77	2.2 (1.1–4.2)	0.01	1.2 (0.7–1.8)	0.40	1.3 (0.8–2.2)	0.22	1.1 (0.7–1.6)	0.72
Hypertension	0.9 (0.3–1.8)	0.56	1.4 (0.6–2.8)	0.78	1.3 (0.8–2.3)	0.25	1.5 (0.8–2.9)	0.17	1.5 (0.9–2.5)	0.08
Diabetes mellitus	0.6 (1.5–2.6)	0.51	1.1 (0.5–2.1)	0.52	1.7 (1.0–2.7)	0.03	1.1 (0.6–2.0)	0.58	0.7 (0.4–1.2)	0.26
Smoking	1.1 (0.4–2.6)	0.76	1.1 (0.5–2.3)	0.63	1.5 (0.9–2.5)	0.10	1.4 (0.8–2.7)	0.23	0.6 (0.3–1.1)	0.10
Hypercholesterolemia	0.1 (0.1–ND)	0.90	1.0 (0.5–2.2)	0.57	0.7 (0.4–1.1)	0.12	0.6 (0.3–1.1)	0.11	0.8 (0.5–1.4)	0.61

HR indicates hazard ratio.
*Adjusted for vascular risk factors, National Institutes of Health stroke scale score (dichotomized), etiology (for ischemic stroke), and acute management (reperfusion therapy for ischemic stroke).

more severe in women, with a 1-month case fatality of 24.7% compared with 19.7% for men. In the Australian stroke clinical registry,[14] women were more likely to be deceased up to 1 year after stroke versus men. The reasons for these disparities have been attributed to advanced age, more severe strokes, less aspirin administration, and likely lower quality of care.[15] Another possible explanation is the physiological differences between men and women, such as hormonal effects (especially in those cases where prothrombotic and autoimmune conditions are more prevalent in women) and the predominance of certain risk factors in women (such as atrial fibrillation and hypertension),[10,11] but these explanations are inconsistent among different registries. In our study, we did not find significant differences between the main vascular risk factors or between stroke subtypes. Nevertheless, these findings require further investigation, especially to facilitate better future healthcare management policy and planning. In addition, further studies are needed to identify biological factors or comorbid diseases that contribute to this sex difference associated with stroke severity and mortality.

Our study is the first multicollaborative study in Latin America to perform a specific analysis on the basis of sex influence on stroke outcome. We report a sex comparison of >4000 patients having their first-ever stroke treated in 18 hospitals across 7 different Latin American countries. Our population presented with similar frequency of hypertension and DM; however, smoking, hypercholesterolemia, and coronary disease were more prevalent in men. Globally, metabolic and environmental risk factors explain 87.9% of IS and 89.5% of hemorrhagic stroke.[2] When comparing the burden attributable to behavioral (smoking, poor diet, and low physical activity), environmental (pollution or lead exposure), and metabolic (high body mass index, high fasting plasma glucose, high systolic blood pressure, high total cholesterol, low glomerular filtration rate) risk factors between men and women since 2013, although globally there were no significant differences among sex, the population attributable factor for stroke-related, age-standardized, disability-adjusted life-years related to behavioral risk factors was higher in low- and middle-income countries, such as those represented in our study.[16] The INTERSTROKE (Study of the Importance of Conventional and Emerging Risk Factors of Stroke in Different Regions and Ethnic Groups of the World) initiative, which reported that 10 simple risk factors (hypertension, smoking, waist-to-hip ratio, physical inactivity, diet risk score, DM, alcohol intake, psychosocial stress, depression, cardiac causes, and apolipoproteins B to A_1) accounted for 90.3% of all stroke, suggested differences in risk-factor association by sex and region, but mainly for waist-to-hip ratio and hypertension.[17] This tendency was also observed in our sample, although our study was not a case-control research model, and the waist-to-hip ratio was not recorded in our data set.

Similar findings have been reported in case-control studies when comparing risk factors by sex for stroke occurrence, with the highest association for hypertension, DM, dyslipidemia, and stress in the preceding 2 weeks of stroke as well as low consumption of green leafy vegetables.[18]

In terms of clinical outcome of stroke, differences according to sex have been explained according to sexual dimorphism in response to drugs (distribution volumes, sex hormone levels, activity of enzymes, and effects of routes of excretion)[19] but also stroke cases in women with older ages (attributable to the higher lifetime risk and life expectancy),[7] which have been reported with the age cutoff of ≥75 years (as seen in our study)[20] and possibly reflecting compounding disability in the older age range. In addition, accessibility to healthcare centers has been postulated as an explanatory or additional condition for this functional outcome: In some registries, women were less likely to present to a medical facility in the acute stroke window compared with men.[21] In general, cardiovascular disease, behavioral health, and access to care are problem areas for women that require immediate attention.[22]

When analyzing healthcare access and quality of medical services in Latin America according to the Healthcare Access and Quality Index from the Global Burden of Disease Study,[23] most Latin American countries scored between the fourth and sixth deciles of the index, indicating an intermediate access to medical services. However, when looking at subnational patterns, Mexico presented with the highest healthcare access inequalities across the states for our region.[23] This observation regarding the medical services across the region could also explain the aforementioned disparate access for women, especially in areas where hospitals, primary attention clinics, medication, and imaging studies availability are more limited.[24,25] In Latin America, the management of stroke patients differs substantially from other regions of the world, especially compared with developed countries.[26] There are substantial problems with the acute phase of stroke treatment: Despite the fact that there are some stroke units, these are available in only a few countries, and their number varies substantially. Given that stroke management is a continuum that begins with the treatment in the acute phase, sex-related factors may be important throughout the entire care process.

Certain study limitations should be acknowledged. First, as this is a retrospective analysis from a multicenter merged database, the study presents the bias of an observational study despite efforts to maintain strict and methodical variable analysis and the sole inclusion of matching information suitable for the analysis. Second, most of the centers represent a tertiary healthcare facility, which could cause an overrepresentation of stroke frequency and not accurately represent the reality of this condition in the entire country, especially because of the access of studies that determined stroke etiology compared with hospitals with less infrastructure or paraclinic access. Furthermore, Latin American regions present differences in every country, and many countries and latitudes are not represented in our analysis; the lack of stroke units (as a formal structure for stroke care) is evident in our registry, which also leads to a difficulty when comparing different centers in our region.[26] Third, association analysis on the basis of covariate adjustment could disregard other variables when explaining the influence of sex on stroke outcome and could overrepresent the magnitude of the effect, especially when comparing accessibility to medical services in every region, therapeutic approaches, and postdischarge medical and rehabilitation attention. Fourth, findings for IS and ICH were relatively similar according to sex. However, a weakness of our registry is the exclusion of cases of subarachnoid hemorrhage, which was reportedly significantly higher in women in other studies.[5]

Conclusions

In the LASE, worse functional outcome and death rates were present in women compared with men. These findings should be considered in Latin America and Hispanic populations abroad when designing and implementing individual management plans for stroke patients, along with secondary prevention and neuro-rehabilitation programs.

Appendix

Co-Investigators and Collaborators of the LASE

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Demographic and clinical characteristics by country.

	Country						
	Mexico N=1229 (%)	**Argentina N=1252 (%)**	**Colombia N=821 (%)**	**Costa Rica N=713 (%)**	**Paraguay N=532 (%)**	**Peru N=210 (%)**	**Ecuador N=31 (%)**
Men	668 (54.4)	762 (60.9)	420 (51.2)	370 (51.9)	316 (59.4)	126 (60.0)	15 (48.4)
Women	561 (45.6)	490 (39.1)	401 (48.8)	343 (48.1)	216 (40.6)	84 (40.0)	16 (51.6)
Age, median (IQR)	65 (52-76)	67 (59-77)	72 (61-83)	67 (55-79)	62 (52-73)	67 (54-77)	61 (47-74)
Risk factors							
Hypertension	756 (61.5)	492 (39.3)	547 (66.6)	553 (77.6)	410 (77.1)	123 (58.6)	23 (74.2)
Diabetes	469 (38.2)	146 (11.7)	146 (17.8)	236 (33.1)	142 (26.7)	48 (22.9)	5 (16.1)
Active Smoking	252 (20.5)	-*	196 (23.9)	139 (19.5)	80 (15.0)	70 (33.0)	7 (22.6)
Hypercholesterolemia	197 (16.0)	453 (36.2)	201 (24.5)	258 (36.2)	38 (7.1)	38 (18.1)	8 (25.8)
Type of stroke							
Ischemic	1042 (84.8)	888 (70.9)	582 (70.9)	579 (81.2)	402 (75.6)	170 (81.0)	23 (74.2)
TIA	95 (7.7)	298 (23.8)	171 (20.8)	23 (3.8)	1 (0.2)	16 (7.6)	3 (9.7)
Hemorrhagic	92 (7.5)	66 (5.3)	68 (8.3)	111 (22.4)	129 (24.2)	24 (11.4)	5 (16.1)
Acute treatment (ischemic stroke)							
IV thrombolysis	49 (5.7)	-*	82 (10.2)	208 (29.2)	-*	23 (12.4)	0 (0)
Mechanical thrombectomy	3 (0.3)	-*	33 (4.1)	2 (0.3)	-*	0 (0)	0 (0)
Functional status (at discharge)							

Good functional outcome (mRs 0-2)	577 (46.9)	1135 (90.7)	514 (62.6)	352 (49.4)	422 (79.3)	116 (55.2)	10 (32.3)
Death	124 (10.1)	22 (1.8)	102 (12.4)	32 (4.5)	37 (7.0)	7 (3.3)	0 (0)
Recurrence							
Ischemic	43 (2.7)	-*	-*	-*	24 (4.5)	11 (5.3)	5 (15.1)
Hemorrhagic	1 (0.1)	-*	*	-*	0 (0)	1 (0.5)	3 (9.7)

* Not available at the dataset.

Table S2. Demographic and clinical characteristics by center.

	Center N (%)								
	Mexico								
	INNN, Mexico City	**PEMEX, Mexico City**	**Hospital Juarez, Mexico City**	**Hospital General, Mexico City**	**Hospital General, Durango**	**PEMEX, Ciudad Madero**	**ISSSTE, Morelia**	**Hospital Civil, Guadalajara**	**ISSSTE, Guadalajara**
Men	162 (50.9)	20 (100)	93 (56.4)	88 (52.4)	133 (55.0)	110 (55.0)	22 (47.8)	19 (63.3)	21 (52.5)
Women	156 (49.1)	0 (0)	72 (43.6)	80 (47.6)	109 (45.0)	90 (45.0)	24 (52.2)	11 (36.7)	19 (47.5)
Age, median (IQR)	57 (39-68)	72 (68-81)	56 (45-66)	62 (54-70)	71 (63-81)	77 (68-83)	63 (56-76)	62 (56-70)	69 (62-75)
Risk factors									
Hypertension	127 (39.9)	-*	86 (52.1)	112 (66.7)	206 (85.1)	153 (76.5)	31 (67.4)	17 (56.7)	24 (60.0)
Diabetes	68 (21.4)	-*	52 (31.5)	76 (45.2)	103 (42.6)	116 (58.0)	25 (54.3)	12 (40.0)	17 (42.5)
Active Smoking	51 (16.0)	-*	33 (20.0)	60 (35.7)	36 (14.9)	38 (19.0)	7 (15.2)	7 (23.3)	20 (50.0)
Hypercholesterolemia	30 (9.4)	-*	2 (1.2)	23 (13.7)	12 (5.0)	112 (56.0)	4 (8.7)	3 (10.0)	11 (27.5)
Type of stroke									
Ischemic	291 (91.5)	10 (50.0)	149 (90.3)	168 (100)	202 (83.5)	119 (59.5)	33 (71.7)	30 (100)	40 (100)
TIA	9 (2.8)	7 (35.0)	0 (0)	0 (0)	17 (7.0)	61 (30.5)	1 (2.2)	0 (0)	0 (0)
Hemorrhagic	18 (3.6)	3 (15.0)	16 (9.7)	0 (0)	23 (9.5)	20 (10.0)	12 (26.1)	0 (0)	0 (0)
Acute treatment (ischemic stroke)									

IV thrombolysis	-*	3 (15.0)	5 (3.4)	18 (10.7)	3 (1.2)	0 (0)	0 (0)	0 (0)	20 (50.0)
Mechanical thrombectomy	-*	0 (0)	1 (0.7)	2 (1.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Functional status (at discharge)									
Good functional outcome (mRs 0-2)	195 (61.3)	20 (100)	53 (32.1)	34 (20.2)	85 (35.1)	132 (66.0)	16 (34.8)	14 (46.7)	28 (70.0)
Death	0 (0)	0 (0)	2 (1.2)	19 (11.3)	74 (30.6)	27 (13.5)	0 (0)	0 (0)	2 (5.0)
Recurrence									
Ischemic	0 (0)	0 (0)	12 (7.3)	8 (4.8)	8 (3.3)	3 (0.6)	1 (2.2)	1 (3.3)	0 (0)
Hemorrhagic	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3.3)	0 (0)

	Center N (%)								
	Colombia			Perú		Argentina	Ecuador	Paraguay	Costa Rica
	UFSF, Bogotá	HUMM, Bogotá	Valle del Lili, Calí	HGGAI, Lima	INCN, Lima	FLENI, Buenos Aires	HPAS, Quito	UNA, Asunción	HRACG, San José
Men	262 (51.8)	60 (42.6)	98 (56.3)	82 (58.2)	44 (63.8)	762 (60.9)	15 (48.4)	316 (59.4)	370 (51.9)
Women	244 (48.2)	81 (57.4)	76 (43.7)	59 (41.8)	25 (36.2)	490 (39.1)	16 (51.6)	216 (40.6)	343 (48.1)
Age, median (IQR)	73 (61-84)	75 (64-83)	68 (58-78)	67 (54-77)	71 (56-80)	67 (59-77)	61 (48-74)	62 (53-73)	67 (56-79)
Risk factors									
Hypertension	331 (65.4)	97 (68.8)	119 (68.4)	73 (51.8)	70 (72.5)	492 (39.3)	23 (74.2)	410 (77.1)	553 (77.6)
Diabetes	101 (20.0)	18 (12.8)	27 (15.5)	38 (27.0)	10 (14.5)	146 (11.7)	5 (16.1)	142 (26.7)	236 (33.1)
Active Smoking	143 (28.3)	27 (19.1)	26 (14.9)	62 (44.0)	8 (11.6)	-*	7 (22.6)	80 (15.0)	139 (19.5)
Hypercholesterolemia	148 (29.2)	16 (11.3)	37 (21.3)	34 (24.1)	4 (5.8)	453 (36.2)	8 (25.8)	38 (7.1)	258 (36.2)
Type of stroke									
Ischemic	383 (75.7)	99 (70.2)	100 (57,5)	105 (74.5)	65 (94.2)	888 (70.9)	23 (74.2)	402 (75.6)	579 (81.2)
TIA	80 (15.8)	28 (19.9)	63 (36.2)	14 (9.9)	2 (2.9)	298 (23.8)	3 (9.7)	1 (0.2)	23 (3.8)

Hemorrhagic	43 (8.5)	14 (9.9)	11 (6.3)	22 (15.6)	2 (2.9)	66 (5.3)	5 (16.1)	129 (24.2)	111 (22.4)
Acute treatment (ischemic stroke)									
IV thrombolysis	67 (13.2)	12 (6.9)	7 (10.4)	3 (2.5)	16 (13.6)	-*	0 (0)	-*	208 (29.2)
Mechanical thrombectomy	26 (5.1)	4 (2.3)	0 (0)	3 (2.5)	0 (0)	-*	0 (0)	-*	2 (0.3)
Functional status (at discharge)									
Good functional outcome (mRs 0-2)	299 (59.1)	78 (55.3)	137 (78.7)	80 (56.7)	36 (52.2)	1135 (90.7)	10 (32.3)	422 (79.3)	352 (49.4)
Death	79 (15.6)	22 (15.6)	1 (0.6)	7 (5.0)	0 (0)	22 (1.8)	0 (0)	37 (7.0)	32 (4.5)
Recurrence									
Ischemic	*	*	*	8 (5.7)	3 (4.3)	-*	5 (15.1)	24 (4.5)	-*
Hemorrhagic	*	*	*	1 (0.7)	0 (0)	-*	3 (9.7)	0 (0)	-*

* Not available at the dataset.