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ORIGINAL RESEARCH

Sex Differences in the Epidemiology of Intracerebral Hemorrhage Over 10 Years in a Population-Based Stroke Registry

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BACKGROUND: We investigated incidence and outcome of spontaneous intracerebral hemorrhage (ICH) in a population-based stroke registry and provided data to inform on the figures of the disease in women and in men.

METHODS AND RESULTS: Our prospective population-based registry included patients with first-ever ICH occurring from January 2011 to December 2020. Incidence rates were standardized to the 2011 Italian and European population, and incidence rate ratios were calculated. Multivariate hazard ratios for 30-day and 1-year fatality were estimated with Cox regression, including components of the ICH score and sex. We included 748 first-ever ICHs (41.3% women). Women were significantly older than men at ICH onset (78.9±12.6 versus 73.2±13.6 years; $P<0.001$) and showed higher clinical severity on presentation (median National Institutes of Health Stroke Scale score, 11 [interquartile range, 6–20] versus 9 [interquartile range, 4–15], respectively; $P=0.016$). The crude annual incidence rate was 20.2 (95% CI, 18.0–22.6) per 100 000 person-years in women and 30.2 (95% CI, 27.4–33.2) per 100 000 person-years in men); incidence was lower in women versus men (incidence rate ratio, 0.67 [95% CI, 0.58–0.78]; $P<0.001$) and did not change over time in both sexes (P for trend=0.073 and 0.904, respectively). Unadjusted comparison showed higher 1-year case-fatality rates in women versus men (48.5% versus 40.1%; $P=0.026$). After adjusting for components of the ICH score, female sex lost significance as a predictor of mortality.

CONCLUSIONS: We found lower ICH incidence in women than in men. However, women showed a higher 1-year case-fatality rate versus men, which was likely related to older age at ICH onset and higher clinical severity. Identification of factors explaining the reported differences is important to develop targeted interventions.

Key Words: case-fatality rate ■ incidence ■ intracerebral hemorrhage ■ prognosis ■ sex

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Intracerebral hemorrhage (ICH) is the second most common subtype of stroke and represents a life-threatening and disabling disease.[1] ICH accounts for ≈10% to 20% of all strokes and is associated with a roughly case-fatality rate of 40% at 1 month and 50% at 1 year.[2,3]

It is important to understand sex differences in ICH, as the peculiarities of ICH occurrence and prognosis in women and men might enable researchers to craft more precise risk assessment, targeted prevention strategies, and tailored treatments. Previous studies on ICH incidence, according to sex, showed controversial findings. Most of European[4–8] and Australasian[9,10] studies have not demonstrated sex differences in ICH incidence. Conversely, studies in North American,[11] Japanese,[12] and Chinese[13] populations documented lower incidence in women. Conflicting results were also reported on the possible sex differences in the

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RESEARCH PERSPECTIVE

What Is New?

- There is a lack of conclusive evidence to describe sex differences in the epidemiology of intracerebral hemorrhage (ICH); using 10-year data from a prospective population-based registry, we found a lower incidence of first-ever ICH in women compared with men.
- In addition, the incidence of ICH did not change over time in both women and men, and women had higher 1-year case-fatality rates than men, which was likely related to their older age at ICH onset and higher clinical severity on presentation.

What Question Should Be Addressed Next?

- Our findings suggest that future research should investigate the peculiarities of pathogenic mechanisms of ICH in women and men to develop tailored approaches to mitigate the worst outcome observed in women.

Nonstandard Abbreviations and Acronyms

ICH	intracerebral hemorrhage
mRS	modified Rankin Scale
NCCT	noncontrast computed tomography
NIHSS	National Institutes of Health Stroke Scale
SBP	systolic blood pressure

outcomes after ICH. Although studies from Finland,[14] Sweden,[15] Greece,[16] Japan,[17] and China[18] showed comparable case-fatality rates between sexes up to a year post-ICH, other research identified female sex as an independent determinant of unfavorable short- and long-term outcomes following ICH.[15,19] Furthermore, more recent studies disclosed that ICH incidence is increasing among both women and men[20] and, although men showed a higher incidence of ICH, especially in younger age groups (<75 years), sex may not significantly impact on ICH-related mortality.[21] Taking all this evidence together, it is important to update existing estimates and address sex differences to align with the evolving demographic features, ICH risk factor diagnosis and management, and the increasing use of anticoagulants. Our study aims to bridge this gap by examining sex differences in spontaneous ICH incidence and their impact on post-ICH outcomes, using a 10-year prospective population-based stroke registry.

METHODS

The complete data set, methods used in the analysis, and materials used to conduct the research will be made available on reasonable request from any qualified researcher to the corresponding author.

Ethical Standards

The study has obtained approval from the Institutional Review Board of the University of L'Aquila (protocol numbers 13/2018 and 57/2019). All subjects gave written informed consent for being included in the study registry.

Study Design and Population

We followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines to report the results of the present study. The study is nested within a prospective population-based registry, including patients with stroke and transient ischemic attack in the population of 298 343 inhabitants of the district of L'Aquila, central Italy.[22] The district of L'Aquila is a mountainous area served by 4 public hospitals with 24/7 availability of brain computed tomography, 5 private hospitals, general practitioners, and the emergency medical service; 2 hospitals have neurology wards, and 1 hospital has a neurosurgical ward. Medical care in the district is completely free of charge, with easy access to medical services for the acute phase of a stroke. The registry complies with epidemiologic criteria for stroke incidence studies and was approved by the Internal Review Board of the University of L'Aquila with protocol numbers 13/2018 and 57/2019. The registry includes all cases of cerebrovascular events occurring in the district, which are regularly reported by local physicians, validated by the study staff, and followed up. Patients were treated according to routine clinical practice and following national and international guidelines.[23] Among all cases of stroke, we registered cases of ICH occurring in the district of L'Aquila over a 10-year period, from January 1, 2011, until December 31, 2020. Diagnoses of ICH were validated according to the presence of focal neurologic deficits along with concomitant evidence of intraparenchymal hemorrhage in the brain.[24] We included only patients with first-ever ICH and excluded those with previous stroke and hemorrhagic transformation of the cerebral infarction. Patients with primary subdural/epidural hematoma or traumatic ICH or hemorrhage attributable to a tumor were also excluded.

Case-Finding Procedures

Each event was identified through active monitoring of inpatient and outpatient health services. All patients admitted for ICH were identified and seen within 7 days

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of symptom onset by a senior physician and then by a consulting neurologist to confirm the event. Event adjudication was based on clinical characteristics and noncontrast brain computed tomography (NCCT) findings, even when brain magnetic resonance imaging was performed. Admission and discharge lists were checked, as well as emergency medical services and emergency department, neuroradiology, neurophysiology, and neurosonology services. Regular contact was also maintained with rehabilitation and long-term care services. The records of patients with a possible diagnosis of transient ischemic attack, dizziness, vertigo, confusion, seizures, headache, and transient global amnesia were also reviewed. Nearby hospitals, rehabilitation centers, and long-term care services were also monitored regularly to identify residents who received cross-boundary medical care. Death certificates were checked monthly, and clinical data of all patients who died with a stroke diagnosis and were not otherwise included in the registry were incorporated. Hot (active identification of all events at the time they occurred) and cold (retrospective identification) pursuits were combined in the ascertainment of cases to ensure a more complete identification.[25]

Data Collection and Follow-Up

Demographic and clinical data were collected through systematic consultation of medical records and stored in a computerized database in a fully anonymized form. We used Research Electronic Data Capture to build and manage online surveys and databases for data input.[26] We collected medical history and cardiovascular and neurologic evaluation findings. Furthermore, we recorded level of consciousness at stroke onset, according to the Glasgow Coma Scale (GCS) score, neurologic impairment on admission, based on the National Institutes of Health Stroke Scale (NIHSS) score,[27] and disability or dependence in the daily activities, assessed by means of the modified Rankin Scale (mRS) score.[28] Specifically, we adjudicated the mRS score before the index event and at discharge; the mRS score at discharge was evaluated in the overall population and reported separately for those who were still alive at discharge. We also recorded vascular risk factors, including arterial hypertension, diabetes, atrial fibrillation, dyslipidemia, cigarette smoking, alcohol abuse, and obesity. Definitions of risk factors are reported in Table S1–S10.

Volume and location of the ICH were assessed retrospectively on the first available brain NCCT scan. NCCT assessment was performed on tridimensional images obtained with multiplanar reformatting. ICH volumes were estimated by a single operator according to the ABC/2 method.[29] ICH location was adjudicated by 2 independent raters, according to the Cerebral Haemorrhage Anatomical Rating Instrument.[30] Specifically, we categorized ICH location into lobar, nonlobar, including all deep and infratentorial anatomic categories (eg, brainstem, cerebellum, caudate, lentiform, and thalamus), and uncertain (eg, large ICH extending into both lobar and nonlobar areas). Disagreements were resolved by consensus before initiating primary analyses.

Statistical Analysis

We provided a global incidence rate, both crude and age adjusted, and an incidence trend over the 10-year observation period. Incidence rates were standardized by age and sex with the direct method to the 2011 Italian and European population.[31] Poisson regression analysis was performed to determine incidence trends and CIs for incidence rates. Overall, annual and age group–related incidence rate ratios were determined according to Poisson distribution in men and women. Descriptive statistics are reported as absolute numbers with percentages or mean±SD, as appropriate. Data were compared using the Wilcoxon test or the Pearson χ^2 test, both used to test the significance of differences between 2 groups for continuous and categorical variables, respectively. ANOVA and Kruskal-Wallis tests were used to assess yearly trends when comparing continuous variables, according to their distribution. Two-sided statistical significance was set at a $P<0.05$.

Missing values were not entered for continuous data when assessing baseline variables; we entered missing values using the median of the variables when performing regression analyses, where applicable. For risk factors, missing data were double checked against patients' treatments to obtain complete information. When not confirmed by the investigators double check against patients' history or treatments, risk factors were considered absent.

The 30-day and 1-year case-fatality rates were reported as numbers and percentages with the corresponding 95% CIs. Overall survival after ICH was estimated using Kaplan-Meier curves. Differences between sex groups were tested using log-rank test. Multivariate estimates of the hazard ratios (HRs) of factors influencing 30-day and 1-year case-fatality rates in men and women were calculated according to the Cox regression analysis, including components of the ICH score[32] and sex.

All statistical analyses were performed with R software, version 4.1.

RESULTS

From January 1, 2011, to December 31, 2020, we identified 748 first-ever ICHs, of which 309 (41.3%) occurred

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in women. Patient race and ethnicity was largely non-Hispanic White in both sex groups (98.6% and 99.6% of women and men, respectively). The mean±SD age at ICH onset was 75.5±13.5 years (age range, 15–99 years); women were significantly older than men (mean age, 78.9±12.6 versus 73.2±13.6 years; *P*<0.001). There was no evidence of changes in mean age at onset over the study period either in women (*P* for trend=0.665) and men (*P* for trend=0.081). All patients were hospitalized, and there was no difference in duration of hospitalization between women and men (interquartile range [IQR], 4–14.5 versus 4.5–18 days, respectively; *P*=0.213). Hospitalization settings did not significantly differ between sex groups (*P*=0.088).

Pre-event median mRS scores were similar in women and men (1 [IQR, 0–2]; *P*=0.102). Women had a greater clinical severity at ICH onset with a median NIHSS score of 11 (IQR, 6–20) compared with men (median, 9 [IQR, 4–15]; *P*=0.016). Although in men there was a significant trend toward lower clinical severity over years (*P* for trend=0.004), we found no changes in ICH severity over the study period in women (*P* for trend=0.189) (Figure S1–S10). Women reported less cigarette smoking (4.6% versus 12.4%; *P*<0.001) and less alcohol abuse compared with men (0.7% versus 8.7%; *P*<0.001) and showed significantly lower mean values of systolic blood pressure (SBP) and diastolic blood pressure on admission (*P*<0.001). Distribution of other risk factors and pre-event drug intake was similar between women and men (Table 1). The proportion of surgically treated patients was low and did not significantly differ between women and men (8.3% versus 6.6%; *P*=0.531).

For neuroimaging, at least 1 NCCT scan was performed in all patients on admission. Brain magnetic resonance imaging was performed in 132 patients, 48 (15.9%) women and 84 (19.5%) men, with a median time of 4 days (IQR, 3–7 days) of admission (*P*=0.203). Considering hemorrhage location, women had more frequently a lobar location of the ICH (45.6% versus 34.2%; *P*<0.001), whereas men had more frequently a nonlobar ICH (59.7% versus 43.4%; *P*<0.001). Mean ICH volume at the first NCCT scan was similar between sexes and showed no significant changes in both women and men over the study period (*P* for trend=0.187 and 0.374, respectively).

Incidence of ICH

The crude annual incidence rate of first-ever ICH in the 2011 to 2020 period was 20.2 (95% CI, 18.0–22.6) per 100 000 person-years in women and 30.2 (95% CI, 27.4–33.2) per 100 000 person-years in men. The corresponding age-adjusted values were 17.3 (95% CI, 15.4–19.4) per 100 000 person-years in women and 35.7 (95% CI, 32.3–39.2) per 100 000 person-years

Table 1. Demographic, Clinical, Laboratory, and Neuroimaging Characteristics

Characteristic	Women (n=309)	Men (n=439)	*P* value
Age, mean±SD, y	78.9±12.6	73.2±13.6	<0.001*
Race and ethnicity, n (%)			0.226
Non-Hispanic White	305 (98.6)	437 (99.6)	
Hispanic	2 (0.7)	1 (0.2)	
Black	2 (0.7)	0 (0.0)	
Asian	0 (0.0)	1 (0.2)	
Time from symptom onset to hospital arrival, n (%)			0.082
≤4.5 h	228 (73.8)	294 (67.0)	
>4.5 h	65 (21.0)	124 (28.2)	
Not available	16 (5.2)	21 (3.8)	
Hospitalization setting, n (%)			0.088
Stroke unit	102 (33.0)	137 (31.2)	
Internal medicine	99 (32.0)	111 (25.3)	
Neurosurgery	54 (17.5)	92 (21.0)	
Intensive care unit	30 (9.7)	64 (14.6)	
Other	24 (5.8)	35 (8.0)	
Pre-event mRS score, median (IQR)	1 (0–2)	1 (0–2)	0.102
NIHSS score at ICH onset, median (IQR)	11 (6–20)	9 (4–15)	0.016*
Risk factors, n (%)			
Arterial hypertension (known)	225 (72.8)	330 (75.2)	0.522
Arterial hypertension (newly diagnosed)	15 (4.9)	13 (3.0)	0.180
Dyslipidemia	61 (19.7)	87 (19.8)	>0.999
Diabetes	62 (20.1)	107 (24.4)	0.194
Atrial fibrillation	21 (6.8)	33 (7.5)	0.817
Obesity	19 (6.1)	28 (6.4)	>0.999
Cigarette smoking	14 (4.5)	53 (12.1)	0.001*
Alcohol abuse	2 (0.7)	38 (8.7)	<0.001*
Ongoing treatment at onset, n (%)			
Lipid-lowering drugs	42 (13.6)	75 (17.1)	0.233
Antihypertensive agents	144 (46.6)	211 (48.1)	0.749
Anticoagulants and antiplatelets			0.146
Warfarin	37 (8.5)	22 (7.2)	
Acenocoumarol	8 (1.8)	8 (2.6)	
DOAC	21 (4.8)	12 (3.9)	
LMWH	12 (2.8)	14 (4.6)	
ASA	96 (22.1)	86 (28.0)	
Clopidogrel	19 (4.4)	12 (3.9)	
Ticlopidine	4 (0.9)	9 (2.9)	
Dipyridamole+ASA	2 (0.5)	0 (0.0)	
ASA+clopidogrel	3 (0.7)	2 (0.7)	
DOAC+ASA	5 (1.2)	3 (1.0)	

Continued

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Table 1. Continued

Characteristic	Women (n=309)	Men (n=439)	*P* value
Blood pressure on admission, mean±SD, mm Hg			
SBP	157.6±33.8	166.4±34.5	<0.001*
DBP	87.1±19.2	92.6±19.8	<0.001*
ICH volume, median (IQR), mL	7.5 (1.5–29.7)	9.8 (2.1–27.8)	0.234
Hemorrhage location, n (%)			<0.001*
Lobar	141 (45.6)	150 (34.2)	
Nonlobar	134 (43.4)	262 (59.7)	
Uncertain	34 (11.0)	27 (6.2)	
Intraventricular extension of ICH, n (%)	102 (33.0)	146 (33.3)	0.961
Acute surgical treatment of ICH, n (%)	19 (8.3)	34 (6.6)	0.531

ASA indicates acetylsalicylic acid; DBP, diastolic blood pressure; DOAC, direct oral anticoagulant; ICH, intracerebral hemorrhage; IQR, interquartile range; LMWH, low-molecular-weight heparin; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and SBP, systolic blood pressure.

*P<0.05.

in men. Overall, we found significantly lower ICH incidence rates in women compared with men (incidence rate ratio, 0.67 [95% CI, 0.58–0.78]; P<0.001) (Table S2). Standardized rates are reported in Table S2. ICH incidence increased with age (P for trend <0.001) in both sexes and was highest in women in the age group of 75 to 84 years and in men in the age group of >85 years (Table S3, Figure 1). There was no evidence of changes in the incidence rates of ICH over time in both women and men (P for trend=0.073 and 0.940, respectively) (Figure 2).

Overall, women showed significantly lower incidence of nonlobar ICH compared with men (incidence rate ratio for women versus men, 0.49 [95% CI, 0.39–0.60]; P<0.001), whereas lobar ICH incidence did not significantly differ between sex groups (incidence rate ratio for women versus men, 0.89 [95% CI, 0.71–1.12]; P=0.335). For ICH location, we did not document significant changes over the study period in the incidence of lobar and nonlobar ICH subtypes overall and separately in women and men (Table S4, Figure S2).

Follow-Up and ICH Case-Fatality Rates

Discharge destinations were similar in women and men (P=0.390). Women showed higher median mRS scores compared with men at discharge, but functional impairment was high in both sex groups (median mRS scores=5 in both women and men [IQR, 4–6 and 3–6, respectively]; P=0.020). When considering only survivors, we observed a clinically important residual disability without significant differences in median mRS scores between women and men (4 [IQR, 2–5] in both sex groups; P=0.162). Median mRS scores at discharge did not change over years in both women (P for trend=0.133) and men (P for trend=0.113).

As reported in Table 2, 39.4% of women and 33.9% of men died within 30 days and 48.5% of women and 40.1% of men died within 1 year from the ICH onset. Unadjusted case-fatality rate comparison showed the 1-year case-fatality rate was significantly higher in women compared with men (P=0.026). The Kaplan-Meier survival analysis indicated that most deaths occurred early following ICH in both women and men. Women showed lower overall survival than men at 1 year (log-rank test; P=0.031; Figure 3).

There were no sex differences in case-fatality rate according to ICH location. We found no evidence of changes in yearly 30-day and 1-year case-fatality rates over the study period overall and in the

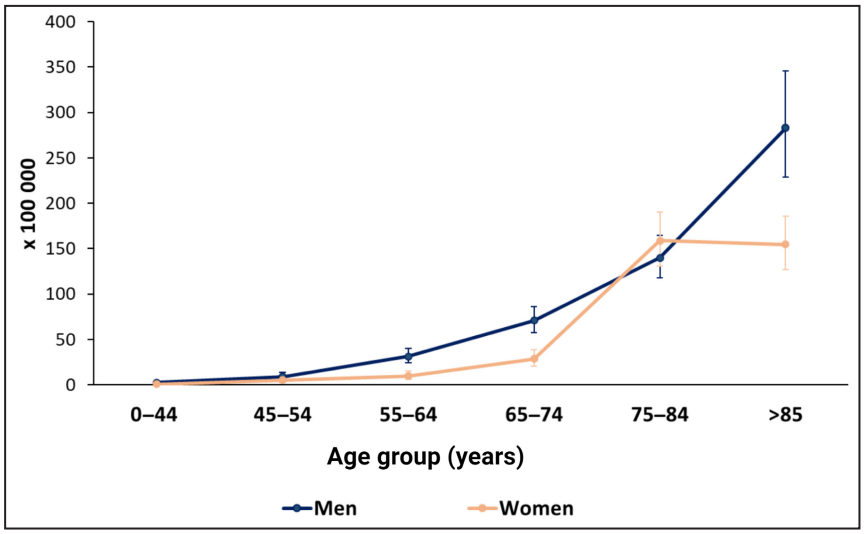

Figure 1. Crude incidence of first-ever intracerebral hemorrhage according to age groups in women and men.

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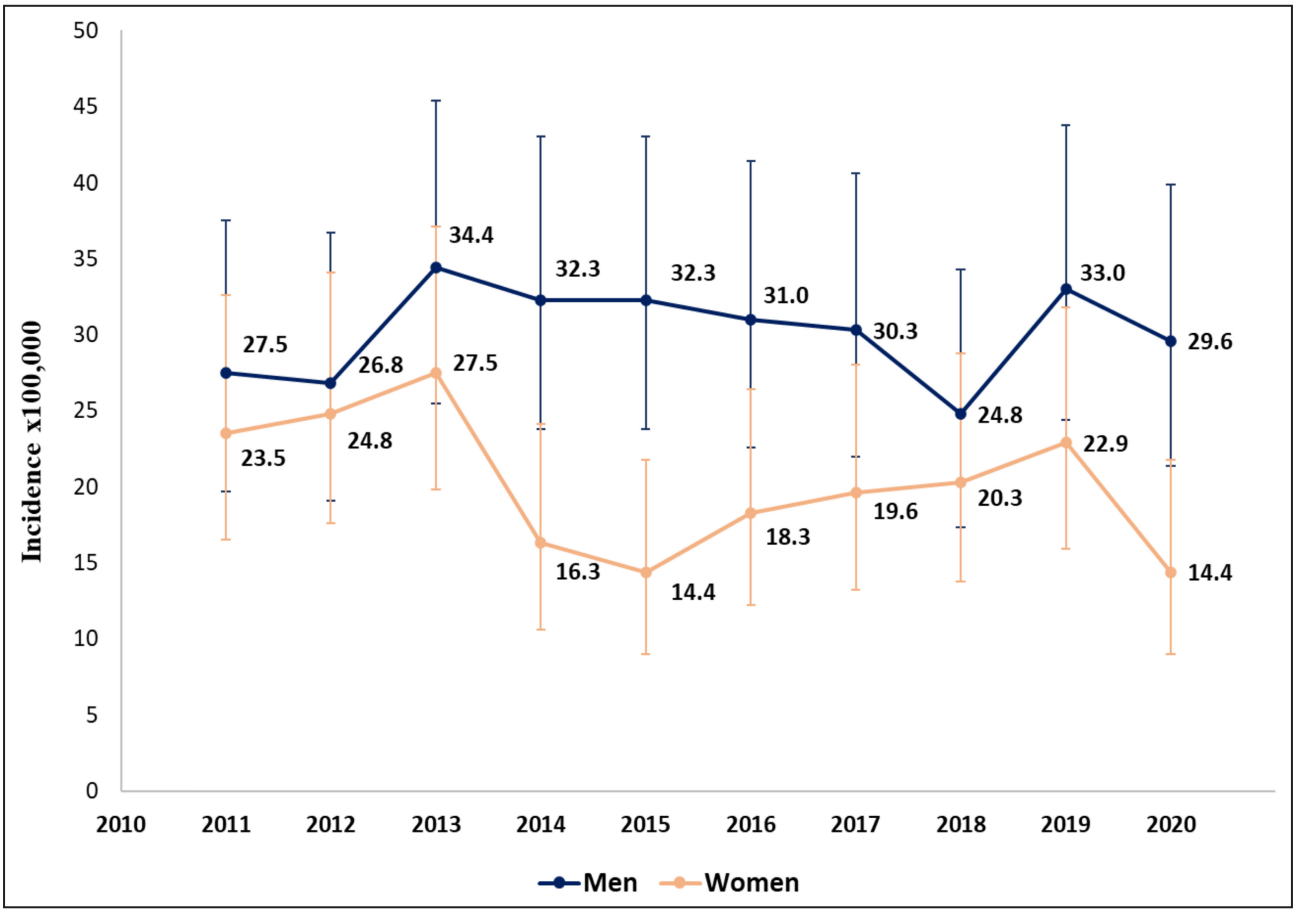

Figure 2. **Incidence trends of first-ever intracerebral hemorrhage over the 2011 to 2020 period in women and men.**

explored subgroups according to sex and ICH location (Tables S5 and S6). Both women and men with atrial fibrillation had a significantly higher 30-day case-fatality rate compared with those without atrial fibrillation (Table S7).

The most frequent cause of death was cerebral death related to the hemorrhage in both women and men. The distribution of death causes did not differ between the 2 sex groups at both 30 days and 1 year (P=0.144 and P=0.466, respectively) (Table 2).

When adjusting for components of the ICH score (ie, age, GCS score, NIHSS score on admission, SBP, ICH volume and location, and intraventricular extension), we found that female sex was not independently associated with 30-day and 1-year case-fatality rate (HR for female sex, 0.90 [95% CI, 0.63–1.29] [P=0.570] and 0.97 [95% CI, 0.70–1.34] [P=0.850], respectively). Among components of the ICH score, ICH volume, intraventricular extension, GCS score, NIHSS score, and SBP on admission were independent predictors of 30-day and 1-year case-fatality rate in the overall population (all P<0.05) (Table S8). When stratifying for sex groups, we found that increasing age, GCS score, and NIHSS score on admission were the only independent predictors of 30-day and 1-year case-fatality rate in women (all P<0.005) (Tables S9 and S10).

DISCUSSION

Our analysis of 10-year data from a prospective population-based stroke registry based in L'Aquila (Italy) revealed some clinically significant sex-related differences in the epidemiology of ICH. One notable observation is that women had ICH at an older age compared with men. This aligns with existing literature that highlights the age-related risk of ICH, as advancing age is consistently recognized as a primary risk factor for ICH across diverse populations.[33] The concept of age-related ICH vulnerability is supported by studies such as the REGARDS (Reasons for Geographic and Racial Differences in Stroke) study, which also emphasizes the age-dependent increase in ICH mortality risks in both sexes.[34] Sex-based interactions with aging in ICH susceptibility should also be considered. One critical facet revolves around the distinct dynamics of sex-specific gonadal hormones, which have been

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Table 2. The 30-Day and 1-Year Case-Fatality Rates and Causes of Death in Patients With a First-Ever ICH, According to Sex Groups

Variable	Women (n=309)	Men (n=439)	*P* value
Discharge destination, n (%)			0.390
Home	90 (29.1)	143 (32.6)	
Hospice/long-term care services	93 (30.1)	141 (32.1)	
mRS score at discharge, median (IQR)			
Overall	5 (4–6)	5 (3–6)	0.020*
Survivors	4 (2–5)	4 (2–5)	0.126
30-d Case-fatality rate, n (%)	122 (39.5)	149 (33.9)	0.140
1-y Case-fatality rate, n (%)	150 (48.5)	176 (40.1)	0.026*
30-d Causes of death, n (%)			0.144
Fatal hemorrhage	99 (81.2)	133 (89.3)	
Cardiac complications	20 (16.4)	11 (7.4)	
Infections (respiratory tract/urinary tract)	2 (1.6)	3 (2.0)	
Undetermined	1 (0.8)	2 (1.3)	
1-y Causes of death, n (%)			0.466
Fatal hemorrhage	114 (76.0)	145 (82.4)	
Cardiac complications	24 (16.0)	20 (11.4)	
Infections (respiratory tract/urinary tract)	11 (7.3)	9 (5.1)	
Undetermined	1 (0.7)	2 (0.1)	

ICH indicates intracerebral hemorrhage; IQR, interquartile range; and mRS, modified Rankin Scale.
*$P<0.05$.

shown to exert beneficial effects on cerebral vasculature integrity and resistance to stressors.[35] Although androgens (more prevalent in men) exhibit gradual and less pronounced decline with the aging process, estrogens (more prevalent in women) abruptly decrease with menopause, thus contributing to increased ICH vulnerability among older women. In addition, the premorbid psychosocial environment, including lifestyle and psychosocial stressors, may diverge between sexes as they progress in age. Such factors could potentially interact with biological dissimilarities to shape the overall risk of ICH at various stages of life.

Furthermore, we observed a lower overall ICH incidence rate in women compared with men (Figure 2), confirming the emerging global trend reported by a multitude of studies.[36,37] Sex-based differences in the ICH incidence were also documented in 5 of the 6 regions in the EROS (European Registers of Stroke)[38] study and in 2 European studies conducted in Norway[39] and Greece.[16] The reasons behind this sex disparity in ICH incidence remain multifactorial and complex. In a North American study,[11] a higher incidence of ICH was found in men aged <65 years and in Black men aged 65 to 74 years (compared with age-matched women of the same race), suggesting that it might be in part explained by the interplay between race and aging.[11] The influence of hormonal fluctuations, genetic factors, along with dissimilarities in lifestyle and behavioral risk factors, such as the lower prevalence of cigarette smoking and alcohol abuse in women (as observed in our population), may all contribute to explain this sex-related difference in ICH incidence. In addition, we did not detect any change in ICH incidence over time, and the overall rate of ICH in our cohort was in line with previous studies on the Italian population.[40,41]

Interestingly, our data also showed intriguing differences in the distribution of ICH subtypes between sexes that should be considered particularly to improve sex-based ICH primary prevention strategies and design clinical trials, including patients with ICH. Specifically, we disclosed a significantly lower incidence of nonlobar ICH in women compared with men. This finding, coupled with the observation of lower mean values of SBP and diastolic blood pressure on admission in women, might empower the well-documented association between hypertension and male sex,[42] thus supporting earlier evidence pointing to a higher risk of hypertensive heart disease and correlated cardiovascular events within this sex category.[43] Conversely, although we identified a greater prevalence of lobar ICH in women, the overall incidence of this subtype remained comparable between sexes. This finding in part contradicts previous studies from North America[11] and Mexico,[44] which showed elevated incidence of lobar ICH in the female sex. Lobar ICH has been associated with cerebral amyloid angiopathy that is strongly related to age and genetic factors.[45] Future studies should investigate whether our findings subtend a novel figure of stable incidence of lobar ICH in women. Together with differences in ICH subtypes, we also found differences in the clinical severity of ICH at onset, with women having more severe clinical events than men. We also found a significant trend over the study period toward lower NIHSS score on admission in our male population (Figure S2), probably reflecting changes in ICH-related risk factor diagnosis and management over the more recent years.

In our study, we confirmed a remarkably high case-fatality rate after ICH in both women and men. Kaplan-Meier curves indicated that most deaths occurred within the first month from ICH in both sexes (Figure 3). Although unadjusted comparison of case-fatality rates showed that women experienced a significantly higher 1-year mortality compared with men, when adjusting for age and other components of the ICH score, sex was not an independent predictor of 30-day and 1-year mortality in our cohort. Conversely to sex, we found that increasing age and higher clinical severity on admission were independently associated with worst prognosis, along with higher SBP values on admission, increased baseline ICH volume, and presence of intraventricular extension (Table S8).

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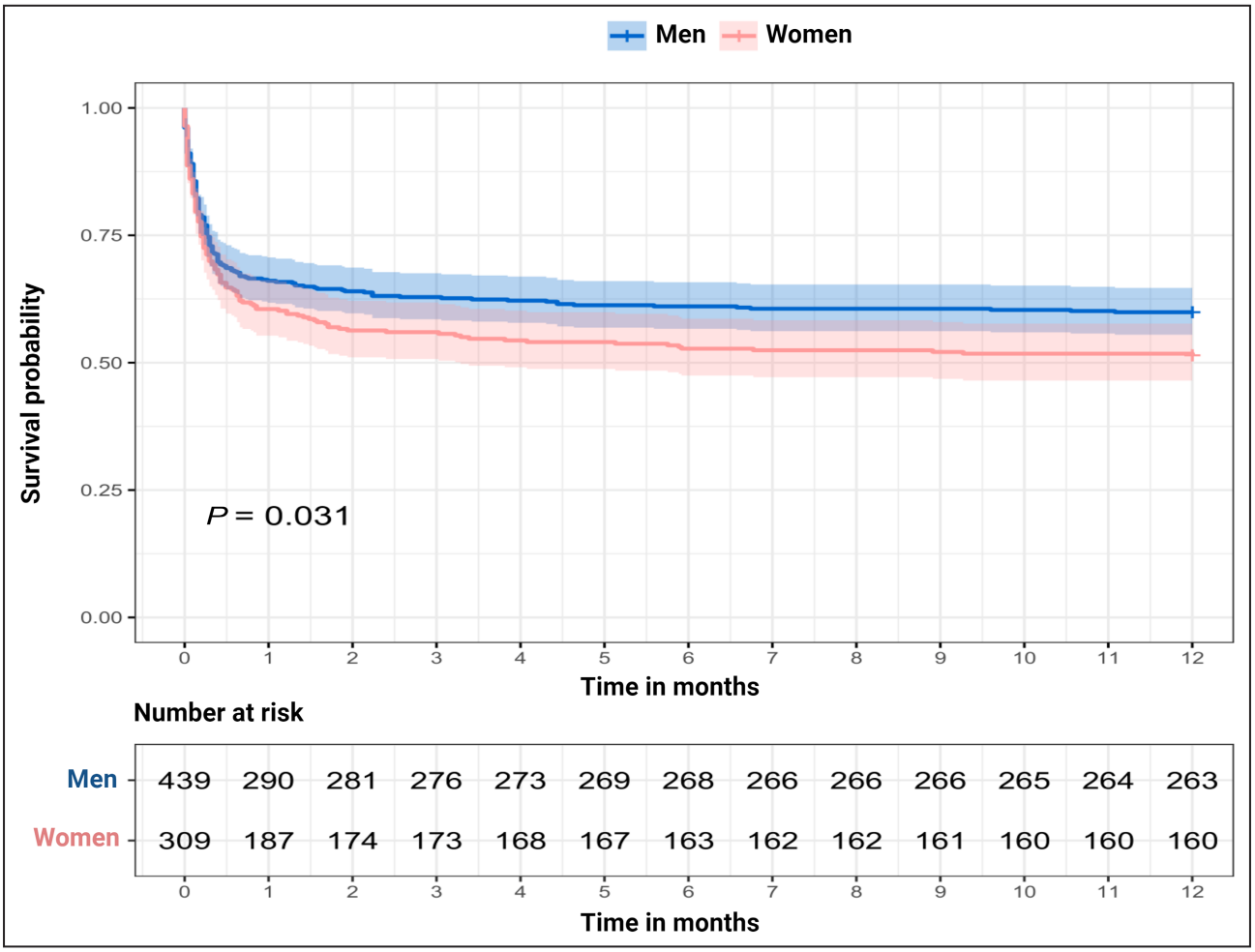

Figure 3. **Kaplan-Meier estimates of survival after intracerebral hemorrhage in women and men.**

Because women presented with older age and higher clinical severity on admission, we can reasonably assume that their higher long-term mortality is largely attributable to these factors, which may enhance vulnerability to ICH complications. In addition, we cannot exclude that disparities in care limitations or diminished adherence to treatment plans for secondary prevention may have played a role in determining the higher 1-year mortality of women within our population, as observed elsewhere.[46] Despite the fact that, in our analysis, we did not find significant differences in the distribution of death causes between sexes, we can speculate that other factors operating in the chronic phase of ICH may also contribute to explain the worst 1-year prognosis observed among women. These could span from intrinsic characteristics of the ICH subtype (eg, worst long-term prognosis of lobar ICH[47]) to potential limitations in post–acute stroke care.

Our study bears some limitations. The possibility of missed cases, including those among nonhospitalized individuals or those who did not seek medical attention because of subtle symptoms or early demise, cannot be entirely ruled out. However, we addressed these concerns through comprehensive case identification from diverse sources (hospitals, outpatient clinics, general practitioners, and death certificates). Moreover, we did not capture data on ICH growth during the hospital stay and on the use of reversal agents in patients on anticoagulant treatment at the time of ICH. Furthermore, the advanced age and the race and ethnicity of our population might limit the generalizability of findings. Also, our study did not detect possible differences between men and women in the withdrawal of life-sustaining treatments, as data were not specifically collected. The local practice on life-sustaining measures for ICH is to maintain treatments in all patients until different indications are provided by consensus between treating physician and patient caregivers. In addition, although we identified significantly higher 30-day case-fatality rates in both women and men with a history of atrial fibrillation, the limited

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prevalence within our study population prevented us from making further assessments about potential differences in the impact of atrial fibrillation on mortality across sex groups. Moreover, we cannot exclude that some of the predictors found in the overall regression analysis lost statistical significance when tested according to sex subgroups (eg, GCS score, hemorrhage location, and intraventricular extension) because of low patient numbers. Last, the use of median imputation instead of multiple imputation techniques for missing data in Cox regressions can be considered as a limitation of the study. However, we recorded a low number of missing data among tested variables (<5% for both GCS and NIHSS score on admission and baseline hematoma volume).

Despite these limitations, our study boasts several strengths. Spanning a decade, our investigation offers a comprehensive and long-term insight into ICH dynamics. Adopting a prospective design, we applied precise and standardized criteria for ICH incidence study. Our inclusion of a sizable, precisely defined stroke population facilitated an observation period spanning at least 100 000 person-years. Notably, 100% of cases underwent at least 1 brain imaging, and survivors were diligently followed up for up to a year post-ICH.

In conclusion, our study investigated sex-related differences in the epidemiology of ICH in a high-income, non-Hispanic White population from 2011 to 2020. Remarkably, the overall incidence of ICH was lower in women than in men. Women had worse long-term prognosis than men, which was likely related to their older age at ICH onset and higher clinical severity on presentation. We additionally disclosed differences in risk factors and ICH location that may reflect differences in the distribution of ICH pathogenesis across sexes. The next step to move forward is to better investigate peculiarities of pathogenic mechanisms in ICH in women and men and to develop tailored approaches to mitigate the worst outcome in women.

ARTICLE INFORMATION

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None.

Supplemental Material

Tables S1–S10
Figures S1–S2
References[48–51]

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