Gender Differences in Patients with Intracerebral Hemorrhage: A Hospital-Based Multicenter Prospective Study

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Key Words
Gender differences • Intracranial hemorrhage • Stroke

Abstract
Gender differences are well described for patients with ischemic stroke. Conversely, sex disparities in stroke presentation, risk factors, treatment, and outcomes for intracerebral hemorrhage (ICH) were not previously studied. Our objective was to compare the frequency of risk factors, management patterns, symptoms at presentation, complication rates, and outcomes between genders in patients with ICH in Fortaleza, Brazil. Methods: Data were prospectively collected from patients admitted to 19 hospitals in Fortaleza with a diagnosis of ICH by trained research coordinators from June 2009 to October 2010. Daily visits to the selected hospitals were performed, and all patients admitted with a diagnosis of ICH were prospectively evaluated. Results: We evaluated 364 patients, 47.5% of whom were women. Men were younger (59.3 ± 14.58 years vs. 66.3 ± 14.6 years, p < 0.001), more frequently smokers (33.1 vs. 16.6%, p < 0.01) and had a higher frequency of alcohol abuse (48.5 vs. 8.2%, p < 0.01) than women. Women had a trend to have more dyslipidemia (41.1 vs. 31.3%, p = 0.12). Clinical presentation was similar between genders including the presence of motor and sensory deficits, headache, and depressed level of consciousness at presentation. Men had more speech disturbances than women (63.6 vs. 52.7%, p = 0.04). The time interval from symptoms onset to hospital admission was longer in women (25.1 ± 82.4 h vs. 7.9 ± 50.3 h, p = 0.08). Complication rates including pneumonia and deep vein thrombosis were not different between genders. Mortality was similar in both
sexes (females: 35.8% vs. males: 33%, p = 0.66). Men were more frequently independent at discharge when evaluated by the modified Rankin Scale (mRS) score (mRS ≤2: 19.7% in men and 8.1% in women, p < 0.01). In the multivariate logistic regression analysis, older age, pre-stroke disability, depressed consciousness at admission, and female gender were independent predictors of poor outcome at discharge. **Conclusion:** Overall risk factors for ICH in men and women were similar in our series. Men had a higher frequency of alcohol abuse and smoking. Women were older, had an increased time length from symptoms onset to hospital admission and had a worse prognosis at discharge. A better understanding of the gender disparities in patients with ICH will hopefully lead to better outcomes in both sexes in the future.

**Introduction**

Depending on the population studied, intracerebral hemorrhage (ICH) can represent from 10 to 15% of all strokes [1, 2]. The condition remains without a treatment of proven benefit and carries a mortality rate of 40–50% [3].

The incidence of stroke is higher in men, but the severity and case fatality at 1 month is worse in women [2, 4]. Gender differences in risk factors, patterns of care, and outcomes are well described for patients with ischemic stroke (IS) [5–9]. Conversely, sex disparities in ICH were not previously studied separately from IS, and therefore the real scenario for ICH is still unknown. Indeed, since most studies evaluating IS and ICH have combined epidemiological and clinical data, they may have led to misinterpreted conclusions on the importance of these variables for each condition [10–12]. Additionally, some of these epidemiological studies have combined subarachnoid hemorrhage with ICH into a single group therefore compromising even further the understanding of gender disparities in ICH care [12, 13].

To address these issues, we used a multicenter hospital-based cohort of patients with primary ICH to compare the frequency of risk factors, management patterns, symptoms at presentation, complication rates, and outcomes between genders in patients diagnosed with ICH in Brazil.

**Patients and Methods**

We conducted a prospective cohort study to evaluate consecutive patients admitted with a new episode of stroke in 19 hospitals (6 public, 4 private, and 9 mixed – public and private) in the city of Fortaleza, Brazil, from June 2009 to October 2010.

Fortaleza has a total of 31 hospitals (11 public, 11 private and 9 mixed – public and private) [14]. In order to identify which hospitals to include in our study, all certificates of deaths attributed to any of the ICD-10 codes related to stroke (I61 through I69) in 2008 in the city of Fortaleza were obtained from the Brazilian Mortality Information System provided by the National Health Ministry [15]. Based on those certificates, 90% of the patients admitted for stroke in the city of Fortaleza died of stroke in one of the 19 selected hospitals.

We used the step-one (conducted exclusively with hospitalized cases) methodology suggested by the Stroke Steps modular program of the World Health Organization [16]. Our trained research coordinators collected data daily using medical records of all ICH patients and interviews with patients and relatives.

In this study, we included patients with first-ever intraparenchymatous cerebral hemorrhage and patients with recurrent ICH, as long as the current admission was due to a new episode. We excluded patients admitted with ICH who died within the first 24 h and who had
no reliable medical record, those with no documented neuroimaging studies, patients with subarachnoid hemorrhage, epidural or subdural hematomas, or ICH secondary to tumors or arteriovenous malformation, and those residing outside the city limits. ICH was defined by universally accepted criteria including clinical and neuroimaging (CT or MRI) findings [17].

A dedicated nurse coordinator with special training in stroke reviewed the medical history of all patients. All patients included in this study were followed until discharge. Controversial data were discussed with two stroke neurologists.

Data collected included demographic characteristics, the presence of stroke risk factors (hypertension, dyslipidemia, diabetes, atrial fibrillation, previous stroke, familiar history of cardiovascular disease, anticoagulant drug use, alcohol abuse, smoking, and obesity), clinical presentation (sensory and speech disturbance, motor deficits, headache, and depressed level of consciousness), modified Rankin Scale (mRS) stroke (pre-stroke and at discharge), brain imaging frequency (CT or MRI), length of stay, use of antihypertensive drugs during admission, frequency of in-hospital rehabilitation (physical and/or speech therapy), and frequency of complications (pneumonia and deep vein thrombosis).

The presence of risk factors was based on the medical records or if medications for known risk factors were used before hospital admission or at discharge.

This study was approved by the institutional review board of each participating institution, and written informed consent was obtained from patients or their representatives.

Means and standard deviations or medians and interquartile intervals were used to describe the patients’ characteristics. The independent samples t test was used to compare means between men and women. Nonparametric data were compared using the Mann-Whitney test. Categorical variables were compared with the χ² test. We used multiple logistic regressions to investigate the influence of the different epidemiological, clinical, and management characteristics upon mRS scores at discharge dichotomized at 2 (mRS ≤2 vs. ≥3). All variables that showed an association in the univariate analysis with a p value of ≤0.10 were included in the multivariate analysis. A two-tailed p value of <0.05 was considered statistically significant. Statistical analysis was performed with SPSS 16.0 software (Chicago, Ill., USA).

Results

During the study period, 2,418 consecutive patients were admitted to the 19 selected hospitals with all types of stroke, 364 (15.2%) of which corresponded to ICH. A total of 173 (47.5%) of the patients admitted with ICH were women. Other stroke subtypes corresponded to ischemic (72.9%), subarachnoid hemorrhage (6.0%), transient ischemic attack (3.0%), and undetermined (2.9%).

Among the ICH patients, men were younger (59.3 ±14.58 years vs. 66.3 ± 14.6 years, p < 0.01), more frequently smokers (33.1 vs. 16.6%, p < 0.01) and had a higher frequency of alcohol abuse (48.5 vs. 8.2%, p < 0.01) than women. Women had a trend to have more dyslipidemia (41.1 vs. 31.3%, p = 0.1), while men had a trend to be more frequently hypertensive (93.7 vs. 88.7%, p = 0.1). There were no differences between genders in the frequency of other epidemiological characteristics and ICH risk factors including race, pre-existing chronic diseases, previous stroke episodes, and family history of cardiovascular disease (table 1).

Clinical presentation, including the presence of motor and sensory deficits, headache, and depressed level of consciousness at presentation, was similar between genders, except for a higher frequency of speech disturbances in men (63.6 vs. 52.7%, p = 0.04) (table 1).

The median interval from symptoms onset to hospital admission tended to be longer for women (8.61 h [1.88–27.00 h]) than for men (1.93–25.15 h, p = 0.08). The median time from
hospital admission to first neuroimaging was 3.55 h (1.28–47.68 h) for women and 3.78 h (1.00–22.05 h) for men, (p = 0.57) (table 1).

No differences between genders were observed for the frequency of the type of brain imaging evaluation used (CT or MRI), length of stay, use of antihypertensive drugs during admission, frequency of in-hospital rehabilitation (physical and/or speech therapy), and frequency of complications as pneumonia and deep vein thrombosis (table 2).

There was no significant difference in mortality between genders (35.8% in women and 33.0% in men, p = 0.66). Men were more frequently independent at discharge when evaluated by the mRS score (mRS $\geq$2: 19.7% in men and 8.1% in women, p < 0.01) (table 2).

Age, depressed level of consciousness at admission, pre-stroke disability (mRS $\geq$1) and female gender were univariate predictors of poor outcomes at discharge (mRS $>$2). After a multivariate logistic regression analysis, older age (OR = 1.05 [1.01–1.08] per additional year, p < 0.01), pre-stroke disability (mRS $\geq$1) (OR = 1.51 [1.13–2.01], p < 0.01), depressed consciousness at admission (OR = 4.61 [1.67–12.71], p < 0.01) and female gender (OR = 2.9 [1.07–8.23], p = 0.03) remained independent predictors of poor outcome at discharge (fig. 1).

**Discussion**

We found that women with ICH were older than men and had a lower frequency of alcohol abuse. Overall, we found no differences in the frequency of other risk factors, patterns of management or complications between genders. After adjusting for other predictors of
functional outcome, female sex was still an independent predictor of poor prognosis at discharge in patients with ICH. Our findings are consistent with previous studies in patients with IS, which have shown that, compared to men, women with stroke tend to be older and are less likely to achieve independence or be discharged home [4, 8, 18, 19].

We have found a higher frequency of alcohol abuse in men than in women admitted for ICH in our cohort. A linear association exists between alcohol consumption and risk of ICH, and it is well documented that women drink less and have a lower prevalence of alcohol abuse than men [20–23]. Secondary prophylaxis of ICH in both genders should therefore specifically address the investigation of alcohol abuse, especially in men. Cigarette smoking was also more common in men in our series. Although smoking definitely increases the risk of IS and subarachnoid hemorrhage, the data on ICH are inconclusive [20–25].

Previous studies suggest that a sex difference exists in reporting of acute stroke symptoms [10, 26, 27]. Typical clinical presentation in patients with ICH involves a sudden onset of focal neurological deficit with or without clinical signs of increased intracranial pressure, such as a decreased level of consciousness, headache, and vomiting [3, 28]. In our series, the unique symptom significantly different between genders was the frequency of speech disturbance, more frequent in men than women. Unfortunately, lesion location was not available in our series in order to better understand this difference.

The age difference between genders observed in our study is probably explained by the fact that worldwide women live about 10 years longer and experience their first stroke later than men [4, 18, 19]. After adjusting for other predictors of functional outcome, female sex
was still an independent predictor of poor prognosis at discharge in patients with ICH in our cohort. In previous studies, including all types of stroke, women often have worse outcomes than men with more physical impairment and limitations in daily activities at long-term follow-up [4, 18, 26]. The underlying reasons of sex disparities in clinical outcomes in patients with ICH have yet to be fully elucidated. Differences in outcomes in patients with all types of stroke are most often explained in the literature by the fact that compared to men, women are older and have a higher frequency of pre-stroke disability [18, 26]. In our cohort, however, women less frequently achieved independence after ICH, independent of age, pre-stroke disability, and depressed consciousness at admission. Stroke severity is also often cited as a potential explanation for sex differences in stroke outcomes, although the available data suggest that differences in stroke severity between genders are small to non-existent [4, 18].

We do not have a specific measure of stroke severity at admission like the National Institutes of Health Stroke Scale, which is an important determinant of outcome in series of patients with stroke. Although it is possible that the gender disparities seen in our patients reflect a higher frequency of more severe strokes in women than in men, the level of consciousness at admission, as a surrogate for stroke severity, suggests that it was not the case.

Our study has some limitations. Our data and conclusions are restricted to discharge outcomes because long-term follow-up was not performed. Additionally, we did not assess important predictors of 30-day mortality after ICH-like hematoma location and volume, the presence of intraventricular hemorrhage, and of pre-ICH cognitive impairment [29, 30]. Finally, we do not have data on the frequency of anticoagulant use before admission. Nevertheless, our cohort was the first to specifically evaluate gender disparities in ICH and serves as hypothesis-generating study.

In conclusion, women less frequently achieve independence after admission for an ICH independent of age, pre-stroke mRS, and the presence of depressed consciousness at presentation. The results reported herein have also indicated that age, alcohol abuse, smoking and speech symptoms are significantly different between genders in ICH. More attention should be given to the differences in risk factors revealed in the current study to devise specific strategies for each gender in order to prevent ICH. A better understanding of the causes of gender disparities in ICH, including risk factors, ICH etiologies, patterns of care and recovery, will hopefully lead to better outcomes in both genders in the future.

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References

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