Gender differences in ischemic stroke intra-hospital mortality: a systematic review

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ABSTRACT

The aim was to evaluate whether intra-hospital mortality from ischemic stroke is different in female patients. Methods. Studies were found in PubMed, Web of Science. We excluded 119 records because they did not include relevant reports or data. Studies were eligible for inclusion if enrolled adult patients with ischemic stroke and if the odds ratio (OR) of intra-hospital mortality in females compared to males is provided. Three retrospective cohort studies were eligible for inclusion criteria and so were included in the analysis. Findings: the random effect model showed a pooled significant higher risk of intra-hospital mortality [OR 1.34 (95% confidence interval 1.04, 1.74), P=0.026] in the female group compared to the male group. Our systematic review shows that intra-hospital mortality was significantly higher in female subjects compared to male.

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Contributions: TC described the study design; AC, TC, and AF conducted the study selection and drafted the manuscript; OVG conducted the statistical analysis; MG, OP, and TC edited and revised the manuscript.

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and exclusion criteria, age, gender, comorbidities, stroke severity, functional outcome, intra-hospital mortality. Titles and abstracts of full texts obtained from researches were analyzed by two authors independently (A.C. and A.F). The quality assessment used for each study was The New Castle-Ottawa-Scale (NOS). The NOS assigns up to a maximum of nine scores in three domains: i) selection of study groups (four scores); ii) comparability of group (two scores); iii) ascertainment of exposure and outcomes (three scores) for case-control and cohort studies, respectively.

Dissents in the evaluation of the quality were resolved by consensus. We included only the articles with a NOS ≥6.

Outcomes

The main outcomes were the OR of intra-hospital mortality for ischemic stroke in female subjects compared to male ones.

Summary measures

Each study contains results of a multivariable logistic regression model with the estimation of OR.

Synthesis of results

Statistical analysis was performed using R version 4.0.0 (2020-04-24) with the metaphor R package version 2.4.0 (2020-03-19). Statistical significance alpha was fixed to 0.05. Considering the methodological difference of included studies, we preferred to use a random-effects model using the generic inverse variance method for pooling results. The model was fitted using the restricted maximum likelihood (REML) method, with the estimation [95% confidence interval (CI)] of summary OR, Q for heterogeneity, and I² (total heterogeneity/total variability).

Results

Study selection and characteristics

Our literature search identified 1319 studies (835 on PubMed and 484 on the Web of Science), of which 1200 were screened, and 3 were included in the meta-analysis.5-7

We excluded 119 records because they did not include relevant reports or data (Figure 1). Three retrospective cohort studies were eligible as per inclusion criteria and so were included in the analysis (Table 1). For the three studies included in the meta-analysis, an adjusted OR for intra-hospital mortality was provided. They are all retrospective cohorts. Park’s and Aziz’s studies adjusted results for several confounding variables. They are all of good methodological and statistical quality with a low risk of bias. Aziz’s and Nardetto’s studies separately showed a significantly higher risk of intra-hospital mortality (OR>1, P<0.05) in female patients compared to male ones.

Synthesis of results

The random-effect model (Figure 2) showed a pooled significant higher risk of intra-hospital mortality [OR 1.34 (95% CI 1.04, 1.74), P=0.026] in the female group compared to the male group. Q for heterogeneity is 18.49 (P<0.0001).

Discussion

It has been reported that gender is an important predictor for the incidence and outcomes in the stroke research field.8 In particular, women manifest stroke differently and have worse outcomes after treatment for acute ischemic stroke than men.9 In this
regard, in our systematic review, we reported a significantly higher risk of intra-hospital mortality in the female group compared to the male group [OR 1.34 (95% CI 1.04, 1.74), P=0.026]. Similar to our findings, most previous studies demonstrated an increased risk of mortality in the female gender, but no studies described intra-hospital mortality by gender in ischemic stroke. Conversely, it has been reported that the male gender is a significant predictor of recurrent ischemic stroke. In 2001, the U.S. Institute of Medicine (IOM) addressed that examining sex differences in clinical and research studies is critical because there is increasing evidence of fundamental sex differences in the biology of disease. In 2015, the American Heart Association (AHA) called for studies of sex differences in car-

### Table 1. The literature search included in the meta-analysis.

| Study                     | Study quality (NOS) | Outcome                          | Exclusions criteria                                                                 | Variables in the multivariate model (adjustments) | Limitation                                                                                       |
|---------------------------|---------------------|----------------------------------|--------------------------------------------------------------------------------------|--------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Park et al., 2012         | 13                  | Accessibility to emergency care - Hospital mortality and disability (mRS) | Age <18 yrs, hemorrhagic stroke                                                     | Age, education, medical history (hypertension, IHD, and stroke), health behavior, and clinical symptoms | No stroke severity; Higher level of ED in Tertiary hospital; Intermediate EMS System; Quality control program for ED stroke began in 2006 |
| Nardetto et al., 2017     | 12                  | Intrahospital mortality          | Incomplete in hospital information                                                  | Age                                              | Under-estimated overall rates of thrombolysis, no long-term outcome data                      |
| Aziz et al., 2016         | 13                  | 30 day in-hospital mortality     | Acute stroke greater than 2 weeks                                                  | Age, race, hypertension, diabetes, high blood cholesterol, and smoking | Age difference between genders; frequency of Malay ethnic patients is high, gender and race adjustment would be required, males had a high prevalence of modifiable risk factors |

IHD, ischemic heart disease; ED, Emergency Department.

### Figure 2. Forest plot of pooled odds ratio for ischemic stroke intra-hospital mortality in females compared to males from random effect model (method=REML). Q=18.49 (P<0.0001). I2 =87.04 (95% CI 48.80- 9.66).
diovascular disease (CVD) consequence because cardiovascular disease may be more deadly for women than it is for men. However, it has been reported that, from the U.S. Framingham Study, female patients with diabetes mellitus (DM) versus those without DM, were at a significantly higher risk of death from CVD and all-cause mortality than their counterparts in males. Other studies have reported that women live longer than men, suffer more severe strokes with higher short-term mortality, worse functional recovery, and are managed differently compared to males. However, other studies reported that females with atrial fibrillation (AF) have a higher incidence of stroke and a higher mortality rate compared to men with AF. In particular, the incidence of AF doubles with every 10-year increase in age, which is particularly important in women, with a higher life expectancy. In this regard, the AHA recommends using the CHA2DS2-VASc score to predict stroke risk and the need for anticoagulation drugs in subjects with AF. Finally, treatment of modifiable cardiovascular risk factors for stroke, including hypertension, obesity, and metabolic syndrome, can be highly effective in women and further optimize AF and stroke prevention. However, another risk factor for female subjects is the peripartum period and early postpartum period. In fact, it is called maternal stroke. During these periods, the risk for ischemic stroke increase.

Conversely, it has been reported that lower levels of education, a lower income, and higher area deprivation were associated with increased risk of stroke among both men and women equally. The mechanisms by which women may have a relatively higher risk of death are not clear. Findings from few studies suggest that women may have an ischemic attack at earlier ages than men; are less likely to undergo procedures to open clogged arteries; are less likely to be on cholesterol-lowering medications than men, and are less likely to have their blood sugar or blood pressure under control than men. Our results could guide the healthcare system towards appropriate cardiovascular prevention by gender and limit expenses related to the disabling stroke outcomes in women.

Conclusions

Our systematic review shows that intra-hospital mortality was significantly higher in female subjects compared to male. The different sex-effect of ischemic stroke with regard to intra-hospital mortality is probably linked to a difference in metabolic disorders by gender. Further studies are needed to assess whether the female gender may benefit from more aggressive vascular risk factors control and treatment strategies for stroke prevention.
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