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

Tiziana Ciarambino,[1] Orazio Valerio Giannico,[2] Amalia Campanile,[3] Antonella Fischetti,[3] Elena Barbagelata,[4] Imma Ambrosino,[5] Ombretta Para,[6] Cecilia Politi,[7] Mauro Giordano[3]

[1]Internal Medicine Department, Hospital of Marcianise, ASL Caserta; [2]Dipartimento di Prevenzione, ASL Taranto; [3]Department of Internal Medicine, University of Campania L. Vanvitelli, Naples; [4]Department of Internal Medicine, Lavagna Hospital, Genova; [5]Local Healthcare Unit of Bari, Health District 10, Post-acute Care Triggiano, Bari; [6]Internal Medicine Department, Ospedale Careggi, University of Florence, Florence; [7]Head of Gender Medicine Area FADOI, Internal Medicine Department, Isernia, Italy

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.

Introduction

Ischemic stroke is the second leading cause of death worldwide.[1] Many researches suggest that ischemic stroke mortality is higher in women.[2,3] Most of these studies assess mortality six months after the acute event, while few studies compared if intra-hospital stroke mortality was different by gender. Current guidelines emphasize the key role of thrombolysis to achieve the best outcome in the prognosis of ischemic stroke patients.[4] The assessment of intra-hospital stroke mortality is crucial to evaluate the efficiency of stroke path.[5] The purpose of this review is to evaluate whether intra-hospital mortality from ischemic stroke is different by gender.

Correspondence: Tiziana Ciarambino, Internal Medicine Department, Hospital of Marcianise, ASL Caserta, Italy.
E-mail: tiziana.ciarambino@gmail.com

Key words: Mortality; ischemic stroke; gender/sex differences; not hemorrhagic stroke.

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.

Conflict of interests: the authors declare no potential conflict of interests.

Received for publication: 27 September 2020.
Revision received: 11 December 2020.
Accepted for publication: 30 December 2020.

Licensee PAGEPress, Italy
Italian Journal of Medicine 2021; 15:124-128
doi:10.4081/itjm.2021.1378

Materials and Methods

Literature search

Studies were identified by PubMed and Web of Science database from inception to June 2020. Key words: mortality, ischemic stroke, gender/sex differences, not hemorrhagic stroke. Bibliographies of recent review and references of articles included were manually searched to identify additional studies. Articles written in a language different from English, pediatric studies, reviews, metanalyses, letters, abstracts for scientific conferences were excluded.

Study selection

We considered randomized and observational studies if: i) enrolled adult patients (≥18 years old); ii) included patients with ischemic stroke and not hemorrhagic stroke; iii) odds ratio (OR) of intra-hospital mortality in females compared to males was provided.

Data extraction and quality assessment

Data extracted from identified studies included clinical setting, Ischemic stroke diagnosis, inclusion

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

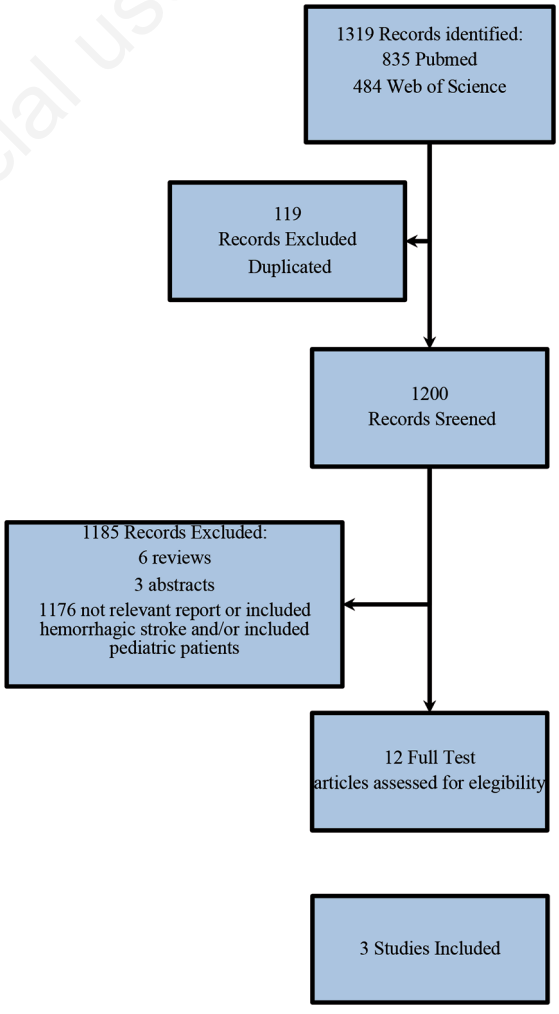

Figure 1. Literature search on PubMed and Web of science.

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.[10] In this regard, 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.[11] 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 (No. patients by treatment group)	Study quality (NOS)	Outcome	Exclusions criteria	Variables in the multivariate model (adjustments)	Limitation
Park *et al.*, 2012[5]	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[6]	12	- Intrahospital mortality	Incomplete in hospital information	Age	Under-estimated overall rates of thrombolysis, no long-term outcome data
Aziz *et al.*, 2016[7]	13	30 day in-hospital mortality - Functional outcome (mRS) - Neurology deficit (NIHSS) - Length of hospital stay - Arrival of ED over 3 h	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.

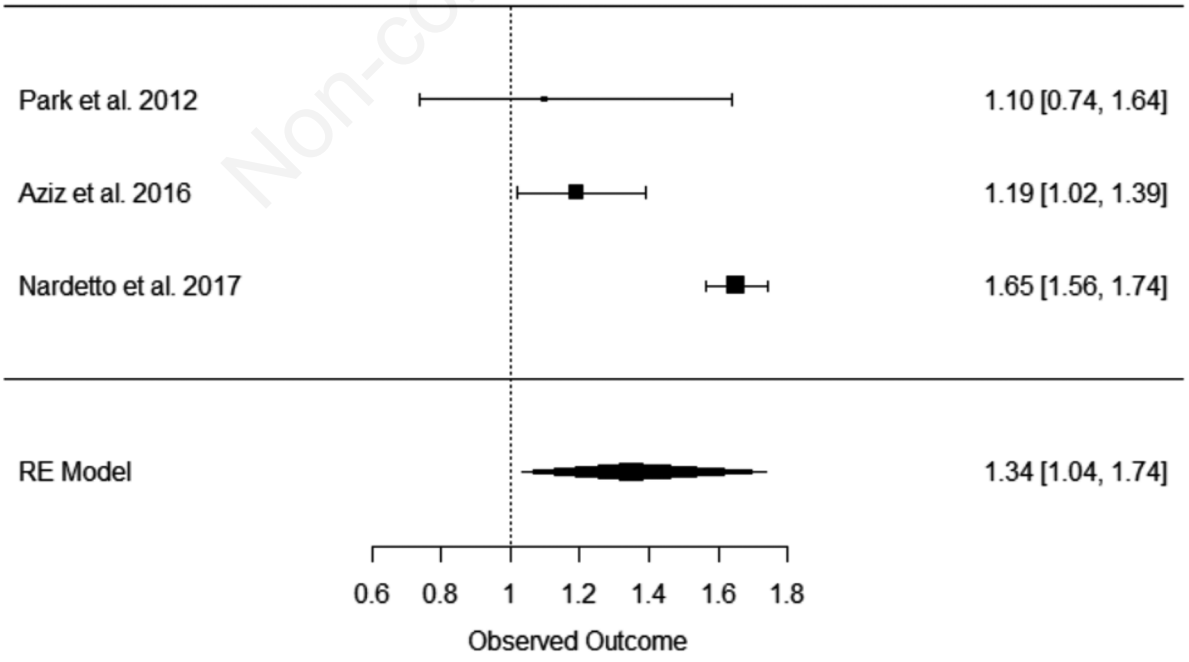

Figure 2. Forest plot of pooled odds ratio for ischemic stroke intra-hospital mortality in females compared to males from random effect model (method=REML). Q=18.49 (P<0.0001). I2 =87.04 (95% CI 48.80- 9.66).

diovascular disease (CVD) consequence because *cardiovascular disease may be more deadly for women than it is for men.*[12] 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.[13] 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.[14-16] 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.[17] In particular, the incidence of AF doubles with every 10-year increase in age,[18] which is particularly important in women, with a higher life expectancy. In this regard, the AHA[19] recommends using the CHA_2DS_2-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.[20,21] In fact, it is called *maternal stroke.*[21] During these periods, the risk for ischemic stroke increase.[20]

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.[12] 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.

References

1. Stepen LJ, Hareden C, Thomson T, Brodie MJ. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2019;18:459-80.
2. Niewada M, Kobayashi A, Sandercock PA, et al. Influence of gender on baseline features and clinical outcomes among 17,370 patients with confirmed ischaemic stroke in the international stroke trial. Neuroepidemiology 2005;24:123-8.
3. Petrea RE, Beiser AS, Seshadri S, et al. Gender differences in stroke incidence and poststroke disability in the Framingham heart study. Stroke 2009;40:1032-7.
4. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2018;49:e46-e110.
5. Park SJ, Shin SD, Young SR, et al. Gender differences in emergency stroke care and hospital outcome in acute ischemic stroke: a multicenter observational study. Am J Emerg Med 2013;31:178-84
6. Nardetto L, Giometto B, Moretto G, et al. Hub-and-spoke stroke network in the Veneto region: a retrospective study investigating the effectiveness of the stroke pathway and trends over time. Neurol Sci 2017;38:2117-21.
7. Aziz ZA, Lee YYL, Sidek NN, et al. Gender disparities and thrombolysis use among patient with first-ever ischemic stroke in Malaysia. Neurol Res 2016;38:406-13.
8. Förster A, Gass A, Kern R, et al. Gender differences in acute ischemic stroke: etiology, stroke patterns and response to thrombolysis. Stroke 2009;40:2428-32.
9. Kapral MK, Degani N, Hall R, et al. Gender differences in stroke care and outcomes in Ontario. Womens Health Issues 2011;21:171-6.
10. Chen CY, Weng WC, Wu CL, Huang WY. Association between gender and stoke recurrence in ischemic stroke patients with high-grade carotid artery stenosis. J Clin Neurosci 2019;67:62-7.
11. Magazines T, Savers S. Exploring the biological contributions to human health: does sex matter? J Womens Health Gend Based Med 2001;10:433-9.
12. Regensteiner JG, Golden S, Huebschmann AG, et al. Sex differences in the cardiovascular consequences of diabetes mellitus: a scientific statement from the American Heart Association. Circulation 2015;132:2424-47.
13. Abbott RD, Donahue RP, Kannel WB, Wilson PW. The impact of diabetes on survival following myocardial infarction in men vs women: the Framingham study. JAMA 1988;260:3456-60.
14. Paolucci S, Bragoni M, Coiro P, et al. Is sex a prognostic factor in stroke rehabilitation? A matched comparison. Stroke 2006;37:2989-94.
15. Gall SL, Tran PL, Martin K, et al. Sex differences in long-term outcomes after stroke. Functional outcomes, handicap, and quality of life. Stroke 2012;43:1982-7.
16. Reeves MJ, Bushnell CD, Howard G, et al. Sex differences in stroke: epidemiology, clinical presentation, medical care, and outcomes. Lancet Neurol 2008;7:915-26.
17. Ball J, Carrington MJ, Wood KA, et al. Women versus men with chronic atrial fibrillation: insights from the

Standard versus Atrial Fibrillation spEcific managemenT studY (SAFETY). PLoS One 2013;8:e65795.
18. Benjamin EJ, Levy D, Vaziri SM, et al. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Study. JAMA 1994;271:840-4.
19. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation 2014;130:e199-e267.
20. Salonen Ros H, Lichtenstein P, Bellocco R, et al. Increased risks of circulatory diseases in late pregnancy and puerperium. Epidemiology 2001;12:456-60.
21. Zambrano MD, Miller EC. Maternal stroke: an update. Curr Atheroscler Rep 2019;21:33.