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Original Article

Female gender and mortality risk in decompensated heart failure

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ABSTRACT

Background: Still there is conflicting evidence about gender-related differences in prognosis among patients with heart failure. This prognostic uncertainty may have implications for risk stratification and planning management strategy. The aim of the present study was to explore the association between gender and one-year mortality in patients admitted with acute decompensated heart failure (ADHF).

Methods: We studied 1513 patients. The Cumulative Incidence Function (CIF) method was used to estimate the absolute rate of mortality, heart transplantation (HT)/ventricular assist device (VAD) implantation, and survival free of HT/VAD implantation at 1 year. An interaction analysis was performed to assess the association between covariates, gender, and mortality risk. Propensity score matching and Cox regression were used to compare mortality rates in the gender subgroups.

Results: The CIF estimates of 1-year mortality, HT/VAD implantation, and survival free of HT/VAD implantation at 1 year were 33.1%, 7.0%, and 59.9% for women and 30.2%, 10.2%, and 59.6% for men, respectively. Except for diabetes, there was no significant interaction between gender, covariates, and mortality risk. In the matched cohort, the hazard ratio of death for women was 1.19 (95% confidence intervals [CIs]: 0.90–1.59; p = .202). After adjusting for age and baseline risk, the hazard ratio of death for women was 1.18 (95% CIs: 0.95–1.43; p = .127). The use of gender-specific predictive models did not allow improving the accuracy of risk prediction.

Conclusions: Our data strongly suggest that women and men have comparable outcome in the year following a hospitalization for ADHF.

1. Introduction

Heart Failure (HF) is a growing global health problem [1]. It is estimated that HF afflicts 61 million people worldwide and > 6 million in either the United States or Western Europe [1–3]. Heart failure causes > 1 million hospitalizations annually in both the United States and Europe [4–6]. Acute decompensated HF (ADHF) is the most common clinical presentation and accounts for most mortality in acute HF [4–6]. Despite advances in medical treatment, prognosis of HF remains grim [7,8]. Among ambulatory HF patients, 1-year mortality can range from 7% to 14%, depending on the studies published [9–11]. In addition, more than one in ten patients with reduced left ventricular function (LVEF) undergo heart transplantation (HT) or ventricular assist device (VAD) implantation within one year [12]. Approximately, 30% of the patients admitted with acute HF die within 1 year [8].

Albeit multiple studies consistently demonstrated important differences in clinical phenotype of HF between males and females in terms of pathophysiology, demography, and clinical presentation, still there is conflicting evidence about gender-related differences in prognosis. While some studies reported a better survival for women compared with men [13–22], other studies showed no difference in mortality after adjustment for age [23–30] or even an increased risk for women [31]. Another study suggests that the impact of gender on the risk of mortality following a hospitalization for DCHF may be time-dependent, with most of the excess risk associated with male gender taking place after the first 6 months following discharge [32]. Among patients on waiting list for HT, the relation between gender and mortality is even more complex, with female gender being associated with an increased risk of death among patients initially listed for heart transplantation as United Network of Organ Sharing (UNOS) status 1A and 1B and a lower risk among those listed as UNOS status 2 [33]. Although differences in etiology and left ventricular function have been

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suggested to explain the better prognosis in women, the causes for the potential gender differences in prognosis remain speculative. Gender inequalities in the provision of care also have been noted [34]. Finally, given the major differences in demographic and clinical characteristics between men and women with ADHF, the effect of covariates on the hazard of death may qualitatively and quantitatively differ in women compared with men [30,35–42]. Some studies, indeed, suggest that natriuretic peptides are stronger predictors of mortality in men than in women, while the opposite was suggested for LVEF and coronary artery disease [35,39,41]. This gender-related heterogeneity in prognostic factors might have implications for developing risk models. However, whether gender-specific risk models allow more accurately estimating mortality risk in ADHF is unknown.

These prognostic uncertainties may have implications for risk stratification and planning management strategy. The aim of the present study was to explore the association between female gender and survival in patients admitted with ADHF and to assess whether the use of gender-specific risk models allows more accurately estimating 1-year mortality risk.

2. Methods

One thousand five hundred twenty eight patients admitted to the cardiology wards of the Niguarda Hospital (Milan) and the Maugeri Institutes of Cassano Murge (Bari) and Tradate (Varese) for ADHF were identified using a computer-generated list obtained from our administrative database and by reviewing electronic medical records. Enrollment period varied among the centers but ran from January 2006 to June 2016 overall. Patients were included according to the following criteria: current hospitalization for ADHF, history of HF of at least 1 year, and chronic treatment with standard therapies. Exclusion criteria were: “de novo” acute HF; cardiogenic shock; acute HF developed after admission for another admitting diagnosis or due to acute myocarditis or restrictive cardiomyopathy; acute coronary syndromes or angina pectoris; recent (< 3 months) cardiac surgical or percutaneous procedures; planned coronary revascularization; congenital heart disease; stenotic valvular disease. The study was approved by the Institutional Review Board. Patients' data were deidentified. The primary outcome was all-cause mortality within 1 year after admission.

2.1. Data collection

Information on demographics, medical history, presenting clinical characteristics, laboratory data at admission, echocardiographic findings, and discharge medications were retrieved from the hospital electronic information system at each participating center. Survival status was ascertained by linking with the Health Regional Information System, by interviewing patients, their relatives, and/or their treating physician, or by direct knowledge.

2.2. Statistical analysis

Data are reported as mean and standard deviation (SD) or median with 25th and 75th percentiles for continuous variables or percentage for categorical variables. We used the Student's *t*-test or the Mann-Whitney test to compare continuous variables and the χ^2 test to compare categorical variables.

To investigate the association between gender and time to death, we performed several landmark analyses. 1) We estimated the one-year probability of death, HT/VAD implantation, and survival free of HT/VAD implantation within each gender-subgroup using the Cumulative Incidence Function (CIF) method that accounts for competing events [43]. 2) We performed an interaction analysis to assess the statistical significance of the between-group differences in the hazard ratios of death using a Z test. 3) Since many background covariates were different between women and men, we performed a propensity score analysis to assembly a propensity score-matched cohort. Propensity scores were calculated using multivariable logistic regression. Nineteen baseline variables that were significantly different between genders were included in the model. Matching was performed in a 1:1 ratio using a caliper width of 0.25 of the standard deviation of the linear predictor of the estimated propensity score [44]. The success of matching was evaluated by computing absolute standardized differences in the distribution of patient characteristics in the matched cohort before and after matching. Post-matching standardized differences < 10% indicate successful balance. We used Cox proportional hazards analysis to estimate the hazard of death for women compared with men in the matched cohort. 4) We used the point-based Acute Decompensated Heart Failure (ADHF)/NT-proBNP risk score to estimate the risk-adjusted hazard of death for women compared with men [45]. The ADHF/NT-proBNP risk score was developed and externally validated to predict 1-year mortality in patients admitted with acute decompensated HF [45]. It is based on variables collected at admission. Briefly, it assigns 2 points to chronic obstructive pulmonary disease (COPD); 1 point to systolic blood pressure (SBP) ≤ 100 mm Hg; 3 points or 1 point to estimated glomerular filtration rate < 30 or 30–59 mL/min/1.73 m^2, respectively; 3 points to serum sodium ≤ 135 mmol/L; 3 points to hemoglobin < 13.0 g/dL in men and < 12.0 mg/dL in women; 3 points to NT-proBNP > 5180 pg/mL; 5 points or 3 points to LVEF ≤ 0.20 or 0.21–0.30, respectively; and 2 points to moderate-severe tricuspid regurgitation [45]. The score for each patient is the sum of the points assigned to each risk marker. We performed multivariable Cox regression analysis to calculate the age- and risk-adjusted hazard of death for women compared with men. The performance of the ADHF/NT-proBNP risk score within gender-subgroups also was assessed. 5) Finally, we investigated whether the use of gender-specific risk models allows more accurately estimating 1-year mortality risk compared with a model derived for the total cohort. We performed separate multivariable Cox regression analyses to identify correlates of 1-year mortality in the total cohort and in female and male subgroups. Thus, three multivariable models were developed, two of which were gender-specific. Each model was developed by using a forward stepwise selection approach with $p < .01$ to retain covariates in the model. Then, the model derived from the total cohort was tested separately within each gender subgroup and its predictive ability compared with that of the gender-specific models. Discrimination was assessed by calculating the Harrell C-index. Calibration was assessed with the Grønnesby and Borgan goodness-of-fit test. All analyses were conducted using STATA software, version 14 (Stata-Corp LP, College Station, Tex).

3. Results

Fifteen of the 1528 patients were lost to follow-up, leaving 1513 patients available for analysis. Table 1 shows baseline characteristics of the patients stratified by gender.

3.1. One-year outcomes

During the 1-year follow-up, 463 patients (139 women and 324 men) died and 138 (29 women and 109 men) underwent HT or VAD implantation. In-hospital mortality was 5.1% in women and 4.9% in men ($p = .909$). Fig. 1 shows CIF curves of survival free of HT/VAD implantation, mortality, and HT or VAD implantation at 1 year for women and men. The CIF estimate of 1-year mortality was 33.1% for women and 30.2% for men ($p = .294$). Almost half of all deaths occurred within the first 3 months. Survival free of HT/VAD was 59.9% for females and 59.6% for males. The incidence of HT/VAD implantation was 31% lower in women compared with men. There was no evidence of interaction between year of admission and the primary outcome.