The Israel Nationwide Heart Failure Survey: Sex Differences in Early and Late Mortality for Hospitalized Heart Failure Patients

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ABSTRACT

Background: Current data on the influence of sex on the prognosis of heart failure (HF) are conflicting, possibly owing to the use of different end points and a heterogeneous heart failure population in earlier studies. We sought to evaluate the effect of sex on the risk of early and late mortality outcomes after hospitalization for acute heart failure.

Methods and Results: The prospective cohort study population comprised 2,212 hospitalized patients with acute HF enrolled in a multicenter national survey in Israel. Cox proportional-hazards regression modeling was used to evaluate the effect of sex on the risk of early (≤6 months) and late (>6 months to 4 years) mortality after the index hospitalization. Among the study patients, 998 (45%) were women. Women with HF displayed significantly different clinical characteristics compared with men, including older age, higher frequency of HF with preserved ejection fraction and hypertensive heart disease, and lower percentage of coronary artery disease (all $P < .001$). The fully adjusted multivariable analyses for mortality outcomes showed that women tended toward an increased risk for early (≤6 months) mortality (hazard ratio [HR] 1.16, 95% confidence interval [CI] 0.96−1.41; $P = .13$), whereas men had significantly increased risk for late (>6 months) mortality (HR 1.25, 95% CI 1.09−1.43; $P = .001$).

Conclusions: There are important differences in the clinical characteristics and the short- and long-term outcomes between men and women hospitalized with acute HF after adjusting for multiple confounding variables. (*J Cardiac Fail 2014;20:193−198*)

Key Words: Preventive cardiology, prospective cohort study, sex differences, mortality outcome.

The influence of sex on the prognosis of heart failure (HF) is both complex and unresolved. Women diagnosed with HF have different clinical characteristics from men, thus confounding survival analysis.[1−3] Heart failure is characterized by a chronic course with scattered acute exacerbations occurring at various points in time, which have a grave impact on survival, and functional capacity of HF patients, regardless of sex.[4] Most studies have failed to show a significant difference in the prognosis of men and women hospitalized with HF,[5−9] or have shown improved outcome among women, especially in the nonischemic HF group.[3,10−12] However, those studies were limited by a heterogeneous patient population, comprising both acute and chronic HF patients, and different outcome measures evaluated at different time points in the HF course. The present study was carried out among 2,212 patients enrolled in the Heart Failure Survey in Israel (HFSIS) and was designed to: 1) investigate whether sex exerts a differential risk on early and late mortality after an acute heart failure event; and 2) identify sex-specific predictors of long-term mortality in this population.

Methods

Study Design

The prospective-cohort HFSIS survey was conducted in March and April 2003 in all 25 public hospitals in Israel. The study

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included 93 of the 98 internal medicine and 24 of the 25 cardiology departments in Israel at that time; its design and methods were previously published in detail.[13−15] Included in that study were 2,212 patients ≥50 years of age who were hospitalized with acute new-onset HF or exacerbation of chronic HF (acute-on-chronic). Data abstracted from the HFSIS files for the present study included patients' baseline characteristics such as medical history, New York Heart Association (NYHA) functional classification, HF etiology, vital signs, findings of physical examination, electrocardiography and radiography results; echocardiography data; laboratory indices; preadmission medications; in-hospital complications; and in-hospital mortality. Longer all-cause mortality outcome, up to 4 years after the index hospitalization, was retrieved from the National Population Registry. The study end point for censoring the surviving patients was set to December 31, 2007. The Ethics Committee at each of the participating hospitals approved the study protocol. All data were recorded and analyzed in an anonymous designated computer file.

End Points and Definitions

The end point of the present study was the occurrence of all-cause mortality during 4 years of follow-up. Early and late mortality were prespecified as within ≤6 months and after >6 months of discharge from the index hospitalization, respectively. In-hospital mortality was included in the early mortality outcome and in the overall 4-year cumulative mortality outcome but not in the subset of late (≥6 months) mortality.

Statistical Analysis

For the univariable analysis, percentages were calculated for categoric variables and means with SDs for continuous variables. The chi-square test in case of categoric variables, with continuity correction for 2×2 tables in case of dichotomous variables, and the Student *t* test in case of continuous variables were used for measuring the significance of differences between the percentages of women and men across the baseline characteristics.

We applied multivariable Cox proportional hazards analyses to estimate the hazard ratio (HR) and its 95% confidence interval (CI) for having all-cause mortality outcome in 2 separate fully multivariable-adjusted Cox models for early and late mortality outcome. In this analysis, late mortality was assessed in a landmark model by starting follow-up time for surviving patients at 6 months after enrollment. The full set of prespecified covariates of heart disease, its management, prognosis, or possible confounders of all-cause mortality included in the multivariable models were: age, NYHA functional class, left ventricular ejection fraction (LVEF), systolic blood pressure (SBP) on admission, plasma glucose, total cholesterol levels, estimated glomerular filtration rate (eGFR), obesity, HF as the primary diagnosis, new-onset or acute-on-chronic HF presentation, a co-morbidity index which was the enumeration of the following: hypertension, diabetes mellitus, peripheral vascular disease, chronic obstructive pulmonary disease, past cerebrovascular stroke or myocardial infarction. Also included were the following preadmission (in the early mortality model) or discharge (in the late mortality model) drugs or drug groups: aspirin, clopidogrel, digoxin, angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), beta-blockers, diuretics, calcium channel blockers (CCBs), amiodarone, digoxin, statins, insulin, oral hypoglycemics, and tranquilizers/antidepressants. Log-minus-log plots were drawn and inspected visually for any violation of the proportional hazards assumption within the 2 time periods (early and late) of the 2 separate multivariable Cox models. Because smoking status in the database was based on 1 general question from the baseline survey, with both current and past smoking status together without the ability to separate between the 2, it could merely reflect the substantial smoking rate differences of the past decades between men and women, and therefore would not add a valid explanatory value to the multivariable models of acute HF hospitalization. As such, using this covariate was excluded from our preplanned study design.

Sex-stratified predictors of death were presented in a separate multivariable-adjusted model for the full follow-up period of 4-year mortality outcome. This model included each covariate-by-sex interaction term at a time. The purpose of the additional model was to present the interactions between each multivariable-adjusted variable in the model with sex. All *P* value calculations were 2 tailed and considered to be statistically significant if their value was <.05. The statistical analyses were performed with IBM SPSS version 20.0 (Chicago, Illinois).

Results

Baseline Characteristics

The HFSIS survey included 2,212 patients hospitalized for congestive HF, of whom 998 (45%) were women. The mean study follow-up duration, until mortality or the study end point, was 2.7 ± 1.9 years. The baseline characteristics of the study patients by sex are presented in Table 1. The mean age of the total survey population was 75 ± 10 years, with women being significantly older than men by a mean of 3.6 years ($P < .001$). Hospitalized women had a significantly lower rate than men of systolic dysfunction ($P < .001$), yet, presented with similar baseline NYHA functional classes III−IV. The HF etiology differed between sexes, with women having a significantly lower rate of coronary artery disease and a higher rate of hypertensive and valvular heart disease.

Consistent with these differences, women had a significantly higher rate of SBP ≥140 mm Hg on admission, higher history rates of hypertension, obesity, and diabetes mellitus, and lower rates of previous myocardial infarction and smoking. Compared with men, women presented with fewer comorbidities. This was particularly evident when multiple (≥3) comorbidities existed (25% in women vs 33% in men; $P < .001$).

Significant differences were observed in the rates of prescribed diuretics at discharge (women 82% vs men 76%; $P = .003$), preadmission statins (men 37% vs women 30%; $P = .001$), statins at discharge (men 44% vs women 36%; $P < .001$), and preadmission and discharge CCBs ($P < .001$; Table 2).

Mortality Outcomes

During 4 years of follow-up, 1,435 study patients died (65% total mortality), of whom 795 (55%) were men and 640 (45%) women. The fully adjusted multivariable