CLINICAL PRACTICE

Risk Stratification in Women Enrolled in the Acute Decompensated Heart Failure National Registry Emergency Module (ADHERE-EM)

Deborah B. Diercks, MD, Gregg C. Fonarow, MD, J. Douglas Kirk, MD, Charles L. Emerman, MD, Judd E. Hollander, MD, Jim Edward Weber, DO, Richard L. Summers, MD, Janet Wynne, MS, W. Franklin Peacock IV, MD, for the ADHERE Scientific Advisory Committee and Investigators

Abstract

Objectives: It has been reported that the mortality risk for heart failure differs between men and women. It has been postulated that this is due to differences in comorbid features. Variation in risk profiles by gender may limit the performance of stratification algorithms available for heart failure in women. This analysis examined the ability of a published risk stratification model to predict outcomes in women.

Methods: The Acute Decompensated Heart Failure National Registry Emergency Module (ADHERE-EM) database was used. Characteristics, treatments, and outcomes for men and women were compared. The ADHERE registry classification and regression tree (CART) analysis was used for the risk stratification evaluation.

Results: Of 10,984 ADHERE-EM patients, 5,736 (52.2%) were women. In-hospital mortality was similar between men and women (p = 0.727). Significant differences (p < 0.0002) were noted by gender in all three variables in the CART model (blood urea nitrogen [BUN] ≥ 43 mg/dL, systolic blood pressure < 115 mm Hg, and serum creatinine ≥ 2.75 mg/dL). However, the CART model effectively stratified both genders into distinct risk groups with no significant difference in mortality by gender within stratified groups.

Conclusions: The ADHERE Registry CART tool is effective at predicting risk in ED patients, regardless of gender.

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INTRODUCTION

Cardiovascular disease is the leading cause of death in women, with heart failure being a major cause of death and disability in this population.[1] Women have a lifetime risk of developing heart failure equal to that of men, estimated at one in five.[2,3] Hospitalizations for heart failure are common, with 1,092,000 primary heart failure discharge diagnoses reported in 2004.[4] Of these discharges, 520,000 (48%) occurred in men and 571,000 (52%) in women. In comparison, there were 309,000 discharges for myocardial infarction in women.[4]

Despite the significant number of women hospitalized for acute decompensated heart failure (ADHF), the clinical characteristics, treatments, outcomes, and risk profiles of these women are inadequately understood, particularly in the emergency setting. Analyses of gender differences in heart failure have primarily originated from clinical trial databases. However, women comprise only about 20% of the enrollment in heart failure clinical trials.[5,6] Thus, robust conclusions regarding gender differences in heart failure cannot be drawn from these datasets.

Treatment disparities in women compared to men have been reported in other areas of cardiovascular disease.[7–9] Gender differences in treatment approaches may also be present among patients with ADHF in the emergency setting, but this hypothesis has not been examined in a large, representative data set. Prior studies have established that the pathophysiology, demographics, and presentation characteristics of women with heart failure are different from men, but it is not clear that these differences influence therapeutic selection or clinical outcome in the acute setting.[10–22] In addition, several studies have identified clinical variables that predict short-term mortality in patients with ADHF, but it is not known whether these prognostic markers ascertain risk equally in men and women.[23–29] It is plausible that risk factors for mortality may be disparate in men and women because of gender differences in heart failure characteristics or pathophysiology.

We used the Acute Decompensated Heart Failure National Registry Emergency Module (ADHERE-EM) database to evaluate gender differences in the presentation, treatment, and outcome of patients with ADHF in the emergency department (ED). Analyses were also performed to ascertain differences in the prevalence of established risk factors according to gender and to evaluate the ability of a previously described risk stratification tool to predict mortality in both men and women in the emergency setting.[24]

METHODS

Study Design

This was a retrospective chart review to examine the ability of a published risk-stratification model to predict outcomes in women. All hospitals obtained institutional review or ethics board approval for participation. The data collection system was designed such that patient informed consent was not required.[30]

Study Setting and Population

The ADHERE-EM database was created as part of the ADHERE registry program, and patients were enrolled between January 2004 and September 2005. ADHERE is a large, national, multicenter registry designed to collect data on the demographics, clinical characteristics, treatment patterns, and outcomes of patients hospitalized for ADHF.[30] The data were collected at 83 hospitals, including 53 academic centers. The goal of ADHERE-EM was to specifically characterize the initial ED evaluation, treatment, and subsequent inpatient management of patients presenting to the ED with ADHF. Therefore, the ADHERE-EM contains detailed data regarding the initial ED presentation, treatment, and disposition not contained in the ADHERE registry. This cohort also included all patients presenting to the ED and identified as having a diagnosis of ADHF regardless of their final disposition.

The registry entries consisted of all consecutive adult patients with either an ED or a hospital discharge diagnosis of ADHF, ADHF that was determined to be clinically present by the patient care team, or ADHF as documented in the diagnosis-related group (DRG) code or ambulatory procedure code. The diagnosis of ADHF was based on the DRG in admitted patients. ADHF had to be the focus of treatment for the patient to be included. Importantly, registry participation did not require any alteration of treatment or ED care, and entry of data into the registry was not contingent on the use of any particular therapeutic agent or treatment regimen. Hospitals of various sizes throughout the United States were represented, and both academic and community hospitals were included.

Measures

Demographic, medical history, clinical presentation, laboratory, treatment course, and clinical outcome data were collected and entered into a Health Insurance Portability and Accountability Act of 1996 (HIPAA)-compliant Web-based electronic data capture system using an electronic case report form. Patient identifiers were not collected.

Data Analysis

Descriptive statistics were used to describe gender differences in presentation, demographics, treatments, and laboratory values. A logistic regression model adjusting for baseline covariates that have previously been shown in the main ADHERE registry to be associated with mortality (blood urea nitrogen [BUN], systolic blood pressure [sBP], serum creatinine [SCr], age, and dyspnea at rest)[24] was performed.

For the risk stratification analysis, patients were categorized according to the five risk groups identified by the previously derived and validated classification and regression tree (CART) analysis of the main ADHERE registry: high risk (BUN ≥ 43 mg/dL, sBP < 115 mm Hg, and SCr ≥ 2.75 mg/dL); intermediate risk 1 (BUN ≥ 43 mg/dL, sBP < 115 mm Hg, and SCr < 2.75 mg/dL); intermediate risk 2 (BUN ≥ 43 mg/dL and sBP ≥ 115 mm Hg); intermediate risk 3 (BUN < 43 mg/dL and sBP < 115 mm Hg); and low risk (BUN < 43 mg/dL

and sBP ≥ 115 mm Hg).[24] A complete case analysis was performed. The predictive value of this model was then assessed by determination of mortality odds ratios (ORs) and 95% confidence intervals (CIs) between risk groups for men and women. These analyses were performed using Version 8.2 of SAS software (SAS Institute, Inc., Cary, NC).

RESULTS

A total of 10,984 patient records were available in the ADHERE-EM database. Of these, 5,248 (47.8%) were men and 5,736 (52.2%) were women. Heart failure was the primary discharge diagnosis in 97%, and 83% had heart failure as the ED admitting diagnosis. The mean age of the overall patient population was 73.1 years,

and men were younger than women (Table 1). In the overall patient population, 76% had a prior history of heart failure, 45% had a history of diabetes, and 79% had a history of hypertension. A slightly higher proportion of men had a history of heart failure or diabetes, and more women had a history of hypertension. Preserved systolic function was present in a significantly greater proportion of women compared to men (Table 1).

In-hospital outcomes and procedures were similar among men and women (Figure 1). In-hospital mortality was 3% for men and 2.8% for women (OR 1.04, 95% CI = 0.83 to 1.30). The risk of death was similar between men and women after adjusting for covariates (OR 1.10, 95% CI = 0.86 to 1.40). No gender differences were present in other important in-hospital clinical

Table 1
Baseline Characteristics

Demographics	Men (n = 5,248)	Women (n = 5,736)	p-Value
Age, years (SD)	70.2 (14.4)	75.7 (14.2)	<0.0001
Race, n (%)			
White	3,629 (69.2)	4,091 (71.3)	0.0299
African American	1,144 (21.8)	1,172 (20.4)	
Asian	28 (0.5)	34 (0.6)	
Hispanic	165 (3.1)	136 (2.4)	
Other	53 (1.0)	52 (0.9)	
Unknown	229 (4.4)	251 (4.4)	
Comorbidities			
Prior heart failure, n (%)	4,049 (77)	4,326 (75)	0.0328
LVEF			
Mean (SD)	34 (15.6)	42.9 (17.1)	<0.0001
<40, n (%)	2,753/4,455 (61.8)	1,884/4,776 (39.4)	<0.0001
Atrial fibrillation, n (%)	1,659 (32)	1,888 (33)	0.1447
Hypertension, n (%)	4,065 (77)	4,650 (81)	<0.0001
Diabetes, n (%)	2,402 (46)	2,518 (44)	0.0488
COPD/asthma, n (%)	1,818 (35)	1,863 (32)	0.0165
Chronic dialysis, n (%)	403 (8)	442 (8)	0.9407
Clinical presentation			
Dyspnea at rest, n (%)	1,831 (34.9)	2,051 (35.8)	0.3423
Edema, n (%)	3,417 (65.1)	3,540 (61.7)	0.0002
Rales, n (%)	3,180 (60.6)	3,608 (62.9)	0.01
Elevated JVP, n (%)	1,066 (35.6)	1,057 (31.2)	0.0002
Fatigue, n (%)	1,338 (25.5)	1,603 (27.9)	0.004
sBP			
mm Hg (SD)	143.4 (32.9)	149.9 (33.9)	<0.0001
>140 mm Hg, n (%)	2,585 (49.4)	3,346 (58.5)	<0.0001
<115 mm Hg, n (%)	1,019 (19.5)	844 (14.8)	<0.0001
Heart rate, beats/min (SD)	89.2 (21.6)	89.7 (22.6)	0.22
Oxygen saturation, % (SD)	94.4 (5.7)	93.8 (6.3)	<0.0001
Chest x-ray congestion, n (%)	3,684 (72.4)	4,163 (74.8)	0.004
Laboratory measures			
BNP, pg/mL (SD)	1,260.6 (1136)	1,204.3 (1114.5)	0.03
BUN*			
mg/dL (SD)	31.1 (20)	29.3 (18.5)	<0.0001
mmol/L (SD)	11.1 (7.1)	10.5 (6.6)	
≥43 mg/dL, n (%)	1,080 (20.9)	1,026 (18.1)	0.0003
SCr†			
mg/dL (SD)	1.9 (1.7)	1.7 (1.5)	
μmol/L (SD)	168 (150.3)	150.3 (132.6)	<0.0001
≥2.75 mg/dL, n (%)	619 (11.9)	550 (9.7)	0.0002
Troponin I, μg/L (SD)	0.2 (1.3), n = 2,913	0.4 (6.2), n = 3,179	0.22
Troponin T, μg/L (SD)	0.2 (2.6), n = 715	0.1 (0.5), n = 768	0.28

Dichotomous variables are reported as n (%), and continuous variables are reported as mean (SD).
COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction; JVP = jugular venous pressure; sBP = systolic blood pressure; BNP = B-type natriuretic peptide; BUN = blood urea nitrogen; SCr = serum creatinine.
*To convert from mmol/L to mg/dL, divide by 0.357.
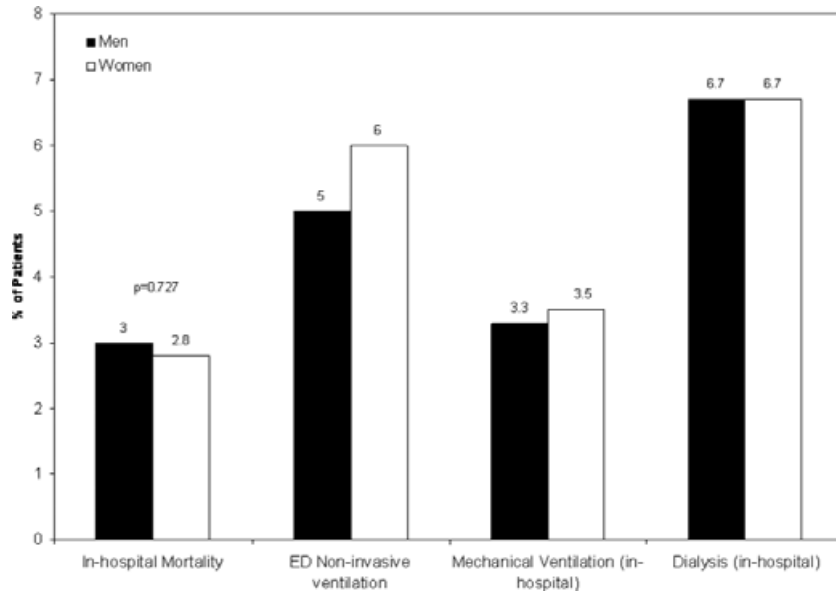†To convert from μmol/L to mg/dL, divide by 88.4.

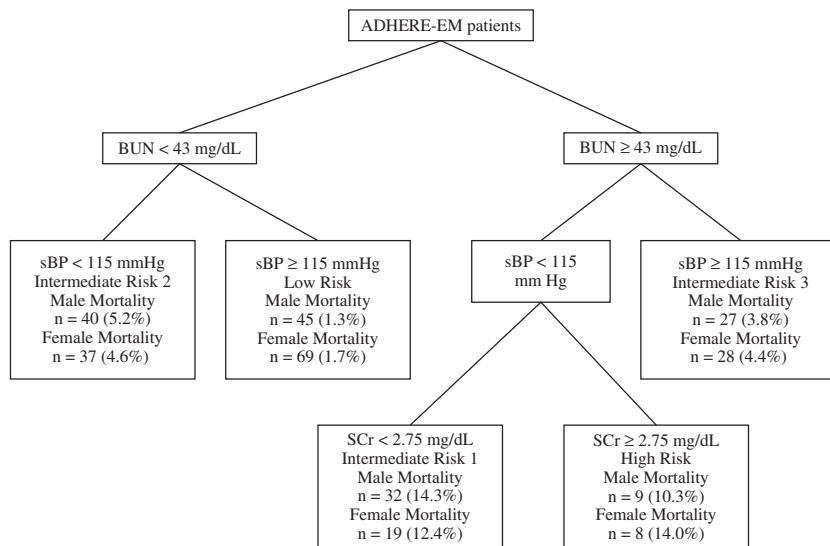**Figure 1.** In-hospital outcomes by gender. (■) Men; (□) women.

Figure 2. Predictors of in-hospital mortality and risk stratification. ADHERE-EM = Acute Decompensated Heart Failure National Registry Emergency Module; BUN = blood urea nitrogen; sBP = systolic blood pressure; SCr = serum creatinine.

procedures, including dialysis or need for mechanical ventilation.

The decision tree generated by CART analysis categorized men and women into high-, intermediate-, and low-risk groups (Figure 2). In the study cohort, 98.5% of all subjects had complete data and were included in the analysis. The clinical characteristics of the five groups by gender are shown in Table 2. Patients in the higher risk groups tended to be older and diabetic and have systolic dysfunction compared to patients in the lower risk groups.

Differences were observed in the proportion of men and women at each risk node. Women were more likely to be in the lowest risk node (OR 1.3, 95% CI = 1.2 to 1.4), while men were more likely to be in the highest risk node (OR 1.7, 95% CI = 1.2 to 2.4). No significant difference in the rate of mortality by gender was

detected within risk categories (Table 3). The risk categorization method stratified in-hospital mortality risk regardless of gender. The mortality OR between the high- and low-risk groups was 9.3 (95% CI = 4.2 to 20.3, p < 0.0001) in women and 8.6 (95% CI = 4.0 to 18.1, p < 0.0001) in men (Table 2). Discrimination between the intermediate-risk and the high-risk group was not as robust.

DISCUSSION

This analysis of the ADHERE-EM registry in ED patients revealed several gender disparities in ADHF clinical characteristics and treatment patterns. Despite these differences, a previously validated risk stratification tool showed good dispersion of risk in both men and women.

Table 2
In-hospital Mortality between Risk Groups

	Females		Males	
	OR (95% CI)	p-Value	OR (95% CI)	p-Value
High vs.				
Low	9.3 (4.2, 20.3)	<0.0001	8.6 (4.0, 18.1)	<0.0001
Intermediate 3	3.6 (1.5, 8.2)	0.0016	2.9 (1.3, 6.4)	0.006
Intermediate 2	3.4 (1.5, 7.7)	0.0018	2.1 (1.0, 4.5)	0.052
Intermediate 1	1.2 (0.5, 2.8)	0.756	0.69 (0.31, 1.5)	0.35
Intermediate 1 vs.				
Low	8.1 (4.7, 13.8)	<0.0001	12.4 (7.7, 20.0)	<0.0001
Intermediate 3	3.1 (1.7, 5.7)	0.0002	4.2 (2.5, 7.2)	<0.0001
Intermediate 2	3.0 (1.7, 5.3)	0.0001	3.0 (1.9, 5.0)	<0.0001
Intermediate 2 vs.				
Low	2.7 (1.8, 4.1)	<0.0001	4.1 (2.7, 6.3)	<0.0001
Intermediate 3	1.0 (0.6, 1.7)	0.8641	1.4 (0.8, 2.3)	0.19
Intermediate 3 vs. low	2.6 (1.7, 4.1)	<0.0001	3.0 (1.8, 4.8)	<0.0001

OR = odds ratio; CI = confidence interval.

Our analysis generated evidence to suggest that in-hospital mortality was not different in men and women at any level of predicted risk based on admission variables. This finding is clinically significant because previous reports have suggested that female gender is associated with a lower mortality risk.[31–38] These previous studies were largely based on clinical trial data sets in the chronic heart failure population, and women have generally been underrepresented in clinical trials.[5,6] In contrast, the ADHERE-EM registry population was 52% women, a factor that enhances the generalizability of our analysis. Consistent with our findings, gender has not been shown to independently predict mortality in other large, representative data sets.[24,25,39] The finding that women have an in-hospital mortality risk similar to that of men has important clinical implications. These data suggest that patients hospitalized with ADHF should receive optimal, evidence-based therapy and appropriate monitoring irrespective of gender. The CART tool, previously developed and validated by Fonarow et al.,[24] effectively predicted in-hospital mortality in both men and women across all risk categories in the ADHERE-EM data set. The ability to accurately risk-stratify patients with ADHF in the ED is critical to ensuring appropriate resource utilization and early implementation of an appropriate therapeutic plan. In addition, utilizing a tool that has good risk differentiation in both men and women may minimize treatment bias attributed to gender.

Systolic blood pressure, SCr, and BUN have been shown in previous models to predict outcome.[23–25,40,41] The predictive risk was not stratified by gender in these analyses. It is plausible that prognostic markers may be gender-specific because of significant differences between men and women in heart failure etiology, pathophysiology, or the prevalence of predictor variables. This has been shown with B-type natriuretic peptide levels. In patients with acute dyspnea, B-type natriuretic peptide values > 500 pg/mL displayed a higher rate of mortality at 24 months in women compared to men (68% vs. 46%, p = 0.015).[42] In addition, women with heart failure tend to be older, and they have higher rates

of hypertension and preserved systolic function.[43–45] Women also tend to present with ischemic heart disease less often.[32] In one study of 5,491 patients admitted with heart failure, women were more likely than men to have a creatinine clearance < 60 mL/minute and a higher left ventricular ejection fraction (LVEF).[36] Data from the ADHERE registry showed that fewer women than men had SCr > 2.0 mg/dL, elevated BUN, or low sBP.[5,39] Differences in the presence of low sBP, SCr ≥ 2.75 mg/dL, and BUN ≥ 43 mg/dL were noted between men and women in this study.

Despite the observed gender differences in the prevalence of discriminatory variables, the CART-derived model was able to stratify risk in men and women to a similar degree. This model performed well in a diverse ED patient population with ADHF identifying a high- and low-risk group, and it also provided useful information independent of gender. This study provides evidence that a model using discriminatory parameters readily available in the ED can be used in conjunction with clinical judgment to identify both men and women who are at highest risk of short-term mortality and who may benefit from a high level of care. In particular, it identified those subjects at either end of the spectrum of risk, which may have the greatest impact on clinical care.

LIMITATIONS

This analysis should be interpreted in the context of several limitations. First, we analyzed episodes of ED presentations and hospitalizations, not unique patients. The treatment differences noted in women with ADHF during the acute management, in-hospital, or discharge time points cannot be solely attributed to disparities in care. Gender-specific variations in pathophysiology, reported symptoms, or preservation of systolic function may require divergent treatment strategies that are clinically appropriate. In addition, the patient's response to the initial diuretic administration was not collected in the database. The data for this analysis were collected by retrospective chart review, and this

Table 3
Clinical Characteristics of Five Risk Groups by Gender

n (%):*	High		Intermediate 1	
	Men, 87 (1.7)	Women, 57 (1.0)	Men, 223 (4.3)	Women, 153 (2.7)
Age, yr (SD)	73.8 (12.4)	78.1 (11.1)	77.0 (12.2)	80.1 (13.3)
Diabetes, n (%)†	44 (50.6)	30 (52.6)	115 (51.6)	65 (42.5)
COPD, n (%)†	39 (44.8)	17 (29.8)	77 (34.5)	51 (33.3)
Systolic dysfunction, n (%) (n = 4,455)†	50 (72.5)	27 (61.4)	149 (73.8)	70 (54.7)
In-hospital mortality, n (%)†	9 (10.3)	8 (14.0)	32 (14.3)	19 (12.4)
Mortality OR (95% CI) (men to women)	0.71 (0.26, 1.95)		1.18 (0.64, 2.17)	

*Percentages are the percentage of gender in each risk group.
†Percentages are the percentage within each column.
COPD = chronic obstructive pulmonary disease; OR = odds ratio; CI = confidence interval.

methodology may not reflect the treating physician's interpretation of symptom severity or acuity, a factor that likely influences treatment. The DRG code was utilized in admitted patients to identify eligible subjects. It is possible that these subjects were not identified as having ADHF in the ED. In addition, the physician's assessment of risk was not obtained; thus, we cannot evaluate the contribution of the risk model above clinical assessment alone. While we observed an association between gender and the ED administration of some therapies, we cannot ascertain from these data whether or not gender was a causative factor in these treatment differences.

This analysis was based on the assumption that discriminatory variables did not differ between the ADHERE-EM and ADHERE core databases. However, the current model defined five distinct categories of risk, suggesting that discriminatory variables were appropriately applied. The intent of this analysis was to identify those at highest risk of death, and therefore in greatest need of aggressive monitoring and care, rather than to determine patients suitable for discharge to home. However, the sample size in the final nodes is small, with wide CIs, therefore limiting the stability of the stratification model. Finally, sites participating in the ADHERE-EM registry were experienced in the management of ADHF, and their treatment approaches may not reflect those of general ED settings.

CONCLUSIONS

We noted variations in clinical parameters included in the CART risk stratification model in women compared to men, in this study of more than 10,000 patients presenting to the ED with ADHF. Women have a risk of in-hospital mortality similar to men, and a risk stratification model accounting for sBP, BUN, and SCr predicted risk similarly between genders. More research is needed to fully understand potential gender differences in ADHF, and future trials should aim to enroll a representative sample of women so that important clinical questions in this population can be addressed.

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Intermediate 2		Intermediate 3		Low	
Men, 766 (14.8)	Women, 811 (14.4)	Men, 706 (13.7)	Women, 640 (11.3)	Men, 3,388 (65.5)	Women, 3,988 (70.6)
72.8 (14.2)	75.6 (14.0)	69.9 (15.2)	74.8 (15.1)	69.2 (14.3)	75.8 (14.1)
461 (60.2)	463 (57.1)	258 (36.5)	231 (36.1)	1,490 (44)	1,691 (42.2)
241 (31.5)	246 (30.3)	262 (37.1)	233 (36.4)	1,172 (34.6)	1,288 (32.3)
352 (56.8)	235 (35.7)	458 (74.4)	265 (50.1)	1,713 (59.0)	1,268 (37.6)
40 (5.2)	37 (4.6)	27 (3.8)	28 (4.4)	45 (1.3)	69 (1.7)
1.15 (0.73, 1.82)		0.87 (0.51, 1.49)		0.76 (0.52, 1.12)	

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