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DIFFERING EFFECTS OF FATIGUE AND DEPRESSION ON HOSPITALIZATIONS IN MEN AND WOMEN WITH HEART FAILURE

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Abstract

Background—In patients with heart failure, worsening of signs and symptoms and depression can affect hospitalization and also each other, resulting in synergistic effects on hospitalizations. A patient's sex may play a role in these effects.

Objectives—To determine the effects of fatigue and depression on all-cause hospitalization rates in the total sample and in subgroups of men and women.

Methods—A secondary analysis was done of data collected January 1, 2010, through December 31, 2012 (N = 582; mean age, 63.2 years [SD, 14.4]). Data were collected on fatigue, depression, sample characteristics, vital signs, results of laboratory tests, medications, and frequency of hospitalization. Patients were categorized into 4 groups on the basis of the *International Classification of Diseases, Ninth Revision*: no fatigue or depression, fatigue only, depression only, and both fatigue and depression. General linear regression was used to analyze the data.

Results—In both the total sample and the subgroups, the number of hospitalizations in patients with both fatigue and depression was greater than the number in patients without either symptom. Among women, the number of hospitalizations in the fatigue-only group and in the depression-only group was greater than that in the group with neither symptom. In men, the number of hospitalizations in the fatigue-only group was greater than that in the group without either symptom.

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Conclusion—Fatigue and depression do not have synergistic effects on hospitalization, but men and women differ in the effects of these symptoms on hospitalization. (*American Journal of Critical Care*. 2016; 25:526–534)

In the United States, the number of patients with heart failure is expected to increase from 5.7 million in 2012 to more than 8 million in 2030.¹ Costs associated with heart failure are expected to skyrocket, from \$31 billion in 2012 to \$70 billion in 2030.¹ Most of these costs are due to high hospitalization rates,^{1,2} and the reason for about 75% of these hospitalizations is exacerbation of signs and symptoms.³ About 50% of patients with heart failure are readmitted to hospitals within 6 months.³ Thus, identifying and managing factors that affect hospitalizations in patients with heart failure are critical.

Fatigue is one of the most common and distressing symptoms in patients with heart failure^{4,5}; about 80% experience it.⁶ Evidence⁷ indicates that fatigue is significantly related to risk for death. In addition, approximately 80% of hospitalized patients who experience heart failure have fatigue before hospitalization.⁸ However, the direct association between fatigue and hospitalizations has not been fully examined. The few investigators^{9,10} who examined factors affecting fatigue found that depression or depressive symptoms were associated with fatigue.

About 30% to 48% of patients with heart failure have depression,^{11,12} and depression has been associated with high rates of hospitalizations in patients with heart failure.^{12,13} In addition, evidence^{10,14,15} suggests that physical signs and symptoms and depression affect each other. Thus, depression and fatigue may have synergistic effects, culminating in hospitalization. However, these synergistic effects have not been examined in patients with heart failure. Because of the high prevalence of fatigue and depression in patients with heart failure, identifying the possible synergistic effects on hospitalizations is important.

Factors that have been associated with hospitalization and either depression or symptoms of heart failure were selected as covariates for hospitalization and for fatigue and depression. Covariates included were demographic factors (eg, age, sex, race or ethnicity, and body mass index),^{16–19} vital signs (eg, blood pressure and heart rate),¹⁷ comorbid conditions (eg, diabetes mellitus, coronary artery diseases, pulmonary disease, renal disease, and cerebrovascular disease),^{16,18} results of laboratory tests (eg, serum levels of creatinine, sodium, hemoglobin, and troponin I),^{9,18} clinical characteristics (eg, left ventricular ejection fraction and New York Heart Association functional class),^{16,18,19} and medications.¹⁶ The results of several studies on heart failure^{19–21} have suggested that fatigue, depression, hospitalization rates, and the factors associated with these 2 symptoms and hospitalization rates differ between men and women. Therefore, we examined the effects of fatigue and depression on hospitalization, including synergistic effects, and compared the effects of fatigue and depression on hospitalization between men and women with heart failure. Adjustments were made for demographic factors, vital signs, comorbid conditions, results of laboratory tests, clinical characteristics, and medications. We compared the effects of both fatigue and depression on hospitalization in 4 groups of patients: those without fatigue and depression (no-symptoms group), those with fatigue only (fatigue-only group), those with

depression only (depression-only group), and those with both fatigue and depression (both-symptoms group).

Methods

Study Design, Setting, and Procedure

This study was a secondary analysis of a database accessed from the University of Arkansas for Medical Sciences, Little Rock, Arkansas, enterprise data warehouse. The study was approved by the University of Arkansas for Medical Sciences institutional review board. The warehouse provided data on all the study variables from January 1, 2010, through December 31, 2012, on patients who had a diagnosis of heart failure as indicated by codes 428 through 428.9 of the *International Classification of Diseases, Ninth Revision (ICD-9)*.²² The warehouse team retrieved data on patients who had heart failure as a primary or secondary diagnosis, and the research team received data on hospitalizations, demographic characteristics (date of birth, sex, marital status, race or ethnicity, and body mass index), vital signs (systolic and diastolic blood pressure and heart rate), comorbid conditions (diabetes mellitus, myocardial infarction, chronic pulmonary heart disease, renal disease, cerebrovascular disease, and cancer), results of laboratory tests (levels of troponin I, albumin, triglycerides, creatinine, sodium, hemoglobin, monocytes, and neutrophils), clinical characteristics (left ventricular ejection fraction and New York Heart Association functional class), and medications (angiotensin-converting enzyme inhibitors, β -blockers, and antidepressants). In addition, data on fatigue and depression were retrieved from data on comorbid conditions by using *ICD-9* codes.

Measures

The number of hospitalizations was the number of all-cause hospitalizations from January 1, 2010, through December 31, 2012 (3 years). Fatigue was defined as a diagnosis of fatigue according to *ICD-9* codes 780.7 through 780.79 at any time during the 3-year period. The *ICD-9* has several diagnoses for fatigue, such as code 780.71 (chronic fatigue syndrome) and code 780.79 (other malaise and fatigue, including fatigue and exhaustion). Depression was defined as a diagnosis of depression as indicated by *ICD-9* codes 296 through 296.36 and 311 at any time during the study period.

Data on demographic and clinical characteristics were used to describe the sample, and some were used as covariates. Age was calculated by subtracting the date of birth from December 31, 2012. Marital status was categorized as never married, married, divorced, widowed, or separated. Race or ethnicity was categorized as white or other races. We used the means of body mass index, vital signs, results of laboratory tests, and clinical characteristics for the 3-year period for our study. Comorbid conditions were identified on the basis of *ICD-9* codes. In addition, data on length of stay (number of hospital days) during all-cause hospitalizations and death were collected.

Data Management and Analysis

Data analysis began with an examination of the variables, including patterns of missing or out-of-range values, frequency distributions, means and standard deviations, and medians

and inter-quartile ranges, as appropriate to the level of measurement of the variables. In the database of 9869 patients, 9287 were excluded because of missing data on covariates. Thus, we used data on 582 patients. The characteristics of this sample are presented in Table 1. Patients in the study sample were younger, had more diagnoses of fatigue and depression, and had a greater number of hospitalizations than did patients excluded from the study. General linear model analysis was used to compare the number of hospitalizations in the 4 symptom groups, with adjustments for covariates. In the model, the symptom group was used as a fixed factor, and socio demographic and clinical characteristics, vital signs, results of laboratory tests, and medications were used as covariates. In the analyses, the both-symptoms group was used as a reference factor to examine the synergistic effects of fatigue and depression on hospitalization. In additional analyses, the no-symptoms group was used as a reference factor to examine whether fatigue only or depression only compared with no symptoms was associated with greater numbers of hospitalizations.

Results

Sample Characteristics

Sample characteristics are presented in Table 1. The mean age of the total sample was 63.2 (SD, 14.4) years. A little more than half of the sample was male (54.6%) and white (51.2%). The mean number of hospitalizations was 3.4 during the 3 years of the study period, and the mortality rate was 37.3%. About 44% of the sample did not experience either fatigue or depression, 29.7% had fatigue only, 10.7% had depression only, and 15.6% had both fatigue and depression. Thus, 45.3% had a diagnosis of fatigue, and 26.3% had a diagnosis of depression. Men and women differed in the patterns of symptoms. More men (50.5%) than women (36.2%) were in the no-symptoms group, more women (14%) than men (7.9%) were in the depression-only group, and more women (21.1%) than men (11%) were in the both-symptoms group. Characteristics of men and women according to symptom groups are presented in Tables 1 and 2. The both-symptoms group had lower heart rates and longer lengths of stay than did all other groups. The both-symptoms group was older and had lower diastolic blood pressure, higher left ventricular ejection fraction, and more emergency department visits than did the no-symptoms group, the depression-only group or the fatigue-only group. Finally, the both-symptoms group had lower systolic blood pressure and more hospitalizations than did the no-symptoms group (Table 2). In addition, more patients in the both-symptoms group were women, were white, and had cerebrovascular disease or cancer compared with patients in some of the other 3 groups.

Effects of Fatigue and Depression on Hospitalization and Factors Associated With Hospitalization

The symptom group variable was associated with the number of all-cause hospitalizations in the total sample and in subgroups of men and women, after adjustments for demographic characteristics, vital signs, comorbid conditions, results of laboratory tests, clinical characteristics, and medications (Table 3). The both-symptoms group had more hospitalizations than the no-symptoms group did ($t = -5.12$; $P < .001$; partial $\eta^2 = .045$) but not more than the depression-only group ($P = .05$) or the fatigue-only group ($P = .39$) in the total sample or in the subgroups of men and women. Thus, fatigue and depression had no

synergistic effects on the number of all-cause hospitalizations. In additional analyses (no table), in the total sample, the depression-only group and the fatigue-only group had more hospitalizations than the no-symptoms group did. The statistics were $t = 2.28$, $P = .02$, partial $\eta^2 = .009$ for depression only, and $t = 5.36$, $P < .001$, and partial $\eta^2 = .050$ for fatigue only. Among men, the fatigue-only group had more hospitalizations than the no-symptom group did ($t = 3.78$; $P < .001$; partial $\eta^2 = .047$), but the depression-only group did not ($P = .23$). In contrast, among women, the fatigue-only group and the depression-only group had more hospitalizations than the no-symptom group did. The statistics were $t = 4.56$, $P < .001$, and partial $\eta^2 = .081$ for the fatigue-only group, and $t = 2.07$, $P = .04$, and partial $\eta^2 = .018$ for the depression-only group.

Furthermore, differences were found between men and women in the factors associated with the number of all-cause hospitalizations (Table 3). In addition to symptom group, in men, age, heart rate, New York Heart Association functional class, diabetes mellitus, cerebrovascular disease, and creatinine level were associated with the number of all-cause hospitalizations, whereas in women, age, myocardial infarction, chronic pulmonary heart disease, renal disease, and hemoglobin level were associated with the number of all-cause hospitalizations.

Discussion

Our findings indicate the importance of fatigue and depression in all-cause hospitalizations in patients with heart failure. The both-symptoms group did not have more hospitalizations than did the fatigue-only group or the depression-only group but did have more hospitalizations than did the no-symptom group. Thus, fatigue and depression did not have synergistic effects on the number of hospitalizations. Our findings also indicate the importance of the diagnoses of fatigue and depression in the number of all-cause hospitalizations and differences between men and women in the relationships between these 2 symptoms and hospitalization. A diagnosis of fatigue was significantly associated with a greater number of all-cause hospitalizations in both men and women, whereas a diagnosis of depression was significantly associated with a greater number of all-cause hospitalizations in women only. Thus, fatigue needs to be addressed in patients with heart failure, and depression needs to be managed, especially in women.

Approximately 80% of patients with heart failure have reported that they experienced fatigue,⁶ and approximately 44% reported that they had profound fatigue.²³ Among our sample, approximately 45% of the patients had a diagnosis of fatigue. Investigators^{4,5} have found that fatigue is one of the most distressing symptoms for patients with heart failure. Fatigue is also associated with mortality risk in heart failure patients.⁷ However, the relationship of fatigue to hospitalization previously had not been fully examined. The findings of the earlier study⁷ and of our study indicate the important roles of fatigue in hospitalization and mortality. Thus, fatigue should be assessed and managed appropriately in patients with heart failure to reduce hospitalization and mortality rates and, in turn, reduce costs. Compared with dyspnea, fatigue improved less during hospitalization, and patients with fatigue at baseline had more experience of worst symptoms at 6 month follow-up ($P = .002$).⁵ These findings imply that more active assessment, diagnosis, and management of

fatigue are needed to lessen fatigue over time. Even though fatigue was reported as one of the most distressing symptoms,^{4,5} not many researchers have investigated factors associated with fatigue.^{9,10} Fink et al⁹ and Evangelista et al¹⁰ found that depression, physical health, and hemoglobin were associated with fatigue.

In addition to the both-symptoms group and the fatigue-only group, the depression-only group had more all-cause hospitalizations than did the no-symptoms group in the total sample and in the subgroup of women. When we combined data on the depression-only group with data on the both-symptoms group, more women (35%) had a diagnosis of depression than did men (19%), and the prevalence of depression in the total sample was approximately 26%. In other studies,^{11,12} prevalence indicated by depressive symptom questionnaires in patients with heart failure has ranged from approximately 30% to 50%. Depression is known to affect hospitalization and mortality in patients with heart failure.^{12,13,24} In addition, the evidence^{10,14,15} suggests that physical signs and symptoms and depression affect each other. Despite the adverse effects of depression on hospitalization, mortality, and physical signs and symptoms, diagnosis and management of depression may be inappropriate in patients with heart failure.

Among our sample, 26% had a diagnosis of depression, and 41% were taking antidepressants. These findings are comparable to those of Jiménez et al.²⁵ In their study of patients with heart failure, approximately 23% of the patients had a diagnosis of depression, 33% were taking antidepressants, and 43% had depressive symptoms, according to scores on the Beck Depression Inventory. Jiménez et al²⁵ also found that 26% of the patients who took anti-depressants did not have a diagnosis of depression when the patients started to take the medications and that cardiologists did not often prescribe anti-depressants. Our findings and those of Jiménez et al²⁵ indicate that clinicians, including cardiologists, need to assess depression more actively, especially in women. Furthermore, in the study by Jiménez et al,²⁵ even though the percentage of patients taking antidepressants was higher than the percentage of patients with a diagnosis of depression, 64% of the depressed patients still had mild to moderate depressive symptoms according to scores on the Beck Depression Inventory. In a study by Faris et al,²⁶ even though 60% of clinically depressed patients with heart failure were taking antidepressants, the depressed patients had higher mortality and hospitalization rates than did nondepressed patients (36% vs 16%, $P = .004$ and 87% vs 74%, $P = .03$, respectively). Thus, more effective treatment and interventions are needed to prevent or reduce the adverse effects of depression on hospitalization and mortality in patients with heart failure.

We found some differences between men and women in factors associated with all-cause hospitalization. Factors associated with number of hospitalizations were age, functional status, comorbid conditions, creatinine level, and symptom group in men and age, comorbid conditions, hemoglobin level, and symptom group in women. The comorbid conditions associated with hospitalization differed between men and women. Thus, these differences should be considered during the development of interventions to reduce hospitalization in these patients.

Our study had some limitations. Patients who were included in the analysis had more fatigue and depression and more severe functional impairment than did those who were excluded. Thus, the generalizability of our findings may be limited. The diagnoses of fatigue and depression were based on data in medical records. In patients with heart failure, the percentage of patients with depression diagnosed by health care providers was less than the percentage of patients with depressive symptoms assessed via a self-report depressive symptom questionnaire.²⁵ Thus, the diagnoses of fatigue and depression might not reflect patients' actual symptom status of fatigue and depression. Dekker²⁷ has divided depressive symptoms into cognitive-affective symptoms and somatic symptoms. Somatic symptoms may overlap with fatigue symptoms, even though when patients with heart failure described depression, they reported cognitive-affective symptoms, not somatic symptoms.²⁷ Because depression in our study was based on *ICD-9* codes, we could not separate depression into cognitive-affective symptoms and somatic symptoms to examine whether symptoms of fatigue and depression overlapped or not. However, our sample included both white patients and patients of other races or ethnic groups and both men and women, and our findings provide a good picture of the relationships of fatigue and depression to hospitalization in heart failure patients with severe conditions. Further studies are needed to develop and test interventions to lessen fatigue and depression and, in turn, reduce hospitalizations of patients with heart failure.

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About 50% of patients with heart failure are readmitted to hospitals within 6 months.

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Depression was defined as a diagnosis of depression as indicated by ICD-9 codes.

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Clinicians, including cardiologists, need to assess depression more actively, especially in women.

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Table 1:

Sample characteristics

Variable	Total sample (N = 582)	Men (n = 317)	Women (n = 265)	Statistics
	Mean (SD)	t	P	
Age, y	63.2 (14.4)	61.4(14.0)	65.4(15.7)	3.30 .001
Blood pressure, mm Hg				
Systolic	135.4(19.6)	133.0 (19.7)	138.2 (19.2)	3.24 .001
Diastolic	78.8 (12.6)	80.2 (13.3)	77.2 (11.5)	-2.91 .004
Heart rate, beats per min	81.2 (12.3)	81.4(12.2)	80.8 (12.3)	-0.58 .56
Body mass index ^a	31.0 (9.1)	30.2 (8.4)	32.1 (9.9)	2.47 .01
LVEF, %	40.8 (15.1)	37.2 (15.0)	45.0 (14.1)	6.41 <.001
Serum levels				
Troponin I, ng/mL	0.7 (3.2)	0.7 (3.0)	0.7 (3.5)	0.04 .97
Albumin, g/dL	.2 (0.6)	3.2 (0.6)	3.2 (0.6)	-0.34 .73
Triglycerides, mg/dL	127.9 (90.9)	117.1 (73.4)	141.1 (106.8)	3.10 .002
Creatinine, mg/dL	1.8 (1.6)	1.9 (1.7)	1.8 (1.6)	-0.48 .63
Sodium, mEq/L	137.1 (2.9)	136.9 (2.9)	137.5 (2.9)	2.46 .01
Hemoglobin, g/dL	11.5 (1.8)	11.8 (1.9)	11.0 (1.6)	-5.75 <.001
Monocytes, x1000/uL ^b	0.7 (0.3)	0.7 (0.3)	0.7 (0.2)	-2.88 .004
Neutrophils, x1000/uL	5.7 (2.5)	5.6 (2.5)	5.8 (2.5)	0.65 .52
No. of hospitalizations ^c	3.4 (3.2)	3.3 (3.3)	3.5 (3.2)	1.05 .42
Length of stay, d	20.7 (26.3)	19.6 (24.6)	21.9 (28.3)	0.82 .29
No. of ED visits ^d	1.8 (3.4)	1.6(2.7)	2.1 (4.0)	1.85 .06
No. (%) of patients				χ^2 P
Male sex	318 (54.6)	NA	NA	NA NA
White race	298 (51.2)	182 (57.4)	116 (43.8)	10.8 .001
Diabetes mellitus	305 (52.4)	159 (50.2)	146 (55.1)	1.4 .24
Myocardial infarction	223 (38.3)	129 (40.7)	94 (35.5)	1.7 .20

Variable	Total sample (N = 582)	Men (n = 317)	Women (n = 265)	Statistics
	Mean (SD)	t	P	
CPHD	85 (14.6)	42 (13.2)	43 (16.2)	1.0 .31
Renal disease	389 (66.8)	212 (66.9)	177 (66.8)	0.0 .98
Cerebrovascular disease	155 (26.6)	71 (22.4)	84(31.7)	6.4 .01
Cancer	145 (24.9)	86 (27.1)	59 (22.3)	1.8 .18
NYHA class II/III	480 (82.5)	256 (80.8)	224 (84.5)	3.4 .18
Use of ACE inhibitors	271 (46.6)	154(48.6)	117 (44.2)	1.1 .29
Use of p-blockers	367 (63.1)	201 (63.4)	166 (62.6)	0.0 .85
Use of antidepressants	241 (41.4)	136 (42.9)	105 (39.6)	0.6 .42
Symptom group				21.2 <.001
No symptoms	256 (44.0)	160 (50.5)	96 (36.2)	
Fatigue only	173 (29.7)	97 (30.6)	76 (28.7)	
Depression only	62 (10.7)	25 (7.9)	37 (14.0)	
Both symptoms	91 (15.6)	35 (11.0)	56 (21.1)	
Death ^e	217 (37.3)	114(36.0)	103 (38.9)	0.5 .47

Abbreviations: ACE, angiotensin-converting enzyme inhibitor; CPHD, chronic pulmonary heart disease; ED, emergency department; LVEF, left ventricular ejection fraction; NA, not applicable; NYHA, New York Heart Association functional class.

SI conversion factors: To convert triglycerides to mmol/L, multiply by 0.0013. To convert creatinine to $\mu\text{mol/L}$, multiply by 88.4.

^aCalculated as weight in kilograms divided by height in meters squared.

^bMonocytes: men, 0.68 (0.24) vs women: 0.74 (0.29).

^cNumber of hospitalizations from January 1, 2010, through December 31, 2012.

^dNumber of ED visits from January 1, 2010, through December 31, 2012.

^eNumber of deaths from January 1, 2010, through December 31, 2012.

Table 2:

Sample characteristics by symptom groups

Variable	Total (N = 582)	No symptom (n = 256)	Depression only (n = 62)	Fatigue only (n = 173)	Both symptoms (n = 91)	Statistics
	Mean (SD)					F P
Age, y	63.2 (14.4)	61.6 (14.0)	59.0 (14.1)	64.5 (14.0)	68.1 (15.2)	6.89 <.001
Blood pressure, mm Hg						
Systolic	135.4(19.6)	137.9 (22.0)	134.6 (15.6)	133.7 (18.3)	131.8 (16.5)	2.89 .04
Diastolic	78.8 (12.6)	80.9 (14.4)	78.1 (11.0)	78.1 (10.9)	74.7 (9.5)	6.03 <.001
Heart rate, beats per min	81.2 (12.3)	81.4(14.0)	83.8 (11.8)	81.4(10.4)	78.2 (9.9)	2.81 .04
Body mass index ^a	31.0 (9.1)	31.6 (9.3)	32.6 (12.5)	29.9 (7.8)	30.7 (8.1)	1.82 .14
LVEF, %	40.8 (15.1)	39.8 (14.9)	43.0 (16.1)	39.6 (14.9)	44.2 (15.0)	2.83 .04
Serum levels						
Troponin I, ng/mL	0.7 (3.2)	0.9 (3.7)	0.6 (2.0)	0.5 (1.7)	0.8 (4.5)	0.62 .60
Albumin, g/dL	3.2 (0.6)	3.2 (0.7)	3.2 (0.6)	3.2 (0.6)	3.1 (0.6)	0.60 .61
Triglycerides, mg/dL	128.0 (90.9)	125.4(83.3)	128.2(80.8)	126.1 (106.1)	138.7(86.9)	0.51 .67
Creatinine, mg/dL	1.8 (1.6)	1.9 (1.5)	1.6 (1.4)	1.9 (1.7)	1.8 (1.9)	0.50 .68
Sodium, mEq/L	137.1 (2.9)	137.1 (3.1)	136.7 (3.1)	137.1 (2.8)	137.5 (2.5)	1.15 .33
Hemoglobin, g/dL	11.5 (1.8)	11.6 (1.9)	11.3 (1.7)	11.4(1.7)	11.3 (1.6)	0.96 .41
Monocytes, x1000/uL ^b	0.7 (0.3)	0.8 (0.3)	0.7 (0.3)	0.7 (0.2)	0.7 (0.2)	3.75 .01
Neutrophils, x1000/uL	5.7 (2.5)	6.1 (2.7)	5.9 (2.7)	5.2(2.1)	5.5 (2.2)	4.85 .002
No. of hospitalizations ^c	3.4 (3.2)	2.4 (1.9)	3.6 (3.0)	4.2 (4.0)	4.5 (4.1)	16.05 <.001
Length of stay, d	20.7 (26.4)	14.4 (20.9)	22.4 (24.3)	23.9 (25.1)	30.9 (37.4)	10.84 <.001
No. of ED visits ^d	1.8 (3.4)	1.2 (2.4)	1.6(2.3)	2.1 (3.5)	2.9 (5.3)	6.80 <.001
No. (%) of patients						
Male sex	317 (54.5)	160 (62.5)	25 (40.3)	97 (56.1)	35 (38.5)	21.2 <.001
White race	298 (51.2)	117 (45.7)	39 (62.9)	86 (49.7)	56 (61.5)	10.5 .01
Diabetes mellitus	305 (52.4)	136 (53.1)	33 (53.2)	87 (50.3)	49 (53.8)	0.4 .93
Myocardial infarction	223 (38.3)	93 (36.3)	19 (30.6)	78 (45.1)	33 (36.3)	5.5 .14

Variable	Total (N = 582)	No symptom (n = 256)	Depression only (n = 62)	Fatigue only (n = 173)	Both symptoms (n = 91)	Statistics	
	Mean (SD)					F	P
CPHD	85 (14.6)	36 (14.1)	6 (9.7)	26 (15.0)	17 (18.7)	2.5	.47
Renal disease	389 (66.8)	163 (63.7)	39 (62.9)	121 (69.9)	66 (72.5)	3.7	.30
Cerebrovascular disease	155 (26.6)	49 (19.1)	17 (27.4)	57 (32.9)	32 (35.2)	14.3	.003
Cancer	145 (24.9)	43 (16.8)	11 (17.7)	53 (30.6)	38 (41.8)	27.6	<.001
NYHA class I/III	480 (82.5)	209 (81.6)	54(87.1)	140 (80.9)	77 (84.6)	2.5	.87
Use of ACE inhibitors	271 (46.6)	124(48.4)	25 (40.3)	77 (44.5)	45 (49.5)	1.9	.59
Use of p-blockers	367 (63.1)	166 (64.8)	38 (61.3)	107 (61.8)	56 (61.5)	0.6	.89
Use of antidepressants	241 (41.4)	109 (42.6)	26 (41.9)	76 (43.9)	30 (33.0)	3.3	.35
Death ^e	217 (37.3)	94 (36.7)	22 (35.5)	66 (38.2)	35 (38.5)	0.2	.97

Abbreviations: ACE, angiotensin-converting enzyme inhibitor; CPHD, chronic pulmonary heart disease; ED, emergency department; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional class.

SI conversion factors: To convert triglycerides to mmol/L, multiply by 0.0013; to convert creatinine to $\mu\text{mol/L}$, multiply by 88.4.

^aCalculated as weight in kilograms divided by height in meters squared.

^bMonocytes: men, 0.68 (0.24) vs women: 0.74 (0.29).

^cNumber of hospitalizations from January 1, 2010, through December 31, 2012.

^dNumber of ED visits from January 1, 2010, through December 31, 2012.

^eNumber of deaths from January 1, 2010, through December 31, 2012.

Table 3:
Effects of fatigue and depression on hospitalization and factors associated with hospitalization

variable	Total sample (N = 582)					Men (n = 317)					Women (n = 265)				
	t	P	95% CI	Partial η^2	t	P	95% CI	Partial η^2	t	P	95% CI	Partial η^2	t	P	95% CI
Age	-3.24	.001	-0.06 to -0.01	.019	-2.89	.004	-0.08 to -0.02	.028	-2.34	.02	-0.06 to <-0.01	.023			
Sex	0.33	.74	-0.44 to 0.63	<.001	NA	NA	NA	NA	NA	NA	NA	NA			
Race	0.96	.34	-0.27 to 0.79	.002	-0.42	.67	-0.90 to 0.58	.001	1.91	.06	-0.03 to 1.64	.015			
Body mass index ^a	-1.30	.20	-0.05 to 0.01	.003	-1.76	.08	-0.09 to <0.01	.011	-0.29	.77	-0.05 to 0.03	<.001			
Blood pressure															
Systolic	-0.43	.67	-0.02 to 0.02	<.001	0.69	.49	-0.02 to 0.04	.002	-1.08	.28	-0.04 to 0.01	.005			
Diastolic	0.51	.61	-0.02 to 0.04	<.001	-1.34	.18	-0.08 to 0.01	.006	1.68	.09	-0.01 to 0.09	.012			
Heart rate	1.08	.28	-0.01 to 0.04	.002	2.45	.02	0.01 to 0.07	.020	-0.84	.40	-0.05 to 0.02	.003			
LVEF	1.72	.09	<-0.01 to 0.04	.005	1.26	.21	-0.01 to 0.04	.005	0.79	.43	-0.02 to 0.04	.003			
NYHA class	2.71	.007	0.22 to 1.38	.013	2.42	.02	0.18 to 1.76	.020	1.64	.10	-0.15 to 1.62	.011			
Use of ACE inhibitors	-0.78	.44	-0.69 to 0.30	.001	-0.47	.64	-0.86 to 0.53	.001	-0.26	.79	-0.81 to 0.62	<.001			
Use of β -blockers	1.66	.10	-0.08 to 0.95	.005	1.03	.30	-0.34 to 1.09	.004	1.10	.27	-0.33 to 1.18	.005			
Use of antidepressants	0.12	.90	-0.44 to 0.51	<.001	-0.51	.61	-0.84 to 0.50	.001	0.43	.67	-0.54 to 0.84	.001			
Diabetes mellitus	2.18	.03	0.06 to 1.09	.009	2.59	.01	0.23 to 1.66	.023	0.78	.44	-0.46 to 1.07	.003			
Myocardial infarction	2.37	.02	0.11 to 1.14	.010	0.32	.75	-0.62 to 0.86	<.001	3.45	.001	0.56 to 2.07	.048			
CPHD	2.94	.003	0.34 to 1.70	.015	1.26	.21	-0.36 to 1.63	.005	2.98	.003	0.48 to 2.37	.036			
Renal disease	3.24	.001	0.37 to 1.50	.019	1.07	.29	-0.36 to 1.23	.004	3.96	<.001	0.84 to 2.50	.062			
Cerebrovascular disease	3.38	.001	0.40 to 1.52	.020	2.69	.008	0.30 to 1.96	.024	1.50	.14	-0.18 to 1.34	.009			
Cancer	1.42	.16	-0.16 to 1.01	.004	0.94	.35	-0.44 to 1.24	.003	1.00	.32	-0.42 to 1.30	.004			
Serum levels															
Troponin I	-0.94	.35	-0.11 to 0.04	.002	-0.40	.69	-0.14 to 0.09	.001	-1.05	.30	-0.16 to 0.05	.005			
Albumin	-0.16	.87	-0.46 to 0.39	<.001	0.27	.79	-0.53 to 0.70	<.001	-0.47	.64	-0.77 to 0.47	.001			
Triglycerides	-1.98	.05	<-0.01 to <-0.01	.007	-1.54	.12	-0.01 to <0.01	.008	-1.34	.18	-0.01 to <0.01	.008			
Creatinine	3.34	.001	0.12 to 0.45	.020	4.03	<.001	0.24 to 0.68	.053	0.20	.84	-0.23 to 0.28	<.001			
Sodium	-0.97	.34	-0.13 to 0.04	.002	0.57	.57	-0.09 to 0.16	.001	-1.25	.21	-0.21 to 0.05	.007			

variable	Total sample (N = 582)					Men (n = 317)					Women (n = 265)				
	t	P	95% CI	Partial η^2	t	P	95% CI	Partial η^2	t	P	95% CI	Partial η^2	t	P	95% CI
Hemoglobin	-2.55	.01	-0.38 to -0.05	.012	-1.37	.17	-0.37 to 0.07	.006	-2.35	.02	-0.57 to -0.05	.023			
Monocytes	-0.40	.69	-1.28 to 0.85	<.001	-0.56	.57	-1.80 to 1.00	.001	-0.36	.72	-2.08 to 1.44	.001			
Neutrophils	1.19	.23	-0.05 to 0.19	.003	1.92	.06	<-0.01 to 0.33	.013	0.23	.82	-0.15 to 0.19	<.001			
Symptom group															
No symptoms	-5.12	<.001	-2.61 to -1.16	.045	-3.23	.001	-3.07 to 0.75	.035	-4.10	<.001	-2.91 to -1.02	.066			
Depression only	-1.94	.05	-1.89 to 0.01	.007	-1.39	.17	-2.71 to 0.47	.007	-1.39	.17	-2.00 to 0.34	.008			
Fatigue only	-0.86	.39	-1.06 to 0.42	.001	-0.61	.54	-1.54 to 0.81	.001	0.02	.98	-0.97 to 0.99	<.001			
Both symptoms			Reference				Reference				Reference				

Abbreviations: ACE, angiotensin-converting enzyme inhibitor; CPHD, chronic pulmonary heart disease; LVEF, left ventricular ejection fraction; NA, not applicable; NYHA, New York Heart Association functional class.

SI conversion factors: To convert triglycerides to mmol/L, multiply by 0.0013. To convert creatinine to $\mu\text{mol/L}$, multiply by 88.4.

^dCalculated as weight in kilograms divided by height in meters squared.