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The Association of Co-morbid Symptoms of Depression and Anxiety with All-Cause Mortality and Cardiac Rehospitalization in Patients with Heart failure

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Abstract

Background—Patients with heart failure (HF) experience multiple psychological symptoms. Depression and anxiety are independently associated with survival. Whether co-morbid symptoms of anxiety and depression are associated with outcomes in patients with HF is unknown.

Objective—To determine whether co-morbid symptoms of depression and anxiety are associated with all-cause mortality or rehospitalization for cardiac causes in patients with HF.

Method—A total of 1,260 HF patients participated. Cox regression analysis was used to determine whether co-morbid symptoms of depression and anxiety independently predicted all-cause mortality and cardiac rehospitalization. Anxiety and depression were treated first as continuous level variables, then as categorical variables using standard published cut points. Patients were then divided into four groups based on the presence of anxiety and depression symptoms.

Results—When entered as a continuous variable, the interaction between anxiety and depression (HR 1.02; 95% CI: 1.01-1.03; $p = 0.002$) was a significant predictor of all-cause mortality in HF patients. When entered as a categorical variable, co-morbid symptoms of depression and anxiety (versus no symptoms, or symptoms of anxiety or depression alone) independently predicted all-cause mortality (HR 2.59; 95% CI: 1.49-4.49; $p = 0.001$). None of the psychological variables was a predictor of cardiac rehospitalization in HF patients whether using the continuous or categorical level of measurement.

Conclusion—To improve mortality outcomes in patient with HF, attention must be paid by healthcare providers to the assessment and management of co-morbid symptoms of depression and anxiety.

Keywords

Heart failure; Depression; Anxiety; Mortality; Rehospitalization

1. Introduction

In the United States, heart failure (HF) is a major public health problem that affects around 5.7 million patients, with 670,000 newly diagnosed patients each year (1). The total costs of HF in the United States are estimated to be \$37 billion each year (1). Although there have been significant therapeutic advances in pharmacological and surgical treatment of HF, the one-year mortality rate of HF patients with progressive symptoms still approaches 40%, which is the same for some types of aggressive cancer (2, 3). Even patients who have less serious HF symptoms usually experience impaired quality of life (3). The high mortality and morbidity rates associated with HF are still not well explained (4). Patients with HF simultaneously experience multiple psychological symptoms that affect health outcomes such as symptoms of depression and anxiety.

Depression is a mood disorder that interferes with an individual's ability to perform daily life activities (5, 6). Depression is characterized by specific symptoms such as changes in appetite, sleep disturbance, fatigue, agitation, feelings of guilt or worthlessness, and concentration problems (7-9). Depression is a significant clinical problem that is found in a

substantial number of patients with HF; around 20% of outpatients who have HF have major depressive symptoms, and up to 48% of outpatients experience clinically significant depressive symptoms (10). Furthermore, HF patients who are depressed are two times more likely to be hospitalized and face death than those who are not depressed (11). Depression is associated with unhealthy behaviors like smoking and unsatisfactory patient compliance (12, 13). Moreover, depression is associated with pathophysiological mechanisms that negatively affect cardiac conditions, such as hypercortisolemia, impaired platelet function, and reduced heart rate variability (14-17).

Anxiety is a negative emotional state resulting from the perception of threat, and is described as the result of a perceived inability to predict, control, or gain from the threatening situation (5, 7). Anxiety is significantly associated with a higher occurrence of adverse cardiac events and cardiac death in the general population and in patients with coronary artery disease (5, 18). Anxiety also has been linked to pathophysiological mechanisms that could mediate negative outcomes such as reduced heart rate variability and baroreflex cardiac control, cardiac arrhythmias, and sudden death (19-21). Patients with HF have a 60% higher level of anxiety compared to healthy elders; 40% percent of patients suffer from major anxiety (7, 22, 23). In addition, patients with HF tend to have higher levels of anxiety compared to other cardiac disease patients or even cancer and lung patients. There are, however, contradictory results about the association between anxiety and health outcomes in patients with HF (24, 25).

Individually, depression and anxiety are associated with survival in HF patients; however, the association of co-morbid symptoms of anxiety and depression with morbidity and mortality in patient with HF is unknown. Thus, the purpose of this study was to examine whether co-morbid symptoms of depression and anxiety are associated with all-cause mortality or rehospitalization for cardiac causes in patients with HF.

2. Method

2.1. Design, sample, and setting

Data from this study were from the Heart Failure Health-Related Quality of Life Collaborative Registry (26), housed at the University of Kentucky College of Nursing. This is a longitudinal database that includes data from patients from across the United States and from several international sites ($n = 4076$). From this database, we analyzed data from all patients who had data on anxiety, depression, and mortality and rehospitalization outcomes ($n = 1,260$). The demographics (i.e., age, gender, and ethnicity) and New York Heart Association (NYHA) class of the sample used in the current study were compared statistically to those in the registry who did not have data on anxiety, depression and outcomes. There were no differences between these two groups on these four variables. The database was accessed through the Research and Interventions for Cardiovascular Health (RICH) program at the University of Kentucky. Inclusion criteria for the original database were patients with a confirmed diagnosis of HF with impaired or preserved left ventricular systolic function. Patients were excluded if they had valvular heart disease, were referred for heart transplantation, had a history of cerebrovascular accident or myocardial infarction in

the past 6 months, had a co-existing terminal illness. Data on mortality and rehospitalization were collected over 12 months (27, 28).

2.2. Measures

2.2.1. Symptoms of Depression and Anxiety

Depressive symptoms: The Patient Health Questionnaire (PHQ-9) (29, 30) was used to measure depressive symptoms in this study. The PHQ-9 is a 9-item, self-reported measure of depression that reflects the severity of depressive symptoms over the past two weeks. (31, 32) Patients respond to each item by using a Likert scale in which responses range from 0 (not at all) to 3 (nearly every day). The total summary score can range from 0 to 27; a higher score reflects more severe depressive symptoms. Good internal consistency, stability, construct and concurrent validity of the PHQ-9 have been supported (28, 32). The standard published cut point of 10 was selected in this study for PHQ-9 to identify those in the sample who were depressed and those who were not depressed (28). This cut point was reported to have 88% sensitivity and 88% specificity for diagnosing major depression.(31, 32)

Anxiety: The Brief Symptom Inventory (BSI) anxiety subscale was used to measure current symptoms of anxiety (33, 34). The subscale consists of 6 questions, each of which are scored by patients using a scale that ranges from 0 (not at all) to 4 (extremely). The total score is calculated by summing all 6 item scores and taking the mean. Thus, the possible range of scores for the anxiety scale is 0 to 4 with higher scores indicative of higher levels of anxiety. The BSI has demonstrated internal consistency, stability, construct and concurrent validity in other studies (33, 34). In this study, the Cronbach's alpha of the anxiety scale was 0.82. A standard published mean of 0.35 was used in this study for BSI to identify those in the sample who were anxious and those who were not anxious (35).

2.2.2. Mortality and Rehospitalization Outcomes—All-cause mortality, or rehospitalization for cardiac causes were the outcome variables in this study. By monthly phone call follow up and by reviewing electronic and non-electronic hospital medical records, all dates of and reasons for hospitalization and death were collected. Furthermore, death certificates were acquired to confirm the cause of death. Patients were followed for at least 12 months.

2.2.3. Demographic and clinical variables—Data on demographic variables and clinical characteristics were collected by reviewing medical records and interviewing patients. These variables included age, gender, ethnicity, and New York Heart Association (NYHA) class. The NYHA class indicates the level of functional impairment reported by patients as a result of symptoms and was rated by trained research nurses. These variables were selected because of their effects on the outcome variable as suggested in the literature (28, 31).

2.3. Statistical Analysis

Data were analyzed using SPSS software, version 20.0 (SPSS Inc., Chicago, IL). Descriptive statistics, including mean, standard deviation and frequency distribution, were

used to describe sample characteristics. In the main analysis, anxiety and depression were treated first as continuous level variables, then as categorical variables. In order to create the categories, variables were created for each individual describing the presence of depression and anxiety using published, standard cut points (10 and 0.35, respectively). Patients were then divided into the following four groups: 1) patients who had neither depression nor anxiety; 2) patients who had depression; 3) patients who had anxiety; and 4) patients who had comorbid anxiety and depression. Sample socio-demographic and clinical characteristics (i.e., age, gender, ethnicity, NYHA class, anxiety level and depression level) between the four groups were compared using χ^2 or ANOVA as appropriate to the level of measurement. Hierarchical Cox regression analyses were used to determine whether co-morbid symptoms of depression and anxiety, independently, predicted mortality alone, or cardiac rehospitalization alone. Data were forced into the regression in order to provide simultaneous control. The following covariates were considered: age, gender, ethnicity, NYHA class, and anxiety and depression. We first tested the interaction term defining the continuous level variables for anxiety and depression, and the outcomes. We next tested the grouping variables identifying co-morbid depression and anxiety status. The assumptions of hierarchical Cox regression were tested and no violation occurred. A p-value of 0.05 was considered statistically significant.

3. Results

Demographic and clinical characteristics of patients (N = 1,260) are summarized in Table 1. The mean levels of anxiety and depression were 0.82 with a SD of 0.92, 7.48 with a SD of 6.22, respectively. Using the clinically defined cut points, 52.9 % of the participants were anxious and 32.5% were depressed. When the sample was divided into the four predefined groups, a total of 5.7% of the patients had depressive symptoms only, 26.1% had anxiety symptoms only, and 26.8% had co-morbid symptoms of anxiety and depression. Eighty-two (6.5%) of the participants died and 182 (14.4%) were hospitalized during the study.

Hierarchical Cox regression was run with anxiety and depression treated as continuous level variables and all-cause mortality as the outcome. In the first block in which demographic variables were entered, only older age was a significant predictor of all-cause mortality. In the second block, NYHA class was entered to the model. Age remained a significant predictor. Additionally, worse NYHA functional class was a significant predictor in this block. In the final block, age (HR 1.03; 95% CI: 1.01-1.05; $p = 0.009$), worse NYHA class (HR 3.90; 95% CI: 2.39-6.36; $p < 0.001$), and higher levels of depression (HR 1.06; 95% CI: 1.01-1.11; $p = 0.012$) were significant predictors of all-cause mortality among HF patients. The interaction between anxiety and depression (HR 1.02; 95% CI: 1.01-1.03; $p = 0.002$) was also a significant predictor of all-cause mortality. However, anxiety (HR 1.07; 95% CI: 0.79-1.45; $p = 0.652$) was not a significant predictor of all-cause mortality (Table 2).

Another hierarchical Cox regression was run with anxiety and depression treated as continuous level variables and cardiac rehospitalization as the outcome. In the first block in which demographic variables were entered, older age, female gender, and ethnicity (African Americans compared to Caucasians, and Caucasians compared to other ethnicities) were significant predictors of cardiac rehospitalization. In the second block, NYHA class was

entered to the model. All previous variables remained significant predictors. Additionally, worse NYHA functional class was a significant predictor in this block. In the final block, anxiety, depression, and the interaction between anxiety and depression were entered to the model. Age (HR 0.99; 95% CI: 0.97-1.00; $p = 0.016$), female gender (HR 1.40; 95% CI: 1.01-1.94; $p = 0.042$), African Americans ethnicity compared to Caucasians ethnicity (HR 2.43; 95% CI: 1.67-3.54; $p < 0.001$), and Caucasians ethnicity compared to other ethnicities (HR 0.30; 95% CI: 0.10 - 0.95; $p = 0.040$), and worse NYHA functional class (HR 2.62; 95% CI: 1.94-3.55; $p < 0.001$) were significant predictors of cardiac rehospitalization among HF patients. However, anxiety (HR 0.93; 95% CI: 0.75-1.15; $p = 0.505$), depression (HR 1.02; 95% CI: 0.99-1.05; $p = 0.290$), and the interaction between anxiety and depression (HR 1.00; 95% CI: 1.00-1.01; $p = 0.648$) were not significant predictor of cardiac rehospitalization (Table 3).

In the next analysis, anxiety and depression were treated as categorical variables and the four categories previously defined were entered in a hierarchical cox regression to predict all-cause mortality (Table 4). In the first block in which demographic variables were entered, only older age was a significant predictor of all-cause mortality. In the second block, NYHA class was entered to the model. Age remained a significant predictor. Additionally, worse NYHA functional class was a significant predictor in this block. In the final block, the four anxiety and depression groups were entered into the model. The final model demonstrated that that older age, worse NYHA class, and comorbid anxiety and depression were the significant predictors of all-cause mortality. In this analysis neither anxiety alone or depression alone were significant predictors of all-cause mortality among HF patients (Figure 1). Based on these results, HF patients with comorbid anxiety and depression are 2.6 times more likely to die compared to those who are neither depressed nor anxious (Table 4 and Figure 1).

A final hierarchical Cox regression was used where anxiety and depression were treated as categorical variables to predict cardiac rehospitalization (Table 5). In the first block in which demographic variables were entered, older age, female gender, African American ethnicity compared to Caucasian, and Caucasian ethnicity compared to other ethnicities were significant predictors of cardiac rehospitalization. In the second block, NYHA class was entered to the model. Age, gender, and ethnicity remained significant predictors. Additionally, worse NYHA functional class was a significant predictor in this block. In the final block, the four anxiety and depression groups were entered into the model. The final model demonstrated that that older age, female gender, African American ethnicity compared to Caucasian, Caucasian ethnicity compared to other ethnicities, and worse NYHA class were the significant predictors of cardiac rehospitalization. In this analysis neither anxiety alone, depression alone, or comorbid anxiety and depression were significant predictors of cardiac rehospitalization among HF patients (Table 5 and Figure 2).

4. Discussion

Several important findings are evident from this study. First, anxiety and depressive symptoms are common and are commonly comorbid in patients with HF. The majority of our sample experienced symptoms of depression or anxiety, or both. Second, we

demonstrated that comorbid anxiety and depressive symptoms, when considered as a clinically relevant categorical variable, was predictive of all-cause mortality, while anxiety and depressive symptoms considered alone were not independent predictors of the same outcome. When treated as continuous level variables, both comorbid depression and anxiety, and depression alone were significant predictors of all-cause mortality. None of the psychological variables were predictive of the cardiac rehospitalization outcome, regardless of whether entered as continuous or categorical level variables. The findings of this study emphasize the hazardous effects of comorbid anxiety and depressive symptoms on the mortality rate of adults with HF.

More than 50% of HF patients suffer from significant symptoms of anxiety or depression (7, 22, 23). HF patients' mortality rate is around 40% within the first year of diagnosis despite current medical and surgical advances (2, 3). Because anxiety and depression have been consistently associated with poorer health outcomes (24, 25), we wanted to examine whether they also explained the high rates of mortality among HF patients.

This study is one of few to investigate comorbid anxiety and depression and its effect on all-cause mortality and cardiac rehospitalization in patients with HF. Frasure-Smith and colleagues found that anxiety and depression were associated with cardiac mortality using a single instrument (the General Health Questionnaire-20) to assess psychological distress. However, these researchers did not control for disease severity, age, and other risk factors. In addition, the additive effect of anxiety and depression was not studied (36). In another study by Doering and colleagues (37), researchers focused on mortality and demonstrated that co-morbid anxiety and depression were predictive of all-cause mortality in patients with coronary artery disease, but did not study hospitalizations. Doering et al. also used the Multiple Adjective Affect Checklist (MAACL-D) to measure depression (37). However, in the HF population, the PHQ-9 is considered one of the best instruments to measure depression (31, 32). In addition, Doering et al treated depression and anxiety as a categorical variables without consideration of these variables treated at the continuous level, which may mask expression of the phenomenon.

Our study is unique in its focus on comorbid anxiety and depression and its effect on cardiac rehospitalization and mortality for all causes in HF patients. Our strengths included the use of valid and reliable instruments to measure depression and anxiety symptoms in patients with HF, and a large sample size. Furthermore, we treated anxiety, depression, and both as continuous-level and categorical-level variables, and we controlled for multiple covariates such as age, gender, ethnicity, and NYHA class.

Our study showed that depression alone, and the interaction of depression and anxiety are the only significant psychological predictors of all-cause mortality among HF patients when we included continuous measures of anxiety, depression, and the interaction between anxiety and depression in our model. When we conducted the analysis using categorical variables, we found that comorbid anxiety and depression was the only significant psychological predictor; neither anxiety nor depression alone was a significant predictor. For depression alone, the lack of significance may be explained by the low number of individuals who had depression alone (n=72). However, when we run the analysis again

using an unadjusted model, depression alone (HR 2.53; 95% CI: 1.04-6.16; $p = 0.042$) was a significant predictor of all-cause mortality among HF patients. This finding suggests that sample size alone does not explain the failure of depression to independently predict the outcome, but rather, suggests that depression, in the company of other psychological, demographic and clinical predictors of outcomes, depression alone is not an independent predictor.

Our results that psychological factors are important mechanisms for the high mortality rate in HF. Anxiety and depression are strongly associated with unhealthy practices such as smoking, drinking, and unsatisfactory patient compliance (12, 13). They are also associated with physiological changes that can lead to hospitalization and death such as hypercortisolemia, impaired platelet function, reduced heart rate variability, cardiac arrhythmias, and sudden death (14-17),(19-21). Thus, these behavioral and physiological factors associated with anxiety and depression likely contribute to the continuing high morbidity and mortality in HF.

5. Study limitations

A potential limitation of our study was the use of self-reported measurement of symptoms of anxiety and depression, rather than diagnostic interviews. However, a strict protocol was used to measure anxiety and depression, and we and others have previously demonstrated the reliability and validity of the self-report instruments used in patients with HF (38-41). Another possible limitation was the absence of treatment, and failure to adjust for some covariate such as smoking and alcohol consumption that may contribute to the phenomena. However, the major covariates, age, gender, ethnicity, and NYHA class, were controlled for in this study. This, along with the large sample size, are strengths of the study.

6. Conclusion

Our findings have clinical and research implications. Comorbid anxiety and depression symptoms are a better predictor of death in HF patients than anxiety or depression alone. Thus, to improve outcomes in patients with HF, attention must be paid by healthcare providers to the assessment and management of co-morbid symptoms of depression and anxiety. Future studies should investigate and evaluate strategies or methods that able to screen and treat depression and anxiety symptoms in HF patients effectively.

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Figure 1.
All-cause mortality according to co-morbid symptoms of depression and anxiety

Figure 2. Cardiac rehospitalization according to co-morbid symptoms of depression and anxiety

Figure 2.
Cardiac rehospitalization according to co-morbid symptoms of depression and anxiety

Table 1

Sample baseline characteristics (N = 1260)

Characteristic	N (%) OR MEAN $\pm$ SD
Age	63.57 $\pm$ 13
Anxiety score	0.82 $\pm$ 0.92
Depressive symptoms score	7.48 $\pm$ 6.22
Gender	
Male	804 (63.8)
Female	456 (36.2)
Ethnicity	
Caucasian	1017 (80.7)
African American	153 (12.1)
Other	90 (7.1)
NYHA class	
I/II	664 (52.7)
III/IV	596 (47.3)
Anxiety and depression categories	
No Anxiety or Depression	521 (41.3)
Depression Only	72 (5.7)
Anxiety Only	329 (26.1)
Co-morbid Anxiety and Depression	338 (26.8)

Table 2

Cox proportional hazard regression of variables associated with all-cause mortality in patients with HF, and anxiety and depression treated as continuous level variables.

Predictor Variables	Exp.(B)	95% CI	P
Age	1.03	1.01 – 1.05	0.009
Female Gender	1.06	0.67 – 1.68	0.805
African American compared to Caucasian	0.30	0.07 – 1.23	0.095
Caucasian compared to ethnicity other than African American	4.85	0.17 – 1.76	0.315
NYHA class III/IV compared to I/II	3.90	2.39 – 6.36	< 0.001
Anxiety	1.07	0.79 – 1.45	0.652
Depression	1.06	1.01–1.11	0.012
Anxiety*Depression	1.02	1.01– 1.03	0.002

Overall Model ($\chi^2 = 60.08$, df. = 6; p <0.001)

Table 3

Cox proportional hazard regression of variables associated with cardiac event-free survival, defined as the composite of cardiac hospitalization or death due to all causes in patients with HF, and anxiety and depression treated as categorical variables.

Predictor Variables	Exp.(B)	95% CI	P
Block I			
Age	1.00	0.99-1.01	0.69
Female Gender	1.29	0.99-1.68	0.06
African American compared to Caucasian	1.78	1.25-2.53	0.001
Caucasian compared to ethnicity other than African American	4.53	1.91-10.72	0.001
Block II			
Age	1.00	0.99-1.01	0.69
Female Gender	1.28	0.98-1.67	0.07
African American compared to Caucasian	1.80	1.25-2.53	0.001
Caucasian compared to ethnicity other than African American	4.58	1.93-10.83	0.001
NYHA class III/IV compared to I/II	2.98	2.31-3.84	<0.001
Block III (Final Model)			
Age	1.00	0.99 – 1.01	0.85
Female Gender	1.33	1.02 – 1.73	0.04
African American compared to Caucasian	1.83	1.28 – 2.60	0.001
Caucasian compared to ethnicity other than African American	4.66	1.97 – 11.04	<0.001
NYHA class III/IV compared to I/II	2.78	2.14 – 3.61	<0.001
Depression Only	1.22	0.71 – 2.08	0.47
Anxiety Only	1.10	0.80 – 1.50	0.56
Comorbid Anxiety and Depression	1.50	1.10 – 2.03	0.01

Overall Model ($\chi^2 = 108.18$, df. = 8; p <0.001)

Table 4

Cox proportional hazard regression of variables associated with all-cause mortality in patients with HF, and anxiety and depression treated as categorical variables.

Predictor Variables	Exp.(B)	95% CI	P
Block I			
Age	1.01	1.00-1.04	0.021
Female Gender	0.94	0.60-1.50	0.806
African American compared to Caucasian	0.30	0.07-1.23	0.094
Caucasian compared to ethnicity other than African American	0.37	0.19-1.88	0.374
Block II			
Age	1.02	1.00-1.04	0.048
Female Gender	0.98	0.62-1.55	0.929
African American compared to Caucasian	0.28	0.07-1.17	0.081
Caucasian compared to ethnicity other than African American	0.56	0.18-1.77	0.323
NYHA class III/IV compared to I/II	4.19	2.58-6.81	<0.001
Block III (Final Model)			
Age	1.03	1.01 – 1.05	0.006
Female Gender	0.92	0.58 – 1.45	0.717
African American compared to Caucasian	0.57	0.18 v 1.80	0.094
Caucasian compared to ethnicity other than African American	4.66	2.20 – 5.94	0.335
NYHA class III/IV compared to I/II	3.62	2.14 – 3.61	<0.001
Depression Only	1.67	0.68 – 4.12	0.263
Anxiety Only	1.35	0.74 – 2.46	0.332
Comorbid Anxiety and Depression	2.59	1.49 – 4.49	0.001

Overall Model ($\chi^2 = 62.78$, df. = 8; p <0.001)

Table 5

Cox proportional hazard regression of variables associated with cardiac rehospitalization in patients with HF, and anxiety and depression treated as categorical variables.

Predictor Variables	Exp.(B)	95% CI	P
Block I			
Age	0.99	0.98-1.00	0.036
Female Gender	0.71	0.52-0.99	0.040
African American compared to Caucasian	2.49	1.71-3.61	<0.001
Caucasian compared to ethnicity other than African American	0.31	0.10-0.97	0.044
Block II			
Age	0.99	0.97-1.00	0.018
Female Gender	0.71	0.52-0.99	0.040
African American compared to Caucasian	2.44	1.69-3.56	<0.001
Caucasian compared to ethnicity other than African American	0.30	0.10-0.94	0.040
NYHA class III/IV compared to I/II	2.60	1.60-3.50	<0.001
Block III (Final Model)			
Age	0.99	0.97 - 0.99	0.035
Female Gender	0.70	0.51 - 1.97	0.034
African American compared to Caucasian	2.47	1.70 - 3.61	<0.001
Caucasian compared to ethnicity other than African American	0.30	0.10 - 0.95	0.040
NYHA class III/IV compared to I/II	2.52	1.85 – 3.43	<0.001
Depression Only	1.07	0.55 – 2.09	0.847
Anxiety Only	1.01	0.70 – 1.47	0.953
Comorbid Anxiety and Depression	1.18	0.81 – 1.71	0.391

Overall Model ($\chi^2 = 88.59$, df. = 8; p <0.001)