

The association of comorbid diabetes mellitus and symptoms of depression with all-cause mortality and cardiac rehospitalization in patients with heart failure

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ABSTRACT

Background: More than 22% of individuals with diabetes mellitus have concomitant heart failure (HF), and the prevalence of diabetes in those with HF is nearly triple that of individuals without HF. Comorbid depressive symptoms are common in diabetes and HF. Depressive symptoms are an independent predictor of mortality in individuals with diabetes alone, as well as those with HF alone and are a predictor of rehospitalization in those with HF. However, the association of comorbid HF, diabetes and depressive symptoms with all-cause mortality and rehospitalization for cardiac causes has not been determined.

Objective: The purpose of this study was to evaluate the association of comorbid HF, diabetes and depression with all-cause mortality and rehospitalization for cardiac cause.

Method: Patients provided data at baseline about demographic and clinical variables and depressive symptoms; patients were followed for at least 2 years. Participants were divided into four groups based on the presence and absence of diabetes and depressive symptoms. Cox regression analysis was used to determine whether comorbid diabetes and depressive symptoms independently predicted all-cause mortality and cardiac rehospitalization in these patients with HF.

Results: Patients (n=663) were primarily male (69%), white (76%), and aged 61±13 years. All-cause mortality was independently predicted by the presence of concomitant diabetes and depressive symptoms (HR 3.71; 95% CI 1.49 to 9.25; p=0.005), and depressive symptoms alone (HR 2.29; 95% CI 0.94 to 5.40; p=0.05). The presence of comorbid diabetes and depressive symptoms was also an independent predictor of cardiac rehospitalization (HR 2.36; 95% CI 1.27 to 4.39; p=0.007).

Conclusions: Comorbid diabetes and depressive symptoms are associated with poorer survival and rehospitalization in patients with HF; effective strategies to regularly evaluate and effectively manage these comorbid conditions are necessary to improve survival and reduce rehospitalization rates.

Key messages

- ▶ The co-occurrence of diabetes mellitus, heart failure and depressive symptoms is high in community dwelling patients.
- ▶ Co-morbid diabetes mellitus and depressive symptoms among patients with heart failure is associated with higher risk of death or rehospitalization.

INTRODUCTION

Nearly 30 million adult Americans, or approximately 12% of the adult population of the USA, has diabetes;¹ the cost of care for these individuals totaled \$245 billion in 2012.^{1,2} Cardiovascular disease is the primary cause of death for individuals with diabetes,¹ and diabetes significantly increases the risk for development of hypertension and dyslipidaemia, two major risk factors for cardiovascular disease. The prevalence of diabetes in individuals with heart failure (HF) ranges from 24% (in those with chronic HF) to 40% (in hospitalized patients with worsening HF).³ In those with diabetes, the risk for acute coronary syndrome is increased by 80%, risk for stroke by 50%, and risk for cardiac death by 70%.² Thus, comorbid diabetes and HF confer a significant risk of cardiovascular morbidity and mortality.

The presence of depressive symptoms and major depression are also associated with greater risk of morbidity and mortality in individuals with HF. Suzuki *et al*⁴ found that depressive symptoms in individuals with HF more than doubled the likelihood of mortality (OR 2.24, CI 1.17 to 4.28, p=0.01), while Fan *et al*⁵ reported that depression nearly doubled the risk for mortality (HR 1.98, CI 1.23 to 3.19). Individuals with diabetes are also at increased risk for depression. Roy *et al*⁶ reported that depression prevalence

ranged from 15% to 66% in individuals with diabetes. Depression and comorbid diabetes were associated with a nearly 50% increase in mortality.⁷ Depression has also been associated with worse self-care, poorer quality of life, higher healthcare costs and greater mortality in those with HF and diabetes.^{7–9}

Although there have been prior studies of these associations in individuals with diabetes alone and HF alone, the association of comorbid HF, diabetes and depressive symptoms in individuals with all-cause mortality and rehospitalization for cardiac cause has not been systematically investigated. Thus, the purpose of this study was to examine whether comorbid depressive symptoms and diabetes were associated with all-cause mortality or rehospitalization for cardiac causes in patients with HF.

METHODS

Design, sample, and setting

We performed a secondary analysis of data from the HF Health-Related Quality of Life Collaborative Registry,¹⁰ housed at the University of Kentucky College of Nursing. The database was accessed through the Research and Interventions for Cardiovascular Health (RICH) program at the University of Kentucky. This is a longitudinal database that included data from patients with HF across the USA (n=4076). We selected cases (n=663) with complete data for the variables of interest that were a representative sample of those with and without diabetes, and with and without depressive symptoms from the database. We compared demographic (ie, age, gender and ethnicity) and clinical variables (New York Heart Association (NYHA) functional class, body mass index (BMI), smoking history, coronary artery disease (CAD) history, hypertension (HTN) history, left ventricle ejection fraction (LVEF) and use of antidepressant medication) of those selected with the remainder of the data set; there were no significant differences between these groups. Thus, this was a representative sample from the data set.

The inclusion criteria for the database included: (1) a confirmed diagnosis of HF with impaired or preserved left ventricular systolic function confirmed by a cardiologist; (2) absence of cognitive dysfunction that precluded giving informed consent; (3) no acute myocardial infarction or stroke within the previous 6 months; (4) prescribed stable doses of HF medications; (5) not on the cardiac transplantation waiting list; and (6) absence of life-threatening comorbidities like active cancer, and end-stage renal or liver failure. Data about mortality and rehospitalization were collected for at least 2 years using a standardized protocol that used regular phone contact with the participant and family, medical record review and death record review as appropriate.^{11 12}

Measures

Demographical and clinical variables

To characterize the study participants and evaluate potential confounding variables, data that included age,

gender, ethnicity, NYHA functional class, smoking history, comorbidity burden (diabetes, CAD history, HTN history), BMI, LVEF and antidepressant use were obtained by patient questionnaire, a brief interview and a thorough medical record review. NYHA functional class was determined by careful patient interview by trained research associates. On the basis of patient report of their ability to perform their usual activities, they were assigned a NYHA classification of: I—ordinary physical activity causes no symptoms of fatigue, dyspnea, angina or palpitations; II—symptoms with ordinary physical activity that slightly limit physical activity; III—symptoms occur with less than ordinary physical activity and markedly limit activity; or IV—symptoms occur at rest.

Depressive symptoms

The Patient Health Questionnaire (PHQ-9)¹³ was used to measure depressive symptoms. It is a 9-item, self-reported measure of depression that reflects the severity of depressive symptoms over the past 2 weeks.¹⁴ Patients respond to each item by using a Likert-type scale, in which responses range from 0 (not at all) to 3 (nearly every day). Scores for each item are summed to provide a total score. The total summary score can range from 0 to 27; a higher score reflects more severe depressive symptoms. Good internal consistency, stability, as well as construct and concurrent validity of the PHQ-9 have been supported.^{12 14} The standard cut point of 10 was used to categorize participants who were and were not depressed.¹² This cut point had an 88% sensitivity and 88% specificity for the diagnosis of major depression.¹⁴

All-cause mortality

All-cause mortality was determined by a combination of medical record review, discussion with patient healthcare providers and family, automated hospital records and review of county death records to obtain date and cause of death. At enrollment, patients were asked for contact information for a close friend or next of kin if the patient was unable to be contacted. For patients who were unable to be reached by telephone, automated hospital records were first evaluated to see if the patient had died. If such evidence was found, the friend or next of kin was contacted. If neither the patient nor these contacts were able to be located or if additional information was needed, the county death records were searched.

Cardiac rehospitalization

Cardiac rehospitalization was determined by a combination of medical record review, hospital administrative records review, and an interview with the patient and family members. Dates and reasons for all hospitalizations were recorded. When patient recall varied from hospital records, we were able to validate the admission using hospital records. For hospital admissions outside the system, discharge reports released to the patient were reviewed.

Procedure

Permission for the conduct of this study was obtained from the University of Kentucky Institutional Review Board. For the original study, eligible patients were approached by a research assistant during a clinic visit. The protocol was explained and informed consent obtained. At that time, an appointment was made for baseline data collection. Demographic and clinical characteristics were collected by patient interview and by review of the medical record. Data were collected at the General Clinical Research Center in a private room. All participating patients completed questionnaires, and were asked to record their future hospitalization history in a log book. We followed up with monthly phone calls to collect hospitalization reports. Finally, we confirmed all dates and causes of hospitalization by review of medical records. For this secondary analysis, we selected a representative sample of cases, compared those selected with those not, examined data distributions and evaluated data for outliers in preparation for analysis.

Statistical analysis

Descriptive statistics were used to characterize the participants. Patients were categorized as those with and without depressive symptoms using the standard cut point of 10 for the PHQ-9.¹² Patients were divided into four groups: (1) those without either diabetes or depressive symptoms; (2) those without diabetes, but with depressive symptoms; (3) those with diabetes, but without depressive symptoms; and (4) those with both diabetes and depressive symptoms. Sample demographic and clinical characteristics (ie, age, gender, ethnicity, NYHA class, smoking history, CAD history, HTN history, BMI, LVEF and antidepressant use) were compared between these four groups using χ^2 analyses or ANOVA based on the level of measurement. Post hoc examination of standardized residuals for χ^2 analyses and of Bonferroni comparisons for ANOVA was used to determine location of significant differences. Unadjusted and adjusted hierarchical Cox regression analyses were used to determine whether comorbid diabetes and depressive symptoms predicted mortality or cardiac rehospitalization in these patients with HF. Data were entered into the regression in three blocks to provide more information about the contribution of each variable to the final prediction model. The following covariates were included in the regression analyses, age, gender, ethnicity, NYHA class, smoking history, CAD history, HTN history, BMI, LVEF and antidepressant use. Data were analyzed using SPSS software, V.20.0 (SPSS Inc, Chicago, Illinois, USA). A p value of <0.05 determined statistical significance.

RESULTS

Characteristics of the participants

Participants (n=663) were primarily white (76%), males (69%), and aged 61±13 years (table 1). A majority of

Table 1 Characteristics of participants (n=663)

Variable	Frequency (%) or mean±SD
Age	61±13 years
Gender	
Male	454 (68)
Ethnicity	
White	502 (76)
African-American	121 (18)
Other	40 (6)
Body mass index	30.1±7.4 kg/m ²
Left ventricular ejection fraction	30±14
NYHA functional class	
I/II	276 (42)
III/IV	387 (58)
Type 2 diabetes mellitus	267 (40)
Depressive symptoms present	221 (33)
Prescribed antidepressants	370 (55.8)
Current smoker	463 (70)
Coronary artery disease	332 (50)
Hypertension	451 (68)
PHQ-9 score	7.51±6.04

NYHA, New York Heart Association; PHQ-9, Patient Health Questionnaire-9.

participants were in NYHA functional classes III and IV (58%) with an LVEF of 30±14%. The mean PHQ-9 score for all participants was 7.51±6; one-third of participants (33%) were classified as having depressive symptoms based on the cut point. However, more than half of the participants were prescribed antidepressant medication (56%). Forty per cent were diagnosed with diabetes, and nearly three-fourths of these participants reported being a current smoker (70%). Half of the participants had a history of CAD; a majority had a history of HTN (68%).

When categorized based on the cut point for the depressive symptoms measure and the presence or absence of diabetes, the largest proportion of participants had neither (40%). Twenty per cent of participants reported depressive symptoms, but were without a diabetes diagnosis. Twenty-seven per cent were with diabetes, but did not have depressive symptoms. Fourteen per cent of participants had both diabetes and depressive symptoms. We compared demographical and clinical variables for these four groups (table 2). Although the overall p value for age was significant (p=0.03), post hoc testing with a Bonferroni comparison revealed no significant differences among the groups. BMI in those with both diabetes and depressive symptoms, and those with diabetes only, was significantly higher than in those in the group with neither diabetes nor depressive symptoms (p<0.001); BMI in those who had diabetes only was also significantly higher than in those who had depressive symptoms only (p≤0.001). LVEF in those participants who had diabetes only was significantly greater than in those with only depressive symptoms (p=0.005). There were fewer women than expected in the group with diabetes only, and more women than expected in

Table 2 Demographic and clinical variable comparisons among four groups categorized by diabetes and depressive symptoms (n=663)

Variable	No diabetes, no depressive symptoms (n=265)	Depressive symptoms only (n=131)	Diabetes only (n=177)	Both diabetes and depressive symptoms (n=90)	p Value
Age in years	62±14	59±13	63±11	60±11	0.027
Male gender	182 (69%)	85 (65%)	136 (77%)*	51 (57%)*	0.006
Ethnicity					
White	51 (19%)	24 (18%)	25 (14%)	21 (23%)	0.194
AA	192 (73%)	101 (77%)	145 (82%)	64 (71%)	
Other	22 (8%)	6 (5%)	7 (4%)	5 (6%)	
LVEF	30±15%	27±14%	33±14†	29±14	0.008
BMI	28.5±6.8	29±7.9	31.8±7‡	32.7±7.7‡	<0.001
NYHA class III/IV	122 (46%)*	92 (70%)	93 (53%)*	80 (89%)*	<0.001
CAD	107 (41%)	60 (46%)	107 (61%)	55 (63%)	<0.001
Hypertension	150 (61%)	85 (68%)	121 (72%)	72 (83%)	0.001
Prescribed antidepressants	129 (49%)	103 (79%)	70 (40%)	68 (76%)	<0.001
Current smoker	179 (68%)	93 (71%)	124 (70%)	67 (74%)	0.647

*Significant difference from predicted proportion $p<0.05$.

†Significantly different from category diabetes only $p<0.05$.

‡Significantly different from category neither diabetes nor depressive symptoms $p<0.05$.

AA, African-American; BMI, body mass index; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional class.

the group with both diabetes and depressive symptoms ($p=0.006$). The group without diabetes or depression had a greater proportion of patients classified as NYHA class I/II than predicted, while those in the diabetes alone group and the group with both diabetes and depressive symptoms had fewer participants than expected in NYHA class I/II.

Predictors of all-cause mortality

During the study follow-up period, 47 (7%) participants died. Diabetes and depression were treated as categorical variables, and the four categories previously defined were entered in a hierarchical Cox regression model to predict all-cause mortality (table 3). Variables were entered into the regression in three blocks to determine predictors of mortality during the follow-up period. In the first block, demographic variables (age, gender, and ethnicity) were entered. In the second block, NYHA functional class, smoking status, CAD and HTN diagnosis, BMI, LVEF and antidepressant prescription were entered. In the final block, the categories (no diabetes or depressive symptoms, depressive symptoms alone, diabetes alone, both diabetes and depressive symptoms) were entered. The final regression model was significant ($\chi^2=82.10$, $p<0.001$). Independent predictors of increased mortality included the presence of both diabetes and depression ($p=0.005$), the presence of depression alone ($p=0.05$), white ethnicity ($p=0.02$), NYHA functional class ($p=0.01$) and prescription of antidepressant medication ($p<0.001$). Patients with HF with both diabetes and depression were 3.7 times more likely to die compared to those participants without either condition; patients with HF with depression alone were 2.3 times more likely to die compared to those with neither

diabetes nor depression (figure 1). Those with white ethnicity were six times more likely to die compared to African-Americans. Those participants in NYHA functional classes III and IV were 2.7 times more likely to die compared to those in functional classes I and II; those prescribed antidepressant medication had a 7.8 times greater likelihood of mortality compared to those not prescribed these medications. Predictors of reduced mortality in the model included absence of a CAD diagnosis ($p=0.001$), increased BMI ($p=0.02$) and greater LVEF ($p=0.002$). Those participants without a CAD diagnosis were 70% less likely to die during the follow-up period. A 1 unit increase in BMI was associated with a 6% reduction in likelihood of mortality; a 1% increase in LVEF was associated with a 4% reduction in likelihood of mortality.

In a sensitivity analysis of these data to confirm these findings, the prior four groups were removed from the analysis and depression was entered as a continuous variable using the total score of PHQ-9; diabetes was entered as a categorical variable. All other variables were entered unchanged. These results demonstrated that diabetes (HR 0.93; 95% CI 0.54 to 1.75; $p=0.929$) was not a significant predictor of mortality. However, depressive symptoms (HR 1.12; 95% CI 1.06 to 1.18; $p<0.001$) were a significant predictor of mortality; for every 1 unit increase in the PHQ-9 score, the likelihood of mortality increased by 12%. In further analyses, we entered β -blocker use, ACE blocker use, diuretic use and other comorbidities. These analyses did not alter the results.

Predictors of cardiac rehospitalization

During the follow-up period, there were 115 (17%) hospitalizations for cardiac reasons. Diabetes and

Table 3 Predictors of all-cause mortality (n=663)

	B	Exp. B	95% CI	p Value
Block 1. Demographic variables				
Age	0.15	1.02	0.99 to 1.04	0.226
Gender (male)	0.70	1.07	0.60 to 2.03	0.830
White ethnicity (AA)	1.365	3.92	0.92 to 16.66	0.065
Other ethnicity (AA)	1.332	3.79	0.34 to 42.04	0.278
Block 2. Clinical variables				
Age	0.019	1.02	0.99 to 1.04	0.137
Gender (male)	-0.501	0.61	0.30 to 1.22	0.162
White ethnicity (AA)	1.645	5.18	1.19 to 22.49	0.028
Other ethnicity (AA)	1.403	0.07	0.34 to 48.32	0.266
NYHA class III/IV (class I/II)	0.991	2.69	1.27 to 5.70	0.01
Current smoker (non-smoker)	0.108	1.11	0.57 to 2.13	0.755
CAD (no CAD)	-0.872	0.42	0.21 to 0.82	0.011
Hypertension (no hypertension)	-0.176	0.84	0.46 to 1.54	0.569
BMI	-0.051	0.95	0.90 to 1.00	0.05
LVEF	-0.040	0.96	0.94 to 0.99	0.002
Antidepressant use (compared to none)	2.145	8.55	3.57 to 21.39	<0.001
Block 3. Patient categories based on diabetes and depressive symptoms				
Age	0.024	1.03	1.00 to 1.05	0.067
Gender (male)	-0.683	0.51	0.24 to 1.05	0.067
White ethnicity (AA)	1.789	5.98	1.38 to 25.99	0.02
Other ethnicity (AA)	1.490	4.44	0.37 to 53.50	0.241
NYHA class III/IV (class I/II)	0.974	2.65	1.23 to 5.69	0.013
Current smoker (non-smoker)	-0.025	0.98	0.48 to 1.98	0.946
CAD (no CAD)	-1.191	0.30	1.47 to 0.63	0.001
Hypertension (no hypertension)	-0.286	0.36	0.41 to 1.38	0.358
BMI	-0.062	0.94	0.89 to 0.99	0.02
LVEF	-0.039	0.96	0.94 to 0.99	0.002
Antidepressant use (compared to none)	2.054	7.8	3.02 to 20.16	<0.001
Depressive symptoms only (No depressive symptoms and no diabetes)	0.827	2.29	1.00 to 5.21	0.05
Diabetes only (No depressive symptoms and no diabetes)	0.810	2.25	0.94 to 5.40	0.070
Both depressive symptoms and diabetes (No depressive symptoms and no diabetes)	1.312	3.71	1.49 to 9.25	0.005

Cox regression—Overall Model $\chi^2=82.10$, $df=14$, $p<0.001$.

Comparison group in parentheses.

AA, African-American; BMI, body mass index; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

depression were again treated as categorical variables, and the four categories previously defined were entered in a hierarchical Cox regression in three blocks to determine predictors of cardiac rehospitalization (table 4). In the first block, demographic variables (age, gender and ethnicity) were entered. In the second block, NYHA smoking history, CAD history, HTN history, BMI, LVEF and antidepressant use were entered. The final block contained the four categories of patients (neither diabetes nor depressive symptoms, diabetes only, depressive symptoms only, both diabetes and depressive symptoms). The final regression model was significant ($\chi^2=42.23$, $p<0.001$). Independent predictors of increased risk for cardiac rehospitalization were the presence of both diabetes and depressive symptoms, and prescription of antidepressant medication. Those participants with both diabetes and depressive symptoms were 2.4 times more likely to be rehospitalized compared to those without either diabetes or depression (figure 2). Patients who were prescribed antidepressant medications were 1.7

times more likely to be rehospitalized compared to those without a prescription. Again, sensitivity analysis was carried out with removal of the four categories of patients and depressive symptoms entered as a continuous variable and diabetes as a categorical variable. Diabetes (HR 1.28; 95% CI 0.89 to 1.86; $p=0.189$) was not a significant predictor of rehospitalization in these patients. However, depressive symptoms (HR 1.06; 95% CI 1.03 to 1.10; $p<0.001$) were a significant predictor of rehospitalization; for each 1 unit increase in the PHQ-9 score, the likelihood of cardiac rehospitalization increased by 6%. In further analyses, we entered β -blocker use, ACE blocker use, diuretic use and other comorbidities. These analyses did not alter the results.

DISCUSSION

We found that the combination of comorbid HF, diabetes and depressive symptoms was associated with shorter survival and an increased likelihood of cardiac

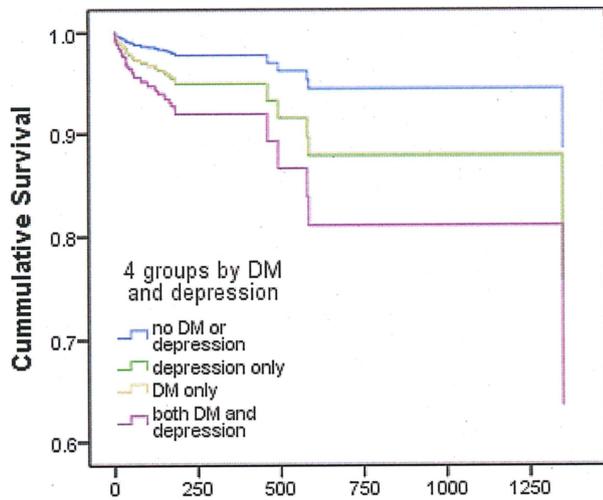


Figure 1 All-cause mortality according to comorbid symptoms of diabetes and depression.

rehospitalization. A diabetes diagnosis alone did not predict either mortality or cardiac rehospitalization. However, depressive symptoms were independently associated with both mortality and cardiac rehospitalization when the PHQ-9 score was used as a continuous variable. The depressive symptoms alone group was also significantly associated with mortality. The likelihood of mortality and rehospitalization increased by 12% and 6%, respectively, with analysis of depressive symptoms as a continuous variable; the presence of depressive symptoms alone increase the likelihood of mortality by 2.3 times compared to those without depressive symptoms. However, the combination of comorbid diabetes and depressive symptoms was associated with a 3.7 times and 2.4 times greater likelihood of mortality and cardiac rehospitalization, respectively. Thus, the presence of diabetes, HF and depressive symptoms demonstrated an apparent cumulative effect on mortality and cardiac rehospitalization.

Table 4 Predictors of rehospitalization (n=663)

	B	Exp. B	95% CI	p Value
Block 1. Demographic variables				
Age	-0.002	1.0	0.98 to 1.02	0.819
Gender (male)	-0.346	0.71	0.45 to 1.11	0.130
White ethnicity (AA)	-0.345	0.71	0.42 to 1.19	0.191
Other ethnicity (AA)	0.246	1.28	0.38 to 4.32	0.693
Block 2. Clinical variables				
Age	-0.008	1.0	0.97 to 1.01	0.391
Gender (male)	-0.328	0.72	0.45 to 1.16	0.180
White ethnicity (AA)	-0.574	0.56	0.33 to 0.96	0.034
Other ethnicity (AA)	0.208	1.23	0.36 to 4.27	0.743
NYHA class III/IV (class I/II)	0.233	1.26	0.84 to 1.90	0.263
Current smoker (non-smoker)	0.365	1.44	0.90 to 2.30	0.127
CAD (no CAD)	0.429	1.54	0.99 to 2.39	0.059
Hypertension (no hypertension)	0.230	1.26	0.81 to 1.96	0.312
BMI	-0.020	0.98	0.95 to 1.01	0.180
LVEF	-0.010	0.99	0.98 to 1.01	0.195
Antidepressant use (none)	0.627	1.87	1.24 to 2.83	0.003
Block 3. Patient categories based on diabetes and depressive symptoms				
Age	-0.007	0.99	0.98 to 1.01	0.473
Gender (male)	-0.345	0.71	0.44 to 1.15	0.165
White ethnicity (AA)	-0.506	0.60	0.35 to 1.03	0.065
Other ethnicity (AA)	-0.373	1.45	0.42 to 5.05	0.558
NYHA class III/IV (class I/II)	0.111	1.12	0.73 to 1.71	0.608
Current smoker (non-smoker)	0.418	1.52	0.94 to 2.45	0.087
CAD (no CAD)	0.316	1.37	0.87 to 2.16	0.172
Hypertension (no hypertension)	0.170	1.19	0.87 to 1.86	0.458
BMI	-0.024	0.98	0.95 to 1.01	0.116
LVEF	-0.010	0.99	0.95 to 1.01	0.220
Antidepressant use (none)	0.548	1.73	1.13 to 2.66	0.012
Depressive symptoms only (No depressive symptoms and no diabetes)	0.212	2.29	0.68 to 2.26	0.490
Diabetes only (No depressive symptoms and no diabetes)	0.164	1.18	0.71 to 1.96	0.527
Both depressive symptoms and diabetes (No depressive symptoms and no diabetes)	0.857	2.36	1.27 to 4.39	0.007

Cox regression—Overall Model $\chi^2=42.23$, $df=14$; $p<0.001$.

Comparison group in parentheses.

AA, African-American; BMI, body mass index; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

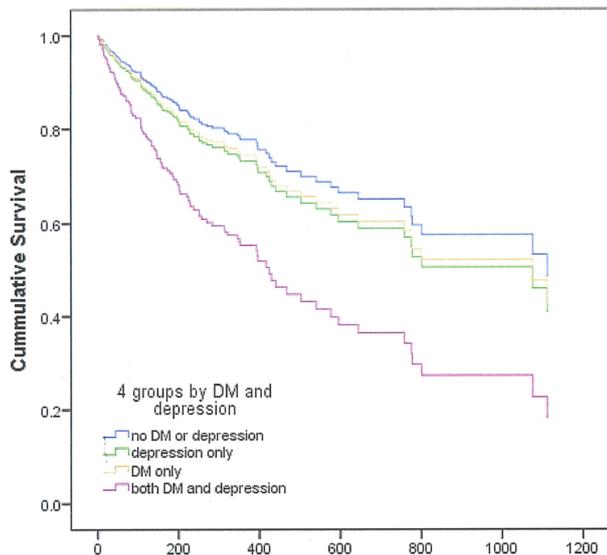


Figure 2 Cardiac re-hospitalization according to comorbid symptoms of diabetes and depression.

Our findings support prior research evidence^{15–21} that established the negative impact of comorbid diabetes and depressive symptoms in patients with HF. We extended the understanding of the association between these comorbid conditions and mortality and rehospitalization with identification of a cumulative effect on outcomes when these three conditions are present. Thus, the triad of HF, diabetes and depressive symptoms should be considered prognostic for poorer outcomes.

Such consideration demands assessment of depression by cardiologists, endocrinologists and other providers who care for patients with HF and diabetes. Such assessments are not common, yet are recommended and can be performed easily in the context of busy clinical practices.²² There are well-defined recommendations for assessing and treating depression in patients with cardiac disease to guide providers.^{22–25} Some providers, believing that depression is natural in the context of chronic illnesses, do not assess or treat depression.^{22–26} This belief discounts the danger of depression and subjects patients to unnecessary risk.

As would be expected, in our sample, patients with diabetes had more severe HF, as reflected by NYHA functional class criteria, than those without diabetes. This is similar to previous studies evaluating HF patients with diabetes.^{21–27} Despite this association, the co-occurrence of diabetes and depression remained independently predictive of both cardiac rehospitalization and all-cause mortality. Thus, HF severity alone does not explain the observed associations.

Comorbid depression and diabetes might be associated with worse outcomes in patients with HF due to shared behavioral pathways. Behaviorally, depressive symptoms likely contribute to poor outcomes by decreasing patient adherence to medical regimens and increasing uptake of risky behaviors.²⁸ Among diabetics, adherence to recommended therapy is poor.^{29–30} Thus,

in patients with concomitant diabetes and depression, adherence could be expected to be even worse than in those with each condition alone.^{31–32}

Physiological mechanisms linking depressive symptoms and diabetes with adverse outcomes in HF are likely related to shared pathophysiology among the three conditions. Neurohormonal activation, rhythm disturbances, inflammation and hypercoagulability have all been implicated in the development, progression and outcomes of HF.³³ Similarly, each of these pathological states is also seen in depressed patients.^{33–36} In patients with diabetes, hyperglycemia has been shown to activate the same intracellular signaling pathways as a mechanical stretch or increased ventricular wall stress (seen in HF), which alters protein kinase C and mitogen-activated proteinkinase.^{37–38} Impaired myocardial performance eventually requires activation of the neurohormonal compensatory systems, including the renin-angiotensin system and the sympathetic nervous system, to avoid systemic hypoperfusion. This compensatory response increases oxidative stress, and upregulates the activity of ACE and other components of the renin-aldosterone system, which contributes to the development of cardiomyopathy.^{39–40} Other pathophysiological links between HF, diabetes and depressive symptoms may include increased levels of circulating cytokines such as tumor necrosis factor; impaired baroreflex sensitivity and decreased heart rate variability.^{37–39}

Limitations: The primary limitation of our study was the use of an existing data set; secondary analyses can only include the existing data previously collected. Other variables cannot be evaluated for their importance. For example, we did not include potential physiological mechanisms in the regression analyses. Another potential limitation of our study was the use of self-report measures of symptoms of depression, rather than diagnostic interviews. However, self-report instruments completed by patients with HF have been shown to be reliable and valid measures. A final limitation of this study is our inability to distinguish patients with type I versus type II diabetes.

CONCLUSIONS

We found that the combination of diabetes and depressive symptoms in patients with HF was associated with a greater likelihood of mortality and cardiac rehospitalization. Diabetes alone was not a predictor of either mortality or cardiac rehospitalization. When analyzed as a continuous variable, depressive symptoms score alone predicted both mortality and rehospitalization. The mechanisms for these associations require further systematic investigation, so that effective interventions can be developed and tested to improve outcomes.

Contributors GR researched the data and wrote part of the manuscript. ASA researched and analyzed the data and wrote part of the manuscript. SKF, JFW and TAL reviewed/edited the manuscript and contributed to discussion. DKM reviewed/edited the manuscript, contributed to discussion and mentored the entire project.

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