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Predictors of the Onset of Depressive Symptoms in Patients With Heart Failure

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OBJECTIVES The objective of this study was to identify the factors associated with the development of depressive symptoms in outpatients with heart failure (HF).

BACKGROUND Depression is common in patients with HF and has been linked to adverse outcomes.

METHODS This was a multicenter prospective cohort study of outpatients with HF and ejection fraction <0.40. Patients were evaluated at baseline and one year with a Medical Outcomes Study-Depression questionnaire, a Kansas City Cardiomyopathy Questionnaire (KCCQ), and a full clinical evaluation including patients' social and economic status.

RESULTS Of 245 patients without depressive symptoms at baseline, 52 (21.2%) developed depressive symptoms one year later. In multivariable analysis, living alone, alcohol abuse, perception of medical care as being a substantial economic burden, and health status as measured by the KCCQ were independent predictors of developing depressive symptoms. For patients without these factors, 7.9% developed depression by one year. When one factor was present, the one-year incidence was 15.5%, when two were present the incidence was 36.2%, and when three were present the incidence was 69.2%. There was a graded relationship between poorer health status and increased risk of developing depression ($p < 0.001$ for trend). No traditional clinical factors or measures of disease severity were significantly associated with the development of depression.

CONCLUSIONS Social factors and health status are predictive of the development of depression in outpatients with HF. Clinicians should be aware of which patients are at risk for the development of depression so that these patients may be targeted for screening and potentially for psychosocial intervention. (J Am Coll Cardiol 2004;44:2333–8) © 2004 by the American College of Cardiology Foundation

Depression is a chronic disease that is associated with limitations in physical and social functioning equal to or greater than those of other common chronic diseases (1) and is associated with increased mortality (2). Depression is more common in patients with cardiovascular disease than in the general population, particularly in patients with heart failure (HF) (3–6). Furthermore, depressive symptoms in patients with HF are strongly associated with a decline in health status (7) and an increase in the risk of hospitalization and death (6,8).

Such data suggest that reducing the burden of coincident depression in patients with HF can improve their health. One possible intervention is to screen patients with HF for depression followed by pharmacologic treatment of those found to be depressed. Yet, even among those HF patients who are not depressed, it would be valuable to identify those patients at elevated risk for developing depression. Identifying such patients could suggest the need for an intervention to reduce the incidence of depression. Previous studies support the notion that depression prevention programs can be effective (9) and are consistent with the Institute of Medicine position that one of the critical changes necessary for transforming American healthcare is for "the system [to] anticipate patient needs, rather than simply react to events" (10). In order to best target depression screening and depression prevention interventions, the factors associated with the onset of depression in patients with HF must be established. To date, the risk factors for developing depression in patients with HF have not been described.

The objective of this study was to identify the sociodemographic and clinical factors associated with the onset of depressive symptoms in outpatients with HF.

METHODS

Study population. All subjects were enrolled in the Kansas City Cardiomyopathy Questionnaire (KCCQ) Interpretability Study. The KCCQ Interpretability Study (11) was conducted by investigators in the Cardiovascular Outcomes Research Consortium (Appendix) at 14 outpatient clinics

From the *University of Colorado Health Sciences Center and †Denver Health Medical Center, Denver, Colorado; ‡Mid-America Heart Institute and University of Missouri-Kansas City, Kansas City, Missouri; and §Denver Veterans Administration Medical Center, Denver, Colorado. The study on which this analysis is based, the Kansas City Cardiomyopathy Questionnaire (KCCQ) Interpretability Study, was sponsored by Pharmacia. Dr. Masoudi is supported by the National Institute on Aging NIH Research Career Award K08-AG01011. Dr. Rumsfeld is supported by a VA Health Services Research Advanced Research Career Development Award (ARCD 98-341-2).

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Abbreviations and Acronyms
HF = heart failure
KCCQ = Kansas City Cardiomyopathy Questionnaire
MOS-D = Medical Outcomes Study-Depression questionnaire

across the U.S. and Canada. Patients were eligible for inclusion if they had an HF diagnosis in their medical record or had been hospitalized for HF during the previous three years, had a left ventricular ejection fraction <0.40, and were at least 30 years of age.

Patients were eligible for this analysis if they did not have significant depressive symptoms at baseline, defined as a Medical Outcomes Study-Depression questionnaire (MOS-D) score of <0.06. The MOS-D (12) is an eight-item screening instrument previously used in case-finding studies of depression and was selected for the current study because it does not assess somatic symptoms that are common in HF. A cutoff of 0.06 has an approximate sensitivity of 85% and specificity of 75% for a diagnosis of major depressive disorder (13). Of the 371 patients in the parent study meeting this criterion, 126 did not have one-year follow-up MOS-D data: 35 (9.4%) died, 22 (5.9%) refused to complete the instrument, 18 (4.8%) had incomplete data, and 51 (13.7%) were lost to follow-up. The remaining 245 patients form the analytic cohort for this study. Eligible patients with incomplete one-year follow-up data were more likely to be black (48% vs. 21%, $p < 0.001$), less likely to have a history of depression requiring treatment (1.2% vs. 9.4%, $p = 0.01$), and more likely to have a history of alcohol abuse. There were no differences in age, gender, body mass index, insurance status, smoking, diabetes, living alone, self-reported difficulty affording healthcare, New York Heart Association functional class, ejection fraction, B-type natriuretic peptide level, 6-min walking distance, KCCQ overall summary score, or baseline MOS-D score.

Data collection. At baseline, all patients completed a standardized history that included questions about social and economic factors and underwent a physical examination, a 6-min walking test, and a survey battery that included the MOS-D and the KCCQ (14). The KCCQ is a 23-item disease-specific health status instrument for patients with HF that measures symptoms, physical functioning, social functioning, self-efficacy, and quality of life. These individual domains can be summarized into an overall summary score with a range from 0 to 100, with higher scores indicating better health status. A previous investigation (11) has defined a clinically significant change as being ≥5 points. As previously reported (7), 30.2% of patients had MOS-D scores consistent with depression.

Patients were contacted by telephone one year after their baseline enrollment to complete both the MOS-D and the KCCQ. A minimum of 10 attempts were made to contact patients and, if all attempts were unsuccessful, a questionnaire packet was sent. A second mailing was sent if the patient did not return his or her initial packet. If there was no reply to the second mailing, the patient was assumed to be lost to follow-up. Institutional Review Board approval at each site was secured before study implementation, and all patients supplied written informed consent.

Statistical analysis. We compared baseline demographic and clinical variables between subjects who did and did not develop depression over the one year of follow-up (i.e., between patients whose follow-up MOS-D score was <0.06 vs. ≥0.06). Chi-squared tests were used for categorical variables and the Student *t* test was used for continuous variables.

The univariate association between each of the candidate predictor variables (those listed in Table 1) and the outcome variable (depression at one year as indicated by an MOS-D score ≥0.06) was determined using simple logistic regression. Then multiple logistic regression was utilized to define the independent association between the candidate predictor variables and one-year depression status. The multivariable model was built by applying backward elimination to those predictor variables that had a univariate p value <0.15 and retaining those variables with $p < 0.05$ in the final model. A c-index was calculated to evaluate model discrimination, and the Hosmer-Lemeshow test was applied to evaluate model calibration.

To better define the relationship between baseline health status and subsequent depressive symptom burden, we compared the incidence of depression for patients in 25-point increments of KCCQ overall score using the Cochran-Armitage test. We also calculated the incidence of depression by the number of risk factors present.

All analyses were conducted using SAS (SAS Institute, Cary, North Carolina) v8.2 software.

RESULTS

Of the 245 patients without depressive symptoms at baseline, 52 (21.2%) had developed significant depressive symptoms at follow-up and 193 had not.

Table 1 compares the characteristics of those subjects with and those without a significant burden of depressive symptoms at one-year follow-up. Patients who developed depressive symptoms were nearly twice as likely to live alone (40.4% vs. 22.9%, $p = 0.015$), were more likely to report medical care as representing a somewhat to severe economic burden for them (59.6% vs. 34.3%, $p = 0.003$), and were more likely to have a history of alcohol abuse (23.1% vs. 11.4%, $p = 0.013$). Mean KCCQ summary scores (59.7 ± 23.1 vs. 71.1 ± 20.4, $p < 0.001$) were significantly worse in those who developed significant depressive symptoms. There was a graded relationship between baseline KCCQ overall summary score and the development of depressive symptoms at one year (Fig. 1).

Table 1. Comparison of Baseline Characteristics Between Those With and Those Without Significant Depressive Symptoms at One Year

	Depressed at 1 Year (n = 52)	Not Depressed at 1 Year (n = 193)	p Value
Age (yrs)	60.5 ± 11.3	63.1 ± 12.5	0.186
Gender (% female)	25.0	25.4	0.954
Race (% white)	65.4	75.0	0.166
Currently married (%)	44.2	57.3	0.321
Living alone (%)	40.4	22.9	0.015
Educational level (%)			0.631
High school or less	53.8	44.3	
Some college	26.9	34.9	
College	11.5	13.5	
Postgraduate	7.7	7.3	
Employment (%)			0.822
Full-time	15.7	16.2	
Part-time	9.8	11.0	
None	74.5	72.8	
Annual income (%)			0.46
<$10,000	20.8	20.2	
$10,000–29,999	52.1	39.9	
$30,000–49,999	12.5	23.5	
$50,000–69,999	6.3	7.7	
≥$70,000	8.3	8.7	
Health insurance (%)	75.0	85.0	0.105
Economic burden of medical care (%)			0.003
Severe	15.4	7.4	
Moderate	11.5	13.7	
Somewhat	32.7	13.2	
A little	13.5	21.6	
None	26.9	44.2	
Access to medical care (%)			0.348
Extremely difficult	2.0	0.5	
Moderately difficult	2.0	3.6	
Somewhat difficult	3.9	5.7	
Not very difficult	47.1	33.9	
No difficulty	45.1	56.3	
Ischemic heart disease (%)	56.0	53.7	0.774
History of hypertension (%)	65.4	52.3	0.093
Chronic lung disease (%)	25.0	19.7	0.402
History of treated depression (%)	9.6	9.3	1.000
History of smoking (%)	59.6	59.6	0.999
Alcohol abuse (%)	23.1	11.4	0.031
Diabetes (%)	44.2	30.6	0.064
NYHA functional class (%)			0.268
I	7.7	16.6	
II	44.2	47.2	
III	44.2	34.2	
IV	3.8	2.1	
Atrial fibrillation (%)	25.0	33.7	0.233
6-min walk (ft)	975.6 ± 398	1019 ± 396	0.504
Ejection fraction (%)	24.1 ± 7.8	25.4 ± 8.6	0.316
BNP (pg/ml)	315 ± 342	376 ± 366	0.393
KCCQ summary score	59.7 ± 23.1	71.1 ± 20.4	<0.001

BNP = brain natriuretic peptide; KCCQ = Kansas City Cardiomyopathy Questionnaire; NYHA = New York Heart Association.

Among the markers of HF disease severity at baseline, New York Heart Association functional class, exercise capacity by the 6-min walking test, ejection fraction, presence of atrial fibrillation, and B-type natriuretic peptide levels did not differ between the groups. Furthermore, there was no difference between the groups with regard to a history of treated depression. Finally, there were no significant differences in baseline use of cardiovascular medications between the two groups.

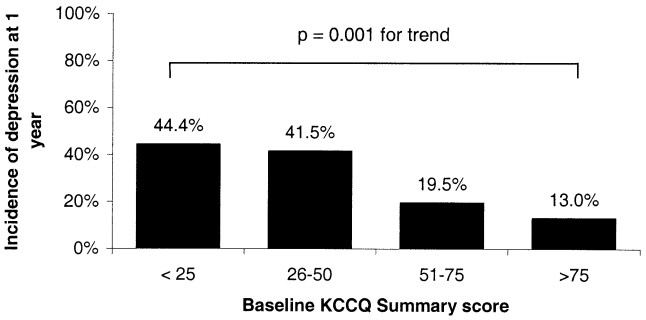

Figure 1. Incidence of depressive symptoms at one year by baseline Kansas City Cardiomyopathy Questionnaire (KCCQ) score.

By multivariable logistic regression analysis, living alone, economic burden associated with the costs of medical care, alcohol abuse, and baseline KCCQ overall summary score <50 were all independent predictors of the development of depressive symptoms (Table 2). The resulting model had a c-statistic of 0.744, indicating moderately good discriminative ability. The Hosmer-Lemeshow statistic for the model was 7.18 (p = 0.517), indicating good fit for the model across the range of predicted probabilities.

For patients who had none of the four risk factors, there was a 7.9% chance of having significant depressive symptoms at one year. The incidence of significant depressive symptoms approximately doubled with each additional risk factor (Fig. 2). For those with one, two, and three risk factors, the incidence of significant depressive symptoms at one year was 15.5%, 36.2%, and 69.2%, respectively. No patient had all four risk factors.

Because 35% of the patients with MOS-D scores >0.06 at baseline had scores ≤0.06 at follow-up, we investigated the possibility that random fluctuation of the scores influenced our results by constructing a second logistic regression model. This model included all 350 patients with baseline and follow-up MOS-D scores, and included baseline MOS-D score as a covariate, in addition to other sociodemographic, clinical, and health status factors. Estimated effects are thus adjusted for regression to the mean. Because we were specifically interested in predictors of developing depressive symptoms, we modeled effects for patients with MOS-D scores ≤0.06 separately from those with scores >0.06. The results of this model appear in Table 3. These results are consistent with those of the prior model. There is attenuation in the odds ratio associated with the KCCQ score from 1.61 to 1.22. Nonetheless, KCCQ score retains a significant association with 1-year depression after accounting for baseline depression score.

Table 2. Summary Statistics for Multivariable Logistic Regression Model of Predictors of Depressive Symptoms at One Year

Variable	Beta	Wald Chi-Squared	p Value	Odds Ratio	95% CI
Living alone	0.972	6.75	0.009	2.64	1.27–5.54
Economic burden	1.106	9.74	0.002	3.02	1.52–6.14
Alcohol abuse	0.9725	5.02	0.025	2.64	1.11–6.16
KCCQ overall score (per 10 points lower score)	−0.0223	7.82	0.005	1.61	1.16–2.27
Intercept	−0.889				

CI = confidence interval; KCCQ = Kansas City Cardiomyopathy Questionnaire.

DISCUSSION

The objective of this study was to identify the factors associated with the development of depression among outpatients with HF. We found four independent predictors of the development of depressive symptoms: living alone, alcohol abuse, financial burden from medical care, and worse baseline HF-specific health status. A sequential doubling of risk with each additional risk factor was observed, resulting in a range of risk for developing depression over one year from 7.9% for patients without any of the four risk factors to 69.2% for patients with three of the four risk factors (no patient had all four risk factors).

To our knowledge, this is the first study to evaluate predictors of the onset of depression in patients with HF. Studies in post-myocardial infarction patients have found low social support, impaired functional status, and higher overall burden of illness to be predictive of depression (15,16). Studies in general populations have found female gender, divorce or separation, unemployment, low educational attainment, and low income to be significant risk factors (17,18). Several of these findings echo the findings of our study. However, we found that living alone increased the risk of depression in HF, whereas previous studies in other populations did not. Also in contrast to previous studies, we did not find female gender to be associated with the development of depressive symptoms. Finally, the results of the current study with regard to the relationship between depression and alcohol consumption are supported by previous studies. In a meta-analysis of eight studies, Hartka et al. (19) documented a clear quantitative relationship between alcohol consumption and subsequent depression.

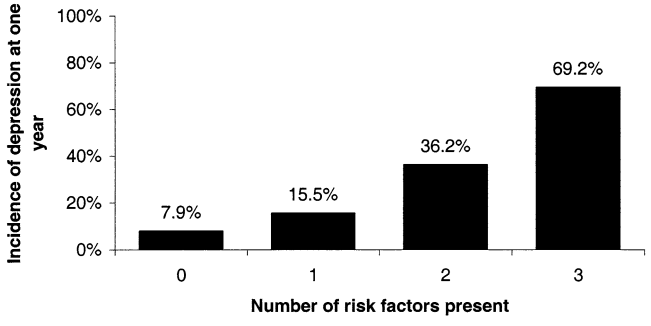

Figure 2. Incidence of depressive symptoms by number of risk factors. The risk factors are the four significant predictors from the multivariable logistic regression model (living alone, significant economic present associated with the costs of medical care, alcohol abuse, and overall Kansas City Cardiomyopathy Questionnaire score <50). No patient had all four risk factors.

The identification of HF patients who are at risk for the development of depression is important because of the prevalence of depression and the association between depression and adverse outcomes in patients with HF. Approximately 30% of patients with HF, including both inpatients and outpatients, have significant depressive symptoms (3–8). Furthermore, depressed HF patients are at increased risk for mortality, HF hospitalization, and worsening of HF symptoms, functional status, and quality of life (6–8). Knowing the risk factors for the development of depression, as delineated in this study, may facilitate the recognition and treatment of depressed HF patients.

There are several implications of this study. First, depression screening may be warranted for all patients with HF, because even among patients without any of the risk factors, about 8% developed depression over one year. However, it may be most critical to screen for depression among those HF patients who have any of the risk factors identified in this study. This screening should probably be serial in nature (i.e., repeated over time) because of the markedly elevated risk for the development of depression in these patients. There are several well-validated and easy-to-use depression screening instruments, such as the Patient Health Questionnaire, that can rapidly identify patients with significant depressive symptoms who may benefit from treatment (20–22). Furthermore, patients with the depression risk factors identified in this study may be targets for psychosocial interventions, such as case management, social worker evaluation, cognitive therapy for social isolation, or alcohol abuse intervention (9). Future studies should be conducted to evaluate whether targeted psychosocial intervention for these patients can reduce the incidence of depression and improve outcomes.

The results of this study also support the use of the KCCQ in evaluating patients with HF. Health status measures have been shown to predict mortality and cardiac events in cardiovascular populations, including HF (5,23–26). The KCCQ scores have previously been associated with subsequent mortality and hospitalization in patients with HF (27). In this study, KCCQ score was one of four independent risk factors for the development of depression among outpatients with HF. Therefore, assessing the health status of HF patients using an instrument like the KCCQ may aid in identification of patients at risk for a wide range

Table 3. Results of Multivariable Logistic Regression Model of Predictors of Depressive Symptoms at One Year Adjusting for Baseline MOS-D Score

Variable	Odds Ratio	95% CI	p Value
Living alone	2.81	1.33–5.99	0.007
Economic burden	2.92	1.45–6.01	0.003
Alcohol abuse	3.02	1.23–7.24	0.014
KCCQ_overall score (per 10 points lower score)	1.22	1.04–1.43	0.015

MOS-D = Medical Outcomes Study-Depression questionnaire; other abbreviations as in Table 2.

of adverse outcomes. Future studies are warranted to evaluate whether health status-guided management of patients with HF can improve outcomes.

The reasons for the elevated incidence of depression in patients with HF are uncertain, but genetic (28), physiologic, and psychodynamic factors have all been postulated as contributors. With regard to genetic factors, recent studies have identified the same genetic polymorphisms to be associated with the development of both depression and cardiovascular disease (29). The G-protein beta-3 825T allele has been associated with depression (28,30) and also with hypertension (31), an important risk factor for HF (32,33). A gene-gene interaction between the G-protein beta-3 825T allele and the angiotensin-converting enzyme D allele (34) has also been implicated in the genesis of both illnesses, and gene-environment interactions have been identified (35). With regard to physiologic factors, increased levels of circulating catecholamines are observed in both illnesses (36,37), and high levels of catecholamines resulting from HF might potentiate depression. Furthermore, patients with HF have elevated levels of cytokines, some of which (particularly interleukin-2) have been shown to cause depressive symptoms (38). Finally, with regard to psychodynamic factors, stressful life events have been demonstrated to precipitate depression (39), and the threat of death and loss of autonomy that accompany HF are consistent with known depression-generating stressors. Our study, although not addressing the contributions of genetic and physiologic factors, demonstrates that environmental factors in the social milieu significantly contribute to the onset of depression in HF.

The current study has several limitations. First, we did not attempt to establish a diagnosis of major depressive disorder through use of a structured interview based on criteria from the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*. However, the validity of the MOS-D as a case-finding instrument in studies of depression is well established (13), and multiple studies have demonstrated the importance of depressive symptoms as predictors of outcome in patients with HF (6–8). Second, our sample was relatively small, limiting the number of variables we could reasonably examine by multivariable analysis. This is unlikely, however, to invalidate the significant predictors that we found. Finally, this study enrolled a convenience sample of outpatients with HF, which could limit generalizability. However, one would expect fewer patients with social risk factors (living alone, alcohol abuse, etc.) to participate in such a study; therefore, we may have underestimated the associations found.

In conclusion, readily measured patient characteristics can identify HF patients at high risk for the development of depressive symptoms. Future studies are needed to evaluate whether interventions aimed at the prevention of depression and/or the treatment of depression in those who screen positive will improve outcomes. In the meantime, clinicians should be aware of the high incidence of depressive symptoms and the risk factors for development of depression in patients with HF.

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APPENDIX

For a list of Cardiovascular Outcomes Research Consortium members who participated in this study, please see the December 21, 2004, issue of *JACC* at http://www.onlinejacc.org.