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The Association between Depressive Symptoms and N-terminal pro-B type natriuretic peptide with Functional Status in Patients with Heart Failure

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Abstract

Background—N-terminal pro-B type natriuretic peptide (NT-proBNP) and depressive symptoms are each associated with functional status in patients with heart failure (HF), but their association together with functional status has not been examined.

Objective—To determine whether functional status scores differ as a function of depressive symptoms and NT-proBNP levels considered together.

Methods—We studied 284 patients with HF who were divided into 4 groups based on the median split of NT-proBNP levels and cut point for depressive symptoms (Beck Depression Inventory 14): 1) low NT-proBNP ≤ 562.5 pg/ml without depressive symptoms, 2) low NT-proBNP ≤ 562.5 pg/ml with depressive symptoms, 3) high NT-proBNP > 562.5 pg/ml without depressive symptoms, and 4) high NT-proBNP > 562.5 pg/ml with depressive symptoms. The Duke Activity Status Index was used to assess functional status.

Results—Nonlinear regression demonstrated that patients without depressive symptoms were more than twice as likely to have higher (better) functional status scores than patients with depressive symptoms regardless of NT-proBNP levels after controlling for age, gender, prescribed antidepressants, and body mass index. Functional status levels of patients with low NT-proBNP did not differ from those with high NT-proBNP in the presence of depressive symptoms.

Conclusion—When examined together, depressive symptoms rather than NT-proBNP levels predicted functional status.

Clinical Implications—Adequate treatment of depressive symptoms may lead to better functional status regardless of heart failure severity.

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Conflicts of Interest: None

Keywords

Depressive symptoms; functional status; heart failure; N-terminal pro-B type natriuretic peptide

Heart failure (HF) is a chronic progressive clinical syndrome, characterized by a variety of symptoms that require ongoing medical care and self-management.^{1,2} Fatigue and dyspnea, hallmark symptoms of HF, contribute to a significant reduction in quality of life and are indicators of HF severity and worsening prognosis.^{2,3} Functional status is considered an important outcome of HF as it describes the impact of HF symptoms on patient's daily physical function.^{3,4} Functional status is an important clinical consideration in HF management.² It has been shown to predict HF symptom severity, quality of life, hospitalization, and mortality.^{3,5}

Depression is a mood disorder commonly seen in patients with HF.⁶ Depression was found to predict increased risk of hospitalization, mortality, and poor functional status measured by both self-reported and objective measures.⁶⁻⁸ Depression is as an important determinant of functional status.^{9,10} Comorbid depression and HF are associated with more impairment in functional status than HF alone.^{7,8,11}

Previous investigators have examined the association of depressive symptoms with functional status in relation to left ventricular ejection fraction (LVEF),^{7,11} and LVEF was found to be a weak predictor of functional status.^{7,8,11} Reduced LVEF was found to have low specificity and sensitivity to the presence of signs and symptoms of HF.^{12,13} Researchers have noted that some patients remain asymptomatic despite severely reduced LVEF while other patients with higher LVEF are symptomatic.^{12,13} Thus, prior studies of patients with HF provided limited insight into how the combination of depressive symptoms with HF severity might affect functional status.

Accordingly, determining the impact of depressive symptoms on functional status using a clinical indicator of HF severity other than LVEF may be valuable. N-terminal pro-B type natriuretic peptide (NT-proBNP) is considered a diagnostic biomarker for HF and a useful indicator of treatment effectiveness and HF prognosis.^{2,14} NT-proBNP is increased in systolic or diastolic dysfunction and markedly increased in decompensated HF.¹⁴ Elevated NT-proBNP is associated with increased HF symptom severity, higher risk of mortality, and worse functional status.^{2,14} In a previous study, we demonstrated that elevated NT-proBNP serum levels were a strong predictor of event-free survival in the presence of depressive symptoms.¹⁵

Thus, given the diagnostic implications of NT-proBNP and its value in determining the severity of HF, a study of the impact of depressive symptoms on functional status in the context of NT-proBNP serum levels may have clinical significance. The purpose of this study was to determine whether functional status scores differ as a function of depressive symptoms and NT-proBNP levels among patients with HF.

Methods

Design and Sample

This was a cross-sectional, secondary data analysis of data from the Heart Failure Quality of Life registry. The registry methods have been previously reported in detail.^{16,17} A sample of 284 patients with HF who had baseline data on DASI, depressive symptoms, and serum NT-proBNP levels were included in this study.

All 7 studies in the registry had similar inclusion and exclusion criteria: documented diagnosis of HF with either reduced ejection fraction (HFrEF; LVEF < 40%) or preserved ejection fraction (HFpEF) confirmed by a cardiologist. Patients were excluded if they were non-English speaking, had been referred for heart transplantation, had a history of cerebral vascular accident or acute myocardial infarction within the previous three months, or had terminal illnesses such as active cancer or end-stage liver failure. Patients were recruited from academic medical centers and community-based clinics in the Southeast and Midwest.

Measures

Depressive symptoms—Depressive symptoms were measured using the Beck Depression Inventory-II (BDI-II). The BDI-II includes 21 items assessing the presence and severity of the cognitive and physical symptoms of depression.¹⁸ Patients rated each depressive symptom on a scale ranging from 0 to 3, with 0 indicating an absence of the symptom and higher values indicating greater severity of the symptom. The total score can range from 0 to 63; the higher the score, the more severe the depressive symptoms. The cut point of 14 was used to indicate the presence of clinically significant depressive symptoms.¹⁹ The reliability and validity of BDI-II have been supported in both non-medical population and individuals with medical diseases.^{20,21}

NT-proBNP—NT-proBNP is released into the blood from left atrial and ventricular myocytes in response to volume overload and increased the filling pressure that occurs with myocardial dysfunction.¹⁴ Elevated NT-proBNP in patients with HF is associated with poor outcomes including functional status impairment.^{2,14} A lower serum NT-proBNP level is an indicator of successful HF management.^{2,14,22} NT-proBNP levels were measured from serum samples that were collected immediately after enrollment using enzyme immunoassay kits (ALPCO Diagnostics). The analytic performance of the enzyme immunoassay was previously reported in detail.²² The analytical range extended from 5 to 1000 fmol/ml.

Functional status—Duke Activity Status Index (DASI) was used to measure functional status. This is a generic measure of functional status, which is more appropriate for determining the impact of different health problems on functional status across different health problems.²³

The DASI is a 12-item self-report scale measuring patients' perception of ability to perform a spectrum of usual daily activities.²⁴ Light-intensity activity levels include the following: activities that need light-mild physical exertion to accomplish (personal care [one item], ambulation [two items], and housework [two items]). Vigorous-intensity activity levels include the following: activities that need moderate-strenuous physical exertion to

accomplish (ambulation [two items], housework [one item], yard work [one item], sexual activity [one item], and recreational activities [two items]). Patients indicated yes or no as a response to their ability to complete each activity comfortably. Ability to perform each activity is weighted by the estimated metabolic equivalents (MET) cost associated with performing that activity (weighting activities ranges from 1.75–8.0 MET). The weighted scores for the 12 activities were summed. Total scores range from 0 – 58.2, with higher scores indicating greater functional status. Determining self-perception of functional status has an important clinical implication as poor perceived functional status is one of the major reasons for frequent physician visits and hospitalization.^{25,26} The DASI has been demonstrated to be responsive to clinical changes associated with cardiac disease.²⁷ The reliability and validity of the DASI have been established.²⁴

Demographic and clinical characteristics—Age, gender, ethnicity, marital status, educational level, employment status, body mass index (BMI), anti-depressant medication therapy, and LVEF were collected by patient interview and medical record review.

Procedure

Appropriate Institutional Review Board approval was obtained from all registry study sites. All patients were referred to the studies by nurses or physicians. Patient eligibility was confirmed from the medical record by trained research nurses. Eligible patients were contacted at their regular clinic visit and gave written informed consent to participate. Participating eligible patients completed DASI and BDI-II measures and provided a blood sample in a tube containing EDTA for NT-proBNP assay. Research nurses read the questionnaire to patients who had difficulty reading. Demographic and clinical characteristics were collected at the same time.

Data analysis

The data were analyzed using SPSS software for Windows (version 23.0; IBM Corporation). Data were examined, verified, and cleaned prior to analysis. Appropriate descriptive statistics (frequencies and percentages or means and standard deviations depending on the level of measurement) were used to characterize the sample.

Patients were divided into 4 groups according to the median split of NT-proBNP levels and presence of depressive symptoms: 1) low NT-proBNP ≤ 562.5 pg/ml without depressive symptoms, 2) low NT-proBNP ≤ 562.5 pg/ml with depressive symptoms, 3) high NT-proBNP > 562.5 pg/ml without depressive symptoms, and 4) high NT-proBNP > 562.5 pg/ml with depressive symptoms. One way analysis of variance (ANOVA) with the Least Significant Difference post hoc tests or chi-square tests were used to examine demographic and clinical differences among 4 groups. A nonlinear regression was run to determine whether group membership predicted higher (better) functional status scores with gender and prescribed antidepressants (yes/no) included as factors and age and BMI as covariates based on previous studies.^{15,28,29} An alpha .05 was considered significant.

Results

Sample Characteristics

Among the 284 patients included in this study, 104 had low NT-proBNP levels and without depressive symptoms, 38 had low NT-proBNP levels with depressive symptoms, 111 had high NT-proBNP levels and without depressive symptoms, and 31 had high NT-proBNP levels with depressive symptoms. Comparisons of group characteristics are summarized in Table 1. The average age of patients was 61 years (range 32 – 89 years). Patients were predominantly male and Caucasian. Nearly half of the patients were obese and most had heart failure with reduced ejection fraction. Clinically significant depressive symptoms were presented in a quarter of the patients and more than a quarter of the patients were prescribed antidepressant medication. On average, the patients in the high NT-proBNP levels and low depressive symptom group were older and had lower mean BMI than patients in the other 3 groups. A greater proportion of patients with depressive symptoms were prescribed antidepressant medication regardless of NT-proBNP levels.

Predictors of DASI Scores

Results of the non-linear regression for predictors of DASI functional status scores are presented in Table 2. Age, gender, prescribed antidepressants, and BMI were not significant predictors of functional status scores. Patients in the groups with no depressive symptoms were more likely to have higher (better) functional status scores than patients in the groups with depressive symptoms, regardless of NT-proBNP levels. Specifically, patients with low NT-proBNP levels and no depressive symptoms were nearly 2.9 times more likely, while patients with high NT-proBNP levels and no depressive symptoms were nearly 2.4 times more likely to have better functional status scores than patients with high NT-proBNP levels and depressive symptoms. There was no significant difference in the likelihood of functional status scores between the 2 groups with depressive symptoms.

Discussion

To achieve the aim of this study, we compared the independent and combined impact of depressive symptoms and high NT-proBNP on functional status. This approach was useful in quantifying the impact of depressive symptoms and HF on functional status in a clinically meaningful manner. We demonstrated that the worst functional status scores were in patients from the groups with depressive symptoms regardless of NT-proBNP serum levels. Between the groups without depressive symptoms, functional status scores were lower (worse) in the higher NT-proBNP group than the lower NT-proBNP group, suggesting NT-proBNP had some effect on functional status scores in the absence of depressive symptoms. However, the results of the nonlinear regression suggest that the primary variable predicting worse functional status scores was depressive symptoms after accounting for age, gender, prescribed antidepressants, and BMI.

Our results concur with previously reported findings.^{8,30,31} Depressive symptoms were found to be associated with decreased functional status based on self-rated measures of ability to perform activities of daily living (ADLs). Our results are also supported by

findings from previous studies in which functional status was measured objectively. Patients with HF and comorbid depressive symptoms were noted to exhibit lower functional ability and lower maximal function on cardiopulmonary exercise test and 6-minute walk test than those without depressive symptoms.^{7,8} Depressive symptoms were found to be associated with a lower physical function in patients with HF as indicated by total daily accelerometer step counts.^{7,32} This suggests that the relationship between depressive symptoms and functional status is similar using either objective or subjective measures of functional status.

Several factors are proposed to explain our findings. First, HF symptoms of dyspnea and fatigue are associated with activity intolerance and decreased functional status.³³ Perceptions of these symptoms are noted to be increased in presence of depressive symptoms resulting in a greater reduction in perceived functional status.^{30,31,34} Second, sedentary lifestyle is often associated with depressive symptoms which can lead to further reduction in functional status.^{8,32,33}

Our finding that patients with increased NT-proBNP serum levels without depressive symptoms have lower functional status scores than non-depressed patients with low NT-proBNP levels is consistent with the previous studies.¹⁴ Increased NT-proBNP serum level was considered a reflection of increased HF severity and poorer prognosis which may be reflected in lower functional status scores.^{2,14} However, our finding demonstrates that presence of depressive symptoms was a stronger predictor of functional status than increased NT-proBNP serum levels. This is in line with prior observations that depressive symptoms were a strong predictor of functional status after controlling for LVEF.^{8,30,32}

Researchers suggested that somatic depressive symptoms included in BDI total scores may overestimate depressive symptoms and its impact on functional status in patients with HF compared with non-medically ill individuals.³⁵ However, the psychometric properties of BDI were previously supported in a large number of studies among different populations with medical illness, which makes BDI one of the most widely used measures of depressive symptoms in clinical studies, including patients with HF.^{35,36} The prevalence of depressive symptoms in this study was approximately 25%, which is comparable to the prevalence reported by previous studies that used different measures of depressive symptoms.^{6,15} In a previous study, somatic depressive symptoms scores on Patient Health Questionnaire were demonstrated to have a weak prediction ability to HF outcomes compared with affective depressive symptoms scores.³⁷ Patients with cardiac disease were noted to have somatic depressive symptoms scores on BDI similar to the outpatients with mental illness matched on age, gender, and affective depressive symptoms.³⁸ Gottlieb et al.⁸ found that severity of HF did not have an impact on BDI total scores including somatic and affective depressive symptoms. Thus, the BDI total score can be used to assess the impact of depressive symptoms on functional status in patients with HF.

It is of interest to note that a large percentage of patients in this study who reported depressive symptoms were prescribed antidepressants. This indicates that depressive symptoms were not adequately treated in these patients. The results of this study suggest that improved treatment of depressive symptoms in patients with HF should also be associated with improved functional status regardless of HF severity. Ongoing assessment of depressive

symptoms with optimization of antidepressant medication, combined with non-pharmacological interventions such as cognitive behavioral therapy has been demonstrated to be effective in decreasing depressive symptoms and improving functional status in patients with HF.³⁹

Several limitations should be considered in interpreting the results of this study. First, the study is cross-sectional which limits the ability to make inferences about causality. Second, most patients in our sample were Caucasian males and, therefore, the results may not be generalizable to other HF populations. Third, we measured NT-proBNP serum level at one time only. NT-proBNP serum level is not a reflection of long-term cardiac function. However, because functional status was measured at the same time at NT-proBNP levels, the levels provide a good reflection of the relationship between NT-proBNP levels and functional status. Fourth, categorizing patients into 4 groups by depressive symptoms and NT-proBNP levels resulted in small sample size in some groups. However, the sample sizes were sufficient to detect meaningful differences among groups.

Conclusion and Clinical Implications

In this study, we showed that the presence of depressive symptoms was a predictor of functional status, regardless of NT-proBNP serum levels. These results suggest that depressive symptoms and NT-proBNP levels may vary limited association with perceived functional status. In patients who have worsening functional status despite lower NT-proBNP serum levels or maximal therapy, consideration must be given for monitoring and treatment of depressive symptoms.

The major finding of this study was that patients with depressive symptoms had the lowest functional status regardless of NT-proBNP levels. Consequently, adequate treatment of depressive symptoms may lead to a greater improvement in patients' functional status.

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What's New?

- Comorbid depression was a stronger predictor of functional status in patients with heart failure than elevated N-terminal pro-B type natriuretic peptide.
- Adequate treatment of depressive symptoms may lead to a greater improvement in patients' functional status across all levels of heart failure severity.

Table 1

Sample Characteristics

	Whole sample (n = 284)	Low BNP/ no depressive symptoms (n = 104)	High BNP/ no depressive symptoms (n = 111)	Low BNP/ depressive symptoms (n = 38)	High BNP/depressive symptoms (n = 31)
Age	61 ± 11.4	58.8 ± 10.6	65.5 ± 11.4 [*]	56.0 ± 9.0	58.0 ± 11.4
Female	91 (32.0)	35 (33.7)	27 (24.3)	17 (44.7)	12 (38.7)
Ethnicity					
Caucasian	227 (79.9)	77 (74.0)	95 (85.6)	31 (81.6)	24 (77.4)
African American	53 (18.7)	26 (25.0)	15 (13.5)	7 (18.4)	5 (16.1)
Other	4 (1.4)	1 (1.0)	1 (0.9)	0 (0)	2 (6.5)
BMI (kg/m ²)	31.7 ± 7.5	32.7 ± 7.6	30.0 ± 7.0 [*]	33.8 ± 7.9	32.1 ± 7.8
LVEF (%)	34.5 ± 14.6	35.4 ± 14.0	32.9 ± 14.9 ^{**}	39.2 ± 14.4	31.7 ± 14.7 ^{**}
HF+HF 40%	202 (71.1)	73 (70.2)	82 (73.9)	24 (63.2)	23 (74.2)
Antidepressant medication	73 (25.7)	16 (15.4)	21 (18.9)	21 (55.3) ^{***}	15 (48.4) ^{***}
DASI Score	15.4 ± 14	19.9 ± 15 [*]	15.8 ± 13 [*]	9.02 ± 11 ^{***}	6.9 ± 6.0 ^{***}

BNP: NT-pro B-type natriuretic peptide; BMI: body mass index; LVEF: left ventricular ejection fraction; HF+HF: reduced ejection fraction; DASI: Duke Activity Status Index. Data are presented as mean ± SD or n (%).

^{*} vs. all other groups; p<.05;

^{**} vs. low NT-proBNP level groups; p<.05;

^{***} vs. no depressive symptom groups; p<.05

Table 2

Predictors of Higher DASI Scores.

Predictor	Exp (B)	95% Confidence Interval	P
Gender	1.09	.83 – 1.4	.501
Prescribed Antidepressant	1.1	.77 – 1.5	.649
Age	.98	.98 – 1.0	.051
BMI	.98	.97 – 1.0	.089
Low BNP/No Depressive Symptoms	2.87	1.82 – 4.4	.000
High BNP/No Depressive Symptoms	2.36	1.5 – 3.7	.000
Low BNP/High Depressive Symptoms	1.4	.82 – 2.5	.237
High BNP/High Depressive Symptoms	Reference		

DASI: Duke Activity Status Index; BNP: NT-proB-type natriuretic peptide; BMI: body mass index