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Depressive symptoms in heart failure: Independent prognostic factor or marker of functional status?

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ABSTRACT

Objective: The prognostic potential of depressive symptoms independent of somatic features of heart failure severity has repeatedly been demonstrated. However, patient-reported functional status has rarely been accounted for in these studies. Thus, it has remained unclear to what extent the predictive power of depressive symptoms may mirror functional status. We therefore aimed to evaluate the prognostic value of depressive symptoms adjusting for patient-reported functional status in a large, well-characterized sample of patients with systolic heart failure.

Methods: Eight hundred sixty-three patients, 67 ± 12 years old, 72% men, and 42% with New York Heart Association functional classes III/IV, who participated in the extended Interdisciplinary Network Heart Failure (INH) study were investigated. We assessed depressive symptoms using the Patient Health Questionnaire (PHQ-9) and patient-reported functional status with the Kansas City Cardiomyopathy Questionnaire (KCCQ). Data on survival was obtained after a follow-up of 18 months (100% complete).

Results: Depressive symptoms predicted mortality risk (HR per PHQ-9 scale point = 1.07, 95% CI 1.04–1.09, $p < .001$), even after adjustment for heart failure severity and co-morbidities (HR = 1.04, 95% CI 1.01–1.07, $p = .017$). However, they were no longer significant predictors (HR = 1.01, 95% CI 0.98–1.05, $p = 0.46$) after additional adjustment for patient-reported functional status, which proved predictive of mortality risk (HR = 0.90, 95% CI 0.82–0.99, $p = .025$).

Conclusion: Our results suggest that the association of depressive symptoms with functional status may at least partly explain the prognostic potential of depressive symptoms.

Introduction

Depression is common in heart failure and associated with adverse outcomes [1]. Although the relationship between depression and mortality may be complex, it is a matter of ongoing debate whether this relation is causal or rather a result of illness severity being the confounding variable of both depression and survival [2,3].

Exploring the association between depression and mortality risk via adjustment for patient-reported functional status has rarely been attempted in heart failure patients so far. Previous research has shown that depression is more closely related to measures of perceived health status than to objective indicators of disease severity such as left ventricular ejection fraction [4]. Thus, the prevalence of depressive symptoms increased with increasing functional limitations according to higher New York Heart Association (NYHA) class ratings [5]. Patients' as opposed to physicians' ratings of functional status might provide a more representative and robust estimate of the impact of heart failure on patients' functioning in everyday life, however.

Patient-reported functional status has been established as an independent predictor of mortality risk in heart failure [6–8]. However, most studies did not adjust for depressive symptoms, and those that did reported inconsistent results [9–11]. No study so far examined whether the relationship between higher levels of depressive symptoms and higher mortality risk was due to an overlap of depressive symptoms with patients' functional status.

Therefore, the present study examined during an 18-month observation period a large, well-characterized heart failure patient sample in order to clarify the potential value of depressive symptoms in predicting mortality risk when at the same time patients' functional

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status is taken into account. We hypothesized that depressive symptoms would predict higher mortality risk, independent of somatic indicators of severity of heart failure. We further hypothesized that adjustment for patient-reported functional status would attenuate this relationship.

Method

Subjects and study design

This study was based on a secondary analysis of data from the extended Interdisciplinary Network for Heart Failure (INH) study (trial registration no. ISRCTN23325295) which evaluated a telephone-based, nurse-coordinated disease management program (*HeartNetCare-HF*™, HNC) for patients with systolic heart failure, i.e. left ventricular ejection fraction ≤40% at hospital discharge. The design of the INH study was published previously [12]. Prior to discharge (baseline), patients underwent a standardized, in-depth evaluation including self-reported depressive symptoms and functional status. The study was approved by the Ethics Committee of the Medical Faculty of the University of Würzburg, Germany, and complied with the Declaration of Helsinki and Good Clinical Practice. All participants provided written informed consent.

Psychometric evaluation and outcome

Depressive symptoms were assessed using the German version of the Patient Health Questionnaire depression module PHQ-9 [13]. This 9-item self-report tool assesses the intensity of 9 symptoms that represent the diagnostic criteria for a depressive episode according to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV), and has been recommended to be used for depression screening in cardiovascular diseases [14]. PHQ-9 scores may range from 0 to 27, with higher scores indicating more severe depressive symptoms.

Patients' self-reported functional status was assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ). Both the original U.S. [15] and the German versions [16] of this widely used tool were found reliable and valid. The Functional Status summary scale covers both physical limitation during everyday activities, such as walking and climbing stairs, and heart failure symptoms including edema, tiredness, and dyspnea. Scores may range from 0 to 100, with higher scores indicating better functional status.

The outcome variable was time from study entry to all-cause death, collected after 18 months from hospital records, death certificates and reports from relatives and physicians. No patient was lost to follow-up.

Data analysis

Cox proportional hazards regression was used to determine the relationship between depressive symptoms and survival, and hazard ratios (HR) with their 95% confidence intervals (CI) were reported. First, we employed univariate analysis (Model A). Second, in a multivariable model (Model B), we adjusted for demographic and somatic correlates of depression and other relevant factors, such as age, sex, New York Heart Association (NYHA) functional class, left ventricular ejection fraction <30%, amino-terminal pro-brain natriuretic peptide (NT-proBNP), systolic blood pressure, heart rate, heart failure etiology, renal dysfunction (estimated glomerular filtration rate [GFR] <60 mL/min/1.73 m^2), anemia (hemoglobin [g/dl] <13 [male], <12 [female]), diabetes, and pharmacotherapy [5]. Third, patient-reported functional status was accounted for by adding the KCCQ Functional Status scale (divided by 10) to the multivariable model (Model C). To quantify possible multicollinearity, we regressed the KCCQ Functional Status scale on all other predictors, obtained the multiple determination coefficient R^2, and calculated the variance inflation factor (VIF), which is $1/(1\text{-}R^2)$. Both, the PHQ-9 and the KCCQ Functional Status scores were included as continuous variables in the Cox models. A two-sided $p < 0.05$ was considered significant. IBM SPSS 19.0 (Armonk, NY) software was used.

Results

Of the 1022 participants of the extended INH Study, 863 provided self-report data at baseline. Baseline characteristics of the study sample by PHQ-9 score are presented in Table 1. Patients were, as a mean, 67 years old, predominantly male (72%) and had multiple comorbidities.

At 18-month follow-up, 154 deaths had occurred. In the univariate analysis, depressive symptoms (PHQ-9 sum score) predicted survival (Table 2, Model A). Each additional point on the PHQ-9 scale (range 0 to 27) conferred a risk increase by 7% ($p < 0.001$).

After adjusting for multiple covariates, including age, sex, indicators of HF disease severity (NYHA functional class, left ventricular ejection fraction, NT-proBNP), risk factors, co-morbidities, and medication, this association remained significant ($p = 0.017$), but the risk increase per PHQ-9 score point reduced to 4% (Table 2, Model B).

The final model included patient-reported functional status as measured by the KCCQ (Table 2, Model C). In this final model, depressive symptoms lost their predictive power, whereas patient-reported functional status predicted survival ($p = 0.025$), the hazard ratio indicating a reduction of survival probability of 10% per 10-point decrement of the KCCQ Functional Status scale.

The correlation coefficient between the PHQ-9 and the KCCQ Functional Status scale was $r = -0.61$ ($p < 0.001$). The variance inflation factor amounted to 2.00, which is not indicative of major multicollinearity between the KCCQ Functional Status scale and the other predictors from Model C, including PHQ-9.

Discussion

We could confirm our first hypothesis showing that depressive symptoms predicted worse survival, not only in the univariate analysis, but also after adjusting for multiple covariates including NYHA class, NT-proBNP, and comorbidities [5,17].

The independent prognostic power of depressive symptoms is consistent with previous research [1,2,18]. Several mechanisms have been proposed to explain the effects of depression on mortality in cardiovascular diseases [19,20]. These include biological pathways, such as autonomic nervous system dysfunction as evidenced by low heart rate variability, inflammation, and endothelial dysfunction. Moreover, impaired therapy adherence [21] and unfavorable health behaviors, particularly less physical activity [22], have also been suggested as

Table 1
Baseline characteristics of the sample.

	Total (n = 863)
Demographics	
Age, mean (SD)	67.0 (12.4)
Female sex, n (%)	239 (27.7)
CAD as cause of HF, n (%)	432 (50.1)
Heart failure severity	
NYHA class III/IV, n (%)	365 (42.3)
LVEF ≤ 30%, n (%)	418 (49.6)
NT-proBNP, pg/ml, mean (SD)	5661 (7498)
Measurements	
Systolic blood pressure, mm Hg, mean (SD)	120.6 (17.9)
Heart rate, beats/min, mean (SD)	79.9 (18.9)
Co-morbidities	
Renal dysfunction, n (%)	341 (39.5)
Anemia, n (%)	275 (31.9)
Diabetes, n (%)	294 (34.1)
Malignant disease, n (%)	102 (11.8)
Pharmacotherapy	
ACE inhibitor/ARB, n (%)	772 (89.5)
Betablocker, n (%)	726 (84.1)
Aldosterone antagonist, n (%)	369 (42.8)
Glycoside, n (%)	303 (35.1)
Diuretic, n (%)	745 (86.3)
Statin, n (%)	407 (47.2)
Psychometric assessment	
PHQ-9 sum score, mean (SD)	7.7 (5.6)
KCCQ Functional Status, mean (SD)	60.0 (25.0)

PHQ, Patient Health Questionnaire; CAD, coronary artery disease; HF, heart failure; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; NT-proBNP, amino-terminal pro-brain natriuretic peptide; ACE, angiotensin converting enzyme; ARB, angiotensin-2 type-1 receptor blocker; KCCQ, Kansas City Cardiomyopathy Questionnaire.