Depression and survival in chronic heart failure: Does gender play a role?

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Abstract

Background: Data regarding the influence of depression on outcome in chronic heart failure are conflicting and neglect possible gender differences.

Aims: To investigate prevalence and prognostic importance of depression in a cohort of patients with symptomatic heart failure and to compare findings in males and females.

Methods: Depression was measured at study entry using a self-reported 9-item Patient Health Questionnaire (PHQ-9) in 231 consecutive outpatients. The median follow-up time was 986 (IQR = 664–1120) days.

Results: The prevalence of suspected major depression was 13% (minor depression, 17%) and was not different between the sexes. Major (but not minor) depression was associated with an increased mortality risk (hazard ratio [HR] = 3.3, 95% confidence interval = 1.8–6.1, \( p < 0.001 \)). This relationship remained significant after adjustment for other prognostically relevant factors as age, sex, heart failure aetiology, degree and type of left ventricular dysfunction, and New York Heart Association functional class. However, testing the effect of the interaction between gender and depression failed to reach significance (\( p = 0.37 \)).

Conclusion: Our data confirm a high prevalence of depression in chronic heart failure. Further, they prove an independent prognostic impact of major, but not minor, depression. Possible gender differences regarding the prognostic impact of depression require further investigation in a larger patient cohort.

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1. Background

In patients with chronic heart failure (CHF), depression is a frequent comorbidity. Among hospitalised patients, the reported prevalence of major and minor depression was 20% and 16% respectively [1]. In patients with left ventricular dysfunction, the respective rates were 14% and 13% [2]; however, in some studies even higher rates have been reported [3,4]. The evidence linking depression and survival in chronic heart failure is inconclusive. Although some studies have found that depression predicts higher mortality [5–10], others have not [11–14]. In particular, it is unclear whether this association results solely from covariance of depression and the severity of heart failure. Moreover, previous studies have not addressed the question of whether the impact of depression on prognosis is comparable in men and women.

2. Aims

We therefore conducted a prospective cohort study addressing the following questions. (1) What is the prognostic impact of depression in patients with chronic heart failure after adjusting for established important variables known to affect survival? (2) Is the prognostic importance of depression comparable in both sexes?
3. Methods

3.1. Subjects

Between June 2002 and December 2003 the prospective cohort study ‘Würzburg Interdisciplinary Network for Heart Failure’ (INH) recruited all consecutive patients presenting with CHF of any aetiology and severity at two Würzburg University Medical Centers \((n=1054)\). Both facilities offer unrestricted access to inpatient cardiology care and outpatient CHF assessment for the general population. Patients were identified using dedicated hospital software screening for ICD codes. Subjects were eligible regardless of their mode of admission. There were no exclusion criteria. Patients gave written informed consent with their obligatory treatment contract signed at hospital entry or on registration with the outpatient department.

Left ventricular (LV) dimensions and fractional shortening were measured by M-Mode echocardiography, and diastolic filling characteristics were assessed by Doppler techniques. Patients were eligible to participate in INH if they had either impaired LV systolic function (ejection fraction <40%) or preserved LV function (ejection fraction ≥40%), with abnormal diastolic filling characteristics in addition to typical signs and symptoms (at least one of the following: raised jugular venous pressure, peripheral oedema, third heart sound, pulmonary congestion at clinical examination or chest X-ray). Baseline laboratory parameters, medication at study entry and medical history were collected using standardized questionnaires. Follow up of the entire population was performed between May and August 2005 (100% complete). All-cause mortality was ascertained either from death certificates, from hospital reports or from general practitioners.

For the purpose of the present study, voluntary psychometric evaluation was offered to all subjects entering the prospective cohort study by the medical staff in charge of the clinical management of these patients. Thus, the sub-sample included all consecutive patients who were willing to sign a separate informed consent form, which was the precondition for participation in the psychometric assessment. No patient providing informed consent was excluded. The study design was approved by the Ethics Committee of the University of Würzburg, Germany.

3.2. Measurements

Depression was assessed using the German version of the Patient Health Questionnaire depression module PHQ-9 [15]. This 9-item self-report screening tool yields the probable diagnosis of a current episode of major or minor depression using a categorical algorithm. A current episode of major depression was suspected, if patients reported that five or more out of nine symptoms were present on more than 50% of the days of the preceding two weeks including at least one of the two following core symptoms, (1) little interest or pleasure in doing things, and (2) feeling down, depressed or hopeless. The diagnosis of an episode of minor depression required two to four of the symptoms on more than 50% of the days of the preceding two weeks. The PHQ-9 diagnosis of depression compares favourably to other screening instruments in validation studies using the Structured Clinical Interviews for ICD-10 [16] or DSM-IV as reference standards [17]. Recently, the PHQ-9 has been recommended as a screening instrument for depression specifically in patients with heart disease as its compactness and diagnostic validity make it a particularly appropriate tool in more severely ill individuals [18].

3.3. Data analysis

The outcome variable was time from study entry to all-cause death. Follow-up assessment of patient survival was performed between May and August 2005. The median follow-up time was 986 (IQR=664–1120) days. No patient was lost to follow-up. Kaplan–Meier probabilities of survival were computed. Cox proportional hazards regression was used to determine the relationship between depression and survival, with and without adjusting for established biomedicai prognostic factors (age, sex, aetiology, ejection fraction, type of left ventricular dysfunction, NYHA functional class). The hazard ratio (HR) is the relative risk attributable to an increase by one unit in the level of a prognostic variable. The assumption of proportional hazards was checked by plotting the log-minus-log functions. A two-sided \(p<0.05\) was considered significant. SPSS 13.0 software (SPSS, Inc., Chicago) was used.

4. Results

Demographics and clinical characteristics of the entire INH study population \((n=1054)\) are described elsewhere [19]. Table 1 shows the baseline characteristics of the sub-sample of patients who participated in this study \((n=231)\). The mean age of participants in the present analysis was lower than in non-participating subjects \((64±13\text{ years versus }73±12\text{ years}, p<0.001)\), and the proportion of men was higher (71% versus 57%, \(p<0.001\)). Heart failure aetiology in the sub-sample was coronary artery disease (CAD) in 43%, dilated cardiomyopathy (CMP) in 22%, hypertension in 14%, and other diseases in 21%. The corresponding figures for the non-participating subjects were 45% CAD, 13% CMP, 18% hypertension, and 24% other causes \((p=0.001)\). One hundred and twenty one (52%) patients in the sub-sample had systolic heart failure with a mean ejection fraction of 33.0%, and 108 (47%) had non-systolic heart failure with a mean ejection fraction of 56.5%; whereas in non-participating subjects 47% had systolic heart failure and 53% non-systolic heart failure \((p=0.117)\). In the present study, the percentage of patients in NYHA functional classes I to IV were 25%, 44%, 25%, and 6% respectively, while NYHA class distribution was 11%/24%/46%/18% in non-participating patients \((p<0.01)\). Thus, in this study patients...
were younger, more often male and had less severe CHF compared with the entire INH cohort.

Of the patients in the sub-sample with systolic heart failure, 77% were males and 23% females, and the distribution of NYHA classes I to IV was 25/43/25/7%. In patients with non-systolic heart failure, 63% were males and 37% females (p=0.022), and the distribution of NYHA classes was 26/45/25/4% (p=0.68).

Male and female participants differed significantly with respect to age and ejection fraction, with women being older (66.6±10.5 vs. 63.3±13.3, p=0.042), with more non-systolic heart failure (59% vs. 42%, p=0.022). In addition, ischaemic aetiology of heart failure was less frequent in women. Moreover, a trend was observed regarding higher NYHA functional class ratings among women. However, these factors were controlled for in the multivariable analyses. Regarding medication, ACE inhibitors were less frequent and diuretics more frequent in women than in men. However, adjustment for these variables did not change the results (detailed data not shown).

At the time of study inclusion, according to the PHQ-9, 31 (13%) patients had a suspected current episode of major depression and 38 (17%) minor depression. Although more women (18%) than men (12%) suffered from major depression, the prevalence rates of major and minor depression among male (12% and 17%, respectively) and female (18% and 16%, respectively) patients did not differ significantly (χ²=1.5, df=2, p=0.47). The proportion of depressed patients doubled from NYHA classes I/II (23%) to III/IV (46%) (χ²=11.6, df=1, p=0.001). The prevalence of depression was independent of age, left ventricular ejection fraction, aetiology (coronary artery disease vs. other), diabetes mellitus, hypertension, obesity, hypercholesterolaemia, renal dysfunction at baseline as well as medical treatment by angiotensin conversion enzyme inhibitors, aldosterone antagonists, diuretics, and beta blockers (Table 1).

During a median follow-up period of 986 (IQR=664–1120) days, 59 (26%) patients died. Among men, the numbers of deaths were 24 (no depression), 7 (minor depression), and 10 (major depression); the respective figures among women were 8, 4, and 6. In the univariate analysis, major depression, as compared to no depression, was predictive of shorter survival (Fig. 1A; Cox proportional hazards regression, HR=3.3, 95% confidence interval [CI]=1.8–6.1, Wald χ²=15.2, df=1, p<0.001). By contrast, the difference between minor depression and no depression was not significant (HR=1.6, 95% CI=0.8–3.1, Wald χ²=1.6, df=1, p=0.20).

In multivariable regression, the association between major depression and shorter survival remained predictive albeit somewhat attenuated (HR=2.4, 95% CI=1.3–4.6, Wald χ²=7.0, df=1, p=0.008) after entering age, sex, aetiology (coronary artery disease vs. other), NYHA functional class, ejection fraction, type of left ventricular dysfunction (systolic vs. non-systolic), and the interaction term between ejection fraction and type of left ventricular dysfunction. However, testing the effect of the interaction between gender and depression failed to reach significance (p=0.37).

Major depression was also predictive of reduced survival when the female sub-sample was studied separately in univariate (HR=2.9, 95% CI=1.1–7.8, Wald χ²=4.6, df=1, p=0.032) and multivariable analyses (HR=4.5, 95% CI=1.3–15.8, Wald χ²=5.4, df=1, p=0.021; Fig. 1C). In men, depression was also predictive in the univariate analysis (HR=3.3, 95% CI=1.6–7.0, Wald χ²=10.1, df=1, p=0.001).
p=0.001), while a suggestive trend was observed in the multivariable analysis (HR=2.4, 95% CI=1.3-4.6, Wald \(\chi^2=3.0, df=1, p=0.08;\) Fig. 1D). Thus, adjusting for additional prognostic variables reduced the predictive power of depression in men while increasing the prognostic relevance in women probably due to elimination of the effect of suppressor variables.

5. Discussion

In this study, we have shown that depression in heart failure confers increased mortality risk. This finding is consistent with previous research [5–10]. Although the adverse effect of depression on prognosis in CAD has previously been documented in women [20,21], this issue has not previously been studied in CHF. Although hazard ratios appeared to be different among women and men, testing the interaction term gender by depression failed to reach significance. Thus, we could not confirm different estimates of mortality risk in depressed males and females. Due to the small sample size, statistical power may have not been sufficient to detect a difference in mortality risk. Therefore, this hypothesis needs to be tested in a larger sample of patients.

In our study, we found that a suspected current episode of major depression was associated with a significantly
increased mortality risk even after adjustment for established prognostic factors including heart failure severity. This is especially remarkable as depression and NYHA functional class share common variance [2]. Thus, a higher functional class may reflect a more severe burden of illness which in itself may contribute to the development of depression. Conversely, depressed patients are likely to experience more pronounced functional impairment, which will result in higher NYHA functional class ratings. Of the previous studies that demonstrated a positive correlation between the suspected diagnosis of depression and impairment of survival, some [5–7], but not all [8–10] adjusted for NYHA functional class.

In our study, a suspected episode of minor depression was not predictive of impaired survival; however, patient numbers may have been too small to detect a less pronounced prognostic effect of minor depression.

Although in our sample more women than men suffered from major depression, the prevalence rates of both major and minor depression were not significantly different between the sexes, probably due to the small size of the female sub-sample. While several publications describe a higher risk of depression in women compared with men in the general population [22,23], in the elderly [24], and in patients with cardiac disease [2,25], our results suggest that there still might be differences regarding the determinants of depression in both sexes. Whereas in males, adjustment for other prognostically relevant factors attenuated the increased hazard ratio, the prognostic effect of depression in females was worsened by this procedure. This seems to indicate differences between males and females regarding the pathogenesis of this comorbidity. Again, larger trials are needed to further address and clarify this issue.

Certain limitations need to be considered in the interpretation of the present findings. We investigated a consecutive heterogeneous cohort of patients with chronic heart failure across all NYHA classes with reduced as well as preserved ejection fraction. Patients participating in our study were more likely to be younger, male and healthier than non-participants. Since functional state and depression are correlated, it is possible that compared with the total cohort the prevalence of depression was lower in our sub-sample because patients with more severe depressive symptoms such as loss of energy might have been more likely to refuse participation. On the other hand, it might also be possible that the prevalence rates of depression were higher in our sub-sample than in the entire INH cohort, as the depressed patients may have made disproportionate use of the opportunity to report on their psychological state. We believe that although our study shares this possible uncertainty regarding patient acquisition with other trials, this may constitute a limitation to generalisation of our findings regarding the prevalence of depression. However, since our findings are in accordance with prevalence rates in previous trials [1–4], this limitation is unlikely to affect the validity of results regarding prognosis. The small sample size of this investigation in relation to the number of events precluded more detailed analyses of confounders and reduced the power of subgroup analyses according to sex. A further limitation is that self-reports of depression were not confirmed by a structured interview. However, excellent sensitivity (98%) and specificity (80%) of the PHQ-9 in particular regarding major depression are well established [17]; moreover, false positive diagnoses of depression in some patients would have weakened rather than incorrectly strengthened the relationship between depression and survival found in this study.

Depression may influence mortality not only via behavioural pathways such as reduced compliance with therapy [26] but also via direct biological mechanisms involved in the pathogenesis of both coronary artery disease and chronic heart failure [27–30]. If depression were a causal risk factor, successful treatment of depression might yield improved survival. So far, such studies have been inconclusive in CAD [31] and are completely lacking in CHF. Prospective randomised trials to address this important issue, including possible sex related differences are urgently needed.

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References


