Depression as an independent prognostic factor for all-cause mortality after a hospital admission for worsening heart failure

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ABSTRACT

Background: Depression is associated with increased mortality amongst patients with chronic heart failure (HF). Whether depression is an independent predictor of outcome in patients admitted for worsening of HF is unclear.
Methods: OPERA-HF is an observational study enrolling patients hospitalized with worsening HF. Depression was assessed by the Hospital Anxiety and Depression Scale (HADS-D) questionnaire. Comorbidity was assessed by the Charlson Comorbidity Index (CCI). Kaplan–Meier and Cox regression analyses were used to estimate the association between depression and all-cause mortality.
Results: Of 242 patients who completed the HADS-D questionnaire, 153, 54 and 35 patients had no (score 0–7), mild (score 8–10) or moderate-to-severe (score 11–21) depression, respectively. During follow-up, 35 patients died, with a median time follow-up of 360 days amongst survivors (interquartile range, IQR 217–574 days). In univariable analysis, moderate-to-severe depression was associated with an increased risk of death (HR: 4.9; 95% CI: 2.3 to 10.2; P < 0.001) compared to no depression. Moderate-to-severe depression also predicted all-cause mortality after controlling for age, CCI score, NYHA class IV, NT-proBNP and treatment with mineralocorticoid receptor antagonist, beta-blocker and diuretics (HR: 3.0; 95% CI: 1.3 to 7.0; P < 0.05).
Conclusions: Depression is strongly associated with an adverse outcome in the year following discharge after an admission to hospital for worsening HF. The association is only partly explained by the severity of HF or comorbidity. Further research is required to demonstrate whether recognition and treatment of depression improves patient outcomes.

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1. Introduction

Psychosocial illness, including depression, is common in people with cardiovascular disease. Depression is particularly common in patients with heart failure (HF) [1]. Probably most patients with HF are depressed by their illness at some time but a meta-analysis suggests that depression affects about a 20% of patients at any time [2].

For patients with HF, depression is associated with an increased rate of adverse outcomes [2,3], such as hospitalization and death. The aggregated risk-estimate derived from 26 studies was an approximately 1.5-fold risk of death in patients with HF if they had depression [3]. However, it can be difficult to disentangle whether depression *causes* a worse outcome, or merely reflects worse HF or more severe co-morbidity. We aimed to assess the prevalence and consequences of

depression in patients admitted to hospital for worsening HF. We analyzed a prospective patient cohort and controlled for common covariates reflecting the severity of both the HF and any comorbidities.

2. Methods

2.1. Study design

OPERA-HF is an ongoing prospective observational study, enrolling patients hospitalized with worsening heart failure (WHF) to the Hull & East Yorkshire Hospitals NHS Trust, UK. The aim of the study is to gather a holistic view of the patients, their general condition and co-morbidities, and to identify predictors of mortality and re-admission to hospital. Clinical and psycho-social data were collected during hospital admission and just prior to discharge. The Charlson Comorbidity Index (CCI) was used to assess comorbidity (Appendix A).

Patients had to fulfill all of the following criteria to be included in the study: age > 18 years; hospitalization for WHF; treatment with loop

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diuretics; and at least one of the following: left ventricular ejection fraction ≤ 40%, left atrial dimension > 4.0 cm or NT-ProBNP > 400 pg/ml (if in sinus rhythm) or >1200 pg/ml (if in atrial fibrillation). Patients unable to understand and comply with the protocol or unable or unwilling to give informed consent were excluded from the study. The study has full ethical approval from the South Yorkshire Research Ethics Committee (REC ref: 12/YH/0344) and is conducted in accordance with ICH-GCP, Declaration of Helsinki, the Data Protection Act 1998 and the NHS Act 2006.

2.2. Depression assessment

Depression was assessed by the Hospital Anxiety and Depression Scale (HADS-D) questionnaire [4] (Appendix B). The HADS-D focuses on questions about depression. The response to each of the 7 questions is graded from 0 to 3, giving a total score that ranges between 0 and 21. A score of 7 or less implies that there is no depression; a score of 8–10 suggests mild depression; and a score of 11 reflects moderate-to-severe depression [4]. Amongst 12 studies assessing the HADS-D questionnaire (total N = 2109 patients), a cut point of 8 for the diagnosis of depression had a mean specificity of 0.79 and a mean sensitivity of 0.83 when compared with a 'gold standard' diagnosis using DSM-III/IV or similar codes [5].

2.3. Mortality

All patients enrolled in the study are followed subsequent to discharge. Readmissions and all-cause mortality are automatically recorded in the hospital's IT system. For the present report, the primary outcome of interest was all-cause mortality.

2.4. Statistical analysis

We report the baseline characteristics of the patients who participated in the study between 14/10/2012 and 16/06/2015 and who completed the HADS-D questionnaire. Follow up was censored at 13/07/2015. The consort diagram is given in Appendix C.

Univariable and multivariable Cox proportional hazard regression models were used to estimate the association between depression and all-cause mortality. Univariable analysis was performed to assess the relation between variables and outcome, including demographics, clinical assessment, echocardiography and medication. In the multivariable model, we adjusted for all the variables found to predict outcome (P ≤ 0.1) in the univariable analysis. Multiple imputation [6] was used to impute missing data when need. The Kaplan–Meier method was used to estimate survival time and produce a survival curve [7]. All analyses were conducted using R 3.1.3 statistical software (The R Foundation for Statistical Computing, Vienna, Austria). In particular, the R package *mice* [8] was used for the multiple imputation and the R package *survival* [9] for the Kaplan–Meier method and the survival analysis.

3. Results

3.1. Baseline characteristics of the study population

The baseline characteristics of the 242 participants who completed the HADS-D questionnaire are reported in Table 1. The median follow-up was 315 days (interquartile range, IQR 167–519) for all patients and 360 days (IQR = 217–574) amongst survivors. The mortality rate estimated from the Kaplan Meier curve was 15% [95% CI 10%–20%] at one year.

3.2. Depression assessment

The median HADS-D score amongst the 242 HF patients was 6 (IQR = 3–9); 153 patients had no (score 0–7), 54 had mild (score 8–10) and 35 had moderate-to-severe (score 11–21) depression, respectively. Patients with moderate-to-severe depression were, on average, in a worse NYHA class, had more likely sinus heart rhythm and were taking more HF medications than those with no depression Table 1.

Patients were more likely to give high (i.e. worse) scores to the questions "*I can laugh and see the funny side of things*" and "*I feel as if I am slowed down*" Table 2.

Table 1
Baseline characteristics stratified by HADS-D group and total population. Characteristics are summarized by their count and fraction (N (%)) for categorical or their median and interquartile range (median [25th–75th]) for continuous variables, respectively; (*) all variables are evaluated at admission apart from NT-proBNP and LVEF which are evaluated at discharge and (**) NYHA class which was evaluated as the worst class during the last 7-days before admission (***) Diuretics: loop diuretics or thiazide.

Depression score	All (N = 242)		0–7 (N = 153)		8–10 (N = 54)		11–21 (N = 35)	
Characteristics (*)	Valid N	Summary	Valid N	Summary	Valid N	Summary	Valid N	Summary
Women, %	242	76 (31%)	153	48 (31%)	54	18 (33%)	35	10 (29%)
Age, years	242	74 [64–80]	153	73 [64–81]	54	74 [67–78]	35	73 [63–80]
CCI, score	221	3 [2–5]	143	3 [2–4]	46	3 [2–6]	32	3 [2–5]
NYHA**: Class I/II, %	209	32 (15%)	132	23 (18%)	48	7 (15%)	29	2 (6%)
NYHA: Class III, %	209	135(65%)	132	87 (66%)	48	32 (67%)	29	16 (55%)
NYHA: Class IV, %	209	42 (20%)	132	22 (17%)	48	9 (19%)	29	11 (38%)
Hypertension, %	235	130 (55%)	150	82 (55%)	53	27 (51%)	32	21 (66%)
NT-proBNP, pg/ml	204	4792 [1694–9784]	130	5022 [1782–9668]	45	3188 [1323–9445]	29	5368 [2830–12,290]
Heart rhythm: sinus, %	242	92 (38%)	153	50 (33%)	54	25 (46%)	35	17 (49%)
LVEF at discharge: ≤40%	216	128(59%)	142	89 (63%)	48	23 (48%)	26	16 (62%)
Main presentation								
Severe peripheral oedema, %	236	24 (10%)	149	19 (13%)	52	3 (6%)	35	2 (6%)
Severe breathlessness at rest, %	236	76 (32%)	149	56 (38%)	52	12 (23%)	35	8 (23%)
Increasing exertional breathlessness, %	236	106(45%)	149	53 (36%)	52	31 (60%)	35	22 (63%)
Chest pain – cardiac, %	236	21 (9%)	149	14 (9%)	52	6 (11%)	35	1 (3%)
Other symptom, %	236	9 (4%)	149	7 (5%)	52	0 (0%)	35	2 (6%)
HF medication (on admission)								
ACE inhibitor, %	242	98 (40%)	153	54 (35%)	54	24 (44%)	35	20 (57%)
ARB, %	242	48 (20%)	153	30 (20%)	54	12 (22%)	35	6 (17%)
Beta-blocker, %	242	126(52%)	153	70 (46%)	54	32 (59%)	35	24 (69%)
Aldosterone Antagonist,%	242	51 (21%)	153	29 (19%)	54	11 (20%)	35	11 (31%)
Digitalis, %	242	35 (14%)	153	19 (12%)	54	9 (17%)	35	7 (20%)
Diuretics***, %	242	128 (53%)	153	71 (46%)	54	30 (56%)	35	27 (77%)

NYHA, New York Heart Association; CCI, Charlson Comorbidity Index; LVEF, left ventricular ejection fraction; SOB, acute shortness of breath; ACE, angiotensin-converting enzyme; ARB: angiotensin receptor blockers.