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Research paper

Depression predicts mortality and hospitalization in heart failure: A six-years follow-up study

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ABSTRACT

Background: The aim of this study is to evaluate the prevalence of depressive symptoms (DS) and its relation on hospitalization for cardiovascular (CV) causes and all-cause mortality risk among outpatients with HF.

Methods: A prospective study was conducted on 130 adult outpatients with HF. The Beck Depression Inventory Scale–second edition (BDI–II) was used to screen for DS. All-cause mortality and hospitalization for CV causes were registered over 6 years. Logistic regression and multinomial logistic regression analysis were used to evaluate the independent prognostic value of DS on mortality and hospitalization for CV causes after adjustment for clinical risk factors.

Results: During a mean follow-up of 6 years, 44% of patients were classified as having DS. Sixty-two participants died for all causes, representing 61% of those with DS and 37% of those without ($p=0.006$); Forty-nine participants (38%) were hospitalized for CV causes, representing 49% of those with DS and 29% of those without ($p=0.027$).

Logistic regression analysis indicated that DS predicted all-cause mortality (OR: 2.905; 95% CI:1.228–6.870; $p=0.006$) and multinomial logistic regression indicated that DS were predictive of hospitalization for CV causes (OR: 3.169; 95% CI: 1.230–8.164; $p=0.027$). These associations were independent of conventional risk factors.

Limitations: Only outpatient sample; measure of DS only at baseline; cause of death was not known.

Conclusion: This study, first held in a portuguese population, showed that DS are independent predictors of death and hospitalization for CV causes among HF patients and its impact persists over 6 years.

1. Introduction

Heart failure (HF) is a serious and progressive medical condition associated with high mortality, morbidity and reduced quality of life (Johansson et al., 2006; Rosamond et al., 2008; The CONSENSUS trial study group, 1987; The SOLVD investigators, 1990). Depression is a common co-morbidity in these patients (Abramson et al., 2001; Joynt et al., 2004; Pelle et al., 2008; Rutledge et al., 2006) and in some studies has been associated with adverse outcomes, as increased risk of hospitalizations (Faris et al., 2002; Jiang et al., 2001; Rozzini et al., 2002); increased health costs (Koenig et al., 1998); functional decline (Rumsfeld et al., 2003; Vaccarino et al., 2001) and death (Sokoreli et al., 2016). The additional effect of depression on mortality in HF has been demonstrated in many studies over periods from 3 months to 3 years (short term effect) however, the long-term effect of depression on clinical outcome among these patients is not well known due to the high mortality verified within 5 years (Adams et al., 2012). Besides that, compared with the end point of mortality, there have been fewer studies evaluating the impact of depression on the end point of hospitalization for CV causes after adjusting for HF severity (in particular using the plasma B-type natriuretic peptide-BNP) and other prognostic factors (Faris et al., 2002; Januzzi, 2013; Jiang et al., 2001; Murberg and Furze, 2004).

Depression may contribute to poor outcome via adverse effects on health behaviour, including smoking, physical inactivity and nonadherence to prescribed treatment plans (Joynt et al., 2003); it has been related to reduced heart rate variability (Carney et al.,

Abbreviations: HF, heart failure; CV, cardiovascular; DS, depressive symptoms; DD, depressive disorders; MMSE, mini mental state examination; BNP, brain natriuretic peptide; NHYA, New York Heart Association; BDI, Beck depression inventory; LVEF, left ventricular ejection fraction

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2001); blunted baroreflex sensitivity (Watkins and Grossman, 1999); heightened sympathetic nervous system activity (Hughes et al., 2004); blood hypercoagulability (Von Kanel et al., 2001); increased inflammation (Kop et al., 2002) and endothelial dysfunction (Sherwood et al., 2005). Each of these disease pathways may act independently or synergistically to increase risk in patients with HF (Sherwood et al., 2007).

The purpose of this study was to evaluate, in a portuguese population, whether DS independently predict long-term mortality due to all-causes or hospitalization for CV causes after adjustment for HF severity and other conventional risk factors of prognosis.

2. Methods

2.1. Participants

A letter describing the study design and inviting participation was sent to 197 patients, diagnosed with HF, identified from medical records held at an urban outpatient`s heart failure clinic at S. João Hospital, Porto Medical School over a period of six months. Eligible subjects were all adults aged ≥ 18 years. Exclusion criteria comprised neuropsychiatric disorders (assessed by a clinical psychiatric interview), cognitive impairments (assessed by the Mini-Mental State Examination – MMSE) and language deficits precluding a valid assessment. The diagnosis of HF was confirmed by clinical, laboratory and echocardiographic criteria.

Of the 197 patients invited to participate, 152 subjects (77%) responded. Illiterate subjects were helped either by relatives or by our staff during the interview. Nineteen elderly subjects scored less than 24 points on the MMSE and were considered unable to provide reliable information. Three patients were excluded because of hearing loss due to increased difficulty in assessing cognitive impairment. A remainder of 130 patients completed the study. Patients characteristics did not differ between the ones included in the study and those who were not.

Patients were followed for 6 years and received usual care from their primary care physicians or their cardiologists. All the patients that met the criteria for major depression at the psychiatric clinical interview were referred for psychiatric consultation (other psychiatrist than the principal investigator).

During the time span between initial interview and survival assessment 62 (48%) patients died from all-causes and 49 (38%) were hospitalized due to CV causes.

The institutional review board approved all study activities and all participants provided informed consent.

2.2. Study variables at baseline

Demographic data including age, marital status, years of education and employment; HF status including etiology of HF (ischemic vs non-ischemic), type of HF (systolic vs diastolic), New York Heart Association (NYHA) functional class (I-IV), left ventricular ejection fraction (LVEF) and brain natriuretic peptides (BNP) levels; existence of comorbidities (diabetes mellitus, cerebrovascular disease, dyslipidemia, renal insufficiency, coronary heart disease and hypertension); medical therapy; use of alcohol and nicotine were collected.

The *Mini-Mental State Examination* (MMSE) was employed to screen patients for cognitive impairment. It is used worldwide both to characterize patient's mental status during the course of a disease and to monitor patient's response to therapeutics.

The staff cardiologist assessed participants clinical status after completing patient's history and physical examination. Each patient condition was rated according to the NYHA functional class. This measure of functional status is based on the degree of activity required to evoke symptoms. The NYHA classifies HF into classes based on functional limitations and severity: Class I (normal), Class II (mild), Class III (moderate) and Class IV (severe). The BNP levels also evaluated HF severity. BNP is a cardiac neurohormone secreted from the ventricles in response to strain and it appears to be one of the most useful predictors of HF prognosis (Januzzi, 2013).

A clinical psychiatric interview was conducted at baseline by a trained psychiatrist to categorize depressive disorders (DD) according to the DSM-IV-TR criteria (Diagnostic and Statistical Manual of Mental Disorders, 2000). The psychometric assessment of patient's depressive symptoms was made through the BDI-II (Coelho et al., 2002). This is a self-administered 21-item questionnaire used to screen the existence and severity of DS. Clinically significant DS were defined as a total BDI-II score of ≥ 13. The decision to use the BDI-II in our analysis took into consideration the fact that some authors found that scores on the BDI test were also linearly and directly associated with mortality in HF patients; that is, for every 1-point increase in total BDI score, mortality increased by 2% points. Furthermore, a BDI score between 5 and 9, which are not severe enough to constitute a psychiatric disorder, was associated with 21% higher mortality compared with a score of <5 (Jiang et al., 2007). Indeed, some studies from depression and CAD literature had already indicate that depression severity is linearly associated with clinical outcomes (Rugulies, 2003), suggesting that the presence of a major depressive episode is not necessary as a standard for intervening. Therefore, if we chose to use in the analysis the clinical diagnosis of major depression we could be underestimated the predictive impact of DS on prognosis (Davidson et al., 2004; Lett et al., 2004; Zuluaga et al., 2010; Kato et al., 2009; Sherwood et al., 2011; Lupón et al., 2008). Besides that, another reason for the use of BDI is that it has the advantage of being the most common tool used in studies with cardiac patients (Hare et al., 2014) and it as been already reported its good sensitivity (91%) and specificity (78%) in this population (Frasure-Smith et al., 2008).

2.3. End points

At follow-up, data on end-points were obtained from medical records and from the information obtained with the attending physicians.

The end points were: all-cause death and hospitalization for CV causes. They were considered separately. Cardiovascular hospitalizations included the occurrence of MI or stroke, treatment of worsening HF and cardiac surgery including coronary artery bypass grafting or pacemaker implantation.

2.4. Statistical analyses

Summary statistics were applied for descriptive analysis. Categorical variables were described by their absolute frequencies (n) and percentages (%). Continuous variables that were symmetrically distributed were described through the mean and standard deviation, whereas the median and interquartile range, were employed in all other cases. The χ^2 test was used for categorical variables comparison (the Fisher exact test was employed when appropriate, i.e., more than 20% of the contingency table cells with frequency lower than 5). The Student t test was used for comparison of symmetrically distributed continuous variables whereas the Mann-Whitney test was applied in all other instances.

Logistic regression analyses were performed to investigate a possible association between DS and an increased risk of all-cause mortality. Multinomial logistic regression analysis was employed to study the relation between DS and hospitalizations for CV