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Hopelessness and cognitive impairment are risk markers for mortality in systolic heart failure patients

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ABSTRACT

Objective: Depression exacerbates the burden of heart failure and independently predicts mortality. The aim of this study was to investigate which specific symptoms of depression predict all-cause mortality in systolic heart failure patients.

Methods: Consecutive outpatients with heart failure and impaired left ventricular ejection fraction (LVEF), attending an Australian metropolitan heart function clinic between 2001 and 2011, were enrolled. The Cardiac Depression Scale (CDS) was completed as a component of usual care. Baseline clinical characteristics were drawn from hospital databases. The primary end-point was all-cause mortality, obtained from the Australian National Death Index.

Results: A total of 324 patients (68.5% male) were included (mean age at enrolment = 66.8 ± 14.36 years), with a median follow-up time of 6.7 years (95% CI 5.97–7.39) and a mortality rate of 50% by the census date. Mean LVEF = 31.0 ± 11.31%, with 25% having NYHA functional class of III or IV. Factor analysis of the CDS extracted six symptom dimensions: Hopelessness, Cognitive Impairment, Anhedonia/Mood, Irritability, Worry, and Sleep Disturbance. Cox regression analyses identified Hopelessness (HR 1.024, 95% CI 1.004–1.045, $p = .018$) and Cognitive Impairment (HR 1.048, 95% CI 1.005–1.093, $p = .028$) as independent risk markers of all-cause mortality, following adjustment of known prognostic clinical factors.

Conclusion: Hopelessness and cognitive impairment are stronger risk markers for all-cause mortality than other symptoms of depression in systolic heart failure. These data will allow more specific risk assessment and potentially new targets for more effective treatment and management of depression in this population.

1. Introduction

Heart failure is a serious medical condition, where the heart can no longer meet the blood flow demands of the body, due to impaired capacity of the heart to fill or eject blood [1].It has been estimated that 26 million people worldwide live with chronic heart failure (CHF) [1]. CHF remains a major public health issue in nearly all developed countries with high mortality, high hospital readmission rates, impaired functional capacity and poor quality of life [2]. There has perhaps been some reduction in 1st hospitalisations with CHF over the years but no overall reduction in mortality despite therapeutic break-throughs in CHF management [3]. Left ventricular ejection fraction (LVEF) is a percentage measure of the amount of blood ejected by the left ventricle in systole and is considered an important objective disease severity measure in heart failure. Whilst there is a heterogeneous group of CHF patients with preserved ejection fraction (HFpEF), heart failure patients with reduced ejection fraction (HFrEF), including some patients now defined as having "mid-range" reduction in left ventricular ejection fraction (LVEF), tend to be better characterised. There are data suggesting that half of all HFrEF patients will have died within five years of diagnosis [4]. The typical CHF disease trajectory is for a continuous decline in function, punctuated by periods of acute exacerbation [5]. There are now an extraordinarily large range of interventions (both medically–based and life-style changes) that have been demonstrated in randomised clinical trials to markedly reduce morbidity and mortality in CHF patients [2]. These interventions can reduce the significant burden on patients, carers and the health care system alike.

Depression is an important sequelae of CHF and also a significant risk marker of a worse outcome [6]. On average, over 20% of CHF patients have major depression, with greater CHF symptom severity

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associated with worse depression [7]. Comorbid depression is linked to increased health-care costs and further exacerbation of their already reduced quality of life [8,9]. Depression seems to be an independent predictor for both developing heart failure [10] as well as an important result of CHF development [11].

Clinical diagnosis of depression is based on observation of depressed mood and/or anhedonia, together with changes in appetite or weight, sleep disturbance, fatigue, feelings of worthlessness or hopelessness, decreased concentration, and suicidal ideation [12]. In other diagnostic cohorts of cardiac patients, there has been some suggestion that certain symptoms of depression have greater prognostic value than others [13]. It has been suggested that research should identify depressive symptom profiles that are particularly cardiotoxic [13,14] in order to advance the development of more targeted treatments to reduce morbidity and mortality in cardiac disease.

Somatic depressive symptoms (such as sleep disturbance, fatigue and weight/appetite change), but not cognitive depressive symptoms (such as depressed mood, anhedonia, decreased concentration, worthlessness/hopelessness), appear to predict mortality in patients with a variety of cardiac diseases, including heart failure [15]. Using the Beck Depression Inventory (BDI) Schiffer et al. [16] found that somatic-affective symptoms, but not cognitive-affective symptoms, predicted all-cause mortality over a follow-up period of around 3 years, adjusted for disease severity variables. Hwang et al. [17] confirmed these findings using the Patient Health Questionnaire (PHQ) whereby somatic-affective symptoms, but not cognitive-affective symptoms, independently predicted mortality in 457 heart failure patients at one year. However, it is possible that somatic features of depression indexed in the BDI and PHQ may be confounded in heart failure settings; representing an extension of cardiac disease severity, rather than symptoms specific to depression [14].

The Cardiac Depression Scale (CDS) [18] offers an alternative assessment tool for depression that has been validated for use in patients with cardiac disease [19]. Factor analysis of the CDS has identified at least six symptom dimensions (generally described as anhedonia, mood, fear/uncertainty, sleep disturbance, cognitive impairment, suicidal ideation and hopelessness) [20] which map well to the diagnostic criteria for depression and includes only those somatic symptoms specific to depression in this population [18]. In a preliminary study using the CDS, Stewart et al. [21] found that Mood/Anhedonia independently predicted mortality at a median follow-up time of 2.4 years in a sample of 374 systolic heart failure patients (adjusted for age, heart failure aetiology, NHYA class and LVEF). Further research is needed that includes other potential biopsychosocial prognostic factors addressed in the CDS, such as cognitive impairment and sleep disturbance [18,20,22] over a longer follow-up time. These data may offer important insights for prognostic algorithms and the development of targeted depression treatments for optimising quality of life and clinical outcomes in heart failure patients.

1.1. Aim

The aim of this study was to investigate whether specific symptoms of depression, as measured by the CDS, could independently predict mortality in patients with HFrEF. It is hypothesised that both overall depression (as measured by the total CDS score) will predict all-cause mortality and that different symptom dimensions of depression will differentially predict all-cause mortality.

2. Method

2.1. Participants

Consecutive CHF patients with a clinical diagnosis of HFrEF, who had an initial out-patient hospital clinic for heart failure during the enrolment period (2001 to 2011 inclusive), were eligible if they had completed a CDS at that visit, and had a transthoracic echocardiogram (TTE) between 6 months prior to or 2 months following their first visit, which included a categorical description of at least *mild* left ventricular dysfunction. These categorical descriptors followed a modified version of the guidelines specified by the American Society of Echocardiography and European Association of Cardiovascular Imaging where *mild* corresponds to an LVEF of < 51% for males and 53% for females [23]. A total of 354 patients met entry criteria, with 30 later excluded because of incomplete data, leaving 324 patients (men = 68.5%; mean age at enrolment = 66.8 ± 14.4), of whom 50% (n = 162) were deceased by the census date.

2.2. Materials and procedure

The investigation conforms with the principles outlined in the *Declaration of Helsinki* and the research protocol was approved by Austin Health (Project No: LNR/13/Austin/185), the National Death Index (Project No EO 2013/4/56) and La Trobe University (LNR/13/Austin/185/O'Halloran). To reduce the likelihood of distress for surviving patients and families of deceased patients, the study was approved with an informed consent waiver.

Patient data were extracted from hospital databases. The primary end-point was all-cause mortality and sourced from the National Death Index (NDI) of the Australian Institute of Health and Welfare (AIHW).

2.3. Cardiac Depression Scale (CDS)

The CDS [20] is a 26-item self-report measure of depressive symptoms in cardiac patients comprising at least six symptom dimensions [19]. The scale comprises mostly negatively worded items, with seven positively worded items interspersed to avoid a standard response set. The instrument utilises a 7-point Likert-type response scale, with descriptors at the extremes to anchor responses. Positively worded items are reversed scored and all items are summed to produce a total CDS score ranging from 26 to 182 (Cronbach's $\alpha = 0.90$), with higher scores indicating a higher level of depressive symptoms. A cut-off score of 100 has been shown to identify severe probable depression, with 88% sensitivity and 84% specificity [20,22]. The CDS has been psychometrically validated for use in cardiac patients [18–20]. The CDS takes about 5 min to complete and 1 min to score [18], making it an efficient tool for use in the clinical setting. As a component of usual care, patients attending the out-patient clinic were approached by staff (including heart failure nurses and/or research staff) to complete the CDS.

2.4. Mortality and survival/follow-up time

All-cause mortality data was extracted from the NDI on 7 May 2014. Survival (or follow-up) time was defined as the time from the first out-patient clinic visit date within the enrolment period (2001 to 2011 inclusive), until the date-of-death or censoring on 7 May 2014. The minimum possible follow-up time for censored patients was 2 years and 4 months.

2.5. Clinical measures

Prognostic factors in heart failure included: demographics, heart failure aetiology, comorbid conditions, medications, pathology results, measures of left ventricular size and dysfunction, and NYHA Class. Percentage LVEF data was sourced from TTEs; where only a categorical descriptor was provided, this was converted to the mid-point of the corresponding percentage range [23].

2.6. Data treatment and statistical analyses

Missing CDS data up to a maximum of 10% were replaced using individual mean replacement. Sixteen of the 26 CDS items contained