# The prevalence and associated distress of physical and psychological symptoms in patients with advanced heart failure attending a South African public hospital

M.E. Lokker, L. Gwyther, J.P. Riley, L. van Zuylen, A. van der Heide, R. Harding

*J Cardiovasc Nurs. 2016 Jul-Aug;31(4):313-22*

## ABSTRACT

**Background.** Despite the high prevalence of heart failure in low- and middle-income countries, evidence concerning patient-reported burden of disease in advanced heart failure is lacking.

**Objective.** The aim of this study is to measure patient-reported symptom prevalence and correlates of symptom burden in patients with advanced heart failure.

**Methods.** Adult patients diagnosed with New York Heart Association (NYHA) stage III or IV heart failure were recruited from the emergency unit, emergency ward, cardiology ward, general medicine wards and outpatient cardiology clinic of a public hospital in South Africa. Patients were interviewed by researchers using the Memorial Symptom Assessment Scale-Short Form, a well-validated multidimensional instrument that assesses presence and distress of 32 symptoms.

**Results.** A total of 230 patients (response, 99.1%) 90% NYHA III and 10% NYHA IV (12% newly diagnosed), with a mean age of 58 years, were included. Forty-five percent were women, 14% had completed high school, and 26% reported having no income. Mean Karnofsky Performance Status Score was 50%. Patients reported a mean of 19 symptoms. Physical symptoms with a high prevalence were shortness of breath (95.2%), feeling drowsy/tired (93.0%), and pain (91.3%). Psychological symptoms with a high prevalence were worrying (94.3%), feeling irritable (93.5%), and feeling sad (93.0%). Multivariate linear regression analyses, with total number of symptoms as dependent variable, showed no association between number of symptoms and gender, education, number of healthcare contacts in the last 3 months, years since diagnosis, or co-morbidities. Increased number of symptoms was significantly associated with higher age ($b$=0.054, $p$=0.042), no income ($b$=-2.457, $p$=0.013) and fewer hospitalizations in the last 12 months ($b$=1.032, $p$=0.017).

**Conclusions.** Patients with advanced heart failure attending a medical centre in South Africa experience high prevalence of symptoms and report high levels of burden associated with these symptoms. Improved compliance with national and global treatment recommendations could contribute to reduced symptom burden. Healthcare professionals should consider incorporating palliative care into the care for these patients.

## INTRODUCTION

Heart failure is a chronic progressive syndrome associated with high morbidity and mortality[1-3]. The prognosis of heart failure is as poor as, or even worse than, that of many cancers[4-10]. Community-based studies have reported mortality rates of 30% to 40% within 1 year of diagnosis and 60% to 70% within 5 years[1 11-13]. Progressive decrease in functional capacity and an increasing frequency of hospitalizations are common in patients who have advanced heart failure[14-16]. Among patients who are hospitalized, mortality rates are even higher[9]. However, when patients are optimized using evidence-based medication, mortality can be reduced[3 17-19].

Multiple investigators have shown that heart failure has a great impact on the health status and quality of life of patients, which can be directly attributed to their symptom burden (e.g., fatigue, shortness of breath, fluid retention) and functional limitations[4 9 20-28]. Unlike most cardiovascular conditions, heart failure is becoming more common[6 7 29 30]. At this moment, cardiovascular diseases account for about 30% of deaths worldwide, with 80% of deaths occurring in the developing world[31]. Heart failure has emerged as a dominant type of cardiovascular disease in Africa[31], and it is a leading cause of death in South Africa[32]. Common causes of heart failure in Africa, such as rheumatic heart disease, peripartum cardiomyopathy, and hypertensive heart disease, are most prevalent in the young[31 33-35]. This is in contrast with developed countries, where heart failure is a condition of the elderly, with a mean age of 76 years[31].

Despite the great burden of heart failure being present in low- and middle-income countries where formal health resources are limited, almost all research concerning advanced heart failure has focused on patients in high-income countries. It remains unclear whether patients with heart failure in developing parts of the world experience the same symptoms and functional limitations. The aims of this study are to measure the prevalence and associated burden of physical and psychological symptoms among patients with New York Heart Association (NYHA) stage III/IV heart failure attending a South African medical centre and to determine which characteristics are associated with the level of symptom burden.

## METHOD

### Design and population

This cross-sectional observational study is part of a longitudinal study investigating symptoms and care needs in patients with advanced heart failure. The Human Research Ethics Committee of the University of Cape Town reviewed and approved this study (HREC REF: 208/2012).

Patients were recruited for this study between August and November 2012 from several inpatient facilities (i.e. emergency unit, emergency ward, cardiology ward, general medicine wards) and the outpatient cardiology clinic of a 900-bed tertiary academic medical centre in South Africa. Patients 18 years or older; able to communicate in English, Afrikaans or isiXhosa; and diagnosed with NYHA stage III/IV heart failure were included. Patients were recruited consecutively by the researcher (M.E.L.) after the attending physicians had indicated that a specific patient met the inclusion criteria. Informed consent was obtained from all participants. The questionnaires used in this study and the information and consent forms were translated from English (forward and back) into Afrikaans and isiXhosa (the main languages of the Western Cape of South Africa).

## Data collection

The following patient demographic and clinical data were collected from the patient: age, gender, education level (primary school, some high school, high school completed, higher education), income (employed with/without payment, unemployed, disability grant, pension, living from private means), number of healthcare contacts during the last 3 months (outpatient visits, telephone contacts, other) and number of previous hospital admission within the past 12 months. The reason for the hospital visit, years since diagnosis, NYHA stage at the time of the interview, aetiology/ comorbidity, current medication, and presence of an implantable cardioverter defibrillator were collected from the medical record.

To describe the functional limitations of the population, functional status was measured with the Karnofsky Performance Status (KPS) scale[36]. The KPS consists of 11 percentage categories denoted in deciles from 100% (asymptomatic, normal function) to 0% (death), which combine information on the patient's ability to function at work and at home, the severity of symptoms, and the need for personal and medical care[37]. The KPS is regarded as the gold standard performance scale for patients with cancer, but use of the instrument has been reported in 3 studies in patients with advanced heart failure and 1 study in patients with acute myocardial infarction[38 39]. Recently, the KPS was described as adding clarification to the description of the heart failure population when used in studies together with the NYHA classification[39.] Interobserver reliability of the KPS varies between 0.66 and 0.97[40-42].

For a 2-dimensional assessment of symptom prevalence and associated burden, we used the Memorial Symptom Assessment Scale-Short Form (MSAS-SF)[43]. The MSAS-SF is a patient-rated instrument in which patients rate the presence of 28 physical symptoms and the frequency of 4 psychological symptoms during the past 7 days. In addition to the 7-day period prevalence, the MSAS-SF also measures the associated burden for each symptom recorded as prevalent. Distress of physical symptoms is rated on a 5-point (0–4) Likert scale (not at all, 0.8; a little bit, 1.6; somewhat, 2.4; quite a bit, 3.2; very much, 4.0). Frequency of psychological symptoms is rated on a 4-point (0-4) Likert scale (rarely, 1; occasionally, 2; frequently, 3; almost constantly, 4). If the symptom is not present, a value of 0 is assigned for the burden index. The MSAS-SF consists of 3 subscales: the global distress index (4 psychological symptoms: feeling sad, worrying, feeling irritable, and feeling nervous, and 6 physical symptoms: lack of energy, pain, lack of appetite, feeling drowsy, constipation, and dry mouth); the physical symptom distress score (12 prevalent physical symptoms: lack of energy, pain, lack of appetite, feeling drowsy, constipation, dry mouth, nausea, vomiting, change in taste, weight loss, feeling bloated, and dizziness), and the psychological symptom distress score (6 prevalent psychological symptoms: worrying, feeling sad, feeling nervous, difficulty sleeping, feeling irritable, and difficulty concentrating). The MSAS-SF has good psychometric properties, with subscale Cronbach's α coefficients of 0.76 to 0.87, and 1-day test-retest reliability correlation coefficients of 0.86 to 0.94[43]. Use of the MSAS-SF has been well reported among patients with heart failure and patients from sub-Saharan Africa with HIV and cancer[20 21 44-46].

Questionnaire items of the MSAS-SF were read aloud by researcher (M.E.L.), and patient's self-report response entered on their behalf. All patients were interviewed in the language of their choice (English, Afrikaans, or isiXhosa). Self-completion was not used because of potential limited literacy in this population. All data were then entered into LimeSurvey (online survey software that was used as data entry tool in this study) and subsequently imported into SPSS version 20.0 for analysis.

### Analysis and statistics

The patient demographic and medical characteristics were described with descriptive statistics. When data were nonnormally distributed, median scores were presented. For each item within the MSAS-SF, prevalence and associated burden were calculated. Scores for the global, physical, and psychological subscales were calculated[47]. The total number of prevalent symptoms for each respondent and the mean number of prevalent symptoms for the sample were also calculated. A high level of symptom burden was defined as the sum of "quite a bit" and "very much" of distress associated with physical symptoms and the sum of "frequently" and "almost constantly" for the frequency of psychological symptoms. Education was measured using 4 groups (primary school, some high school, high school completed, and higher education). The high school completed and the higher education group both contained a very low number of patients, making a 3-group division (ie, lower, middle, and higher education) not possible. Therefore, education was divided into 2 groups of primary school versus more than primary school (including some high school, high school completed, and higher education). Income was measured using 6 groups (employed with payment, employed without payment, unemployed, disability grant, pension, living on own private means), but could not be categorized into levels of income (low, middle, and high); therefore, income was divided into no income (employed without payment and unemployed) versus income (employed with payment, disability grant, pension, and living on own private means).

Linear regression analyses were used to identify associations with symptom burden. Five models were constructed, with the following dependent variables: global distress (model 1), physical distress (model 2), psychological distress (model 3), total MSAS (model 4) and total number of symptoms (model 5). Univariate linear regression analyses were performed to test the association of different patient characteristics with the dependent variables: age (continuous), gender (two levels of male/female), education (two levels of primary high school / > primary high school), income (two levels of yes/no), years since diagnosis (two levels of 0 / > 0 years), number of prior hospital admission within the past 12 months (continuous), number of healthcare contacts during the last three months (two levels of 0/>0) and number of co morbidities (continuous). Following each univariate regression, multivariate regression models were constructed. Independent variables were entered stepwise into the multivariate model if they were significant in univariate analyses at the conservative 25% level.[45] For each model, the 95% confidence interval of the unstandardized *b* coefficient was calculated.

## RESULTS

### Sample characteristics

A total of 232 patients met the inclusion criteria for this study, and of these, 2 patients declined participation. Therefore, a total of 230 patients (response 99.1%) were included in the study (Table 1). The mean (SD) age was 58 (16.7) years (median, 60 years; min-max, 18-90 years); 45% were women, 14% completed high school, and 26% reported having no income. Most patients included in this study had been admitted to the hospital because of an exacerbation of their illness. Eighty-eight percent had been diagnosed with heart failure before their hospital visit. The most prevalent stage of heart failure in this population was NYHA stage III (90%). Comorbidity was common; only 19 patients were reported having no other illnesses. The most prevalent comorbidities were hypertension (70%) and diabetes (38%). Mean KPS was 50% (“requires considerable assistance and frequent medical care”). On average, patients had been previously admitted to hospital on 1 occasion during the past year. Sixty-eight percent of all patients had not had any contact with a healthcare professional during the previous 3 months. According to the medical records, angiotensin-converting enzyme (ACE) inhibitors, were used by 57% of patients with an existing diagnosis; β-blockers, by 47%; angiotensin receptor blockers by 4%; mineralocorticoid receptor antagonists(MRA), by 12%; diuretics other than MRA, by 92%; and digoxin, by 11%. Five percent of patients had an implantable cardioverter-defibrillator (ICD).

### Symptom prevalence and burden

The 7-day period symptom prevalence and associated burden are reported in Table 2. Patients reported a mean of 19 symptoms (not in table). Eighteen symptoms were reported by more than 50% of all patients. Physical symptoms with highest prevalence were shortness of breath (95.2%), feeling drowsy/tired (93.0%) and pain (91.3%). Psychological symptoms with highest prevalence were worrying (94.3%), feeling irritable (93.5%) and feeling sad (93.0%). Symptoms associated with highest burden were shortness of breath (93.1%), numbness/tingling in hands or feet (90.5%) and “I do not look like myself” (89.9%).

**Table 1.** Sample Characteristics (n=230)

| **Patient demographic characteristics** | | | **Patient medical characteristics** | | |
|---|---|---|---|---|---|
| Age median ± SD, y | 60 | ± 16.7 | Aetiology/ comorbidity cardiovascular diseases | | |
| Gender | | | Hypertension | 70% | 161 |
| Male | 45% | 103 | Ischemic Heart disease | 13% | 30 |
| Female | 55% | 127 | Valvular heart disease | 3% | 7 |
| Education level | | | Rheumatic heart disease | 3% | 6 |
| Primary school | 49% | 112 | Post-partum cardiomyopathy | 1% | 2 |
| Some high school | 37% | 86 | Congenital heart disease | 1% | 2 |
| High school completed | 11% | 25 | Hypertrophic obstructive cardiomyopathy | 0,4% | 1 |
| Higher education | 3% | 7 | Aetiology/ comorbidity other diseases | | |
| Income | | | Diabetes type 2 | 24% | 55 |
| Employed with payment | 22% | 50 | Diabetes type 1 | 14% | 31 |
| Employed without payment | 2% | 5 | Renal Failure | 12% | 28 |
| Unemployed | 24% | 55 | COPD | 8% | 19 |
| Disability grant | 10% | 24 | Asthma | 7% | 16 |
| Pension | 41% | 94 | HIV | 7% | 15 |
| Living on own private means | 1% | 2 | Tuberculosis | 4% | 8 |
| **Patient medical characteristics** | | | Cancer | 1% | 2 |
| Heart failure diagnosis | | | Comorbidity per patient, mean (interval) | 2 | 0-4 |
| Years since diagnosis[a] median/ interval | 1 | 0-18 | Karnofsky Performance Score, mean (interval) | 50% (90%-20%) | |
| Newly diagnosed | 12% | 27 | Reason for hospital visit | | |
| NYHA stage at time of interview | | | Acute admission | 86% | 197 |
| III | 90% | 207 | Outpatient clinic[b] | 13% | 29 |
| IV | 10% | 23 | Planned admission | 2% | 4 |
| Contact with healthcare professionals | | | Medication use (patients with an existing diagnosis n=201) | | |
| Prior hospital admissions last year (mean/interval) | 1 | 0-4 | ACE-inhibitors | 57% | 115 |
| Prior healthcare contacts last 3 months | | | β-blockers | 47% | 94 |
| 0 | 63% | 144 | Angiotensin receptor blockers | 4% | 7 |
| 1 | 28% | 64 | Digoxin | 11% | 22 |
| ≥ 2 | 10% | 22 | MRA | 12% | 25 |
| Implantable Cardioverter Defibrillator (ICD) | 5% | 11 | Diuretics other than MRA | 92% | 184 |

Data are presented as percentage and number, unless otherwise indicated. Abbreviations: ACE, angiotensin-converting enzyme; COPD, chronic obstructive pulmonary disease; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.

[a] Number of years since diagnosis missing for 2 patients.

[b] Includes patients following recent hospitalization and for scheduled follow-up.

Table 2. 7-day-Period Symptom Prevalence[a] and Associated Symptom Burden (N=230)[b]

| Symptoms | Prevalence | Burden (Total 100%) | | | | |
|---|---|---|---|---|---|---|
| | | Not at All | A Little Bit | Somewhat | Quite a Bit | Very Much |
| Physical problems | | | | | | |
| Shortness of breath | 95.2% (n=219) | 0.9% (n=2) | 2.7% (n=6) | 3.2% (n=7) | 11.4% (n=25) | 81.7% (n=179) |
| Feeling drowsy/ tired | 93.0% (n=214) | 0.5% (n=1) | 3.7% (n=8) | 6.5% (n=14) | 23.4% (n=50) | 65.9% (n=141) |
| Pain | 91.3% (n=210) | 1.4% (n=3) | 2.4% (n=5) | 12.4% (n=26) | 24.8% (n=52) | 59.0% (n=124) |
| "I don't look like myself" | 90.4% (n=208) | 1.4% (n=3) | 2.4% (n=5) | 6.3% (n=13) | 15.9% (n=33) | 74.0% (n=154) |
| Weight loss | 84.8% (n=195) | 5.6% (n=11) | 12.3% (n=24) | 21.5% (n=42) | 20.0% (n=39) | 40.5% (n=79) |
| Lack of energy | 82.2% (n=189) | 1.1% (n=2) | 2.6% (n=5) | 14.3% (n=27) | 18.0% (n=34) | 64.0% (n=121) |
| Swelling of arms or legs | 81.3% (n=187) | 2.1% (n=4) | 2.7% (n=5) | 9.1% (n=17) | 32.6% (n=61) | 53.5% (n=100) |
| Difficulty sleeping | 77.0% (n=177) | 1.1% (n=2) | 2.3% (n=4) | 13.6% (n=24) | 28.8% (n=51) | 54.2% (n=96) |
| Numbness/tingling in hands or feet | 73.5% (n=169) | 2.4% (n=4) | 2.4% (n=4) | 4.7% (n=8) | 20.1% (n=34) | 70.4% (n=119) |
| Changes in way food tastes | 73.0% (n=168) | 3.6% (n=6) | 5.4% (n=9) | 7.7% (n=13) | 29.8% (n=50) | 53.6% (n=90) |
| Lack of appetite | 72.2% (n=166) | 3.6% (n=6) | 7.8% (n=13) | 14.5% (n=24) | 39.8% (n=66) | 34.3% (n=57) |
| Difficulty concentrating | 67.4% (n=155) | 7.7% (n=12) | 13.5% (n=21) | 33.5% (n=52) | 32.9% (n=51) | 12.3% (n=19) |
| Difficulty swallowing | 55.7% (n=128) | 4.7% (n=6) | 5.5% (n=7) | 17.2% (n=22) | 38.3% (n=49) | 34.4% (n=44) |
| Problems with sexual interest/ activity | 52.6% (n=121) | 25.6% (n=31) | 25.6% (n=31) | 33.9% (n=41) | 7.4% (n=9) | 7.4% (n=9) |
| Cough | 49.1% (n=113) | 5.3% (n=6) | 8.8% (n=10) | 18.6% (n=21) | 23.0% (n=26) | 44.2% (n=50) |
| Nausea | 42.2% (n=97) | 6.2% (n=6) | 15.5% (n=15) | 24.7% (n=24) | 25.8% (n=25) | 27.8% (n=27) |
| Dizziness | 41.3% (n=95) | 4.2% (n=4) | 24.2% (n=23) | 24.2% (n=23) | 17.9% (n=17) | 29.5% (n=28) |
| Feeling bloated | 36.1% (n=83) | 6.0% (n=5) | 7.2% (n=6) | 33.7% (n=28) | 25.3% (n=21) | 27.7% (n=23) |
| Dry mouth | 35.7% (n=82) | 8.5% (n=7) | 22.0% (n=18) | 28.0% (n=23) | 25.6% (n=21) | 15.9% (n=13) |
| Problems urinating | 32.2% (n=74) | 2.7% (n=2) | 14.9% (n=11) | 32.4% (n=24) | 24.3% (n=18) | 25.7% (n=19) |
| Itching | 28.3% (n=65) | 13.8% (n=9) | 29.2% (n=19) | 29.2% (n=19) | 15.4% (n=10) | 12.3% (n=8) |
| Changes in skin | 27.0% (n=62) | 14.5% (n=9) | 22.6% (n=14) | 12.9% (n=8) | 16.1% (n=10) | 33.9% (n=21) |

Table 2. 7-day-Period Symptom Prevalence[a] and Associated Symptom Burden (N=230)[b] (continued)

| Symptoms | Prevalence | Burden (Total 100%) | | | | |
|---|---|---|---|---|---|---|
| | | Not at All | A Little Bit | Somewhat | Quite a Bit | Very Much |
| Constipation | 26.1% (n=60) | 1.7% (n=1) | 20.0% (n=12) | 21.7% (n=13) | 28.3% (n=17) | 28.3% (n=17) |
| Vomiting | 25.7% (n=59) | 6.8% (n=4) | 15.3% (n=9) | 27.1% (n=16) | 33.9% (n=20) | 16.9% (n=10) |
| Sweats | 25.2% (n=58) | 10.3% (n=6) | 12.1% (n=7) | 19.0% (n=11) | 36.2% (n=21) | 22.4% (n=13) |
| Hair loss | 13.9% (n=32) | 18.8% (n=6) | 21.9% (n=7) | 18.8% (n=6) | 15.6% (n=5) | 25.0% (n=8) |
| Mouth sores | 12.6% (n=29) | 27.6% (n=8) | 20.7% (n=6) | 17.2% (n=5) | 17.2% (n=5) | 17.2% (n=5) |
| Diarrhea | 12.2% (n=28) | 25.0% (n=7) | 10.7% (n=3) | 17.9% (n=5) | 21.4% (n=6) | 25.0% (n=7) |

| Symptoms | Prevalence | Burden (total 100%) | | | |
|---|---|---|---|---|---|
| | | Rarely | Occasionally | Frequently | Almost constantly |
| Psychological problems | | | | | |
| Worrying | 94.3% (n=217) | 31.3% (n=68) | 35.9% (n=78) | 24.9% (n=54) | 7.8% (n=17) |
| Feeling irritable | 93.5% (n=215) | 38.6% (n=83) | 31.2% (n=67) | 22.3% (n=48) | 7.9% (n=17) |
| Feeling sad | 93.0% (n=214) | 28.5% (n=61) | 51.9% (n=111) | 11.7% (n=25) | 7.9% (n=17) |
| Feeling nervous | 92.2% (n=212) | 25.0% (n=53) | 20.8% (n=44) | 31.1% (n=66) | 23.1% (n=49) |

Distress of physical symptoms is rated on a 5-point (0-4) Likert scale (not at all, 0.8; a little bit, 1.6; somewhat, 2.4; quite a bit, 3.2; very much, 4.0). Frequency of psychological symptoms is rated on a 4-point

(0-4) Likert scale (rarely, 1; occasionally, 2; frequently, 3; almost constantly, 4). If the symptom is not present, a value of 0 is assigned for the burden index.

[a] Symptom prevalence in descending order of prevalence.

[b] Symptom prevalence presented for N = 230 without missing values.

## Correlates of symptom burden

Univariate and multivariate regression analyses to determine associations with symptom burden are presented in Table 3. Age, income, and prior hospital admission were found to be consistent correlates for the multivariate models. In the multivariate analyses, age, income and prior hospital admission were correlated to global distress (model 1: b=0.007, *P*=0.030; b=-0.270, *P*=0.029 and b=-0.168, *P*<0.001 respectively), physical distress(model 2: b=0.007, *P*=0.037; b=-0.298, *P*=0.013 and b=-0.211, *P*<0.000 respectively), number of symptoms (model 5: b=0.053, *P*=0.038; b=-2.233, *P*=0.021 and b=-1.498, *P*<0.001 respectively), psychological distress (model 3: prior hospital admission only, b=-0.116, *P*=0.023) and total distress (model 4: prior hospital admission only, b=-0.168, *P*<0.001). In these models, a higher symptom burden was associated with having a higher age, having no income (dichotomous variable; having no income compared to income) and having fewer hospital admissions within the past 12 months. Multivariate analyses showed no association between the different models and the independent variables of gender, education, healthcare contacts, years since diagnosis, or comorbidities.

**Table 3. Associations With Symptom Burden**

| Independent variables | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | b | *P* | 95% CI for b | b | *P* | 95% CI for b |
| Model 1: Global distress Subscale, $r^2$ =9,0% | | | | | | |
| Age | 0.002 | 0.449 | -0.003, 0.008 | **0.007** | **0.030** | **0.001, 0.014** |
| Gender | -0.102 | 0.280 | -0.287, 0.083 | | | |
| Education | -0.060 | 0.525 | -0.244, 0.125 | | | |
| Income | -0.157 | 0.140 | -0.366, 0.052 | **-0.270** | **0.029** | **-0.512, -0.028** |
| Years since diagnosis | -0.042 | 0.772 | -0.326, 0.242 | | | |
| Prior hospitalizations | **-0.172** | **<0.000** | **-0.264, 0.080** | **-0.168** | **<0.000** | **-0.260, -0.076** |
| Healthcare contacts | 0.137 | 0.156 | -0.053, 0.327 | 0.160 | 0.091 | -0.026, 0.347 |
| Co-morbidity | 0.022 | 0.661 | -0.077, 0.122 | | | |
| Model 2: Physical distress Subscale, $r^2$ = 13,0% | | | | | | |
| Age | 0.001 | 0.729 | -0.005, 0.006 | **0.007** | **0.037** | **0.000, 0.013** |
| Gender | -0.140 | 0.132 | -0.322, 0.043 | -0.112 | 0.204 | -0.285, 0.061 |
| Education | -0.021 | 0.823 | -0.203, 0.161 | | | |
| Income | **-0.221** | **0.035** | **-0.426, -0.016** | **-0.298** | **0.013** | **-0.532, -0.064** |
| Years since diagnosis | -0.088 | 0.534 | -0.368, 0.191 | | | |
| Prior hospitalizations | **-0.216** | **<0.000** | **-0.305, -0.128** | **-0.211** | **<0.000** | **-0.300, -0.122** |
| Healthcare contacts | 0.074 | 0.438 | -0.114, 0.262 | 0.106 | 0.247 | -0.074, 0.286 |
| Co-morbidity | -0.024 | 0.625 | -0.123, 0.074 | | | |

**Table 3. Associations With Symptom Burden (continued)**

| Independent variables | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | b | *P* | 95% CI for b | b | *P* | 95% CI for b |
| | Model 3: Psychological distress Subscale $r^2$ = 2,8% | | | | | |
| Age | 0.001 | 0.762 | -0.005, 0.007 | | | |
| Gender | -0.115 | 0.251 | -0.311, 0.082 | -0.116 | 0.247 | -0.312, 0.081 |
| Education | 0.045 | 0.653 | -0.151, 0.241 | | | |
| Income | -0.121 | 0.284 | -0.344, 0.101 | | | |
| Years since diagnosis | -0.027 | 0.859 | -0.332, 0.277 | | | |
| Prior hospitalizations | -0.114 | 0.024 | -0.214, -0.015 | **-0.116** | **0.023** | **-0.215, -0.016** |
| Healthcare contacts | 0.038 | 0.711 | -0.164, 0.241 | | | |
| Co-morbidity | 0.008 | 0.885 | -0.098, 0.144 | | | |
| | Model 4: Total MSAS Score, $r^2$ =8,8% | | | | | |
| Age | 0.001 | 0.749 | -0.004, 0.005 | | | |
| Gender | -0.122 | 0.119 | -0.275, 0.032 | -.0124 | 0.100 | -0.271, 0.024 |
| Education | -0.029 | 0.709 | -0.182, 0.124 | | | |
| Income | -0.159 | 0.072 | -0.333, 0.014 | | | |
| Years since diagnosis | -0.072 | 0.547 | -0.308, 0.164 | | | |
| Prior hospitalizations | **-0.171** | **<0.000** | **-0.246 -0.095** | **-0.168** | **<0.000** | **-.0243, -0.093** |
| Healthcare contacts | 0.055 | 0.492 | -0.103, 0.213 | | | |
| Co-morbidity | -0.016 | 0.695 | -0.099, 0.066 | | | |
| | Model 5: Number of symptoms, $r^2$ =10,7% | | | | | |
| Age | 0.010 | 0.666 | -0.034, 0.054 | **0.053** | **0.038** | **0.003, 0.104** |
| Gender | -1.391 | 0.061 | -2.847, 0.066 | -1.177 | 0.101 | -2.584, 0.229 |
| Education | -0.446 | 0.548 | -1.91, 1.013 | | | |
| Income | **-1.669** | **0.047** | **-3.316, -0.021** | **-2.233** | **0.021** | **-4.124, -0.341** |
| Years since diagnosis | -0.415 | 0.716 | -2.661, 1.832 | | | |
| Prior hospitalizations | **-1.530** | **<0.000** | **-2.250 -0.809** | **-1.498** | **<0.000** | **-2.218, -0.778** |
| Healthcare contacts | 0.238 | 0.756 | -1.270, 1.746 | | | |
| Co-morbidity | -0.268 | 0.503 | -1.056, 0.520 | | | |

Bold values correspond with significant outcomes (P = .05).
Abbreviations: CI, confidence interval; MSAS, Memorial Symptom Assessment Scale.

## DISCUSSION

This study is the first to assess the prevalence, burden, and correlates of physical and psychological symptoms in patients with NYHA stage III and IV heart failure in a developing country. We found that these patients report a high prevalence of symptoms and high levels of burden associated with these symptoms. Higher symptom burden is associated with a higher age, having no income and fewer hospital within the past 12 months.

The prevalence figures reported in this study are high compared with findings of several other studies who used the MSAS[9 20 27 48]. Focussing on the most prevalent physical and psychological symptoms in this study, varying percentages have been reported for the prevalence of shortness of breath (95.2% vs 56.3%-85.0%[9 20 27 48]), feeling drowsy/tired (93.0% vs 52.0%-90.0%[9 20 27 48]), pain (91.3% vs 52,0%-56,0%[20 27]), worrying (94.3% vs 43.7%-61.5%[9 27]), feeling irritable(93.5% vs 33.0%-53.7%[9 27]) and feeling sad(93.0% vs 42.7%-54.7%[9 27]). The high prevalence figures found in the current study are striking, especially in this group, with a high rate of patients being diagnosed with NYHA stage III. The discrepancies in symptom prevalence between our findings and previous studies could be explained by several factors: Not all studies restricted their inclusion to NYHA stage III or IV but also included NYHA stage I and II, measurements were done at different locations (i.e. at home, during an outpatient clinic visit, during an hospital admission) and at different points in the course of the illness (during an exacerbation, during a chronic period), studies reported on patients with a higher average age (having a younger age has been associated with a higher symptom burden in patients with cancer[49 50]), and studies were carried out in developed parts of the world (i.e. Europe and North America). It is possible that the prevalence figures in the current study are higher compared with earlier findings because most patients in the current study were interviewed at the time of an exacerbation of their illness (86% of patients were at the hospital for an acute admission). Also, the KPS in our study was quite low compared with that in 3 other studies in patients with advanced heart failure (50% vs 69%-76%), which seems to confirm this hypothesis. Another possible explanation for the difference in prevalence figures is related to the prescription rates of recommended treatment. Treatment guidelines in South Africa[51 52] are in line with those for Europe and North America[53 54] in their recommendation for the use of ACE inhibitors, ß-blockers, and spironolactone as an important part of heart failure treatment. The reported levels of medication in our study are, however, lower than recommended and also low compared to other studies, in which ACE-inhibitors were used by 47% to 82% of patients[27 44 48 55-58] (vs 57% in our study); ß-blockers, by 34% to 88%[27 44 48 55-58] (vs. 47%); and MRAs, by 18% to 72%[44 48 56-58] (vs. 12%). Under-treatment has been reported as a problem in heart failure treatment and does not seem to be limited to developing counties[30 56].

The symptoms shortness of breath, numbness/ tingling in hands or feet and “I do not look like myself were considered most distressing by our study group. We found 2 previous studies that reported on distress of symptoms in an advanced heart failure population. Blinderman et al.[9] studied a sample of 103 community-dwelling patients with NYHA stage III/IV heart failure in the United States. According to this sample, the most distressing symptoms were other pain (in this study, pain was differentiated into cardiac pain and other pain), problems with sexual interest/activity and lack of energy. Zambroski et al.[27] studied a sample of 53 patients with NYHA stage II to IV heart failure visiting a heart failure clinic in the United States. Patients in this study judged lack of energy, difficulty sleeping and shortness of breath to be the most distressing symptoms. Patients in the studies of Blinderman et al. and Zambroski et al. and the current study seem to disagree about which symptoms are most distressing to them. This discrepancy could be related to the differences in symptom prevalence and ranking of most prevalent symptoms. Numbness or tingling in hands or feet can be caused by swelling of the arms or legs or associated with peripheral neuropathy secondary to diabetes. Prevalences of the symptom swelling of the arms or legs and of diabetes were higher in the current study compared with the studies of Blinderman et al. and Zambroski et al (81.3% vs 32.0-47.2% and 38% vs 33-32%, respectively[9 27]). It could by hypothesized that patients who report feeling that they do not look like themselves do so because of the presence of disfiguring symptoms such as swelling of arms or legs and weight loss (84.8% vs 19.4%-32.1%[9 27]), which were both more prevalent in our study. To be able to focus care on the most distressing symptoms, communication about symptom-related distress is key.

Having a higher age, having no income, and having fewer hospital admissions within the past 12 months were associated with higher symptom burden. The association with age is in accordance with previous studies that have shown an increased risk of heart failure hospitalization with increasing age[15 59]. The association with income is in line with studies that have looked at the relationship between socioeconomic status (SES) and the risk of heart failure hospitalizations[59-61]. A lower SES is associated with a higher risk for heart failure and heart failure-related hospital admissions. Hospitalizations are usually due to an exacerbation of heart failure. The association of higher symptom burden with fewer hospital admissions is therefore rather surprising. It could be that patients who have been admitted have been well cared for, including receiving the recommended treatment, leading to lower symptom burden in the group with previous hospital admissions. Another explanation could be related to the association with no income. In South Africa, healthcare access for all is constitutionally enshrined, but great inequities in access to and the subsequent use of healthcare remain[62]. Studies have indicated that low-income groups in South Africa cannot “afford” to be ill and therefore underreport or “ignore” illness[62 63]. Also, no money for transport, out-of-pocket payments, delays due to a belief that the illness was not serious enough to warrant immediate care, or that care would be ineffective have been reported as access barriers for the low-SES group[62]. It is startling that the number of healthcare contacts was not associated with symptom burden; therefore, we can presume that pain and symptom burden are not adequately addressed in routine existing care.

Many of the symptoms that are being reported by patients with advanced heart failure are not generally thought of as being caused by heart failure[4 20]. Some symptoms may be related to medication used to treat heart failure, such as dry mouth or constipation, or with comorbidities, which are highly prevalent in this population[20 64 65]. Although the causes of various symptoms, such as pain[5 8 66], remain unclear, these diverse symptoms together are responsible for a major portion of the decrease in quality of life associated with heart failure[20]. Advanced heart failure has been described as having one of the largest effects on quality of life of any advanced disease[20 28]. To optimally treat patients with heart failure, attention needs to be paid to all symptoms that are present , irrespective of their aetiology. Several authors have emphasized the need for incorporating palliative care in advanced heart failure care[4 8 53 67-69]. Palliative care is care tailored to the needs of patients; it is a holistic approach to the care for patients and their families who are facing the problems associated with a life-threatening illness.

There are some limitations to this study. First, concerning generalizability of the results, the patients were recruited from 1 medical centre and may therefore not be representative for the total population with heart failure residing in community settings; although patients were recruited consecutively during an inclusion period of 3 months, most patients who were included in the study were diagnosed with stage III heart failure. It is therefore possible that our results are not completely generalizable to patients with stage IV heart failure. We hypothesize that patients with stage IV heart failure are often too ill to visit the hospital and are taken care of at home. Second, concerning reliability and completeness of data collected from the medical record, it is not clear to what extent these medical records were complete and thus completely reflected the medical history and current health status of the patient. We did not collect data on ejection fraction, and therefore, we cannot fully reflect on the reported levels of medication in this study. Third, the cross-sectional design provides us with a “snapshot” of the symptom burden experienced by patients with advanced heart failure. Symptom burden is expected to change during the course of the disease. A longitudinal follow-up is needed to know how symptom burden changes over time in patients with advanced heart failure, and these longitudinal data will follow in subsequent reporting. The strength of this study lies in the use of patient-reported data, instruments with good psychometric properties and multiple language options, the high response rate, and multiple recruitment points throughout the medical centre.

In conclusion, patients with advanced heart failure attending an academic medical centre in South Africa experience a high prevalence of symptoms and report high levels of burden associated with these symptoms. Current treatment seems not to be in accordance with national and global recommendations. Improved compliance with national and global treatment recommendations could contribute to reduced symptom burden. Attention should be paid to high prevalent symptoms, symptoms associated with high distress, and symptoms that are not generally thought of as being caused by heart failure. Incorporating palliative care into the care for these patients could contribute to the provision of tailored care.

## REFERENCELIST

1. Roger VL, Weston SA, Redfield MM, et al. Trends in heart failure incidence and survival in a community-based population. JAMA 2004;292(3):344-50.
2. Levy D, Kenchaiah S, Larson MG, et al. Long-term trends in the incidence of and survival with heart failure. N Engl J Med 2002;347(18):1397-402.
3. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33(14):1787-847.
4. Howlett JG. Palliative care in heart failure: addressing the largest care gap. Curr Opin Cardiol 2011;26(2):144-8.
5. Nordgren L, Sorensen S. Symptoms experienced in the last six months of life in patients with end-stage heart failure. Eur J Cardiovasc Nurs 2003;2(3):213-7.
6. McMurray JJ, Stewart S. Epidemiology, aetiology, and prognosis of heart failure. Heart 2000;83(5):596-602.
7. Petrie M, McMurray J. Changes in notions about heart failure. Lancet 2001;358(9280):432-4.
8. Gadoud A, Jenkins SM, Hogg KJ. Palliative care for people with heart failure: Summary of current evidence and future direction. Palliat Med 2013
9. Blinderman CD, Homel P, Billings JA, et al. Symptom distress and quality of life in patients with advanced congestive heart failure. J Pain Symptom Manage 2008;35(6):594-603.
10. Stewart S, MacIntyre K, Hole DJ, et al. More 'malignant' than cancer? Five-year survival following a first admission for heart failure. Eur J Heart Fail 2001;3(3):315-22.
11. Bleumink GS, Knetsch AM, Sturkenboom MC, et al. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam Study. Eur Heart J 2004;25(18):1614-9. doi:
12. Cowie MR, Wood DA, Coats AJ, et al. Survival of patients with a new diagnosis of heart failure: a population based study. Heart 2000;83(5):505-10.
13. Ho KK, Pinsky JL, Kannel WB, et al. The epidemiology of heart failure: the Framingham Study. J Am Coll Cardiol 1993;22(4 Suppl A):6A-13A.
14. Strachan PH, Ross H, Rocker GM, et al. Mind the gap: Opportunities for improving end-of-life care for patients with advanced heart failure. Can J Cardiol 2009;25(11):635-40.
15. Cowie MR, Fox KF, Wood DA, et al. Hospitalization of patients with heart failure: a population-based study. Eur Heart J 2002;23(11):877-85.
16. Kruse W. Early readmission of elderly patients with congestive heart failure. J Am Geriatr Soc 1991;39(10):1045-6.
17. The British Society for Heart Failure. National Heart Failure Audit. London: National Institute for Cardiovascular Outcomes Research (NICOR), 2012.
18. Stewart S, Ekman I, Ekman T, et al. Population impact of heart failure and the most common forms of cancer: a study of 1 162 309 hospital cases in Sweden (1988 to 2004). Circ Cardiovasc Qual Outcomes 2010;3(6):573-80.
19. Jhund PS, Macintyre K, Simpson CR, et al. Long-term trends in first hospitalization for heart failure and subsequent survival between 1986 and 2003: a population study of 5.1 million people. Circulation 2009;119(4):515-23.
20. Bekelman DB, Havranek EP, Becker DM, et al. Symptoms, depression, and quality of life in patients with heart failure. J Card Fail 2007;13(8):643-8.

21. Bekelman DB, Rumsfeld JS, Havranek EP, et al. Symptom burden, depression, and spiritual well-being: a comparison of heart failure and advanced cancer patients. J Gen Intern Med 2009;24(5):592-8.
22. Benedict CR, Weiner DH, Johnstone DE, et al. Comparative neurohormonal responses in patients with preserved and impaired left ventricular ejection fraction: results of the Studies of Left Ventricular Dysfunction (SOLVD) Registry. The SOLVD Investigators. J Am Coll Cardiol 1993;22(4 Suppl A):146A-53A.
23. Goebel JR, Doering LV, Shugarman LR, et al. Heart failure: the hidden problem of pain. J Pain Symptom Manage 2009;38(5):698-707.
24. Janssen DJ, Spruit MA, Wouters EF, et al. Daily symptom burden in end-stage chronic organ failure: a systematic review. Palliat Med 2008;22(8):938-48.
25. Rumsfeld JS, Havranek E, Masoudi FA, et al. Depressive symptoms are the strongest predictors of short-term declines in health status in patients with heart failure. J Am Coll Cardiol 2003;42(10):1811-7.
26. Rutledge T, Reis VA, Linke SE, et al. Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. J Am Coll Cardiol 2006;48(8):1527-37.
27. Zambroski CH, Moser DK, Bhat G, et al. Impact of symptom prevalence and symptom burden on quality of life in patients with heart failure. Eur J Cardiovasc Nurs 2005;4(3):198-206. [published Online First: 2005/05/27]
28. Adler ED, Goldfinger JZ, Kalman J, et al. Palliative care in the treatment of advanced heart failure. Circulation 2009;120(25):2597-606.
29. McMurray JJ, Petrie MC, Murdoch DR, et al. Clinical epidemiology of heart failure: public and private health burden. Eur Heart J 1998;19 Suppl P:P9-16.
30. McMurray JJ, Stewart S. The burden of heart failure. . Eur Heart J Suppl 2002;4(suppl D):D50-D58.
31. Ntusi NB, Mayosi BM. Epidemiology of heart failure in sub-Saharan Africa. Expert Rev Cardiovasc Ther 2009;7(2):169-80.
32. Statistics South Africa. Mortality and causes of death in South Africa, 2010: Findings from death notification. Pretoria, 2013.
33. Amoah AG, Kallen C. Aetiology of heart failure as seen from a National Cardiac Referral Centre in Africa. Cardiology 2000;93(1-2):11-8.
34. Marijon E, Mirabel M, Celermajer DS, et al. Rheumatic heart disease. Lancet 2012;379(9819):953-64. doi: S0140-6736(11)61171-9
35. WHO. Rheumatic fever and rheumatic heart disease : report of a WHO Expert Consultation. Geneva, Switserland, 2004.
36. Karnofsky DA, Burchenal JH. The Clinical Evaluation of Chemotherapeutic Agents in Cancer. In: MacLeod CM, ed. Evaluation of Chemotherapeutic Agents. New York: Columbia University Press 1949:196.
37. Schaafsma J, Osoba D. The Karnofsky Performance Status Scale re-examined: a cross-validation with the EORTC-C30. Qual Life Res 1994;3(6):413-24.
38. Brezinski D, Stone PH, Muller JE, et al. Prognostic significance of the Karnofsky Performance Status score in patients with acute myocardial infarction: comparison with the left ventricular ejection fraction and the exercise treadmill test performance. The MILIS Study Group. Am Heart J 1991;121(5):1374-81.
39. Johnson MJ, Bland JM, Davidson PM, et al. The relationship between two performance scales: New York Heart Association Classification and Karnofsky Performance Status Scale. J Pain Symptom Manage 2014;47(3):652-8.
40. Mor V, Laliberte L, Morris JN, et al. The Karnofsky Performance Status Scale. An examination of its reliability and validity in a research setting. Cancer 1984;53(9):2002-7.

41. Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: reliability, validity, and guidelines. J Clin Oncol 1984;2(3):187-93.
42. Yates JW, Chalmer B, McKegney FP. Evaluation of patients with advanced cancer using the Karnofsky performance status. Cancer 1980;45(8):2220-4.
43. Chang VT, Hwang SS, Feuerman M, et al. The memorial symptom assessment scale short form (MSAS-SF). Cancer 2000;89(5):1162-71.
44. Bekelman DB, Nowels CT, Allen LA, et al. Outpatient palliative care for chronic heart failure: a case series. J Palliat Med 2011;14(7):815-21.
45. Harding R, Selman L, Agupio G, et al. Prevalence, burden, and correlates of physical and psychological symptoms among HIV palliative care patients in sub-Saharan Africa: an international multicenter study. J Pain Symptom Manage 2012;44(1):1-9.
46. Harding R, Selman L, Agupio G, et al. The prevalence and burden of symptoms amongst cancer patients attending palliative care in two African countries. Eur J Cancer 2011;47(1):51-6.
47. Chang VT, Hwang SS, Thaler HT, et al. Memorial symptom assessment scale. Expert Rev Pharmacoecon Outcomes Res 2004;4(2):171-8. doi: 10.1586/14737167.4.2.171
48. Song EK, Moser DK, Rayens MK, et al. Symptom clusters predict event-free survival in patients with heart failure. J Cardiovasc Nurs 2010;25(4):284-91.
49. Kirkova J, Rybicki L, Walsh D, et al. Symptom prevalence in advanced cancer: age, gender, and performance status interactions. Am J Hosp Palliat Care 2012;29(2):139-45.
50. Walsh D, Donnelly S, Rybicki L. The symptoms of advanced cancer: relationship to age, gender, and performance status in 1,000 patients. Support Care Cancer 2000;8(3):175-9.
51. The National Department of Health, Republic of South Africa. Standard treatment guidelines and essential medicines list Primary Health Care: The National Department of Health, Pretoria, South Africa; 2008 [Available from: http://www.kznhealth.gov.za/edlphc2008.pdf05-08-2013.
52. The National Department of Health, Republic of South Africa. Standard treatment guidelines and essential medicines list for South Africa Hospital Level Adults: The National Department of Health, Pretoria, South Africa; 2012 [Available from: http://www.kznhealth.gov.za/edlphc2008.pdf05-08-2013.
53. Jessup M, Abraham WT, Casey DE, et al. 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation 2009;119(14):1977-2016.
54. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2012;14(8):803-69.
55. Janssen DJ, Spruit MA, Uszko-Lencer NH, et al. Symptoms, comorbidities, and health care in advanced chronic obstructive pulmonary disease or chronic heart failure. J Palliat Med 2011;14(6):735-4
56. Rutten FH, Heddema WS, Daggelders GJ, et al. Primary care patients with heart failure in the last year of their life. Fam Pract 2012;29(1):36-42.
57. Setoguchi S, Glynn RJ, Stedman M, et al. Hospice, opiates, and acute care service use among the elderly before death from heart failure or cancer. Am Heart J 2010;160(1):139-44.
58. Son YJ, Lee Y, Song EK. Adherence to a sodium-restricted diet is associated with lower symptom burden and longer cardiac event-free survival in patients with heart failure. J Clin Nurs 2011;20(21-22):3029-38.

59. Borne Y, Engstrom G, Essen B, et al. Country of birth and risk of hospitalization due to heart failure: a Swedish population-based cohort study. Eur J Epidemiol 2011;26(4):275-83.
60. Benderly M, Haim M, Boyko V, et al. Socioeconomic status indicators and incidence of heart failure among men and women with coronary heart disease. J Card Fail 2013;19(2):117-24.
61. Hawkins NM, Jhund PS, McMurray JJ, et al. Heart failure and socioeconomic status: accumulating evidence of inequality. Eur J Heart Fail 2012;14(2):138-46.
62. Harris B, Goudge J, Ataguba JE, et al. Inequities in access to health care in South Africa. J Public Health Policy 2011;32 Suppl 1:S102-23.
63. Sauerborn R, Adams A, Hien M. Household strategies to cope with the economic costs of illness. Soc Sci Med 1996;43(3):291-301.
64. Braunstein JB, Anderson GF, Gerstenblith G, et al. Noncardiac comorbidity increases preventable hospitalizations and mortality among Medicare beneficiaries with chronic heart failure. J Am Coll Cardiol 2003;42(7):1226-33.
65. Tevendale E, Baxter J. Heart failure comorbidities at the end of life. Curr Opin Support Palliat Care 2011;5(4):322-6.
66. Godfrey C, Harrison MB, Medves J, et al. The symptom of pain with heart failure: a systematic review. J Card Fail 2006;12(4):307-13.
67. Jaarsma T, Beattie JM, Ryder M, et al. Palliative care in heart failure: a position statement from the palliative care workshop of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2009;11(5):433-43.
68. Johnson MJ, Booth S. Palliative and end-of-life care for patients with chronic heart failure and chronic lung disease. Clin Med 2010;10(3):286-9.
69. Lemond L, Allen LA. Palliative care and hospice in advanced heart failure. Prog Cardiovasc Dis 2011;54(2):168-78.