Influence of depression and gender on symptom burden among patients with advanced heart failure: Insight from the pain assessment, incidence and nature in heart failure study

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ABSTRACT

Introduction: Patients with advanced heart failure (HF) experience many burdensome symptoms that increase patient suffering.
Methods: Comparative secondary analysis of 347 patients with advanced HF. Symptom burden was measured with the Memorial Symptom Assessment Scale-HF. Depression was measured using the Patient Health Questionnaire-9.
Results: Mean number of symptoms was 13.6. The three most frequent symptoms were non-cardiac pain, shortness of breath, and lack of energy. Patients with depression reported higher symptom burden. Symptom burden differed when compared by gender. Women reported higher symptom burden for other pain, dry mouth, swelling of the arms and legs, sweats, feeling nervous, nausea, and vomiting. Men reported higher symptom burden with sexual problems.
Conclusions: Given the high rates of symptoms and distress, interventions are needed to alleviate the symptom burden of patients with advanced HF. Reported symptom burden in patients with advanced heart failure was higher when depressive symptoms were present. Women reported varied number and severity of symptoms than men.

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Introduction

The number of people with heart failure (HF) continues to grow with approximately 6.5 million Americans being diagnosed in the years 2011−2014,[1] and projections for the year 2030 show an increase of 46%.[2] Advanced HF is associated with many burdensome symptoms that occur as a result of altered cardiac function and neurohormonal activation.[3,4] One of the major goals of HF care is alleviation of symptoms and the associated suffering that diminishes quality of life.[3] Therefore, it is important that symptoms are measured using a questionnaire that is valid, reliable, and comprehensive. The Memorial Symptom Assessment Scale for Heart Failure (MSAS-HF) is one such questionnaire that can be used to assess the wide array of symptoms that patients experience.

The frequency and severity of symptoms reported by HF patients may be influenced by depression level.[3,5−7] Depression has been found in approximately 22−42% of HF patients and poses additional threats to effective advanced HF management.[8] Depressive symptoms such as hopelessness, concentration difficulties, and apathy make following guideline recommendations more difficult, thus decreasing quality of life. In addition, patients with HF and depression have been shown to have 57% increased rate of hospital admission.[9]

While the prevalence of HF is similar for women and men, mortality rates are higher in women than men, demonstrating the need to include adequate numbers of women with HF in studies.[10] The average percentage of women participating in HF studies remains low at 32%.[11] Without adequate representation of women in studies, generalizability of the data to women is limited.[11]

Systematic review of symptom clusters in cardiovascular disease patients found the majority of the studies done with HF patients only included 8−10 symptoms with 1 study using 14 symptoms.[12] Of the

six HF studies, none of them focused on patients with advanced HF, with the majority of the studies included patients in all NYHA classes.[13−18] One goal of this study was to determine how many symptoms advanced HF patients endorse when a broader range of symptom choices are assessed. This study evaluated 32 different symptoms in advanced HF patients.

The aims of this study were to: 1) characterize symptom burden defined as, presence, frequency, severity, and level of distress the symptoms provoked; 2) evaluate differences in symptom burden between patients with high and low depressive symptoms and between women and men; and 3) determine sociodemographic (i.e., age, gender, marital status, education), psychosocial (i.e., depression, social support), and clinical (ejection fraction, comorbidity) variables that explain symptom burden (composite of each symptom how often, severity, and distress) among patients with advanced HF.

Methods

Design, sample, setting

A retrospective explanatory design was used for this study. The data were obtained for this comparative analysis from a multisite study Pain Assessment, Incidence and Nature in Heart Failure in which 347 patients with advanced HF were recruited from 10 different outpatient clinics and 5 home hospice programs across the United States who were involved with the Palliative Care-Heart Failure Education and Research Trials collaborative. Institutional review boards approved the original study and the current study.[19] All patients completed written informed consent prior to data collection. The purpose of the parent study was to fully evaluate pain among community dwelling patients with advanced HF, the impact of pain on activity and quality of life, and determine its relationship to health status.[19] Inclusion criteria were advanced HF patients who were at least 18 years old. Advanced HF was defined as dyspnea or fatigue at rest or with minimal exertion. HF providers confirmed the presence of HF. Both patients with reduced and preserved ejection fraction were enrolled. Only patients with reduced ejection fraction (40%), needed to be receiving optimal medical therapy for at least one month before enrollment as recommended by the American Heart Association/American College of Cardiology guidelines, as there are not recommendations for patients with preserved ejection fraction.[19] Exclusion criteria were: cognitive or other impairments that prevented accurate assessment of symptoms or resulted in inability to provide informed consent; HF due to recent onset of acute viral or peripartum myocarditis; hemodialysis or mechanical ventilation; received non-approved Federal Drug Administration investigational agents or devices; previous cardiac transplantation or destination therapy with left ventricular assistive device; cor pulmonale or right ventricular HF in the absence of left ventricular systolic dysfunction; and awaiting cardiac transplantation or destination therapy with left ventricular assistive device.[19]

The theoretical framework guiding this study is the Theory of Unpleasant Symptoms. In this theory, it is proposed that symptoms have antecedent factors that can be categorized as physiological, psychological, situational or environmental.[20−21] The symptoms are interactive and reciprocal as they relate to one another and improvement of one or more symptoms may contribute to the management or improvement of others.[21] Data to support the theory focuses on symptom timing/how often, intensity, duration, quality and distress experienced by the patient.[21] Due to the high number of symptoms patients with advanced HF have reported in past studies, this theory provides guidance to explain symptom experience as well as improve symptom management by accounting for the cumulative effects of multiple symptoms.[13,19] For example, depression magnifies pain experience, pain lengthens the time needed for successful treatment of depression, and concurrent pain and depression reduce a person's coping skills.[22]

Measures

Symptom burden was measured using the Memorial Symptom Assessment Scale-HF (MSAS-HF). The MSAS-HF is based on the Memorial Symptom Assessment Scale, an instrument developed for patients with cancer.[23] For the MSAS-HF, cancer-specific symptoms were removed and HF-specific symptoms were added.[24,25] The MSAS-HF is a 32-item questionnaire on which patients are asked to report how often, severity, and distress each symptom evoked in the past week. Individual scores are summed for each symptom present, rating frequency, severity, and distress to obtain a total symptom score for each symptom with a possible range of 0−13. MSAS-HF response scales are as follows: 1) symptom present 0="no", 1="yes"; 2) how often 1="rarely", 2="occasionally", 3="frequently", 4="almost constantly"; 3) severity 1="slight", 2="moderate", 3="severe", 4="very severe"; and 4) distress 0="not at all", 1="a little bit", 2="somewhat", 3="quite a bit", 4="very much". The total symptom scores are summed to obtain a final grand total symptom burden score that includes all 32 symptoms with a possible score range of 0−416.[23] Higher scores indicate greater symptom burden. In previous studies, the internal consistency of the MSAS-HF was supported by Cronbach's alpha 0.92 among 52 patients recruited from a HF clinic.[24,26] Content validity, construct validity, and internal consistency reliability were demonstrated.[26] The MSAS-HF reliability was satisfactory in this sample with a Cronbach's alpha of 0.90.

Depression was measured using the Patient Health Questionnaire (PHQ-9). The PHQ-9 is based on the Diagnostic and Statistical Manual of Mental Disorders for clinical depression diagnostic criteria.[27] Patients are asked to rate each of the 9 items as to how often they were bothered by each symptom over the past two weeks. The items are on 4 point response scales of 0= "not at all", 1= "several days", 2= "more than half the days", 3= "nearly every day". Possible scores range from 0- 27, with higher scores indicating greater likelihood of depression. In past studies, a total score of ≥ 10 had a sensitivity and specificity of 88% in diagnosis of major depression.[27] Therefore, ≥ 10 was used as the cut off for a positive screen for depression in this analysis. Construct validity of the PHQ-9 was supported among 308 HF patients[9] and internal consistency was supported with Cronbach's alpha of 0.82 among 249 patients with HF.[28] The reliability of the PHQ-9 in this sample was satisfactory with Cronbach's alpha of 0.85.

The Enriched Social Support Instrument was used to measure perceived social support. This instrument was developed to include items about structural, instrumental, and emotional support previously found to be significant predictors of mortality among patients with cardiovascular conditions.[29] Patients were asked to rate 6 items based on their current situation. The item response scales include: 1 = "none of the time", 2 = "a little of the time", 3 = "some of the time", 4 = "most of the time", and 5 = "all of the time". On the final item, patients are asked if they are currently married or living with a partner, with a 4= "yes" and 2= "no".[6] Items are summed to obtain a total score with higher scores indicating greater perceptions of social support. Total possible scores range from 0 to 31. Internal consistency reliability was reported with an estimated Cronbach's alpha 0.86, and convergent validity was supported by a moderate correlation (r = 0.62) with the Perceived Social Support Scale among 196 myocardial infarction patients.[29] Reliability was satisfactory in this study with a Cronbach's alpha of 0.88.

The Charlson Comorbidity Index is a method of evaluating comorbidities among patients and is based on the International Classification of Diseases diagnosis.[30] Diagnoses are included for the following conditions if they were present in the patients' medical records: myocardial infarction, congestive HF, peripheral vascular disease,

cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, liver disease, moderate or severe renal disease, hemiplegia, leukemia, lymphoma, metastatic solid tumor, any tumor, human immunodeficiency virus with or without acquired immunodeficiency syndrome, and diabetes with or without end organ damage.[30] Each comorbidity is assigned an associated weight and the sum of the weighted scores is the final comorbidity index score.[30] Higher scores reflect more comorbidity burden.[30] Predictive validity was supported by 3496 community dwelling older adults in primary care.[30]

Chart review and patient interview were used to collect data on age, sex, race, ethnicity, living situation, household income, education level, and left ventricular ejection fraction.

Statistical analysis

Descriptive statistics were used to examine sociodemographic variables and to describe the presence, frequency, and severity of symptoms during the previous week, and the level of distress the symptoms evoked. Chi-square, independent t-tests, and Mann-Whitney U, were computed for aim two comparing patient characteristics and evaluating the differences in symptom burden by depression score (PHQ-9 score < 10 or ≥ 10) and gender.[27] To determine the influence of explanatory variables on "grand total symptom burden," multicollinearity and other violations of the assumptions of multiple regression were assessed and no violations were found. Explanatory variables of grand total symptom burden were then evaluated using simultaneous multiple regression with pairwise deletion. Independent variables entered into the regression model were age, gender, marital status, education level, depression score, social support score, ejection fraction, and comorbidity score. A post-hoc analysis was done to test if there was an interaction effect between depression and gender on grand total symptom burden. Only those patients with complete data for all study variables were included in the regression analysis (N = 323). Significance level was set at p ≤ 0.05.

Results

The sample featured 35% women and 65% men, 79% White and 19% Black, and 8% Hispanic. Fifty-five percent were married, 49% reported having more than a high school education, and 89% reported having a household income over $25,000 (Table 1). The mean age of the sample was 66 years old, mean left ventricular ejection fraction was 30%, and the mean Charlson Comorbidity Index was 3.64. Most patients (76.6%) had advanced HF with reduced ejection fraction (≤ 40%), 89% were prescribed diuretics, 94% were prescribed beta-blockers, 79% were prescribed angiotensin-modulating agents, and 52% had an internal cardiac defibrillator, based on patient medical records. Only 8% of the patients who had reduced ejection fraction were unable to tolerate beta blockers and/or angiotensin-modulating agents. The mean PHQ 9 depression score was 7.69 (SD 6.24), with 224 participants with a score less than 10 and 105 with 10+ (Table 1). No differences in prevalence of depression was found between genders (p = 0.221) as shown in Table 1.

The number of symptoms present based on the MSAS-HF ranged from 0−32. The mean and standard deviation (SD) of the total number of symptoms reported were 13.6 and 6.8, respectively. Each symptom reported as present by at least 50% of the patients in order of most common included: pain other than chest pain (77%), shortness of breath (76%), lack of energy (76%), feeling drowsy (62%), numbness/tingling (60%), dry mouth (60%), and difficulty sleeping (59%) as shown in Table 2.

The three most frequent symptoms, pain other than chest pain, shortness of breath, and lack of energy had the highest mean scores for total symptom score (7.4−6), how often (2.5−3), severity (1.7−2), and distress (1.6−1.9) except sexual problem which had the third highest mean in how often (2.9) (Table 2).

The mean MSAS-HF grand total symptom burden score was 96 (SD=58), with a range of 0−336, the 25th and 75th percentiles were 52 and 125, respectively. Differences were found in total symptom

Table 1
Sociodemographic characteristics for total sample and compared by depression and gender

Variable	Total n or mean/SD***	PHQ-9 (<10) n or mean/SD	PHQ-9 (10+) n or mean/SD	Male n or mean/SD	Female n or mean/SD
Gender					
Male	222	148	62		
Female	123	76	43		
Race**					
White	225	164	80	172	81
Other	72	43	23	37	34
Household income**					
<25,000	154	102	44	84	70
25,000+	139	91	43	102	35
Education**					
High school or less	168	119	43	95	71
More than high school	158	98	52	109	48
Marital status**					
Not married	158	109	40	80	77
Married	190	116	66	142	46
Ethnicity					
Hispanic	23	18	5	13	10
Not hispanic	305	194	94	192	104
Age*	66.26 (14.86)	68.61 (14.65)	61.61 (13.71)	66.11 (13.99)	66.77 (16.17)
Left ventricular ejection fraction**	0.30 (0.15)	0.293 (0.14)	0.32 (0.15)	0.28 (0.13)	0.34 (0.17)
40+	72				
<40	262				
Social support*	22.94 (5.18)	23.52 (4.81)	21.87 (2.17)	22.99 (5.49)	22.80 (4.56)
Charlson comorbidity index	3.64 (2.22)	3.62 (2.17)	3.72 (2.25)	3.59 (2.24)	3.75 (2.19)
PHQ 9	7.69 (6.24)				
<10	224				
10+	105				

*Significant difference in depression scores p-value ≤0.05, **Significant difference in gender p-value ≤0.05, ***SD = standard deviation.

Table 2
Symptom frequency, severity and distress in order of most reported to least[a] (n = 326)

	Symptom	Overall presence n (%)	Total score Range 0−13 Mean (SD[2])	How often Range 1−4 Mean (SD)	How severe Range 1−4 Mean (SD)	Distress Range 0−4 Mean (SD)
1	Other pain	251 (77)	**6.5** (4.2)	**2.9** (0.9)	**1.8** (1.2)	**1.8** (1.4)
2	Shortness of breath	248 (76)	**6.0** (4.1)	2.5 (0.9)	**1.7** (1.2)	**1.6** (1.4)
3	Lack of energy	248 (76)	**7.4** (4.1)	**3.0** (0.9)	**2.0** (1.2)	**1.9** (1.5)
4	Feeling drowsy	202 (62)	4.5 (4.1)	2.5 (0.9)	1.3 (1.2)	1.0 (1.3)
5	Numbness/tingling	196 (60)	4.5 (4.4)	2.6 (1.0)	1.3 (1.3)	1.1 (1.4)
6	Dry mouth	196 (60)	4.3 (4.3)	2.6 (1.0)	1.2 (1.2)	1.0 (1.4)
7	Difficulty sleeping	192 (59)	5.1 (4.7)	2.7 (1.0)	1.4 (1.4)	1.4 (1.5)
8	Difficulty breathing when lying flat	160 (49)	3.0 (3.5)	.5 (0.5)	1.3 (1.6)	1.2 (1.6)
9	Worrying	157 (48)	3.7 (4.3)	1.2 (1.4)	1.0 (1.2)	1.0 (1.3)
10	Cough	157 (48)	3.6 (3.6)	2.2 (0.9)	1.0 (1.0)	.7 (1.1)
11	Difficulty concentrating	157 (48)	3.2 (3.8)	2.2 (0.9)	.8 (1.0)	.8 (1.3)
12	Swelling of arms and legs	147 (45)	2.0 (2.6)	0	.9 (1.1)	.7 (1.2)
13	Feeling bloated	147 (45)	3.4 (4.2)	2.3 (1.0)	.9 (1.2)	.9 (1.4)
14	Sweats	143 (44)	2.4 (3.7)	2.2 (0.9)	.7 (1.1)	.5 (1.1)
15	Feeling sad	143 (44)	3.0 (3.9)	2.1 (0.9)	.8 (1.1)	.8 (1.2)
16	Dizziness	140 (43)	3.1 (3.9)	2.1 (0.8)	.8 (1.1)	.8 (1.3)
17	Feeling irritable	140 (43)	2.8 (3.7)	2.0 (0.8)	.8 (1.1)	.7 (1.2)
18	Chest pain	134 (41)	2.8 (3.8)	1.9 (0.8)	.8 (1.2)	.8 (1.3)
19	Palpitations	127 (39)	1.8 (3.2)	2.0 (0.8)	.5 (0.9)	.4 (1.0)
20	Feeling nervous	124 (38)	2.5 (3.6)	2.2 (0.9)	.7 (1.0)	.7 (1.2)
21	Itching	117 (36)	2.5 (3.7)	2.2 (0.9)	.7 (1.0)	.6 (1.1)
22	Sexual problems	111 (34)	3.1 (4.8)	**2.9** (1.1)	.9 (1.5)	.9 (1.5)
23	Lack of appetite	108 (33)	2.2 (3.5)	2.3 (1.1)	.7 (1.1)	.4 (1.0)
24	Waking up breathless	108 (33)	2.4 (3.9)	2.2 (1.)	.7 (1.1)	.7 (1.3)
25	Weight gain	104 (32)	1.5 (2.5)	.29 (0.5)	.6 (1.0)	.6 (1.2)
26	Urination problem	104 (32)	2.3 (3.8)	2.4 (1.4)	.6 (1.1)	.6 (1.2)
27	Nausea	101 (31)	2.0 (3.4)	2.0 (1.0)	.6 (1.0)	.5 (1.1)
28	Diarrhea	78 (24)	1.6 (3.2)	1.9 (0.8)	.5 (1.0)	.4 (1.0)
29	Food taste change	75 (23)	1.2 (2.4)	0	.5 (1.0)	.4 (1.0)
30	Weight loss	65 (20)	0.7 (1.7)	0	.4 (0.8)	.2 (0.7)
31	Constipation	62 (19)	1.4 (2.5)	0	.6 (1.0)	.6 (1.1)
32	Vomiting	39 (12)	.8 (2.4)	1.8 (0.9)	.2 (0.7)	.2 (0.8)

[a] Higher number indicates higher frequency, severity, and distress. [2]SD = standard deviation, **bold**=top 3 highest.

burden based on depression scores (10+ vs. <10) for 31 of the 32 symptoms (Table 3). Patients with higher depression scores reported higher symptom burden. In addition, patients with higher depression scores experienced higher overall symptom burden as determined by grand total symptom burden score of 70 versus 137 (p < 0.001).

Compared with men, women had significantly greater symptom burden in the following areas: pain other than chest pain (p = 0.005), feeling nervous (p = 0.041), dry mouth (p = 0.022), nausea (p = 0.0021), vomiting (p = 0.015), sweats (p = 0.043), and swelling of the arms and legs (p = 0.015). Men reported significantly more symptom burden from sexual problems than women (p ≤ 0.001) (Table 3). No significant differences were found in grand total symptom burden score (p = 0.141).

The overall multiple regression model was significant ($R^2 = 0.413$, p < 0.001) when the MSAS-HF grand total symptom burden score was entered as the dependent variable and age, gender, marital status, education level, depression score, social support, left ventricular ejection fraction, and comorbidity score were entered as independent variables. An interaction term of depression and gender was also evaluated and found to be non-significant (p = 0.078). Depression and education were the only significant explanatory variables of the MSAS-HF grand total symptom burden score (Table 4) with depression accounting for most of the explained variance. Patients with high levels of depression had higher MSAS-HF grand total symptom burden scores, meaning that those with higher depression levels reported greater symptom burden. Compared with patients with education level of more than high school, patients with high school education level or less had lower grand total symptom burden indicating that patients with lower education levels reported less symptom burden.

Discussion

Patients with advanced HF reported a large number of symptoms (mean 13.6 with SD 6.8) with moderate burden levels despite the majority (92%) of patients receiving optimal medical management of HF. In another study, investigators reported that patients with advanced HF had a similar number of symptoms (12, SD=5.8) using the MSAS-HF.[31] They reported the same top 6 symptoms as the current study found despite a smaller sample (N = 40).[31] With the mean number of 12 and 13.6 symptoms being reported in each study, additional research looking at symptoms clusters is likely needed as only 6−9 symptoms were assessed in previous HF symptom cluster work.[13,17,32,33] Key information that would further inform clinical practice maybe missing due to the few number of symptoms included. Additional research investigating symptoms clusters using a measure of more symptoms with the inclusion of pain and depression is needed.

The most commonly reported symptom in this study was pain other than chest pain (77%).[19] This finding is a somewhat surprising because the hallmark symptoms of HF are shortness of breath and lack of energy.[34−36] Non-cardiac pain has been investigated in HF patients because of the impact of comorbidities on HF patients and the corresponding increase in symptom burden.[37−41] This study supports the need for additional non-cardiac pain assessment and proper treatment among patients with advanced HF.

The next most commonly reported symptoms were shortness of breath and lack of energy, both with an overall presence of 76% is consistent with existing scholarly literature. Wilson and colleagues found both symptoms to be among the three most commonly reported with shortness of breath at 65%, and lack of energy at 70%.[31] By definition,

Table 3
MSAS-HF[a] symptom total scores compared by depression and gender

Symptom	Depression			Gender		
	Not depressed (N = 225) Median (25,75 percentile)	Depressed 10+ (N = 106) Median (25,75 percentile)	P value =/≤	Male (N = 222) Median (25,75 percentile)	Female (N = 123) Median (25,75 percentile)	P value =/≤
Difficulty concentrating	0 (0,4)	6.5 (0,9)	0.001	0 (0,6)	3 (0,7)	0.063
Chest pain	0 (0,5)	1 (0,8)	0.002	0 (0,6)	0 (0,6)	0.538
Other pain	7 (0,9)	9 (6,11)	0.001	7 (0,9)	8 (6,10)	**0.005**
Cough	3 (0,5)	4.5 (0,8)	0.001	4 (0,6)	3 (0,6)	0.424
Feeling nervous	0 (0,4)	1 (0,7)	0.001	0 (0,5)	0 (0,6)	**0.041**
Dry mouth	3 (0,7)	5.5 (2,9)	0.001	4 (0,7)	5 (0,9)	**0.022**
Nausea	0 (0,0)	0 (0,7)	0.001	0 (0,3)	0 (0,5)	**0.021**
Feeling drowsy	4 (0,7)	7 (0,9)	0.001	0 (0,8)	0 (0,9)	0.541
Numbness tingling	3 (0,7)	7 (0,10)	0.001	5 (0,9)	5 (0,8)	0.973
Difficulty sleeping	3 (0,8)	9 (0,11)	0.001	6 (0,10)	5 (0,9)	0.830
Feeling bloated	0 (0,6)	5 (0,9)	0.001	0 (0,6)	0 (0,7)	0.173
Urination problem	0 (0,3)	0 (0,6)	0.017	0 (0,3)	0 (0,3)	0.152
Palpitations	0 (0,0)	0 (0,6)	0.001	0 (0,3)	0 (0,4)	0.317
Lack of energy	7 (4,10)	10 (7,12)	0.001	8 (5,10)	8 (6,11)	0.251
Waking up breathless	0 (0,0)	0 (0,8)	0.001	0 (0,5)	0 (0,4)	0.916
Vomiting	0 (0,0)	0 (0,1)	0.001	0 (0,0)	0 (0,0)	**0.015**
Shortness of breath	6 (0,8)	9 (6,10)	0.001	7 (3,9)	6 (3,9)	0.795
Diarrhea	0 (0,0)	0 (0,4)	0.004	0 (0,0)	0 (0,0)	0.933
Feeling sad	0 (0,4)	6.5 (0,9)	0.001	0 (0,6)	0 (0,6)	0.655
Sweats	0 (0,3)	0 (0,7)	0.001	0 (0,4)	0 (0,6)	**0.043**
Worrying	0 (0,5)	7 (0,10)	0.001	0 (0,7)	5 (0,8)	0.089
Sexual problems	0 (0,3)	3 (0,11)	0.001	0 (0,9)	0 (0,0)	**0.001**
Itching	0 (0,4)	0 (0,6)	0.008	0 (0,5)	0 (0,5)	0.471
Lack of appetite	0 (0,0)	3 (0,7)	0.001	0 (0,4)	0 (0,5)	0.257
Dizziness	0 (0,5)	5 (0,7)	0.001	0 (0,7)	0 (0,6)	0.569
Feeling irritable	0 (0,4)	5 (0,9)	0.001	0 (0,6)	0 (0,6)	0.945
Food taste change	0 (0,0)	0 (0,3)	0.056[b]	0 (0,0)	0 (0,3)	0.119
Weight loss	0 (0,0)	0 (0,2)	0.001	0 (0,0)	0 (0,0)	0.115
Constipation	0 (0,0)	0 (0,4)	0.003	0 (0,1)	0 (0,4)	0.111
Swelling of arms and legs	0 (0,3)	2 (0,5)	0.014	0 (0,3)	2 (0,4)	**0.015**
Weight gain	0 (0,2)	0 (0,6)	0.001	0 (0,3)	0 (0,3)	0.758
Difficulty breathing when lying flat	0 (0,5)	5 (0,8)	0.001	0 (0,6)	2 (0,7)	0.321
MSAS-HF grand total	70 (42,106)	137 (95,180)	0.001	86 (49,125)	90 (67,125)	0.141

[a] MSAS-HF = Memorial Symptom Assessment Scale-Heart Failure.
[b] only symptom not sig for depression analysis, **bold**= significant gender difference variables.

advanced HF occurs when symptoms are present at rest despite optimal medical therapy.[4] More research is needed to understand how to optimize management of shortness of breath and exertional fatigue to reduce symptom burden to more manageable levels.[42]

Not surprisingly, in addition to being more frequent, pain other than chest pain, shortness of breath, and lack of energy were most severe, and distressing symptoms; therefore, they were the most burdensome among these patients with advanced HF. Wilson and colleagues found similar results among patients with HF enrolled in hospice, with seven

Table 4
Multiple regression analysis for total symptom burden score (n = 326)[a]

Variable	B	Standard error B	β	t	P-value
Age	−0.171	0.199	−0.044	−0.862	0.389
Gender 0=male 1=female	0.025	5.794	0.000	0.004	0.997
Marital status 0=not married 1= married	−3.119	6.024	−0.027	−0.518	0.605
Education 1=HS or less 2= more than HS	−13.063	5.288	−0.112	−2.470	0.014
Depression	5.890	0.447	0.632	13.168	≥ 0.001
Social support	−0.241	0.571	−0.021	−0.421	0.674
LVEF	27.274	19.038	0.068	1.433	0.153
Charlson comorbidity index	1.123	1.224	0.043	0.918	0.359

[a] Overall R^2 =0.428, adjusted R^2 =0.413, F (8, 292) = 28.364, p < 0.001, MSAS-HF Grand total score regressed on 8 factors.

of the most common symptoms being the same symptoms reported in the current study.[31] Differences between Wilson's study and the current study included symptoms of weight loss (20% vs 53%) and change in taste (23% vs 50%).[31] It is unclear why the percentage of patients reporting weight loss and change in taste is higher in the current study. One possible explanation is that the sample size was larger in the current study, or patients maybe have been on different medication regimens. The sample size in the current study was larger and the majority of patients (92%) were prescribed optimal medical treatment for HF.[43,44]

Results from the current study demonstrated that patients with higher depression scores reported higher symptom burden. This important result is consistent with the theory and past studies as discussed in the introduction section.[3,5,7,45] In addition to assessing for expected and unexpected HF symptoms, using a valid depression screening tool (such as the PHQ 9) is important for all HF patients, particularly those patients with advanced HF where rates of depression are highest.

The prevalence of depression was not different between genders (p = 0.221) in our study, which is different from previous studies in people with myocardial infarction.[46] Recent estimates from the CDC of men and women living in the United States, aged 51+ with clinically significant depressive symptoms, ranged between 9–14% in men and 15–19% in women, between the years 2006–2014.[47] Similar findings are available for European countries although differing methods of measurement used by different countries make generalized estimates of major depression more difficult.[46] While depressive symptoms have many of the same risk factors as the general population (e.g., stressful life events), gender is only a significant predictor of depression in some studies.[46]

Symptoms of significance varied by gender, although grand total symptom burden did not. Women were more likely to report higher scores of other pain, feeling nervous, dry mouth, nausea, vomiting, sweats, and swelling of the arms and legs. This finding suggests that women may require more extensive or different treatment options and requires further exploration. Further research is also needed to determine if women experience more symptoms at all stages of HF or just with advanced HF.

The issue of sexual problems in HF can include erectile dysfunction, orgasmic difficulties, lack of interest in sex, being afraid to have sex, and partner fear of having sex.[48] Of the studies involving sexual dysfunction in HF, no gender differences were found that would explain the differences in reporting we have found here, as both genders reported problems in other studies.[49] One explanation maybe that only those who have a sexual partner may report having a sexual issue and many of the women in this study were not married where as more of the men were (p ≤ 0.001).[50]

Depression and education were significant explanatory variables of higher grand total symptom burden. It is possible those with lower level of education reported less symptoms due to lower health literacy or inability to express their symptoms accurately.[33] The more important finding of the study is a substantial part of the variance (41%) in grand total symptom burden was accounted for by depression. Thus, the clinical implication is by treating depressive symptoms we may improve patients overall symptom burden.

Limitations

This study has a few limitations. First, the sample was comprised of mainly White patients and results may not be generalizable to patients from other racial groups. Second, the sample was comprised of unequal numbers of women and men. The greater percentage of men may have influenced results. Third, the majority (92%) of the patients in this study with reduced EF were prescribed optimal medical therapies and results may not be generalizable to patients who are not prescribed these therapies. Finally, there were multiple significance testing completed on the 32 items of the MSAS-HF, which may have influenced the study findings. These results need to be confirmed in a prospective study among a more diverse group of patients.

Conclusion

The results of this study suggest a need to test the impact of clinical assessment including wider variety of symptoms in patients with advanced HF, and of clinical interventions aimed at effectively managing the high symptom burden. Given the high rates of symptoms and associated distress, novel interventions need to be developed and tested to alleviate the symptom burden of patients with advanced HF. Furthermore, lack of energy was reported as the most bothersome symptom and little is known about how to treat fatigue (or lack of energy) in advanced HF. Knowing the frequency and overall burdensome nature of multiple symptoms is important for future interventions, as many symptoms were present despite optimal medical management of HF. Additional research focusing on the reciprocal nature of multiple symptoms is also needed by expanding on symptom cluster work by adding assessment of additional symptoms.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.hrtlng.2019.02.002.

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