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Symptom clusters predict event-free survival in patients with heart failure

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INTRODUCTION

Heart failure (HF) is a leading cause of hospitalization and death in individuals over 65 years of age worldwide.[1,] 2Although overall survival rate has improved over time,3 the one year mortality rate is still as high as 20%.2 The prevalence of HF has increased along with the aging of the population, resulting in increased hospitalizations and death in South Korea.[4] Approximately, one in five person die within 1-year following a diagnosis of HF in Korea, while readmission rates for HF exacerbation within 6 months post discharge have been reported to be as high as 50%.[5, 6]

Patients with HF commonly experience a variety of physical symptoms concurrently including shortness of breath, dyspnea at rest, paroxysmal nocturnal dyspnea, lack of energy, difficulty sleeping, swelling of legs or ankles, and lack of appetite.[7-14] More than 90% of patients with HF experienced at least two of six common physical HF symptoms.[15] Dyspnea and fatigue were correlated to each other,[16, 17] and fatigue was associated with difficulty sleeping.[17] Additionally, dyspnea and edema were correlated.[18] Elderly patients with a history of HF were more likely to experience a symptom cluster of severe fatigue, difficulty sleeping, and shortness of breath in prior studies.[19, 20] This may suggest that a number of physical symptoms are inter-related and their co-existence in a cluster may increase the perceived severity of each symptom.[8, 21-23] Worsening symptoms are a key reason for patients with HF to visit the hospital or seek treatments from health care providers.[10, 21, 22, 24] Consequently, it may be important for patients with HF to be aware of clustering of symptoms to recognize impending exacerbation of HF. Failure to do so could lead to delay in seeking treatment and timely management.[25] Thus, identifying physical symptoms clusters associated with adverse outcomes in patients with HF may increase our ability to help patients recognize when treatment is warranted to prevent rehospitalization.

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To date, only the effect of individual physical symptom such as breathlessness or fatigue on adverse outcomes has been demonstrated.[26] The impact of physical symptom clusters on adverse outcomes has not been examined. Given the importance of early awareness for worsening symptoms in preventing unnecessary hospitalizations, it is important to identify symptom clusters and their impact on adverse outcomes in patients with HF. Therefore, the purposes of this study were to 1) determine which symptoms occur in clusters in patients with HF and 2) identify whether these symptom clusters predict cardiac rehospitalization and cardiac mortality for 12-months follow-up period after discharge, controlling for age, gender, etiology of HF, body mass index (BMI), New York Heart Association (NYHA) functional class, left ventricular ejection fraction (LVEF), duration of HF, total comorbidity score, and prescribed medications.

METHODS

Design, Participants, and Setting

This was a prospective study to identify symptom clusters and their potential impact on cardiac-related rehospitalization and death in patients with HF. The distress of physical HF symptoms were assessed at the beginning of the enrollment and then the time to first cardiac rehospitalization or mortality was measured over the 12-months follow-up period.

Patients with HF were recruited during an index hospitalization for exacerbation of chronic HF at two large tertiary medical centers in Seoul, South Korea, between September 1, 2005 and December 31, 2006. As part of standard care prior to discharge from the index hospitalization, patients were instructed to monitor their physical symptoms daily and to call their clinician if symptoms worsened. Eligibility criteria for participation in this study were: (1) confirmed diagnosis of chronic HF and having either non-preserved left ventricular systolic function (left ventricular ejection faction [LVEF] < 40%) or preserved systolic function (LVEF ≥ 40%); (2) taking stable doses of HF medications for at least 3 months; (3) no acute myocardial infarction within the previous 6 months (4) no cognitive impairment (defined as a diagnosis of cerebrovascular accident or dementia); (5) no history of cancer, severe thyroid disease, liver or renal failure.

A total of 455 patients were eligible for this study. Fifteen patients declined to participate, eight patients withdrew, and thirteen patients were lost to follow-up. Thus, data from 421 patients were included in this study.

Measurements of variables

The prevalence and distress of physical symptoms—The prevalence and perceived distress of the following physical symptoms specific to HF were assessed by using the modified Memorial Symptom Assessment Scale-Heart Failure (MSAS-HF)[27]: shortness of breath, lack of energy, difficulty sleeping, difficulty breathing when lying flat, waking up breathless at night, swelling of legs or ankles, dizziness, chest discomfort, palpitations, and lack of appetite. Patients were asked to indicate for the previous two weeks whether a symptom was present or not, and then to report the level of perceived distress associated with that symptom on a 4-point Likert scale using the stem: “For the previous two weeks, how much were you bothered or distressed by each symptom”. Symptom distress was rated from 1 to 4 as follows: 1 = Not at all; 2 = A little, mildly; 3 = A great deal, moderately; and 4 = Extremely, could not have been worse. The original version of MSAS had well-established reliability and validity among cancer population.28 The validity of the modified MSAS-HF was previously established in patients with HF to assess the degree of symptom distress.[7, 29, 30] The modified MSAS-HF had acceptable reliability with a Cronbach's α coefficient of 0.87.[7] In this study, the Cronbach's α coefficient was 0.81.

Other clinical variables—Age, gender, etiology of HF, NYHA functional class, LVEF, duration of HF, total comorbidity score measured by the Charlson comorbidity index,[31] and prescribed medications were obtained through patient interview and review of medical records. These covariates have been identified to be associated with higher risk for adverse outcomes in patients with HF in previous studies.[32-37] Body weight and height were measured by a trained research assistant using a calibrated scale and a professional grade stadiometer at discharge. BMI (kg/m^2) was defined as the individual's body weight (kg) divided by the square of his or her height (meter).

Adverse outcomes—Cardiac rehospitalization-free survival was defined as time to first rehospitalization for exacerbation of HF or cardiac-related problems during the 12-months follow-up period. Data about rehospitalization (i. e., readmission date and discharge date, reason for readmission) were obtained from telephone interviews with patients every month by asking following several questions. “For the past 1 month, have you been rehospitalized?” “If you were hospitalized for the past 1 month, could you please tell me the reason for readmission, the date of readmission and discharge, and hospital name?” Cardiac death-free survival was defined as time to cardiac-related death during the 12-month follow-up period. Reported rehospitalizations and death determined during telephone interviews with family members and physicians were confirmed by review of medical records and death certificates.

Procedure

This study was approved by the Institutional Review Board at each medical center. The cardiologists at each medical center referred eligible patients to the primary investigator. Medical records were double-screened by the primary investigator and a trained research assistant to determine if the patient met the eligibility criteria. Patients who were considered eligible by both screeners were recruited for the study. The primary investigator explained the study purposes and protocols and obtained written informed consent from each patient. Patients were given a series of questionnaires to complete when they were medically stable, usually within 1 to 2 days before discharge, approximately 9-10 days of hospitalization. A trained research assistant reviewed the questionnaires to ensure completeness and then gave all participants a $15 gift certificate to compensate them for their time. After discharge, telephone follow-up interviews to obtain data about rehospitalization and death were conducted every month for 12 months.

Statistical Analysis

Statistical analyses were conducted using SPSS for Windows 16.0. Three physical HF symptoms, dizziness, chest discomfort, and palpitations, were excluded from the analyses because they occurred in less than 20% of patients. An agglomerative hierarchical clustering approach with Ward's method was used to identify symptom clusters. Cluster analysis is one way to classify based on similarity within clusters while maximizing dissimilarity between clusters.[38] An agglomerative hierarchical clustering approach begins with each symptom as a separate cluster and successively merges symptoms into larger clusters. Clusters were formed based on symptom similarity defined as the distance between ratings of symptom distress, which was calculated using squared Euclidian distances. Data were pictorially displayed using the dendrogram. The distance score ranges from 0 to 25 on the dendrogram; the lower the distance score, the more similar the symptoms being clustered together. A mean distress score was calculated for each symptom cluster by averaging the distress scores of the symptoms within the cluster.

The mean distress score for each symptom cluster was used in hierarchical Cox proportional hazards regressions. The hierarchical Cox proportional hazards regression was used to identify the impact of symptom clusters on adverse outcomes, after controlling for age, gender, etiology

of HF, BMI, NYHA functional class, LVEF, duration of HF, total comorbidity score, ACE inhibitors, and beta-blockers. The proportional hazard assumption of each hazard ratio (HR) over the follow-up periods was examined and found to be met. A HR along with 95% confidence intervals (CIs) for cardiac rehospitalization and death was obtained for all independent variables.

RESULTS

Sample characteristics

Sample characteristics are shown in Table 1. Patients were primarily male with an age range of 23 to 97 years. In accordance with the obesity categories recommended by the World Health Organization for Asian people,[39] 22% of patients were obese and 6.4% were underweight. The majority of patients were in NYHA functional classes II and III. Half the patients had ischemic heart disease as the underlying etiology of HF. The most common co-morbidities were hypertension, diabetes mellitus, and atrial fibrillation. Approximately 55% of patients had been diagnosed with HF for 2.5 years or more. The majority of patients were prescribed diuretics, beta-blockers, and ACE inhibitors.

The prevalence and distress of physical symptoms

The most common physical symptoms were shortness of breath, lack of energy, and difficulty sleeping. Other symptoms were reported with less frequency but by 50% or more of the sample. More than 60% of patients experienced at least two physical symptoms. Approximately 80% had both lack of energy and shortness of breath. Lack of energy was rated as the most distressful physical symptom, while difficulty breathing when lying flat was rated as the least distressful physical symptoms (Table 2).

The symptom clusters

The dendrogram presented in Figure 1 shows that two distinct symptom clusters emerged. Shortness of breath, difficulty breathing when lying flat, and waking up breathless at night were clustered into a symptom cluster that we named the Dyspneic symptom cluster. Lack of energy, lack of appetite, and difficulty sleeping were clustered into a symptom cluster that we named the Weary symptom cluster. Swelling of legs or ankles was not included in either cluster. In the Weary symptom cluster, difficulty sleeping branched off from the other symptoms at a distance score of 15 which indicated difficulty sleeping was the least related symptom to the other symptoms within the Weary symptom cluster. In the Dyspneic cluster, waking up breathless at night and difficulty breathing when lying flat were the most closely related symptoms.

The impact of symptom clusters on adverse outcomes

During the 12-month follow-up periods after discharge, 34 patients (8.1%) died and 164 patients (39.0%) were rehospitalized due to HF exacerbation and cardiac-related cause.

Higher distress from the Dyspneic symptom cluster did not predict cardiac rehospitalization-free survival, but did independently predict cardiac death-free survival after controlling for age, gender, etiology of HF, BMI, NYHA functional class, LVEF, duration of HF, total co-morbidity score, ACE inhibitors, and beta-blockers ($p = .012$). Each one unit increase in mean distress score in the Dyspneic symptom cluster doubled the risk for cardiac death (Table 3). In contrast, higher distress from the Weary symptom cluster independently predicted cardiac rehospitalization-free survival after controlling for same clinical variables ($p = .011$). The risk of cardiac rehospitalization increased by 1.5 times for each one unit increase in mean distress

score in the Weary symptom cluster (Table 3). Distress from the Weary symptom cluster did not predict cardiac death-free survival.

DISCUSSION

Only a small number of studies have been conducted to explore symptom clusters in patients with cardiovascular disease[19, 20, 40] and none in patients with HF. This was the first study to identify symptom clusters in patients with HF and demonstrate a relationship between symptom clusters and adverse outcomes. Two distinct symptom clusters were identified in this study; the Dyspneic (shortness of breath, difficulty breathing when lying flat, and waking up breathless at night) and Weary symptom cluster (lack of energy, lack of appetite, and difficulty sleeping). The presence of these symptom clusters conveyed considerable risk for adverse outcomes. Patients with HF who experienced more distress from the Weary symptom cluster had a 50% higher risk of rehospitalization within one-year of discharge from a hospitalization for exacerbation of HF. Patients with higher distress from the Dyspneic symptom cluster were approximately twice as likely to have a cardiac death within one-year following discharge. Available evidence from previous studies describing the negative impact of physical symptoms on clinical outcomes focused on quality of life and functional status as outcomes.[7, 29, 30, 41, 42] The majority of these investigators examined the impact of individual physical symptoms on outcomes in patients with HF.[29, 43, 44] The relationship of HF symptoms to hospitalization and death was examined in only one previous study by Ekman and colleagues[26] who reported findings consistent with our results. In their study, breathlessness (a component of the Dyspneic symptom cluster in the our study) was an independent predictor of all-cause mortality but not hospitalization, while fatigue (a component of the Weary symptom cluster in our study) was an independent predictor of hospitalization for worsening HF but not mortality after adjusting for other risk factors. Our study explains these findings by demonstrating that these symptoms are components of different symptom clusters that respectively predict the different outcomes.

Dyspneic cluster symptoms, shortness of breath, difficulty breathing when lying flat, and waking up breathless at night have been considered the typical symptom of HF exacerbation.[45] Subsequently, monitoring of these symptoms has been frequently emphasized to identify when treatment should be sought to prevent hospitalization.[46-48] The atypical Weary symptom cluster comprised of lack of energy, lack of appetite, and difficulty sleeping was also associated with higher risk for cardiac rehospitalization. This finding suggests that monitoring these symptoms for co-occurrence is also necessary to identify when timely management should be sought to prevent rehospitalization.

Teaching patients to self-monitor for presence of symptom clusters, however, poses several challenges. First, regular self-monitoring of symptom in not routinely performed.[49] Only 9% of hospitalized patients with HF reported actively monitoring their symptoms prior to hospitalization.[50] Second, the co-occurrence of multiple symptoms may impair the ability of patients to recognize changes in any one symptom.[7] The delay in seeking treatment of acute onset of severe dyspnea is approximately five hours.[8, 21] This may be because only 5% of the patients realized that their worsening symptoms were related to HF when they were hospitalized.[10] Investigators have reported that patients with gradually increasing physical symptoms tended to wait more than three days after the onset of their symptoms before seeking treatment.[8, 21, 22, 51] Additionally, many patients associate their symptom with other co-morbid conditions or with aging.[10, 52] Teaching focused on monitoring for symptom clusters may help address these issues by assisting patients to gain a better appreciation of the importance of regular symptom monitoring. Also, patient education targeting to symptom cluster may assist them to better interpret physical symptoms in relationship to worsening HF.

There are potential limitations to be acknowledged in this study. This study assessed the prevalence and distress of physical symptoms one time during an index hospitalization 1 to 2 days before discharge when all patients were medically stable. Although accurate recall of the average symptom experiences for a 2-week period has been reported,[9, 53] patients recall of symptom distress for the 2 previous weeks could be influenced by current hospitalization. Any conclusions drawn from this single measurement of the symptom experiences may not indicate the prevalence and distress of symptoms over longer time periods. Self-reported rehospitalization and death were confirmed by review of medical records or death certificates. It is possible that some hospitalizations that were not self-reported were missed. Nonetheless, the predictive ability of this single measure suggests that it is clinically meaningful. Future researchers may want to consider the pattern or change of symptom experiences through repeated measurements to further clarify their respective roles in prognosis in different settings such as community setting or outpatient clinics.

In this study, only physical symptom clusters were examined. Psychosocial symptoms, primarily depressive symptoms and anxiety, are common in patients with HF. They can affect the perceived level of symptom severity and may also occur as components of already identified symptoms clusters or as additional clusters.[9, 54, 55] Future research is needed to examine the combined clustering of psychological and physical symptoms. This is necessary to develop new teaching strategies that consider the relationships among symptoms and interactive effects of psychosocial and physical symptoms on symptom monitoring and clinical outcomes. Research is also needed to examine whether an educational intervention for monitoring of the particular symptom clusters found from this study is feasible and improves health outcomes.

CONCLUSIONS

Distinct symptom clusters, the Weary and the Dyspneic, occurred in patients with HF. Higher distress from the Weary symptom cluster and the Dyspneic symptom cluster remained independent predictor for cardiac rehospitalization and cardiac mortality within one-year following discharge in patients with HF, respectively. These finding could be used by health care providers to assess patient status and guide treatments. These results also suggest that self-monitoring for symptom clusters rather than individual symptoms should be emphasized in patient education. However, additional research is needed to examine the combined clustering of psychological and physical symptoms and determine the best teaching strategies.

Summary and Implications

Patients with heart failure (HF) experience distinct symptom clusters, the Weary and the Dyspneic symptom clusters. Patients with increased distress from the Weary and the Dyspneic symptom cluster are likely to be rehospitalized or die within one-year post discharge. Therefore, to prevent rehospitalization or death in patients with HF, health care providers can follow these steps:

- Emphasize the importance of self-monitoring for symptom clusters rather than individual symptoms in patient education
- Develop new strategies to help patients monitor their symptom regularly and recognize early worsening symptom on a daily basis

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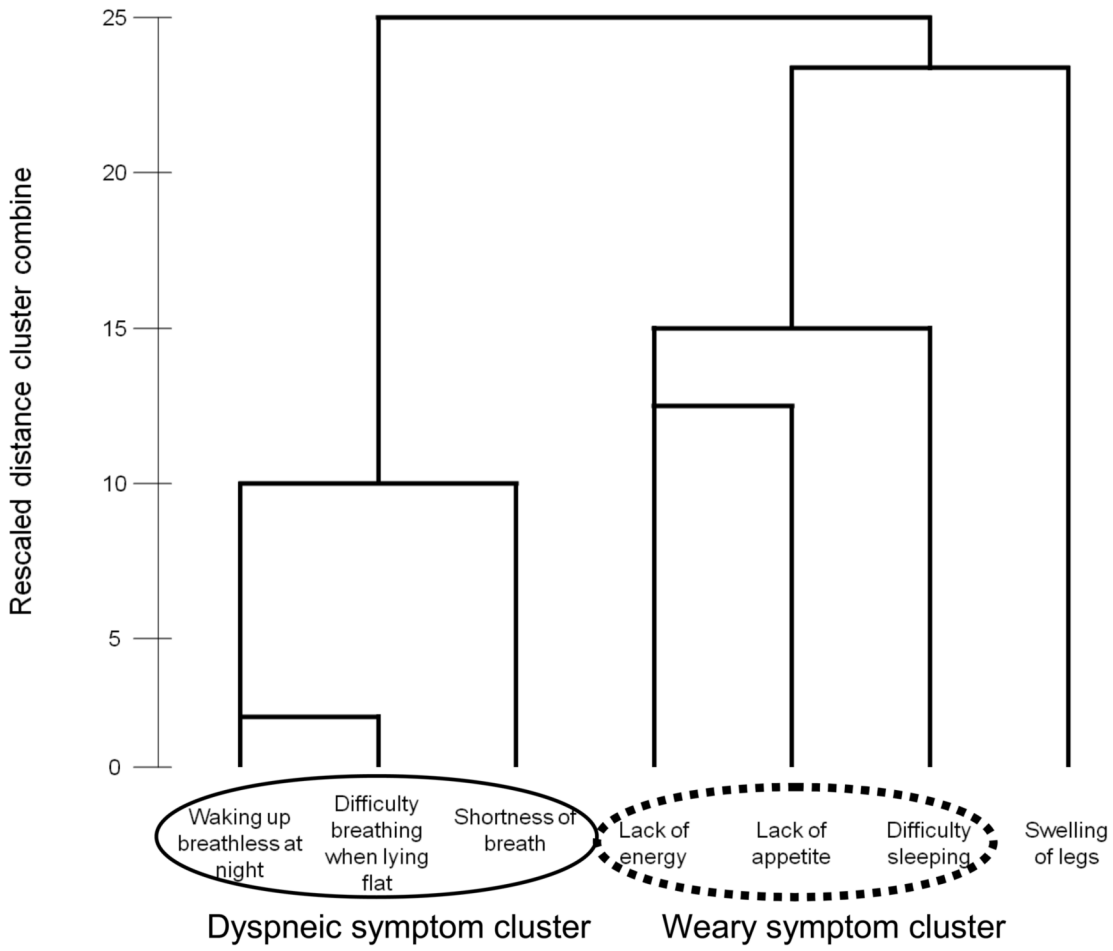

Figure 1.
The symptom clusters

Table 1

Patient characteristics

	Characteristics	N (%)	Mean (±SD)
Age (years)			62 (±14)
Gender	Male	254 (60.3)	
	Female	167 (39.7)	
Body mass index (kg/m^2)			24.3 (±4.0)
	Underweight (< 18.5)	27 (06.4)	
	Normal weight (18.5 to 22.99)	147 (34.9)	
	Overweight (23.0 to 27.59)	153 (36.3)	
	Obese (≥ 27.60)	94 (22.3)	
NYHA functional class	I	73 (17.3)	
	II	161 (38.2)	
	III	144 (34.2)	
	IV	43 (10.2)	
Underlying etiology of heart failure	Non-ischemic heart disease	213 (50.6)	
	Ischemic heart disease	208 (49.4)	
Left ventricular ejection fraction (%)			39.8 (±16.7)
Total comorbidity score			2.7 (±1.2)
	Hypertension	227 (53.9)	
	Diabetes	137 (32.5)	
	Atrial fibrillation	143 (34.0)	
Duration of heart failure (months)			36.3 (±18.7)
Length of stay (days)			10.2 (±9.5)
Medication	ACE inhibitors	304 (72.2)	
	Angiotension II receptor blocker	65 (15.4)	
	Digoxin	153 (36.3)	
	β blocker	345 (81.9)	
	Diuretics	292 (69.4)	
	Aldosterone antagonist	130 (30.8)	

ACE, angiotensin-converting enzyme; NYHA, New York Heart Association

Table 2

Prevalence and distress of physical symptoms

Physical symptoms	Prevalence	Distress
	N (%)	Mean (±SD)
Lack of energy	378 (89.8)	2.88 (±0.94)
Shortness of breath	355 (84.3)	2.78 (±1.02)
Difficulty sleeping	299 (71.0)	2.42 (±1.11)
Lack of appetite	258 (61.3)	2.13 (±0.83)
Difficulty breathing when lying flat	251 (59.6)	1.93 (±0.94)
Waking up breathless at night	249 (59.1)	1.99 (±0.99)
Swelling of legs or ankles	238 (56.5)	1.99 (±1.03)

Table 3

The impact of symptoms clusters on adverse outcome in patients with heart failure

Characteristics		Cardiac rehospitalization			Cardiac death		
		Adjusted HR	95% CI	*p*	Adjusted HR	95% CI	*p*
Age (year)		1.00	0.99 - 1.01	NS	1.02	0.99 - 1.05	NS
Female gender		0.84	0.58 - 1.21	NS	0.41	0.17 - 1.02	NS
Body mass index (kg/m^2)		0.93	0.89 - 0.97	.001	0.96	0.88 - 1.05	NS
NYHA functional class	II	0.93	0.54 - 1.62	NS	0.35	0.10 - 1.28	NS
	III	0.73	0.42 - 1.27	NS	0.41	0.13 - 1.23	NS
	IV	0.82	0.40 - 1.65	NS	1.26	0.33 - 4.82	NS
IHD as etiology of HF		1.17	0.83 - 1.64	NS	1.74	0.76 - 3.99	NS
LVEF (%)		0.99	0.98 - 1.00	.047	0.96	0.93 - 0.99	.005
Total comorbidity score		1.20	1.02 - 1.41	.030	1.00	0.66 - 1.51	NS
Duration of HF (months)		1.00	0.99 - 1.01	NS	1.00	0.96 - 1.02	NS
ACE inhibitors		1.03	0.69 - 1.55	NS	1.52	0.51 - 4.51	NS
β blocker		1.46	0.88 - 2.42	NS	2.87	0.91 - 9.09	NS
Dyspneic symptom cluster		1.25	0.99 - 1.58	NS	2.00	1.16 - 3.34	.012
Weary symptom cluster		1.45	1.09 - 1.93	.011	1.76	0.89 - 3.46	NS
Swelling of legs or ankles		1.16	0.98 - 1.37	NS	0.80	0.54 - 1.18	NS

HR, hazard ratio; CI, confidence interval; NYHA, New York Heart Association; IHD, ischemic heart disease; HF, heart failure; LVEF, left ventricular ejection fraction; NS, non-significant