Title

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Journal

Heart & Lung, 49(2)

ISSN

0147-9563

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Publication Date

2020-03-01

DOI

10.1016/j.hrtlng.2019.11.004

Peer reviewed

Published in final edited form as:

Heart Lung. 2020 ; 49(2): 151–157. doi:10.1016/j.hrtlng.2019.11.004.

Cross-Classification of Physical and Affective Symptom Clusters and 180-Day Event-Free Survival in Moderate to Advanced Heart Failure

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Abstract

Background: The relationship between physical and affective symptom clusters in heart failure (HF) is unclear.

Objectives: To identify associations between physical and affective symptom clusters in HF and to quantify outcomes and determinants of symptom subgroups.

Methods: This was a secondary analysis of data from two cohort studies among adults with HF. Physical and affective symptom clusters were compared using cross-classification modeling. Cox proportional hazards modeling and multinomial logistic regression were used to identify outcomes and determinants of symptom subgroups, respectively.

Results: In this young, mostly male sample (n=274), physical and affective symptom clusters were cross-classified in a model with acceptable fit. Three symptom subgroups were identified: congruent-mild (69.3%), incongruent (13.9%), and congruent-severe (16.8%). Compared to the congruent-mild symptom group, the incongruent symptom group had significantly worse 180-day event-free survival.

Conclusion: Congruence between physical and affective symptom clusters should be considered when identifying patients at higher risk for poor outcomes.

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Declaration of Conflicting Interests

None Declared

Keywords

Heart Failure; Symptoms; Event-Free Survival

Introduction

Despite significant advances in the management of heart failure (HF),[1] symptom burden continues to be a problem for the millions of adults living with HF worldwide.[2] Higher symptom burden is associated with worse quality of life[3] and clinical outcomes among adults with HF.[4] In addition to common physical symptoms such as dyspnea and sleep-wake disturbances, many adults with HF report multiple affective symptoms such as depression and anxiety.[2] Moreover, adults with HF report an average of 9 symptoms,[5] with over 20 symptoms reported towards the end of life.[6] As such, there is a need to understand different experiences of HF symptom burden across multiple physical and affective symptoms collectively, which will help to identify those at greater risk for poor outcomes and aid in the development of targeted interventions.

Given the considerable heterogeneity of symptoms experienced by adults with HF, clustering symptoms has emerged as a useful approach for characterizing naturally-occurring symptom patterns and providing important insight into how symptom patterns may inform outcomes.[7] There are two common conceptual approaches to examining symptom clusters, which are generally defined as two or more symptoms that occur simultaneously and are related.[8] The first approach involves identification of de novo symptom clusters based on individual symptoms using techniques such as factor analysis or hierarchical agglomerative cluster analysis, and the second approach involves identification of subgroups of patients based on their experience with symptom clusters using techniques such as latent class mixture modeling.[9] Both of these techniques have been used in HF symptom cluster research.[10] Studies have demonstrated that symptoms generally fall into two clusters (physical and affective/emotional)[11–14] and that patient's experiences with symptom clusters can be grouped based on symptom severity (e.g. mild, moderate, severe)[15–17] with many of these symptom clusters and profiles linked to clinical outcomes such as quality of life, hospitalizations, and death. What is not well understood, however, is how independent physical and affective symptom clusters are associated based on symptom severity, and whether characterizing symptoms in this way would provide insight into clinical outcomes.

Accordingly, the purpose of this paper was to 1) identify associations between physical and affective symptom clusters in HF using cross-classification modeling (i.e. latent class mixture modeling with multiple classes), 2) quantify the influence of symptom subgroups on 180-day event-free survival (all-cause mortality or cardiovascular hospitalization or emergency room admission), and 3) characterize the determinants of symptom subgroups.

Methods

We performed a secondary analysis of baseline data collected during two prospective cohort studies of symptoms among adults with HF.[18,19] Participants were recruited through a single outpatient HF clinic in the Pacific Northwest between 2010 and 2013. Key inclusion criteria

(identical between studies) were age 21 years or greater with New York Heart Association (NYHA) functional class of II-IV HF (i.e. current HF symptoms). Exclusion criteria included prior transplantation, prior mechanical circulatory support, and a diagnosis of major cognitive impairment. Both studies were approved by our institutional review board, and written consent was obtained from all participants.

Measurement

Data on age, gender, marital status, race, and education were obtained using an identical socio-demographic questionnaire in both studies. Functional status (i.e. NYHA) was assessed by an attending HF cardiologist during the same visit as enrollment. History, etiology, and treatment of HF were collected through a review of the electronic medical record. Clinical characteristics, including last known echocardiographic and right heart catheterization parameters and laboratory values, were collected during an in-depth review of participants' electronic medical record. Comorbid conditions were summarized using the Charlson Comorbidity Index.[20] The Seattle HF Model (SHFM) score was calculated based on the model developed by Levy and colleagues (2006); this model uses objective clinical variables and HF treatments to generate a composite risk score.[21]

Physical symptoms.—We measured dyspnea and sleep-wake disturbances as physical symptoms as they are consistently reported among adults with HF[2,22] but have minimal overlap with the measurement of affective symptoms. The Heart Failure Somatic Perception Scale (HFSPS; v.3) was used to measure dyspnea.[23] The HFSPS asks how much the participant was bothered by physical symptoms and provides 6 response options ranging from 0 (I did not have this symptom) to 5 (extremely bothersome). For this analysis, we used the 6-item Heart Failure Somatic Perception Scale-Dyspnea (HFSPS-D). Scores on the HFSPS-D range from 0–30 with higher scores indicating worse dyspnea. The reliability and validity of the HFSPS-D has been established recently.[23] Cronbach α on the HFSPS-D was 0.90 in this sample.

The Epworth Sleepiness Scale (ESS)[24] was used to measure sleep-wake disturbances. The ESS asks respondents to rate how likely they would be to doze off in 8 different situations by choosing response options that range from 0 (would never doze) to 3 (high chance). Scores on the ESS range from 0–24 with higher scores indicating worse sleep-wake disturbances. The ESS correlates significantly with sleep latency measures.[24] Cronbach α on the ESS was 0.85 in this sample.

Affective symptoms.—We measured depression and anxiety as affective symptoms as they are highly prevalent among adults with HF.[25] The 9-Item Patient Health Questionnaire (PHQ9)[26] was used to measure depression. The PHQ9 scores each of the 9 related DSM-IV criteria for depression. Scores on the PHQ9 range from 0 to 27 with higher scores indicating worse depression. The PHQ9 is a valid and reliable measure of depression in HF.[27] Cronbach α on the PHQ-9 was 0.88 in this sample.

The 6-item Brief Symptom Inventory anxiety scale (BSIANX)[28] was used to measure anxiety. Scores on the BSIANX (calculated by adding the ratings and dividing the total by the number of items in the subscale) range from 0 to 4 with higher scores indicating higher

anxiety. The BSIANX is a valid and reliable measure of anxiety in HF.[29] Cronbach α on the BSIANX was 0.86 in this sample.

Clinical events.—We assessed time to first event (all-cause death or cardiovascular hospitalization or emergency room admission) as a cumulative endpoint at 180 days after enrollment. We extracted clinical events and associated dates from the electronic medical record. Additionally, clinical events were assessed by contacting participants by telephone as needed to inquire about events that may have occurred outside the healthcare system and network of medical records.

Statistical analysis

We used standard descriptive statistics (proportions, means, and standard deviations) to describe the sample. Latent class mixture modeling with cross-classification was used to first identify latent classes of physical symptoms and affective symptoms separately (clustered based on severity) and then quantify the relationship between physical and affective symptom clusters (Figure 1). Model convergence (entropy near 1.0), and posterior probabilities (average posterior probabilities for the most likely class membership near 100%) were used to judge how well physical and affective symptom clusters fit together and the certainty of the classification of participants based on both physical and affective symptom clusters. We also used comparative statistics (Kendall's tau-*b* and chi-square tests) to compare physical symptom clusters versus affective symptom clusters. Student's t-test was used to compare differences in symptom severity between clusters (HFSPS-D and ESS scores for the physical symptom cluster, and PHQ-9 and BSIANX scores for the affective symptom cluster). Symptom subgroups were then labeled based on severity of individual physical and affective symptom clusters (i.e. mild, severe) and congruence between combined symptom clusters (i.e. congruent, incongruent).

Cox proportional hazards modeling was used for analysis of time to first event within 180 days (all-cause death or cardiovascular hospitalization or emergency room admission). Hazard ratios (HR) with 95% confidence intervals (CI) were calculated to quantify the influence of symptom subgroups on 180-day cardiovascular event-free survival. In the final model, we adjusted for the SHFM risk score to account for clinically relevant prognostic variables.

Comparative statistics were used to compare sociodemographic and clinical factors between symptom subgroups. Specifically, we used F statistics from analysis of variance and χ^2 to evaluate differences. Factors that were significantly different at a p value < 0.20 were moved into a multinomial logistic regression model to identify determinants of the symptom subgroups. NYHA functional class was not included in the multinomial regression due to the significant measurement overlap with symptom measures.

Results

The average age of the sample (n = 274) was 57.2±13.2 years, and most were male (61.0%) (Table 1). A majority of participants were classified as NYHA Class III HF (57.3%), and most had non-ischemic etiology (63.7%). Cross-classification modeling revealed two

physical symptom clusters based on severity, severe physical (n = 72; 26.3%) and mild physical (n = 202; 73.7%), and two affective symptom clusters based on severity, severe affective (n = 58; 21.2%) and mild affective (n = 216; 78.8%). There were significant differences in HFSPS-D scores ($t = 7.35$, $p < 0.001$) and ESS scores ($t = 16.80$, $p < 0.001$) between the two physical symptom clusters, and there were significant differences in PHQ-9 scores ($t = 22.06$, $p < 0.001$) and BSIANX scores ($t = 7.87$, $p < 0.001$) between the two affective symptom clusters (Figure 2). Then, cross-classification modeling indicated acceptable model fit in the association between physical and affective symptom clusters (entropy = 0.80) (Table 2). Additionally, traditional comparative statistics (Kendall's tau-*b* and chi-square tests) showed that subjects with the severe physical symptom cluster were more likely to have the severe than the mild affective symptom cluster, and those with the mild physical symptom cluster were more likely to have the mild than the severe affective symptom cluster (Table 2). Those with mild physical and affective symptom clusters were labeled congruent-mild symptom group (n = 190; 69.3%) and those with severe physical and affective symptom clusters were labeled congruent-severe symptom group (n = 46; 16.8%). Given the small numbers of participants with mild physical/severe affective symptom clusters and severe physical/mild affective symptom clusters, these participants were combined into one group labeled incongruent symptom group (n = 38; 13.9%).

In this sample, 86 participants had a clinical event within 180 days. There were 5 deaths, 66 participants were admitted to the hospital for a cardiovascular cause, and 15 participants were admitted to the emergency room for a cardiovascular cause. Only 5 participants (1.8%) were lost to follow-up. Using Cox proportional hazards regression and adjusting for the SHFM risk score (Figure 3), those in the incongruent symptom group were 98% more likely to have an event within 180 days ($p = 0.014$) compared with those in the congruent-mild symptom group (model likelihood ratio $\chi^2 = 20.95$, $p = 0.0001$; Harrell's *C* statistic = 0.65). Adjusting for the SHFM score, those in the congruent-severe symptom group were not significantly more likely to have an event within 180 days ($p = 0.261$) compared with those in the congruent-mild symptom group.

There were a few significant differences in sociodemographic and clinical characteristics between the symptom subgroups (Table 3). Namely, NYHA Class and antidepressant/anxiolytic use were significantly different across symptom subgroups. When characteristics at $p < 0.20$ were moved into a multivariate multinomial logistic regression model (with congruent-mild as the referent group), there were a few significant determinants of membership in the incongruent and congruent-severe symptom groups (Table 4). Namely, a significant determinant of the incongruent symptom group membership was lack of diuretic use, and significant determinants of congruent-severe symptom group membership were aldosterone antagonist use and antidepressant/anxiolytic use.

Discussion

While we know that adults with HF experience high symptom burden, we lack an understanding of how independent physical and affective symptom clusters align based on symptom severity and how naturally-occurring patterns of alignment predict outcomes. In this sample of 274 adults with HF, we found a strong association between physical and

affective symptom clusters by symptom severity. Those who had the mild physical symptom cluster were more likely to have the mild affective symptom cluster, and similarly, those who had the severe physical symptom cluster were more likely to have the severe affective symptom cluster. There was, however, a small group of adults with HF who had incongruent physical and affective symptom clusters, meaning that they had one mild symptom cluster and one severe symptom cluster. Moreover, those in the incongruent symptom group had significantly worse 180-day event-free survival.

HF symptom clusters have been explored previously.[10] For example, Song and colleagues identified two physical symptom clusters (i.e. dyspneic and weary profiles) that were associated with clinical event risk.[12] Hertzog and colleagues identified three symptom clusters based on physical symptoms and one measure of depression, and these profiles were linked with functional capacity and quality of life.[16] Lee and colleagues found a physical symptom cluster and an emotional/cognitive symptom cluster, but only the emotional/cognitive symptom cluster predicted a higher cardiac event risk.[13] Our group has profiled physical and psychological symptoms together and found three symptom profiles (mild, moderate, and severe) that were associated with a graded increase in one-year clinical event risk.[17] What this paper adds is a patient-level examination of how physical and affective symptom clusters are related based on severity to identify symptom subgroups of patients. Not surprisingly, there was a strong association between physical and affective symptom clusters. Moreover, a novel and important finding of this study is that we found a small group of adults with HF who had incongruent symptom clusters.

Our findings suggest that having discordant severity of physical and affective symptoms has clinical relevance as those in the incongruent symptom group had worse clinical outcomes. Compared with those in the congruent-mild symptom group, after adjusting for a commonly used risk prognostication score, we found that those in the incongruent symptom group (i.e. mild physical/severe affective or severe physical/mild affective) had significantly worse 180-day event-free survival. One potential reason for this finding may be that the discordant presentation of physical and affective symptoms may be difficult for patients and providers to interpret and manage. For example, a dramatic improvement in physical symptoms may lead to reduced follow-up and affective symptoms may remain unalleviated. We also found that a significant determinant of membership in the incongruent symptom group was not being on a diuretic medication. One potential reason for this may include intolerance of a diuretic as a result of multiple comorbidities[1] or under-treatment. Moreover, although not statistically significant, the numerically higher prevalence of atrial fibrillation among those in the incongruent symptom group may contribute to discordant symptoms.

While the majority of the participants in this sample were in the congruent-mild symptom group, there were also a number of participants in the congruent-severe symptom group. Being on an aldosterone antagonist and an antidepressant/anxiolytic were significant determinants of membership within the congruent-severe symptom group. These are likely patients with more advanced disease requiring more aggressive medical management, as demonstrated by the high proportion of NYHA Class III/IV patients in this group. However, those in the congruent-severe symptom group did not have significantly worse 180-day event-free survival compared with those in the congruent-mild symptom group. This may be

due to better utilization of guideline-directed medical therapy or the relatively short follow-up period (180 days).

These symptom subgroups may be helpful in understanding common pathophysiological mechanisms and sequential processes that underlie physical and affective symptoms among adults with moderate to advanced HF. HF symptoms are often the result of the pathogenesis of HF itself (e.g. congestion, neurohormonal dysregulation). However, symptoms may also be the result of other comorbidities and/or aging. Thus, identifying how symptom clusters are related or not related may inform the underlying pathology of symptom presentation. Particularly for those in the incongruent symptom group, the pathophysiology may differ for these patients; future research should explore the biological underpinnings of incongruent physical and affective symptoms. For example, as an extension of our previous findings,[30,31] varying degrees of sympathetic overactivation may underlie both physical and affective symptom clusters.

Clinically, these findings demonstrate that while it is important to identify symptom clusters in HF, it is also important to understand the association between symptom clusters (e.g. physical and affective) at the patient-level. Information about the symptom experience is imperative for both optimizing clinical management strategies and self-care. Those in the congruent-mild and congruent-severe symptom groups would likely require a graded clinical and self-care approach in managing both physical and affective symptoms. Those in the incongruent symptom group, however, may require a more nuanced approach to symptom management. It is important to recognize that reducing one aspect of symptomatology may not reduce other aspects. Moreover, the mismatch between the severity of physical and affective symptoms is perhaps an indicator that closer follow-up may be needed for these patients. Additionally, an awareness of both physical and affective symptom clusters may inform HF self-care strategies.[32] Patients, caregivers, and clinicians should prioritize the recognition and inventory of both their physical and affective symptoms, especially when one or a grouping of symptoms becomes progressively worse out of proportion with other symptoms.

Strengths and Limitations

This is the first known study to use cross-classification modeling to characterize how physical and affective symptom clusters are related to one another at the patient-level. In addition to studying individual symptoms, an important aspect of HF symptom science is to examine how symptoms cluster together,[33] and this study takes it one-step further by examining how symptom clusters are linked together. Cross-classification modeling allowed us to quantify model fit of symptom clusters and group membership. Additionally, this approach revealed a group of participants who were not classified into traditional mild versus severe symptom groups. Another strength of this study is that we assessed physical and affective symptoms using robust, domain-specific measures as opposed to quality of life measures and/or provider assessments of symptoms.

There are a few noted limitations. First, this was a predominantly young, male, and non-Hispanic Caucasian sample of patients with moderate to advanced HF recruited from one advanced HF clinic in the Pacific Northwest. As such, these results may not be generalizable

to all patients with HF. Second, this was an analysis of how symptoms cluster at one time point, and the temporal relationship between physical and affective symptom cluster trajectories, including changes in clinical characteristics and treatments, cannot be identified in this study. Third, while we examined two physical symptoms (dyspnea and sleep-wake disturbances) and two affective symptoms (depression and anxiety), we did not include the full range of possible symptoms experienced by HF patients, such as pain and gastrointestinal symptoms. Finally, given the low numbers of those in the mild physical/severe affective symptom group and those in the severe physical/mild affective symptom group, we combined the two into one group. Thus, we were unable to identify specific determinants and outcomes of the smaller groups, which should be the focus of future work.

Future Research

Future research should include other highly prevalent symptoms in HF, such as pain[34] and gastrointestinal symptoms (e.g. loss of appetite, nausea).[35] Moreover, as we have done in this study, symptoms should be measured with symptom-specific measures as opposed to using quality of life measures or provider assessment as proxies for symptoms. Future research should also explore how symptom clusters in HF vary depending on comorbidities (e.g. atrial fibrillation) and with advancing age. Finally, physical and affective symptom clusters should be examined over time to understand how they change independently and concurrently, mechanisms and antecedents of worsening symptom clusters, and how different treatments (e.g. antidepressants and/or anxiolytics) for symptoms affect congruence between symptom clusters and ability to recognize symptom clusters.

Conclusion

There is a strong association between physical and affective symptom clusters in HF. While those with mild physical symptom clusters were more likely to have mild affective symptom clusters and those with severe physical symptom clusters were more likely to have severe affective symptom clusters, there was a group with incongruent symptom clusters. Moreover, those in the incongruent symptom group had worse 180-day event-free survival. Therefore, the congruence between physical and affective symptom clusters should be considered when identifying patients at higher risk for poor outcomes.

Disclosures and Acknowledgments

Dr. Denfeld is currently supported as a Scholar of the Oregon Building Interdisciplinary Research Careers in Women's Health K12 Program funded by the Eunice Kennedy Shriver National Institute of Child Health & Human Development of the NIH under Award Number K12HD043488. This work was supported, in part, by an award from the National Institutes of Health/National Institute of Nursing Research (F31NR015936; Denfeld), an award from the American Heart Association (11BGIA7840062; Lee), and an award from the Eunice Kennedy Shriver National Institute of Child Health & Human Development of the NIH under Award Number K12HD043488 (Lee). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or the American Heart Association.

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Highlights

- Adults with heart failure experience numerous physical and affective symptoms
- Physical and affective heart failure symptom clusters are strongly associated
- Three symptom subgroups based on heart failure symptom clusters were identified
- Those in the incongruent symptom subgroup had worse 180-day event-free survival
- Congruence between severity of symptom clusters is relevant

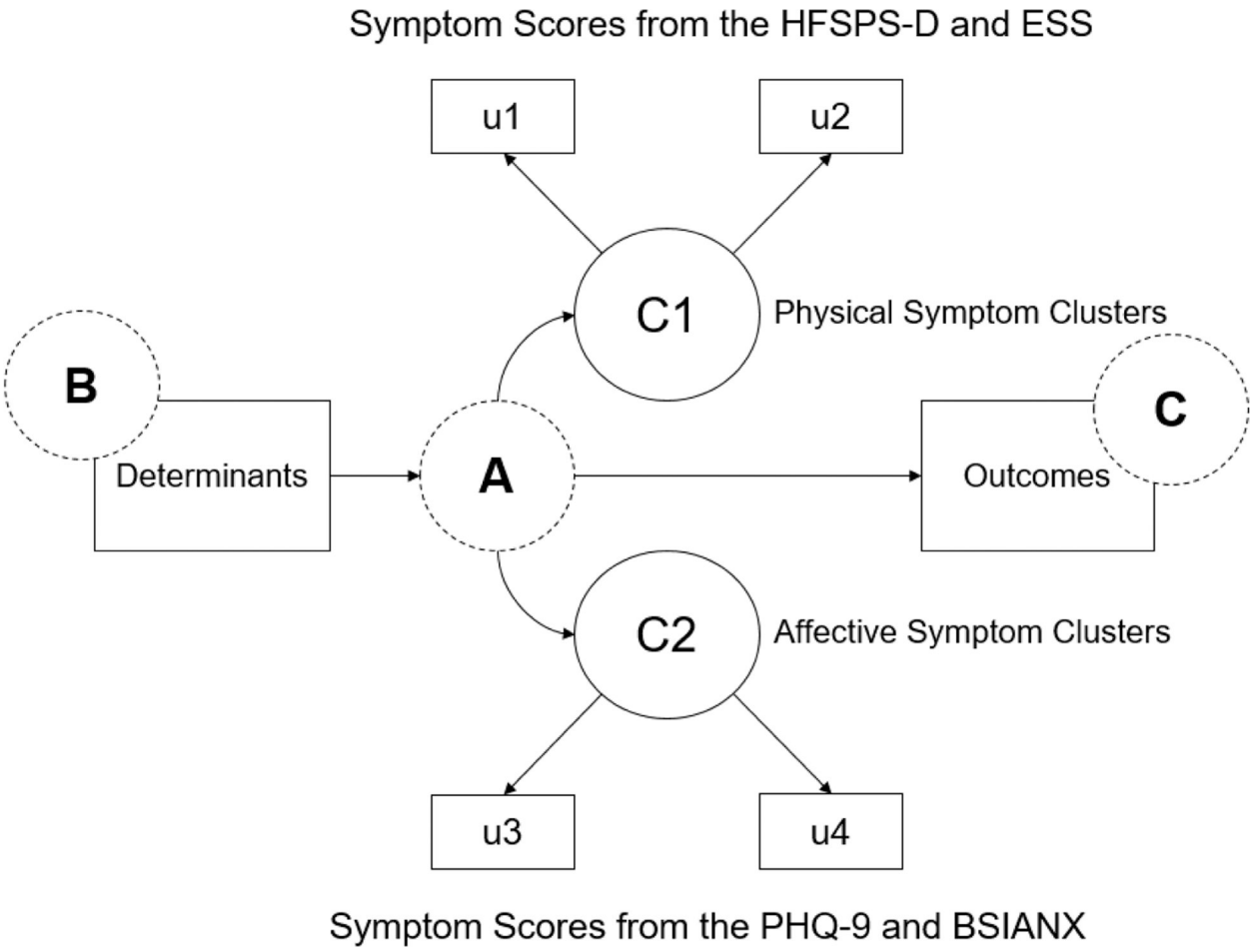

Figure 1. Identifying classes of physical and affective symptom clusters and determinants and outcomes symptom groups.

The analytic approach involved using latent class mixture modeling to identify distinct classes of severity of physical symptom clusters (C1) and severity of affective symptom clusters (C2) based on scores from the HFSPS-D and ESS (physical) and PHQ-9 and BSIANX (affective). Then cross-classification modeling was used to quantify the relationship between identified classes of physical symptom clusters and affective symptom clusters (A). Generalized linear modeling was used to identify determinants of symptom groups (B) and Cox proportional hazards modeling was used to identify determinants of symptom groups (C). Abbreviations: BSIANX, Brief Symptom Inventory Anxiety Subscale; ESS, Epworth Sleepiness Scale; HFSPS-D, Heart Failure Somatic Perception Scale-Dyspnea; PHQ9, Patient Health Questionnaire-9.

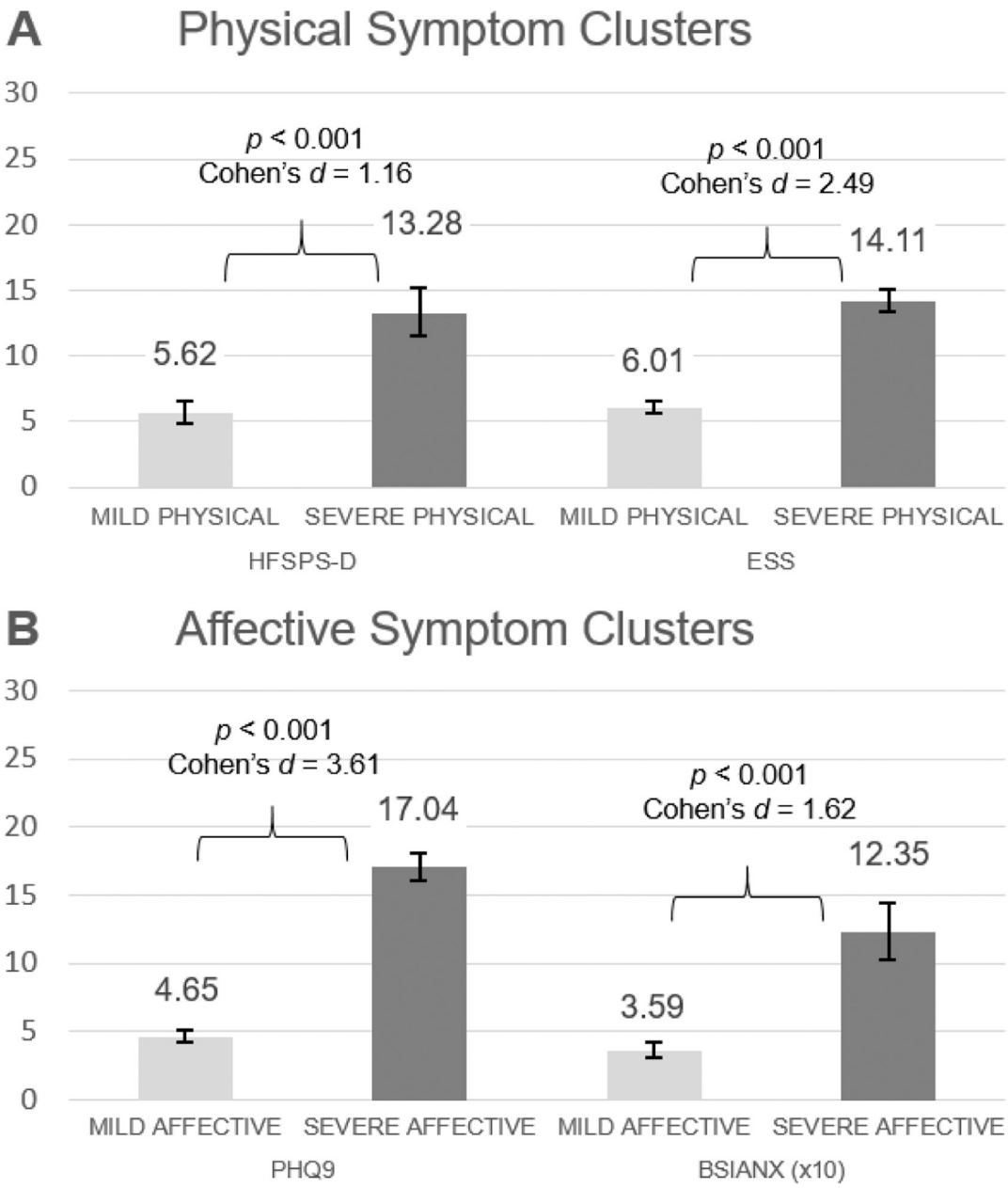

Figure 2. Physical and affective symptom clusters.

There were significant differences in HFSPS-D and ESS scores between the mild (73.7%) and severe (26.3%) physical symptom clusters (A). There were significant differences in PHQ9 and BSIANX scores between the mild (78.8%) and severe (21.2%) affective symptom clusters (B). Cohen's *d* is reported for effect sizes. Abbreviations: BSIANX, Brief Symptom Inventory Anxiety Subscale; ESS, Epworth Sleepiness Scale; HFSPS-D, Heart Failure Somatic Perception Scale-Dyspnea; PHQ9, Patient Health Questionnaire-9.

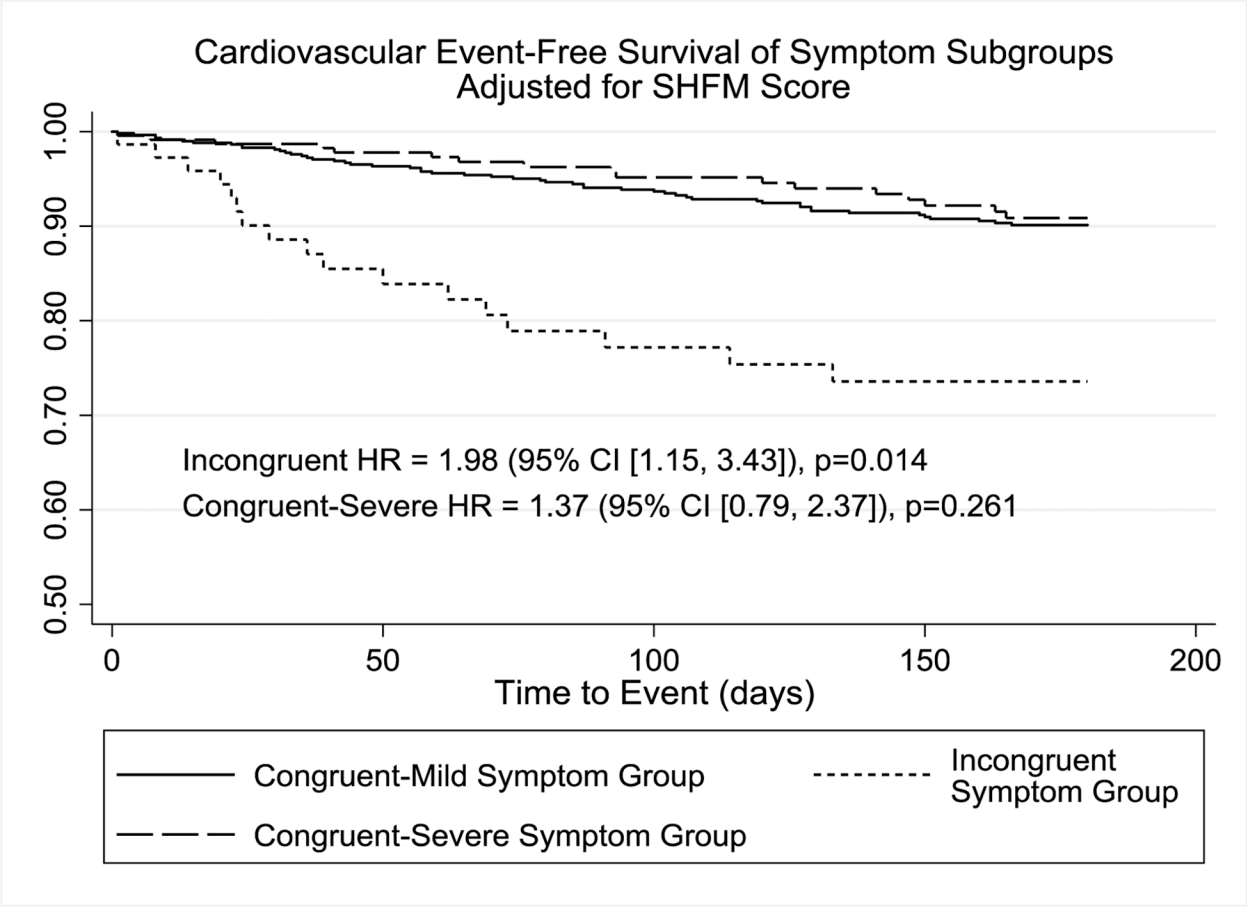

Figure 3. Symptom subgroups and 180-day cardiovascular event-free survival.

Composite risk of first cardiovascular event (cardiovascular hospitalization or emergency room admission or death) for those in the incongruent and congruent-severe symptom groups compared with those in the congruent-mild symptom group, adjusting for the SHFM score. Abbreviations: CI, confidence interval; HR, hazards ratio; SHFM, Seattle Heart Failure Model.

Table 1:

Characteristics of the sample (n = 274)

	Mean±SD, or N (%)
Patient Characteristics:	
Age (years)	57.2±13.2
Male	167 (61.0)
Non-Hispanic Caucasian	231 (90.4)
Married/living with partner	173 (63.1)
Education level	
Less than high school	90 (32.9)
>High school but < college	122 (44.5)
College degree	62 (22.7)
Body Mass Index (kg/m^2)	31.0±7.4
Charlson Comorbidity Index (weighted)	2.3±1.4
Atrial Fibrillation	108 (39.4)
Stage 3 Chronic Kidney Disease	40 (14.6)
General Heart Failure Characteristics:	
Time with Heart Failure in years: median [IQR]	4.0 [1.0–7.6]
NYHA Functional Class	
Class II	107 (39.1)
Class III	157 (57.3)
Class IV	10 (3.7)
Non-ischemic etiology	174 (63.7)
Prescribed a β-blocker	249 (90.9)
Prescribed an ACE-I or ARB	224 (81.8)
Prescribed an aldosterone antagonist	120 (43.8)
Prescribed an antidepressant and/or anxiolytic	100 (36.5)
ICD or Biventricular ICD	168 (61.3)
Serum sodium (mEq/L)	137.8±3.3
Serum hemoglobin (g/dL)	13.1±2.1
Serum BUN:creatinine ratio	20.2±9.5
Heart rate	79.1±14.9
Left ventricular internal end-diastolic diameter (cm)	6.1±1.1
Left ventricular ejection fraction (%)	28.3±12.4
Pulmonary capillary wedge pressure (mm/Hg)	19.0±8.5
Right atrial pressure (mm/Hg)	9.6±5.5
Cardiac index (L/min/m^2 by Fick equation)	2.1±0.5

Abbreviations: ACE-I, Angiotensin Converting Enzyme-Inhibitor; ARB, Angiotensin Receptor Blocker; ICD, implantable cardioverter defibrillator; IQR, interquartile range; NYHA, New York Heart Association; SD, Standard Deviation

Table 2:

Relationship Between Physical and Affective Symptom Clusters

	N (%)	
	Mild Physical	**Severe Physical**
Mild Affective	190 (69.3)	26 (9.5)
Severe Affective	12 (4.4)	46 (16.8)

Comparative statistics: Kendall's tau b = 0.62±0.06; χ^2= 106.82, p < 0.001. Model fit statistics: entropy = 0.80; posterior probabilities for belonging in the most likely combined symptom cluster of mild physical/mild affective, severe physical/mild affective, mild physical/severe affective, and severe physical/severe affective = 0.94, 0.71, 0.73, and 0.86, respectively.

Table 3:

Characteristics by Symptom Groups (n=274)

	M±SD or N (%)			
	Congruent-Mild (*n* = 190)	**Incongruent (*n* = 38)**	**Congruent-Severe (*n* = 46)**	***p* value[a]**
Age (years)	58.3±13.5	56.1±13.9	53.7±10.9	0.085
Female	73 (38.4)	18 (47.4)	16 (34.8)	0.475
Non-Hispanic Caucasian	171 (90.0)	34 (89.5)	41 (89.1)	0.855
Married/living with partner	124 (65.3)	25 (65.8)	24 (52.2)	0.239
Highest education level				0.914
High school or less	61 (32.1)	12 (31.6)	17 (37.0)	
> High school but < college	84 (44.2)	17 (44.7)	21 (45.7)	
College degree or higher	45 (23.7)	9 (23.7)	8 (17.4)	
Body mass index (kg/m^2)	31.1±7.3	30.4±7.9	30.9±7.4	0.856
Charlson Comorbidity Index (weighted)	2.2±1.2	2.4±1.9	2.4±1.4	0.560
Atrial fibrillation	74 (38.9)	20 (52.6)	14 (30.4)	0.114
Stage 3 chronic kidney disease	28 (14.7)	4 (10.5)	8 (17.4)	0.672
Time with heart failure (years)	5.4±5.5	4.8±4.7	5.7±6.8	0.738
NYHA functional class				
Class II	88 (46.3)	11 (28.9)	8 (17.4)	0.001
Class III	97 (51.1)	24 (63.2)	36 (78.3)	
Class IV	5 (2.6)	3 (7.9)	2 (4.3)	
Non-ischemic etiology	121 (63.7)	27 (71.1)	20 (43.5)	0.382
Prescribed a diuretic	166 (87.4)	28 (73.7)	41 (89.1)	0.068
Prescribed a β-blocker	174 (91.6)	32 (84.2)	15 (93.5)	0.283
Prescribed an ACE-I or ARB	160 (84.2)	28 (73.7)	36 (78.3)	0.246
Prescribed an aldosterone antagonist	78 (41.1)	16 (42.1)	26 (56.5)	0.161
Prescribed antidepressant and/or anxiolytic	58 (30.5)	16 (42.1)	26 (56.5)	0.003
ICD or Biventricular ICD	113 (59.5)	24 (63.2)	31 (67.4)	0.594
Serum sodium (mEq/L)	137.8±3.5	137.9±3.2	137.9±2.9	0.967
Serum hemoglobin (g/dL)	13.0±2.1	13.1±2.3	13.1±1.8	0.976
Serum BUN:Creatinine	20.9±10.0	19.0±7.6	18.2±8.1	0.187
Resting heart rate	77.8±14.9	80.9±15.5	82.8±13.8	0.091
Left ventricular end-diastolic diameter (cm)	6.1±1.1	5.7±1.2	6.1±1.3	0.177
Left ventricular ejection fraction (%)	28.2±13.0	31.0±12.2	26.7±9.9	0.287
Right atrial pressure (mmHg)	9.4±5.4	10.9±5.8	9.6±5.6	0.493
Pulmonary capillary wedge pressure (mmHg)	18.9±8.5	21.0±8.3	17.8±8.5	0.424
Cardiac index (L/min/m^2 by Fick equation)	2.1±0.5	2.0±0.6	2.1±0.5	0.533

[a] *p* values for oneway ANOVA (F ratios), χ^2, or Fisher's exact tests

Abbreviations: ACE-I, Angiotensin Converting Enzyme-Inhibitor; ARB, Angiotensin Receptor Blocker; BUN, blood urea nitrogen; ICD, implantable cardioverter defibrillator; NYHA, New York Heart Association; SD, standard deviation.

Table 4:

Determinants of Incongruent and Congruent-Severe Symptom Groups[a]

	RRR [95%CI]			
	Incongruent	**p value**	**Congruent-Severe**	**p value**
Age (years)	0.97 [0.94, 1.01]	0.137	0.98 [0.95, 1.02]	0.352
BUN/Creatinine ratio	0.97 [0.92, 1.03]	0.361	0.95 [0.90, 1.01]	0.080
Atrial Fibrillation	2.47 [0.99, 6.20]	0.053	0.61 [0.24, 1.53]	0.291
Prescribed an AA	1.62 [0.61, 4.30]	0.332	2.52 [1.08, 5.86]	0.032
LVIDd	0.76 [0.52, 1.10]	0.150	0.99 [0.70, 1.41]	0.962
Pulse	1.02 [0.99, 1.05]	0.115	1.02 [0.99, 1.05]	0.178
Prescribed a diuretic	0.27 [0.09, 0.86]	0.026	1.23 [0.29, 5.30]	0.779
Prescribed an antidepressant and/or anxiolytic	1.16 [0.49, 2.76]	0.742	3.00 [1.35, 6.68]	0.007
Model Pseudo R^2	10.8%			

[a]Compared to the Congruent-mild symptom group

Abbreviations: AA, aldosterone antagonist; BUN, blood urea nitrogen; LVIDd, left ventricular internal end-diastolic diameter; RRR, relative risk ratio.