Symptom-Hemodynamic Mismatch and Heart Failure Event Risk

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Abstract

Background—Heart failure (HF) is a heterogeneous condition of both symptoms and hemodynamics.

Objective—The goal of this study was to identify distinct profiles among integrated data on physical and psychological symptoms and hemodynamics, and quantify differences in 180-day event-risk among observed profiles.

Methods—A secondary analysis of data collected during two prospective cohort studies by a single group of investigators was performed. Latent class mixture modeling was used to identify distinct symptom-hemodynamic profiles. Cox proportional hazards modeling was used to quantify difference in event-risk (HF emergency visit, hospitalization or death) among profiles.

Results—The mean age (n=291) was 57±13 years, 38% were female, and 61% had class III/IV HF. Three distinct symptom-hemodynamic profiles were identified. 17.9% of patients had concordant symptoms and hemodynamics (i.e. moderate physical and psychological symptoms matched the comparatively hemodynamic profile), 17.9% had severe symptoms and average hemodynamics, and 64.2% had poor hemodynamics and mild symptoms. Compared to those in the concordant profile, both profiles of symptom-hemodynamic mismatch were associated with a markedly increased event-risk (severe symptoms hazards ratio = 3.38, p=0.033; poor hemodynamics hazards ratio = 3.48, p=0.016).

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Conclusions—A minority of adults with HF have concordant symptoms and hemodynamics. Either profile of symptom-hemodynamic mismatch in HF is associated with a greater risk of healthcare utilization for HF or death.

Keywords

heart failure; symptoms; symptom clusters; hemodynamics

Introduction

Heart failure (HF) is a complex and heterogeneous condition and an epidemic among industrialized nations.[1, 2] As a clinical syndrome, the diagnosis of HF and the evaluation of treatment effectiveness is largely based on symptoms like dyspnea and fatigue.[3] Beyond their importance to clinical care, symptoms are also key determinants of self-care behaviors[4, 5] and quality-of-life,[6, 7] and principal antecedents to urgent healthcare utilization[8, 9] among adults with HF. It is well-known that both hemodynamics (e.g. metrics of contractility, pressure and flow)[10–12] and symptoms[13, 14] are important and independent predictors of clinical outcomes in HF. Despite their mutual importance in HF, however, we are bereft of insight into the relationship between hemodynamics and what patients experience as physical and psychological symptoms.

Investigations into the link between objective markers of HF severity (e.g. those derived from right heart catheterization, echocardiographic, cardiopulmonary stress test and laboratory parameters) and symptoms have collectively concluded that there is limited-to-no association between the two.[15–20] In the absence of a single test for HF or responsiveness to HF therapies, clinicians must integrate objective and subjective data to personalize treatment strategies.[21] For example, integrating data on current heart function and physical symptoms may allow clinicians to tailor monitoring strategies and/or promote effective self-care behaviors to enhance the patient's quality of life and reduce healthcare utilization. But, the general lack of association between hemodynamics and symptoms makes it difficult to integrate this information in planning care, particularly for patients who have symptoms that are markedly worse than anticipated based on their hemodynamics and those who are surprisingly asymptomatic despite severely decompensated hemodynamics. Moreover, the clinical relevance of these types of symptom-hemodynamic mismatch in HF is unknown.

Accordingly, the purpose of this study was to identify common profiles among integrated data on physical and psychological symptoms and hemodynamics among adults with HF. To gain insight into the symptom biology of this heterogeneous syndrome, our main hypothesis was that distinct profiles of symptoms and hemodynamics could be identified. Further, we sought to position the clinical relevance of symptom-hemodynamic mismatch by comparing 180-day HF-related clinical event-risk (i.e. emergency room visits, hospitalizations or death) among the observed profiles; we hypothesized that there would be significant differences in event-risk among observed profiles.

Methods

Study Design

We completed a secondary analysis of data collected on 291 unique participants from two prospective cohort studies conducted by a single team of HF investigators from 2010–2013. The goal of the first study was to quantify the prognostic values of physical and psychological symptoms in HF,[22] and the goal of the second study was to describe profiles of HF symptom response behaviors.[23] All participants were recruited through a single outpatient HF clinic in the Pacific Northwest that specializes in evaluating patients for advanced HF therapies. Written informed consent was obtained from all interested participants by study staff not directly involved in patient care. Both studies were approved by our institutional review board.

The sampling frame for each study was community-dwelling adults with symptomatic HF (i.e. New York Heart Association (NYHA) class II–IV HF). Formal inclusion criteria (identical for both studies) included; 1) being willing and able to provide informed consent, 2) being 21 years of age or greater, 3) having the ability to read and comprehend 5th grade English, 4) experiencing current HF symptoms (i.e. NYHA class II–IV), 5) being on optimal HF treatment or having HF treatment optimized in the opinion of the treating cardiologist, and 6) receiving health services locally or by a referral practice to facilitate follow-up. Patients were deemed ineligible if they had a diagnosis of major cognitive impairment in the medical record (e.g. Alzheimer's disease), had received a heart transplant or long-term mechanical circulatory support, or were otherwise unable to complete the study requirements.

Measurement

Socio-demographic and Clinical Data—Socio-demographics were assessed by self-report using a questionnaire asking about gender, age, marital/partnership status, ethnicity/race and employment. NYHA functional classification was assessed on the same day as enrollment by the treating attending cardiologists. Comorbidities were assessed with the Charlson Comorbidity Index[24] during a review of the electronic medical record.

Clinical and treatment characteristics, including last known left ventricular ejection fraction (LVEF) and left ventricular internal end-diastolic diameter (LVIDd) from echocardiographic assessments, and pulmonary capillary wedge pressure (PCWP), right atrial pressure (RAP) and cardiac index (calculated by the Fick principle) from right heart catheterization, were collected during an in-depth review of participants' electronic medical record. As this sample was comprised of adults with NYHA class II–IV HF and was having treatment optimized or being evaluated for advanced therapies, the median time from echocardiographic assessment to symptom measurement was 42 days (interquartile range = 8–90 days prior) and the median time from right heart catheterization to symptom assessment was 9 days (interquartile range = 60 days prior to 11 days afterward).

Mild cognitive dysfunction was assessed using the Montreal Cognitive Assessment (MoCA).[25] The MoCA has a sensitivity of 90% and specificity of 87% to detect mild cognitive impairment with the cutoff score of 26 (i.e. below a score of 26 out of 30) in the

general population.[25] Use of the MoCA in persons with HF has been validated,[26] and it was administered in-person immediately following informed consent.

Symptom Measurement—In the absence of a single comprehensive symptom measure in HF, multiple symptom measures with established psychometric properties and frequent use in HF were chosen to capture common physical and psychological domains. Beyond the physical symptoms that are hallmarks of HF,[3] depression, anxiety and hostility are common psychological symptoms experience by adults with HF.[27–30] Moreover, wake disturbances are a common and distressing symptoms associated with HF.[31]

Physical symptoms were measured using the 18-item Heart Failure Somatic Perception Scale (HFSPS).[32] Participants rated how much they were bothered by 18 common HF symptoms; four response options are provided that range from 0 (not at all) to 5 (extremely). Scores were calculated by summing responses; higher values on the HFSPS (range 0–90) indicate worse physical symptoms. Theta reliability of the original HFSPS was 0.71–0.78.[33]

Wake disturbances (a.k.a. daytime sleepiness) were measured using the 8-item Epworth Sleepiness Scale (ESS).[34] The ESS asks respondents to rate how likely they would be to doze off or fall asleep in 8 soporific situations (e.g. sitting in traffic) by choosing response options that range from 0 (would never doze) to 3 (high chance). The ESS correlates significantly with sleep latency measures, and scores distinguish normal sleep patterns, obstructive sleep apnea syndrome, narcolepsy, idiopathic hypersomnia, and insomnia.[34] Scores were calculated by summing responses. Higher ESS scores (range 0–24) indicate worse wake disturbances.

Depression was measured with the 9-Item Patient Health Questionnaire (PHQ9).[35] The PHQ9 scores each of the 9 related DSM-IV criteria providing four response options ranging from 0 (not at all) to 3 (nearly every day). The PHQ9 has 70% sensitivity and 92% specificity for major depression among adults and is a valid and reliable measure of depression in HF.[36] Higher score (range 0–27) indicate worse depression; scores of 10 are indicative of moderate or greater depression.[35]

Anxiety and hostility were measured using the Brief Symptom Inventory (BSI).[37] The BSI asks about feelings during the past seven days and provides five response options ranging from 0 (no) to 4 (extreme). Subscale scores (ranging from 0 to 4) are calculated by adding the ratings and dividing the total by the number of items in the subscale, with higher scores indicating worse anxiety or hostility.[37] In adults with HF, Cronbach's alpha was 0.80 for the BSI hostility score and 0.86 for the BSI anxiety score.[22]

Clinical Events—We completed a review of the electronic medical record at 180 days looking specifically for emergency room visits or hospitalizations for HF and HF-related mortality. Our sample received care locally and/or was part of an extensively-linked electronic medical record system (i.e. Epic® Care Everywhere Network). Thus, for the vast majority of events data were extracted directly from discharge summaries. We also contacted study participants by phone every 90 days to inquire about events that may have occurred outside of the health system and network. In such instances, we solicited sufficient

detail directly from participants whether or not the event was primarily related to their HF or for other reasons.

Statistical Analysis

Descriptive statistics (mean ± standard deviation (SD), proportions, and medians with inter-quartile ranges) were used to describe the sample at large. Latent class mixture modeling (LCMM) was used to identify distinct profiles among symptom (HFSPS score, ESS score, PHQ9 cutoff for moderate or greater depression (dichotomous), and the BSI anxiety and hostility score) and HF hemodynamics (LVEF, LVIDd, cardiac index, PCWP, and RAP). LCMM is a type of clustering that accommodates continuous and categorical data and allows for the quantification of uncertainty in classification. The Lo-Mendell-Rubin adjusted likelihood ratio test (LMRT)[38] and parametric bootstrap likelihood ratio test (PBLRT) (p-value for both), model convergence (entropy near 1.0), the size of the observed profiles (not less than 5% of the sample), and posterior probabilities (average posterior probabilities for most likely class near 1.0) were used to assess the performance of alternative models (e.g. 3 vs. 2 profiles).[39] Neither the number nor composition of the profiles is predetermined using LCMM; thus, the resulting profiles are distinct, common and naturally-occurring.

Comparative statistics (F-statistics from analysis of variance, and χ^2) were used to compare factors among the observed profiles. The profiles were then labeled according to key differentiating characteristics. Cox proportional hazards modeling was used to quantify 180-day HF event-risk (emergency room visit or hospitalization for HF or all-cause death). The proportional hazards assumption was justified based on Schoenfeld residuals. We present three Cox models; a) unadjusted models (just the observed profiles), b) adjusted models (including the observed profiles and any clinical or socio-demographic factor that was different across the three profiles with p<0.20), and c) backward selection (p-values < 0.2) using all baseline clinical and socio-demographic characteristics (e.g. comorbid conditions, cognitive dysfunction, HF medications, demographics). These three approaches to Cox modeling were undertaken to demonstrate that the influence of the profiles on clinical event-risk was not a function of the groups being otherwise imbalanced and was that the relationship robust to other confounding factors that are known to be directly related to HF clinical event-risk. Hazard ratios (HR) and 95% confidence intervals (CI) are presented. LCMM was generated using Mplus v7.11 (Los Angeles, CA); all other analyses were performed using Stata MP v13 (College Station, TX).

Results

Socio-demographic and clinical characteristics of the sample are presented in Table 1. In brief, the majority of participants were male and Caucasian, and the average age of the sample was just under 57 years. A majority (61.2%) of participants had NYHA class III/IV HF, and a majority of the sample was prescribed beta adrenergic blockers (90.4%) and angiotensin converting enzyme-inhibitors (ACE-I) or angiotensin receptor blockers (ARBs) (81.8%). Eighty-one (27.8%) participants reported symptoms indicative of moderate or greater depression, and 31.3% of the sample had mild cognitive dysfunction.

Three distinct profiles of symptoms and hemodynamics were identified (entropy = 0.84; LMRT = 131.15, p=0.0218; PBLRT p<0.001; and posterior probabilities exceeded 0.9, all supporting a good model). Significant differences in physical symptoms, depression, anxiety, hostility, wake disturbances, LVIDd, LVEF, and cardiac index were observed across the three profiles; the differences in PCWP and RAP, however, were not significant among the profiles (Table 2).

Approximately 18% of the sample (n=52) had what we labeled as 'concordant' symptoms and hemodynamics. That is, the moderate physical and psychological symptoms matched the comparatively good hemodynamic profile; 50% of those whose characteristics fit the concordant profile had HF with preserved ejection fraction (i.e. LVEF >40). We also observed two profiles wherein there was a mismatch in symptoms and hemodynamics. First, there was a mismatch profile (n=52 (17.9%)) that was characterized by 'severe symptoms' compared with the relatively moderate hemodynamic profile (i.e. they had the worst symptoms across all measures, and hemodynamic values close to sample averages). Second, there was a mismatch profile (n=187 (64.2%)) that had 'poor hemodynamics' and a flat symptom profile (i.e. they had the worst hemodynamics but lowest symptom burden across all measures) (Figure 1).

There were a few differences in socio-demographic and clinical characteristics among the three symptom and hemodynamic profiles (Table 3). Namely, there were statistically significant or numerical differences with p-values <0.20 in age, gender, level of education and prescribed HF therapies (i.e. ACE or ARB, and aldosterone antagonists). The HF event rate at 180 days was 22.3% (65 events in 44,492 at-risk days of observation). Compared with patients in the concordant profile and adjusting for observed difference among profiles, patients classified in the severe symptom profile were 3.3 times as likely to have a clinical HF event, and those in the poor hemodynamic profile were 3.9 times as likely to have a clinical HF event (Table 4). Adjusted HRs derived from backward covariate selection were similar (Figure 2).

Discussion

In this sample of 291 adult patients with moderate to advanced HF, we identified three profiles among integrated data on physical and psychological symptoms and hemodynamic parameters that are commonly used to help guide HF management and evaluate treatment effectiveness. A 'concordant' profile was characterized by moderate symptoms and comparatively good hemodynamics that were largely comparable. We also identified two profiles of symptom-hemodynamic mismatch; a 'severe symptom' profile identified participants who experienced the worst symptoms and average hemodynamics, and a 'poor hemodynamic' profile identified those with the lowest symptom burden but very poor hemodynamics. Compared to those with concordant symptoms and hemodynamics, patients with the severe symptom profile and those with the poor hemodynamic profile had markedly increased 180-day HF event-risk. To the best of our knowledge, ours is the first study to identify distinct profiles of symptom-hemodynamic mismatch in HF and quantify significant and clinically-meaningful associations with clinical event-risk.

We know very little about how symptoms relate to the underlying pathogenesis of HF. For example, Shah[15] found that invasive right heart catheterization parameters are not associated significantly with dyspnea. Rector[16] observed that several common objective measures of HF severity, including LVEF, blood pressure, and serum creatinine and hemoglobin, were not independently associated with HF symptoms. Meyers[17] identified that symptoms of HF correlate poorly with objective measures of exercise capacity (i.e. peak oxygen uptake). Finally, Guglin[20] recently concluded that there was no association between HF symptoms and multiple clinical factors that predict morbidity and mortality, including peak oxygen uptake, LVEF, Nt-proBNP, right heart catheterization parameters, and echocardiographic parameters. Our approach was different from prior research in that our goal was to identify distinct and common profiles among integrated data on symptoms and hemodynamics. In doing so, we identified three profiles that capture differences in the relationship among symptoms and hemodynamic, with one congruent profile and two profiles of symptom-hemodynamic mismatch. Thus, clustering combined data on symptoms and hemodynamics may be an avenue to gain new insights into relationships among symptoms and their biological and non-biological underpinnings.

Several symptom clusters have been identified in prior clinical HF research. For example, Song and colleagues[14] identified a symptom cluster centered on dyspnea and another centered on lack of energy and difficulty sleeping. Hertzog and group[40] identified three physical symptom profiles. Finally, Jurgens et al.,[41] and Lee and colleagues[13] both identified clusters among physical and psychological symptoms in HF. Our findings build upon prior work in HF symptom clustering by integrating hemodynamics data with both physical and psychological symptoms. Importantly, symptom clusters have been shown by others to independently predict clinical event-risk. Specifically, Lee and colleagues[13] identified an emotional cluster that predicted event-free survival (HR=1.18), and Song and colleagues[14] recognized a weary symptom cluster that predicted hospitalization (HR=1.45) and a dyspnea cluster that predicted mortality (HR=2.00). Thus, our research is a logical extension of prior work on symptom clusters and survival by linking symptom-hemodynamic mismatch profiles to significant differences in HF event risk. It is worth noting that these prior studies exemplify the two main approaches to symptom clustering in HF (i.e. clustering symptoms themselves and clustering patients based on symptoms). Hence, the aims and analyses of these prior studies varied according to the overall approach to symptom clustering. The patient, not the symptom, was the unit of analysis in this study.

Our most important finding is that symptom-hemodynamic mismatch of either kind was associated with a greater 180-day HF event-risk. Simply put, the clinical relevance of the symptom-hemodynamic mismatch we observed is centered on future urgent healthcare resource utilization. We have learned from large HF registries that the vast majority (89–93%) of patients who are hospitalized for HF present with symptoms like dyspnea, are hypertensive, and have preserved ejection fraction.[42, 43] We also know that poor hemodynamics, when not assessed along with symptoms, are predictive of poor clinical outcomes in HF.[12, 44] The novel findings of our research are a) the majority of adults with HF do not have concordant symptoms and hemodynamics, and b) that either severe symptoms or poor hemodynamics is associated with greater event-risk.

Implications and Directions for Future Research

Our findings don't change the fact that a detailed history and examination remain the cornerstones of evaluation of HF and the responsiveness to therapy.[3] Further, it would be well beyond the scope of this paper to provide specific treatment recommendations that differ from those detailed in international guidelines. There are, however, clear implications based on what we have observed about the nature of the relationship between hemodynamics and symptoms. First, a minority of patients in our sample had symptoms and hemodynamics that were on par with one another. These patients were also significantly older and had more education than those in the mismatched profiles and half had HF with preserved ejection fraction. Thus, the relative symptom-hemodynamic concordance we observed may be a function of these or other factors. Second, patients with severe symptom and average hemodynamics have a markedly elevated event-risk compared to those with symptom-hemodynamic concordance. Thus, what patients have to tell us about their experience in living with this condition, even if that does not match what we can objectively measure, is important in predicting future healthcare resource utilization. Interventions that could be particularly helpful with this type of symptom-hemodynamic mismatch may be centered on assessing and removing barriers to effective symptom management strategies to prevent unnecessary hospitalization. Third, patients with mild-to-no symptoms and poor hemodynamics also had a markedly elevated event-risk compared with those who had concordant symptoms and hemodynamics. Hence, minimal symptoms, particularly in the context of poor hemodynamics, should not be interpreted as a sign that all is well. Instead, patients with this type of symptom-hemodynamic mismatch may require more intensive monitoring of hemodynamics or even advanced therapies to prevent hospitalization and/or death. Fourth, the only right heart catheterization parameter that was helpful in differentiating among the three types of symptom-hemodynamic congruence or mismatch was cardiac index. That is, PCWP and RAP were not different among the three profiles, and there were minimal differences in cardiac index. Thus, profiles of symptom-hemodynamic mismatch can be observed in the general cardiology population with a good history and physical examination and echocardiogram. Finally, our results once again highlight how little we know about HF in general, and about HF symptom biology in particular.

Accordingly, future research is needed to: a) gain insight into the biological and non-biological underpinning of physical and psychological symptoms in HF, b) validate and/or find new profiles of symptom-hemodynamic mismatch that are associated with significant differences in clinical and patient-oriented outcomes, and c) determine how symptom-hemodynamic concordance and mismatch may change over the course of HF progression and in response to HF therapies. Additional research is needed to test tailored disease management and self-care strategies according to profiles of symptom-hemodynamic mismatch.

Strengths and Limitations

Our approach to this study has several strengths. First, we used a robust method to identify unique patterns of similarity among a population of patients that is notoriously heterogeneous with respect to symptoms and underlying hemodynamics. Second, we

integrated data on symptoms and hemodynamics to gain insight into how, and in whom, these subjective and objective data are related. Third, we used two approaches to adjust our estimates of event hazard associated with the profiles of symptom-hemodynamic mismatch, one that results in balancing among groups based on observed differences, and the other that helps choose covariates that are also strongly related to the risk of clinical events.

There are several potential limitations to our work that must also be acknowledged and taken into consideration when interpreting our findings. First, our study is a non-experimental study and therefore prone to bias that is associated with all observational research. Second, we make no claim about the temporal relationship between symptoms and hemodynamics and present our findings as associations not causal mechanisms. Third, we sought to identify difference in clinical and socio-demographic determinants among the observed profiles to effectively adjust for those differences in our hazards modeling. There may be other determinants of the types of symptom-hemodynamic concordance or mismatch that we did not test. Finally, this research was on relatively young adults with symptomatic HF. Thus, these results may not be generalizable to all cohorts of adults with HF.

Conclusion

A minority of adults with HF had concordant symptoms and hemodynamics. Two profiles of symptom-hemodynamic mismatch were identified. Adults with severe symptoms and average hemodynamics had three times the risk of having HF events within 180 days compared to those with concordant symptoms and hemodynamics. Those with poor hemodynamics and mild symptoms had nearly four times the risk of having HF events within 180 days compared to those with concordant symptoms and hemodynamics. These results have implications for researchers and clinicians alike who are interested in improving clinical outcomes of HF.

Acknowledgment

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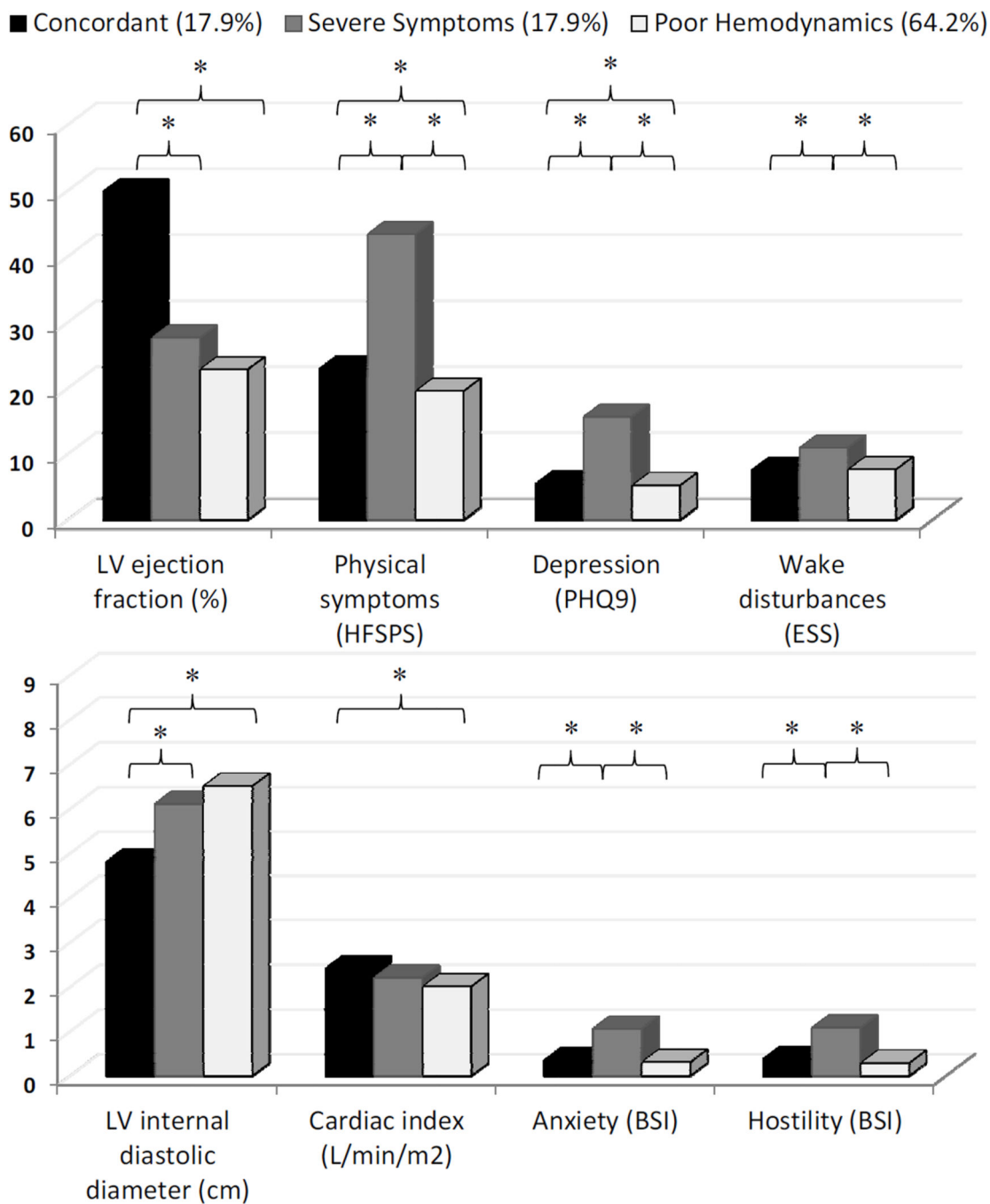
Figure 1.
Bar graphs present significant differences in four hemodynamic values and four symptom measures among the three symptom-hemodynamic profiles. All measures were significantly different across the three groups based on overall -tests with p-values <0.0001.
* = statistically significant between-group tests with p<0.01 corrected for multiple comparisons.

Abbreviations: BSI = Brief Symptom Inventory, ESS = Epworth Sleepiness Scale, HFSPS = Heart Failure Somatic Perception Scale, LV left ventricle, PHQ9 = Patient Health Questionnaire.

Heart Failure Event-Free Survival

Profiles of Symptom-Hemodynamic Mismatch:

Severe Symptoms: HR = 3.19 (95%CI = 1.04-9.81), p= 0.043

Poor Hemodynamics: HR = 4.01 (95%CI = 1.43-11.22), p=0.008

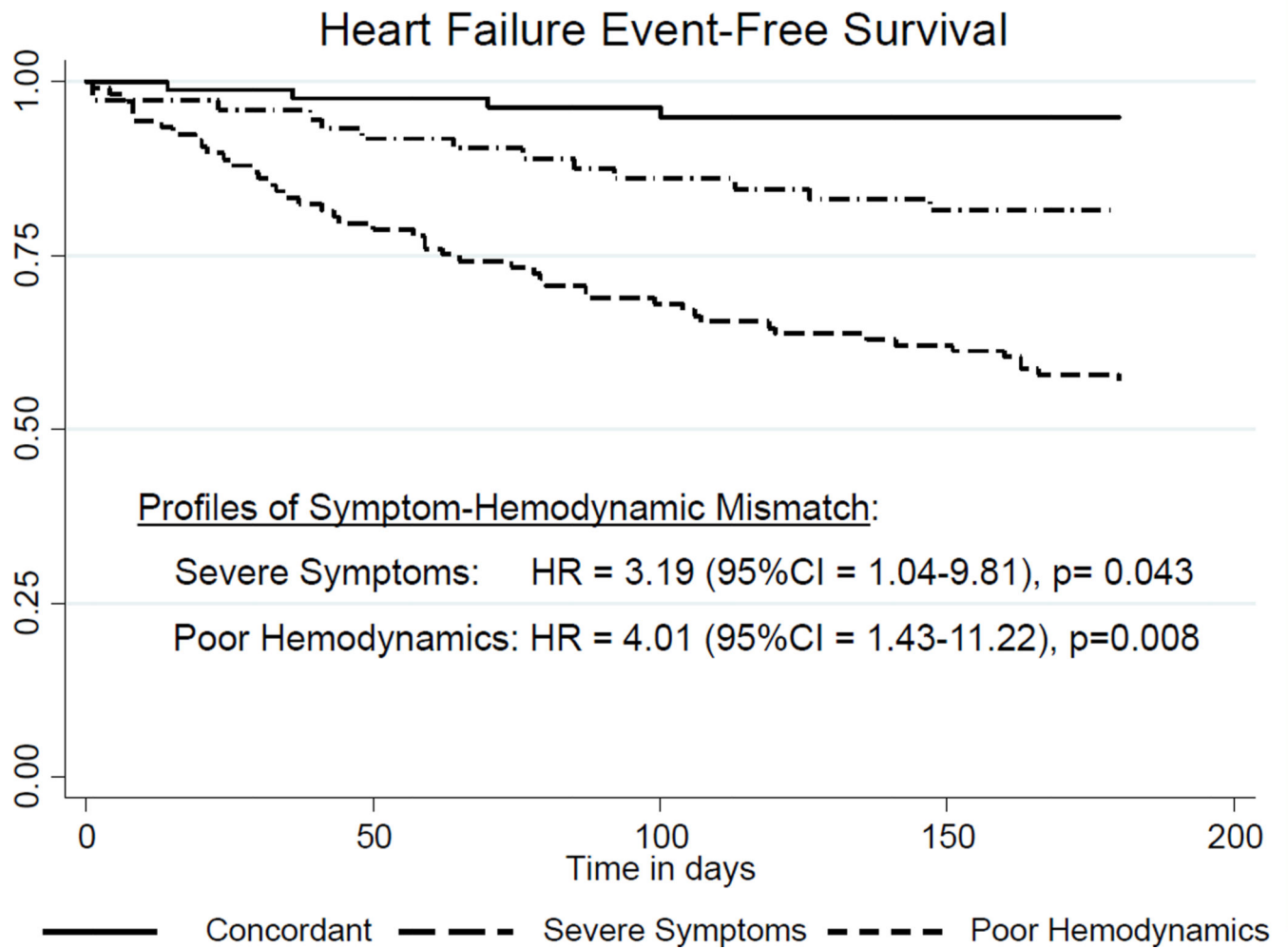Concordant — — - Severe Symptoms - - - - Poor Hemodynamics

Figure 2.
Heart failure event-free survival by observed profiles of symptoms and hemodynamic mismatch. Hazards ratios are relative to patients with concordant symptoms and hemodynamics and adjusted for mild cognitive dysfunction, and treatment with a β-adrenergic blocker, and treatment with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker.

Abbreviations: CI = confidence interval, HR = adjusted hazards ratio

Table 1

Characteristics of the sample (n=291)

Patient Characteristics:	mean±SD, n (%), or median [IQR]
Age (years)	56.7±13.3
Female	111 (38.1%)
Non-Hispanic Caucasian	237 (81.6%)
Married/Living with Partner	184 (63.2%)
Body Mass Index (kg/m^2)	31.0±7.5
Charlson Comorbidity Index (weighted)	2.3±1.4
Atrial fibrillation	111 (38.1%)
Stage 3 chronic kidney disease	42 (14.4%)
General Heart Failure Characteristics:	
Time with heart failure in months:	48 [20–96]
NYHA Functional Class:	
Class II	113(38.8%)
Class III	164 (56.4%)
Class IV	14 (4.8%)
Ischemic Heart Failure	101 (34.8%)
Prescribed a β-blocker	263 (90.4%)
Prescribed an ACE-I or ARB	238 (81.8%)
Prescribed an aldosterone antagonist	129 (44.3%)
Serum sodium (mEq/L)	137.8±3.3
Serum hematocrit (%)	39.0±5.7
Serum BUN-to-creatinine ratio (mg/dL:1)	20.2±9.4
Heart Failure Hemodynamics:	
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)	18.8±8.4
Right atrial pressure (mm/Hg)	9.5±5.5
Cardiac index (L/min/m^2 by Fick equation)	2.1±0.5
Symptoms:	
Physical symptoms (HFSPS; 0–90)	24.6±16.7
Wake disturbances (ESS; 0–24)	8.2±4.9
Depression (PHQ9; 0–27)	7.2±6.1, 6 [2–10.5]
Anxiety (BSI; 0–4)	0.33 [0–0.88]
Hostility (BSI; 0–4)	0.20 [0–0.60]

Abbreviations: ACE-I = Angiotensin Converting Enzyme-Inhibitor, ARB = Angiotensin Receptor Blocker, BSI = Brief Symptom Inventory, ESS = Epworth Sleepiness Scale, HFSPS = Heart Failure Somatic Perception Scale, IQR = interquartile range, NYHA = New York Heart Association, PHQ9 = Patient Health Questionnaire, SD = standard deviation.

Table 2

Mixture model of heart failure symptoms and hemodynamics

Symptoms and Hemodynamics	Concordant (17.9%)	Severe Symptoms (17.9%)	Poor Hemodynamics (64.2%)	F, p-value
Physical HF symptoms (HFSPS)	22.9±15.6	43.3±15.3	19.5±13.2	57.1, p<0.0001
Wake disturbances (ESS)	7.5±5.5	10.9±5.1	7.6±4.3	10.7, p<0.0001
Depression (PHQ9)	5.4±4.6	15.6±5.3	5.2±4.3	109.3, p<0.0001
Anxiety (BSI)	0.34±0.46	1.53±0.67	0.30±0.32	168.4, p<0.0001
Hostility (BSI)	0.37±0.47	1.07±0.81	0.28±0.36	52.6, p<0.0001
LV internal diastolic diameter (cm)	4.8±0.7	6.1±1.2	6.5±1.0	48.7, p<0.0001
LV ejection fraction (%)	49.8±9.9	27.6±8.0	22.8±6.4	258.2, p<0.0001
Cardiac index (L/min/m^2)	2.4±0.6	2.2±0.5	2.0±0.5	7.8, p=0.0006
Wedge pressure (mm/Hg)	16.4±8.5	19.8±8.4	19.0±8.4	1.3, p=0.2674
Right atrial pressure (mm/Hg)	10.2±5.6	10.8±8.4	9.1±5.1	1.6, p=0.1982

Abbreviations: BSI = Brief Symptom Inventory, ESS = Epworth Sleepiness Scale, HF = heart failure, HFSPS = Heart Failure Somatic Perception Scale, LV = left ventricle, PHQ9 = 9-item patient health questionnaire.

Table 3

Characteristics by observed profiles of symptoms and hemodynamics

	Concordant (17.9%)	Severe Symptoms (17.9%)	Poor Hemodynamics (64.2%)	*F* or χ^2, p-value
Age (years)	62.6±15.1	52.8±12.9	56.5±12.6	5.9, p=0.003
Female	51.1%	32.7%	37.7%	3.9, p=0.145
Married/Living with Partner	61.7%	53.9%	66.3%	2.7, p=0.257
Non-Hispanic Caucasian	84.0%	84.6%	80.1%	12.0, p=0.445
Body Mass Index (kg/m^2)	31.4±7.4	31.5±9.1	30.8±7.1	0.3, p=0.764
Charlson Comorbidity Index	2.2±1.3	2.3±1.2	2.3±1.4	0.1, p=0.943
College Education	39.2%	13.5%	27.7%	13.8, p=0.008
Mild Cognitive Dysfunction [*]	29.4%	34.6%	30.6%	0.9, p=0.627
Heart failure duration (months)	57.9±57.8	70.2±82.0	71.7±67.8	0.79, p=0.454
Ischemic Etiology	28.0%	36.5%	36.2%	1.2, p=0.537
Prescribed a β-blocker	92.2%	86.5%	91.0%	1.1, p=0.566
Prescribed an ACE-I or ARB	74.5%	76.9%	85.1%	4.03, p=0.133
Prescribed an aldosterone antagonist	29.4%	50.0%	46.8%	5.74, p=0.057

Abbreviations: ACE-I = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker

[*] = assessed with the Montreal Cognitive Assessment

Table 4

180-day heart failure event-risk by profile of symptoms and hemodynamics

Characteristic	HR (95%CI), p-value	HR[†] (95%CI), p-value	HR[‡] (95%CI), p-value
Symptom and Hemodynamic Profile			
Severe Symptoms[*]	3.38 (1.10–10.37), p=0.033	3.27 (1.07–10.08), p=0.039	3.19 (1.04–9.81), p=0.043
Poor Hemodynamics[*]	3.48 (1.26–9.66), p=0.016	3.85 (1.38–10.77), p=0.010	4.01 (1.43–11.22), p=0.008
Other Factors			
Age	-	0.99 (0.98–1.02), p=0.987	-
Male	-	1.23 (0.73–2.06), p=0.442	-
College Education	-	0.64 (0.34–1.21), p=0.167	-
ACE/ARB	-	0.46 (0.26–0.83), p=0.009	0.47 (0.27–0.83), p=0.010
Aldosterone antagonist	-	1.03 (0.62–1.69), p=0.918	-
Cognitive dysfunction[¶]	-	-	1.68 (1.02–2.75), p=0.040
B-adrenergic blocker	-	-	0.55 (0.28–1.10), p=0.090

[*] = relative to participants in the concordant profile.

[†] = adjusted for among-group differences in age, gender, education, angiotensin converting enzyme inhibitor/angiotensin receptor blocker, and aldosterone antagonist.

[‡] = retained factors from backward selection with removal of factors with a p-value >0.20. Factors entered into the model were age, gender, married/living with partner, race, body mass index, Charlson comorbidity index, education, mild cognitive dysfunction, heart failure duration, ischemic etiology, prescribed a β-adrenergic blocker, prescribed an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and prescribed an aldosterone antagonist.

[¶] = assessed with the Montreal Cognitive Assessment

Abbreviations: CI = confidence interval, HR = hazards ratio, ACE/ARB= angiotensin converting enzyme inhibitor/ angiotensin receptor blocker