Background and Design of the Biological and Physiological Mechanisms of Symptom Clusters in Heart Failure (BIOMES-HF) Study

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ABSTRACT

Background: Symptoms, which often cluster together, are a significant problem in heart failure (HF). There is considerable heterogeneity in symptom burden, particularly in the vulnerable transition period after a hospitalization for HF, and the biological underpinnings of symptoms during transitions are unclear. The purpose of this article is to describe the background and design of a study that addresses these knowledge gaps, entitled Biological and Physiological Mechanisms of Symptom Clusters in Heart Failure (BIOMES-HF).

Methods and Results: BIOMES-HF is a prospective gender- and age-balanced longitudinal study of 240 adults during the 6-month transition period after a HF hospitalization. The aims are to (1) identify clusters of change in physical symptoms, (2) quantify longitudinal associations between biomarkers and physical symptoms, and (3) quantify longitudinal associations between physical frailty and physical symptoms among adults with HF. We will measure multiple symptoms, biomarkers, and physical frailty at discharge and then at 1 week and 1, 3, and 6 months after hospitalization. We will use growth mixture modeling and longitudinal mediation modeling to examine changes in symptoms, biomarkers, and physical frailty after HF hospitalization and associations therein.

Conclusions: This innovative study will advance HF symptom science by using a multibiomarker panel and the physical frailty phenotype to capture the multifaceted nature of HF. Using advanced quantitative modeling, we will characterize heterogeneity and identify potential mechanisms of symptoms in HF. As a result, this research will pinpoint amenable targets for intervention to provide better, individualized treatment to improve symptom burden in HF.

Lay Summary: Adults with heart failure may have significant symptom burden. This study is designed to shed light on our understanding of the role of biological and physiological mechanisms in explaining heart failure symptoms, particularly groups of co-occurring symptoms, over time. We explore how symptoms, biomarkers, and physical frailty change after a heart failure hospitalization. The knowledge generated from this study will be used to guide the management and self-care for adults with heart failure. (*J Cardiac Fail 2022;28:973–981*)

Key Words: Heart failure, biomarkers, frailty, symptoms, quantitative.

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Despite advances in the management of heart failure (HF),[1] symptom burden persists for many of the 6.2 million adults living with HF in the United States.[2] Symptoms, such as dyspnea and fatigue,[3] decrease quality of life and increase clinical event risk in HF.[4,5] However, there is considerable heterogeneity in symptoms, often manifesting in symptom clusters,[6] that is particularly critical in the vulnerable transition period after a HF hospitalization.[7] Although symptoms improve for some patients and they have periods of relative stability, others are plagued by enduring symptoms leading to poor outcomes, including rehospitalization.[8] There is little to no association between common clinical markers (eg, ejection fraction) and symptoms in HF,[9,10] meaning that clinical efforts to optimize stability during a hospitalization may not translate to symptom improvement after hospitalization. Understanding how and why symptoms develop and/or persist for some patients versus others will aid in the development of interventions to mitigate symptom burden and decrease HF rehospitalizations.

The purpose of this article is to describe the background and design of a prospective observational study entitled Biological and Physiological Mechanisms of Symptom Clusters in Heart Failure" (BIOMES-HF). This biobehavioral study was developed to identify how symptom clusters change after a HF hospitalization and quantify longitudinal associations between symptoms, biomarkers, and physical frailty. Overall, we propose that a multibiomarker panel and the physical frailty phenotype might better capture the multifaceted nature of HF symptoms than current markers. In this article, we describe the relevant background and the overall research design and methods for this study. We conclude with a discussion of anticipated results and implications for clinical practice and research.

Background

HF is the fastest growing cardiovascular condition in the United States[11] and the most common reason for hospitalization and rehospitalization among older adults.[12] With more than 1 million hospital admissions annually,[2] patients hospitalized for HF are vulnerable to poor outcomes with readmission rates of up to 50% by 6 months.[12] Symptom burden is a key risk factor precipitating readmissions.[8] However, our understanding of HF symptoms during the transition from hospital to home remains limited.

Many of those living with HF experience significant symptom burden (eg, dyspnea, pain),[3] which persists across all subgroups (eg, women and men, HF with reduced and preserved ejection fraction),[13,14] decreasing quality of life and increasing clinical event risk.[4,15] Adults with HF report a multitude of co-occurring symptoms,[15] often manifesting as HF symptom clusters.[4,5,16] Moreover, in addition to hallmark physical symptoms such as dyspnea, adults with HF commonly report affective symptoms such as depression and anxiety, which often compound the overall symptom burden.[4,5] Although we can cluster HF symptoms together and link HF symptom clusters with poor outcomes, we do not yet know how symptom clusters change after a HF hospitalization.

Moreover, most research into the biological underpinnings of symptoms in HF has focused on conventional clinical markers (eg, ejection fraction).[9,10] Across studies, however, there is little to no association between these clinical markers and symptoms, which presents several clinical problems. First, we do not know the mechanisms of symptoms in HF; thus, symptom science in HF lags behind other chronic conditions such as cancer. Second, clinical management strategies are limited in their ability to mitigate symptom burden in HF. For instance, optimizing hemodynamic stability during a HF hospitalization may not translate to better symptoms after hospitalization. Similarly, focusing on symptoms only may result in suboptimal improvement in hemodynamics.

Many studies have shown that HF is not just a hemodynamic, "pump failure" problem,[17] but it is a multifactorial, multisystem condition involving processes such as inflammation,[18] sympathetic dysregulation,[19] and endothelial dysfunction.[20] Biomarkers of these processes can serve as an indicator of disease prognosis and/or response to an intervention,[21] and they may provide insight into the biological mechanisms of symptoms. Additionally, there is increasing recognition of the intersection between HF and physical frailty,[22] which is defined as decreased physiological reserves and increased vulnerability to adverse outcomes.[23] Physical frailty affects about 50% of adults with HF[24] and is associated with worse clinical outcomes.[25] The biological mechanisms of physical frailty in HF are unknown; however, it is hypothesized that the pathophysiological processes of HF mirror those of physical frailty,[26] including a strong association with symptoms in HF.[27] In sum, a multibiomarker panel and the physical frailty phenotype that capture the multifaceted nature of HF might tell us more about symptoms in HF than our current markers.

Methods

Theoretical Framework

The research is based on the integration of 2 theories: Lenz's Theory of Unpleasant Symptoms[28] and Fried's cycle of frailty (Fig. 1).[23] Theory of Unpleasant Symptoms focuses on understanding the

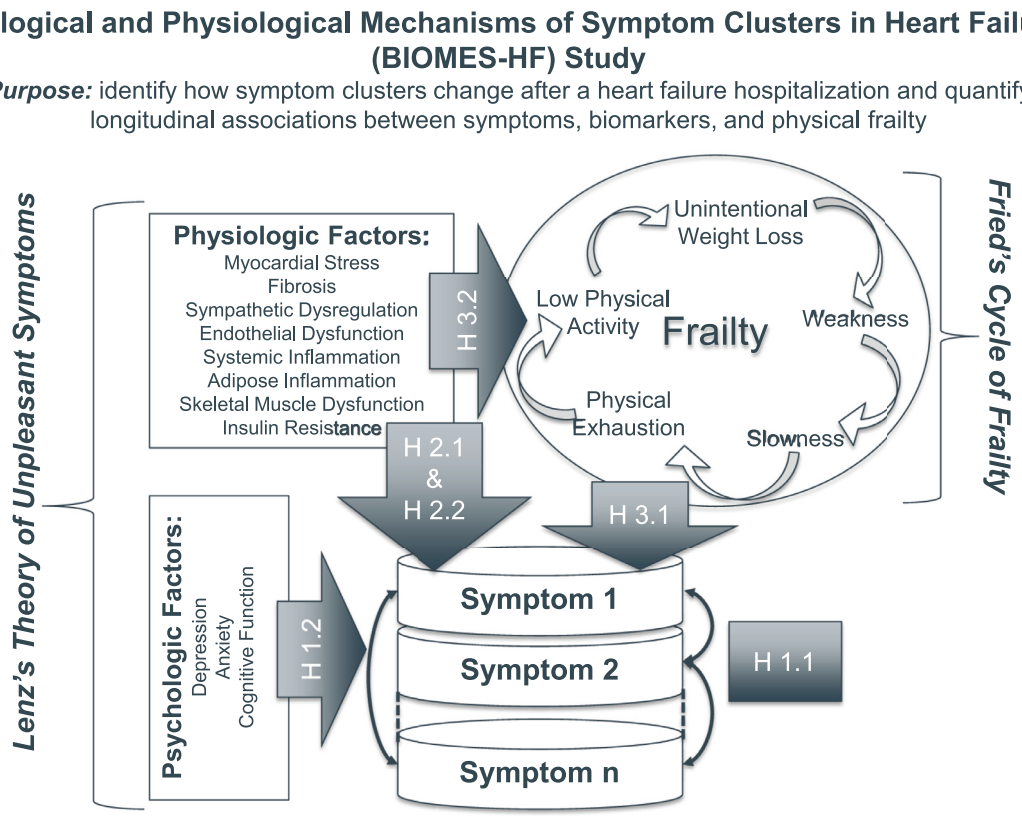

Fig. 1. Overview of theoretical approach and hypotheses. We incorporated Lenz's Theory of Unpleasant Symptoms and Fried's cycle of frailty in our approach. Abbreviations: H, hypothesis.

relationships among multiple symptoms, the influencing factors of symptoms, and the outcome or effect of the symptom experience. In particular, this study focuses on how multiple physical symptoms cluster and influential physiologic factors (ie, biomarkers and physical frailty) and psychologic factors (ie, affective symptoms) to identify mechanisms of symptoms in HF.[28]

To expand on the role of physical frailty in HF, we also incorporate the cycle of frailty as described by Fried et al.[23] The cycle of frailty unifies the markers of frailty that are associated with decreased physiological reserves and energetics; when there is a critical mass of these markers, the syndrome of frailty is identified. We propose that the multifaceted systemic interaction of aging, HF pathogenesis, and comorbidities results in the entry point into the cycle of frailty. We also hypothesize that, through the cycle of frailty, symptoms in HF become more pronounced and worsen over time.

Study-Specific Aims and Hypotheses

The overarching goal of this study is to identify how symptom clusters change longitudinally in the 6-month period after a HF hospitalization and quantify longitudinal associations between symptoms, biomarkers, and physical frailty. Our central hypothesis is worsening symptoms after a HF hospitalization will be associated with worsening biomarkers and physical frailty. We address the following aims.

Specific Aim #1: Identify clusters of change in physical symptoms among adults with HF.

Hypothesis 1.1: At least 2 distinct clusters in physical symptoms will be identified (eg, stable and worsening).

Hypothesis 1.2: Worsening physical symptom clusters will be associated with worsening affective symptoms.

Specific Aim #2: Quantify longitudinal associations between biomarkers and physical symptoms among adults with HF.

Hypothesis 2.1: A change in biomarkers will be associated significantly with a change in physical symptoms.

Hypothesis 2.2: Worsening biomarkers will be associated with worsening physical symptom clusters.

Specific Aim #3: Quantify the longitudinal associations between physical frailty and physical symptoms among adults with HF.

Hypothesis 3.1: Persistent physical frailty will be associated significantly with worsening physical symptoms.

Table 1. Schedule of Assessments

	Measurement	Reliability (α)	Baseline	1 Week	1 Month	3 Months	6 Months
Clinical characteristics							
Sociodemographics	Sociodemographic questionnaire	–	x				
Comorbidities	Charlson Comorbidity Index[30]	–	x	x	x	x	x
HF Clinical characteristics	Chart Abstraction (SHFM[31] and AHA/ACC guidelines[29])	–	x	x	x	x	x
Symptoms							
Dyspnea	Heart Failure Somatic Perception Scale-Dyspnea[34]	0.92*	x	x	x	x	x
Sleep-related impairment	PROMIS Sleep-Related Impairment[33]	0.92*	x	x	x	x	x
Pain interference	PROMIS Pain Intensity and Interference[33]	0.96*	x	x	x	x	x
Depressive symptoms	Patient Health Questionnaire-9[37]	0.88*	x	x	x	x	x
Anxiety	PROMIS Emotional Distress-Anxiety[33]	0.96*	x	x	x	x	x
Cognitive function	PROMIS Cognitive Function[33]	0.97*	x	x	x	x	x
Physical frailty[38]		–					
Shrinking	Unintentional weight loss >10lb/year	–	x		x	x	x
Weakness	Grip strength and 5-repeat chair stands	–	x		x	x	x
Slowness	4-meter gait speed	–	x		x	x	x
Physical exhaustion	FACIT-F[39]	0.94*	x		x	x	x
Low physical activity	CHAMPS[40]	–	x		x	x	x
Plasma biomarkers	See Table 3 for details	–	x	x	x	x	x
Clinical events	Emergency room, hospitalization, death, heart transplantation, ventricular assist device	–		x	x	x	x

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; CHAMPS, Community Health Activities Model Program for Seniors; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue Scale; PROMIS, Patient Reported Outcomes Measurement Information System; SHFM, Seattle Heart Failure Model.

*Cronbach's α based on the same population of HF patients enrolled in our previous research study.[32]

Hypothesis 3.2: Physical frailty will mediate the relationship between biomarkers and physical symptoms.

Study Design

We will use a prospective, observational study design to address the study aims. Data will be collected at the following time points: approximately 24 hours before hospital discharge, then 1 week and 1, 3, and 6 months after hospitalization (Table 1). These assessments will allow us to capture symptoms, biomarkers, and physical frailty at critical and clinically relevant time points after a hospitalization (eg, 1 week to prevent readmission; 1 month to determine likely trajectory).

Sample. The sampling frame is adult women and men with a confirmed diagnosis of stage C or D HF (by documented history, physical examination, and echocardiographic evidence) of 3 or more months who are responsible for their own decisions and have been hospitalized with a primary diagnosis of acute decompensated HF (with reduced or preserved ejection fraction). See Table 2 for the complete inclusion and exclusion criteria. All eligible patients will be approached for voluntary participation when they are admitted to hospital and meet the criteria; research study staff will work with clinical staff (led by S.A.C.) in approaching eligible patients. We will use convenience sampling to enroll up to 290 participants to reach our final evaluable and analytic sample of 240 (ie, participants who complete all study visits, allowing for 20% attrition).

Inclusion of Women, Minorities, and Adults across the Lifespan. To address critically important sex/gender differences that occur in HF, we will use a 1:1 male:female enrollment strategy. To address noted health disparities by race and ethnic categories, we will enroll at least 30% minorities, including enrolling approximately 15% of participants who self-identify as Hispanic or Latino (having Spanish versions of surveys and interpreters available). Additionally, in order to address the entire aging-HF continuum, we will enroll patients from across the adult lifespan ($\geq$18 years).

Data Collection Procedures

A schedule of assessments is presented in Table 1. After participants provide written informed consent, we will schedule baseline data collection at or around 24 hours before discharge, after which, we

Table 2. Formal Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Willing and able to provide informed consent	Previous heart transplant or ventricular assist device
Age ≥18 years	Major diagnosed cognitive impairment (eg, Alzheimer's)
Able to read and comprehend 5th grade English or Spanish	Major and uncorrected hearing dysfunction
Reachable by telephone/email/texting for the duration of the study	Active psychosis or substance use that would preclude study participation
Confirmed diagnosis of HF by physical exam and echocardiographic evidence of ≥3 months prior	Concomitant terminal illness that would impede participation in a longitudinal study (eg, under hospice care)
Hospitalized with HF as primary diagnosis	Discharged to a long-term care facility
Current HF symptoms (ie, NYHA functional class II–IV HF; AHA/ACC stage C or D HF)[68,69]	Other medical conditions that would interfere with participant safety or data collection (eg, life-threatening illness)

AHA/ACC, American Heart Association/American College of Cardiology; HF, heart failure; NYHA, New York Heart Association.

will schedule participants for follow-up data collection (1 week [±2 days], 1 month [−1 week and + 2 weeks], 3 months [±2 weeks], and 6 months [±2 weeks] after hospitalization). Data will be collected from the participant using paper or electronic data collection (via our Research Electronic Data Capture [REDCap] system) and from the medical record; all data will be stored in REDCap.

Measurement

We will collect sociodemographic and clinical variables, including HF history (eg, etiology, duration of HF), diagnostics (eg, laboratory values, echocardiographic metrics), medications (eg, diuretics, beta-blockers), and treatment (eg, implantable cardiac defibrillator placement).[29] We will assess comorbidities with the Charlson Comorbidity Index.[30] We will also collect data specific to the calculation of the Seattle Heart Failure Model score,[31] which will be used to account for the severity of HF.

Symptoms. We will use both HF-specific and universal symptom measures that have well-established psychometric properties in clinical populations. Reliabilities of these measures within our HF population[32] are presented in Table 1. The universal symptom measures will include measures developed within the National Institutes of Health–sponsored Patient Reported Outcomes Measurement Information System (PROMIS) Initiative.[33] For PROMIS measures, the raw score is translated into a T-score, resulting in a standardized score with a mean of 50 and a standard deviation of 10.

Dyspnea will be measured with the 6-item Heart Failure Somatic Perception Scale Dyspnea Subscale (HFSPS-D).[34] The HFSPS-D asks participants how much they were bothered by common HF symptoms, ranging from 0 (did not have this symptom) to 5 (extremely bothersome). We will ask additional questions about bendopnea[35] and loss of appetite.[36] Sleep-related impairment will be measured with the 8-item PROMIS Sleep-Related Impairment Short Form.[33] The Sleep-Related Impairment Short Form focuses on self-reported perceptions of alertness, sleepiness, and tiredness during usual waking hours, including the perceived functional impairments, with response options ranging from 1 (not at all) to 5 (very much). Pain intensity will be measured with the 1-item PROMIS Pain Intensity Short Form.[33] The Pain Intensity Short Form assesses how much a person hurts, on average, ranging from 0 (no pain) to 10 (worst imaginable pain). Pain interference will be measured with the 4-item PROMIS Pain Interference Short Form.[33] The Pain Interference Short Form measures the self-reported consequences of pain on relevant aspects of one's life, ranging from 1 (not at all) to 5 (very much).

Depressive symptoms will be measured with the Patient Health Questionnaire-9.[37] The Patient Health Questionnaire-9 scores each of the 9 related *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, criteria providing 4 response options ranging from 0 (not at all) to 3 (nearly every day). Anxiety will be measured with the 8-item PROMIS Emotional Distress-Anxiety Short Form.[33] The Anxiety Short Form measures self-reported fear, anxious misery, hyperarousal, and somatic symptoms related to arousal with response options ranging from 0 (never) to 4 (always). Cognitive function will be measured with the 6-item PROMIS Cognitive Function Short Form.[33] The Cognitive Function Short Form assesses perceived cognitive deficits, including mental acuity, concentration, and memory with response options ranging from 5 (never) to 1 (very often, several times a day).

Physical Frailty. Physical frailty will be measured based on the validated Frailty Phenotype Criteria[23] as adapted for the HF population (described in Denfeld et al[38]) using 5 physical frailty criteria. Unintentional weight loss will be measured by a self-report of unintentional weight loss of 10 or more pounds in the past year. Weakness of both the upper and lower extremities will be assessed using grip strength and 5-repeat chair stands, respectively. Physical exhaustion will be assessed using the 13-item Functional Assessment of Chronic Illness

Therapy Fatigue Scale,[39] which captures self-reported tiredness and inability to perform activities of daily living as a result of fatigue. Slowness (ie, gait speed) will be measured by clocking the time it takes a participant to walk 4 meters at their usual pace. Physical activity will be measured with the Community Healthy Activities Model Program for Seniors scale.[40] Scoring will be as follows: no criterion met = no physical frailty, 1−2 criteria met = pre-physical frailty, and $\geq$ 3 criteria met = physical frailty.

Biomarkers. Along with symptom and physical frailty assessments, participants will provide fasting blood samples. Samples will be transported on ice and processed and stored in our National Center for Advancing Translational Sciences-sponsored research core laboratory. The biomarkers will be assayed either in the research core laboratory, our hospital clinical core laboratory, and in the laboratory of one of our authors (B.A.H.). We selected a panel of 8 plasma biomarkers to capture the multifaceted pathogenesis of HF (Table 3).[21] We will measure N-terminal pro-B-type natriuretic peptide as a marker of myocardial stress and hemodynamic congestion[41] and soluble suppressor of tumorigenicity-2, a member of the IL-1 receptor family, as a marker of fibrosis and vascular stress[42] given their important role in HF prognostication.[43] We will measure norepinephrine and its primary metabolite as markers of sympathetic dysregulation given heightened sympathetic activity in HF.[44] We will measure soluble E-selectin as a marker of endothelial dysfunction owing to decreased endothelial nitric oxide bioavailability and formation of reactive oxygen species in HF.[20] We will measure soluble tumor necrosis factor α receptor-1 as a marker of systemic inflammation as inflammation is a common feature of HF[45] and posited as a link between HF and physical frailty.[26] We will measure adiponectin (ie, cytokine secreted by adipose tissue) as it reflects a wasting, cachexic profile and increased mortality in HF.[46] We will measure myostatin, also known as growth differentiation factor 8, as a marker of skeletal muscle dysfunction as HF can be characterized by marked alterations in skeletal muscle size and function.[47] Finally, we will measure fasting glucose and insulin as a marker of insulin resistance, which is a predominant feature of HF pathophysiology.[48]

Table 3. Biomarkers

Process	Biomarker	Method
Myocardial stress	NT-proBNP[41]	Chemiluminescent immunoassay
Fibrosis/vascular stress	sST2[42]	ELISA
Sympathetic dysregulation	NE:DHPG ratio[70]	HPLC-ED
Endothelial dysfunction	sE-selectin[71]	ELISA
Systemic inflammation	sTNFαR1[45]	ELISA
Adipose inflammation	Adiponectin[72]	RIA
Skeletal muscle dysfunction	Myostatin[47]	ELISA
Insulin resistance*	Insulin[48]	ELISA
	Glucose	Colorimetric

Abbreviations: DHPG, dihydroxyphenolglycol; ELISA, enzyme-linked immunosorbent assay, HPLC-ED, high performance liquid chromatography with electrochemical detection; NE, norepinephrine; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RIA, radioimmunoassay; sST2, soluble suppressor of tumorigenicity-2; sTNFαR1, soluble tumor necrosis factor α receptor-1.

*Insulin and glucose are both used to calculate homeostasis model of assessment-insulin resistance index.

Clinical Events. Because these patients will be at high risk for clinical events, we will complete a review of the electronic medical record at each follow-up to record the following: emergency room visits, hospitalizations, mortality, heart transplantation, ventricular assist device implantation, or being alive without an event. We will explore the influence of events on the primary measures of the study and incorporate into statistical analyses as appropriate.

Statistical Analysis Plan

Standard descriptive statistics of frequency, central tendency, and dispersion will be used to describe the sample. We will use comparative statistics (eg, the Student *t* test, Pearson's correlation) to quantify associations between potential covariates and symptoms, biomarkers, and physical frailty. Throughout our modeling procedures described below, we will control for (at minimum) the Seattle Heart Failure Model score[31] plus the Charlson Comorbidity Index,[30] which will account for relevant clinical characteristics. Analyses will be performed using StataMP v.17 (College Station, TX) and Mplus v.8 (Los Angeles, CA).

Overview of Growth Mixture Modeling. Growth mixture modeling (GMM) is a type of clustering designed to identify distinct, naturally occurring patterns of change that vary around different means, have unique estimates of variance, and homogenous within-trajectory growth.[49] Based on conditional probabilities, cases are assigned to the most likely class or pattern of change over time. Changes over time are modeled as random effects, non-normal distributions and nonlinear patterns of change are accommodated well, and there are several metrics to help judge comparative fit between models in GMM.[50] Our approach to latent model specification is based on common procedures.[49] We will use Bayesian Information Criteria, the Lo−Mendell−Rubin adjusted likelihood ratio test,[51] parametric bootstrap likelihood ratio,[52] entropy, posterior probabilities, and the proportion of

sample to compare alternative models (eg, 3 vs 2 distinct clusters of change).[52,53]

Overview of Longitudinal Mediation Modeling. Mediation modeling is useful in describing the way in which one variable has an effect on another variable through its influence on some intermediate variable.[54] Compared with cross-sectional mediation models, the advantage of longitudinal mediation approaches is the ability to leverage panel data (ie, all variables have been measured at the same time points) to make stronger causal claims by using prior time points to predict future time points. This approach allows for more accurate modeling of causal relationships that take time to unfold and provides a stronger foundation for specifying and testing mediation hypotheses where there is some question as to the direction of the causal arrow.[54] Parallel process modeling[55] is 1 way to perform mediation analysis by modeling simultaneous trajectories of change while accounting for intraindividual variability in change.[56]

Handling Missing Data. If the data are missing completely at random or missing at random, we will use a full-information maximum likelihood estimation, which uses all available data to calculate parameter estimates and is less biased and more efficient than other techniques such as mean imputation or last observation carried forward. Principled methods of multiple imputation[57] will be used to account for dropout patterns considered missing not at random, if necessary.

Aim #1: Change in Physical Symptom Clusters. To address Hypothesis 1.1, we will develop latent growth curve models of each physical symptom measure (dyspnea, sleep-related impairment, and pain intensity) to capture average change, dispersion, and the shape of change over time.[58,59] Then, we will generate parallel process models[60,61] for all 2-way symptom comparisons to quantify congruence or discordance between symptom measures over time using common thresholds of fit (ie, comparative fit indices and Tucker–Lewis indices of $\geq$0.95, root mean square errors of approximation of $<$0.08, and standardized root mean square residuals of $<$0.10),[62] as well as random effect estimates between intercepts, slopes, and quadratic terms for nonlinear patterns. Next, we will develop a GMM for complementary or nonredundant symptom measures to identify distinct and naturally occurring clusters of change in physical symptoms over time. We will decide on the number of classes based on Bayesian Information Criteria (lower absolute value comparing k to k−1 classes), Lo–Mendell–Rubin adjusted likelihood ratio test (*P* value), parametric bootstrap likelihood ratio (*P* value), model entropy (closest to 1.0), class proportions ($\geq$5% of the sample), and posterior probabilities (closest to 1.0).[49] We anticipate testing four models to identify the number of classes. Using the above metrics (with a primary emphasis on Lo–Mendell–Rubin adjusted likelihood ratio test) in conjunction with content expertise, we will generate a new categorical variable that identifies multiple clinically meaningful physical symptom cluster trajectories (eg, a 2-class solution: stable symptoms, worsening symptoms). To address Hypothesis 1.2, we will develop latent growth curve models of each affective symptom measure (depressive symptoms, anxiety, and cognitive function) to capture average change, dispersion and the shape of change over time.[58,59] Then, we will compare each affective symptom by the known trajectories of physical symptom clusters identified in Hypothesis 1.1.

Aim #2: Change in Physical Symptoms and Biomarkers. To address Hypotheses 2.1 (individual symptom trajectories) and 2.2 (symptom clusters), we will develop latent growth curve models of each biomarker to capture average change, dispersion, and the shape of change over time (after using log transformation to approximate normality where appropriate).[58,59] Then, we will generate parallel process models[60,61] for all 2-way biomarker comparisons to quantify congruence and discordance over time using the same thresholds of fit as described as described under Aim #1 analysis. Next, we will generate parallel process models[60,61] for all 2-way biomarker vs physical symptom comparisons to quantify congruence and discordance over time. Because the risk of false discovery is high with so many possible comparisons, our primary comparisons will be between dyspnea and biomarkers of myocardial stress and fibrosis; other comparisons will be adjusted for false discovery by adjusting the p values using the Benjamini and Hochberg method.[63] Then, we will compare trajectories of each biomarker by physical symptom clusters.

Aim #3: Change in Physical Symptoms and Physical Frailty. To test Hypothesis 3.1, we will categorize changes in physical frailty over 6 months. For example, if a participant is physically frail at all 3 assessments, they would be considered to have persistent physical frailty. In contrast, if a participant changes category from frail to prefrail or nonfrail, they would be considered as having improving physical frailty. Then, we will compare trajectories of each physical symptom or identified physical symptom cluster by the known trajectories of physical frailty.

To test Hypothesis 3.2, which is more exploratory, we will first determine the direction of the causal arrow using cross-lagged panel models,[54,64] which are ideal when 2 variables are measured longitudinally, and we want to determine which is the cause and which is the effect. Once this is known, we will

quantify potential mediating factors using parallel process mediation models. Intercepts and slopes will be estimated for all 3 variables involved in the proposed mediation (ie, symptoms, biomarkers, and physical frailty). We will test several different model specifications given the exploratory nature of this hypothesis. A first model will be specified such that the baseline value (intercept) for the *X* variable (ie, biomarker) will predict change (slope) in the *M* mediator variable (ie, physical frailty) from baseline to 3 months, and change (slope) in the *M* mediator variable (ie, physical frailty) will predict change in the *Y* outcome variable (ie, physical symptom) from 3 months to 6 months. Alternative models will be fit using different time intervals, as needed. To test for longitudinal mediation, the mediating (or indirect) effect of this path will be estimated and tested for significance. Similar models will be fit for each of the mediation paths for both individual and clustered physical symptoms and each of the biomarkers, adjusting for false discovery.

Sample Size Justification. No universal approach has been adopted for sample size considerations in GMM. With 3 symptoms over 5 time points in our most complex model in Aim 1, however, our *n*-to-items ratio far exceeds sample size recommendations for related approaches (10−20:1).[65] Although there are simulation methods to estimate sample size for GMM, these methods require known values for all model parameters and are not scientifically defensible given all the unknowns in this context. In previous studies,[66] our group has shown that symptoms were highly variable among adults with moderate HF; this variability fosters detection of multiple clusters over time. Assuming 80% power, a 2-sided α of 0.05, and our reported variability in biomarkers,[66] we will detect differences between 2 equal sized symptom clusters of as small as 503.3 pg/mL (N-terminal pro-B-type natriuretic peptide) and 11.3 ng/mL (soluble suppressor of tumorigenicity-2) as being significant.[67] Assuming 80% power, a 2-sided α of 0.05, and our reported variability in symptoms described elsewhere in this article, we will detect differences in HFSPS-D scores between 2 equal sized physical frailty groups of as small as 3.3 points as significant.

Associated Risks

Although this observational study is considered minimal risk by our institutional review board (#20644), there are risks associated with this study. There are extremely rare risk associated with having blood drawn, such as hematoma or infection. Participants may become fatigued while completing the questionnaires. There are rare musculoskeletal and fall risks associated with the grip strength, chair stand, and gait speed assessments. We may detect previously undiagnosed major depression. Finally, there is a minimal risk of loss of confidentiality.

Anticipated Results and Implications

First, we anticipate finding at least 2 unique clusters of change in physical symptoms over time (eg, stable symptoms, worsening symptoms) and that there will be differences in trajectories of affective symptoms by clusters of change in physical symptoms. Second, we anticipate a significant association between a change in biomarkers and a change in physical symptoms, and that worsening biomarkers are associated with worsening physical symptom clusters. Finally, we expect that persistent physical frailty is associated with worsening physical symptoms or symptom clusters and that physical frailty mediates the relationship between biomarkers and symptoms in HF.

The anticipated results of this study have potentially important implications for research and clinical practice. In the future, the identified symptom clusters could be used to risk stratify patients based on symptom burden, providing anticipatory guidance to patients, families, and providers. The identified associations between symptoms, biomarkers, and physical frailty will be used to pinpoint mechanisms and identify specific therapies for certain groups of patients. Finally, the overall goal of this study is to use these results to design biobehavioral interventions, possibly involving exercise, nutritional, and/or symptom management interventions, to mitigate symptom burden. Moreover, our data may provide direction as to which existing therapies (eg, medications, cardiac rehabilitation) to prioritize for which groups of patients.

Conclusion

The purpose of this study is to characterize heterogeneity and potential mechanisms of symptoms after a HF hospitalization. This innovative study will advance HF symptom science by using a multibiomarker panel and the physical frailty phenotype to capture the multifaceted nature of HF. By examining the longitudinal associations between symptoms, biomarkers, and physical frailty, we hope to identify targets for intervention to relieve the significant symptom burden experienced by millions of adults living with HF.

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Supplementary materials

Supplementary material, including references #31-72,[†] associated with this article can be found in the online version at doi:10.1016/j.cardfail.2022.01.003.

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[†]References #31-72 are located in Supplementary Material.