# Candidate biomarkers of physical frailty in heart failure : An exploratory cross-sectional study

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# Candidate Biomarkers of Physical Frailty in Heart Failure: An Exploratory Cross-Sectional Study

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## Abstract

**Aims:** Physical frailty is highly prevalent and predictive of worse outcomes in heart failure (HF). Candidate biomarker analysis may help in understanding the mechanisms underlying physical frailty in HF. We aimed to identify candidate biomarkers associated with physical frailty in HF using a multimarker strategy of distinct pathophysiological processes.

**Methods and Results:** We collected data and plasma samples from 113 adults with New York Heart Association Functional Class I-IV HF. Physical frailty was measured with the Frailty Phenotype Criteria. Plasma biomarkers included: N-terminal pro-B-type natriuretic peptide, norepinephrine, dihydroxyphenylglycol, soluble tumor necrosis factor alpha receptor 1, adiponectin, insulin, glucose, insulin-like growth factor-1, and myostatin. Comparative statistics and multivariate linear regression were used to test group differences and associations. The average age was 63.5±15.7 years, half were women (48%), and most had a non-ischemic etiology of HF (73%). Physical frailty was identified in 42% and associated with female sex, higher body mass index and percent body fat, more comorbidities, and HF with preserved ejection fraction. Adjusting for Seattle HF Model projected survival score, comorbidities, body composition, and

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**Tweet:** Candidate biomarkers of #frailty in #HeartFailure (affects ~50% of adults) could involve markers r/t adipose tissue + poor skeletal muscle quality & performance. Further clinical & research validation may help identify targeted #CVD strategies.

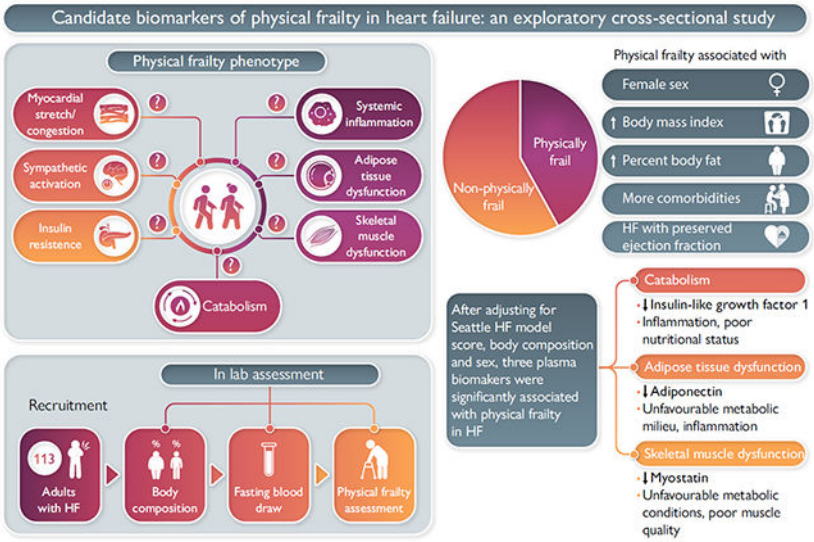
Declaration of Conflicting Interests
None

sex, physically frailty was associated with significantly lower plasma adiponectin (β±Standard Error (SE) −0.28±0.14, $p = 0.047$), insulin-like growth factor-1 (β±SE −0.21±0.10, $p = 0.032$), and myostatin (β±SE −0.22±0.09, $p = 0.011$). In sex-stratified analyses, insulin-like growth factor-1 and myostatin were significantly associated with physical frailty in men but not women.

**Conclusion:** We identified biomarkers involved in adipose tissue and skeletal muscle development, maintenance, and function that were associated with physical frailty in HF.

## Graphical Abstract

Abbreviations: HF, heart failure




### Keywords

Heart Failure; Biomarkers; Frailty; Sex Differences

## Introduction

Physical frailty is highly prevalent and strongly associated with adverse outcomes among adults with heart failure (HF).[1,2] Defined as decreased physiological reserves across multiple systems and increased vulnerability to stressors,[3] physical frailty is commonly associated with both chronological aging and accelerated biological aging, especially among adults with cardiovascular disease.[4] Physical frailty in HF is associated with increased symptom burden,[5,6] potentially impacts self-care behaviors,[7] and increases healthcare utilization.[8] As such, there is a need to develop strategies to mitigate this significant personal and healthcare burden. Identifying relevant biomarkers for physical frailty in HF is one strategy that may provide clues into the mechanisms of this condition, identify relevant interventions, and offer a means for tracking outcomes longitudinally.

Common pathophysiological mechanisms may explain the strong association between physical frailty and HF. One possible link is neurohormonal activation, such as increased sympathetic activation.[9] For example, we previously showed that physical frailty is

associated with decreased cardiac output and increased heart rate in HF.[10] In addition, inflammatory pathways are hypothesized to explain physical frailty in HF,[11] especially given their major role in HF.[12] Insulin resistance also has been postulated to play a role in HF,[13] and a few research studies have demonstrated links between insulin resistance and physical frailty.[14] Finally, skeletal muscle dysfunction and sarcopenia are considered components of physical frailty[15] and are often found in patients with HF (i.e. the skeletal muscle hypothesis).[16] Hence, we sought to identify biomarkers associated with physical frailty in HF using a candidate multimarker strategy that reflects multiple distinct pathophysiological processes, including neurohormonal activation, inflammation, insulin resistance, and skeletal muscle dysfunction. Secondarily, building on our previous finding of women being significantly more likely to be physically frail than men,[17] we explored sex differences in expression of these biomarkers in relation to physical frailty in HF.

## Methods

### Study Design and Sample

This was an observational cross-sectional study of adults with HF that was designed to quantify sex differences in physical frailty phenotypes in HF, as previously described.[17] Briefly, we collected data on clinical characteristics and symptoms, assessed physical frailty, measured parameters of body composition, and obtained fasting plasma samples for biomarker identification. Inclusion criteria were age 21 years or older, ability to read and comprehend 5$^{th}$ grade English, confirmed diagnosis of HF, and New York Heart Association (NYHA) functional classification I-IV. Exclusion criteria were documented major cognitive impairment (e.g. Alzheimer's disease) or active psychosis that would preclude study participation, prior heart transplantation or durable mechanical circulatory support, major and uncorrected hearing dysfunction, or were otherwise unable to complete the requirements of the study (e.g. life-threatening illness). Between May 2018 and February 2020, eligible patients from HF and general cardiology clinics at Oregon Health & Science University were screened and approached ($n$ = 202). Of these, 152 patients were consented and enrolled (exclusion reasons described previously[17]). Then, of these, 115 participated in study visits (non-completers described previously [17]), but two were unable to provide blood samples and excluded from this analysis providing a final analytic sample of $n$ = 113. This study was approved by the Institutional Review Board and adheres to the principles outlined in the Declaration of Helsinki,[18] and written informed consent was obtained from all participants.

### Measurement

**Sociodemographic and clinical data.—**Data on age, marital status, race, and education were collected using a sociodemographic questionnaire. We performed a medical record review to collect data on HF history, etiology, NYHA functional class, clinical and laboratory data, and treatment of HF. The Charlson Comorbidity Index[19] was used to summarize comorbid conditions. The Seattle HF Model (SHFM) 1-year projected survival was calculated based on the model developed by Levy et al; the model includes relevant clinical characteristics such as age, ejection fraction, lab values, medications, and other clinical parameters.[20]

**Physical frailty.—**Physical frailty was measured using the Frailty Phenotype Criteria.[3] Briefly, the criteria were as follows: 1) unintentional weight loss of > 10 pounds over the last year by self-report, 2) weakness of the lower extremities using 5-repeat chair stands, 3) slowness with gait speed assessed over 4 meters, 4) physical exhaustion, and 5) reduced physical activity by asking how much time was spent exercising over the past week.[10] After completing the measures for each of the 5 criteria, the scores were totaled (range 0 to 5). Each participant was then classified as either “non-physically frail” (i.e. “non-frail” [0 criteria met] or “pre-frail” [1-2 criteria met]) or “physically frail” (i.e. ≥ 3 criteria met).

**Body composition.—**Whole body composition was determined by dual energy x-ray absorptiometry (DXA) (Hologic-QDR Discovery Wi; APEX software, v.4.02). For this analysis, we used measured whole body percent fat and calculated appendicular lean mass by summing the bone-free lean mass for all 4 extremities.

**Biomarkers.—**Whole blood was collected from participants after fasting for 8 hours and abstaining from caffeine consumption and exercise prior to the blood draw. Blood samples were immediately placed on ice and transported to the university Research Core Lab. Plasma was aliquoted and immediately stored at −80°C until processing. Samples were thawed only once prior to completing the biomarker assays. Performance characteristics of each assay are listed in Supplemental Table 1.

**Neurohormonal activation.:** We measured plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) as a marker of neurohormonal activation, specifically related to myocardial stretch and hemodynamic congestion;[21] NT-proBNP plays an important role in HF prognostication.[22] Plasma NT-proBNP was measured using a chemilumenscent immunoassay on a Siemens Vista 1500 chemistry analyzer. Higher concentrations of NT-proBNP reflect more myocardial stretch and congestion. We also measured plasma norepinephrine (NE) and its main metabolite, 3,4-dihydroxyphenylglycol (DHPG) as markers of sympathetic dysfunction given heightened sympathetic activity in HF.[23] The catechols were separated by reversed-phase high performance liquid chromatography on C18 column (Agilent Microsorb, 150x4.6 mm, 5 μm) and measured by an electrochemical detector (Coulochem III; ESA, Bedford, MA) using an oxidation-reduction protocol (electrodes set to +300 mV, +150mV, and −350 mV), as described previously.[24] Higher concentrations of NE and DHPG reflect more sympathetic activation.

**Inflammation.:** We measured soluble tumor necrosis factor α receptor-1 (sTNFαR1) as a marker of systemic inflammation, a common feature of HF[12] that is posited as a link between HF and physical frailty.[11] sTNFαR1 was measured using an enzyme-linked immunosorbent assay (R&D Systems; Minneapolis, MN, USA). Higher concentrations of sTNFαR1 reflect more systemic inflammation. We measured adiponectin, a cytokine secreted from adipose tissue, as a marker of inflammation, fatty acid metabolism, and glucose regulation; it reflects a wasting, cachexic profile and increased mortality in HF.[25] Adiponectin was measured using a radioimmunoassay (EMD Millipore Corporation; St. Louis, MO, USA). Generally, lower adiponectin concentrations reflect increased

inflammation; however, in advanced HF, higher adiponectin concentrations are associated with worsening HF severity, cachexia, and increased mortality.[25]

**Insulin Resistance.:** We measured insulin and glucose as markers of insulin resistance, which is a predominant feature of HF pathophysiology.[13] Glucose was measured using a colorimetric assay (BioAssay Systems; Hayward, CA, USA). Insulin was measured using an enzyme-linked immunosorbent assay (Mercodia; Uppsala, Sweden). We also calculated homeostatic model of assessment-insulin resistance (HOMA-IR)[26] from fasting plasma glucose and insulin concentrations: HOMA-IR = (fasting glucose (mmol/L) x fasting insulin (μU/mL))/22.5.[27] Higher levels of HOMA-IR reflect increased insulin resistance.

**Skeletal muscle dysfunction.:** We measured insulin-like growth factor-1 (IGF-1) as a marker of catabolism using an enzyme-labeled chemiluminescent immunometric assay on an Immulite 1000 (Siemens Medical Solutions; Malvern, PA, USA). Decreased levels of IGF-1 reflect increased catabolism. We measured myostatin as a marker of skeletal muscle dysfunction, as HF can be characterized by marked alterations in skeletal muscle size and function,[28] using an enzyme-linked immunosorbent assay (Immundiagnostik AG; Bensheim, Germany). There is not a consensus on the implications of myostatin as it has been reported to be decreased and increased in both HF and frailty.[29,30]

## Statistical Analysis

Characteristics of the sample are presented using standard descriptive statistics, including measures of central tendency and dispersion. Due to the severe skewness of the biomarker data, we used a natural log transformation of the data to approximate normality. Comparative statistics (Student's *t*-, Mann-Whitney *U*, Fisher exact, or the Pearson $\chi^2$ tests) were used to determine significant differences in clinical characteristics and biomarkers between physically frail and non-physically frail adults with HF. Pairwise correlations with Bonferroni corrections were used to quantify relationships among biomarkers. Multivariate linear regression was used to quantify differences in the natural log of biomarkers between physical frailty groups (non-frailty as the referent group), adjusting for SHFM 1-year projected survival, Charlson Comorbidity Index, and sex in adjusted model 1 and adding in whole body percent fat and appendicular muscle mass in adjusted model 2. For the exploratory sex difference analysis, we used comparative statistics to quantify sex-stratified differences in biomarkers between physically frail and non-physically frail adults with HF, along with interaction testing. Effect sizes were also calculated using Hedge's *g* (0.20 = small effect; 0.50 = medium effect; 0.80 = large effect) and Spearman's rho. Significance was set at $\alpha < 0.05$. There was < 2% missing data for NE, DHPG, insulin, and myostatin; all other data and biomarkers were complete. We were missing DXA data on 7 participants, but there were no significant differences in sex, age, or physical frailty status between those with and without completed DXA scans. All analyses were performed using Stata/MP version 17MP (StataCorp, College Station, TX).

## Results

Characteristics of the sample ($n$ = 113), overall and stratified by level of physical frailty, are presented in Table 1. The average age of the patients was 63.5±15.7 years, 48% were women, and 84% were non-Hispanic Caucasian. Most participants were classified as HF with reduced ejection fraction and had non-ischemic etiologies. Physical frailty was identified in 42% of the sample with significant sex differences (27% of men and 59% of women were frail). Physically frail adults were more likely to have HF with preserved ejection fraction, more comorbidities, higher ejection fraction, higher body mass index, higher percent body fat, and lower hemoglobin. Plasma IGF-1 was significantly lower among those physically frail compared with those non-physically frail (Table 1; median: 67.9 ng/mL vs. 95.4 ng/mL, $p$ = 0.004). Plasma myostatin also was significantly lower among those physically frail compared with those non-physically frail (median: 2123 pg/mL vs. 2890 pg/mL, $p < 0.0001$).

Pairwise correlations among plasma biomarkers across the entire sample are presented in Table 2. There were a few moderately strong, significant correlations between biomarkers ($r$ = 0.30-0.54) but not much overlap, indicating that biomarkers are representing distinct physiological processes.

Unadjusted and adjusted differences in the natural log of biomarkers between physical frailty groups are shown in Table 3. In Model 1 (adjusting for SHFM score, comorbidities, and sex), plasma adiponectin, IGF-1, and myostatin were significantly lower among those physically frail compared with those non-physically frail. These results remained significant after adding in body composition metrics in Model 2. There were no significant differences in the other biomarkers. To further understand the IGF-1 and myostatin findings, we examined the relationship between these biomarkers and two physical performance criteria of frailty (slowness by gait speed and weakness by chair stands), adjusting for appendicular lean mass. Lower IGF-1 was significantly associated with meeting the slowness criterion (OR = 0.34, 95%CI 0.12-0.93, p = 0.036) but not weakness criterion (OR = 0.74, 95%CI 0.28-1.96, p = 0.54). Lower myostatin was significantly associated with meeting the slowness (OR = 0.18, 95%CI 0.05-0.58, p = 0.004) and weakness criteria (OR = 0.23, 95%CI 0.07-0.78, p = 0.017).

Since women were more likely to be physically frail, we explored biomarkers in sex-stratified analyses using traditional significance testing and calculating effect sizes (Table 4). Physically frail men had significantly lower IGF-1 and myostatin compared with non-physically frail men; whereas none of the biomarkers were significantly different between physically frail and non-physically frail women. However, there were no significant interactions by sex in the relationship between biomarker and physical frailty. Adjusting for SHFM score, comorbidities, and body composition metrics, for men, IGF-1 was no longer significant, but myostatin remained significant; for women, all results remained non-significant (*data not shown*).

## Discussion

In this study of 113 adults with HF, we preliminarily identified several candidate adipose tissue and skeletal muscle biomarkers associated with physical frailty in HF (Central Illustration). Specifically, plasma IGF-1, adiponectin, and myostatin were significantly lower among physically frail compared with non-physically frail adults with HF. Although the pathophysiology of physical frailty in HF has been suggested,[11,31] there is little evidence that pinpoints candidate biomarkers of this condition. The findings reported here suggest potential mechanisms underlying physical frailty in HF, which in turn may help drive targeted intervention development (e.g. self-care, exercise, nutrition interventions) and track outcomes for physically frail adults with HF.

We showed that IGF-1, an effector peptide of growth hormone that prevents skeletal muscle atrophy and other metabolic effects,[32] was significantly associated with physical frailty. It is well known that IGF-1 levels decline with age, and there is evidence that lower levels of IGF-1 are associated with frailty.[33] In HF, there is increasing interest in IGF-1 as a relevant biomarker associated with worsening HF, specifically linked to exercise intolerance and catabolism.[34] Our study builds on previous findings and shows that IGF-1 is a potential biomarker of physical frailty in HF. Impaired anabolic drive, as a result of inflammation and poor nutritional status,[32] could play a significant role in the development of physical frailty in HF and may be an important target for interventions.

We also showed that adiponectin, an adipokine that augments insulin sensitivity[35] and also has anti-inflammatory and anti-atherogenic properties, is significantly lower among those physically frail compared with those non-physically frail. Among individuals with obesity and diabetes, an association with reduced adiponectin could link adipose tissue function (typically size) with increased inflammation and decreased insulin sensitivity, both of which are linked with frailty.[14,35] However, findings are mixed on whether decreased or increased adiponectin levels are associated with frailty.[36,37] Furthermore, among adults with HF (particularly those with advanced HF), higher levels of adiponectin have been associated with higher mortality rates.[25] In the current study, our finding of lower adiponectin levels being associated with physical frailty may indicate a hypothetical mechanism in which increased inflammation, independent of percent body fat and other comorbidities (e.g., insulin resistance), may be playing a role.

In our participants, myostatin (a.k.a. growth-differentiation factor 8), a metabolic marker of skeletal muscle wasting, is also significantly associated with physical frailty. Evidence linking myostatin levels with frailty among older adults shows conflicting relationships.[30,33] For example, Arrieta et al. showed that myostatin levels are higher in fitter, more active older adults.[38] In HF, it is recognized that there are often significant skeletal muscle changes, including decreased skeletal muscle size and function, muscle atrophy, contractile dysfunction, and reduced oxidative capacity.[39] As such, skeletal muscle dysfunction may underpin some of the adverse functional capacity and symptoms in HF. Some studies have shown that myostatin is increased in HF,[40] possibly due to feedback loops to mitigate cardiac hypertrophy, which in turn depletes skeletal muscle. However, other studies have shown the opposite where HF is associated with decreased myostatin (compared with

controls), and decreased strength is associated with decreased myostatin.[29] In fact, it is thought that decreased myostatin may be in response to unfavorable metabolic conditions.[30] Since adjustment for appendicular lean mass did not change the results, two possible mechanistic hypotheses are: 1) low myostatin is the effect, and not the cause, of physical frailty, and 2) low myostatin reflects poor muscle quality given the association with the physical performance criteria.

Interestingly, we did not observe significant differences in NT-proBNP, NE and DHPG, sTNFαR1, insulin, glucose, or HOMA-IR between physically frail and non-physically frail adults with HF. We may not have observed a significant relationship between markers of neurohormonal dysfunction as this was a sample of HF patients who are likely optimized or closely optimized on guideline-directed medical therapy. Neurohormonal dysfunction may be uncovered as a contributor of physical frailty in HF if we had a control group of non-HF matched participants. Furthermore, this lack of a significant finding highlights the need to consider other systems beyond the heart in HF. The lack of a relationship between systemic inflammation and physical frailty in HF is interesting; perhaps our candidate marker of systemic inflammation was not specific enough to discern physical frailty compared with other studies.[14] Finally, despite finding associations between physical frailty and both type 2 diabetes and adiponectin, there was no significant relationship between biomarkers of insulin resistance and physical frailty, which could indicate that physical frailty in HF is the result of downstream effects of insulin resistance on skeletal muscle.

Given that female gender was a strong predictor of physical frailty overall (and in 4 out of 5 of the physical frailty criteria) in our previous findings [17], we conducted a secondary exploration of our candidate biomarkers in relation to physical frailty by sex. We found that myostatin and IGF-1 were only significant for discerning physical frailty in men but not women, although the directions of the effects were the same and there was not a significant biomarker by sex interaction. We were underpowered to quantify sex differences, and thus, we examined effect sizes to explore the findings, especially since the differences were in the expected directions for all biomarkers, and to provide a starting point for future larger studies.

There are limitations to this study. While we achieved sex balance, this was a relatively young, racially homogenous sample recruited from one single academic medical center in the Pacific Northwest, and these results may not be generalized to the entire HF population. Moreover, this was a sample comprised of mostly non-ischemic, HF with reduced ejection patients, which also limits the generalizability. Also, because this was an exploratory cross-sectional study, we are unable to determine any causal mechanisms, and we were potentially underpowered to detect significant differences; however, our findings provide a starting point for future larger and longitudinal studies. Finally, there are limitations to the use of DXA to quantify lean mass, which may have impacted the adjusted model.

Our findings point to the need for further research. First, given the nascent state of this area in HF and the exploratory nature of our investigation, it will be important to test and validate these targeted biomarkers in larger groups of patients, especially in ages across the lifespan, as well as expansion to included non-targeted approaches (e.g. omics-based

analyses). Additionally, once validated, causal pathways can be explored in relation to age, comorbidities, and HF pathogenesis, among others. Second, given the emerging findings linking adipose tissue and skeletal muscle structure and function to physical frailty, it would be helpful to elucidate changes in body composition in relation to these biomarkers. For example, future studies could use better methods to quantify muscle mass using such as D3-creatine dilution[41] and muscle density using computed tomography.[42] Third, sex differences in physical frailty phenotypes remain greatly understudied and our preliminary data suggest that the biological mechanisms underpinning physical frailty may be fundamentally different between women and men with HF. Finally, because this was an exploratory study, much work will need to be done before implementing biomarker analysis in clinical practice. Once validated, however, we envision that a multidisciplinary clinical team may be able to use these biomarkers and pathways to implement targeted strategies, such as self-care, exercise, and nutritional interventions, that mitigate physical frailty. Nurses would be particularly well-positioned to lead these efforts.

## Conclusions

We identified biomarkers involved in adipose tissue and skeletal muscle development, maintenance, and function that were significantly associated with physical frailty, independent of body composition. Physical frailty in HF may be, in part, underpinned by dysfunctional peripheral processes involving the adipose tissue and skeletal muscle. Future research should validate these biomarkers and identify causal pathways to elucidate the development of physical frailty in HF. With improved mechanistic understanding, we may have an opportunity to develop clinical interventions to mitigate the significant symptom burden and physical frailty in adults with HF using these biomarkers to quantify how patients are responding to interventions.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Data Availability Statement

Data are available on reasonable request to the corresponding author. Code also available upon request to the corresponding author.

## Abbreviations:

| | |
|---|---|
| **HF** | heart failure |
| **DHPG** | 3,4-dihydroxyphenylglycol |

| | |
|---|---|
| **HOMA-IR** | homeostatic model of assessment-insulin resistance |
| **IGF-1** | insulin-like growth factor-1 |
| **NE** | norepinephrine |
| **NT-proBNP** | N-terminal pro-B-type natriuretic peptide |
| **NYHA** | New York Heart Association |
| **SHFM** | Seattle Heart Failure Model |
| **sTNFαR1** | soluble tumor necrosis factor α receptor-1 |

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**Table 1.**

Characteristics of the sample and by level of physical frailty

| | Total ($n$ = 113) | Non-Physically Frail ($n$ = 65)* | Physically Frail ($n$ = 48) | $p$ value† |
|---|---|---|---|---|
| **Patient Characteristics** | | | | |
| Age (years) | 63.5±15.7 | 61.2±15.9 | 66.7±15.0 | 0.07 |
| Sex | | | | **0.001** |
| Women | 54 (48%) | 22 (34%) | 32 (67%) | |
| Men | 59 (52%) | 43 (66%) | 16 (33%) | |
| Non-Hispanic Caucasian | 95 (84%) | 54 (83%) | 41 (85%) | 0.73 |
| **Clinical Characteristics** | | | | |
| Body mass index (kg/m$^2$) | 31.3±8.3 | 29.5±7.1 | 33.6±9.1 | **0.012** |
| Charlson Comorbidity Index (weighted) | 3.2±2.0 | 2.8±1.7 | 3.8±2.1 | **0.018** |
| Atrial fibrillation | | | | 0.28 |
| Yes | 54 (48%) | 28 (43%) | 26 (54%) | |
| No | 59 (52%) | 37 (57%) | 22 (46%) | |
| Stage 3 chronic kidney disease | | | | **0.039** |
| Yes | 31 (27%) | 13 (20%) | 18 (38%) | |
| No | 82 (73%) | 52 (80%) | 30 (63%) | |
| Type 2 diabetes | | | | **0.001** |
| Yes | 46 (41%) | 18 (28%) | 28 (58%) | |
| No | 67 (59%) | 47 (72%) | 20 (42%) | |
| % body fat | 37.8±8.8 | 35.4±8.7 | 41.2±7.8 | **0.001** |
| Appendicular lean mass (kg) | 22.3±6.2 | 23.1±6.5 | 21.1±5.6 | 0.09 |
| **Heart Failure Characteristics** | | | | |
| Time with heart failure (years) | 3.5 [1.4-7.2] | 4.0 [1.8-8.4] | 3.0 [1.2-5.4] | 0.14 |
| New York Heart Association functional class | | | | 0.11 |
| Functional class I/II | 57 (50%) | 37 (57%) | 20 (42%) | |
| Functional class III/IV | 56 (50%) | 28 (43%) | 28 (58%) | |
| Etiology | | | | 0.75 |
| Ischemic | 30 (27%) | 18 (28%) | 12 (25%) | |
| Non-ischemic | 83 (73%) | 47 (72%) | 36 (75%) | |

| | Total ($n$ = 113) | Non-Physically Frail ($n$ = 65)* | Physically Frail ($n$ = 48) | $p$ value† |
|---|---|---|---|---|
| Heart failure type‡ | | | | **0.003** |
| Heart failure with reduced ejection fraction | 80 (71%) | 53 (82%) | 27 (56%) | |
| Heart failure with preserved ejection fraction | 33 (29%) | 12 (18%) | 21 (44%) | |
| Left ventricular end-diastolic diameter (cm) | 5.4±1.0 | 5.4±1.0 | 5.3±1.0 | 0.33 |
| Left ventricular ejection fraction (%) | 43.0±16.0 | 40.0±15.3 | 47.1±16.1 | **0.020** |
| Serum sodium (mEq/L) | 138.5±3.0 | 138.7±3.3 | 138.3±2.5 | 0.51 |
| Serum hemoglobin (g/dL) | 13.3±3.6 | 13.8±4.3 | 12.5±2.0 | **0.031** |
| Serum BUN:Creatinine ratio | 21.4±7.7 | 21.2±8.1 | 21.6±7.0 | 0.77 |
| Prescribed a β-blocker | | | | 0.08 |
| Yes | 97 (86%) | 59 (91%) | 38 (79%) | |
| No | 16 (14%) | 6 (9%) | 10 (21%) | |
| Prescribed an angiotensin-converting enzyme-inhibitor or angiotensin II receptor blocker | | | | **0.002** |
| Yes | 81 (72%) | 54 (83%) | 27 (56%) | |
| No | 32 (28%) | 11 (17%) | 21 (44%) | |
| Prescribed an aldosterone antagonist | | | | 0.16 |
| Yes | 51 (45%) | 33 (51%) | 18 (38%) | |
| No | 62 (55%) | 32 (49%) | 30 (63%) | |
| SHFM one year projected survival (%) | 96 [89-97] | 96 [92-98] | 92 [87-97] | **0.014** |
| **Biomarkers** | | | | |
| lnNT-proBNP (pg/mL) | 6.18±1.51 | 6.13±1.39 | 6.26±1.67 | 0.67 |
| lnNE (pmol/mL) | 1.42±0.58 | 1.39±0.59 | 1.46±0.57 | 0.49 |
| lnDHPG (pmol/mL) | 2.67±0.35 | 2.69±0.37 | 2.65±0.32 | 0.47 |
| lnNE:lnDHPG Ratio | 0.53±0.23 | 0.52±0.22 | 0.56±0.23 | 0.35 |
| lnsTNFαR1 (pg/mL) | 0.97±0.29 | 0.94±0.30 | 1.00±0.26 | 0.23 |
| lnAdiponectin (ug/mL) | 2.49±0.75 | 2.58±0.70 | 2.37±0.79 | 0.15 |
| lnGlucose (mg/dL) | 7.75±0.31 | 4.72±0.32 | 4.78±0.28 | 0.33 |
| lnInsulin (mU/L) | 2.27±0.88 | 2.18±0.83 | 2.39±0.94 | 0.21 |
| HOMA-IR | 2.4 [1.3-5.5] | 2.1 [1.3-4.7] | 2.9 [1.4-9.1] | 0.23 |
| lnIGF-1 (ng/mL) | 4.39±0.44 | 4.49±0.44 | 4.27±0.41 | **0.008** |
| lnMyostatin (pg/mL) | 7.80±0.45 | 7.94±0.43 | 7.60±0.40 | **<0.0001** |

Mean±SD, N (%), or Median [IQR]

[*] Non-physically frail includes both non-frail ($n$ = 10) and pre-frail ($n$ = 55)

[†] p values comparing physically frail versus non-physically frail

[‡] Heart failure with reduced ejection fraction was defined as left ventricular ejection fraction <40% and heart failure with preserved ejection fraction was defined as left ventricular ejection fraction >50% on initial presentation at diagnosis. Midrange ejection fraction (40-50%) was adjudicated by attending cardiologist to determine most appropriate phenotype based on clinical characteristics.

*Abbreviations:* BUN, blood urea nitrogen; DHPG, dihydroxyphenylglycol; HOMA-IR, homeostatic model of assessment-insulin resistance; IGF-1, insulin-like growth factor 1; ln, natural log; NE, norepinephrine; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SHFM, Seattle Heart Failure Model; sST2, soluble suppressor of tumorigenicity-2; sTNFαR1, soluble tumor necrosis factor α receptor-1.

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**Table 2:**

Linear relationships among candidate biomarkers*

| | NT-proBNP | NE | DHPG | sTNFαR1 | Adiponectin | Glucose | Insulin | IGF-1 |
|---|---|---|---|---|---|---|---|---|
| **NE** | 0.241 | | | | | | | |
| **DHPG** | 0.198 | **0.304**† | | | | | | |
| **sTNFαR1** | 0.236 | 0.144 | −0.133 | | | | | |
| **Adiponectin** | **0.538**† | 0.204 | 0.273 | 0.105 | | | | |
| **Glucose** | −0.062 | −0.148 | −0.169 | 0.260 | −0.292 | | | |
| **Insulin** | −0.274 | −0.134 | −0.235 | 0.150 | **−0.533**† | 0.529† | | |
| **IGF-1** | −0.077 | −0.099 | 0.069 | **−0.314**† | −0.046 | −0.099 | 0.031 | |
| **Myostatin** | −0.114 | 0.046 | **0.364**† | −0.280 | 0.043 | −0.038 | −0.044 | −0.119 |

*natural log of biomarkers

†$p < 0.05$

*Abbreviations:* DHPG, dihydroxyphenylglycol; IGF-1, insulin-like growth factor 1; NE, norepinephrine; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sTNFαR1, soluble tumor necrosis factor α receptor-1.

**Table 3:**

Unadjusted and adjusted differences in candidate biomarkers between levels of physical frailty

| | Unadjusted* | | Model 1 Adjustment*† | | Model 2 Adjustment*‡ | |
|---|---|---|---|---|---|---|
| | β±SE | *p* value | β±SE | *p* value | β±SE | *p* value |
| lnNT-proBNP (pg/mL) | 0.12±0.29 | 0.66 | −0.09±0.28 | 0.75 | 0.27±0.26 | 0.31 |
| lnNE:lnDHPG ratio | 0.04±0.04 | 0.35 | 0.02±0.05 | 0.72 | 0.00±0.05 | 0.94 |
| lnsTNFαR1 (pg/mL) | 0.06±0.05 | 0.24 | −0.02±0.06 | 0.74 | −0.03±0.06 | 0.56 |
| lnAdiponectin (ug/mL) | −0.21±0.14 | 0.14 | −0.42±0.14 | **0.003** | −0.28±0.14 | **0.047** |
| lnInsulin (mU/dL) | 0.22±0.17 | 0.20 | 0.19±0.18 | 0.31 | −0.18±0.15 | 0.25 |
| lnGlucose (mg/dL) | 0.06±0.06 | 0.34 | 0.05±0.06 | 0.41 | −0.02±0.07 | 0.81 |
| HOMA-IR | 1.47±1.14 | 0.20 | 1.37±1.26 | 0.28 | −0.91±1.08 | 0.40 |
| lnIGF-1 (ng/mL) | −0.22±0.09 | **0.008** | −0.20±0.09 | **0.023** | −0.21±0.10 | **0.032** |
| lnMyostatin (pg/mL) | −0.35±0.08 | **<0.001** | −0.20±0.08 | **0.014** | −0.22±0.09 | **0.011** |

*Slope coefficient for physically frail participants (versus non-physically frail)

†Adjusting for Seattle Heart Failure Model 1-year survival score (a composite of clinical variables and heart failure treatments), Charlson Comorbidity Index, and sex

‡Adjusting for Seattle Heart Failure Model 1-year survival score (a composite of clinical variables and heart failure treatments), Charlson Comorbidity Index, sex, appendicular lean mass, and total % body fat

*Abbreviations*: DHPG, dihydroxyphenylglycol; IGF-1, insulin-like growth factor 1; ln, natural log; NE, norepinephrine; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SE, standard error sTNFαR1, soluble tumor necrosis factor α receptor-1.

**Table 4.**

Candidate biomarkers of physical frailty by sex

| | Women | | | | Men | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Non-Physically Frail (*n* = 22)** | **Physically Frail (*n* = 32)** | ***p* value** | **Effect size** | **Non-Physically Frail (*n* = 43)** | **Physically Frail (*n* = 16)** | ***p* value** | **Effect Size** | **Interaction *p* value** |
| lnNT-proBNP (pg/mL) | 6.05±1.44 | 6.08±1.58 | 0.96 | 0.02 | 6.17±1.38 | 6.61±1.83 | 0.39 | 0.29 | 0.49 |
| lnNE:lnDHPG ratio | 0.55±0.26 | 0.54±0.22 | 0.88 | 0.04 | 0.50±0.21 | 0.59±0.24 | 0.19 | 0.41 | 0.26 |
| lnsTNFαR1 (pg/mL) | 0.98±0.26 | 1.01±0.27 | 0.74 | 0.11 | 0.92±0.32 | 1.00±0.25 | 0.33 | 0.26 | 0.64 |
| lnAdiponectin (ug/mL) | 2.75±0.56 | 2.44±0.69 | 0.08 | 0.48 | 2.49±0.76 | 2.22±0.98 | 0.33 | 0.32 | 0.91 |
| lnInsulin (mU/dL) | 2.32±0.71 | 2.38±0.91 | 0.76 | 0.07 | 2.10±0.88 | 2.41±1.04 | 0.30 | 0.33 | 0.50 |
| lnGlucose (mg/dL) | 4.67±0.28 | 4.77±0.30 | 0.22 | 0.34 | 4.75±0.34 | 4.80±0.24 | 0.53 | 0.16 | 0.70 |
| HOMA-IR | 2.4 [1.3-4.1] | 2.9 [1.4-8.3] | 0.62 | 0.07 | 2.1 [1.3-5.0] | 2.9 [1.4-9.4] | 0.31 | 0.14 | 0.86 |
| lnIGF-1 (ng/mL) | 4.47±0.43 | 4.33±0.45 | 0.24 | 0.31 | 4.49±0.44 | 4.15±0.31 | **0.002** | 0.82 | 0.24 |
| lnMyostatin (pg/mL) | 7.74±0.51 | 7.54±0.43 | 0.13 | 0.42 | 8.05±0.33 | 7.72±0.29 | **0.001** | 1.02 | 0.45 |

Mean±SD or Median [IQR]

*Abbreviations*: DHPG, dihydroxyphenylglycol; IGF-1, insulin-like growth factor 1; ln, natural log; NE, norepinephrine; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SE, standard error sTNFαR1, soluble tumor necrosis factor α receptor-1.