Clinical Investigation

Lower Extremity Function Is Independently Associated With Hospitalization Burden in Heart Failure With Preserved Ejection Fraction

WHITNEY E. HORNSBY, PHD,[1,2] MOHAMED-ALI SAREINI, BS,[1,2] JESSICA R. GOLBUS, MD,[1,2] CRISTEN J. WILLER, PHD,[1,2,3,4] JENNIFER L. MCNAMARA, MS,[1,2] MATTHEW C. KONERMAN, MD,[1,2] AND SCOTT L. HUMMEL, MD, MS[1,2,5]

Ann Arbor, Michigan

ABSTRACT

Background: Frailty reflects decreased resilience to physiological stressors; its prevalence and prognosis are not fully defined in heart failure with preserved ejection fraction (HFpEF).

Methods: The Short Physical Performance Battery (SPPB) was prospectively obtained in 114 outpatients with HFpEF. The SPPB tests gait speed, tandem balance, and timed chair rises, each scored from 0 to 4 points. Severe and mild frailty were respectively defined as an SPPB score ≤6 and 7−9 points. We used risk-adjusted logistic, Poisson, and negative binominal regression, respectively, to assess the relationship between SPPB score and risk of death or all-cause hospitalization, number of hospitalizations, and days hospitalized or dead longer than 6 months.

Results: Patients were similar to other HFpEF cohorts (age 68 ± 13 years, 58% female, body mass index 36 ± 8 kg/m^2, multiple comorbidities). Mean SPPB score was 6.9 ± 3.2, and 80% of patients were at least mildly frail. Over a 6-month period, the SPPB score independently predicted death or all-cause hospitalization (odds ratio 0.81 per point, 95% confidence interval [CI] 0.69−0.94, $P = .006$), number of hospitalizations (incidence rate ratio 0.92 per point, 95% CI 0.86−0.97, $P = .006$), and days hospitalized or dead (incidence rate ratio 0.85 per point, 95% CI 0.73−0.99, $P = .04$).

Conclusions: Lower extremity function, as measured by the SPPB, independently predicts hospitalization burden in outpatients with HFpEF. Additional studies are warranted to explore shared mechanisms and treatment implications of frailty in HFpEF. (*J Cardiac Fail 2019;25:2−9*)

Key Words: Elderly, diastolic heart failure, older adults, hospitalization, frailty.

Heart failure with preserved ejection fraction (HFpEF) has reached epidemic proportions in the developed world and now represents approximately half of heart failure (HF) cases. Patients with HFpEF are typically older adults who have multiple additional comorbid illnesses. As the population ages and associated comorbidities become more common, the prevalence of HFpEF is expected to rise sharply in the years ahead.[1] Unfortunately, outcomes remain poor despite multiple large clinical trials of well-reasoned cardiovascular therapies, possibly because many deaths and hospitalizations in patients with HFpEF are noncardiovascular.[2] The cardinal manifestation of HFpEF is exercise intolerance, but not all exertional limitations in patients with HFpEF relate to cardiac dysfunction.[3]

The geriatric syndrome of frailty is broadly defined as decreased resilience and ability to compensate for physiological stressors. The presence of physical frailty markedly

increases adverse event rates after complex cardiovascular procedures that are often performed in older patients with multimorbid illness, such as transcatheter aortic valve replacement[4] and left ventricular assist devices.[5] In unselected older hospitalized patients with HF, frailty increases the risk of functional decline, readmission, and death.[6] Moderate-intensity aerobic exercise is the primary modality with the potential to reverse the frailty syndrome[7] and appears particularly beneficial in patients with HFpEF.[8–10]

We sought to prospectively define the prevalence and prognostic implications of frailty in a cohort of patients referred to an academic center's HFpEF clinic. We performed the Short Physical Performance Battery (SPPB), which assesses gait speed, balance, and leg muscle strength to provide a multidomain measure of lower extremity function. Low SPPB scores signify frailty and are associated with risk of functional decline, hospital admission, and death in community-dwelling older adults,[11] as well as in those after acute-care hospitalization.[12] We hypothesized that baseline SPPB scores would independently predict the combined risk of hospitalization and death and overall hospitalization burden over the subsequent 6 months in outpatients with HFpEF.

Methods

Study Design and Population

The Cardiovascular Health Improvement Project (CHIP) Biorepository is a longitudinal observational cohort study of patients at the University of Michigan with a clinical diagnosis of cardiovascular disease (predominantly, thoracic/abdominal aortic disease or HF). We enrolled participants into the CHIP Biorepository cohort who presented for evaluation in a speciality HFpEF clinic between February 2016 and June 2017. All study participants signed informed consent and were prospectively followed up for at least 6 months. The University of Michigan's institutional review board approved this protocol (HUM00128472).

The diagnosis of HFpEF was confirmed by the treating cardiologist and primarily followed the criteria established by the 2016 European Society of Cardiology guidelines, which includesymptoms and signs of HF, left ventricular ejection fraction ≥50%, signs and symptoms of HF, at least mild elevation in natriuretic peptide levels, and cardiac structural (eg, left atrial enlargement) or functional abnormalities (eg, diastolic dysfunction) associated with HfpEF.[13] Participants could also be diagnosed with HFpEF after hospitalization for decompensated HF requiring intravenous diuresis or if increased left ventricular filling pressures were documented on catheterization, regardless of the natriuretic peptide level.

Lower Extremity Functional Assessment

Lower extremity function was assessed by the SPPB, which evaluates the frailty domains of slowness, weakness, and balance impairment through a series of 3 timed physical performance tests (gait speed, chair rises, and tandem balance). Each test is scored from 1 to 4, representing approximate quartiles based on specific cut-points described in the following (Table 1), although a 0 score indicates "unable to perform" for 1 of the these reasons: (1) those who tried but were unable; (2) the interviewer or subject felt it was unsafe; or (3) for other health issues, such as pain or orthopedic limitation.[14] The SPPB has been shown to be reliable, valid, and sensitive to change. Intraclass correlation coefficients range from .88 to .92 for measures made 1 week apart, with a 6-month average correlation coefficient of .78.[15] For this analysis, a total composite SPPB score ≤6, which represents a population at high risk for progressive disability,[11] was used to define severe frailty, and an SPPB score between 7 and 9 points denoted mild frailty.[16]

Demographics, Clinical Variables, and Outcomes

Clinical and demographic variables recorded include age, self-reported race, sex, body mass index, blood urea

Table 1. Short Physical Performance Battery

SPPB Components	Operational Definition	Scoring
5-m gait speed test	Patient is instructed to walk at a comfortable pace for 5 m; cue to trigger stopwatch is first footfall after start line and first footfall after finish line; repeated 3 times and averaged.	0 = Unable to perform 1 = ≥11.6 s (≤0.43 m/s) 2 = 8.3−11.5 s (0.44−0.60 m/s) 3 = 6.5−8.2 s (0.61−0.77 m/s) 4 = ≤6.4 s (≥0.78 m/s)
Chair rise test	Patient is seated on a straight-backed chair and asked to stand up 5 times as quickly as possible with arms folded across chest; time to complete 5 chair rises is recorded (cue to stop stopwatch is when patient is standing after fifth chair rise).	0 = Unable to perform 1 = ≥16.7 s 2 = 13.7−16.6 s 3 = 11.2−13.6 s 4 = ≤11.1 s
Balance test	Patient is asked to stand in a semitandem position for 10 seconds; if patient is able, then he/she is asked to stand in full tandem position for 10 seconds; if patient is not able, then he/she is asked to stand in side-by-side position for 10 seconds.	0 = Side by side 0−9 s or unable to perform 1 = Side by side 10 s 2 = Full tandem 0−2 s 3 = Full tandem 3−9 s 4 = Full tandem 10 s
SPPB composite score		≥10 = Nonfrail 7−9 = Mild frailty present ≤6 = Severe frailty present

BMI, body mass index; SPPB, Short Physical Performance Battery.

nitrogen, estimated glomerular filtration rate (calculated with the Modification of Diet in Renal Disease equation), B-type natriuretic peptide, left ventricular ejection fraction, the most recently assessed New York Heart Association (NYHA) functional class, and the dates of previous all-cause medical hospitalizations. Data were also collected on comorbid conditions including hypertension, diabetes mellitus, dyslipidemia, obesity, coronary artery disease, stroke/transient ischemic attack, atrial arrhythmias, chronic obstructive pulmonary disease, and sleep apnea. These data were obtained from the CHIP Biorespository REDCap database[17] and from electronic medical record review.

All-cause medical hospitalizations and length of hospital stays at the University of Michigan are tracked automatically through the electronic medical record, Admissions at outside hospitals were manually obtained through chart review of office visits with providers, through review of electronic medical records available remotely from other local hospitals, and through review of HF telemangement nurse calls. Dates of death are obtained from periodic queries of the Social Security Death Index, supplemented by information gained from electronic medical record review and HF telemanagement nurse calls. All patients not listed as having died by these methods were confirmed alive at 6 months of follow-up. Previous work by our group suggests these methods miss few outcomes in our HF clinic population.[18] All hospitalizations were directly reviewed by a cardiologist (J.R.G. or M.C.K,) blinded to frailty data, to attribute the hospitalization to HF, other cardiovascular illness, or noncardiovascular cause.

Heart Failure Patient Severity Index

The Heart Failure Patient Severity Index (HFPSI) was developed within the University of Michigan's HF subspecialty population and validated in the Ann Arbor Veterans Affairs Health System HF clinic. In brief, the HFPSI uses known prognostic factors, including biomarkers, functional status, comorbidities, and recent clinical course, to predict the risk of all-cause hospitalization or death in outpatients with HF over the next 6 months.[18] The variables comprising the HFPSI include blood urea nitrogen; B-type natriuretic peptide; NYHA class; the presence of diabetes or atrial arrhythmias; and prior all-cause hospitalizations, the strongest predictor of hospital admission in patients with HF. A simple integer score effectively divides patients with HF into 4 risk strata.[19] For this analysis, we calculated the HFPSI score using data available at the time of SPPB assessment in the HFpEF clinic (Supplementary Table S3 provides a score calculation). The HFPSI score groups 1−4 were used to risk-adjust the relationship between SPPB score and the study primary outcome of all-cause hospitalization or death.

Statistical Analysis

Demographics and clinical characteristics were compared between frail and nonfrail participants using an unpaired t test or chi-square test, as appropriate. Univariable and multivariable logistic regression was used to evaluate the odds ratio for all-cause hospitalization or death at 180 days of follow-up. Exploratory analyses were performed to evaluate the relationship between the primary outcome and the individual HFPSI and SPPB components. A sensitivity analysis was also performed adding age and number of comorbid conditions to the model containing HFPSI group and SPPB score. C-statistics, reflecting the area under the receiver-operating curve, were used to describe model discrimination. A categorical net reclassification index, using risk cutoffs for death or all-cause hospitalization of 10%, 40%, and 70%, as well as an integrated discrimination index, were calculated.

Univariable and multivariable Poisson regression was used to obtain the incidence rate ratio for total number of all-cause hospitalizations. Poisson models were adjusted for the offset factor of log-transformed days alive (of 180) to include patients who died during the follow-up period. Owing to overdispersion of count data, univariable and multivariable negative binomial regression was used to obtain the incidence rate ratio for days hospitalized or dead (of 180 follow-up days).

Results

Study Population

A total of 122 patients with HFpEF were enrolled in the CHIP program during the study interval; 116 agreed to SPPB testing, and 114 of these participants had at least 6 months of clinical follow-up after baseline evaluation. This latter group forms the cohort for this analysis. Details regarding demographics, comorbidities, risk stratification, and frailty are provided in Tables 2 and 3. In general, as in other cohorts,[20,21] patients with HFpEF were older adults, more commonly female than male, and had multiple comorbid conditions, most commonly obesity and systemic hypertension.

Association Between Frailty and Risk

The mean SPPB score across the cohort as a whole was 6.9 ± 3.2 points; 39 of 114 (34%) were severely frail, as defined by an SPPB score ≤6 points,[11] and 53 of 114 (46%) had an SPPB score ≤9 points, the threshold that defines frailty in community-dwelling older adults.[16] Frail patients were more likely than nonfrail patients to have been recently hospitalized and to have poor functional status as reflected by provider-assigned NYHA class and hence more commonly had a high-risk HFPSI score (Table 3).

Association Between SPPB and Death or All-Cause Hospitalization

Over 6 months of follow-up, 6 (5%) patients died and 44 (39%) died or had at least 1 unplanned all-cause hospitalization. As a whole, the cohort had 94 all-cause hospitalizations, of which 38 were primarily for cardiovascular causes

Table 2. Demographics and Comorbidities

Variables	All Patients	Severely Frail*N = 39 (34%)	Mildly FrailN = 53 (46%)	NonfrailN = 22 (19%)	P Value
Age (y)	68 ± 13	72 ± 13	67 ± 12	64 ± 13	.05
Male (% yes)	48 (42)	14 (36)	22 (42)	12 (55)	.36
Race (% Caucasian)	100 (88)	35 (90)	44 (83)	21 (95)	.59
BMI (kg/m^2)	36 ± 8	37 ± 8	35 ± 8	35 ± 9	.45
Comorbid conditions					
Hypertension	92 (81)	32 (82)	40 (75)	20 (91)	.29
Diabetes mellitus	52 (46)	18 (46)	26 (49)	8 (36)	.60
Obesity	86 (75)	31 (79)	41 (77)	14 (64)	.35
Coronary artery disease	41 (36)	16 (41)	20 (38)	5 (23)	.34
Dyslipidemia	76 (67)	29 (74)	35 (66)	12 (55)	.29
Obstructive sleep apnea	69 (61)	26 (67)	30 (57)	13 (59)	.61
Atrial arrhythmias	55 (48)	24 (62)	22 (42)	9 (41)	.12
Chronic kidney disease	47 (41)	18 (46)	21 (40)	8 (36)	.72
COPD	33 (29)	15 (39)	14 (26)	4 (18)	.21
Stroke/TIA	14 (12)	8 (21)	4 (8)	2 (9)	.15
Total comorbidities	4.8 ± 2.1	5.5 ± 2.2	4.6 ± 2.0	4.1 ± 2.1	.03
Total medications	14 ± 7	17 ± 7	14 ± 6	11 ± 5	.003

Data are presented as mean ± standard deviation for continuous and n (% yes) for categorical variables.

BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; COPD, Chronic obstructive pulmonary disease; TIA, transient ischemic attack; other abbreviations as in Table 1.

*Severe frailty: SPPB ≤6 points; mild frailty: SPPB 7−9 points; nonfrail: SPPB ≥10 points.

(including HF) and 33 for HF specifically. The HFPSI group and the SPPB score were each significantly associated with the primary outcome on a univariable basis. Independent of the HFPSI group, the SPPB score was significantly associated with the primary outcome, occurrence of death or all-cause hospitalization at 6 months (Table 4).

The C-statistic for death or all-cause hospitalization was 0.77 for the HFPSI group as a single variable, with similar discrimination for HF and noncardiovascular hospitalizations. The C-statistic increased to 0.82 when the SPPB score was added to the HFPSI group, with 3-category net reclassification of 23% (P =.04) and integrated discrimination improvement of 6% (P = .02).[22] The SPPB score was also independently associated with the total number of days hospitalized or dead and the number of all-cause hospitalizations over the same 6-month period (Table 4).

In exploratory analyses, the SPPB remained an independent predictor when the individual components of the HFPSI were each analyzed separately. When considering the individual components of the SPPB, gait speed and chair rise time also were independently associated with

Table 3. Associations Between Frailty and Risk

Variables	All Patients	Severely Frail*N = 39 (34%)	Mildly FrailN = 53 (46%)	NonfrailN = 22 (19%)	P Value
Gait speed (m/s)[†]	0.85 ± 0.25	0.61 ± 0.18	0.86 ± 0.23	1.03 ± 0.17	<.001
Chair rise time (s)[†]	17.0 ± 5.5	21.4 ± 9.0	17.2 ± 3.4	13.2 ± 2.2	<.001
Balance test (points)[†]	2.9 ± 1.3	1.6 ± 1.3	3.4 ± 0.8	3.8 ± 0.4	<.001
SPPB score (points)	6.9 ± 3.2	3.2 ± 2.5	8.2 ± 0.8	10.5 ± 0.8	<.001
NYHA class					<.001
1	7 (6)	0	4 (8)	3 (14)	
2	39 (34)	6 (15)	20 (38)	13 (59)	
3	63 (55)	28 (72)	29 (55)	6 (27)	
4	5 (4)	5 (13)	0	0	
BNP (pg/mL)	109 (56-259)	141 (65-274)	108 (40-246)	87 (54-153)	.33[§]
BUN	29 ± 14	32 ± 14	27 ± 13	26 ± 15	.11
Atrial arrhythmias	55 (48)	24 (62)	22 (42)	9 (41)	.12
Diabetes mellitus	52 (46)	18 (46)	26 (49)	8 (36)	.60
Prior hospitalization					
Within 1 mo	22 (19)	13 (33)	7 (13)	2 (9)	.02
Within 2−6 mo	55 (48)	28 (72)	20 (38)	7 (32)	.001
HFPSI risk group					<.001
1	18 (25)	2 (5)	11 (21)	10 (45)	
2	17 (24)	8 (21)	22 (42)	3 (14)	
3	23 (32)	12 (31)	12 (23)	7 (32)	
4	13 (18)	17(44)	8 (15)	2 (9)	

HFPSI, Heart Failure Patient Severity Index; NYHA, New York Heart Association; other abbreviations as in Tables 1 and 2.

*Severe frailty: SPPB ≤6 points; mild frailty: SPPB 7−9 points; nonfrail: SPPB ≥10 points.

[†]In patients able to perform test; total numbers of patients unable: 19 (gait speed), 13 (balance), 23 (chair rises).

[§]Statistical comparison based on log-transformed values.

Table 4. Prediction of Death or All-Cause Hospitalization at 180 Days

Variables	Logistic Regression (death or all-cause hospitalization)				Negative Binomial Regression (days hospitalized or dead)				Poisson Regression (no. of all-cause hospitalizations)*			
	Univariable OR (95% CI)	P Value	Multivariable OR (95% CI)	P	Univariable IRR (95% CI)	P Value	Multivariable IRR (95% CI)	P	Univariable IRR (95% CI)	P Value	Multivariable IRR (95% CI)	P Value
HFPSI Risk Group	1 (reference)		1 (reference)		1 (reference)		1 (reference)		1 (reference)		1 (reference)	
2	0.32 (0.08–1.24)	.10	0.18 (0.04–0.79)	.02	0.27 (0.08–1.24)	.06	0.19 (0.05–0.73)	.04	0.26 (0.10–0.68)	.005	0.21 (0.08–0.55)	.001
3	1.44 (0.46–4.54)	.53	0.84 (0.24–2.92)	.78	1.45 (0.39–5.45)	.58	1.48 (0.41–5.35)	.55	1.72 (0.95–3.08)	.07	1.33 (0.72–2.48)	.37
4	8.0 (2.25–28.48)	.001	3.89 (0.99–15.23)	.051	9.77 (2.52–37.84)	.001	6.63 (1.26–21.13)	.02	2.17 (1.21–3.91)	.01	1.54 (0.81–2.94)	.18
SPPB† total score	0.78 (0.69–0.90)	<.001	0.81 (0.69–0.94)	.006	0.76 (0.64–0.91)	.003	0.85 (0.73–0.99)	.04	0.90 (0.85–0.95)	<.001	0.92 (0.86–0.97)	.006

CI, confidence interval; IRR, incidence rate ratio; OR, odds ratio; other abbreviations as in Tables 1 and 3.
*Adjusted for offset factor: log (days surviving of 180).
†ORs and IRRs (46) are per 1-unit change in the SPPB total score. Multivariable models include the SPPB score and HFPSI categories.

death or all-cause hospitalization, and the balance test score trended toward significance ($P = .06$). The SPPB remained an independent predictor of the primary outcome when adjusted by HFPSI group, age, and the number of comorbid illnesses (odds ratio 0.79, 95% confidence interval 0.66−0.93, $P = .006$; C-statistic 0.85 for the full model). When the 22 patients who had been discharged from the hospital within the 30 days before frailty assessment were removed from the cohort, the SPPB remained independently associated with the primary outcome (odds ratio 0.79, 95% confidence interval 0.66−0.92, $P = .004$; C-statistic 0.79).

Discussion

The principal finding of this study is that in outpatients referred for evaluation of HFpEF, the baseline SPPB score was independently associated with all-cause hospitalization or death over the subsequent 6 months. In addition, the SPPB independently predicted the overall burden of adverse events, as evidenced by both the number of all-cause hosptializations and total days dead or hospitalized over this time frame. Our findings extend prior work highlighting the high prevalence and poor prognosis of frailty among older adults with cardiovascular disease.[14,23,24]

To our knowledge, this is the first study to describe the prognostic implications of the SPPB in outpatients with HFpEF. Based on the SPPB score, 80% of this HFpEF cohort was frail when compared with healthy community-dwelling older adults,[16] and 34% were severely frail.[11] The SPPB score overlapped significantly with other important predictors of adverse outcome in HF, including worsened NYHA class and previous hospitalizations,[19] yet provided prognostic information separate from these factors. The SPPB scores were lower than previously reported in HFpEF by Reeves et al,[25] but patients with any recent hospitalizations were excluded from that analysis. Frailty may be initiated or worsened by hospitalization[26], but importantly in the present study, the SPPB remained predictive in patients who had not been hospitalized in the previous month.

A recent meta-analysis of 17 studies ($n = 16,534$, mean age 76 ± 3 years) with the SPPB used as a measure of frailty reported that a score ≤9 predicted increased all-cause mortality.[27] Volpato et al[12] evaluated the SPPB at hospital admission, discharge, and 1 month after discharge in patients aged ≥65 years admitted for HF, pneumonia, and chronic obstructive pulmonary disease. Patients with low SPPB scores at hospital discharge (0−4) had more than 5 times greater risk of rehospitalization or death compared with those with higher SPPB scores, independent of comorbidities and self-reported functional status. Our findings are also consistent with a recent study by Pulignano et al,[28] who reported that reduced gait speed was independently associated with death, hospitalization for HF, and all-cause hospitalization.

In community-dwelling older adults, frailty is associated with cardiovascular dysfunction that predicts incident

HFpEF,[29] suggesting that there may be common underlying mechanisms. In addition, patients with HFpEF often have multiple proinflammatory noncardiac illnesses that promote frailty,[30,31] and noncardiac hospitalizations are more common in HFpEF than in HF with reduced ejection fraction.[32] When compared with healthy older adults, several abnormalities of skeletal muscle are present in patients with HFpEF, including altered fiber type distribution, increased intermuscular fat, decreased capillary-to-fiber ratio, and reduced mitochondrial density and oxidative function.[3,29] These observations overlap substantially with those in frail older adults, independent of the presence of HF. For example, in a large prospective Italian cohort study,[33] frail older adults had lower muscle mass and higher fat content than nonfrail participants.

Regular moderate-intensity aerobic exercise training is the most promising treatment modality with the potential to improve or reverse the frailty phenotype in older adults with cardiovascular disease.[7] Despite multiple large-scale randomized medication trials, regular physical activity has been the most successful treatment for HFpEF to date, consistently improving peak oxygen consumption and exertional capacity.[7,8,10,34] Contrary to classical expectations in HF, in HFpEF the improvements in peak oxygen consumption appear related more to improved oxygen utilization in the periphery than increases in cardiac output. This suggests that the benefits of aerobic exercise in HFpEF stem at least in part from improving perfusion or metabolism in skeletal muscle.[35]

It is worth considering how frailty could affect treatment strategies in HFpEF. Sarcopenic obesity is defined by the combination of reduced skeletal muscle mass and excess fat mass. Although body composition was not measured, the high average body mass index (75% were obese) and prevalence of frailty suggest a high prevalence of sarcopenic obesity in this HFpEF cohort.[36] In a recent study, Kitzman et al[8] randomized 92 obese HFpEF patients to 20 weeks of caloric restriction, moderate-intensity aerobic exercise, or both. Peak oxygen consumption increased significantly in both the exercise and the caloric restriction groups, with additive improvement when both interventions were combined. Although frailty was not described in that study, the increase in peak oxygen consumption was positively associated with increases in the percentage of lean body mass and the thigh muscle to intermuscular fat ratio. Deficits in leg strength and balance in the present study were individually associated with poor outcomes, suggesting that a multidomain exercise program incorporating these domains[37] would be more effective in frail patients with HFpEF.

Our study highlights the complexity faced by health care providers and their patients with HFpEF. Multiple comorbidities and polypharmacy were very common in this cohort and were present to a greater degree in frail patients (Table 2). Frailty often overlaps with other "geriatric conditions," such as malnutrition and cognitive impairment[38–40]; depression and social isolation are also frequently present.[41] A recent position paper advocated for consideration of these geriatric domains as an integral part of the care plan for HF.[42] The implications are that cardiology teams may need to develop familiarity with these issues and partner with geriatric experts to improve outcomes in this vulnerable population.

Limitations

This single-center analysis is limited by the small sample size, lack of racial/ethnic diversity (88% Caucasian), and younger age than in some other cohorts.[43–46] Selection bias is also likely, because patients in this cohort were referred to an academic center's HFpEF program. However, the gender distribution, high prevalence of obesity and hypertension, and burden of multimorbid illness are broadly representative of HFpEF, and the findings are consistent with previous literature as outlined earlier. We used the SPPB because of its ease of measurement, as well as its association with outcomes in both community-dwelling and recently hospitalized older adults. In addition, the SPPB could be obtained serially to track decline in physical function or positive response to intervention. However, many methods can be used to assess frailty,[14] and it is possible that another instrument would provide additional insight or better prognostic capability.

Conclusions

Poor lower extremity function, a proxy for frailty measured by the SPPB, is an independent risk factor for all-cause hospitalization or death and overall hospitalization burden in outpatients with HFpEF. Additional studies are warranted to explore shared mechanisms and the implications of treating frailty in patients with HFpEF.

Disclosures

Acknowledgments

Supplementary Data

Supplementary data related to this article can be found at doi:10.1016/j.cardfail.2018.09.002.

References

1. Eaton CB, Pettinger M, Rossouw J, Martin LW, Foraker R, Quddus A, et al. Risk factors for incident hospitalized heart failure with preserved versus reduced ejection fraction in a multiracial cohort of postmenopausal women. Circ Heart Fail 2016;9:e002883.

2. Zile M, Gaasch W, Anand I, Haass M, Little WC, Miller AB, et al. Mode of death in patients with heart failure and a preserved ejection fraction: results from the Irbesartan in Heart Failure With Preserved Ejection Fraction Study (I-Preserve) trial. Circulation 2010;121:1393–405.

3. Kitzman DW, Nicklas B, Kraus WE, Lyles MF, Eggebeen J, Morgan TM. Skeletal muscle abnormalities and exercise intolerance in older patients with heart failure and preserved ejection fraction. Am J Physiol Heart Circ Physiol 2014;306: H1364–70.

4. Afilalo J, Lauck S, Kim DH, Lefèvre T, Piazza N, Lachapelle K, et al. Frailty in older adults undergoing aortic valve replacement: The FRAILTY-AVR Study. J Am Coll Cardiol Physiol 2017;70:689–700.

5. Chung CJ, Wu C, Jones M, Kato TS, Dam TT, Givens RC, et al. Reduced handgrip strength as a marker of frailty predicts clinical outcomes in patients with heart failure undergoing ventricular assist device placement. J Card Fail 2014;20:310–5.

6. Vidan MT, Blaya-Novakova V, Sanchez E, Ortiz J, Serra-Rexach JA, Bueno H. Prevalence and prognostic impact of frailty and its components in non-dependent elderly patients with heart failure. Eur J Heart Fail 2016;18:869–75.

7. Bibas L, Levi M, Bendayan M, Mullie L, Forman DE, Afilalo J. Therapeutic interventions for frail elderly patients: part I. Published randomized trials. Prog Cardiovasc Dis 2014;57: 134–43.

8. Kitzman DW, Brubaker P, Morgan T, Haykowsky M, Hundley G, Kraus WE, et al. Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart failure with preserved ejection fraction: a randomized clinical trial. JAMA 2016;315:36–46.

9. Kitzman DW. Exercise training in heart failure with preserved ejection fraction: beyond proof-of-concept. J Am Coll Cardiol 2011;58:1792–4.

10. Edelmann F, Gelbrich G, Düngen H-D, Fröhling S, Wachter R, Stahrenberg R, et al. Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: results of the Ex-DHF (Exercise training in Diastolic Heart Failure) pilot study. J Am Coll Cardiol 2011;58:1780–91.

11. Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. N Engl J Med 1995;332:556–62.

12. Volpato S, Cavalieri M, Sioulis F, Guerra G, Maraldi C, Zuliani G, et al. Predictive value of the Short Physical Performance Battery following hospitalization in older patients. J Gerontol A Biol Sci Med Sci 2011;66:89–96.

13. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016;18:891–975.

14. Afilalo J, Alexander KP, Mack MJ, Maurer MS, Green P, Allen LA, et al. Frailty assessment in the cardiovascular care of older adults. J Am Coll Cardiol 2014;63:747–62.

15. Ostir GV, Volpato S, Fried LP, Chaves P, Guralnik JM. Reliability and sensitivity to change assessed for a summary measure of lower body function: results from the Women's Health and Aging Study. J Clin Epidemiol 2002;55:916–21.

16. Bandinelli S, Lauretani F, Boscherini V, Gandi F, Pozzi M, Corsi AM, et al. A randomized, controlled trial of disability prevention in frail older patients screened in primary care: the FRASI Study. Design and baseline evaluation. Aging Clin Exp Res 2006;18:359–66.

17. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377–81.

18. Hummel SL, Ghalib HH, Ratz D, Koelling TM. Risk stratification for death and all-cause hospitalization in heart failure clinic outpatients. Am Heart J 2013;166:895–903. e1.

19. Hummel SL, Katrapati P, Gillespie BW, Defranco AC, Koelling TM. Impact of prior admissions on 30-day readmissions in medicare heart failure inpatients. Mayo Clin Proc 2014;89:623–30.

20. Hummel SL, DeFranco AC, Skorcz S, Montoye CK, Koelling TM. Recommendation of low-salt diet and short-term outcomes in heart failure with preserved systolic function. Am J Med 2009;122:1029–36.

21. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006;355:251–9.

22. Pencina MJ, D' Agostino RB, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27:157–72.

23. Afilalo J, Karunananthan S, Eisenberg MJ, Alexander KP, Bergman H. Role of frailty in patients with cardiovascular disease. Am J Cardiol 2009;103:1616–21.

24. Chiarantini D, Volpato S, Sioulis F, Bartalucci F, Del Bianco L, Mangani I, et al. Lower extremity performance measures predict long-term prognosis in older patients hospitalized for heart failure. J Card Fail 2010;16:390–5.

25. Reeves GR, Whellan DJ, Patel MJ, O'Connor CM, Duncan P, Eggebeen JD, et al. Comparison of frequency of frailty and severely impaired physical function in patients ≥60 years hospitalized with acute decompensated heart failure vs chronic stable heart failure with reduced and preserved left ventricular ejection fraction. Am J Cardiol 2016;117:1953–8.

26. Krumholz HM. Post-hospital syndrome—an acquired, transient condition of generalized risk. N Engl J Med 2013;368:100–2.

27. Pavasini R, Guralnik J, Brown JC, di Bari M, Cesari M, Landi F, et al. Short Physical Performance Battery and all-cause mortality: systematic review and meta-analysis. BMC Med 2016;14:215.

28. Pulignano G, Del Sindaco D, Di Lenarda A, Alunni G, Senni M, Tarantini L, et al. Incremental value of gait speed in predicting prognosis of older adults with heart failure: insights from the IMAGE-HF Study. JACC Heart Fail 2016;4:289–98.

29. Nadruz Jr W, Kitzman D, Windham BG, Kucharska-Newton A, Butler K, Palta P, Griswold ME, et al. Cardiovascular dysfunction and frailty among older adults in the community: the ARIC Study. J Gerontol A Biol Sci Med Sci 2017;72:958–64.

30. Bellumkonda L, Tyrrell D, Hummel SL, Goldstein DR. Pathophysiology of heart failure and frailty: a common inflammatory origin? Aging Cell 2017;16:444–50.

31. Walston J, McBurnie MA, Newman A, Tracy RP, Kop WJ, Hirsch CH, et al. Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities: results from the Cardiovascular Health Study. Arch Intern Med 2002;162:2333–41.

32. Ather S, Chan W, Bozkurt B, Aguilar D, Ramasubbu K, Zachariah AA, et al. Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population

with heart failure and preserved versus reduced ejection fraction. J Am Coll Cardiol 2012;59:998–1005.

33. Cesari M, Leeuwenburgh C, Lauretani F, Onder G, Bandinelli S, Maraldi C, et al. Frailty syndrome and skeletal muscle: results from the Invecchiare in Chianti study. Am J Clin Nutr 2006;83:1142–8.

34. Kitzman D, Brubaker P, Morgan T, Stewart K, Little W. Exercise training in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. Circ Heart Fail 2010;3:659–67.

35. Haykowsky MJ, Brubaker PH, Stewart KP, Morgan TM, Eggebeen J, Kitzman DW. Effect of endurance training on the determinants of peak exercise oxygen consumption in elderly patients with stable compensated heart failure and preserved ejection fraction. J Am Coll Cardiol 2012;60:120–8.

36. Upadhya B, Haykowsky MJ, Eggebeen J, Kitzman DW. Sarcopenic obesity and the pathogenesis of exercise intolerance in heart failure with preserved ejection fraction. Curr Heart Fail Rep 2015;12:205–14.

37. Reeves GR, Whellan DJ, O'Connor CM, Duncan P, Eggebeen JD, Morgan TM, et al. A novel rehabilitation intervention for older patients with acute decompensated heart failure: the REHAB-HF Pilot Study 2017;5:359–66.

38. Bollwein J, Volkert D, Diekmann R, Kaiser MJ, Uter W, Vidal K, et al. Nutritional status according to the mini nutritional assessment (MNA) and frailty in community dwelling older persons: a close relationship. J Nutr Health Aging 2013;17:351–6.

39. Dorner TE, Luger E, Tschinderle J, Stein KV, Haider S, Kapan A, et al. Association between nutritional status (MNA-SF) and frailty (SHARE-FI) in acute hospitalised elderly patients. J Nutr Health Aging 2014;18:264–9.

40. Murad K, Goff Jr DC, Morgan TM, Burke GL, Bartz TM, Kizer JR, et al. Burden of comorbidities and functional and cognitive impairments in elderly patients at the initial diagnosis of heart failure and their impact on total mortality: the Cardiovascular Health Study. JACC Heart Fail 2015;3:542–50.

41. Uchmanowicz I, Wleklik M, Gobbens RJ. Frailty syndrome and self-care ability in elderly patients with heart failure. Clin Intervent Aging 2015;10:871–7.

42. Gorodeski EZ, Goyal P, Hummel SL, Krishnaswami A, Goodlin SJ, Hart LL, et al. Domain management approach to heart failure in the geriatric patient: present and future. J Am Coll Cardiol 2018;71:1921–36.

43. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006;355:251–9.

44. Gurwitz JH, Magid DJ, Smith DH, Goldberg RJ, McManus DD, Allen LA, et al. Contemporary prevalence and correlates of incident heart failure with preserved ejection fraction. Am J Med 2013;126:393–400.

45. Sharma K, Kass DA. Heart failure with preserved ejection fraction: mechanisms, clinical features, and therapies. Circ Res 2014;115:79–96.

46. Roth GA, Johnson CO, Abate KH, Abd-Allah F, Ahmed M, Alam K, et al. The burden of cardiovascular diseases among US states, 1990-2016. JAMA Cardiol 2018;3:375–89.