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Lower extremity function is independently associated with hospitalization burden in heart failure with preserved ejection fraction

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Abstract

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

Methods and Results: 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 0-4 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 binomial regression, respectively, to assess the relationship between SPPB score and risk of death and/or all-cause hospitalization, number of hospitalizations, and days hospitalized or dead over six months. Patients were similar to other HFpEF cohorts (age 68 ± 13 years, 58% female, BMI 36 ± 8 kg/m², multiple comorbidities). Mean SPPB score was 6.9 ± 3.2 , and 80% of patients were at least mildly frail. Over a six-month period, the SPPB score independently predicted death or all-cause hospitalization (odds ratio [OR] 0.81 per point, 95% CI 0.69-0.94, $p=0.006$), number of hospitalizations (incidence rate ratio [IRR] 0.92 per point, 95% CI 0.86-0.97, $p=0.006$) and days hospitalized or dead (IRR 0.85 per point, 95% CI 0.73-0.99, $p=0.04$).

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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.

Graphical Abstract

Keywords

Elderly; diastolic heart failure; older adults; hospitalization; frailty

INTRODUCTION

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 non-cardiovascular (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 following complex cardiovascular procedures that are often performed in older patients with multimorbid illness, e.g. 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 multi-domain 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 following 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 six 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 have been prospectively followed for at least six 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, i.e. symptoms and signs of HF, left ventricular ejection fraction $\leq 50\%$, signs and/or symptoms of HF, at least mild elevation in natriuretic peptide levels, and cardiac structural (e.g. left atrial enlargement) and/or functional abnormalities (e.g. diastolic dysfunction) associated with HFpEF (13). Participants could also be diagnosed with HFpEF following hospitalization for decompensated HF requiring intravenous diuresis and/or if increased left ventricular filling pressures were documented on catheterization, regardless of natriuretic peptide level.

Lower Extremity Functional Assessment

Lower extremity function was assessed by the Short Physical Performance Battery (SPPB) which evaluates the frailty domains of slowness, weakness, and balance impairment through a series of three timed physical performance tests (gait speed, chair rises, and tandem balance). Each test is scored 1 to 4, representing approximate quartiles based on specific cut-points described below (Table 1) while a zero score indicates "unable to perform," for one of the following reasons: (1) those who tried but were unable; (2) the interviewer or subject felt it was unsafe; or, (3) for other health issues, e.g. 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 between 7-9 points denoted mild frailty (16).

Demographics, Clinical Variables, and Outcomes

Clinical and demographic variables recorded include age, self-reported race, gender, body mass index, blood urea nitrogen (BUN), estimated glomerular filtration rate (calculated with the Modification of Diet in Renal Disease equation), B-type natriuretic peptide (BNP), 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 telemanagement 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 six 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, in order to attribute the hospitalization to HF, other cardiovascular illness, or non-cardiovascular cause.

Heart Failure Patient Severity Index (HFPSI)

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 six months (18). The variables comprising the HFPSI include BUN, BNP, NYHA class, the presence of diabetes and/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 four risk strata (19). For this analysis, we calculated the HFPSI score using data available at the time of SPPB assessment in HFpEF clinic (see Supplementary Table for 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 and/or death.

Statistical Analysis

Demographics and clinical characteristics were compared between frail and non-frail participants using 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 and/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) in order to include patients who died during the follow-up period. Due 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 six 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 non-frail 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 six months of follow-up, six (5%) patients died and 44 (39%) died and/or had at least one unplanned all-cause hospitalization. As a whole, the cohort had 94 all-cause hospitalizations, of which 38 were primarily for cardiovascular causes (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 and/or all-cause hospitalization at six 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 non-cardiovascular hospitalizations. The c-

statistic increased to 0.82 when the SPPB score was added to the HFPSI group, with three-category net reclassification of 23% ($p=0.04$) and integrated discrimination improvement of 6% ($p=0.02$) (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 six-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 death and/or all-cause hospitalization, and the balance test score trended toward significance ($p=0.06$). The SPPB remained an independent predictor of the primary outcome when adjusted by HFPSI group, age, and the number of comorbid illnesses (OR 0.79, 95% CI 0.66-0.93, $p=0.006$; c-statistic 0.85 for full model). When the 22 patients who had been discharged from the hospital within the 30 days prior to frailty assessment were removed from the cohort, the SPPB remained independently associated with the primary outcome (OR 0.79, 95% CI 0.66-0.92, $p=0.004$; 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 six months. In addition, the SPPB independently predicted the overall burden of adverse events, as evidenced by both the number of all-cause hospitalizations 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., but patients with any recent hospitalizations were excluded from that analysis (25). 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) using SPPB as a measure of frailty reported that a score ≥ 9 predicted increased all-cause mortality (27). Volpato and colleagues evaluated the SPPB at hospital admission, discharge, and 1-month following 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 a 5 times greater risk of rehospitalization or death compared with those with higher SPPB scores (12), 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 pro-inflammatory non-cardiac illnesses that promote frailty (30,31), and non-cardiac 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 one large prospective Italian cohort study (33), frail older adults had lower muscle mass and higher fat content than non-frail 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, 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. While 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 and colleagues 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. While frailty was not described in that study, the increase in peak oxygen consumption was positively associated with increases in percent lean body mass and thigh muscle:intermuscular fat ratio (8). Deficits in leg strength and balance in the present study were individually associated with poor outcomes, and suggest that a multi-domain exercise program incorporating these domains (37) would be more effective in frail patients with HFpEF.

Our study highlights the complexity faced by healthcare 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 (see 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 (43–45). Selection bias is also likely, as 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 is broadly representative of HFpEF and the findings are consistent with previous literature as outlined above. 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.

Conclusion

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

(CHIP)	Cardiovascular Health Improvement Project
(HFpEF)	Heart failure with preserved ejection fraction
(HF)	Heart failure
(BNP)	Bran natriuretic peptide
(BUN)	Blood urea nitrogen
(NYHA)	New York Heart Association

(SPPB)	Short Physical Performance Battery
(TIA)	Transient ischemic attack

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Highlights

- Heart failure with preserved ejection fraction (HFpEF) has poor long-term outcomes
- Frailty is common in older adults with multiple medical conditions
- The Short Physical Performance Battery (SPPB) tests leg function to measure frailty
- Three-quarters of outpatients with HFpEF were at least mildly frail by the SPPB
- The SPPB independently predicts hospitalization and death in patients with HFpEF

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.

Table 2.

Demographics and Comorbidities

Variables	All Patients	Severely Frail [*] N=39 (34%)	Mildly Frail N = 53 (46%)	Nonfrail N = 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 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.

Table 3.

Associations Between Frailty and Risk

Variables	All Patients	Severely Frail [*] N = 39 (34%)	Mildly Frail [*] N = 53 (46%)	Nonfrail [*] N = 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.