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Frailty Measures of Patient-reported Activity and Fatigue May Predict 1-year Outcomes in Ambulatory Advanced Heart Failure: A Report From the REVIVAL Registry

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ABSTRACT

Background: The Fried Frailty Phenotype predicts adverse outcomes in geriatric populations, but has not been well-studied in advanced heart failure (HF). The Registry Evaluation of Vital Information for Ventricular Assist Devices (VADs) in Ambulatory Life (REVIVAL) study prospectively collected frailty measures in patients with advanced HF to determine relevant assessments and their impact on clinical outcomes.

Methods and Results: HF-Fried Frailty was defined by 5 baseline components (1 point each): (1) weakness: hand grip strength less than 25% of body weight; (2) slowness based on time to walk 15 feet; (3) weight loss of more than 10 lbs in the past year; (4) inactivity; and (5) exhaustion, both assessed by the Kansas City Cardiomyopathy Questionnaire. A score of 0 or 1 was deemed nonfrail, 2 prefrail, and 3 or greater was considered frail. The primary composite outcome was durable mechanical circulatory support implantation, cardiac transplant or death at 1 year. Event-free survival for each group was determined by the Kaplan−Meier method and the hazard of prefrailty and frailty were compared with nonfrailty with proportional hazards modeling. Among 345 patients with all 5 frailty domains assessed, frailty was present in 17%, prefrailty in 40%, and 43% were nonfrail, with 67% ($n = 232$) meeting the criteria based on inactivity and 54% ($n = 186$) for exhaustion. Frail patients had an increased risk of the primary composite outcome (unadjusted hazard ratio [HR] 2.82, 95% confidence interval [CI] 1.52−5.24; adjusted HR 3.41, 95% CI 1.79−6.52), as did prefrail patients (unadjusted HR 1.97, 95% CI 1.14−3.41; adjusted HR 2.11, 95% CI 1.21−3.66) compared with nonfrail patients, however, the predictive value of HF-Fried Frailty criteria was modest (Harrel's C-statistic of 0.603, $P = .004$).

Conclusions: The HF-Fried Frailty criteria had only modest predictive power in identifying ambulatory patients with advanced HF at high risk for durable mechanical circulatory support, transplant, or death within 1 year, driven primarily by assessments of inactivity and exhaustion. Focus on these patient-reported measures may better inform clinical trajectories in this population. (*J Cardiac Fail 2021;00:1−10*)

Key Words: Heart failure, frailty, left ventricular assist device, heart transplant, outcomes.

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Frailty is defined as a decreased physiological reserve that renders patients vulnerable to stress and is assessed by a variety of measures. Among patients with heart failure (HF), the prevalence of frailty has been reported across a broad range from 25% to 78% based on the patient population being assessed and measures used .[1,2] HF and frailty share common symptoms that can be attributed to either condition (eg, fatigue, exhaustion, weight loss).[3] As such, distinguishing the aspects of the frailty syndrome that are reversible with a therapeutic intervention for HF (eg, mechanical circulatory support [MCS] or cardiac transplantation) vs those that are independent, is critical.[4]

Several frailty indices have been proposed, some of which are center or study specific,[5] or focus on select measures/maneuvers such as the hand grip strength test[6] and gait time,[7] or are extrapolated from quality of life questionnaires such as the Short-Form 12.[8] The most commonly used frailty measure is the Fried Frailty Phenotype (FFP), which defines frailty by measures of weakness, slowness, inactivity, exhaustion, and shrinking,[9] likely owing to its ease of assessment and generalizability. There are limitations to the FFP, however, that are important to consider with respect to its application in an advanced HF population: (1) the measure was developed in an ambulatory geriatric patient population with a low prevalence of HF; (2) weight fluctuations owing to fluid retention are common in patients with HF and may mask unintended weight loss; and (3) the questionnaire used to assess patient inactivity is the Minnesota Leisure Time Activity scale, which is likely irrelevant to patients with advanced HF, who rarely participate in activities such as jogging or bowling.[10]

Thus, although the FFP is the most widely used measure of frailty, it remains to be validated in the setting of advanced HF owing to inconsistent application and criteria used in existing publications. The Registry Evaluation of Vital Information for VADs in Ambulatory Life (REVIVAL) prospectively collected frailty measures in ambulatory patients with advanced HF (Interagency Registry for Mechanically Assisted Circulatory Support [INTERMACS] 4−7) to determine the relevant components of frailty to this population and their individual as well as collective impact on clinical outcomes. As such, this registry offers the unique opportunity to determine how measurements of frailty correlate with worsening severity of HF requiring advanced therapies. Using the rigor of a prospective, multicenter clinical study, we hypothesized that HF-specific modified FFP criteria (HF Fried Frailty) when applied to ambulatory patients with advanced HF, would be strongly associated with the 1-year composite outcome of durable MCS, cardiac transplantation, or death.

Methods

Data Source

The REVIVAL study was a prospective, observational cohort study of patients with ambulatory systolic HF recruited from 21 United States heart transplant/MCS centers; enrollment occurred between July 2015 and June 2016. Patients were eligible for enrollment if they had persistent New York Heart Association functional classes II−IV symptoms despite optimal medical therapy as well as an additional high-risk feature such as a recent nonelective HF hospitalization, heart transplant listing, objective functional limitation, or evidence of neurohormonal activation. Patients were excluded if they had a significant noncardiac condition that would limit functional capacity or expected survival to less than 2 years, intravenous inotrope use, or chronic kidney disease with a creatinine of 3.0 mg/dL or greater, or were on dialysis. Detailed entry criteria and study design have previously been published.[11] Patient demographic characteristics including age, sex, race, and current HF status, including INTERMACS profile, were captured at the time of enrollment. During this visit, a 6-minute-walk test was performed, handgrip strength was assessed, and quality of life questionnaires were completed. An independent observational study monitoring board oversaw the conduct of the REVIVAL study. The institutional review board at each center and at the Data Coordinating Center at the University of Michigan approved the study. All subjects provided written informed consent before study participation.

The HF Fried Frailty Criteria

HF Fried Frailty was defined by 5 components: (1) weakness, (2) slowness, (3) weight loss, (4) inactivity, and (5) exhaustion. For weakness, the handgrip strength was performed using a Jamar dynamometer. Peak grip strength was measured 3 times in the dominant and nondominant hand. The average of all measures was indexed to body weight, and less than 25% of body weight was considered as meeting criterion for weakness.[6] To assess for slowness based on the 15-feet walk time, 7 seconds or more was considered to meet the criterion for men 5′8″ or shorter and 6 seconds or more for men taller than 5′8″. For women 5′3″ or shorter, 7 seconds or more met the threshold for slowness, and for women taller 5′3″, 6 or more seconds qualified.[9] An unintentional pound weight loss or 10 lbs or more was considered meeting the criterion for weight loss, collected at baseline visit from prior visits or by report. For inactivity, answers of extremely limited or quite a bit limited on the Kansas City Cardiomyopathy Questionnaire (KCCQ) for any of the 5

activity questions (including dressing oneself, showering/bathing, walking 1 block on level ground, doing yardwork/housework/carrying groceries, and climbing 1 flight of stairs without stopping) were considered to represent inactivity. The question on hurrying or jogging was excluded given the advanced nature of disease in this population. Finally, an answer of extremely limited to moderately limited for either fatigue question was considered to constitute exhaustion[10] (Appendix). For each frailty domain in which the frailty criterion was met, patients received 1 point. These were summed and the total score was used to form the following categories: nonfrail (0−1 points), prefrail (2 points), or frail (≥3 points) (Central Illustration).

Outcomes

The primary end point of interest was the 1-year composite outcome of durable MCS, transplant (as a United Network for Organ Sharing previous status 1A or 1B), or death from any cause. Of note, because MCS and transplantation were components of the primary composite outcome, death following either of these procedures was not assessed. Although the REVIVAL registry followed patients for 2 years, the 1-year end point was selected as a time period during which the impact of baseline frailty could exert its effect in the context of other baseline characteristics.

Statistical Analysis

Categorical data were presented as number (%) and continuous data were reported as mean ± standard deviation or median [interquartile range]. Patient baseline characteristics were compared between the three frailty classification groups using Pearson's χ^2 or the Kruskal−Wallis tests for categorical and continuous variables, respectively. Event-free survival for each frailty group was determined by the Kaplan−Meier method and the risks of prefrailty and frailty compared with nonfrailty were determined with proportional hazards modeling.

With regard to identifying which of the 5 modified FFP components are needed to optimize risk prediction for the primary composite outcome, each component was considered individually in a univariable analysis followed by multivariable analysis. All variables in the univariable analyses were entered into a backward elimination multivariable analysis. The multivariable model was further adjusted for body mass index because it was thought that exhaustion, inactivity, and slow gait time may be more commonly present in obese patients. The KCCQ overall summary score and clinical summary score were also assessed for association with the composite outcome, as were the individual components of the KCCQ to evaluate whether there was an incremental predictive value of the HF-Fried Frailty criteria over KCCQ. Further, contributions of the inactivity and exhaustion domains of the KCCQ were compared with the overall predictive value of the KCCQ. To assess potential biased resulting from missing components of HF-Fried data, Fisher's exact and 2-sample Wilcoxon rank-sum tests were used to compare selected categorical and continuous patient characteristics between the groups with missing and nonmissing FFP data.

Results

Baseline Characteristics

Of the 400 enrolled patients, 345 patients had assessments for all 5 frailty components at baseline. Among this advanced HF cohort, the mean age was 60 years, 75% were men, more than two-thirds were INTERMACS profile 6 or 7, and nearly 60% had a history of chronic kidney disease. The mean left ventricular ejection fraction was 20% and the mean 6-minute-walk test distance was 336 m (Table 1). The characteristics of the patients for whom all 5 components of the HF-Fried Frailty index were not available ($n = 55$) were not significantly different from the remainder of the study sample with the exception of a higher proportion of African American patients, and higher blood urea nitrogen and international normalized ratio (Supplemental Table 1).

With respect to the individual components of the HF Fried Frailty index, 232 patients (67%) met the criteria for inactivity and 186 (54%) met the criteria for exhaustion. More than one-quarter of the sample ($n = 89$ [26%]) met the criteria for weakness by handgrip strength, whereas only 28 (8%) patients had a slow gait time and a negligible proportion of patients reported a weight loss or more than 10 lbs (3 patients [0.9%]). Based on these assessments, 149 patients (43%) were classified as nonfrail with 0−1 points, 139 patients (40%) were classified as prefrail with 2 points, and 57 patients (17%) were classified as frail with 3 or more points (Table 2).

There were no differences in age between the 3 groups; however, 50% of the frail group were women compared with approximately 20% in the prefrail and nonfrail cohorts ($P < .001$). Body mass index was noted to higher in the frail patients than in the nonfrail patients (32.7 ± 6.8 vs 29.1 ± 5.7, $P = .001$). Importantly, patients with the most severe HF (INTERMACS profile 4) constituted a larger percentage of the frail group than of the prefrail or nonfrail groups (14% vs 8.6% vs 6%, respectively; $P = .001$) and New York Heart Association functional class tracked similarly. Functional capacity was also correspondingly more impaired in the frail group as

Table 1. Baseline Characteristics Based on Frailty Classification

Characteristic	(1) Not frail (n = 149)	(2) Prefrail (n = 139)	(3) Frail (n = 57)	Total (n = 345)	P value
Age (years)	62 [53−68]	62 [54−69]	61 [56−67]	62 [54−68]	.92
Male sex	120 (80.5)	110 (79.1)	28 (49.1)	258 (74.8)	<.01
Race					.21
African American/Black	34 (22.8)	24 (17.3)	18 (31.6)	76 (22.0)	
American Indian/Alaskan Native	0 (0.0)	0 (0.0)	1 (1.8)	1 (0.3)	
Asian	3 (2.0)	4 (2.9)	0 (0.0)	7 (2.0)	
More than one race	1 (0.7)	3 (2.2)	0 (0.0)	4 (1.2)	
Other/none of the above	2 (1.3)	4 (2.9)	0 (0.0)	6 (1.7)	
Unknown/undisclosed	1 (0.7)	1 (0.7)	0 (0.0)	2 (0.6)	
White	108 (72.5)	103 (74.1)	38 (66.7)	249 (72.2)	
Hispanic/Latino	9 (6.1)	11 (8.3)	4 (7.1)	24 (7.1)	.78
BMI, kg/m^2	28.4 [24.9−32.5]	29.3 [25.4−34.5]	32.7 [27.5−37.1]	29.2 [25.4−34]	<.01
New York Heart Association functional class					<.01
I	5 (3.4)	1 (0.7)	0 (0.0)	6 (1.7)	
II	54 (36.2)	32 (23.0)	9 (15.8)	95 (27.5)	
III	89 (59.7)	102 (73.4)	44 (77.2)	235 (68.1)	
IV	1 (0.7)	4 (2.9)	4 (7.0)	9 (2.6)	
INTERMACS profile					<.01
4	9 (6.0)	12 (8.6)	8 (14.0)	29 (8.4)	
5	18 (12.1)	42 (30.2)	10 (17.5)	70 (20.3)	
6	58 (38.9)	50 (36.0)	27 (47.4)	135 (39.1)	
7	64 (43.0)	35 (25.2)	12 (21.1)	111 (32.2)	
Hypertension	8 (5.4)	4 (2.9)	3 (5.5)	15 (4.4)	.54
Diabetes (n = 344)	55 (36.9)	49 (35.3)	25 (44.6)	129 (37.5)	.46
Chronic kidney disease	88 (59.1)	79 (56.8)	39 (68.4)	206 (59.7)	.32
Peripheral vascular disease	4 (2.7)	7 (5.1)	2 (3.6)	13 (3.8)	.57
COPD	20 (13.4)	20 (14.4)	3 (5.3)	43 (12.5)	.19
History of stroke or TIA?	12 (8.1)	18 (13.0)	8 (14.0)	38 (11.0)	.30
Atrial fibrillation	17 (11.4)	10 (7.2)	7 (12.3)	34 (9.9)	.39
Creatinine, mg/dL	1.30 [1.09−1.60]	1.30 [1.01−1.63]	1.27 [1.06−1.67]	1.30 [1.05−1.61]	.84
BUN, mg/dL	23 [18−34]	24 [18−35]	26 [19−37]	24 [18−36]	.68
AST, U/L	25 [21−31.5]	24 [19−32]	23 [18−29]	24 [20−32]	.16
Albumin, g/L	4.2 [3.9−4.45]	4.2 [3.9−4.4]	4.1 [3.9−4.4]	4.2 [3.9−4.4]	.60
INR (n = 335)	1.2 [1.1−1.9]	1.2 [1−2]	1.2 [1−2]	1.2 [1−2]	.98
Hemoglobin, g/dL	13.4 [12.5−14.6]	13.7 [12.4−14.7]	13.1 [12.3−14.2]	13.4 [12.4−14.5]	.19
Left ventricular ejection fraction (%)	20 [15−25]	20 [17−25]	22 [18−30]	20 [15−25]	.10
ECG: LV dimension (d)	68 [62.05−75.20]	65.65 [61.60−73.05]	64.80 [57.85−70.60]	66.50 [61.05−73.85]	.04
6-Minute walk distance (m)	364 [326−439]	335 [270−384]	273 [183−335]	341 [280−402]	<.01
Systolic blood pressure, mm Hg	108 [98−120]	106 [98−114]	109 [97.5−117]	107 [98−117]	.76
Heart rate, bpm	72 [65−84]	76 [65−84]	72.5 [66−82.5]	74 [65−84]	.71
Beta-blocker	141 (94.6)	136 (97.8)	52 (91.2)	329 (95.4)	.12
ACE inhibitor	67 (45.0)	62 (44.6)	26 (45.6)	155 (44.9)	.99
ARB	43 (28.9)	30 (21.6)	9 (15.8)	82 (23.8)	.11
ARNI	19 (12.8)	24 (17.3)	12 (21.1)	55 (15.9)	.30
ACE inhibitor/ARB/ARNI	129 (86.6)	116 (83.5)	47 (82.5)	292 (84.6)	.67
Hydralazine	27 (18.1)	19 (13.7)	9 (15.8)	55 (15.9)	.59
Nitrates	35 (23.5)	32 (23.0)	15 (26.3)	82 (23.8)	.88
Mineralocorticoid receptor antagonist (spiro/eplerenone)	120 (80.5)	97 (69.8)	43 (75.4)	260 (75.4)	.11
Loop diuretic	138 (92.6)	125 (89.9)	53 (93.0)	316 (91.6)	.65

Nonfrail, prefrail, and frail defined as a Fried Frailty Phenotype score of 0−1, 2, and 3−5, respectively.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; INR, international normalized ratio; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LV, left ventricular; TIA, transient ischemic attack.

*Categorical data presented as number (%), continuous data presented as median [interquartile range].

Table 2. The Proportion of Patients With Each Component of Frailty

Frailty Component	Total Cohort (N = 345)	Nonfrail (n = 149 [43%])	Prefrail (n = 139 [40%])	Frail (n = 57 [17%])
Inactivity	232 (67.3)	50 (33.6)	127 (91.4)	55 (96.5)
Exhaustion	186 (53.9)	17 (11.4)	115 (82.7)	54 (94.7)
Weak hand grip strength	89 (25.8)	14 (9.4)	26 (18.7)	49 (86.0)
Slow gait time	28 (8.1)	2 (1.3)	9 (6.5)	17 (29.8)
Weight loss	3 (0.9)	0	1 (0.7)	2 (3.5)

Values are number (%).

assessed by the 6-minute-walk test distance (262 ± 106 m vs 325 ± 92 m in the prefrail group and 375 ± 85 m in the nonfrail group ($P < .001$)).

Relationship to Outcome

At 1 year, 75 patients (22% of the entire cohort) experienced the primary composite outcome of durable MCS ($n = 41/75$ [55% of composite]), urgent cardiac transplant ($n = 10/75$ [13% of composite]), or death ($n = 24/75$ [32% of composite]) and 14 patients were lost to follow-up. Patients categorized as nonfrail had the greatest probability of survival free of the primary composite end point (86.6%), followed by patients classified as prefrail (73.8%); patients deemed frail had the lowest probability (64.9%, $P = 0.003$) (Figure 1). Durable MCS implantation was the most frequent outcome of the composite and occurred most frequently in the frail group followed by the prefrail and finally nonfrail group (19% vs 15% vs 6%, respectively) (Table 3).

Univariable and Multivariable Association of Frailty and Primary End Point

The difference in hazards of the primary composite end point was significantly different between the frail and nonfrail groups (unadjusted hazard ratio [HR] 2.82, 95% confidence interval [CI] 1.52−5.24, $P = .001$; adjusted HR 3.41, 95% CI 1.79−6.52, $P < .001$), as well as between the prefrail and nonfrail group (unadjusted HR 1.97, 95% CI 1.14−3.41, $P = .016$; adjusted HR 2.11, 95% CI 1.21−3.66, $P = .008$). There was, however, no significant increased hazard in the frail vs prefrail group (unadjusted HR 1.44, 95%CI 0.83−2.49, $P = .198$) (Table 4). INTERMACS profile was associated with the primary composite outcome (profiles 4 and 5 vs 7 had a higher risk of durable MCS, transplantation, or death than profile 7 on univariable analysis) but age, sex, and body mass index were not. Last, a higher left ventricular ejection fraction was expectedly protective against the primary end point (HR 0.96, 95% CI 0.93−0.99 per 1% increase).

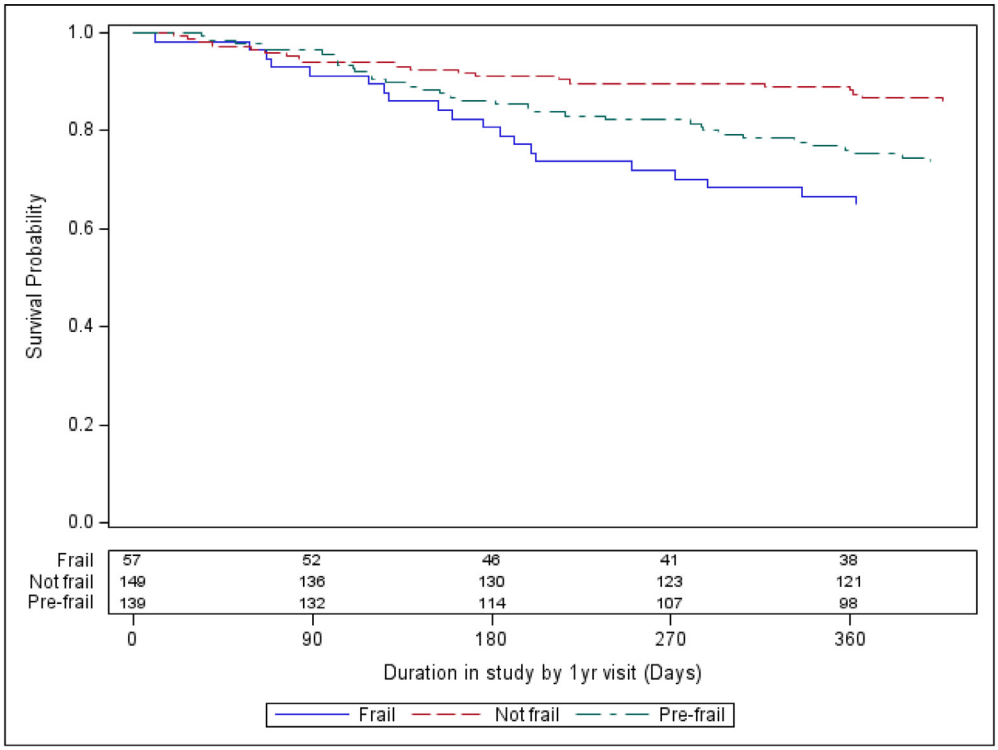
The overall Harrell's c-statistic of the HF-Fried Frailty index in predicting the composite outcome was 0.60. When considering the value of the individual components of the HF-Fried Frailty index, questions on inactivity and exhaustion drove predictive power. The Harrell's c-statistic for inactivity was c = 0.58 (HR 2.44, 95% CI 1.34−4.44, $P = .035$), and for exhaustion c = 0.62 (HR 2.81, 95% CI 1.67−4.72, $P = .0001$) (Table 5). Including both inactivity and exhaustion, the c-statistic improved to 0.64, (95% CI 0.578−0.69). Even though KCCQ questions on inactivity and exhaustion constitute just 2 of many components of the Clinical and Overall Summary Scores, the multivariable Cox model including just the KCCQ inactivity and exhaustion components had similar predictive ability to the KCCQ Clinical Summary Score: c = 0.64 (HR 0.98, 95% CI 0.97−0.99, $P < .0001$); and the Overall Summary Score: c = 0.63 (HR 0.98, 95% CI 0.97−0.99, $P < .0001$) (Table 5).

Discussion

We used data from a prospective multicenter registry to assess the predictive value of 5 HF-specific frailty measures, called the HF-Fried Frailty criteria, among ambulatory patients with advanced HF to report several meaningful findings. First, more than one-half of the patients were classified as prefrail or frail. Second, exhaustion and inactivity were the most common frailty components observed. Third, markers of frailty using a 5-component HF-Fried Frailty index, tracked with ambulatory INTERMACS profiles 4−7, with sicker patients being more frail. Finally, prefrailty or frailty was associated with a 2- to 3-fold risk of death or needing advanced therapies at 1 year, driven by patient reports of inactivity and fatigue severity. The predictive value was modest, however, suggesting these frailty assessments, originally appreciated in an elderly population, may be less relevant in this younger cohort.

Assessment of Frailty in Advanced HF

Frailty is a syndrome characterized by an accumulation of deficits, resulting in a depleted physiological reserve and limited ability to overcome stressors.[12] Its detection can be elusive; the syndrome relies on the characterization of symptoms shared by both advanced HF and biological aging,[3] and certain components (eg, inactivity and exhaustion) are not precisely measurable. The original Fried construct used the Minnesota Leisure Time Activities Questionnaire to assess inactivity wherein activities such as running, dancing, and tennis, are often beyond the physical abilities of patients with advanced HF. [10,13] Although prior HF frailty publications have assessed inactivity and exhaustion using a variety of techniques,[14] we chose to use domains of the extensively validated KCCQ.[10] The KCCQ inactivity and extent of exhaustion questions are more relevant to HF and include challenges (if any) in dressing, showering, and light housework as well as frequency of fatigue with regular activities. The advanced nature of disease in the REVIVAL cohort is evidenced by high overall event rates compared with other contemporary clinical trials in HFrEF. For example, in REVIVAL 22% of patients had the composite end point at 1 year compared with 22% in PARADIGM-HF[15] at 27 months or 19% in EMPEROR-REDUCED[16] at 16 months. Importantly, in REVIVAL, HF hospitalizations were not included in the primary composite end point of left ventricular assist



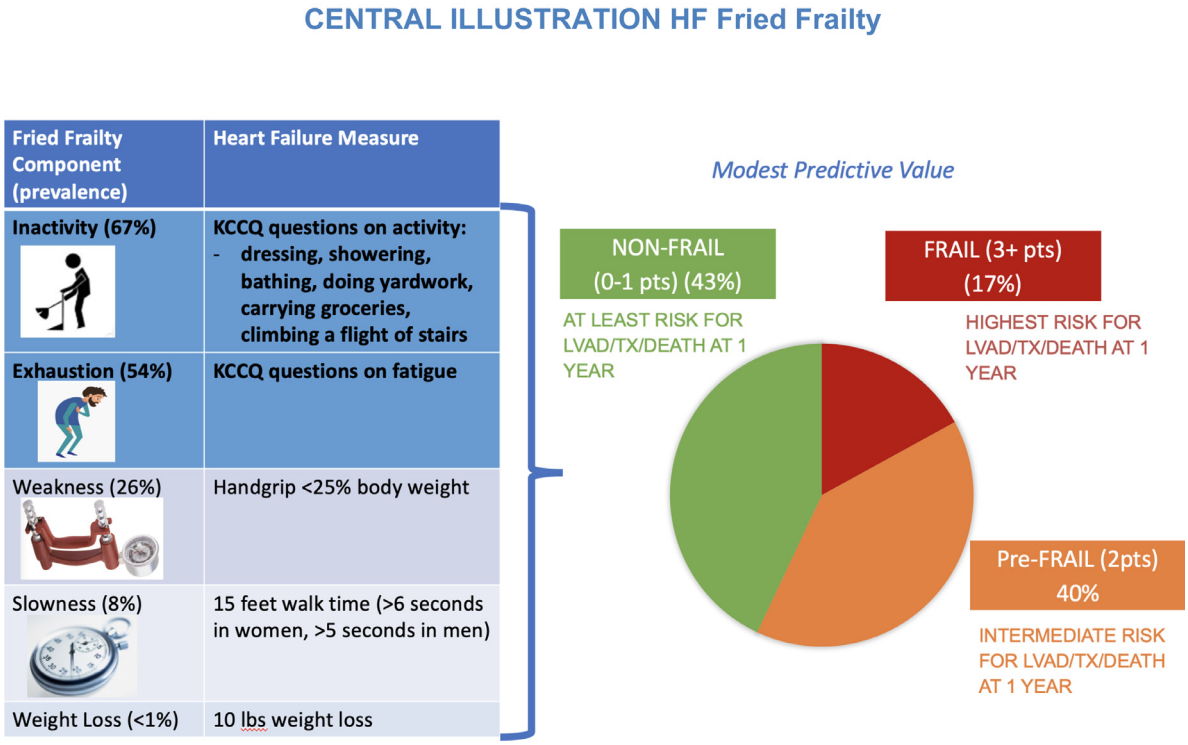


Figure 1. Survival free of primary composite end point.

device implantation, transplantation, or death. If cardiovascular mortality and HF hospitalizations were assessed, 36% of REVIVAL patients experienced this composite at 12 months and 48% by 24 months.

Prevalence of Frailty

Frailty measures are increasingly assessed to reflect biologic age rather than chronologic age in efforts to better prognosticate outcomes in patients

Table 3. Clinical Outcomes at 1 Year by Frailty Category

Clinical Outcome	Nonfrail (*n* = 149)	Prefrail (n = 139)	Frail (*n* = 57)
Primary composite end point	20 (13.4)	35 (25.2)	20 (35.1)
Durable MCS implantation	9 (6.0)	21 (15.1)	11 (19.3)
Urgent cardiac transplant	1 (0.7)	6 (4.3)	3 (5.3)
Death	10 (6.7)	8 (5.8)	6 (10.5)

Values are number (%). MCS, mechanical circulatory support.

with advanced HF. Yet the absence of a HF-specific frailty tool has been a significant limitation.[12] The FFP is used to predict outcomes, particularly in elderly patients and in the surgical settings[9]; thus, its applicability to predict clinical trajectories among patients with ambulatory advanced HF is of interest. The HF-Fried Frailty criteria used in this study included HF-specific assessments of weight loss, hand grip strength, gait time, inactivity, and exhaustion. Using this definition, 57% of patients with advanced HF were considered prefrail or frail, with 40% classified as prefrail with 2 domains positive (with >80% owing to inactivity and exhaustion) and less than one-fifth of patients (17%) classified as frail with 3 or more domains positive. Poor handgrip strength was the most common qualifying assessment after inactivity and exhaustion.

Clinical Characteristics of Patients With HF With Frailty

Frailty has typically been considered a comorbid condition of the elderly. In scenarios of advanced end-organ disease, however, the recognition of frailty is important regardless of biological age, with a similar age distribution for frail and non-frail patients among patients referred for heart transplantation.[17] The present cohort is relatively young, so measures outside the Fried construct may be more meaningful. Although more women were frail than men (consistent with prior frailty publications in elderly patients with and without HF),[18] sex was not a significant factor when assessing the impact of frailty on outcomes.[19,20] We observed that patients with more severe heart failure (e.g., lower INTERMACS Profile) had a higher prevalence of frailty than less ill patients.

In our analysis, we also surprisingly found that prefrail and frail patients had a higher body mass index than nonfrail patients. This paradox highlights a few important observations: (1) objective frailty assessment over eyeball tests is important to permit accurate prognostication among patients with HF [21,22]; (2) frail patients suffer from sarcopenia, and sarcopenia can coexist in obese individuals, also known as obese sarcopenia[23,24]; and (3) the combination of HF and obesity can enhance systemic inflammation, muscle catabolism, and may precipitate frailty.[25]

Table 5. Discriminatory Power of the Components of the Heart Failure Fried Frailty Toward the Primary Composite End Point

Frailty Characteristic	Harrel's C-Statistic	Hazard Ratio [95% CI]	*P* Value
Weak handgrip strength	0.509	1.1 [0.665−1.823]	.71
Slow gait time	0.511	1.2 [0.56−2.67]	.61
Inactivity	0.580	2.4 [1.34−4.44]	.004*
Exhaustion	0.615	2.81 [1.67−4.72]	.0001*
Overall HF-FF	0.603		.004*
Prefrail		1.97 [1.14−3.41]	.016
Frail		2.82 [1.52−5.24]	.001
Modified KCCQ	0.635		
Inactivity		1.71 [0.90−3.23]	.099
Exhaustion		2.34 [1.34−4.07]	.003*

HF-FF, heart failure Fried Frailty index; KCCQ, Kansas City Cardiomyopathy Questionnaire.

Association of Frailty With Outcomes in Patients With HF

In line with previous publications, the current study also shows worse outcomes among patients

Table 4. Univariable and Multivariable Analyses (Models) of the Primary End Point

	Univariable Model		Final Multivariable Model	
Characteristic	Hazard Ratio [95% CI]	*P* Value	Hazard Ratio [95% CI]	*P* Value
Age (years)	1.00 [0.98−1.01]	.652		
Sex (male)	0.96 [0.58−1.61]	.883		
BMI (kg/m^2)	1.00 [0.96−1.03]	.810	0.98 [0.95−1.02]	.344
INTERMACS profile (IPP)		.027		
IPP 4 vs 7	2.83 [1.24−6.46]			
IPP 5 vs 7	2.51 [1.28−4.91]			
IPP 6 vs 7	1.81 [0.98−3.35]			
Creatinine (mg/dL)	1.12 [0.86−1.44]	.404		
Albumin (g/dL)	1.51 [0.84−2.71]	.172		
LVEF (%)	0.97 [0.93−1.00]	.057	0.96 [0.93−0.99]	.018
Frailty		.004		<.001
Prefrail vs nonfrail	1.97 [1.13−3.41]	.016	2.11 [1.21−3.66]	.008
Frail vs nonfrail	2.82 [1.52−5.24]	.001	3.41 [1.79−6.52]	<.001

CI, confidence interval; LVEF, left ventricular ejection fraction. Other abbreviations as in Table 1.

found to be frail. For example, a systematic review demonstrated that frailty increases the risk for HF hospitalizations by 30% and all-cause mortality by 60%.[20] In advanced HF, Jha et al[17] demonstrated that the prevalence of frailty confers a higher risk of needing an left ventricular assist device or transplantation. In addition, the presence of preoperative frailty in heart transplant recipients was associated with inferior survival after transplant.[17,26] The current study focuses not only on the assessment and prevalence of frailty, but also uniquely demonstrated its association with the combined trajectory outcome of durable MCS, transplant or death at 1 year. Prior HF frailty publications have not assessed risk associated with the presence of prefrailty alone and our findings suggest that prefrailty confers increased risk of HF progression.

Individual Domains of the HF-Fried Frailty Index

The overall discriminatory power of the HF-Fried Frailty index for the primary composite end point was modest, with a Harrel's c-statistic of 0.60, with varying discriminatory power among the 5 frailty domains assessed. Overall, handgrip strength and 15-foot gait time had poor predictive power, with a c-statistic of approximately 0.5. This finding is distinct from prior publications, which have suggested that handgrip strength among candidates for left ventricular assist device implantation was highly predictive of outcomes after left ventricular assist device implantation.[6] We also identified a low prevalence of weight loss (approximately 1% of patients) similar to that reported by Reeves et al, but disparate from the 38% reported by Vidan et al,[29] likely owing to the advanced age of their cohort compared with the current analysis. In fact, in the REVIVAL population body-mass index was actually higher with increasing degree of frailty.[27,28] Assessment of weight changes in HF is challenging owing to fluctuations in volume status, where loss of muscle mass may be masked by hypervolemia, again suggesting that weight loss may not be a critical component of the frailty assessment in patients living with HF. [12,24,25]

Perhaps most interestingly, the modest predictive power of the HF-Fried Frailty index in this population of patients with HF was driven primarily by questions on inactivity and exhaustion. The importance of assessing these domains has been similarly noted in prior HF frailty studies, where they were observed to be more predictive of one-year mortality than gait time, weight loss, or grip strength.[29] It also suggests that the KCCQ, which is extensively validated and used in HF, contains domains that can be used to quantitatively assess exhaustion and inactivity as part of the HF frailty assessment. Further, assessments based on the questions of inactivity and fatigue had equivalent predictive performance to the clinical summary and overall KCCQ scores, underscoring their specific relevance to this HF population.

Limitations

There are limitations to this analysis that warrant mention. Despite multiple reports demonstrating the association of frailty with worse outcomes in HF, a gold standard for frailty has yet to be defined in this population. Two components of the HF-Fried Frailty criteria previously validated in other contexts, namely, handgrip strength and 15-foot gait time, should be evaluated in other HF samples to reassess their performance before dismissing them as not valuable indicators of frailty in HF. Indeed, different thresholds have been used to qualify for weakness using handgrip strength.[30] REVIVAL excluded patients with severe chronic kidney disease and end-stage renal disease who often meet outlined criteria for frailty, and as such our findings cannot be extrapolated to such a population. We also adjusted for a modest number of covariates and did not evaluate the impact of cognitive impairment or depression,[2,26] which may modulate frailty-associated risk.[31] Three-quarters of the REVIVAL population were men, lending to an under-representation of women in the current analysis; however, this proportion is in line with studies of patients with advanced HF awaiting transplantation or MCS.[32,33] Outcomes were assessed up until 1 year, and a longer follow-up may influence the results.[34] Finally, it could be that the employment of another frailty tool or measure might have detected a higher prevalence of frailty and yielded different association with the primary composite end point. Still, studies have found that frailty screens and measures have been at least moderately correlated with one another, reflecting the detection of a common underlying phenotype.[1]

Conclusions

Understanding the best way to assess frailty and its association with outcomes is undeniably important to better risk stratify and care for patients with advanced HF. We report the modest predictive value of applying the HF-Fried Frailty criteria to determine clinical trajectory in HF including death, or the requirement for advanced therapies over 1 year. Notably, assessments of inactivity and exhaustion are readily translated to the clinical environment and provide important prognostic information.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2021.10.014.

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