Received: 21 December 2021 | Revised: 15 February 2022 | Accepted: 18 February 2022

DOI: 10.1111/jgs.17736

Journal of the
American Geriatrics Society

Prognostic value of functional capacity after transitional rehabilitation in older patients hospitalized for heart failure

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Abstract

Background: Poor functional status is highly prevalent among older patients hospitalized for HF and marks a downward inflection point in functional and prognostic trajectories. We assessed the prognostic value of 6-min walk test after transitional cardiac rehabilitation in older patients hospitalized for heart failure (HF).

Methods: We studied 759 patients aged ≥60 years who had been transferred to six inpatient rehabilitation facilities (IRF) from acute care hospitals after a hospitalization for acute HF. The primary outcome was 3-year all-cause mortality. We used multivariable Cox analysis to determine the association between 6-min walk distance (6MWD) at discharge from the IRFs and the primary outcome, adjusting for established predictors of death. The optimal cutoff for 6MWD was considered as the one that maximized the chi-square statistic.

Results: Mean age was 75 ± 8 years. 6MWD significantly increased from admission to discharge (145 to 210 m; $p < 0.001$). The optimal cutoff for 6MWD was 198 m. After full adjustment, the hazard ratio for each 50 m-increase in discharge 6MWD was 0.90 (0.87–0.94; $p < 0.001$) and that for discharge 6MWD dichotomized at the optimal cutoff 0.48 (0.38–0.60; $p < 0.001$). The incidence rate of death/100 person-years for the patients who walked >198 m was 13.0 (10.0–15.5) compared with 30.8 (26.9–35.4) for those who walked <198 m. A statistically significant interaction of discharge 6MWD with left ventricular ejection fraction (EF) on the risk of death was observed (p value for interaction 0.047).

Conclusions: A rehabilitation intervention provided in the critical hospital-to-home transition period to older patients hospitalized for HF resulted in improved functional capacity. Increasing levels of functional capacity following rehabilitation were closely associated with decreasing risk of death; this association was significantly stronger for the subgroup with preserved EF.

KEYWORDS
cardiac rehabilitation, functional capacity, heart failure, survival

INTRODUCTION

Heart failure (HF) is an increasingly prevalent clinical syndrome, especially among older people, and a major cause of cardiovascular mortality, morbidity and disability.[1–3] Although HF survival has modestly improved in the last two decades due to advances in the treatment, median survival remains at ≈5 years.[4] Moreover, HF is a leading cause of hospitalization and the most common condition for hospital admission in elderly people.[5] Functional disability and loss of independence are hallmark features of HF. The Global Burden of Disease study showed that HF contributes to a significant percentage of all years lived with disability associated with chronic conditions.[6]

Hospitalization has a central role in precipitating, worsening and perpetuating functional disability in older persons.[7,8] New or worsening functional disability, likely resulting from the interaction of patients' vulnerability and resilience with hospitalization factors,[8] is common in older patients admitted for HF. Around 50% of older patients hospitalized for HF present with moderate-to-severe functional disability, which often progresses during hospitalization, and one in four develop new disability that was not present before admission.[9] In most cases, the hospitalization-associated functional decline persist, or even progresses, after discharge and is associated with adverse prognosis, worse health-related quality of life, and increased care needs,[8–12] indicating that functional status trajectory is an important outcome in older patients hospitalized for HF. Thus, more aggressive efforts are warranted to enhance restorative interventions in the subacute and outpatient settings.[7,8] Cardiac rehabilitation (CR) is recommended for HF patient in order to improve functional capacity, quality of life, and clinical outcomes.[2] Some studies also suggest that CR has beneficial effects on mortality.[13–16] Despite practice guideline recommendations,[2,17] however, only a minimal fraction of older patients is referred to outpatient or inpatient CR after a HF hospitalization.[18,19] In the Rehabilitation Therapy in Older Acute Heart Failure Patients (REHAB-HF) trial, Kitzman et al investigated the effects of a transitional rehabilitation intervention on physical function in older patients hospitalized for acute HF.[20] Three hundred forty-nine patients aged 60 years or older were randomized to usual care or the rehabilitation intervention. The mean 6-min walk distance (6MWD) at baseline was <200 m, indicating severe functional impairment. The rehabilitation intervention resulted in significantly greater improvement in functional capacity, as assessed by exercise endurance and 6MWD, than usual care.[20] Whether improved functional status after CR translates into improved survival in older HF patients hospitalized for HF remains unknown.

Key points

- Poor functional status is highly prevalent among older patients hospitalized for heart failure and marks a downward inflection point in functional and prognostic trajectories.
- The recently published Rehabilitation Therapy in Older Acute Heart Failure Patients (REHAB-HF) trial demonstrated that a transitional rehabilitation intervention resulted in significantly greater improvement in functional capacity than usual care in older patients hospitalized for heart failure.
- A scientific statement from the American Heart Association emphasized the importance of prioritizing functional capacity as a principal end-point for therapies oriented to older adults with cardiovascular disease.

Why does this paper matter?

Our findings, by showing that the level of functional capacity achieved after transitional cardiac rehabilitation is closely associated with long-term survival, add to the REHAB-HF trial results and provide further supportive evidence for prioritizing improvement in functional capacity as a therapeutic option in older patients hospitalized for heart failure. Further randomized or cohort control studies are however needed to warrant promotion of transitional cardiac rehabilitation for older patients hospitalized for heart failure.

The 6-min walk test (6MWT) is the most widely used test to measure functional capacity of HF patients in the CR setting.[21] There is evidence that 6MWT performs better as a prognostic tool for HF patients with severely impaired functional capacity, in whom daily activity level is likely to approach maximal exercise capacity.[22–24] The aim of the present study was to assess the prognostic value of 6MWT after CR in older patients hospitalized for HF.

METHODS

This was a multicenter observational retrospective study including all discharges with a primary diagnosis of HF (International Classification of Diseases, Ninth Revision codes: 402.01, 402.11, 402.91, 404.01, 404.03,

404.11, 404.13, 404.91, 404.93, and 428.xx) from six inpatient CR units of a nationwide Research Institute in the field of Rehabilitation Medicine in Italy between January 2013 and December 2016.[15] All participating centers are part of a single department of CR, share a common formal rehabilitation program, and are certified ISO9001 Quality Management Systems for activities of rehabilitation. Activities of rehabilitation and conformity with national regulatory rules for admission to inpatient CR[25,26] are subject to periodic external audit by independent auditors of the Regional Health Agencies. During the study period, 3301 patients experienced 5312 admissions. In the case of multiple admissions, the first admission was selected for inclusion in the study. Patients were eligible for inclusion in the study if they were 60 years of age or older and had been transferred to CR from acute care hospitals after a hospitalization for acute HF.[20] Patients who were younger than 60 years, who were admitted from the community, who died or were readmitted back to acute care during the inpatient rehabilitation period or developed adverse clinical events that precluded rehabilitation completion, who had previous disabling stroke or dementia or were lost to follow-up were excluded. Of the 1022 patients who met the selection criteria, 759 had available data for 6MWT at admission and discharge and 263 had missing data for 6MWT at admission (N. 203) or at discharge (N. 60). Thus, 759 patients were available for analysis. Figure 1 displays the flow-chart of patient selection.

In each participating center, the multidisciplinary CR team comprises the following professionals: cardiologist, physiatrist, physiotherapist, psychologist, dietitian, and nurse. Our formal multidisciplinary program is led by cardiologists and is designed to promote stable clinical conditions, improve physical function through a supervised exercise training plan tailored to the individual level of functional ability at presentation, provide specialized medical assistance, and optimize medical treatment. Available services in each participating center include an on-site 24-h service of on-call cardiologist, a subintensive area with monitored beds, and an echo lab.

The exercise program consisted of a supervised training program including active/passive mobilization; assisted ambulation; respiratory, musculoskeletal flexibility, movement coordination, and/or callisthenic exercises, and training on a (unloaded) bedside/upright cycle ergometer. The types of exercises and exercise intensity were gradually progressed throughout the rehabilitation period, according to the individual functional and clinical conditions. During each training session, heart rate, rhythm, symptoms, and perceived exertion were monitored. In more severely ill patients, the training program was started once symptoms at rest had subsided and clinical stability had been achieved. Experienced physiotherapists performed a standardized 6MWT at admission to and discharge from CR.[27] If a patient was not able to walk, a distance equal to 0 meters was recorded.[28,29]

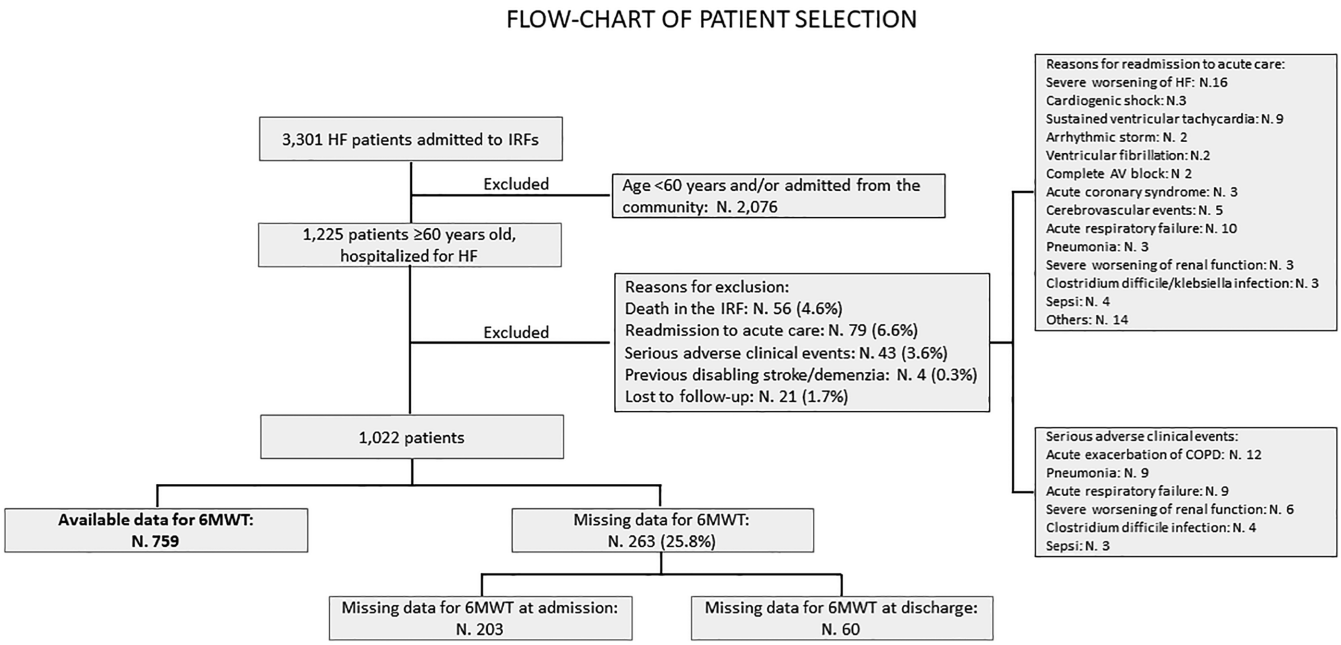

FIGURE 1 Flow-chart of patient selection. Abbreviations: IRF, denotes inpatient rehabilitation facility, HF, heart failure, 6MWT, 6-min walking test, COPD, chronic obstructive pulmonary disease

Data collection

The data were extracted from the electronic Hospital Information System shared between the participating centers and entered into a REDCap database. Baseline measurements were obtained at the time of admission to inpatient CR. All patients provided a written consent to the use of their data in an anonymous form for scientific purposes. Any identifying information was removed from the database and replaced with an identification number. The Ethics Committee of our Institution approved the study. Survival status was ascertained by linkage to the national Health Information System. The patients were followed-up until death or November 30, 2019.

Primary outcome

The primary outcome was 3-year all-cause mortality after discharge from CR.

Statistical analysis

Data are reported as mean and standard deviation (SD) or median with 25th and 75th percentiles for continuous variables and as number and percentage for categorical variables. We used the Student's t-test or the Mann–Whitney test to compare continuous variables and the χ^2 test to compare categorical variables. Cumulative mortality rates were estimated using the Kaplan–Meier method and a log-rank test was used to compare groups. Annualized incidence rates of death were calculated per 100 patient-years and the 95% confidence intervals were estimated using the Poisson distribution. The effect size of CR on 6MWD was calculated as standardized mean difference (mean difference in 6MWD between admission and discharge, divided by the SD of change).[30] We used multivariable Cox proportional hazard regression analysis to determine the association between 6MWD at discharge from CR and the primary outcome. Three models were developed. Model 1 (baseline risk model) included the following prognostic factors: age; sex; diabetes; chronic obstructive pulmonary disease; NYHA class, systolic blood pressure, left ventricular ejection fraction (LVEF), estimated glomerular filtration rate, blood urea nitrogen, sodium, and hemoglobin measured at admission to CR; and treatment with beta-blockers or renin angiotensin system inhibitors. These variables were selected because they were identified in previous studies as being the most consistent and strongest prognostic factors in HF.[31,32] Missing data for systolic blood pressure (3.9%) were replaced by the median of observed values.[33] Model 2 included model 1 plus discharge 6MWD modeled as per 50-m increase or as binary variable dichotomized at the optimal cutoff. The optimal cutoff was considered as the one that maximized the chi-square statistic. Model 3 included model 2 plus 6MWD at admission to CR. To test for a potential nonlinear association between discharge 6MWD and risk of mortality, a likelihood ratio test comparing the model with only the linear term of 6MWD with the model with both the linear and the restricted cubic spline terms was used, with $p < 0.05$ denoting significant nonlinearity. In addition, we assessed the prognostic value of change in 6MWD from admission to discharge dichotomized at the optimal cutoff adjusting for baseline model plus baseline 6MWD. To assess the incremental value of discharge 6MWD in addition to the baseline risk model for predicting the primary outcome, we calculated the improvement in global χ^2 values. Risk reclassification was assessed using the category-free net reclassification index (NRI) and the integrated discrimination improvement (IDI).[34] Confidence intervals for NRI and IDI were calculated considering a normal distribution of their estimates.[34] Category-free NRI is a measure of risk reclassification and defines upward and downward movement among cases and non-cases as any change in predicted probabilities[35]; the IDI "integrates net reclassification over all possible cut-offs for the probability of the outcome".[36] The Cox analyses were repeated in the subgroup of patients with available data for NT-proBNP. Finally, we tested for any statistically significant interaction between discharge 6MWD and age, sex, NYHA class, and LVEF for the primary outcome. The available sample size of 759 patients with 331 events was sufficient to detect a HR of 0.95 for each 50 m-increase in 6MWD and a HR of 0.70 for 6MWD above the optimal cutoff with a statistical power of 90% at a significance level of 5%.[37] Values of $p < 0.05$ were considered significant. All analyses were conducted using STATA software, version 14 (Stata-Corp LP, College Station, Tex).

RESULTS

Baseline characteristics

Table 1 displays patient baseline characteristics. Mean age was 75 years and six in ten patients were males, the burden of prognostically relevant comorbidities was high, 45% patients had NYHA class III/IV symptoms, mean 6MWD was 145 m, the median NT-proBNP was 2990 (1217–5998), and one third presented with total/severe dependence in performing activities of daily living. Table S1 displays the baseline characteristics of the

TABLE 1 Baseline characteristics

	Missing N (%)	All patients (N. 759)
Demographics		
Age (years), mean (SD)	–	75 (8)
>75 years, N (%)		385 (50.7)
Male sex, N (%)	–	472 (62.2)
Body mass index, mean (SD)	30 (3.9)	26.4 (6.4)
Comorbidities		
Hypertension, N (%)	–	503 (66.3)
Diabetes mellitus, N (%)	–	255 (33.8)
Chronic obstructive pulmonary disease, N (%)	–	217 (28.6)
Chronic kidney disease, N (%)	–	526 (69.3)
Stage 3a (eGFR 45–59 mL/min/1.73 m^2)		185 (24.4)
Stage 3b (eGFR 30–44 mL/min/1.73 m^2)		203 (26.7)
Stage 4 (eGFR 15–29 mL/min/1.73 m^2)		129 (17.0)
Stage 5 (eGFR <15 mL/min/1.73 m^2)		9 (1.2)
Anemia (hemoglobin <13 g/dL in men and < 12 g/dL in women), N (%)	–	426 (56.1)
Atrial fibrillation, N (%)	–	343 (45.2)
Clinical findings		
Transferred from acute care after a hospitalization for HF, N (%)		759 (100)
NYHA, N (%)	–	
I		88 (11.6)
II		282 (37.2)
III		293 (38.6)
IV		48 (6.3)
Indeterminable		48 (6.3)
ICD/CRT-D, N (%)	–	136 (17.9)
ICD/CRT-D in patients with LVEF ≤0.40, N (%)	–	120 (26.9)
Systolic blood pressure (mm Hg), mean (SD)	30 (3.9)	113 (16)
Systolic blood pressure < 100 mm Hg, N (%)	30 (3.9)	104 (14.7)
Diastolic blood pressure (mm Hg), mean (SD)	30 (3.9)	68 (8)
LVEF (%), mean (SD)	–	39.3 (14.3)
LVEF ≤0.40, N (%)	–	446 (58.8)
Treatment with i.v. inotropes at admission. N (%)		11 (1.4)
Treatment with i.v. vasodilators at admission. N (%)		116 (15.3)
Laboratory findings		
Hemoglobin (g/dL), mean (SD)	–	12.3 (2.0)
BUN (mg/dL), mean (SD)	–	36 (20)
Creatinine (mg/dL), (mean (SD)	–	1.49 (0.67)
eGFR (mL/min/1.73 m^2), mean (SD)	–	51 (23)
Sodium (mEq/L), mean (%)	–	139.2 (3.7)
Sodium <136 mEq/L, N (%)		118 (15.5)
NT-proBNP (pg/mL), median (IQR)	281 (37.0)	2990 (1217–5998)
Functional status at admission		
Barthel index	127 (16.7)	
0–20 (total dependence), N (%)		44 (7.0)
21–60 (severe dependence), N (%)		167 (26.4)
61–90 (moderate dependence), N (%)		235 (37.2)
91–99 (slight dependence), N (%)		47 (7.4)
100 (independence), N (%)		139 (22.0)
Six-min walking distance at admission (meters), mean (SD)	–	145 (142)
Six-min walking distance at discharge (meters), mean (SD)	–	210 (172)
Length of stay in the IRFs (days), mean (SD)	–	23 (10)
Treatment at admission to IRF	–	
All patients		
Beta-blockers, N (%)		421 (55.5)
RAAS-Is, N (%)		363 (47.8)

TABLE 1 (Continued)

	Missing N (%)	All patients (N. 759)
Beta-blockers plus RAAS-Is, N (%)		246 (32.4)
Treatment at discharge from IRF	–	
All patients		
Beta-blockers, N (%)		640 (84.3)
RAAS-Is, N (%)		555 (73.1)
Beta-blockers plus RAAS-Is, N (%)		474 (62.5)

Abbreviations: BUN, denotes blood urea nitrogen, CRT, cardiac resynchronization therapy, eGFR, estimated glomerular filtration rate, ICD, implantable cardioverter defibrillator, IRF, inpatient rehabilitation facility, LVEF, left ventricular ejection fraction, NYHA, New York Heart Association, N, number of patients, RAAS-Is, renin angiotensin aldosterone system inhibitors, SD, standard deviation, SEM, standard error.

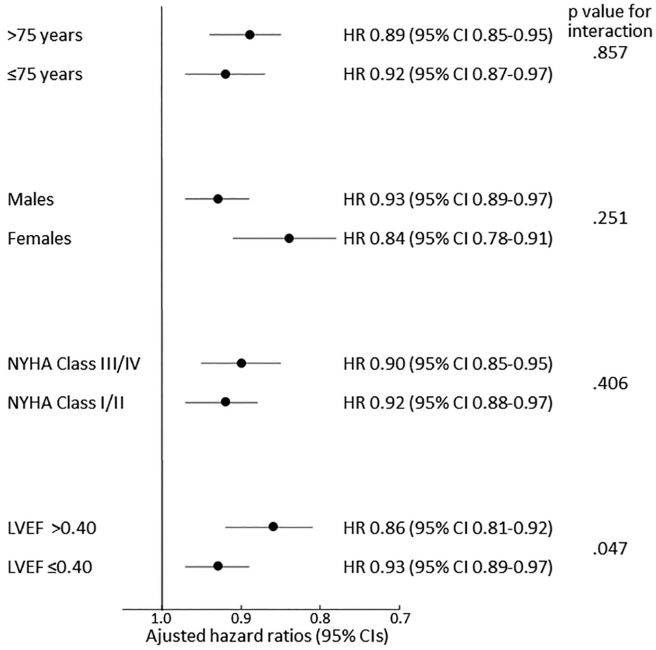

FIGURE 2 Multivariable-adjusted hazard ratios of the primary outcome according to age, sex, NYHA class and left ventricular ejection fraction. Hazard ratios are for 50 m increase in 6MWD

patients with missing data for 6MWT at admission (N. 203) or at discharge (N. 60). For these patients, no reason for not performing the test could be retrieved from our electronic Health Information System.

Prognostic value of discharge 6MWD

In the whole cohort, mean 6MWD significantly increased from admission to discharge (145 to 210 m; $p < 0.001$) (Table 1). The effect size was 0.69 (95% CI 0.62–0.76). The optimal cutoff for discharge 6MWD was 198 m. During a total follow-up of 1653 person-years, 331 deaths (20.0 deaths/100 person-years; 95%CI 18.0–22.3) occurred. The incidence rate of death/100 person-years for the patients who walked ≥198 m was 13.0 (95% CIs 10.0–15.5) compared with 30.8 (95% CIs 26.9–35.4) for those who walked <198 m ($p < 0.001$). Figure S1 shows Kaplan–Meier estimates of cumulative incidence of mortality for patients stratified by the optimal cutoff. In model 2, discharge 6MWD emerged as the most important variable to predict long-term mortality, based on Wald statistics (Table S2). The association between discharge 6MWD and risk of mortality was approximately linear (Figure S2), and the test for nonlinearity was not significant ($p = 0.064$). The adjusted HR for each 50 m-increase in discharge 6MWD was 0.90 (95% CI 0.87–0.94; $p < 0.001$) and that for discharge 6MWD dichotomized at the optimal cutoff 0.48 (95% CI 0.38–0.60; $p < 0.001$). After further adjustment for admission 6MWD (model 3), the HRs were 0.93 (95% CI 0.87–0.99; $p = 0.024$) and 0.51 (95% CI 0.36–0.72; $p < 0.001$), respectively. The adjusted HR for change in 6MWD from admission to discharge dichotomized at the optimal cut-off was 0.71 (95% CI 0.56–0.89; $p = 0.003$). No significant interaction of discharge 6MWD with age, sex, or NYHA class on the risk of death was observed (Figure 2). The interaction between discharge 6MWD and LVEF was statistically significant (Figure 2). Table S3 displays baseline characteristics by LVEF. Compared with the patients with LVEF ≤0.40, those with LVEF >0.40 were older and more often females, had a higher comorbid burden and presented with a poorer functional status at admission.

In the subgroup of 478 patients with available data for NT-proBNP, mean 6MWD significantly increased (145 to 205 m; $p < 0.001$). The optimal cutoff for discharge 6MWD was 220 m. During a total follow-up of 1038 person-years, 204 deaths (19.7 deaths/100 person-years; 95% CI 17.1–22.5) occurred. After adjustment, the HR for each 50 m-increase in discharge 6MWD was 0.94 (95% CI 0.90–0.98; $p = 0.007$) and that for discharge 6MWD dichotomized at the optimal cutoff 0.56 (95% CI 0.41–9.76; $p < 0.001$).

Incremental prognostic value of discharge 6MWD

The addition of discharge 6MWD to the baseline risk model significantly improved model fit and risk classification

TABLE 2 Incremental prognostic value of discharge 6-min walking distance for 3-year mortality

	Model 1 (Baseline risk model[a])	Model 2 (Baseline risk model plus discharge 6MWD [per 50 m-increase])	*p* value	Model 2 (Baseline risk model plus discharge 6MWD dichotomized at the optimal cutoff)	*p* value
All patients (N.759)					
Global χ^2 values	154.14	183.90	<0.001	194.49	<0.001
Category-free NRI (95% CI)		0.440 (0.297–0.584)	<0.001	0.522 (0.378–0.665)	<0.001
NRI for event (95% CI)		0.118 (0.010–0.226)	0.032	0.208 (0.101–0.316)	<0.001
NRI for non-event (95% CI)		0.322 (0.228–0.417)	<0.001	0.313 (0.218–0.408)	<0.001
IDI (95% CI)		0.030 (0.018–0.042)	<0.001	0.039 (0.025–0.053)	<0.001
Patients with available data for NT-proBNP (N. 478)[b]					
Global χ^2 values	145.85	153.07	0.007	160.09	<0.001
Category-free NRI (95% CI)		0.339 (0.158–0.520)	<0.001	0.486 (0.305–0.667)	<0.001
NRI for event (95% CI)		0.098 (−0.039–0.235)	0.161	0.275 (0.137–0.412)	<0.001
NRI for non-event (95% CI)		0.241 (0.122–0.359)	<0.001	0.212 (0.093–0.330)	<0.001
IDI (95% CI)		0.012 (0.002–0.022)	0.014	0.022 (0.008–0.036)	0.002

Abbreviations: 6MWD, 6-min walking distance, NRI, net reclassification improvement, IDI, integrated discrimination improvement.
[a]The baseline risk model includes age, sex, diabetes, chronic obstructive pulmonary disease, NYHA class, systolic blood pressure, left ventricular ejection fraction, estimated glomerular filtration rate, blood urea nitrogen, sodium, hemoglobin, and treatment with beta-blockers or renin angiotensin system inhibitors.
[b]The baseline risk model includes age, sex, diabetes, chronic obstructive pulmonary disease, NYHA class, systolic blood pressure, left ventricular ejection fraction, estimated glomerular filtration rate, blood urea nitrogen, sodium, hemoglobin, treatment with beta-blockers or renin angiotensin system inhibitors and NT-proBNP.

(Table 2). Comparable results were obtained in the subgroup with available data for NT-proBNP (Table 2).

DISCUSSION

Although poor functional status is highly prevalent among older patients hospitalized for HF and marks a downward inflection point in functional and prognostic trajectories, it is generally not addressed in clinical care pathways.[22] Three major findings emerged from this study (Figure 3). First, functional capacity significantly improved after transitional CR. Second, increasing levels of functional capacity following CR were independently associated with decreasing long-term risk of death. Third, the level of functional capacity following CR provided incremental prognostic information over well-established, powerful prognostic factors. To the best of our knowledge, the present study is the first to show that improved functional capacity after transitional CR confers a survival benefit in older patients hospitalized for HF. Despite the substantial limitations of this observational, uncontrolled, retrospective study, we demonstrated that functional capacity at discharge from CR was significantly associated with long-term survival in older adults recovering from acute HF after adjustment for well-established conventional and disease-focused prognostic factors and for baseline functional capacity and provided incremental prognostic information. Since the observational design of the study limits the inference about causality, a prospective randomized or cohort control trial would be needed to validate our findings.

The baseline characteristics of the patients enrolled in the present study are indicative of a cohort of vulnerable, severely disabled patients. In such patients, a 6MWT may represent maximal effort[38] and its responsiveness is greatest.[23,24,39] The benefit of CR on functional capacity in HF is well-established.[38,40] Consistent with the REHAB-HF trial,[20] a significant improvement in functional capacity was achieved after transitional rehabilitation. The effect size was 0.69, suggesting a moderate-to-large improvement. The level of functional capacity at discharge, as assessed by the 6MWD, was closely associated with the incidence of the primary outcome, on top of the baseline risk model including established demographic, clinical and laboratory prognostic factors. Notably, 6MWD ranked as the most important variable to

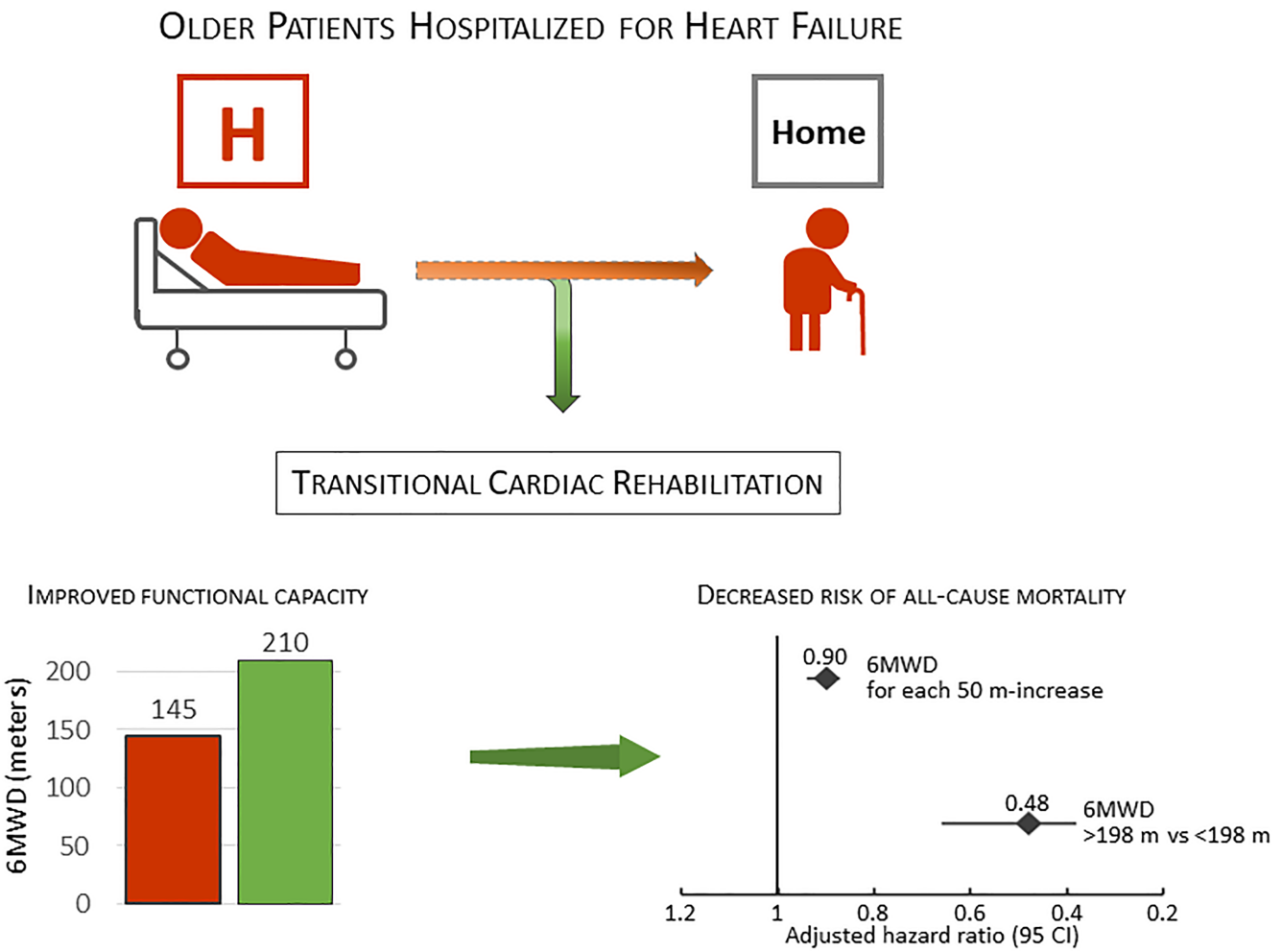

FIGURE 3 The level of functional capacity achieved after transitional rehabilitation is closely associated with long-term survival in older patients hospitalized for heart failure. 6MWD, 6-min walking distance

predict long-term mortality. After full adjustment, each 50 m-increase in discharge 6MWD was associated with a 10% decreased risk for the primary outcome. When 6MWD was analyzed as binary variable, longer distances were associated with a 52% decreased risk of the primary outcome. The patients who walked <198 meters had an annual death rate 2.4 times higher than that of the patients who walked >198 meters. Further adjustment for baseline functional capacity or for NT-proBNP did not affect the relationship between discharge 6MWD and the primary outcome.

Heart failure patients with preserved EF (HFpEF) are a key subgroup, particularly relevant to older persons.[41] We observed a statistically significant interaction of discharge 6MWD with LVEF on the risk of death, suggesting a potentially larger survival benefit in patients with HFpEF than in those with HFrEF. This finding is in line with a companion paper from REHAB-HF trial.[42] In that study, "patients with HFpEF appeared to potentially be more responsive to the rehabilitation intervention and had significantly greater benefit for all-cause death and global rank end point", including death + all-cause hospitalization + global physical function, than patients with HFrEF.[42] Of interest, based on the results of an economic analysis of the REHAB-HF trial, Chew suggested that longer-term benefits of the rehabilitation intervention, particularly in the subgroup of patients with HFpEF, may yield good value to the health care system.[43] Taken together, these findings provide important background and context for a future randomized clinical trial aimed at determining the impact of transitional CR on clinical outcomes of HFpEF patients after a hospitalization for HF, "a large and growing population of high-risk patients for whom limited evidence-based treatments are available".[42] Conversely, no significant interaction between NYHA class and 6MWD on the risk of death was observed. This finding does not contradict the concept that 6MWD is inversely correlated with NYHA functional classification levels.[44]

A remarkable finding of our study is that the addition of discharge 6MWD to established demographic, clinical

and laboratory prognostic factors - including NT-proBNP, which is generally regarded as the most powerful predictor of death in HF - significantly improved the outcome prediction. Furthermore, reclassification improvement analyses showed that the addition of discharge 6MWD to the baseline risk model yielded an improvement of risk stratification.

Currently, only a minimal proportion of elderly patients hospitalized for HF participate in CR.[18,19] A scientific statement from the American Heart Association emphasized the importance of prioritizing functional capacity as a principal end-point for therapies oriented to older adults with cardiovascular disease.[38] However, there is a dearth of research specifically addressing the diverse population of older patients hospitalized for HF. In the recent REHAB-HF trial,[20] a transitional rehabilitation intervention resulted in greater improvement in physical function than usual care in older patients hospitalized for HF. Our findings, by showing that the level of functional capacity achieved after transitional CR is closely associated with long-term survival, add to the REHAB-HF trial results and provide further supportive evidence for prioritizing improvement in functional capacity as a therapeutic target in older patients hospitalized for.[45]

Limitations

Some limitations must be acknowledged. First, this study was retrospective in nature. Although we adjusted for well-established prognostic factors, other unmeasured factors might have influenced the association between the exposure and outcome. Second, the patients' baseline characteristics are indicative of a cohort with severe functional impairment. Such patients are at high risk of poor prognosis. Moreover, for severely disabled, ill patients, outpatient rehabilitation may not be a feasible management option. This limits generalizability of the results. Third, there was no control group. Thus, a residual confounding effect resulting from spontaneous, though unlikely,[10] improvement in 6MWD cannot be excluded. Fourth, 203 patients had missing data for 6MWT at admission and 60 at discharge. For these patients, no reason for not performing the 6MWT could be retrieved from our electronic Health Information System. Compared to the patients with available data for 6MWT, those with missing data for admission 6MWT were older, had a higher prevalence of moderate-to-severe anemia (hemoglobin <11 g/dL) and higher NT-proBNP levels, and more often presented with total/severe dependence in activities of daily living (Table S1). These data suggest that the test may have been perceived as too demanding or unwarranted for these high-risk patients by the treating cardiologist. Consistent with this hypothesis, the patients with missing data for 6MWT at admission had a markedly higher annual death rate than the included patients (Table S1). Conversely, no differences in baseline characteristics between patients with missing data for 6MWT at discharge and those with available data were observed, except for a significantly longer distance walked at admission by the patients with missing data (Table S1), suggesting administrative reasons or unwillingness to perform the test as the most plausible reasons for missingness. Fifth, for the subgroup with HFpEF (Table S3), background therapies differ considerably from those that are considered guidelines directed medical treatments in the U.S.; this may limit generalizability of the results. It should however be considered that nine in ten patients with preserved EF were hypertensive (Table S3) and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and beta blockers are recommended treatments for hypertensive patients with HFpEF, based on expert consensus.[46] This may at least partially account for the high prescription rate of these therapies in the subgroup with HFpEF. Finally, since this was a retrospective study, we could not provide details about the rehabilitation sessions.

Conclusions

A rehabilitation intervention provided in the critical hospital-to-home transition period to older patients hospitalized for HF resulted in improved functional capacity. Increasing levels of functional capacity following CR were closely associated with decreasing long-term risk of death. These findings may contribute to promote referral of older patients to CR after a hospitalization for HF, increase the awareness of the benefits of transitional rehabilitation in this diverse patient population, and promote prospective randomized or cohort control trial to assess causality.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest. The Authors declare that no relationship with industry exists.

AUTHOR CONTRIBUTIONS

Domenico Scrutinio and Pietro Guida conceived, planned and supervised the research. Pietro Guida performed the statistical analysis. Domenico Scrutinio wrote the manuscript with the support of Andrea Passantino and Roberta Ruggieri All Authors discussed the results and approved the final version of the manuscript.

SPONSOR'S ROLE

This research did not receive any specific grant from funding agencies in the public or commercial sectors.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

Table S1. Baseline characteristics of the patients with missing data for 6-min walking test compared with enrolled patients.
Table S2. Significant predictors of the primary outcome.
Table S3. Baseline characteristics by left ventricular ejection fraction.
Figure S1. Kaplan–Meier estimates of cumulative incidence of mortality for patients stratified by the optimal cutoff of discharge 6-min walking distance.
Figure S2. All-cause mortality by 6-min waking distance: restricted cubic spline plot.

How to cite this article: Scrutinio D, Guida P, Ruggieri R, Passantino A. Prognostic value of functional capacity after transitional rehabilitation in older patients hospitalized for heart failure. *J Am Geriatr Soc*. 2022;70(6):1774-1784. doi:10.1111/jgs.17736