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Functional Limitations Predict the Risk of Rehospitalization Among Patients With Chronic Heart Failure

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Writing group on behalf of the PTMaTCH collaborators

Background: Although functional limitations (FLs) can predict clinical deterioration in chronic heart failure (CHF), few studies have focused on the associated clinical significance. The aim of the present study was to examine the association between FL and changes in the related time course with subsequent hospital readmission in CHF patients.

Methods and Results: FLs were analyzed using the Performance Measure for Activities of Daily Living-8 (PMADL-8; higher scores indicate worse FLs) for 215 CHF patients at 1 and 3 months after discharge in a multicenter cohort study. The mean follow-up was 20 months. In a multivariate Cox regression analysis including covariates, only the PMADL-8 score remained significantly related to rehospitalization of CHF (hazard ratio, 2.49; 95% confidence interval: 1.27–4.90; P<0.01). Event-free survival differed significantly among the 4 PMADL-8 time-course groups (P<0.01). The persistent low-FL group had lower event rates than the other 3 time-course groups (P<0.01).

Conclusions: FLs as measured by the PMADL-8 and the time course of the PMADL-8 score predict readmission in CHF patients after discharge. Accordingly, FL assessment is recommended as part of the clinical management because it not only identifies decline in physical function but also guides prognosis in CHF patients. (*Circ J* 2012; **76:** 1654–1661)

Key Words: Chronic heart failure; Functional limitation; Rehospitalization

Chronic heart failure (CHF) is characterized by limited exercise performance, which is mainly determined by disease-specific factors, such as diminished cardiac output, abnormal ventilatory response, and low perfusion in skeletal muscles, which lead to skeletal muscle dysfunction.[1] Exercise intolerance and symptoms may lead to activity restriction and further functional deterioration with the progression of CHF.[2] Declines in physical function in CHF patients are therefore one of the key aspects of clinical management.

To date, few studies have focused on physical functional decline in patients with CHF. Although some reports have studied functional outcomes, these measures were commonly used for symptom or quality-of-life assessments,[3,4] and the results of these studies may not be sufficient to provide information about functional status.[5] In the process of functional decline, it is critical to measure the onset of "difficulty" in performing daily physical activities (functional limitations [FLs]).[6] Indeed, FLs are important risk factors for subsequent disability, institutionalization,[7] and also coronary heart disease mortality.[8] In addition, difficulty with physical performance due to HF reflects the existence of a clinical condition according to the New York Heart Association (NYHA) functional classification. Severe FL has been suggested to be associated with increased risk for rehospitalization and mortality in CHF patients.[9,10]

Therefore, FLs are not only a marker of functional decline but also have the potential to predict clinical status in CHF patients. Both standardized measures for FL and prospective cohort studies are needed in order to examine this relationship. The Performance Measure for Activities of Daily Living-8 (PMADL-8) is a new self-administered questionnaire developed to provide a measure of FL in CHF patients.[11] It has been proven to be reliable and valid and has been shown to discriminate between mild and severe CHF. It is unknown, however, whether FLs, as measured by PMADL-8, can identify patients at high risk for further deterioration in clinical status associated with hospital readmission.

Therefore, the aim of the present study was to examine the association between FL and subsequent hospital readmission

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by prospective and continuous follow-up over a period of 2 years in a multicenter cohort of CHF patients. Furthermore, to improve the clinical applicability of FL assessments, we also investigated whether the time-course change of the FLs was associated with rehospitalization in CHF patients after discharge.

Methods

Study Design and Patients

Patients were recruited through the Preventive Effect of Exercise for Management of Daily Functioning in Patients with CHF (PTMaTCH) study – a rehabilitation cohort study of CHF patients. A list of participating investigators and institutions is provided in **Appendix 1**. The goal of this multicenter cohort study was to describe the natural course of daily functioning of CHF patients after discharge. Details of the inclusion and exclusion criteria and study design have been provided previously.[12] Briefly, 254 patients with an admission diagnosis of CHF, left ventricular ejection fraction (LVEF) ≤40%, or plasma B-type natriuretic peptide (BNP) level ≥80 pg/ml as well as NYHA functional classification II–IV were followed up serially at 1, 3, 5, 12, and 24 months after discharge. FL assessments were performed using the PMADL-8. Exclusion criteria included (1) inability to walk a minimum distance (50 m) with or without a walking aid; (2) Mini-Mental State Examination (MMSE) score[13] ≤18; (3) cardiac surgery during hospitalization; (4) obstructive pulmonary disease (COPD); or (5) severe mental illness. Because 95% of the healthy population >65 years old scored ≥19 points,[14] the MMSE score was set at ≤18 as part of the exclusion criteria. The institutional review board or ethics committee at each site involved in the PTMaTCH study approved the protocol, and all patients provided written informed consent before enrollment.

Measures

Demographic and Physical Function Variables Patients were interviewed and assessed at the time of discharge for demographic information and physical function variables (6-min walk distance [6MWD], handgrip strength, and knee extensor muscle strength). The following clinical information was documented by the attending cardiologist: cause of HF and comorbidities, LVEF, laboratory tests at discharge, and discharge medications. BNP levels were measured during hospitalization. Estimated glomerular filtration rate (eGFR) was calculated using the following equation: eGFR ($ml \cdot min^{-1} \cdot 1.73\,m^{-2}$) = $194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287} \times 0.739$ (if female).[15] Patients with previous myocardial infarction were defined as having CHF due to ischemic heart disease. Details of the methods of measurement are published elsewhere.[12]

FL FLs were assessed using the PMADL-8, which is a self-administered and disease-specific FL measure for patients with CHF.[11] The scale consists of 8 items and assesses the difficulty in performing specified daily physical activities using a 4-category response scale (**Table 1**) for the past 1 month. Raw summary scores were transformed to interval-level scores along the same difficulty continuum, which was established using Rasch methods. Scores range from 8 to 32, with higher scores reflecting more severe FLs. The validity and reproducibility of the PMADL-8 have been previously established in subjects with CHF.[11]

The PMADL-8 is also associated with peak oxygen uptake (peak $\dot{V}O_2$). A receiver operating characteristic analysis showed 3 PMALD-8 cut-off points for discriminating FL in terms of peak $\dot{V}O_2$ as follows: PMADL-8 ≥18, peak $\dot{V}O_2$ <18 $ml \cdot kg^{-1} \cdot min^{-1}$; PMADL-8 ≥20, peak $\dot{V}O_2$ <16 $ml \cdot kg^{-1} \cdot min^{-1}$; and PMADL-8 ≥22, peak $\dot{V}O_2$ <14 $ml \cdot kg^{-1} \cdot min^{-1}$.[16] These peak $\dot{V}O_2$ values indicate an important level of physical fitness for having FLs[17] or poor prognosis of CHF.[18] Because the focus of the current study was the investigation of PMADL-8 prognosis information, the PMADL-8 score was converted into categorical variables in statistical analysis based on the aforementioned 3 threshold scores obtained from our previous study. In addition, we collected the PMADL-8 after discharge, not at discharge. Because the PMADL-8 focuses on difficulty in daily physical activity during the past 1 month, we note that the PMADL-8 at discharge does not reflect real daily physical activity because of hospitalization, and, in turn, PMADL-8 score at discharge may reflect unusual activity, which is not correct FL by definition.

Table 1. Performance Measure for Activities of Daily Living-8

1, very easy; 2, somewhat easy; 3, somewhat hard; 4, very hard
1. Getting up and off the floor without tools
2. Washing your body and hair
3. Walking upstairs without a handrail
4. Vacuuming your room
5. Pulling and closing a heavy sliding door
6. Getting into and out of a car
7. Walking at the same speed with someone of the same age
8. Walking up a slight slope for 10 min

Outcomes

Outcome included rehospitalization for CHF exacerbation during the follow-up period. Rehospitalization was determined by cardiologists at each of the enrolling sites and obtained via 3-month follow-up calls by research staff. The follow-up period was defined as the time from discharge until (1) death or rehospitalization for CHF; (2) death or prolonged hospitalization for non-cardiovascular reasons; (3) occurrence of motor disorders; (4) refusal to participate any further; or (5) the end of follow-up.

Statistical Analysis

Categorical data are presented as n (%) and continuous variables as mean±SD. Differences between patient groups were evaluated using the Student's t-test, Wilcoxon rank-sum test, or 1-way analysis of variance for continuous variables and chi-squared analysis for categorical variables. To assess and compare the prognostic values of different parameters, Cox proportional hazard regression analysis was performed using PMADL-8 scores at 1 month after discharge. At first, the unadjusted association between 1-month PMADL-8 and the outcome was tested through Cox regression analysis to compare the prognostic values. Then, multivariate Cox regression analysis was performed. Model covariates included candidate predictor variables[19–21] (**Table 2**) that had a significant difference with the outcome variable (rehospitalization during follow-up). The models were built stepwise, and the P-value for entering and staying in the model was set at 0.05.

To assess the relative importance of the course of FLs as predictors of outcome in CHF, we also conducted additional analysis. Using the difference in the PMADL-8 score (significant PMADL-8 best threshold scores of the outcome) from 1 month to 3 months after discharge, the patients were divided into the following 4 groups: (1) high cut-off points at 1 and 3

Table 2. Patient Characteristics

	Total	PMADL-8 <20	PMADL-8 ≥20	P-value
n	215	115	100	
Age (years)	69±11	66±11	72±10	<0.001
Male	133 (61.9)	80 (69.6)	53 (53.0)	<0.01
BMI (kg/m^2)	22.0±3.6	22.1±3.5	22.0±3.7	0.78
Cause of heart failure				
Ischemic	97 (45.1)	46 (40.0)	51 (51.0)	0.06
Dilated cardiomyopathy	49 (22.7)	33 (28.6)	16 (16.0)	0.02
Hypertrophic cardiomyopathy	10 (4.7)	4 (3.5)	6 (6.0)	0.29
Valvular	24 (11.2)	8 (7.0)	16 (16.0)	0.03
Hypertensive	19 (8.8)	9 (7.8)	10 (10.0)	0.63
Other	16 (7.4)	15 (13.0)	1 (1.0)	<0.01
Comorbidities				
Hypertension	131 (60.9)	72 (62.6)	59 (59.0)	0.34
Diabetes	73 (34.0)	35 (30.4)	38 (38.0)	0.15
Coronary artery bypass surgery	26 (12.1)	15 (13.0)	11 (11.0)	0.40
eGFR <60 ml·min^{-1}·1.73 m^{-2}	113 (62.4)	57 (49.6)	59 (59.0)	0.21
Stroke	13 (6.0)	4 (3.5)	9 (9.0)	0.08
Medications				
ACE inhibitor/ARB	164 (76.3)	93 (80.9)	71 (71.0)	0.09
β-blockers	159 (74.0)	91 (79.1)	68 (68.0)	0.06
Diuretics	181 (84.2)	92 (80.0)	89 (89.0)	0.07
Digoxin	46 (21.4)	24 (20.9)	22 (22.0)	0.49
LVEF (%)	40.0±15.5	38.6±15.6	41.8±15.3	<0.001
BNP (pg/ml)	395 (600)	351 (510)	528 (623)	0.02
Serum hemoglobin (g/dl)	12.5±2.2	13.2±2.1	11.8±2.0	<0.001
Serum albumin (g/dl)	3.7 (0.6)	3.8 (0.5)	3.6 (0.7)	<0.001
Serum sodium (mmol/L)	139 (4)	139 (4)	139 (3)	0.68
NYHA functional class on admission				0.39
II	51 (23.7)	31 (27.0)	20 (20.0)	
III	90 (41.9)	44 (38.3)	46 (46.0)	
IV	74 (34.4)	40 (34.8)	34 (34.0)	
Six-min walk distance (m)	359±116	392±101	321±120	<0.001
Grip strength (kg)	25±10	28±10	22±9	<0.001
Knee extensor muscle strength (Nm/kg)	1.1±0.6	1.3±0.6	0.9±0.5	<0.001

Data given as n (%), mean±SD, or median (IQR).
PMADL-8, Performance Measure for Activities of Daily Living-8; BMI, body mass index; eGFR, estimated glomerular filtration rate; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; LVEF, left ventricular ejection fraction; BNP, brain natriuretic peptide; NYHA, New York Heart Association.

months (high-high; persistent severe FL); (2) low cut-off points at both time points (low-low; persistent low FL); (3) high cut-off at 1 month and low cut-off at 3 months (high-low; decreased severity of FL); and (4) low cut-off at 1 month and high cut-off at 3 months (low-high; increased severity of FL). To compare event-free survival between patient groups, a Kaplan-Meier analysis was performed using the log-rank test for statistical differences.

All data were analyzed using SPSS version 19.0 for Windows (SPSS, Chicago, IL, USA). P<0.05 was considered statistically significant.

Results

Patient Characteristics

Of the 254 patients enrolled in the PTMaTCH study, 215 provided 1-month PMADL-8 data. Characteristics of those 215 are included in Table 2. Before the 1-month post-discharge follow-up, 2 patients had died, 8 were re-hospitalized with acute exacerbation, 1 was hospitalized for reasons other than HF, 3 were excluded due to COPD, 2 were excluded due to severe mental illness, 6 withdrew from the study, 14 did not answer the PMADL-8 at 1 month, and 3 were lost to follow-up for other reasons. There were no differences in the characteristics of the 215 patients compared with the full cohort of 254 enrolled individuals. Of the 215 patients followed in this study, 41 were rehospitalized due to worsening HF, and 1 patient died of HF during the 24-month follow-up period (mean, 20±8 months). The total number of endpoints was 41 (19.1%). A total of 15 patients were rehospitalized due to HF exacerbation within the 1–3-month follow-up period, and an additional 26 were rehospitalized by the 24-month follow-up. Of these 215 patients, 181 provided 3-month PMADL-8 data. Of the 34 patients who were not followed up with the PMADL-8 at 3 months, 15 were rehospitalized due to HF, 2 died of reasons other than HF, and 17 failed to complete the PMADL-8 at 3 months. No significant differences in age, gender, CHF etiology, or physician classification of CHF status were found

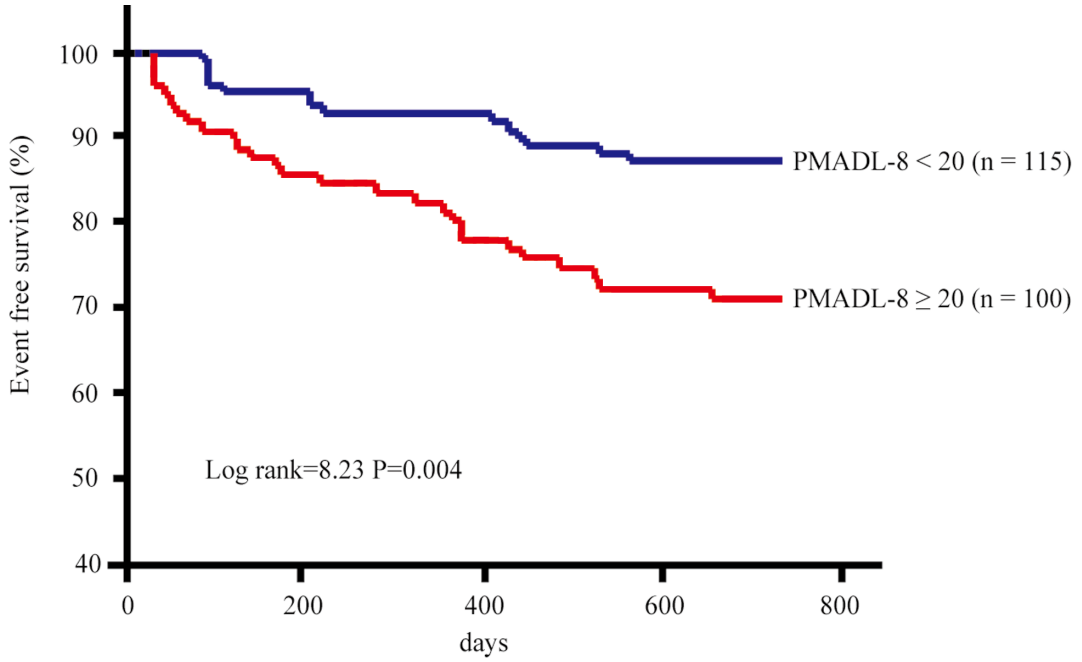

Figure 1. Kaplan-Meier curves for event-free survival according to the Performance Measure for Activities of Daily Living-8 (PMADL-8) score at 1 month.

between those with and without complete PMADL-8 assessments at 3 months.

The PMADL-8 score at 1 month for the entire group was 19±6 (median, 19), which reflected moderate FL. At 3 months, the PMADL-8 scores for the patients who survived to the 3-month follow-up had decreased to 18±6 (median, 18), meaning that FL had improved slightly. The PMADL-8 score at 1 month was ≥18 in 129 patients (60.0%), ≥20 in 100 patients (46.5%), and ≥22 in 75 patients (34.9%). The characteristics of the PMADL-8 score group are listed in Table 2. Patients with PMADL-8 ≥20 at 1 month were older, with higher LVEF, lower serum hemoglobin level, lower serum albumin level, and lower physical function (grip strength, knee extensor muscle strength, 6MWD) compared to those with PMADL-8 <20.

Prognostic Value of the PMADL-8 Score

PMADL-8 ≥20 at 1 month was a significant univariate predictor of CHF rehospitalization (hazard ratio [HR], 2.49; 95% confidence interval [CI]: 1.31–4.75; P=0.01). Other cut-off points, PMADL-8 ≥18 and ≥22 at 1 month, were not significantly associated with CHF rehospitalization (P=0.11 and P=0.60, respectively). Using multivariate Cox regression analysis, PMADL-8 ≥20 remained predictive of CHF rehospitalization after adjustment for covariates (HR, 2.49; 95%CI: 1.27–4.90; P=0.008). Model covariates that had a significant difference with the outcome variable included BNP, hypertrophic cardiomyopathy, and grip strength (P<0.10). A PMADL-8 score ≥20 at 1 month was an independent predictor of CHF rehospitalization. This finding was further confirmed on Kaplan-Meier analysis. The group of patients with PMADL-8 ≥20 at 1 month (event rate, 27.0%; 27/100) had a significantly worse prognosis in comparison to patients with PMADL-8 <20 (event rate, 12.2%; 14/115; log-rank test P<0.01; Figure 1). At 6 months after discharge, Kaplan-Meier estimates of rehospitalization for CHF were 14% in patients who had PMADL-8 ≥20 and 4% in patients who had PMADL-8 <20; at 12 months after discharge, these proportions were 19% and 7%, respectively. The PMADL-8 assessment characteristics for the prognosis of CHF rehospitalization yielded a positive predictive value of 27% and a negative predictive value (NPV) of 88%.

Time Course of PMADL-8

Using a cut-off of 20 for the PMADL-8, patients were separated into 4 time-course groups: (1) persistent severe FLs (high-high; PMADL-8 ≥20 at 1 and 3 months); (2) persistent low FLs (low-low; PMADL-8 <20 at 1 and 3 months); (3) decreased-severity FLs (high-low; PMADL-8 ≥20 at 1 month and PMADL-8 <20 at 3 months); and (4) increased-severity FLs (low-high; PMADL-8 <20 at 1 month and PMADL-8 ≥20 at 3 months). The clinical characteristics of these 4 groups are described in Table 3. Patients with higher FLs were older and had lower albumin levels, lower hemoglobin levels, and lower levels of physical function, as indicated by the lower grip strength, knee extensor muscle strength, and 6MWD. Event-free survival (survival without hospital readmission) in the persistent low-FL group differed significantly from that in the other 3 groups (overall log-rank test P<0.01). Patients with persistent low FL had significantly lower event rates (5.4%) than the other 3 time-course groups (vs. 20.0% in high-high P<0.01; vs. 25.0% in high-low P<0.01; vs. 50.0% in low-high P<0.001; Figure 2).

Discussion

The present cohort study demonstrates that FLs measured on the PMADL-8 and the time course of the PMADL-8 score after discharge predicted further adverse events in CHF pa-

Table 3. Patient Characteristics vs. PMADL-8 Score at 1 and 3 Months

	Low-low	Low-high	High-low	High-high	P-value
n	93	8	20	60	
Age (years)	65±11	71±9	71±7	73±10	<0.001
Male	65 (69.9)	5 (62.5)	13 (65.0)	31 (51.7)	0.16
BMI (kg/m^2)	22.0±3.7	20.9±2.8	20.9±3.1	22.4±4.1	0.36
Cause of heart failure					
Ischemic	36 (38.7)	3 (37.5)	9 (45.0)	31 (51.7)	0.40
Dilated cardiomyopathy	28 (30.1)	1 (12.5)	2 (10.0)	6 (10.0)	0.01
Hypertrophic cardiomyopathy	2 (2.2)	2 (25.0)	1 (5.0)	5 (8.3)	0.03
Valvular	8 (8.6)	0 (0)	3 (15.0)	11 (18.3)	0.20
Hypertensive	8 (8.6)	0 (0)	2 (10.0)	7 (11.7)	0.72
Other	11 (11.8)	2 (25.0)	3 (15.0)	0 (0.0)	0.02
Comorbidities					
Hypertension	60 (64.5)	2 (25.0)	14 (70.0)	37 (61.7)	0.14
Diabetes	26 (28.0)	3 (37.5)	6 (30.0)	27 (45.0)	0.18
Coronary artery bypass surgery	12 (12.9)	1 (12.5)	1 (5.0)	7 (11.7)	0.80
eGFR <60 ml·min^{-1}·1.73 m^{-2}	52 (55.9)	5 (62.5)	15 (75.0)	41 (68.3)	0.34
Stroke	3 (3.2)	0 (0)	0 (0)	7 (11.7)	0.08
Medications					
ACE inhibitor/ARB	74 (79.6)	8 (100.0)	18 (90.0)	38 (63.3)	0.01
β-blockers	71 (76.3)	6 (75.0)	13 (65.0)	42 (70.0)	0.69
Diuretics	74 (79.6)	8 (100.0)	19 (95.0)	51 (85.0)	0.19
Digoxin	22 (23.7)	1 (12.5)	4 (20.0)	13 (21.7)	0.89
LVEF (%)	38.1±15.5	40.9±16.4	38.3±13.4	43.3±16.6	0.23
BNP (pg/ml)	338 (530)	315 (321)	523 (564)	531 (748)	0.29
Serum hemoglobin (g/dl)	13.2±2.0	12.3±2.6	11.9±1.9	11.9±2.0	<0.001
Serum albumin (g/dl)	3.8 (0.5)	4.1 (0.5)	3.6 (0.7)	3.7 (0.7)	0.04
Serum sodium (mmol/L)	139 (4)	139 (5)	140 (5)	139 (3)	0.96
NYHA functional class on admission					0.80
II	26 (28.0)	1 (12.5)	5 (25.0)	13 (21.7)	
III	40 (43.0)	3 (37.5)	7 (35.0)	28 (46.7)	
IV	27 (29.0)	4 (50.0)	8 (40.0)	19 (31.7)	
Six-min walk distance (m)	386±103	384±75	349±127	313±116	0.001
Grip strength (kg)	29±10	23±14	24±11	21±8	<0.001
Knee extensor muscle strength (Nm/kg)	1.2±0.6	1.3±0.3	1.1±0.7	0.9±0.4	0.003
PMADL-8 at 1 month (points)	14±3	17±2	22±2	25±3	<0.001
PMADL-8 at 3 months (points)	13±3	22±3	17±2	24±3	<0.001

Data given as n (%), mean±SD, or median (IQR).
P-value indicates a difference among the following 4 groups: high-high, PMADL-8 ≥20 at 1 and 3 months; low-low, PMADL-8 <20 at 1 and 3 months; high-low, PMADL-8 ≥20 at 1 month and PMADL-8 <20 at 3 months; and low-high, PMADL-8 <20 at 1 month and PMADL-8 ≥20 at 3 months.
Abbreviations as in Table 2.

tients after discharge. PMADL-8 had a relationship with readmission even after adjustment for demographic characteristics and clinical factors. In those with PMADL-8 ≥20 at 1 month after discharge, the rate of HF rehospitalization was 2-fold greater when compared with patients with PMADL-8 <20. Accordingly, patients with PMADL-8 <20 at both 1 and 3 months after discharge had the lowest readmission rate during the 2-year follow-up period. These results extend our recently reported study that described an association of PMADL-8 with disease severity.[11] In addition, the present study was a multicenter cohort study including patients with a broader range of CHF etiologies, which avoided the potential selection biases of a single-center study. All of these considerations underline the prognostic importance of FLs in CHF patients.

The present findings add new information to the existing body of literature on FLs in patients with CHF. The present subjects included high-risk patients after an acute exacerbation of CHF because almost one-half of all patients admitted for decompensated CHF are readmitted within 6 months after discharge.[22] In the present study, within the 6 months after discharge, we found a sharp increase in the readmission rate among patients with PMADL-8 ≥20 at 1 month. Thus 1-month PMADL-8 assessment may identify patients who are at high risk for further readmission in post-discharge care. Although 3-month PMADL-8 ≥20 was also an independent predictor of CHF hospitalization (data not shown), early post-discharge follow-up for high-risk patients may be effective to reduce readmission rates and improve health-care outcomes for patients with CHF.[23]

The present findings have some implications for the treatment of CHF patients after discharge. First, it was found that the PMADL-8 provides additional prognostic information to

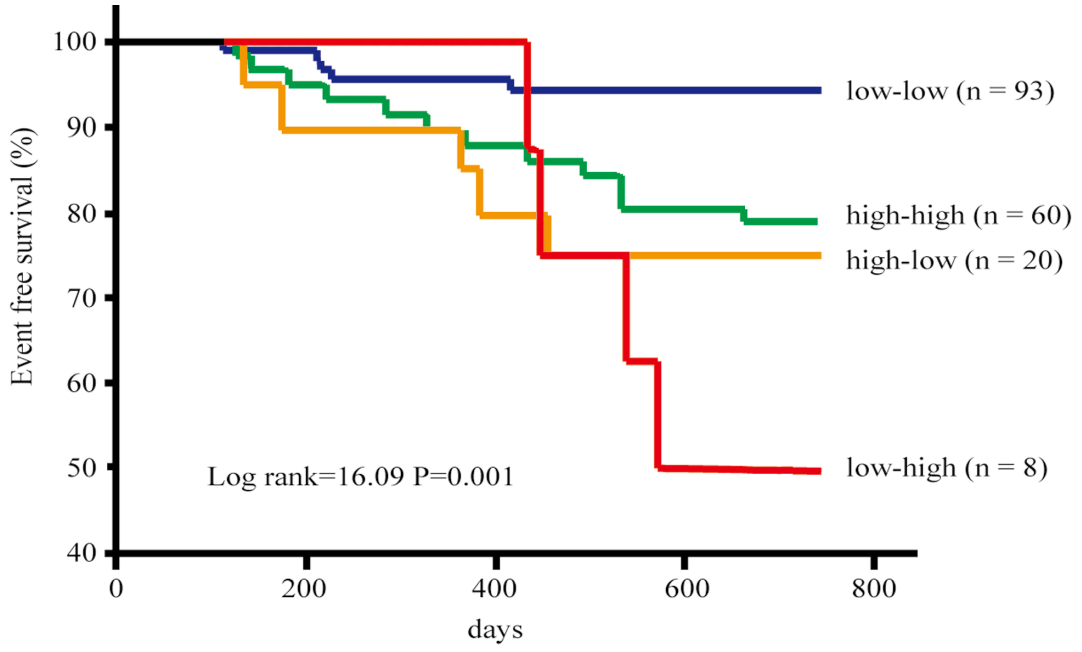

Figure 2. Kaplan-Meier curves for event-free survival according to the Performance Measure for Activities of Daily Living-8 (PMADL-8) score at 1 and 3 months. High–high, PMADL-8 ≥20 at 1 and 3 months; low–low, PMADL-8 <20 at 1 and 3 months; high–low, PMADL-8 ≥20 at 1 month and PMADL-8 <20 at 3 months; and low–high, PMADL-8 <20 at 1 month and PMADL-8 ≥20 at 3 months.

standard demographic, clinical, and laboratory data. Specifically, the results showed that PMADL-8 can serve as an independent predictor of readmission. In addition, previous studies established a correlation between the PMADL-8 and muscle strength and peak exercise $\dot{V}O_2$.[11,16] Therefore, the PMADL-8 provides supplementary information to the objective functional or physical aspect of the disease and the prognosis can be improved through use of the FL assessment. Second, we found that some patients exhibit increases in FLs even after hospitalization. Few studies have investigated the course of CHF FLs after discharge. Worsening conditions will often provoke emotional responses that make the patient feel more severely affected by symptoms.[24,25] The rate of rehospitalization was markedly higher in the low-high group (50.0%) compared with the other 3 groups (high-high, high-low, low-low). Therefore, the present findings suggest that CHF patients need to be followed up for FL periodically after hospitalization. Finally, increased FLs or a continuing lower level of FLs after discharge may be a sign that the possibility of cardiac rehospitalization needs to be estimated. In terms of time-course changes after discharge, lower PMADL-8 scores were associated with better long-term event-free survival. In addition, PMADL-8 <20 was associated with high NPV (approximately 90%) for readmission. These results show that patients with persistent low FLs have a decreased risk for rehospitalization, and support the use of the PMADL-8 to augment the quality of patient care. Further study is needed to examine whether improvement of FLs will result in a better cardiac rehospitalization rate.

The mechanisms through which FL may exert its effects on readmission are unclear, but the data regarding optimal PMADL-8 cut-off points in readmission provide some suggestions. We have demonstrated that only PMADL-8 ≥20 has a clinically significant predictive value. In previous work, PMADL-8 ≥20 represented peak $\dot{V}O_2$ <16 $ml \cdot kg^{-1} \cdot min^{-1}$,[16] which is similar to a cut-off level of physical fitness for having difficulty in performing daily tasks (functional disability).[17] These results may reflect skeletal muscle deterioration, which may underlie disease severity.[26,27] Further study is needed to clarify the cause-effect relationship between PMADL-8 and rehospitalization. In addition, future studies are needed to assess physiological measures that are known to be abnormal in CHF patients and that are relevant with respect to FLs, such as measures of decreased muscle mass,[28] inflammatory markers,[29,30] and/or the parameters of cardiopulmonary exercise testing.[31,32]

Although it is preferable to use validated instruments for measuring symptoms or the health-related quality of life, few instruments focused on FLs are available for CHF, and none are applicable for repetitive measurements. NYHA functional classification, routinely used as an FL measure, is determined by a clinician and is also influenced by knowledge of the severity of cardiac dysfunction, prior medical history, and the likely prognosis. A limitation of the NYHA classification is its poor interobserver and intraobserver reproducibility. The NYHA classification has poor interobserver concordance,[33] whereas the PMADL-8 has good repeatability[11] and predictive validity, as shown in the present study. The PMADL-8 is a simple tool that can be used in the clinical setting. It has the great advantage of being an absolute score, and it can be used repeatedly with no cost. Patients with persistent severe FLs are potential targets for future clinical research initiatives, as recognized by the European Society of Cardiology (ESC).[34] Simple and easily used questionnaires based on FLs, such as the PMADL-8, may be a useful adjunct to current outpatient care. The present study increases the generalizability and the

potential applicability of the PMADL-8 in clinical care.

Several limitations should be considered in the interpretation of the present findings. First, this observational study may have introduced bias related to the prognostic variables that are unknown or were not collected here. Second, the rehospitalization rate in the present study was substantially better than previously reported estimates, in which the readmission rate of CHF has been as high as 33.4% in the same Japanese CHF population.[35] It is possible that selection bias (eg, in the avoidance of refractory end-stage CHF patients) may have influenced the observed event rate. Third, the present study might have underestimated covariate effects in the Cox regression model because the PMADL-8 and covariates were not collected at the same time. In particular, the BNP level is probably time and disease-severity dependent, so it may change with the duration of time between discharge and post-discharge assessments. Finally, because the FLs occur with either increased disease severity or decline of physical function, the other limitations of the present study include the absence of known biomarker assessments at the time of evaluation of PMADL-8 after discharge. Nevertheless, considering skeletal muscle function as a disease symptom,[36] the present findings provide a possible new aspect of disease management for CHF patients.

In conclusion, FL determined by PMADL-8 assessment can predict rehospitalization for CHF. Accordingly, FL assessment is recommended as part of clinical management because it not only identifies decline in physical function but also guides prognosis in CHF patients.

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Appendix 1

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