Quality of Life as an Independent Predictor for Cardiac Events and Death in Patients With Heart Failure

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Background: Little is known about health-related quality of life (QOL) in Japanese patients with heart failure. The purpose of this study was to identify factors related to QOL using a disease-specific QOL instrument, and to clarify whether QOL independently predicts clinical outcomes among Japanese patients with heart failure.

Methods and Results: A total of 114 outpatients with heart failure were enrolled (mean age 64.7 ± 15.8 years; 73.7% males). The Minnesota Living with Heart Failure Questionnaire (MLHFQ) to assess patient's QOL was used. At baseline, depressive symptoms and chronic kidney disease were significantly associated with worse QOL in multiple regression analysis. During a 2-year follow up, patients with a MLHFQ score ≥ 26 , indicating worse QOL, had a higher incidence of the combined endpoint of cardiac death or hospitalization for heart failure, and a higher all-cause mortality than those with a score < 26 (25.3% vs. 7.5%, $P=0.011$; 18.5% vs. 6.4%, $P=0.018$; respectively). Multivariate Cox proportional hazard models demonstrated that a higher MLHFQ score was significantly associated with increased risks of cardiac events (hazard ratio, 1.02, 95% confidential interval, 1.001–1.05, $P=0.038$) and of all-cause death (hazard ratio, 1.04, 95% confidential interval, 1.02–1.07, $P=0.001$).

Conclusions: Depressive symptoms and chronic kidney disease are major determinants of impaired QOL, and the MLHFQ score is an independent predictor of both cardiac events and death among Japanese patients with heart failure. (*Circ J* 2011; **75**: 1661–1669)

Key Words: Heart failure; Hospitalization; Mortality; Quality of life

Heart failure is a universally prevalent, money-consuming, and long-standing condition associated with heavy symptom burden, high mortality, and frequent hospital admission.^{1,2} Since recent advances in treatment have prolonged life expectancy, greater attention has now been paid to improving health-related quality of life (QOL) in patients with heart failure. Heart failure patients experience high levels of physical, functional and emotional distress. Their QOL is not able to be normalized even with optimal treatment,^{3–5} and are usually worse than other common chronic diseases (ie, hypertension, angina, chronic lung disease, or arthritis).⁵

Comprehension of factors associated with patient's QOL could help health professionals to outline strategies during management of heart failure, and not only focus on objective goals, but also on the patient's perception. Prior studies have shown limited associations between heart failure severity and

health status measures including symptoms, functional status and QOL,^{6,7} suggesting that other factors than disease severity might be important in determining the health status of patients with heart failure. Depressive symptoms could be one of such factors,^{8–10} but it still needs to be elucidated. Moreover, most of the previous studies investigating QOL of heart failure patients were performed mainly in the USA and Europe; there has been only a few studies in Japan.^{3,4} The Japanese studies investigating QOL of heart failure patients used the generic QOL instruments such as Short-Form 36, and did not focus on identifying factors associated with QOL.^{3,4} In order to assess more precisely the symptoms and health impacts of heart failure, heart failure-specific QOL instruments have been widely used.¹¹

According to the literature, a lot of markers seem to have prognostic values and might be used for risk stratification in heart failure. Recently, a systematic review has revealed that

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health status assessed by the QOL instruments is a strong predictor of the combined endpoint of death and hospitalization, but is not predictive of all-cause mortality.¹² Moreover, previous results of the predictability of the QOL score in clinical outcomes after adjustment for disease severity and other prognostic factors have been inconsistent.^{13–18} Thus, it remains unclear whether the QOL score provides useful prognostic information in addition to objective indicators.

The purpose of this study was therefore: (1) to identify factors related to QOL using the heart failure-specific QOL instrument; (2) to clarify whether the QOL score predicts the combined endpoint of cardiac death or hospitalization for heart failure as well as all-cause death and (3) to examine whether the QOL score can be an independent prognostic factor in Japanese patients with heart failure.

Methods

Study Design and Study Patients

This study was a prospective cohort study of outpatients with heart failure. The institutional review board of the University of Tokyo approved this study. All participants provided informed consent. The detail of this study design was described previously.^{19–21} In brief, all consecutive outpatients with heart failure who were making scheduled visits to the cardiovascular outpatient clinic of the University Hospital in Tokyo between July 2006 and November 2006 were enrolled. The attending physician determined whether each patient met our criteria based on medical records and the patient's symptoms. Patients were included when they were diagnosed with heart failure in accordance with Framingham heart failure criteria,²² were at least 20 years of age, and did not undergo hemodialysis.²³ Exclusion criteria were physical inability to complete the questionnaire and inability or unwillingness to give informed consent. Patients were followed up for a median period of 2.1 years, and they received usual care from their primary care physicians and/or their cardiologists.

Endpoints

The primary endpoint was the combined endpoint of cardiac death or hospitalization for heart failure. Hospitalization for heart failure was defined as an admission primarily diagnosed with heart failure. We considered all-cause death as secondary endpoints. The information on endpoints was collected from medical records. We also mailed a follow-up letter to all patients or their family approximately 2 years after the initial assessment to enquire about the patients' clinical outcomes. If the requested information was not received within 4–6 weeks after the mailing, we asked the attending physicians about the patient's clinical outcomes.

Heart Failure-Specific QOL Instrument

We used the Minnesota Living with Heart Failure Questionnaire (MLHFQ),²⁴ which is one of the most widely used questionnaires to evaluate heart failure specific QOL.¹¹ The MLHFQ assesses the perception of the effect of heart failure and its treatment on the life of the patients. It is made up of 21 items that cover heart failure related physical, psychological, and social impairments. The patient's perception of such impairment is assessed on a scale ranging from no (score of 0) to very much (5). The total MLHFQ score is obtained by adding the scores for all 21 items (range, 0–105), and a higher score indicates a worse QOL. In addition, it is possible to calculate a summary score of the impact of heart failure on physical dimensions constructed on the basis of 8 items (range, 0–

40), and another summary score of its impact on emotional dimensions constructed on the basis of 5 items (range, 0–25). Psychometric properties of the original and Japanese version of the MLHFQ have been confirmed.^{24,25}

Clinical Characteristics

The following clinical information was collected from medical records at baseline: etiology of heart failure; duration of heart failure; prior hospitalizations for heart failure; New York Heart Association (NYHA) functional class; B-type natriuretic peptide (BNP); left ventricular ejection fraction (LVEF); left ventricular end-diastolic diameter; left arterial diameter by ultrasound cardiography; systolic/diastolic blood pressure; heart rate; atrial fibrillation including paroxysmal atrial fibrillation; hemoglobin concentration; estimated glomerular filtration rate (GFR) [calculated using the formula for Japanese,²⁶ that is, estimated $GFR = 194 \times \text{age}^{-0.287} \times \text{creatinine}^{-1.094}$ (and, if female, $\times 0.739$)]; comorbidity such as diabetes mellitus; and medication including β -blockers, angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin II receptor blockers (ARBs), and warfarin.

Demographic and Psychosocial Characteristics

Patients were asked to complete a self-administered questionnaire to collect demographic and psychosocial variables including gender, age, marital status, educational level, employment, living situation, and depressive symptoms. Depressive symptoms were measured using the Japanese version of the Center for Epidemiologic Studies Depression Scale (CES-D).^{27,28} The CES-D is a 20-item self-report questionnaire designed for screening of depressive symptoms on a 4-point Likert scale ranging from 0 to 3. A higher score indicates a greater tendency toward depressive symptoms. A total score of ≥ 16 indicates the presence of depressive symptoms, and we classified patients with scores ≥ 16 as suffering from depressive symptoms. Validity and reliability of the CES-D Japanese version have been confirmed by Shima et al.²⁸

Statistical Analysis

Categorical data are presented as frequencies and percentages. For continuous variables with a normal distribution, the mean and standard deviations are reported. For variables not normally distributed, the median and inter-quartile ranges (IQR) are reported. In order to identify variables that related to QOL, univariate analysis was initially performed. The dependent variable was the total MLHFQ score, and independent variables were demographic, psychosocial, and clinical variables. Pearson's product-moment correlation coefficient or Spearman's rank-correlation coefficient was calculated for continuous variables, and the Student's t-test or Mann-Whitney U-test was used to evaluate differences between the 2 groups. After assessing the multicollinearity, multiple regression analysis was conducted, which included the variables related to the total MLHFQ score at $P < 0.10$ in univariate analysis.

The difference in survival between patients grouped by median of the total MLHFQ score was evaluated with a log-rank test using Kaplan–Meier curves. A Cox proportional hazards model was constructed to assess the relationship between the MLHFQ score and subsequent endpoints after adjustment for the prognostic factors. The selection methods for the potential prognostic factors are described below. After we assessed multicollinearity, variables that were related to each endpoint at $P < 0.10$ in univariate Cox regression analysis were entered into the model. They were then selected

Table 1. Baseline Characteristics of Study Patients (n=114)

	n (%)
Gender, male	84 (73.7)
Age, years	64.7±15.8
Marital status	
Married	81 (71.1)
Unmarried, divorced, widowed	33 (28.9)
Education	
>12 years	51 (44.7)
≤12 years	63 (55.3)
Employment	
Employed	52 (45.6)
Unemployed	62 (54.4)
Living alone	15 (13.2)
Depressive symptoms	27 (23.7)
Ischemic etiology of HF	33 (28.9)
Duration of HF, years	2.8 (1.0–5.6)
Prior hospitalization for HF	50 (43.9)
NYHA functional class, I or II	95 (83.3)
BNP, pg/ml	121.6±163.9
LVEF, %	53.1±13.3
LVEF ≥50	69 (60.5)
LVDd, mm (n=112)	53.5±8.2
LAD, mm (n=111)	45.0±11.5
LAD ≥42	63 (56.8)
Systolic BP, mmHg	125.3±20.8
Diastolic BP, mmHg	71.2±11.4
Heart rate, beats/min	71.1±12.3
Atrial fibrillation	41 (36.0)
Hemoglobin, g/dl	13.2±2.2
Estimated GFR, ml·min ⁻¹ ·1.73 m ⁻²	61.4±20.8
Estimated GFR <60	57 (50.0)
Diabetes mellitus	39 (34.2)
Medication	
β-blockers	60 (52.6)
ACE inhibitors and/or ARBs	75 (65.8)
Digoxins	36 (31.6)
Diuretics	76 (66.7)
Warfarin	53 (46.5)
The MLHFQ score	
Total score	31.6±23.0
Physical summary score	14.1±10.5
Emotional summary score	7.6±6.2

HF, heart failure; NYHA, New York Heart Association; BNP, B-type natriuretic peptide; LVEF, left ventricular ejection fraction; LVDd, left ventricular end-diastolic diameter; LAD, left atrial diameter; BP, blood pressure; GFR, glomerular filtration rate; ACE, angiotensin-converting-enzyme; ARB, angiotensin II receptor blocker; MLHFQ, the Minnesota Living with Heart Failure Questionnaire. Values are n (%), mean±standard deviation, or median (interquartile range).

using the backward method (the significance level required for retention in the model was 0.10).

All statistical tests were 2-tailed, and statistical significance was defined as $P<0.05$. All analyses were performed with the SAS version 9.1 for Windows (SAS Institute Inc, Cary, NC, USA).

Table 2. Factors Associated With Quality of Life Among HF Patients in Univariate Analysis (n=114)

	Total MLHFQ score	P value
Gender		
Female	42.4±25.2	0.002
Male	27.7±20.9	
Age, years	0.081	0.390
Marital status		
Married	32.9±22.8	0.344
Unmarried	28.4±23.3	
Education		
>12 years	30.5±21.3	0.645
≤12 years	32.5±24.3	
Employment		
Employed	28.2±20.9	0.153
Unemployed	34.4±24.3	
Living alone		
Yes	28.9±25.6	0.632
No	32.0±22.6	
Depressive symptoms		
Yes	52.5±23.1	<0.001
No	25.1±18.7	
Ischemic etiology of HF		
Yes	34.9±23.1	0.323
No	30.2±22.9	
Duration of HF, years	−0.056	0.551
Prior hospitalization for HF		
Yes	35.0±22.3	0.168
No	29.0±23.3	
NYHA functional class		
I or II	29.0±22.6	0.006
III	44.8±20.8	
Log BNP, pg/ml	0.251	0.007
LVEF, %	−0.049	0.602
≥50	30.9±23.6	0.672
<50	32.7±22.2	
LVDd, mm (n=112)	−0.036	0.707
LAD, mm (n=111)		
≥42	35.0±24.1	0.041
<42	26.3±18.9	
Systolic BP, par 10 mmHg	−0.037	0.698
Diastolic BP, par 10 mmHg	−0.036	0.701
Heart rate, beats/min	0.090	0.343
Atrial fibrillation		
Yes	36.0±25.4	0.125
No	29.1±21.3	
Hemoglobin, g/dl	−0.270	0.004
Estimated GFR, ml·min⁻¹·1.73 m⁻²		
≥60	24.9±22.9	0.002
<60	38.3±21.2	
Diabetes mellitus		
Yes	32.8±23.1	0.677
No	30.9±23.0	

(Table 2 continued next page.)

Medication	Total MLHFQ score	P value
β -blockers		
Yes	28.8 $\pm$ 17.8	0.171
No	34.7 $\pm$ 27.4	
ACE inhibitors and/or ARBs		
Yes	31.5 $\pm$ 23.9	0.968
No	31.7 $\pm$ 21.4	
Digoxins		
Yes	38.3 $\pm$ 29.5	0.033
No	28.5 $\pm$ 18.6	
Diuretics		
Yes	35.6 $\pm$ 22.5	0.008
No	23.6 $\pm$ 22.0	
Warfarin		
Yes	34.8 $\pm$ 24.8	0.162
No	28.8 $\pm$ 21.0	

Quality of Life was assessed with the Minnesota Living with Heart Failure Questionnaire; higher scores represent more impaired quality of life. Values are mean $\pm$ SD, Pearson's product-moment correlation coefficient, or Spearman's rank-correlation coefficient. Abbreviations as per Table 1.

Results

Baseline Characteristics of Study Patients

A total of 124 patients participated in the survey. Ten patients were excluded for the following reasons: 2 patients did not return the questionnaire, more than 80% of all items were missing in the questionnaire of 7 patients, and the medical data of 1 patient was not available at baseline. Thus, 114

Table 3. Independent Determinants of Quality of Life Among HF Patients in Multiple Regression Analysis (n=111)

	s β	P value
Depressive symptoms	0.44	<0.001
Estimated GFR, <60 ml·min ⁻¹ ·1.73 m ⁻²	0.18	0.038
Female	0.13	0.158
Digoxin	0.11	0.198
Diuretics	0.09	0.327
Hemoglobin, g/dl	-0.09	0.399
Log BNP, pg/ml	-0.05	0.642
Left atrium diameters, $\geq$ 42 mm	0.02	0.816
R ² (Adjusted R ²)	0.362	(0.312)

Quality of Life was assessed with the Minnesota Living with Heart Failure Questionnaire; higher scores represent more impaired quality of life.

s β , standard partial regression coefficients. Other abbreviations as per Table 1.

After we assessed the multicollinearity, variables that were related to the quality of life score at P<0.10 in univariate analysis (Table 2) were entered into the multivariate model. Because there was a significant relationship between log BNP level and NYHA functional class, we used the variables of log BNP instead of NYHA functional class in multiple regression analyses.

patients were included in the final analysis. The effective response rate was 91.9%. Characteristics of patients were not different between patients who were included in the study and those who were not.

Characteristics of study patients are shown in Table 1. The patients were 64.7 years old, and 73.7% were male. Heart failure of ischemic etiology was present in 28.9% of the patients. The mean BNP was 121.6 $\pm$ 163.9 pg/ml. The mean LVEF

Table 4. Association of Baseline Characteristics With Clinical Outcomes in Univariate Cox Regression Analyses (n=110)

	Cardiac death or hospitalization for HF		All-cause death	
	HR (95%CI)	P value	HR (95%CI)	P value
The MLHFQ score				
Total score	1.03 (1.02–1.05)	<0.001	1.04 (1.02–1.06)	<0.001
Physical summary score	1.08 (1.03–1.12)	<0.001	1.10 (1.04–1.16)	<0.001
Emotional summary score	1.12 (1.05–1.20)	0.001	1.15 (1.05–1.25)	0.002
Gender, female vs. male*	2.68 (1.06–6.79)	0.038	3.57 (1.15–11.09)	0.028
Age, years	1.03 (0.99–1.06)	0.170	1.02 (0.98–1.07)	0.324
Marital status				
Married vs. others*	1.10 (0.39–3.10)	0.850	0.86 (0.26–2.86)	0.808
Education >12 vs. ≤12*, years	0.61 (0.23–1.63)	0.325	0.41 (0.11–1.50)	0.177
Employment				
Employed vs. unemployed*	0.58 (0.22–1.54)	0.271	0.37 (0.10–1.38)	0.139
Depressive symptoms	4.14 (1.64–10.44)	0.003	5.79 (1.84–18.28)	0.003
Ischemic etiology of HF	0.96 (0.34–2.70)	0.940	0.80 (0.22–2.96)	0.740
Duration of HF, years	1.001 (0.91–1.10)	0.982	1.07 (0.97–1.17)	0.192
Prior hospitalization for HF	3.32 (1.19–9.33)	0.023	1.68 (0.53–5.28)	0.379
NYHA functional class				
III vs. I or II*	14.58 (5.42–39.21)	<0.001	8.49 (2.69–26.88)	<0.001
Log BNP	2.92 (1.85–4.61)	<0.001	2.07 (1.20–3.57)	0.009
LVEF, %	0.96 (0.93–0.998)	0.038	0.98 (0.94–1.02)	0.259
LVEF ≥50 vs. <50*, %	0.41 (0.16–1.06)	0.064	0.64 (0.21–1.98)	0.437
LVDd, mm	0.998 (0.94–1.06)	0.946	0.94 (0.88–1.01)	0.077
LAD, ≥42 vs. <42*, mm	1.85 (0.65–5.24)	0.250	2.13 (0.57–8.04)	0.264
Systolic BP, par 10 mmHg	0.75 (0.58–0.96)	0.024	0.84 (0.64–1.12)	0.237
Diastolic BP, par 10 mmHg	0.58 (0.39–0.86)	0.006	0.70 (0.44–1.11)	0.127
Heart rate, beats/min	1.01 (0.98–1.05)	0.496	1.01 (0.97–1.06)	0.572
Atrial fibrillation	1.97 (0.78–4.96)	0.151	1.38 (0.44–4.36)	0.579
Hemoglobin, g/dl	0.64 (0.50–0.82)	0.001	0.71 (0.53–0.95)	0.022
Estimated GFR				
<60 vs. ≥60*, ml·min ⁻¹ ·1.73 m ⁻²	5.39 (1.56–18.62)	0.008	3.02 (0.82–11.14)	0.098
Medication				
β-blockers	0.15 (0.04–0.52)	0.003		
ACE inhibitors and/or ARBs	0.30 (0.12–0.78)	0.014	0.15 (0.04–0.55)	0.004
Digoxins	3.87 (1.50–9.98)	0.005	2.46 (0.79–7.68)	0.121
Diuretics	4.32 (0.99–18.77)	0.051	2.59 (0.57–11.83)	0.219
Warfarin	1.97 (0.76–5.09)	0.160	1.97 (0.76–5.09)	0.160

For the MLHFQ, higher scores represent more impaired quality of life. *Reference category. HR, hazard ratio; CI, confidence interval. Other abbreviations as per Table 1.

was 53.1% and a left atrial diameter of more than 42 mm was present in 56.8% of the patients. Forty-one patients (36.0%) had atrial fibrillation, including 7 patients (6.1%) with paroxysmal atrial fibrillation. Twenty-seven patients (23.7%) were classified as patients with depressive symptoms. And half of patients had chronic kidney disease defined as an estimated GFR of less than 60. Regarding medication, ACE inhibitors and/or ARBs, and β-blockers were prescribed to 65.8% and 52.6% of patients, respectively. Fifty-three patients (46.5%) were treated with warfarin. The total MLHFQ score was 31.6±23.0.

Factors Associated With QOL

Table 2 compares the total MLHFQ score between the 2 populations stratified by various patients' characteristics. Female and patients with depressive symptoms had the higher total score of the MLHFQ, indicating a worse QOL (P=0.002 and

P<0.001, respectively). As to heart failure severity, the log BNP level and NYHA functional class but not LVEF was positively associated with a worse QOL (r=0.251, P=0.007; and P=0.006; respectively). Additionally, a lower level of hemoglobin and the presence of an estimated GFR <60 were significantly associated with impaired QOL (P=0.004 and P=0.002, respectively).

Because there was a significant relationship between log BNP level and NYHA functional class (ρ=0.404, P<0.001), we used the variables of log BNP instead of NYHA functional class in multivariate analyses. Multiple regression analysis revealed that depressive symptoms [standard partial regression coefficients (sβ)=0.44, P<0.001] and the estimated GFR of less than 60 (sβ=0.18, P=0.038) were significant predictors of a worse QOL (**Table 3**).

Table 5. Association of Quality of Life With Clinical Outcomes in Multivariate Cox Regression Analyses (n=110)

	HR (95%CI)	P value
Cardiac death or hospitalization for HF		
Total MLHFQ score	1.02 (1.001–1.05)	0.038
LVEF, %	0.93 (0.89–0.97)	0.002
β -blockers	0.12 (0.03–0.48)	0.002
Estimated GFR, $<60 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$	5.28 (1.36–20.47)	0.016
Systolic BP, par 10 mmHg	0.79 (0.64–0.98)	0.035
ACE inhibitors and/or ARBs	0.32 (0.11–0.95)	0.039
Hemoglobin, g/dl	0.80 (0.64–1.003)	0.053
All-cause death		
Total MLHFQ score	1.04 (1.02–1.07)	0.001
Log BNP	0.11 (0.03–0.44)	0.002
ACE inhibitors and/or ARBs	1.76 (0.94–3.30)	0.078

Quality of Life was assessed with the Minnesota Living with Heart Failure Questionnaire; higher scores represent more impaired quality of life.

Abbreviations as per Tables 1, 4.

After we assessed the multicollinearity, variables that were related to each endpoint at $P < 0.10$ in univariate Cox regression analysis (Table 4) were entered into the multivariate model. They were then selected using the backward method (the significance level required for retention in the model was 0.10). Because there were significant relationships between log BNP level and NYHA functional class, and between systolic and diastolic BP levels, we used the variables of log BNP instead of NYHA functional class and of systolic BP instead of diastolic BP in multivariate analyses.

Association of QOL With Clinical Outcomes

The median follow-up period was 756 days (IQR, 738–781). Of the 114 patients, the vital status data were available in 110 patients (96.5%). During follow up, 18 patients had the combined endpoint of cardiac death or hospitalization for heart failure. Fifteen patients were hospitalized for decompensated heart failure, and 12 patients died, 8 of them from a cardiac cause. For all patients, the cumulative 1- and 2-year combined endpoint rates and mortality were 13.7% and 16.5%,

and 4.6% and 10.3%, respectively.

In heart failure patients with a total MLHFQ score of ≥ 26 , an indicating worse QOL score, the rate of cardiac death or heart failure hospitalization was greater compared with those with a score of < 26 [25.3% vs. 7.5%, $P = 0.011$, **Figure 1**; hazard ratio (HR) 1.95; 95% confidence interval (CI), 1.12–3.40; $P = 0.018$]. **Table 4** shows the results of univariate Cox regression analysis. The total MLHFQ score was related to an increased risk for cardiac death or hospitalization for heart

failure (HR, 1.03 for each 1 unit increase; 95%CI, 1.02–1.05; $P<0.001$). Similar trends were observed in the physical summary score (HR, 1.08; 95%CI, 1.03–1.12; $P<0.001$) and the emotional summary score (HR, 1.12; 95%CI, 1.05–1.20; $P=0.001$). Factors associated with increased cardiac death or hospitalization for heart failure in univariate analysis were as follows: female, depressive symptoms, prior hospitalization for heart failure, higher NYHA functional class, higher BNP level, lower LVEF, lower systolic blood pressure, lower diastolic blood pressure, lower hemoglobin level, estimated GFR <60 , non-use of β -blockers, non-use of ACE inhibitors and/or ARBs, and use of digoxins.

In addition to the significant relationship between log BNP level and NYHA functional class described above, there was a strong association between systolic and diastolic blood pressure levels ($\rho=0.704$, $P<0.001$). Thus, we used the variables of systolic blood pressure instead of diastolic blood pressure, as well as the variable of log BNP instead of NYHA functional class in multivariate analyses. Multivariate Cox regression analyses revealed that the MLHFQ score was significantly associated with an increased risk for the combined endpoint of cardiac death and hospitalization for heart failure, independent of other prognostic factors including LVEF, use of β -blockers, and the presence of estimated GFR <60 (HR, 1.02; 95%CI, 1.001–1.05; $P=0.038$; **Table 5**).

With respect to all-cause death, patients with a total MLHFQ score of ≥ 26 had a higher mortality than those with a score of <26 (18.5% vs. 6.4%; $P=0.018$; **Figure 2**; HR, 2.27; 95%CI, 1.06–4.86; $P=0.034$). The total MLHFQ score was associated with an increased mortality (HR, 1.04; 95%CI, 1.02–1.06; $P<0.001$; **Table 4**). The physical summary score (HR, 1.10; 95%CI, 1.04–1.16; $P<0.001$) and emotional summary score (HR, 1.15; 95%CI, 1.05–1.25; $P=0.002$) were also related to mortality. Univariate analyses showed that female, depressive symptoms, higher NYHA functional class, higher BNP level, lower hemoglobin level, and non-use of ACE inhibitors and/or ARBs were significantly associated with increased mortality (**Table 4**). Because none of the deceased patients were prescribed β -blockers, we could not calculate the hazard ratio concerning use of β -blockers. In multivariate analyses, the total MLHFQ score was again a significant predictive factor for all-cause death, which was independent of the use of ACE inhibitors and/or ARBs and BNP level (HR, 1.04; 95%CI, 1.02–1.07; $P=0.001$; **Table 5**).

Discussion

This study was a 2-year prospective follow-up study among Japanese outpatients with mild to moderate heart failure. We showed that depressive symptoms and chronic kidney disease were risk factors for worse QOL independently of disease severity in patients with heart failure. We also demonstrated that the QOL score could predict both the combined endpoint of cardiac death or hospitalization for heart failure, and all-cause death, independently of other prognostic factors in Japanese patients with heart failure. This suggests that knowledge of health status, as measured by the MLHFQ, might both provide a unique window into their clinical status and be prognostically important, such that it can enhance secondary prevention intervention by means of identifying high-risk patients at a relatively low cost.

Determinants of QOL

Depressive symptoms were strongly associated with impaired QOL, independently of disease severity assessed by BNP

level, which expands the results of earlier studies.^{8,9} Prior studies have also shown that impaired QOL was predictive of the development of depression.²⁹ Comorbid depressive symptoms, which is common in patients with heart failure, has an additional impact on patients' increased morbidity and mortality^{19,30} as well as negatively influencing a patient's adherence to therapy.³¹ Given the severe restrictions in QOL because of depressive symptoms and the resulting pronouncedly negative effect on the course and prognosis of patient's cardiac disease, our finding suggests that an accurate diagnosis of depressive comorbidity in patients with heart failure is essential when it comes to initiating adequate treatment.

An interesting finding was that chronic kidney disease, defined as an estimated GFR of less than 60 was an independent risk factor for worse QOL in heart failure patients. Although chronic kidney disease has been established as a predictor for morbidity and mortality,^{32,33} it has not well-known as an independent risk factor for impaired QOL in patients with heart failure. A study of 1186 chronic kidney disease patients has found that a history of cardiovascular co-morbidity was associated with impaired QOL.³⁴ These observations highlight the profound impact of chronic kidney disease on heart failure, and suggest potential areas that can be targeted for therapeutic intervention.

Regarding LVEF, our result was consistent with that from the CHARM study.³⁵ The re-hospitalization rate as well as QOL in heart failure patients with preserved EF has shown to be similar compared with those with reduced EF.^{2,35} Improvement in QOL and preventing re-hospitalization are important objectives in all patients with heart failure, irrespective of LVEF.

Relationship of QOL With Clinical Outcomes

It is noteworthy that the MLHFQ score predicted all-cause death as well as the combined endpoint of cardiac death or hospitalization for heart failure, independently of the established prognostic factors and medication. In previous studies, there has been a discrepancy in the association between the QOL score and subsequent mortality, and it has not been consistent whether the QOL score predicts clinical outcomes after fully adjusting for prognostic factors.¹² Our results support that the QOL score could provide prognostic information in addition to conventional factors such as LVEF and estimated GFR.^{12–15,18} Moreover, recent sub-analyses from EPHEUS has shown that the QOL score predicted resource use and the cost over the next year for stable heart failure patients after myocardial infarction.³⁶ Taking these observations into consideration, self-reported health status, including QOL, is useful for identifying high-risk heart failure patients who might be candidates for more intensive therapy including cardiology referral and a heart failure management program.

With respect to the mechanism between QOL and subsequent clinical outcomes, the worse QOL score has been shown to be related to inflammatory burden including interleukin-6, implying a close relationship between self-reported health status and the biochemical pathogenetic mechanisms of heart failure progression.³⁷ Immune activation has been shown to be associated with increased emotional distress and depressive symptoms.³⁸ This pathophysiological aspect might possibly explain the relationship of impaired QOL with depressive symptoms and clinical outcomes.

Study Limitations

Our study has several potential limitations. First, the gener-

alizability of this study was limited as all patients were recruited from a cardiovascular outpatient clinic at a single university hospital in Tokyo. Second, a cross-sectional assessment of variables including depressive symptoms, chronic kidney disease and the MLHFQ score cannot confirm a causative relationship. Third, small sample size and low frequency of clinical events in this study limited the number of variables examined in multivariate analyses and the statistical significance of our findings; additional variables might have significant contributions in a larger study. Fourth, we did not assess adherence to treatment. Adherence to pharmacological and non-pharmacological treatment is likely to have an influence on patient's QOL and clinical outcomes. Finally, QOL was assessed at only baseline in this study; using only 1 snapshot assessment might miss the true nature of QOL in a given individual. The relationship of a change of QOL and subsequent clinical outcomes needs to be investigated in future research.

Conclusions

This study has found that depressive symptoms and chronic kidney disease are risk factors for impaired QOL, independently of disease severity among patients with heart failure. We have also demonstrated that the MLHFQ score is associated with increased risk of all-cause death as well as the combined endpoint of cardiac death or hospitalization for heart failure. The MLHFQ score is an independent risk factor for the prognosis of heart failure patients. Future effort to improve the QOL of patients with heart failure should include a focus on depressive symptoms and chronic kidney disease. Measurement of QOL is an attractive and inexpensive method of estimating a heart failure patient's prognosis for healthcare professionals interested in identifying high-risk patients for specific intervention.

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