【 ORIGINAL ARTICLE 】

Patient Health Questionnaire-2 Screening for Depressive Symptoms in Japanese Outpatients with Heart Failure

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Abstract:

Objective Depression is common in patients with heart failure (HF) and is a possible risk factor for adverse outcomes. The aim of this study was to determine the prevalence of depression assessed by the 2-item Patient Health Questionnaire (PHQ-2) and the effect of depression on outcomes in Japanese outpatients with HF.

Methods This sub-analysis of a prospective observational study assessed 976 patients with HF (mean age 66±13 years; 26.7% female; 42.7% with an ischemic etiology). Depression was defined as a PHQ-2 score ≥3. The main composite outcome was death from any cause or hospitalization due to worsening HF. PHQ-2 items were extracted from the PHQ-9 results. To evaluate the association of PHQ-2 scores with outcomes, Cox proportional hazards models were evaluated.

Results Fifty-seven (5.8%) patients were diagnosed with depression. During a median follow-up of 21 months, the incidence rates for death from any cause and hospitalization due to worsening HF in patients with and without depression were 2.2 vs. 0.9 per 100 person-years and 6.7 vs. 1.6, p<0.001, respectively. There was a higher incidence of the main outcome in patients with depression than in those without depression (p<0.001). After adjustment for conventional risk factors, depression (PHQ-2 ≥3) was an independent predictor of the main outcome (hazard ratio 2.41, 95% confidence interval 1.14-4.67, p=0.022), and a score for item 1 of the PHQ-2 (loss of interest or pleasure) ≥2 was also an independent risk factor (hazard ratio 3.57, 95% confidence interval 1.85-6.46, p<0.001).

Conclusion Depression as assessed by the PHQ-2 was identified in 5.8% of Japanese outpatients with HF and was associated with outcomes.

Key words: depression, heart failure, Japanese, outcomes, outpatients, PHQ-2

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Introduction

Depression is common in patients with heart failure (HF) and is a possible risk factor for adverse outcomes (1-5). The American Heart Association (AHA) recommends routine depression screening in patients with coronary artery disease using the 9-item Patient Health Questionnaire (PHQ-9) (6). This method is also useful for depression screening in patients with HF, and depression assessed using the PHQ-9 is independently associated with adverse outcomes in patients

with HF (7-9). Furthermore, the shorter PHQ-2, which consists of only the first 2 items of PHQ-9, might also be useful for depressive symptom screening and predicting an increased risk of adverse outcome in hospitalized patients with HF (9-11).

However, some items of the PHQ-9, i.e. abnormalities in sleep, feeling tired or little energy, poor appetite, feeling bad and having trouble concentrating, overlap with HF symptoms. PHQ-2 items, namely the loss of interest or pleasure (anhedonia) and a depressed mood, serve as the two core symptoms of major depression as defined in the Diagnostic

and Statistical Manual of Mental Disorders (12). Although the PHQ-2 has not been established for use in providing a final diagnosis or as a tool for monitoring depression severity, it may function as a useful questionnaire to screen for depressive symptoms in patients with HF. However, there are no data concerning the utility of the PHQ-2 in outpatients with HF in Japan. In addition, a short questionnaire is convenient for use in an outpatient clinical setting where time is limited.

The aim of this study was to determine the prevalence of depression as assessed by the PHQ-2 and the effect of depression as assessed by the PHQ-2 on outcomes in Japanese outpatients with HF.

Materials and Methods

Patients

We conducted a substudy of a prospective observational study in Japanese outpatients who visited the outpatient cardiology clinics of Tokyo Women's Medical University Hospital (between March 2013 and May 2013), Tokyo Women's Medical University Medical Center East (between December 2013 and February 2014) and Tokyo Women's Medical University Aoyama Hospital (March 2014). Patients with dementia, delirium, or other conditions (e.g. end-stage of other life-threatening diseases) that make it difficult to complete a self-report written questionnaire were excluded. A total of 1,453 outpatients with cardiovascular disease were enrolled in this study. Among them, 976 patients with American College of Cardiology Foundation (ACCF)/ AHA Stage C or D HF who completed the questionnaire were included in this study. Study details are reported elsewhere (13).

The institutional review board of Tokyo Women's Medical University approved the study. This study was conducted in accordance with the Declaration of Helsinki. All patients provided their written informed consent (UMIN-CTR No. UMIN 000023514).

The assessment of depression

Depressive symptoms were assessed using the Japanese version of the PHQ-9 (14). The PHQ-9 is a self-reported scale containing 9 symptoms that reflect the diagnostic criteria for depression. Overall scores range from 0 to 27. Kroenke et al. reported that PHQ-9 scores ≥10 had a sensitivity of 88% and a specificity of 88% for major depression (15), and Muramatsu et al. reported that PHQ-9 scores ≥10 on the Japanese version had a sensitivity of 84% and a specificity of 95% for major depression in Japanese patients (14). In our main study, depression was defined as a PHQ-9 score ≥10. The PHQ-2 consists of 2 questions about the frequency of experiencing a depressed mood and anhedonia over the past 2 weeks (16). In this questionnaire, patients are asked, "Over the past 2 weeks, how often have you been bothered by 1) little interest or pleasure in doing things, and 2) feeling down, depressed or hopeless?". Over-

all scores range from 0 to 6. Kroenke et al. reported that PHQ-2 scores ≥3 exhibit a sensitivity of 83% and a specificity of 92% for major depression (16), and Inagaki et al. reported that PHQ-2 scores ≥3 on the Japanese version exhibit a sensitivity of 77% and a specificity of 95% for major depression in Japanese patients in general internal medicine settings (17). Therefore, depression was defined as a PHQ-2 score ≥3 in this study. We extracted the PHQ-2 items from the PHQ-9 results.

Follow-up

Patients were observed as outpatients at our hospital or at their general practitioner's clinic at 1- to- 3-month intervals up to December 2015. Patients receiving pacing-device therapy, including pacemakers, cardiac resynchronization therapy and implantable cardioverter defibrillators (ICDs), were also followed every 3 to 6 months at our pacemaker/ICD clinic. Information about deceased subjects was obtained from medical records, family members, their general practitioner and the admitting hospital. Five (0.5%) patients were lost to follow-up.

Clinical outcomes

The main outcome was the composite of death from any cause and hospitalization due to worsening HF from the time of enrollment to the first event. Worsening HF was defined by signs and symptoms, such as dyspnea, rales and ankle edema, as well as the need for treatment with diuretics, vasodilators, positive inotropic drugs or an intra-aortic balloon pump. The second outcome was death from any cause and hospitalization due to worsening HF.

Statistical analyses

Data are presented as the mean ± standard deviation (SD), number, median and range. Baseline clinical data were compared between groups with and without depression using Student's t-test and the Mann-Whitney U test. Categorical variables were subjected to chi-square analysis. Cumulative event-free rates were calculated using the Kaplan-Meier method. Differences in event-free rates were compared using the log-rank test. To evaluate the association of PHQ-2 scores with the main outcome, subsequent death or hospitalization due to worsening HF, Cox proportional hazards models were evaluated and adjusted for age, sex, cardiovascular disease, left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) functional class, hemoglobin, serum albumin, estimated glomerular filtration rate (eGFR) by the Modification of Diet in Renal Disease formula and medication use. A p value <0.05 was considered significant. Data analyses were performed using the JMP statistical software program (version 13, SAS Institute, Cary, USA).

Table 1.   Patient Characteristics.

	PHQ-2 ≥3 (n=57)	PHQ-2<3 (n=919)	p value
Age (years)	66±14	66±13	0.964
Female	21 (36.8)	239 (26.0)	0.086
Cardiovascular disease			<0.001
Coronary artery disease	21 (36.8)	396 (43.1)	
Nonischemic cardiomyopathy	28 (49.1)	346 (37.6)	
Valvular heart disease	4 (7.0)	115 (12.5)	
Congenital heart disease	5 (8.8)	42 (4.6)	
Others	0	19 (2.1)	
NYHA functional class			0.002
I/II	52 (91.2)	899 (97.8)	
III/IV	5 (8.8)	20 (2.2)	
LVEF (%)	48±12	49±12	0.583
Hemoglobin (g/dL)	13.3±1.9	13.8±1.7	0.056
Serum albumin (g/dL)	4.2±0.5	4.2±0.4	0.176
eGFR (mL/min/1.73m^2)	55±25	57±14	0.200
Plasma BNP (pg/mL)	51 (4-1,632)	244 (4-3,358)	0.920
Medical comorbidities			
Hypertension	27 (47.4)	485 (52.8)	0.477
Diabetes	20 (35.1)	120 (13.1)	0.273
Dyslipidemia	26 (44.8)	447 (48.6)	0.750
Hemodialysis	2 (3.5)	9 (0.9)	0.834
Cerebrovascular disease	2 (3.5)	8 (0.8)	0.105
COPD	2 (3.5)	5 (0.5)	0.085
Major depression	1 (1.7)	1 (0.1)	0.008
Implanted pacing devices			0.460
Pacemaker/CRT-P	3 (5.2)	61 (6.6)	
ICD/CRT-D	7 (12.3)	63 (6.9)	
Medications			
Beta-blockers	39 (68.4)	651 (70.8)	0.554
ACE inhibitors/ARBs	41 (71.9)	638 (69.4)	0.566
MRAs	11 (19.3)	204 (22.2)	0.783
CCBs	11 (19.3)	245 (26.7)	0.210
Antiplatelets	18 (31.6)	305 (33.2)	0.870
Anticoagulants	14 (24.6)	366 (39.8)	0.832
Amiodarone	8 (14.0)	133 (14.5)	0.873
Living status			
Living alone	11 (19.3)	141 (15.3)	0.462
Work status			
Unemployed/retired	40 (70.2)	488 (53.1)	0.011

Values are n (%) or means±SD or median (range).
ACE: angiotensin-converting enzyme, ARB: angiotensin II receptor blocker, BNP: brain natriuretic peptide, CCB: calcium channel blocker, COPD: chronic obstructive pulmonary disease, CRT: cardiac resynchronization therapy, CRT-D: CRT with a defibrillator, CRT-P: CRT with a pacemaker, eGFR: estimated glomerular filtration rate, ICD: implantable cardioverter defibrillator, LVEF: left ventricular ejection fraction, MRA: mineralocorticoid receptor antagonists, NYHA: New York Heart Association, PHQ: Patient Health Questionnaires

Results

Prevalence and characteristics of depression

Fifty-seven patients (5.8%) met the criteria for depression as assessed by the PHQ-2. Patient characteristics and results of the comparison of patients with depression (PHQ-2 score ≥3) to those without depression are presented in Table 1. No significant differences in age or sex were noted between the two groups. The proportions of patients with non-ischemic cardiomyopathy and a higher NYHA functional class were higher in patients with depression than in those without. However, no significant difference in the rates of medication
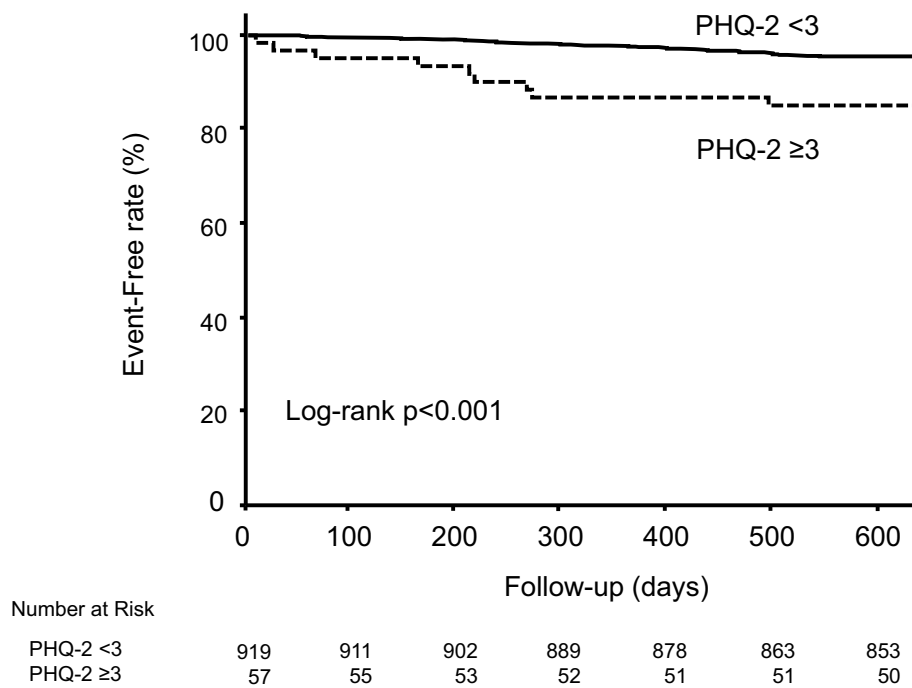
Figure.   **Kaplan-Meier curves for the main outcome (death from any cause or hospitalization due to worsening HF) in HF outpatients with a PHQ-2 score ≥3 or <3.**

use, including beta-blockers, was noted between patients with and without depression. Two patients (0.2%) who were diagnosed with major depression by a psychiatrist had taken antidepressants, and their PHQ-2 scores were ≥3 and <3.

Compared with patients without depression PHQ-2 score <3, more patients with PHQ-2 score ≥3 were unemployed/retired. A multivariate analysis revealed that NYHA functional class III/IV (hazard ratio 3.71, 95% confidence interval 1.33-10.40, p=0.012) and unemployment status (hazard ration 2.00, 95% confidence interval 1.09-3.68, p=0.025) were significantly associated with depression.

Depression and clinical outcomes

During a median follow-up of 21 months (interquartile range, 18 to 22 months), 2 (3.5%) patients with a PHQ-2 score ≥3 and 14 (1.5%) patients with a PHQ-2 score <3 died; incidence rate 2.2 per 100 person-years versus 0.9 per 100 person-years. Six (10.5%) patients with a PHQ-2 score ≥3 and 24 (2.6%) patients with a PHQ-2 score <3 required hospitalization for worsening HF (incidence rate: 6.7 per 100 person-years versus 1.6 per 100 person-years, p<0.001). Kaplan-Meier curves for the main outcome are presented in Figure. The incidence rate of the main outcome was higher in patients with a PHQ-2 score ≥3 than those with in those with a PHQ-2 score <3.

After adjusting for the age, sex, cardiovascular disease, LVEF, NYHA functional class, hemoglobin, serum albumin, eGFR and medications, a PHQ-2 score ≥3 was found to be an independent risk factor for the main outcome and hospitalization due to HF but not for all-cause mortality. To further evaluate the relationship between each core depressive symptom and the outcome, we separately examined the cor-

relation of item 1 (loss of interest or pleasure) and item 2 (depressed mood) with outcome. A response of at least "more than half the days" (≥2) for any item was defined as a positive response. Among PHQ-2 items, an item 1 (loss of interest or pleasure) score ≥2 was an independent risk factor for the main outcome and hospitalization due to worsening HF (Table 2).

Discussion

Our study revealed that the prevalence of depression assessed by the PHQ-2 was 5.8% in Japanese outpatients with HF. A significantly higher incidence of the main outcome, namely, death from any cause and hospitalization due to worsening HF, was noted in patients with depression than in those without depression. After adjusting for confounders, depression defined as a PHQ-2 score ≥3 was an independent factor for a worse clinical outcome in patients with HF, especially hospitalization due to worsening HF. Among items of the PHQ-2, a loss of interest or pleasure (anhedonia) was also an independent risk factor.

Previous studies that aimed to evaluate the relationship between depression defined by PHQ-2 and clinical outcomes have targeted hospitalized patients with HF (9-11). These studies included patients with systolic HF (LVEF<40%) and the proportion of patients with NYHA functional class III/IV was 42.3% (9) and 61.1% (10, 11), respectively. The proportion of patients with a PHQ-2 score ≥3 was 33.5% (9) and 78.8% (10, 11). In general, the prevalence of depression in outpatients with cardiovascular diseases is lower than in hospitalized patients. National Health Interview Survey data of 30,801 US adults reported that the 12-month prevalence

Table 2.   Adjusted Main Outcome, All-cause Mortality and Hospitalization due to Worsening HF.

	Main outcome[a]		All-cause mortality		Hospitalization due to worsening HF	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
PHQ-2 ≥3	2.41 (1.14-4.67)	0.022	1.04 (0.12-5.16)	0.962	2.78 (0.92-6.91)	0.066
Items of PHQ-2						
Item 1 (loss of interest or pleasure) ≥2	3.57 (1.85-6.46)	<0.001	0.83 (0.09-4.09)	0.848	3.13 (1.31-7.53)	0.029
Item 2 (depressed mood) ≥2	1.81 (0.74-3.83)	0.177	1.05 (0.11-5.49)	0.959	1.57 (0.40-4.61)	0.478

CI: confidence interval, HF: heart failure, HR: hazard ratio, PHQ: Patient Health Questionnaires

[a]Composite outcome of death from any cause or hospitalization due to worsening HF.

*Adjusted for age, sex, cardiovascular disease, left ventricular ejection fraction, New York Heart Association functional class, hemoglobin, serum albumin, estimated glomerular filtration rate and medication use.

of major depression was 7.9% in those with HF (18). Although the methods for measuring depression and the patient characteristics differed, the prevalence rate (approximately 5.8% regardless of the use of PHQ-2 or PHQ-9) of depression in our outpatients with HF was comparable to that reported previously (18).

Depression is associated with poor outcomes in patients with HF, and this relationship is similar in both outpatients and inpatients with HF (19). Although the pathophysiologic mechanisms are not completely understood, depression is an important risk factor for adverse cardiovascular events (20). Bhatt et al. noted that the PHQ-9 effectively identifies outpatients with HF at risk for hospitalization, increased health care resource utilization and reduced the quality of life (21). In our study, after adjusting for conventional risk factors, PHQ-2 score ≥3 was a risk factor for hospitalization due to worsening HF. Among the PHQ-2 items, a loss of interest or pleasure (anhedonia) alone was a significant risk factor. Kessing et al. reported that anhedonia was associated with a poor adherence to self-care in HF patients independent of disease severity (22). In our study, however, item 2 (depressed mood) was not an independent risk factor. A depressed mood may be influenced by physical factors, such as general fatigue derived from the symptoms of HF. Fink et al. reported that a depressed mood was associated with HF-related fatigue (23). Particularly, loss of interest or pleasure (anhedonia) is a core depressive symptom independent of HF symptoms, and the assessment of a loss of interest or pleasure (anhedonia) may be important for HF patients in clinical practice.

Study limitations

Several limitations associated with the present study warrant mention. First, depression defined by this self-reported questionnaire was not re-confirmed by diagnostic interviews including a structured clinical interview. Second, this was a cohort study involving university hospitals. The clinical characteristics of our patients might not reflect those of general cardiovascular patients with HF. Our results limit the generalizability of our findings to Japanese patients with HF in clinical practice. Third, these outpatients with HF were

relatively stable and exhibited a lower risk than hospitalized patients with HF. Therefore, the sample size of this substudy was relatively small. Fourth, a patient in the non-depressive group received antidepressants due to major depression diagnosed prior to the study.

Conclusion

Our results suggested that 5.7% of Japanese outpatients with HF exhibited depressive symptoms, which were defined as a PHQ-2 score ≥3, and depressive symptoms are associated with outcomes. PHQ-2, especially a loss of interest or pleasure (anhedonia), may be a useful questionnaire for outpatients with HF in clinical practice.

The authors state that they have no Conflict of Interest (COI).

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