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 20 had a sensitivity of 88% and a specificity of 88% for major depression (15), and Muramatsu et al. reported that PHQ-9 scores 20 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 210. 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?”.

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 Inc., Cary, NC, 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/1.73m²)   | 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

|                        |                 |                 |         |
| Pacemaker/CRT-P        | 3 (5.2)         | 61 (6.6)        | 0.460   |
| 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 mean±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
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<3, more patients with PHQ-2 ≥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 ratio 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 correlation 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...
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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**References**

1. MacMahon KM, Lip GY. Psychological factors in heart failure: a review of the literature. Arch Intern Med 162: 509-516, 2002.
2. Jiang W, Alexander J, Christopher EJ, Kuchibhatla M, Gaulden LF, Cuffe MS, et al. Relationship of depression to increased risk of mortality and rehospitalization in patients with congestive heart failure. Arch Intern Med 161: 1849-1856, 2001.
3. Vaccarino V, Kasl S, Abramson J, Krumhoz H. Depressive symptoms and risk of functional decline and death in patients with heart failure. J Am Coll Cardiol 38: 199-205, 2001.
4. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure: a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. J Am Coll Cardiol 48: 1527-1537, 2006.
5. Sherwood A, Blumenthal JA, Trivedi R, Johnson KS, O’Connor AM, Adams KF, et al. Relationship of depression to death or hos-

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

| Main outcome* | All-cause mortality | Hospitalization due to worsening HF |
|---------------|---------------------|-----------------------------------|
| PHQ-2 ≥3      |                     |                                   |
| HR (95% CI)   | p value             | HR (95% CI)                       | p value |
| 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 (0.40-6.41) | 0.478 |

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

*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.
pitalization in patients with heart failure. Arch Intern Med 167: 367-373, 2007.

6. Lichtman JH, Bigger Jr JT, Blumenthal JA, Frasure-Smith N, Kaufmann PG, et al. Depression and Coronary Heart Disease Recommendations for Screening, Referral, and Treatment. Circulation 118: 1768-1775, 2008.

7. Moraska AR, Chamberlain AM, Shah ND, Vickers KS, Rummons TA, Dunlay SM, et al. Depression, healthcare utilization, and death in heart failure: a community study. Circ Heart Fail 6: 387-394, 2013.

8. Beach SR, Januzzi JL, Mastromauro CA, Healy BC, Beale EE, Celano CM, et al. Patient Health Questionnaire-9 score and adverse cardiac outcomes in patients hospitalized for acute cardiac disease. J Psychosom Res 75: 409-413, 2013.

9. Piepenburg SM, Faller H, Gelbrich G, Störk S, Warrings B, Ertl G, et al. Comparative potential of the 2-item versus the 9-item patient health questionnaire to predict death or rehospitalization in heart failure. Circ Heart Fail 8: 464-472, 2015.

10. Rollman BL, Herbeck Belnap B, Mazumdar S, Houck PR, He F, Alvarez RJ, et al. A positive 2-item Patient Health Questionnaire depression screen among hospitalized heart failure patients is associated with elevated 12-month mortality. J Card Fail 18: 238-245, 2012.

11. Deveney TK, Belnap BH, Mazumdar S, Rollman BL. The prognostic impact and optimal timing of the Patient Health Questionnaire depression screen on 4-year mortality among hospitalized patients with systolic heart failure. Gen Hosp Psychiatry 42: 9-14, 2016.

12. American Psychiatry Association. Diagnostic and Statistical Manual of Mental Disorders. 5th Edition. American Psychiatric Association, Washington, DC, 2013.

13. Suzuki T, Shiga T, Omori H, Tatsumi F, Nishimura K, Hagiwara N. Depression and outcomes in Japanese outpatients with cardiovascular Disease - A Prospective Observational Study. Circ J 80: 2482-2488, 2016.

14. Muramatsu K, Miyakawa H, Kamijima K, Muramatsu Y, Yoshida M, Otsubo T, et al. The Patient Health Questionnaire, Japanese version: validity according to the Mini-International Neuropsychiatric Interview-Plus. Psychol Rep 101 (3 Pt 1): 952-960, 2007.

15. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 16: 606-613, 2001.

16. Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: validity of a two-item depression screener. Med Care 41: 1284-1292, 2003.

17. Inagaki M, Yonemoto N, Kawashima Y, Saitho A, Okawa Y, et al. Validity of the Patient Health Questionnaire (PHQ)-9 and PHQ-2 in general internal medicine primary care at a Japanese rural hospital: a cross-sectional study. Gen Hosp Psychiatry 35: 592-597, 2013.

18. Egede LE. Major depression in individuals with chronic medical disorders: prevalence, correlates and association with health resource utilization, lost productivity and functional disability. Gen Hosp Psychiatry 29: 409-416, 2007.

19. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure: a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. J Am Coll Cardiol 48: 1527-1537, 2006.

20. Hare DL, Toukhati SR, Johansson P, Jaarsma T. Depression and cardiovascular disease: a clinical review. Eur Heart J 35: 1365-1372, 2014.

21. Bhatt KN, Kalogeropoulou AP, Dunbar SB, Butler J, Georgiopoulou VV. Depression in heart failure: Can PHQ-9 help? Int J Cardiol 221: 246-250, 2016.

22. Kessing D, Pelle AJ, Kupper N, Szabó BM, Denollet J. Positive affect, anhedonia, and compliance with self-care in patients with chronic heart failure. J Psychosom Res 77: 296-301, 2014.

23. Fink AM, Sullivan SL, Zerwic JJ, Piano MR. Fatigue with systolic heart failure. J Cardiovasc Nurs 24: 410-417, 2009.

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