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ORIGINAL ARTICLE

Comprehensive symptom assessment using Integrated Palliative care Outcome Scale in hospitalized heart failure patients

Yasuhiro Hamatani[1]*, Moritake Iguchi[1], Yurika Ikeyama[2], Atsuko Kunugida[2], Megumi Ogawa[2], Natsushige Yasuda[3], Kana Fujimoto[4], Hidenori Ichihara[4], Misaki Sakai[2,5], Tae Kinoshita[5], Yasuyo Nakashima[3] and Masaharu Akao[1]

[1]*Department of Cardiology, National Hospital Organization Kyoto Medical Center, 1-1, Mukaihata-cho, Fukakusa, Fushimi-ku, Kyoto, 612-8555, Japan;* [2]*Department of Nursing, National Hospital Organization Kyoto Medical Center, Kyoto, Japan;* [3]*Department of Rehabilitation, National Hospital Organization Kyoto Medical Center, Kyoto, Japan;* [4]*Department of Pharmacy, National Hospital Organization Kyoto Medical Center, Kyoto, Japan; and* [5]*Department of Palliative Care Medicine, National Hospital Organization Kyoto Medical Center, Kyoto, Japan*

Abstract

Aims Patients with heart failure (HF) may have variable unrecognized symptom burdens. We sought to investigate the details, determinants, and prognostic significance of symptom burden in hospitalized patients with HF.

Methods and results We prospectively evaluated consecutive hospitalized patients with HF as primary diagnosis at our institution using the Integrated Palliative care Outcome Scale (IPOS) both on admission and at discharge. The IPOS, which is a well-validated multi-dimensional symptom assessment scale among advanced illness, consists of 17 questions for enquiring about physical symptoms (10 items), emotional symptoms (4 items) and communication and practical issues (3 items) using a 5-point Likert scale (0 [best]–4 [worst] points). Clinically relevant symptoms were defined as $\geq$2 points for each IPOS item. Worsening symptom burden was defined as the total IPOS score at discharge being poorer than that on admission. Of 294 patients (mean age: 77.5 ± 12.0 years, male: 168 patients, New York Heart Association class IV: 96 patients, mean left ventricular ejection fraction [LVEF]: 44%, and median N-terminal pro B-type natriuretic peptide [NT-proBNP] level: 4418 ng/L), the median (IQR) total IPOS score on admission was 19 (12, 27) and they were widely distributed (minimum: 0 – maximum: 52). The total IPOS score on admission was not correlated with the HF severity, including LVEF (Spearman's $\rho = -0.05$, $P = 0.43$), NT-proBNP levels (Spearman's $\rho = 0.08$, $P = 0.20$) or in-hospital mortality prediction model (GWTG-HF risk score) (Spearman's $\rho = 0.01$, $P = 0.90$). Total IPOS scores significantly decreased during hospitalization as a whole (median [IQR]: 13 [6, 21] at discharge; $P < 0.001$ vs. those on admission). All of the four emotional symptoms (patient anxiety, depression, family anxiety and feeling at peace) remained in the top 5 of clinically relevant symptoms at discharge, whereas none of 10 physical symptoms were nominated. Worsening symptom burden was noted in 28% of the patients during hospitalization, and was independently associated with higher all-cause mortality after discharge (hazard ratio: 2.28, 95% confidence interval: 1.02–5.09; $P = 0.044$) even after adjustment by age and HF mortality prediction model (MAGGIC risk score).

Conclusions We revealed that hospitalized patients with HF had multi-dimensional symptom burdens which varied among individuals and were not correlated with the disease severity. Emotional symptoms, such as anxiety and depression, were the main clinically relevant symptoms at discharge. A worsening IPOS score was noted in a quarter of patients with HF and was associated with a poor prognosis, suggesting the importance of holistic symptom assessment during the course of hospitalization for HF.

Keywords Heart failure; Integrated Palliative care Outcome Scale; Psychological symptoms

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**Correspondence to: Yasuhiro Hamatani, Department of Cardiology, National Hospital Organization Kyoto Medical Center, 1-1, Mukaihata-cho, Fukakusa, Fushimi-ku, Kyoto 612-8555, Japan. Tel: +81-75-641-9161; Fax: +81-75-643-4325. Email: y.hamatani1114@gmail.com*

Introduction

Heart failure (HF) is a progressive disease with a poor prognosis and it is a major growing public health concern in aging societies.[1] In the course of HF, patients typically have a high symptom burden, including physical, psycho-social and spiritual issues.[2,3] Thus, holistic symptom assessment is recommended for patients with advanced HF.[4,5] However, we previously found that their symptoms are poorly recognized and addressed by healthcare professionals.[6] Patients with HF are often admitted to the hospital repeatedly,[7] and hospitalization may be an ideal opportunity for holistic assessment and management because multidisciplinary team intervention can be easily introduced. To date, there is a paucity of studies regarding holistic symptom assessment during the course of hospitalization for HF.

Patient-reported outcome measurements (PROMs) are patient-completed questionnaires proposed to provide a subjective evaluation of the patients, and are the gold standard in symptom assessment.[8] The Integrated Palliative care Outcome Scale (IPOS) is one of the PROMs with a 17-item multi-dimensional tool for enquiring about physical and psycho-social symptoms, which enables a holistic approach.[9] The IPOS is widely accepted among patients with advanced illness, and established in clinical care and research.[10,11] Previous studies suggested that the IPOS is also feasible and acceptable for patients with HF,[12,13] and recent European guideline for HF recommends the IPOS as one of the symptom assessment tools among advanced HF patients.[14] The use of IPOS is expected to increase in the near future; however, studies on the implementation of IPOS in consecutive patients with HF are lacking. An understanding of the symptom burden using IPOS may be of clinical value, and form the foundation for the holistic assessment and management of hospitalized patients with HF.

Accordingly, the aim of this study was to investigate the prevalence, determinants, temporal change and prognostic significance of symptom burden using IPOS in consecutive hospitalized patients with HF in a Japanese cardiovascular department.

Methods

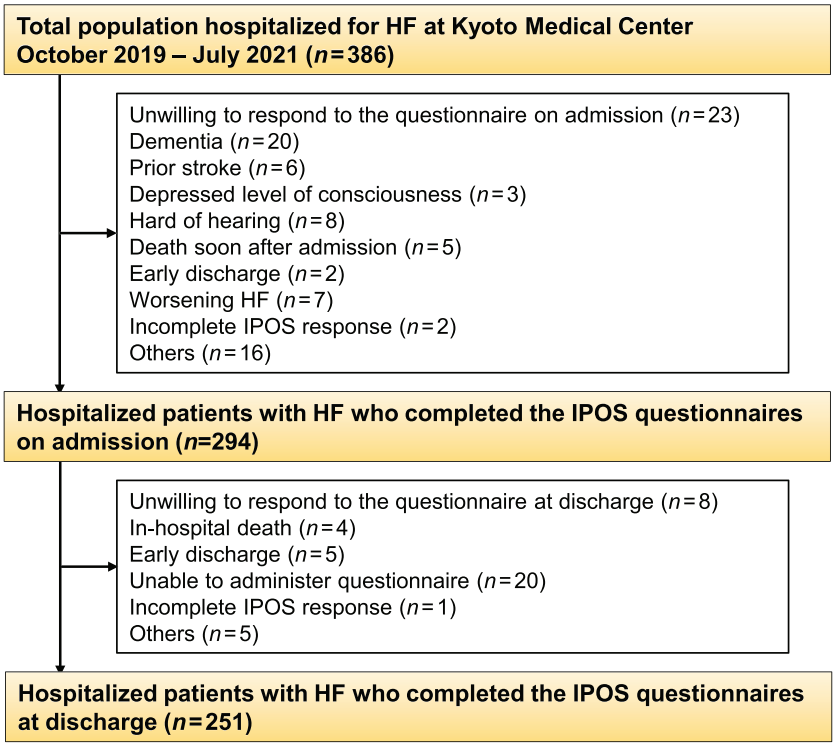
Study population

This single-centre HF registry is an ongoing, prospective, observational study including consecutive patients hospitalized with HF as primary diagnosis at the National Hospital Organization Kyoto Medical Center, Kyoto, Japan. The details of the registry were described previously.[15] Briefly, the diagnosis of HF was confirmed based on the Framingham definition of HF by two or more cardiologists at a conference at the cardiology department of the hospital.[16] The objective of this registry is to evaluate the current status of symptom burden (such as physical, psychological, social, and spiritual symptoms) using validated scales in a holistic manner among hospitalized patients with HF, and to investigate the predictors and prognostic significance of these symptoms in patients with HF. We herein report the baseline characteristics, determinants, temporal change and short-term prognostic significance of symptom burden in patients with HF who were hospitalized at our institution between October 2019 and July 2021. Follow-up was censored on 9 August 2021. We excluded patients who were unable to fill out the IPOS questionnaires. The reasons for exclusion in this study were as follows: unwillingness to respond to the questionnaire, dementia, prior stroke, depressed level of consciousness, hard of hearing, death soon after admission, early discharge, worsening HF, incomplete IPOS response and others (*Figure 1*). For patients with multiple admissions, only the first hospitalization during the study period was analysed. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the ethical committees of the National Hospital Organization Kyoto Medical Center (20-014).

Symptom assessment scale

Symptom burden was evaluated by the IPOS questionnaires.[9] The IPOS has been translated into Japanese, and its validity and reliability were previously evaluated.[17] The IPOS assesses the symptoms using a 5-point Likert scale (0–4 points) with a 17-item questionnaire comprising three subscales: physical symptoms (10 items; pain, shortness of breath, weakness, nausea, vomiting, poor appetite, constipation, dry mouth, drowsiness and poor mobility), emotional symptoms (4 items; patient anxiety, family anxiety, depression and feeling at peace) and communication and practical issues (3 items; sharing feelings, enough information and practical issues).[18,19] The physical symptoms are graded according to the severity. Emotional symptoms and communication issues are graded by frequency. The practical issue is scaled for the occurrence of the addressed problem. A higher score indicates higher symptom levels and clinically relevant symptoms were defined as $\geq$2 points for each item according to a previous study.[20] The values of the individual IPOS scores were added up to a total score ranging from 0 (minimum burden) to 68 (maximum burden).[10,20] We used a Japanese translation of the IPOS patient version 3 day recall period in this study. A clinical research coordinator at our department guided the patients through the answering of the questionnaires if necessary and it took approximately 10 minutes to complete the questionnaires. There was an extra item in the IPOS questionnaire asking if they filled out the questionnaire alone or with the help of healthcare staff or family/

Figure 1 Flow diagram of this study. HF, heart failure; IPOS, Integrated Palliative care Outcome Scale.



friends. We obtained IPOS questionnaires both on admission and at discharge during hospitalization for HF. When we were unable to obtain the questionnaires, we assessed the reason for non-response in each case. We excluded patients lacking ≥1 IPOS items (defined as incomplete IPOS response). The results of IPOS questionnaires were not shared with the attending physicians during the study period.

Variables

We obtained data on the patient background, laboratory and echocardiographic data, and details of HF treatment on admission from a medical chart review. We also calculated the Get With the Guidelines–Heart Failure (GWTG-HF) risk score using variables on admission for predicting in-hospital mortality,[21] and calculated the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score using variables at discharge for prognostication after discharge.[22]

Statistical analysis

Continuous variables are presented as the mean ± standard deviation when normally distributed, and as the median and interquartile range (IQR) when non-normally distributed. Distribution was assessed using a histogram. Comparisons of differences among groups were performed by the unpaired Student's *t*-test, Mann–Whitney *U*-test or Kruskal–Wallis test for continuous variables. Comparisons were performed by the chi-squared test or Fisher's exact test for dichotomous variables as appropriate.

First, we investigated the distribution and details of symptom burden revealed by IPOS questionnaires on admission in hospitalized patients with HF. Then, we divided the entire population into two groups according to the median value of the total IPOS score on admission, and compared the clinical backgrounds and disease severity between the two groups. The relationship between total IPOS score on admission and important baseline characteristics (GWTG-HF risk score, N-terminal pro B-type natriuretic peptide [NT-proBNP] levels and left ventricular ejection fraction [LVEF]) was determined by Spearman correlation analysis. Second, we investigated the distribution and details of the IPOS score at discharge. We evaluated the prevalence of clinically relevant symptoms (≥2 points for each item) among 17 items during hospitalization for HF, and ranked the frequency of symptoms based on the framework of three subscales (10 physical symptoms, 4 emotional symptoms, and 3 communication/practical issues). Third, we evaluated the temporal changes in IPOS score during hospitalization for HF. The paired Wilcoxon test was applied to assess the difference between the IPOS score on admission and at discharge. Thereafter, we defined worsening symptom burden as the IPOS

score at discharge being higher than that on admission, and compared the baseline characteristics between patients with worsening symptom burden and those without it. Lastly, we investigated the association of worsening symptom burden during hospitalization with mortality after discharge. The Kaplan–Meier method was used to estimate the cumulative incidence of all-cause mortality and log-rank testing was performed to assess differences among groups. The hazard ratio of the events was calculated using Cox proportional hazards model. We adjusted the results by age and MAGGIC risk score in multivariable Cox models. All tests were two-tailed and a value of $P < 0.05$ was considered significant. All analyses were performed using JMP version 14.2.0.

Results

Study flowchart and baseline characteristics

A flowchart of this study is presented in *Figure 1*. Of the total 386 patients with HF hospitalized at our institution between October 2019 and July 2021, 294 (76%) completed the IPOS questionnaires on admission. None of the patients were complicated with coronavirus disease 2019 during the study period. Of 294 patients, the mean age was 77.5 ± 12.0 years and 168 (57%) were male. There were 96 patients classified as NYHA functional class IV (33%), the median NT-proBNP level was 4418 ng/L and the mean LVEF was 44% on admission (*Table 1*). Among 294 patients with IPOS questionnaire data on admission, 251 (85%) responded to the questionnaires at discharge. Demographic and clinical characteristics among the total hospitalized patients, and those of patients with IPOS questionnaires on admission and at discharge are presented in the Supporting Information, *Table S1*.

Distribution and determinants of Integrated Palliative care Outcome Scale score on admission

The distribution of the total IPOS score on admission is shown in *Figure 2A*. The median (IQR) for the total IPOS score on admission was 19 (12, 27) and they were widely distributed (minimum: 0 – maximum: 52). The median (IQR) duration from hospital admission to the day of IPOS evaluation on admission was 2 (1, 4) days. One hundred and fifty-two patients with HF responded the IPOS questionnaire by themselves (52%), 136 responded with the help of the clinical research coordinator (47%), 4 responded with the help of their family/friends (1%), and the results of the remaining 2 were missing. The details of each IPOS item on admission are described in *Figure 2B* and *2C*.

Baseline characteristics stratified by median total IPOS score on admission are shown in *Table 1*. Patients with a higher IPOS score (≥20 points [above median value]) were younger (75.6 ± 12.7 vs. 79.3 ± 11.0 years; $P = 0.008$), had a higher prevalence of a history of depression (11 [8%] vs. 3 [2%]; $P = 0.029$) and had a lower prescription rate of renin-angiotensin system inhibitor (58 [40%] vs. 80 [54%]; $P = 0.019$) than those with a lower IPOS score (≤19) (*Table 1*). On the other hand, other demographic characteristics did not differ among the two groups stratified by the median total IPOS score. The total IPOS score on admission was comparable between patients stratified by NYHA functional class ($P = 0.066$), HF stage ($P = 0.46$) and history of HF hospitalization ($P = 0.31$). The total IPOS score was not correlated with GWTG-HF risk score (Spearman's $\rho = 0.01$, $P = 0.90$), NT-proBNP level (Spearman's $\rho = 0.08$, $P = 0.20$) or LVEF (Spearman's $\rho = -0.05$, $P = 0.43$).

Details of Integrated Palliative care Outcome Scale score during hospitalization for heart failure

The distribution of total IPOS score at discharge is shown in *Figure 3A*. The median (IQR) for the total IPOS score at discharge was 13 (6, 21) and scores were also widely distributed (minimum: 0 – maximum: 44), as well as on admission. The median (IQR) duration from the day of IPOS evaluation at discharge to hospital discharge was 1 (1, 2) day. One hundred and forty-eight patients with HF responded the IPOS questionnaire at discharge by themselves (59%) and 103 responded with the help of the clinical research coordinator (41%).

The details of each item at discharge are described in *Figure 3B* and *3C*. When compared with physical symptoms, most emotional symptoms persisted during hospitalization for HF. The prevalence of clinically relevant symptoms (≥2 points for each IPOS item) on admission and at discharge is presented in *Figure 4*. Of note, more than half of the patients had clinically relevant symptoms of family anxiety even at discharge. All four emotional symptoms (patient anxiety, depression, family anxiety and feeling at peace) were ranked in the top 5 at discharge, whereas none of 10 physical symptoms were nominated.

Temporal changes in Integrated Palliative care Outcome Scale score during hospitalization

During hospitalization for HF, the total IPOS score significantly decreased as a whole (19 [12, 27] on admission vs. 13 [6, 21] at discharge; $P < 0.001$). On the other hand, worsening symptom burden (IPOS score at discharge being higher than that on admission) was noted in 71 patients (28%). Baseline characteristics stratified by the worsening IPOS score during hospitalization are shown in *Table 2*. The patient characteristics were almost comparable between patients with

Table 1 Baseline characteristics among total population and stratified by the IPOS scores on admission

Variables	Total population $n = 294$	IPOS ≥20 $n = 145$	IPOS ≤19 $n = 149$	*P*-value
Backgrounds				
Age, years	77.5 ± 12.0	75.6 ± 12.7	79.3 ± 11.0	0.008
Male sex	168 (57%)	79 (55%)	89 (60%)	0.36
Body mass index, kg/m^2	24.6 ± 5.5	24.7 ± 5.1	24.6 ± 5.9	0.79
Stage D HF	26 (9%)	11 (8%)	15 (10%)	0.45
NYHA class IV on admission	96 (33%)	54 (37%)	42 (28%)	0.10
Acute on chronic HF	124 (42%)	64 (44%)	60 (40%)	0.50
Systolic blood pressure, mmHg	139 ± 30	138 ± 32	140 ± 27	0.59
Pulse rate, beats per minute	94 ± 27	94 ± 24	95 ± 30	0.75
Aetiology of HF				
Ischaemic cardiomyopathy	60 (20%)	33 (23%)	27 (18%)	0.43
Non-ischaemic cardiomyopathy	50 (17%)	24 (17%)	26 (17%)	
Valvular heart disease	52 (18%)	22 (15%)	30 (20%)	
Hypertensive	36 (12%)	21 (14%)	15 (10%)	
Arrhythmia	66 (22%)	28 (19%)	38 (26%)	
Others	30 (10%)	17 (12%)	13 (9%)	
Co-morbid conditions				
History of HF hospitalization	86 (29%)	48 (33%)	38 (26%)	0.15
Atrial fibrillation	166 (56%)	85 (59%)	81 (54%)	0.46
Coronary artery disease	79 (27%)	38 (26%)	41 (28%)	0.80
Cerebrovascular disease	48 (16%)	23 (16%)	25 (17%)	0.83
Hypertension	227 (77%)	108 (74%)	119 (80%)	0.27
Diabetes mellitus	89 (30%)	37 (26%)	52 (35%)	0.080
Chronic kidney disease	227 (77%)	111 (77%)	116 (78%)	0.79
History of anxiety	12 (4%)	8 (6%)	4 (3%)	0.25
History of depression	14 (5%)	11 (8%)	3 (2%)	0.029
Oral medication on admission				
ACE-I/ARB/ARNi	138 (47%)	58 (40%)	80 (54%)	0.019
Beta-blockers	122 (42%)	62 (43%)	60 (40%)	0.66
MRA	56 (19%)	30 (21%)	26 (17%)	0.48
SGLT2i	7 (2%)	4 (3%)	3 (2%)	0.72
Loop diuretics	150 (51%)	79 (54%)	71 (48%)	0.24
Anxiolytic agents on admission	12 (4%)	8 (6%)	4 (3%)	0.25
Antidepressants on admission	16 (5%)	12 (8%)	4 (3%)	0.041
Echocardiography				
LVDd, mm	51.8 ± 8.9	52.4 ± 9.0	51.2 ± 8.9	0.23
LVEF, %	44.0 ± 17.9	43.7 ± 18.0	44.4 ± 17.9	0.73
LVEF < 40%	134 (46%)	68 (47%)	66 (45%)	0.69
Laboratory data				
NT-proBNP, ng/L	4418 (1869, 8749)	4882 (1862, 9566)	4112 (1869, 7971)	0.29
Troponin I, ng/L	32.6 (15.9, 87.9)	36.2 (20.1, 91.1)	27.8 (15.0, 79.6)	0.086
eGFR, mL/min/1.73 m^2	44.3 (28.2, 57.1)	45.5 (27.8, 57.3)	42.2 (30.6, 57.3)	0.99
Haemoglobin, g/dL	11.9 ± 2.3	12.0 ± 2.4	11.8 ± 2.3	0.40
Sodium, mEq/L	140 ± 4	140 ± 4	140 ± 4	0.37
Albumin, g/dL	3.6 ± 0.5	3.5 ± 0.6	3.6 ± 0.5	0.52
Management during hospitalization				
Intensive care unit admission	152 (52%)	73 (50%)	79 (53%)	0.65
Intravenous drug administration	198 (67%)	97 (67%)	101 (68%)	0.87
Cardiac rehabilitation	271 (92%)	132 (91%)	139 (93%)	0.47
Psychiatrist counselling	24 (8%)	15 (10%)	9 (6%)	0.18
Hospitalization length, days	17 (13, 23)	17 (13, 25)	16 (13, 22)	0.38
Risk scores				
GWTG HF risk score, points	42 ± 8	42 ± 8	42 ± 8	0.80
MAGGIC risk 1-year mortality, %	19 ± 8	18 ± 9	20 ± 11	0.13
MAGGIC risk 3-year mortality, %	40 ± 16	40 ± 15	42 ± 17	0.17

Data are expressed as mean ± SD, median (interquartile range), or number (%).
ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor neprilysin inhibitor; eGFR, estimated glomerular filtration rate; GWTG HF, Get With The Guideline Heart Failure; HF, heart failure; IPOS, Integrated Palliative care Outcome Scale; LVDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; MAGGIC, The Meta-Analysis Global Group in Chronic Heart Failure; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; SGLT2i, sodium glucose co-transporter 2 inhibitor.

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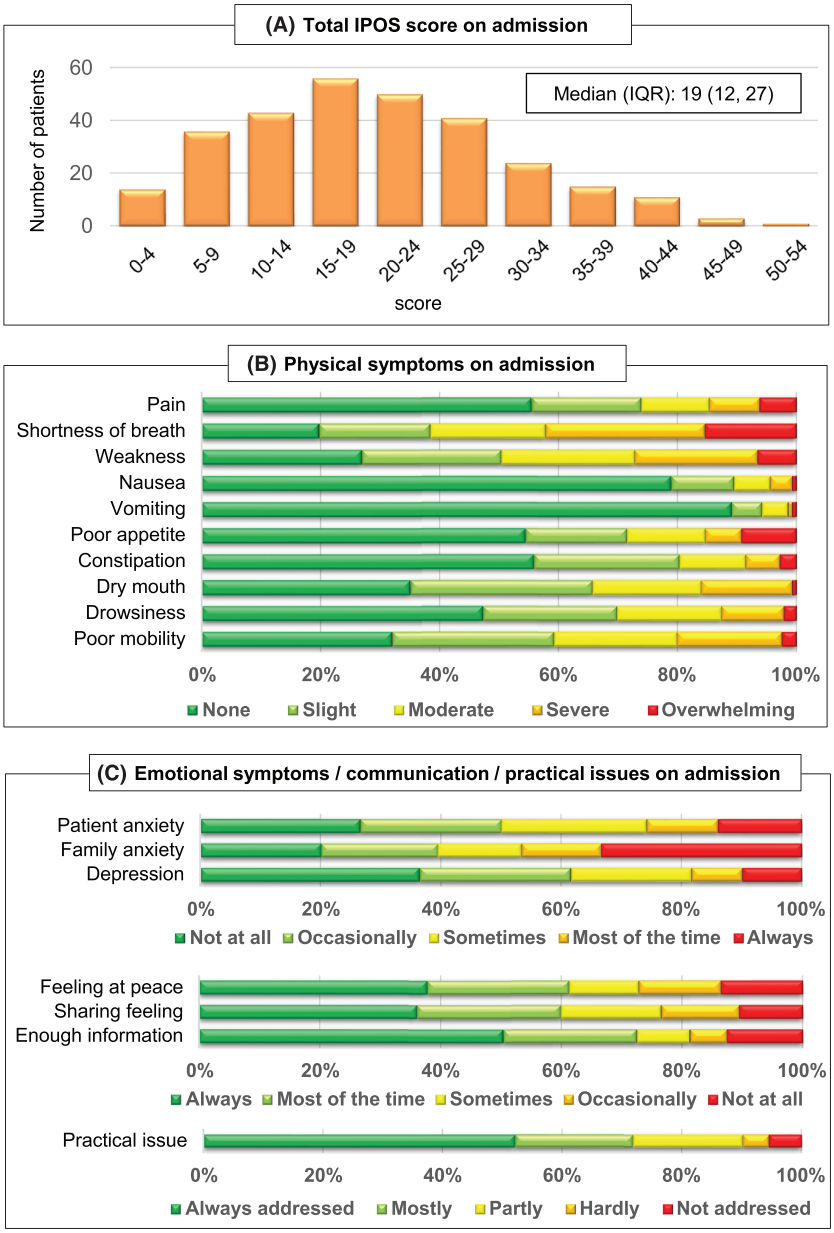
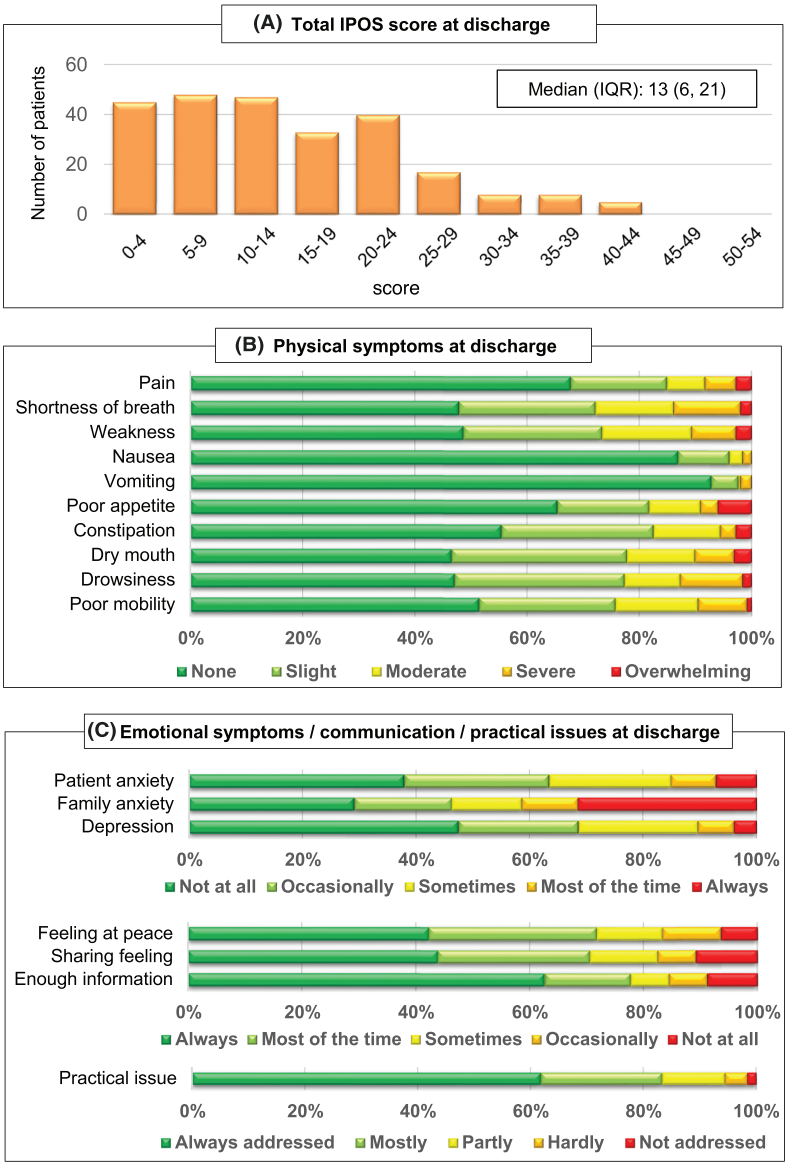
Figure 2 Distribution of the total IPOS score and details of each IPOS item on admission among hospitalized patients with heart failure. (A) Total IPOS score on admission; (B) Physical symptoms on admission; (C) Emotional symptoms, communication and practical issues on admission. IPOS, Integrated Palliative care Outcome Scale; IQR, interquartile range.



worsening IPOS score and those without, except that those with a worsening IPOS score had a higher prevalence of a history of chronic kidney disease (61 [86%] vs. 133 [74%]; $P = 0.041$) than those without (*Table 2*).

The cumulative incidence of events is shown in *Table 3*. A total of 25 patients (10%) died during the median (IQR) follow-up period of 238 (100, 416) days. The Kaplan–Meier curve for the incidence of all-cause mortality after discharge stratified by the worsening IPOS score during hospitalization is shown in *Figure 5*. Patients with a worsening IPOS score had a higher risk of all-cause mortality (log-rank; $P = 0.027$, unadjusted hazard ratio: 2.37, 95% confidence interval: 1.07–5.23; $P = 0.032$). After adjustment by age and MAGGIC-risk score in the multivariable Cox regression analysis, worsening IPOS score during hospitalization remained an independent predictor of all-cause mortality after discharge (hazard ratio: 2.28, 95% confidence interval: 1.02–5.09; $P = 0.044$) (*Table 3*).

Figure 3 Distribution of the total IPOS score and details of each IPOS item at discharge among hospitalized patients with heart failure. (A) Total IPOS score at discharge; (B) Physical symptoms at discharge; (C) Emotional symptoms, communication and practical issues at discharge. IPOS, Integrated Palliative care Outcome Scale; IQR, interquartile range.



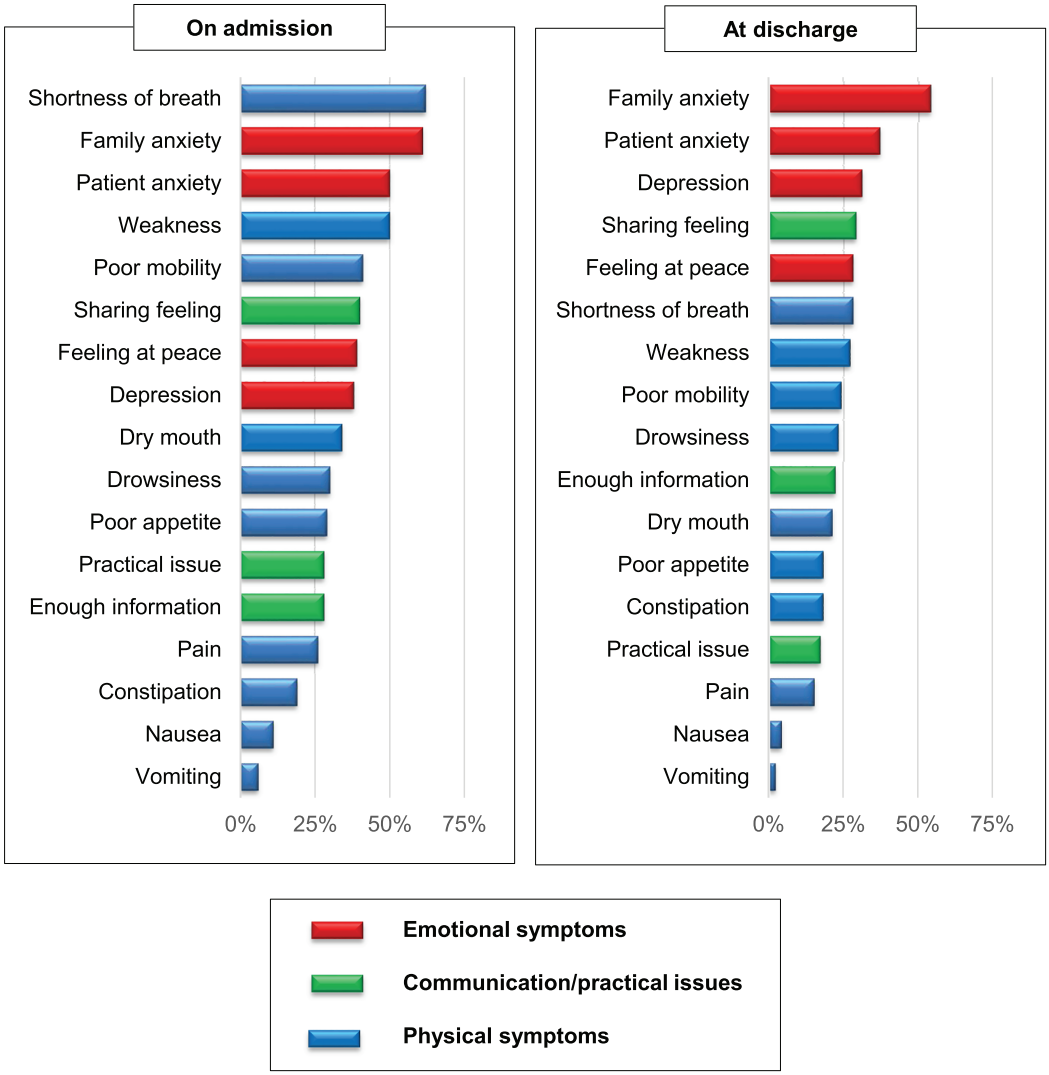
Discussion

Our study revealed the following: First, hospitalized patients with HF exhibited a multi-dimensional symptom burden, including physical, emotional and social issues. Importantly, these symptoms varied among individuals and were not correlated with the disease severity. Second, the symptom burden somewhat improved during hospitalization but existed to some extent even at discharge. Of note, all four emotional symptoms, including family anxiety, were ranked in the top 5 distressing symptoms at discharge. Third, approximately a quarter of hospitalized patients with HF exhibited a worsening symptom burden, which was unable to be predicted by baseline characteristics. We found a possible association between the temporal worsening of IPOS during hospitalization and subsequent poor prognosis in patients with HF.

Symptom burden and related factors in hospitalized patients with heart failure

The IPOS has been confirmed to be a valid and reliable PROM,[10] and translated into many languages.[17,23–25] The IPOS is characterized by its inclusion of social and spiritual is-

Figure 4 Frequency of clinically relevant symptoms (IPOS score ≥2 points) among 17 IPOS items on admission and at discharge. IPOS, Integrated Palliative care Outcome Scale.



sues as well as physical and psychological symptoms. In this study, comprehensive symptom assessment using IPOS identified a large symptom burden, including physical, psycho-social and spiritual issues, in hospitalized patients with HF. Ideally, symptom burden should be routinely and regularly evaluated in the course of HF; however, it is difficult to keep track of this in a busy cardiovascular medical service. Under such circumstances, hospitalization constitutes a convenient and suitable time point to start holistic symptom assessment because hospitalization is a hallmark that can easily be identified and is a strong predictor for poor prognosis in patients with HF. Moreover, hospitalization is considered to be a great opportunity for the multi-disciplinary team to become involved in the management of patients with HF. We believe that assessment using the IPOS by multi-disciplinary team including nurses can be integrated into hospital management, complementing existing practice without requiring additional equipment.

Of note, the symptom burden varied among individuals (range: 0–52), and the total IPOS score was not associated with the baseline characteristics such as NYHA class, HF stage, history of hospitalization, LVEF and natriuretic peptide levels. While HF is associated with a variety of co-morbidities, there was no significant association between IPOS score and co-morbid conditions except for a history of depression. Previous studies also demonstrated that no clinical background factors correlated with PROMs, including the Kansas City Cardiomyopathy Questionnaires (KCCQ), the Minnesota Living with Heart Failure Questionnaire and the Euro-QoL 5D scores.[26,27] Taken together, we were unable to predict the impaired PROMs using the patient background and symptom burden can only be identified by asking the patients, suggesting the

Table 2 Baseline characteristics according to the change of IPOS during hospitalization for HF

Variables	With worsening IPOS score [a] $n = 71$	Without worsening IPOS score [a] $n = 180$	*P*-value
Backgrounds			
Age, years	78.8 ± 11.5	76.9 ± 12.5	0.26
Male sex	45 (63%)	93 (52%)	0.093
Body mass index, kg/m^2	24.5 ± 7.1	24.8 ± 5.1	0.68
Stage D HF	8 (11%)	13 (7%)	0.30
NYHA functional class IV on admission	21 (30%)	65 (36%)	0.33
Acute on chronic HF	27 (38%)	77 (43%)	0.49
Systolic blood pressure, mmHg	138 ± 27	142 ± 32	0.36
Pulse rate, beats per minute	92 ± 27	97 ± 27	0.13
Aetiology of HF			
Ischaemic cardiomyopathy	12 (17%)	39 (22%)	0.11
Non-ischaemic cardiomyopathy	12 (17%)	27 (15%)	
Valvular heart disease	19 (27%)	23 (13%)	
Hypertensive	8 (11%)	26 (14%)	
Arrhythmia	16 (23%)	44 (24%)	
Others	4 (6%)	21 (12%)	
Co-morbid conditions			
History of HF hospitalization	20 (28%)	52 (29%)	0.91
Atrial fibrillation	39 (55%)	105 (58%)	0.62
Coronary artery disease	17 (24%)	47 (26%)	0.72
Cerebrovascular disease	9 (13%)	30 (17%)	0.43
Hypertension	59 (83%)	137 (76%)	0.23
Diabetes mellitus	22 (31%)	53 (29%)	0.81
Chronic kidney disease	61 (86%)	133 (74%)	0.041
History of anxiety	4 (6%)	7 (4%)	0.54
History of depression	3 (4%)	7 (4%)	0.90
Oral medication on admission			
ACE-I/ARB/ARNi	35 (49%)	85 (47%)	0.77
Beta-blockers	24 (34%)	77 (43%)	0.19
MRA	11 (15%)	36 (20%)	0.41
SGLT2i	3 (4%)	4 (2%)	0.41
Loop diuretics	35 (49%)	91 (51%)	0.86
Anxiolytic agents on admission	4 (6%)	7 (4%)	0.54
Antidepressants on admission	4 (6%)	9 (5%)	0.76
Echocardiography			
LVDd, mm	50.5 ± 7.4	52.2 ± 9.1	0.16
LVEF, %	43.2 ± 17.4	44.1 ± 17.8	0.74
LVEF <40%	30 (43%)	86 (48%)	0.44
Laboratory data			
NT-proBNP, ng/L	4991 (1932, 9656)	4351 (1978, 8324)	0.49
Troponin I, ng/L	56.7 (14.9, 124.2)	32.0 (16.6, 79.4)	0.43
eGFR, mL/min/1.73 m^2	42.1 (27.3, 51.3)	45.4 (28.3, 59.6)	0.13
Haemoglobin, g/dL	11.5 ± 2.3	12.1 ± 2.4	0.11
Sodium, mEq/L	140 ± 4	140 ± 4	0.48
Albumin, g/dL	3.5 ± 0.4	3.6 ± 0.5	0.24
Management during hospitalization			
Intensive care unit admission	39 (55%)	95 (53%)	0.76
Intravenous drug administration	44 (62%)	133 (74%)	0.062
Cardiac rehabilitation	68 (96%)	167 (93%)	0.57
Psychiatrist counselling	4 (6%)	14 (8%)	0.79
Hospitalization length, days	17 (13, 22)	17 (14, 24)	0.59
Risk scores			
GWTG HF risk score, points	43 ± 8	41 ± 8	0.21
MAGGIC risk 1-year mortality, %	20 ± 10	18 ± 9	0.092
MAGGIC risk 3-year mortality, %	43 ± 17	39 ± 16	0.095

Data are expressed as mean ± SD, median (interquartile range), or number (%).

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor neprilysin inhibitor; eGFR, estimated glomerular filtration rate; GWTG HF, Get With The Guideline Heart Failure; HF, heart failure; IPOS, Integrated Palliative care Outcome Scale; LVDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; MAGGIC, The Meta-Analysis Global Group in Chronic Heart Failure; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; SGLT2i, sodium glucose co-transporter 2 inhibitor.

[a]Worsening IPOS score was defined as total IPOS score at discharge being poorer than that on admission.

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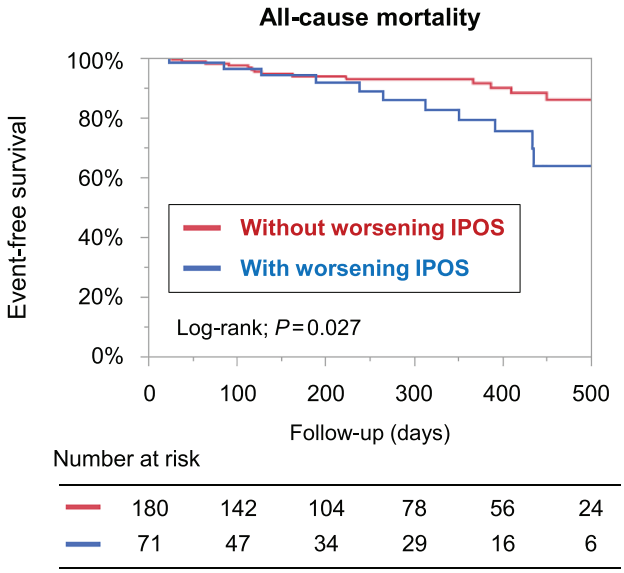
Table 3 Incidences of events after discharge according to the change of IPOS during hospitalization

	With worsening IPOS score $n = 71$	Without worsening IPOS score $n = 180$	*P*-value
All-cause death			
Cumulative event number	11	14	
Incidence rate, per person-year	23.9%	10.3%	0.027[a]
Unadjusted hazard ratio (95% CI)	2.37 (1.07–5.23)	Reference	0.032
Adjusted hazard ratio (95% CI)[b]	2.28 (1.02–5.09)	Reference	0.044

CI, confidence interval; IPOS, Integrated Palliative care Outcome Scale; MAGGIC, The Meta-Analysis Global Group in Chronic Heart Failure.
[a]Calculated by log-rank test.
[b]Adjusted by age and MAGGIC risk score.

Figure 5 Kaplan–Meier curve for the incidence of all-cause mortality among patients with and without a worsening IPOS score during hospitalization. IPOS, Integrated Palliative care Outcome Scale.



importance of holistic symptom assessment using validated screening tools in all patients with HF. Indeed, a European position statement recommends that a symptoms and needs assessment-based approach be provided regardless of disease severity.[28]

Unmet symptoms during hospitalization in patients with heart failure

We administered the IPOS questionnaires not only on admission but also at discharge, and identified which symptoms persisted during hospitalization. We revealed that emotional symptoms remained at discharge, as shown in *Figure 4*, in hospitalized patients with HF. Anxiety, depression and psychological needs were reportedly the most frequent concerns among patients receiving interventions by the palliative care team (mainly those with cancer).[29] The course of HF is characterized by uncertainty and loss of control, thus patients with HF can develop emotional distress similar to those with cancer. Indeed, we recently demonstrated that both anxiety and depression are common among hospitalized patients with HF using the Hospital Anxiety and Depression Scale.[15] Psychological symptoms might be under-diagnosed and under-treated in daily practice unless healthcare staff pays attention to them. However, psychological symptoms are associated with increased mortality and rehospitalization in patients with HF. Therefore, addressing psychological symptoms is recommended as a multi-domain approach for HF,[30,31] and our studies strongly support the importance of screening psychological symptoms in patients with HF.

The unique feature of the IPOS when compared with other PROMs is that it integrates the patients' perspectives and views on the concerns of their families. Our survey using the IPOS revealed that more than half of the patients had family anxiety even at discharge, which was the most common clinically relevant symptom at discharge. Self-assessment tools for caregivers revealed that family anxiety is highly ranked in patients with advanced illness.[32,33] HF is considered to be a disease that places burdens on their family. Indeed, previous small studies suggested that the majority of caregivers of patients with HF, mainly their family, had anxiety.[34,35] These studies and ours underline the importance of holistic care for relatives as well as for patients. From this perspective, IPOS, which encompasses the domain of family anxiety, is considered to be a more useful PROM than other scales among patients with HF.

Temporal changes and prognostic significance of Integrated Palliative care Outcome Scale in patients with heart failure

By applying the questionnaires both on admission and at discharge, we clarified the temporal changes in IPOS score during hospitalization for HF, which has not been addressed in previous studies.[12,13,20] The total IPOS score significantly decreased during hospitalization among the overall population; however, the IPOS score of more than a quarter of patients with HF (28%) deteriorated. As shown in *Figure 5* and *Table 3*,

a worsening IPOS score during hospitalization was associated with a poor prognosis after discharge.

PROMs, such as KCCQ or Minnesota Living with Heart Failure Questionnaire, are independently associated with subsequent death in patients with HF,[36,37] although the precise pathophysiological mechanisms remain unknown. In addition, change in KCCQ is associated with a poor prognosis in these patients.[38] To date, the prognostic significance of temporal IPOS changes during hospitalization has not been reported. Deterioration of the IPOS score may merely indicate the progression of HF; however, there were little differences in disease severity between patients with and without a worsening IPOS score in our study (*Table 2*). Although the relationship between temporal IPOS changes and adverse outcomes remains to be elucidated, holistic symptom assessment during the course of HF may constitute a starting point for more customized care, and our study suggested that it is imperative for health care providers to evaluate PROMs from the acute phase to the chronic phase in patients with HF. The IPOS is easy to respond because of its briefness and minimization of the text, and enables healthcare staff to identify and rank the patients' symptom burdens. Indeed, a substantial proportion of hospitalized patients with HF were willing to complete the questionnaires and no adverse effects were reported or conceptually occurred by this intervention, indicating that the IPOS can be routinely used during the course of hospitalization for HF. Specific referral criteria for palliative care have not been determined in daily practice. We hope implementation of palliative care based on IPOS questionnaires will be able to improve the quality of life among patients with HF.

Limitations

Our study had several limitations. First, some of the analyses were cross-sectional, limiting the ability to address the causal relationship between symptom burden and demographic variables. Second, our analysis was based on patients hospitalized at only one location in Japan and generalizability is limited. Further multi-cultural cohort studies and external validation of the results are strongly warranted. Third, approximately one-fourth of the total hospitalized patients were unable to respond the IPOS questionnaire, possibly introducing selection bias. Indeed, patients with IPOS data on admission were younger, less often NHYA class IV and had a lower NT-proBNP level on admission than those without (*Table S1*). However, IPOS can be used as a proxy assessment in patients who are unable to complete the questionnaires, even though we did not investigate its utility in this study. Fourth, the coordinator who guided the patients through answering the questions did not receive any specific training for administrating the IPOS questionnaires, resulting in some unavoidable bias. In addition, we did not collect the data about acceptability or feasibility of IPOS questionnaires in this study. Fifth, we did not obtain the quantitative scale about frailty which could be associated with symptom burdens in patients with HF. Sixth, family anxiety was assessed from the perspective of the patient rather than the family themselves. Ideally, this needs to be validated by the families.

Conclusions

We revealed that multi-dimensional symptom burdens exist in hospitalized patients with HF, which cannot be predicted by HF disease severity. Psychological symptoms, including family anxiety, were the main clinically relevant symptoms at discharge, indicating the necessity for addressing these symptoms in hospitalized patients with HF. A worsening IPOS score was noted in a quarter of patients with HF and was associated with a poor prognosis, suggesting the importance of holistic symptom assessment during the course of HF hospitalization. Further studies are warranted to investigate whether screening and intervention for multi-dimensional symptoms using validated scale like IPOS can improve the quality of life in patients with HF.

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Conflict of interest

All authors reported that they have no relationships relevant to the content of this paper to disclose.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline characteristics among total population and those with IPOS data on admission or at discharge.

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