

[ORIGINAL ARTICLE]

Gender Differences in the Social Determinants of the Long-term Prognosis for Severely Decompensated Acute Heart Failure in Patients over 75 Years of Age

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Abstract:

Objective The aim of present study was to elucidate the gender differences in social determinants among patients with acute heart failure (AHF).

Methods A total of 1,048 AHF patients were enrolled, and the 508 AHF patients who were ≥75 years old and the 540 patients who were <75 years old were evaluated as the elderly and non-elderly cohorts, respectively. Participants who met one of the three marital status-, offspring-, and living status-related criteria were considered socially vulnerable, and subjects were thus classified into socially vulnerable and non-socially vulnerable groups by gender in both the non-elderly and elderly cohorts. Social vulnerability was significantly more common in the elderly cohort (n=246, 48.4%) than in the non-elderly cohort (n=197, 36.5%) and significantly more common in the elderly women (n=157, 69.4%) than in the elderly men (n=89, 31.5%). Kaplan-Meier curves showed that the survival rate of the socially vulnerable group was significantly poorer than that of the non-socially vulnerable group in the elderly male cohort (p=0.010). Social vulnerability was an independent predictor of the 1,000-day mortality in the elderly male cohort (hazard ratio: 1.942, 95% confidence interval: 1.102-3.422) but not in the elderly female cohort according to a multivariate analysis.

Conclusion Social vulnerability was shown to be more common in elderly female AHF patients than in elderly men, although it was associated with a poor prognosis in elderly men. Reinforcing the social structure of elderly male AHF patients might help improve their prognosis.

Key words: acute heart failure syndrome, socioeconomic status, living condition, marital status, mortality, aging society

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Introduction

The number of heart failure (HF) patients has been rapidly increasing, such that the situation is now referred to as the 'HF pandemic'. Worldwide, approximately 26 million patients are living with HF (1, 2). HF will become a more serious issue in the near future with the epidemiological transition and aging of the population (3).

In this era of aging and an "HF pandemic", the population of socially vulnerable acute HF (AHF) patients (i.e., those with no partner or children or who are living alone) is expected to increase. The evaluation of the social status of each AHF patient is therefore important for preventing re-admission due to HF and a poor prognosis. Several groups have systemically investigated the impact of social determinants or isolation on the prognosis of AHF patients (4-7). Lu et al. reported that the marital status and living condi-

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tions were correlated with the mortality and readmission rate among African Americans with HF (5). Specifically, being married and living with family independently predicted a low 1-year all-cause mortality and a low 30-day readmission rate.

We also recently described the adverse prognosis of socially vulnerable AHF patients, especially those who are elderly (6). Social vulnerability has been confirmed to be an independent factor predicting the 1,000-day mortality in HF patients, and such patients have a number of factors that may lead to repeated admission and adverse outcomes after their discharge. The gender differences in characteristics among AHF patients have also been discussed in some previous reports (8-10). However, gender differences in the proportion of socially vulnerable patients and in the prognosis based on the presence of social vulnerability in AHF have not yet been reported. Such differences might be an important factor in determining the association between social factors and the HF prognosis. Investigations of the gender differences in social vulnerability might therefore help improve the social service of socially vulnerable patients.

In the present study, we newly defined socially vulnerable patients as those who met one of three criteria [marital status (without a partner), offspring status (without children), and living status (living alone)] and investigated the impact of gender differences on the relationship between social determinants and the long-term prognosis of AHF.

Materials and Methods

Subjects

A total of 1,048 patients [540 patients <75 years of age (non-elderly cohort) and 508 patients ≥75 years of age (elderly cohort)] admitted to the intensive-care unit (ICU) at Nippon Medical School Chiba Hokusoh Hospital between February 2000 and December 2014 and who had data available on social determinants were enrolled. Patients with HF caused by acute coronary syndrome were excluded from the study.

Based on the 2016 European Society of Cardiology (ESC) guidelines for the diagnosis of AHF, we diagnosed AHF according to the plasma natriuretic peptide level [b-type natriuretic peptide (BNP) ≥ 100 pg/mL] (Class I, level A), a 12-lead electrocardiogram (Class I, level C), laboratory measurements (troponins, blood urea nitrogen (11), creatinine, sodium, potassium, glucose, liver function and complete blood counts) (Class I, level C) and echocardiography (Class I, level C) (12). The treating physician at the emergency department diagnosed AHF within 30 minutes of admission. AHF presented as either new-onset or decompensated chronic HF with symptoms sufficient to warrant hospitalization. The patients who met any of the following criteria were admitted to the ICU: 1) those who required high-projectile oxygen inhalation (including mechanical support) to treat orthopnea; 2) those who required inotrope or me-

chanical support due to low blood pressure; and 3) those who required various types of diuretics to improve general or lung edema. The treatment strategy was chosen by each physician. In all cases, diuretics or vasodilators were administered for the treatment of AHF. All of the patients had a New York Heart Association (NYHA) functional class of either III or IV.

Procedure

Patients who met one of the three marital status-, offspring status-, and living status-related criteria were considered to be socially vulnerable. With regard to the marital status, patients without a partner (including those who had never been married or were divorced or widowed) were classified as socially vulnerable. With regard to the offspring status, patients who had no children were classified as socially vulnerable. With regard to the living status, patients who lived alone were classified as socially vulnerable. Patients who met at least one of these criteria were classified as socially vulnerable, and all others were classified as non-socially vulnerable.

The patients were defined as non-socially vulnerable or socially vulnerable in each cohort as follows: non-elderly male cohort [non-socially vulnerable (n=260) and socially vulnerable (n=154)], non-elderly female cohort [non-socially vulnerable (n=83) and socially vulnerable (n=43)], elderly male cohort [non-socially vulnerable (n=193) and socially vulnerable (n=89)], elderly female cohort [non-socially vulnerable (n=69) and socially vulnerable (n=157)]. We defined the elderly cohort as those ≥75 years of age, which is the population referred to as “the late elderly” in Japanese society. The Japanese Heart Failure Society provided a statement about the management of elderly HF targeting those ≥75 years of age in 2016. Furthermore, the Acute Decompensated Heart Failure Syndromes (ATTEND) registry showed that Japanese HF patients ≥75 years of age had a higher mortality rate than those <75 years of age (13). The present study therefore focused on HF patients ≥75 years of age.

We compared the patients' characteristics among the groups, including their age, gender, presence of *de novo* or recurrent HF, etiology of HF, risk factors for atherosclerosis (diabetes mellitus, hypertension and dyslipidemia), vital signs [systolic blood pressure (SBP) and heart rate], left ventricular ejection fraction (LVEF) on echocardiography, NYHA class, arterial blood gas data, laboratory data [blood urea nitrogen (11), total bilirubin, hemoglobin, BNP, C-reactive protein (CRP) and other variables], nutritional status [prognostic nutritional index (PNI) and controlling nutritional status (CONUT) score], medications administered during ICU admission and duration of admission (duration of ICU stay and hospital stay). All data were collected from the patients' medical records.

The PNI was calculated according to the following formula: $10 \times \text{serum albumin (g/dL)} + 0.005 \times \text{lymphocyte count } (\mu\text{L})$ (lower = worse). The CONUT score was calculated using the serum albumin, lymphocytes and total cho-

lesterol (range 0-12, higher = worse). In this scoring system, point values are assigned to different ranges of laboratory measurements, as follows: serum albumin ≥ 3.5 g/dL, 0 points; 3.49-3, 2 points; 2.99-2.5, 4 points; and < 2.5 , 6 points; lymphocytes $\geq 1,600$ μL^{-1} , 0 points; 1,200-1,599, 1 point; 800-1,199, 2 points; and < 800 , 3 points; and total cholesterol ≥ 180 mg/dL, 0 points; 140-179, 1 point; 100-139, 2 points; and < 100 , 3 points. The lymphocyte count and total cholesterol were not obtained from 181 and 21 patients, respectively, so the PNI and CONUT score were calculated from the data of 869 and 867 AHF patients, respectively.

The long-term prognosis, including the 1,000-day all-cause mortality, was evaluated as the primary endpoint. The patients were routinely followed-up at an outpatient clinic. The prognoses of the patients who were followed at other institutes were determined by telephone contact. The prognostic value for 1,000-day mortality was evaluated using a Cox regression hazard model and Kaplan-Meier curves. In addition, the long-term prognosis was compared between the non-socially vulnerable and socially vulnerable groups in reduced LVEF (LVEF $\geq 40\%$, HF_rEF) and preserved LVEF (LVEF $< 40\%$, HF_pEF) patients as a sub-group analysis.

Statistical analyses

All of the statistical analyses were performed using the SPSS 22.0 software program (SPSS Japan Institute, Tokyo, Japan). All numerical data were expressed as the mean \pm standard deviation or the median (25-75% interquartile range), depending on normality. If the data were normally distributed, the values were expressed as the mean \pm standard deviation. If the data were not normally distributed, the values were expressed as the median (25-75% interquartile range). Normality was assessed using the Shapiro-Wilk W-test. The Mann-Whitney U-test was used for comparisons between two groups. The chi-squared test was used to compare proportions. P values of < 0.05 were considered to indicate statistical significance.

The prognostic value of social vulnerability was assessed by comparing the socially vulnerable group to the non-socially vulnerable group using a Cox regression hazard model. A Cox regression analysis was performed to determine the hazard ratio (HR) for the 1,000-day mortality. All clinically relevant factors affecting the prognosis, including the age (per 1.0-year increase), SBP (≥ 140 mmHg), estimated glomerular filtration rate (eGFR) (per 10-mL/min/1.73 m² increase), total bilirubin (per 0.1-mg/dL), sodium (per 1.0-mmol/L increase), CRP (per 1.0-mg/dL increase), hemoglobin (per 1.0-mg/dL increase), LVEF (per 10% increase), and BNP (per 10-pg/mL increase) at admission, were included in a multivariate Cox regression hazard model to investigate factors associated with the 1,000-day all-cause mortality. A multivariate Cox regression hazard model with simultaneous forced entry was used to analyze the impact of a socially vulnerable status and all clinically relevant factors (adjusted factors). The cumulative survival rates in each of

group were analyzed using Kaplan-Meier curves, and the log-rank test was used to calculate the statistical significance of the differences.

Ethics review board

The research ethics committee of Nippon Medical School Chiba Hokusoh Hospital approved the study protocol. Regarding informed consent, we described the contents of the present study in a poster displayed at our institute, and we also shared the contents on our homepage, where it could be easily seen by anyone in accordance with the advice of the ethics committee.

Results

Patient characteristics

The percentage of socially vulnerable patients was compared between the non-elderly cohort (n=540) and the elderly cohort (n=508); in addition, the percentage was also compared between men and women in both cohorts. The socially vulnerable patients numbered 246 (48.4%) in the elderly cohort and 197 (36.5%) in the non-elderly cohort. The proportion of socially vulnerable patients was significantly higher in the elderly cohort than in the non-elderly cohort ($p < 0.001$) (Fig. 1A). In the non-elderly cohort, there were 154 (37.2%) socially vulnerable men and 43 (34.2%) socially vulnerable women, a non-significant difference (Fig. 1B); in contrast, in the elderly cohort, there were 89 (31.5%) socially vulnerable men and 157 (69.4%) socially vulnerable women, a significant difference ($p < 0.001$) (Fig. 1C). These results suggest that elderly female AHF patients are more likely to be socially vulnerable than elderly male AHF patients in Japanese society.

Among male patients in the non-elderly cohort, the mean age in the socially vulnerable group was significantly younger than in the non-socially vulnerable group. Furthermore, the patients in the socially vulnerable group were less likely to have ischemic disease than those in the non-socially vulnerable group (Table 1). Among female patients in the non-elderly cohort, there were no significant differences in most factors (Table 1). However, among patients of both genders in the elderly cohort, the mean age in the socially vulnerable group was significantly older than in the non-socially vulnerable group (Table 2). These results suggest that aging and social vulnerability are strongly associated in both women and men with AHF.

The prognosis

The median follow-up period was 546 (144-1,000) days. There were 104 (9.9%) in-hospital deaths, and 242 patients (23.1%) died within 1,000 days. The Kaplan-Meier curves for the socially vulnerable patients in each category are shown in Figs. 2 and 3.

The rates of all-cause mortality were not significantly different between the socially vulnerable and non-socially vul-

Gender differences in social vulnerability

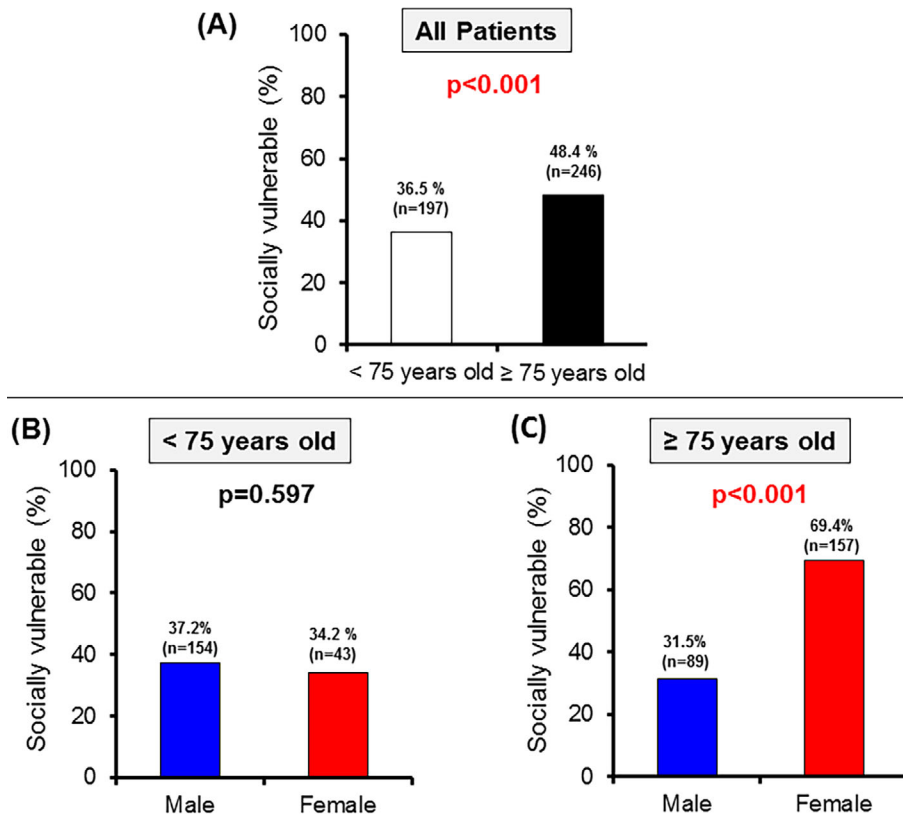


Figure 1. (A) Social vulnerability was significantly more likely in the elderly cohort (n=246, 48.4%) than in the non-elderly cohort (n=197, 36.5%) (p<0.001). (B) The rate of social vulnerability was not significantly different between the non-elderly men (n=154, 37.2%) and non-elderly women (n=43, 34.2%). (C) Social vulnerability was significantly more likely in the elderly female cohort (n=157, 69.4%) than in the elderly male cohort (n=89, 31.5%) (p<0.001).

nerable groups in non-elderly patients of either gender (Fig. 2). Interestingly, the rate of all-cause mortality in the socially vulnerable group was significantly higher than in the non-socially vulnerable group in elderly men (p=0.010) but not in elderly women (p=0.344) (Fig. 3). The univariate Cox regression analysis showed that a socially vulnerable status was a predictor of the 1,000-day mortality in the elderly male cohort [HR: 1.868, 95% confidence interval (CI) 1.151-3.031, p=0.011]; however, it was not a predictor in the elderly female cohort (Table 3). The multivariate Cox regression model revealed that a socially vulnerable status was an independent predictor of the 1,000-day mortality only in the elderly male cohort (HR: 1.942, 95% CI: 1.102-3.422, p=0.022) (Table 3). Furthermore, the rate of all-cause mortality in the socially vulnerable group was significantly higher than in the non-socially vulnerable group in elderly men with a reduced LVEF (p<0.001) but not in elderly women with a reduced LVEF (p=0.428), elderly men with a preserved LVEF (p=0.176), and elderly women with a preserved LVEF (p=0.538) (Fig. 4).

Discussion

The present study showed that the proportion of socially vulnerable patients was higher in elderly female AHF patients than in elderly male AHF patients. However, social vulnerability was only associated with a poor prognosis in the elderly male AHF cohort.

We previously reported that social vulnerability is correlated with a poor outcome of AHF. In addition, we showed in the present study that the socially poor AHF cohort included a large number of elderly women. Since the life expectancy of women is longer than that of men in Japan, elderly women tend to lose their partners and consequently become socially vulnerable. We also reported that being an elderly woman is independently associated with a worse mortality in patients with AHF (9). From this perspective, we hypothesized that the major reason for the poor prognosis in socially vulnerable elderly patients with AHF may be due to the fact that many such patients tend to be widowed women, which means that social vulnerability may thus be more strongly associated with a poor prognosis in the elderly female cohort than in the elderly male cohort.

Table 1. Characteristics of the Patients in the Non-elderly Cohort.

	<75 years old					
	Male		p value	Female		p value
	Non-socially vulnerable (n=260)	Socially vulnerable (n=154)		Non-socially vulnerable (n=83)	Socially vulnerable (n=43)	
Status and vital signs						
Age (years old)	66 (61-71)	62 (56-69)	0.001	66 (58-71)	69 (61-72)	0.343
Type (readmission, %)	88 (33.8%)	51 (33.1%)	0.915	19 (22.9%)	12 (27.9%)	0.663
LVEF (%)	31 (22-42)	31 (23-45)	0.901	39 (30-52)	34 (26-45)	0.074
NYHA (IV, %)	216 (83.1%)	128 (83.1%)	1.000	58 (69.9%)	35 (81.4%)	0.202
Systolic blood pressure (mmHg)	158 (125-186)	172 (147-199)	0.024	152 (125-179)	160 (113-180)	0.839
Pulse (beats/min)	110 (95-131)	120 (103-138)	0.005	122 (98-140)	112 (93-128)	0.115
Etiology						
Ischemia (yes, %)	132 (51.0%)	60 (39.0%)	0.014	23 (27.7%)	14 (32.6%)	0.680
Past medical history						
Hypertension (yes, %)	183 (70.4%)	112 (72.7%)	0.654	54 (65.1%)	26 (60.5%)	0.697
Diabetes mellitus (yes, %)	129 (49.6%)	74 (48.1%)	0.761	39 (47.0%)	18 (41.9%)	0.706
Dyslipidemia (yes, %)	129 (49.6%)	81 (52.6%)	0.611	41 (49.4%)	21 (48.8%)	1.000
Arterial blood gas						
pH	7.35 (7.21-7.43)	7.33 (7.17-7.43)	0.341	7.33 (7.23-7.44)	7.34 (7.22-7.42)	0.994
PCO ₂ (mmHg)	40.1 (32.0-54.6)	42.2 (34.3-60.7)	0.061	44.7 (31.6-55.7)	38.6 (33.0-50.1)	0.517
PO ₂ (mmHg)	83.5 (65.2-124.8)	86.7 (67.1-125.8)	0.407	90.9 (65.6-114.4)	93.6 (69.3-129.5)	0.837
HCO ₃ ⁻ (mmol/L)	21.5 (19.2-23.5)	22.0 (19.4-23.8)	0.200	22.3 (19.6-24.3)	21.1 (18.8-23.3)	0.222
SaO ₂ (%)	95 (89-98)	96 (90-98)	0.555	95 (91-98)	97 (93-98)	0.246
Lactate (mmol/L)	1.9 (1.3-3.7)	1.7 (1.2-3.2)	0.367	2.8 (1.2-4.5)	1.9 (1.0-3.6)	0.427
Laboratory data						
Total bilirubin (mg/dL)	0.6 (0.4-0.9)	0.6 (0.4-1.1)	0.998	0.6 (0.4-0.9)	0.5 (0.3-1.1)	0.713
Uric acid (mg/dL)	7.0 (5.9-8.2)	7.5 (6.0-8.7)	0.060	6.6 (5.0-7.6)	6.0 (4.6-7.8)	0.498
Sodium (mmol/L)	140 (137-142)	140 (138-142)	0.044	139 (137-141)	139 (138-142)	0.760
Potassium (mmol/L)	4.3 (3.9-4.8)	4.1 (3.8-4.4)	0.004	4.1 (3.8-4.5)	4.1 (3.6-4.6)	0.817
Hemoglobin (g/dL)	13.5 (11.4-15.3)	14.2 (12.3-15.8)	0.017	12.3 (10.9-13.7)	12.3 (10.6-13.3)	0.636
BUN (mmol/L)	23.3 (17.7-32.8)	21.8 (16.5-32.2)	0.313	21.9 (17.3-28.9)	22.2 (16.5-30.6)	0.896
Creatinine (g/dL)	1.27 (1.00-1.89)	1.24 (0.97-1.93)	0.449	0.93 (0.69-1.18)	1.02 (0.69-1.37)	0.353
CRP (mg/dL)	0.75 (0.23-2.51)	0.50 (0.21-1.62)	0.095	0.66 (0.21-2.30)	0.79 (0.15-1.87)	0.686
BNP (pg/mL)	685 (389-1,256)	716 (410-1,337)	0.548	571 (267-1,129)	942 (496-1,897)	0.005
Nutritional status						
PNI	44.7 (39.8-48.3)	45.4 (40.6-49.6)	0.295	44.2 (38.8-48.9)	42.9 (39.7-48.7)	0.931
CONUT score	3 (1-4)	2 (1-4)	0.242	3 (1-4)	3 (1-4)	0.911
Albumin (g/dL)	3.7 (3.4-4.0)	3.8 (3.4-4.1)	0.508	3.8 (3.3-4.1)	3.6 (3.3-3.9)	0.348
Lymphocyte count (/μL)	1,306 (948-1,687)	1,394 (987-1,789)	0.590	1,310 (814-1,745)	1,339 (1,025-1,687)	0.420
Total cholesterol (mg/dL)	162 (138-187)	174 (145-203)	0.065	179 (145-222)	187 (170-204)	0.633
Medication (cases) during ICU						
Furosemide (yes, %)	238 (91.5%)	141 (91.6%)	1.000	80 (96.4%)	39 (90.7%)	0.229
Nitroglycerin (yes, %)	174 (66.9%)	111 (72.1%)	0.323	51 (61.4%)	24 (55.8%)	0.570
Nicorandil (yes, %)	40 (15.4%)	18 (11.7%)	0.310	9 (10.8%)	7 (16.3%)	0.407
Carperitide (yes, %)	128 (49.2%)	96 (62.3%)	0.011	40 (48.2%)	19 (44.2%)	0.710
Dopamine (yes, %)	77 (29.6%)	39 (25.3%)	0.367	17 (20.5%)	11 (25.6%)	0.508
Dobutamine (yes, %)	76 (29.2%)	36 (23.4%)	0.209	17 (20.5%)	7 (16.3%)	0.639
ACE-I/ARB (yes, %)	105 (40.4%)	73 (47.4%)	0.182	41 (49.4%)	16 (37.2%)	0.257
β-blocker (yes, %)	71 (27.3%)	45 (29.2%)	0.734	18 (21.7%)	8 (18.6%)	0.818
Spironolactone (yes, %)	102 (39.3%)	60 (39.0%)	1.000	36 (43.4%)	20 (46.5%)	0.850
Outcome						
ICU hospitalization (days)	5 (3-8)	5 (3-7)	0.812	5 (3-7)	4 (3-6)	0.068
Total hospitalization (days)	28 (18-46)	27 (18-48)	0.577	27 (18-52)	28 (18-54)	0.769
In-hospital mortality (yes, %)	28 (10.8%)	12 (7.8%)	0.391	8 (9.6%)	6 (14.0%)	0.553

LVEF: left ventricular ejection fraction measured by echocardiography, NYHA: New York Heart Association, BUN: blood urea nitrogen, CRP: C-reactive protein, BNP: brain natriuretic peptide, PNI: prognostic nutritional index, CONUT: controlling nutritional status, ACE-I: angiotensin-converting enzyme inhibitor, ARB: angiotensin II receptor blocker, ICU: intensive-care unit

The p values between the non-socially vulnerable and socially vulnerable group were determined using the Mann-Whitney U-test or the χ^2 test.

All numerical data are expressed as the median (25-75% interquartile range).

Table 2. Characteristics of the Patients in the Elderly Cohort.

	≥75 years old					
	Male		p value	Female		p value
	Non-socially vulnerable (n=193)	Socially vulnerable (n=89)		Non-socially vulnerable (n=69)	Socially vulnerable (n=157)	
Status and vital signs						
Age (years old)	78 (77-82)	83 (79-86)	<0.001	81 (78-85)	84 (80-87)	0.002
Type (re admission, %)	80 (41.5%)	39 (39.3%)	0.795	21 (30.4%)	44 (28.0%)	0.751
LVEF (%)	35 (28-47)	30 (23-42)	0.017	41 (33-56)	43 (30-59)	0.923
NYHA (IV, %)	150 (77.7%)	72 (80.9%)	0.639	55 (79.7%)	131 (83.4%)	0.571
Systolic blood pressure (mmHg)	160 (128-180)	160 (140-180)	0.576	151 (136-180)	154 (130-180)	0.739
Pulse (beats/min)	106 (86-123)	106 (90-126)	0.428	110 (90-121)	107 (90-128)	0.894
Etiology						
Ischemia (yes, %)	100 (51.8%)	43 (48.3%)	0.610	24 (34.8%)	45 (28.7%)	0.433
Past medical history						
Hypertension (yes, %)	147 (76.2%)	61 (68.5%)	0.192	56 (81.2%)	125 (79.6%)	0.858
Diabetes mellitus (yes, %)	82 (42.5%)	27 (30.3%)	0.065	27 (39.1%)	67 (42.7%)	0.662
Dyslipidemia (yes, %)	80 (41.5%)	34 (38.2%)	0.695	32 (46.4%)	60 (38.2%)	0.304
Arterial blood gas						
pH	7.32 (7.19-7.42)	7.32 (7.23-7.41)	0.995	7.32 (7.18-7.37)	7.34 (7.24-7.42)	0.013
PCO ₂ (mmHg)	43.2 (32.9-58.5)	42.0 (35.1-52.5)	0.826	48.8 (39.6-62.2)	43.8 (35.1-54.2)	0.017
PO ₂ (mmHg)	87.6 (65.2-133.0)	87.4 (64.3-133.0)	0.846	84.5 (70.4-141.0)	103.0 (65.5-155.0)	0.939
HCO ₃ ⁻ (mmol/L)	22.2 (19.6-24.4)	22.0 (18.8-24.7)	0.519	22.2 (19.9-24.4)	22.0 (19.9-25.7)	0.651
SaO ₂ (%)	96 (89-98)	95 (89-98)	0.642	95 (91-98)	97 (91-98)	0.360
Lactate (mmol/L)	1.7 (1.1-3.2)	1.9 (1.2-3.3)	0.939	1.7 (1.3-3.2)	1.4 (1.0-2.6)	0.174
Laboratory data						
Total bilirubin (mg/dL)	0.5 (0.4-0.8)	0.6 (0.4-0.9)	0.262	0.6 (0.4-0.9)	0.5 (0.4-0.8)	0.294
Uric acid (mg/dL)	6.4 (5.3-7.7)	7.4 (6.3-8.3)	0.003	6.3 (4.9-7.7)	5.9 (4.8-7.5)	0.664
Sodium (mmol/L)	139 (137-142)	140 (138-142)	0.207	141 (139-142)	140 (137-142)	0.035
Potassium (mmol/L)	4.3 (3.9-4.8)	4.4 (3.9-4.7)	0.954	4.2 (3.8-4.6)	4.3 (3.8-4.8)	0.592
Hemoglobin (g/dL)	12.1 (10.6-13.9)	12.1 (10.8-13.9)	0.909	11.2 (9.8-12.7)	11.1 (10.0-12.4)	0.714
BUN (mmol/L)	26.2 (19.2-39.1)	28.3 (19.8-43.5)	0.223	25.2 (16.6-35.7)	24.9 (18.8-34.1)	0.779
Creatinine (g/dL)	1.40 (1.06-1.81)	1.36 (1.02-2.28)	0.689	1.04 (0.79-1.64)	1.00 (0.82-1.47)	0.700
CRP (mg/dL)	0.70 (0.24-2.50)	0.72 (0.18-3.04)	0.855	0.49 (0.19-1.30)	0.50 (0.14-1.89)	0.625
BNP (pg/mL)	736 (484-1,222)	967 (534-1,500)	0.049	1,020 (556-1,588)	870 (457-1,630)	0.634
Nutritional status						
PNI	42.6 (38.3-47.0)	42.5 (37.7-46.8)	0.687	42.0 (38.2-44.5)	42.6 (38.0-47.8)	0.388
CONUT score	3 (2-5)	3 (2-5)	0.771	3 (2-5)	3 (2-5)	0.518
Albumin (g/dL)	3.7 (3.3-3.9)	3.6 (3.2-3.8)	0.238	3.7 (3.3-4.0)	3.7 (3.3-3.9)	0.887
Lymphocyte count (μL)	1,249 (929-1,529)	1,157 (831-1,591)	0.468	1,009 (804-1,352)	1,058 (703-1,504)	0.795
Total cholesterol (mg/dL)	155 (135-182)	160 (140-180)	0.628	164 (141-191)	176 (151-206)	0.052
Medication (cases) during ICU						
Furosemide (yes, %)	184 (95.3%)	87 (97.8%)	0.511	64 (92.8%)	147 (93.6%)	0.778
Nitroglycerin (yes, %)	125 (64.8%)	58 (65.2%)	1.000	50 (72.5%)	105 (66.9%)	0.440
Nicorandil (yes, %)	41 (21.2%)	15 (16.9%)	0.698	11 (15.9%)	15 (9.6%)	0.179
Carperitide (yes, %)	109 (56.5%)	53 (59.6%)	0.426	32 (46.4%)	72 (45.9%)	1.000
Dopamine (yes, %)	49 (25.4%)	17 (19.1%)	0.291	12 (17.4%)	37 (23.6%)	0.381
Dobutamine (yes, %)	37 (19.2%)	16 (18.0%)	0.871	11 (15.9%)	26 (16.6%)	1.000
ACE-I/ARB (yes, %)	64 (33.1%)	33 (37.1%)	0.590	27 (39.1%)	47 (29.9%)	0.218
β-blocker (yes, %)	54 (28.0%)	24 (27.0%)	0.887	14 (20.3%)	25 (15.9%)	0.448
Spironolactone (yes, %)	52 (26.9%)	30 (33.7%)	0.261	24 (34.8%)	46 (29.3%)	0.437
Outcome						
ICU hospitalization (days)	4 (3-7)	4 (3-7)	0.810	5 (3-7)	4 (3-7)	0.553
Total hospitalization (days)	26 (16-39)	23 (16-46)	0.768	35 (22-45)	28 (16-50)	0.025
In-hospital mortality (yes, %)	11 (5.7%)	11 (12.4%)	0.059	8 (11.6%)	20 (12.7%)	1.000

LVEF: left ventricular ejection fraction measured by echocardiography, NYHA: New York Heart Association, BUN: blood urea nitrogen, CRP: C-reactive protein, BNP: brain natriuretic peptide, PNI: prognostic nutritional index, CONUT: controlling nutritional status, ACE-I: angiotensin-converting enzyme inhibitor, ARB: angiotensin II receptor blocker, ICU: intensive-care unit

The p values between the non-socially vulnerable and socially vulnerable group were determined using the Mann-Whitney U-test or the χ^2 test. All numerical data are expressed as the median (25-75% interquartile range).

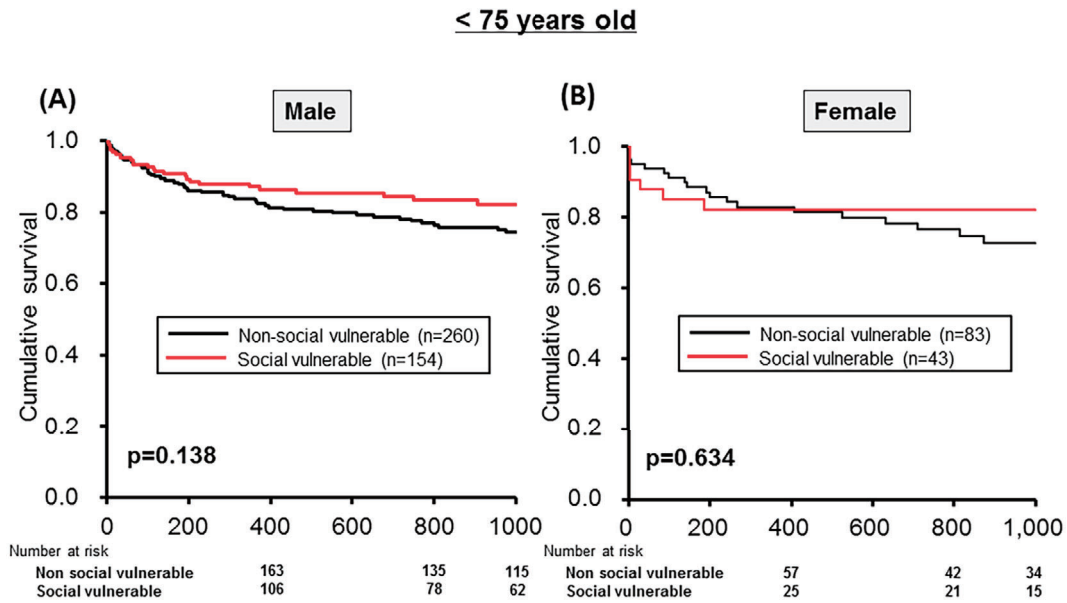


Figure 2. (A) The Kaplan-Meier survival curves showed that the prognosis, including all-cause death, was not significantly different between the socially vulnerable group and the non-socially vulnerable group in men <75 years of age. (B) The Kaplan-Meier survival curves showed that the prognosis, including all-cause death, was not significantly different between the socially vulnerable group and the non-socially vulnerable group in women <75 years of age.

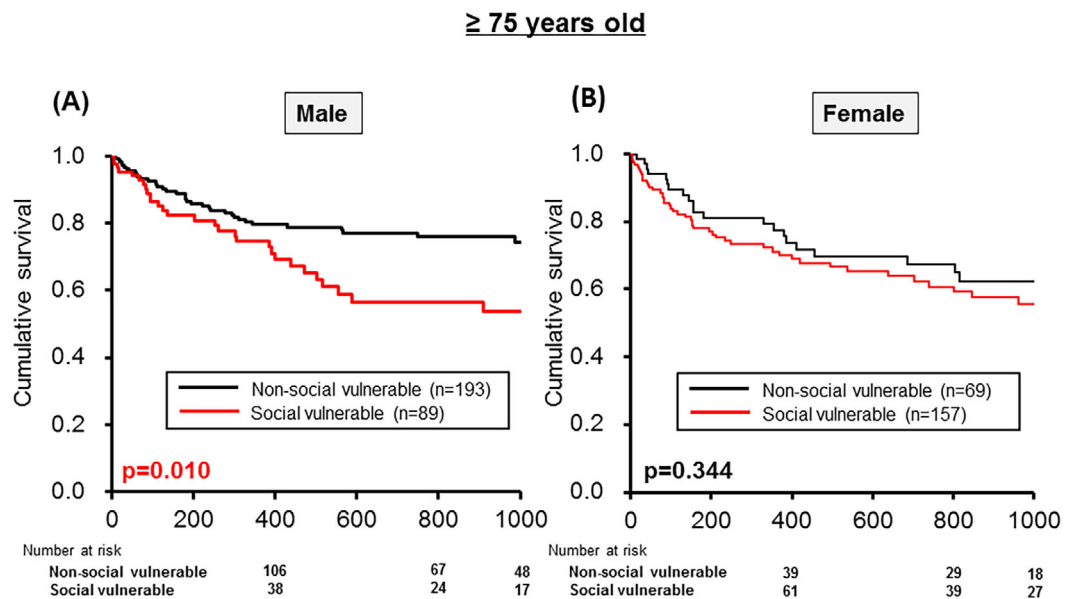


Figure 3. (A) The Kaplan-Meier survival curves showed that the prognosis, including all-cause death, was significantly poorer in the socially vulnerable group than in the non-socially vulnerable group in men ≥ 75 years of age ($p=0.010$). (B) The Kaplan-Meier survival curves showed that the prognosis, including all-cause death, was not significantly different between the socially vulnerable group and the non-socially vulnerable group in women ≥ 75 years of age.

Contrary to our expectations, however, the present study showed that social vulnerability was not associated with a poor prognosis in the elderly female cohort but was associated with such an outcome in the elderly male cohort. This result indicates that female patients can maintain control of their environment even if they become socially poor (having

no partner or children or living alone) in their elderly years. In contrast, male patients may not be able to manage as well when they become socially poor.

Definition of socially vulnerable HF patients

The present study defined social vulnerability as not hav-

Table 3. The Univariate and Multivariate Analyses of the Associations between the Clinical Findings and 1,000-day All-cause Mortality.

	Univariate			Multivariate		
	HR	95% CI	p value	HR	95% CI	p value
Age ≥75 years, male						
Socially vulnerable (yes)	1.868	1.151 - 3.031	0.011	1.942	1.102 - 3.422	0.022
Laboratory data						
Age (per 1-year increase)	1.029	0.976 - 1.085	0.288	0.980	0.918 - 1.045	0.533
SBP (≥140 mmHg)	0.487	0.301 - 0.788	0.003	0.505	0.290 - 0.881	0.016
eGFR (per 10-mL/min/1.73 m ² increase)	0.879	0.769 - 1.004	0.058	0.977	0.843 - 1.132	0.759
Total bilirubin (per 1.0-mg/dL increase)	1.009	0.963 - 1.057	0.715	1.045	0.986 - 1.107	0.137
Sodium (per 1.0-mmol/L increase)	0.960	0.914 - 1.009	0.111	0.998	0.948 - 1.051	0.951
CRP (per 0.1-mg/dL increase)	1.001	0.986 - 1.016	0.897	1.001	0.982 - 1.020	0.950
Hemoglobin (per 1.0-mg/dL increase)	0.836	0.758 - 0.922	<0.001	0.888	0.783 - 1.006	0.063
LVEF (per 10% increase)	0.983	0.849 - 1.139	0.824	1.000	0.840 - 1.190	0.997
BNP (per 10-pg/mL increase)	1.003	1.002 - 1.005	<0.001	1.002	1.001 - 1.004	0.002
Age ≥75 years, female						
Socially vulnerable (yes)	1.281	0.767 - 2.142	0.344	1.007	0.614 - 1.889	0.795
Laboratory data						
Age (per 1-year increase)	1.053	1.002 - 1.107	0.040	1.043	0.983 - 1.107	0.166
SBP (≥140 mmHg)	0.655	0.405 - 1.059	0.085	0.640	0.369 - 1.110	0.112
eGFR (per 10-mL/min/1.73 m ² increase)	0.881	0.773 - 1.004	0.057	0.846	0.724 - 0.989	0.036
Total bilirubin (per 1.0-mg/dL increase)	1.014	0.970 - 1.061	0.531	0.997	0.939 - 1.060	0.932
Sodium (per 1.0-mmol/L increase)	0.932	0.884 - 0.982	0.009	0.928	0.873 - 0.987	0.017
CRP (per 0.1-mg/dL increase)	1.005	0.947 - 1.066	0.882	0.927	0.844 - 1.018	0.113
Hemoglobin (per 1.0-mg/dL increase)	1.043	0.920 - 1.181	0.511	1.150	0.981 - 1.348	0.086
LVEF (per 10% increase)	0.920	0.794 - 1.066	0.267	0.970	0.821 - 1.147	0.724
BNP (per 10-pg/mL increase)	1.002	1.000 - 1.004	0.046	1.002	1.000 - 1.004	0.111

HR: hazard ratio, CI: confidence interval, SBP: systolic blood pressure, eGFR: estimated glomerular filtration rate, CRP: C-reactive protein, LVEF: left ventricular ejection fraction measured by echocardiography, BNP: brain natriuretic peptide

ing a partner (including patients who had never married or were divorced or widowed), not having any children, or living alone, as in our previous report (6). Previous studies have considered household incomes, health insurance, occupation, and educational background as components of being socially poor (14, 15). However, the Japanese medical service system basically covers all people, regardless of their income, medical insurance type, occupation, or educational background. We therefore did not regard these factors as important social factors. In addition, social isolation (being unmarried, divorced, or widowed; not having children; or living alone) is an independent risk factor of cardiovascular disease (CVD), as a previous study has already shown (16). We therefore conclusively defined socially vulnerable HF according to the existence of partners or family members in the present study.

The prognosis of HF in socially vulnerable patients

Several explanations have been proposed for the association between social determinants and patient outcomes. Previous studies have shown that chronic HF patients with symptoms of depression caused by psychological stress or minor depression were at a higher risk of poor self-care than those without symptoms of depression (17). The symptoms

of depression might be exacerbated after admission in AHF patients and might be further exacerbated in socially vulnerable patients. Second, the lack of medical supervision is also a major problem for these patients. Medication adherence is reported to be involved in the relationship between marital status and the event-free survival in patients with HF (18). Patients with a better socioeconomic status might therefore be more likely to keep taking their prescribed medications. This might be the strongest predictor of a better outcome in connection with the socioeconomic status. Third, chronic HF is sometimes complicated by malnutrition, which can lead to muscle weakness, cognitive impairment and dysphagia; thus, the nutrition status (i.e. extremely low body mass index) is also reported to be a predictor of an adverse outcome in patients with AHF (19, 20). Living alone is suggested to be associated with a poor-quality diet and poor dietary patterns (21). Finally, these patients would have found it more difficult to visit a hospital immediately after the manifestation of symptoms than those with a partner or children.

The prognosis of socially poor HF patients according to gender differences

Among patients with coronary artery disease, male patients who are divorced or widowed show a poorer prognosis

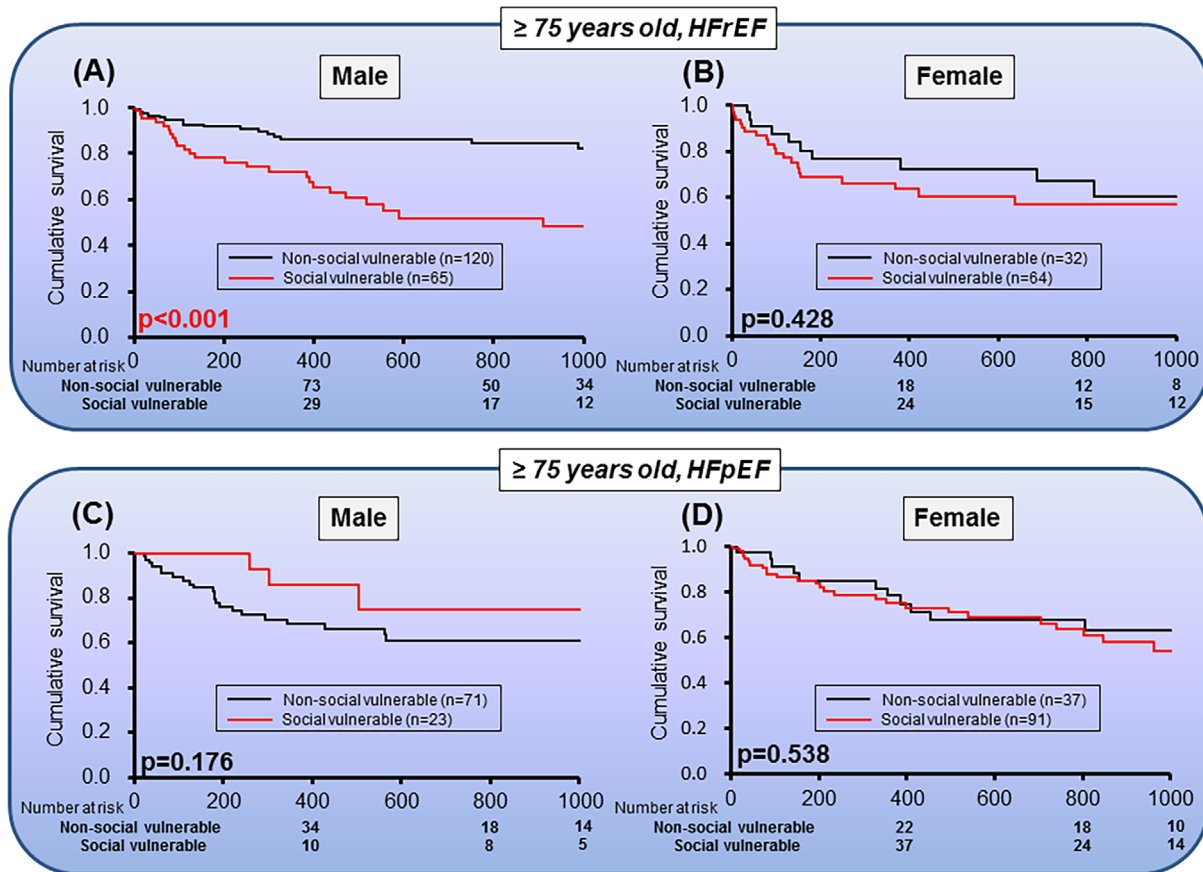


Figure 4. (A) The Kaplan-Meier survival curves showed that the prognosis, including all-cause death, was significantly poorer in the socially vulnerable group than in the non-socially vulnerable group in men ≥ 75 years of age and reduced LVEF ($p < 0.001$). (B) The Kaplan-Meier survival curves showed that the prognosis, including all-cause death, was not significantly different between the socially vulnerable group and the non-socially vulnerable group in women ≥ 75 years of age and reduced LVEF ($p = 0.428$). (C) The Kaplan-Meier survival curves showed that the prognosis, including all-cause death, was not significantly different between the socially vulnerable group and the non-socially vulnerable group in men ≥ 75 years of age and preserved LVEF ($p = 0.176$). (D) The Kaplan-Meier survival curves showed that the prognosis, including all-cause death, was not significantly different between the socially vulnerable group and the non-socially vulnerable group in women ≥ 75 years of age and preserved LVEF ($p = 0.176$). HF rEF: heart failure reduced ejection fraction, HF pEF: heart failure preserved ejection fraction, LVEF: left ventricular ejection fraction

sis than married male patients (22, 23). Furthermore, according to the Cancer Prevention Study-II report, among Caucasians, the HR for the all-cause mortality was higher in non-married men than in non-married women (24). However, there have been some reports showing that women are more sensitive and vulnerable to psychosocial stress, financial stress, or social isolation than men, which might affect the progression of HF and CVD (25-27). Thus, whether or not gender difference affects the prognosis of socially poor patients with cardiovascular heart disease remains controversial.

However, there have been no reports describing the prognosis of socially poor HF according to gender differences. The present study regarding AHF showed that only elderly male socially vulnerable patients suffered an adverse outcome. While the mechanism underlying this effect has not

yet been clarified, several studies have explored the mechanism involved in the mortality discrepancy between genders in socially vulnerable patients with CVD (11, 23, 28). Women historically manage the household and assume a nurturing role, potentially imbuing them with better self-care skills than their male counterparts. In addition, women socialize differently than men and may have stronger social networks outside of their homes than men. This may lead to a better outreach situation for female CVD patients, who would then demonstrate better attendance to physician appointments or cardiac rehabilitation. Furthermore, psychological stress, medication adherence and nutrition status may also be responsible for the gender differences in the prognosis of socially vulnerable HF (17, 18, 21). Women can therefore maintain control of their life environment even if they become socially poor (having no partner or children or

living alone) in later life. Further investigations will be required to clearly elucidate the mechanisms underlying this gender-based difference by examining each factor potentially associated with socially poor HF by gender.

A multifactorial program involving physicians and social workers (i.e. home health services and home healthcare provided by visiting doctors, nurses, social workers, and physicians) as well as other options, such as discharge to institutions like nursing homes, elderly care facilities that provide intensive care, and group homes, may be necessary to avoid repeated admission for elderly male AHF patients. Such efforts might help reduce the rates of morbidity and mortality of socially vulnerable elderly male AHF patients. Nursing homes in particular may provide better care to elderly patients with poor social support than to non-elderly patients. In addition, frequent outpatient clinic visits may also help prevent social isolation among elderly men. Based on the results of the present study, we should consider implementing new management practices to prevent repeated admissions and eventually reduce the rate of mortality for elderly socially vulnerable male AHF patients.

Study limitations

The present study is associated with several limitations. First, this was a retrospective study that was performed at a single center. It is therefore possible that unmeasured variables or missing data affected the results. Second, our study population was limited to patients who were admitted to the ICU; thus, AHF patients who were admitted to the general ward were excluded from this study. The patients were treated in a “closed ICU” at our institute. All of the physicians in our “closed ICU” are cardiologists. Thus, the majority of patients with severely decompensated AHF were admitted to the ICU. Third, the present study defined social vulnerability based on the marriage status (widowed, divorced, or unmarried), offspring status (no children), and living status (living alone). It is unclear whether this definition can be used to accurately select socially vulnerable patients. The results might have differed if other social determinants (i.e. the level of education or household income) had been used. In addition, patients living in a nursing home were considered to be socially vulnerable in the present study, as they were classified as “living alone”. It is difficult to judge whether or not such patients are actually socially vulnerable. As a reference, however, Lu et al. reported that nursing home patients showed a poor prognosis (5). Finally, the present study was a retrospective one, and the data were only collected from medical records. While we can obtain accurate data on “single status” at the time of admission from medical records, it can be difficult to judge the details clearly (widowed, divorced, or unmarried). The status of divorced or widowed was not clear based on the medical records; furthermore, there might have been some interaction between divorced and widowed status. This may be a major limitation associated with the present study. Further prospective studies will be required to evaluate this issue.

Conclusion

Social vulnerability was more common in elderly AHF patients, especially female AHF patients, than in non-elderly AHF patients. However, social vulnerability was not associated with a poor prognosis in elderly female AHF patients; instead, such an association was only noted in elderly male AHF patients. Elderly women might manage their condition reasonably well even if they are socially vulnerable. Interventions to improve the social structure of socially vulnerable patients, especially elderly men, may help improve the prognosis of these patients in light of the oncoming AHF pandemic.

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

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