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Clinical characteristics and prognostic factors in elderly patients with chronic heart failure -A report from the CHART-2 study-

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ABSTRACT

Background: Since most of the randomized clinical trials for heart failure (HF) were designed to exclude elderly patients, limited data are available on their clinical characteristics, prognosis, and prognostic factors.

Methods: We compared clinical characteristics, prognosis, and prognostic factors among Stage C/D HF patients in our CHART-2 Study (N = 4876, mean 69 years, women 32%, 6.3-year follow-up) by age (G1, ≤64 years, N = 1521; G2, 65–74 years, N = 1510; and G3, ≥75 years, N = 1845).

Results: From G1 to G3, the prevalence of women, left ventricular ejection fraction (LVEF) and plasma levels of B-type natriuretic peptide (BNP) increased (all P < 0.001). Similarly, 5-year mortality increased (9.9, 17.3 to 39.9%, P < 0.001) along with a decrease in proportion of cardiovascular death and an increase in non-cardiovascular death in both sexes. While all-cause and cardiovascular mortality was comparable between the sexes, women had significantly lower incidence of non-cardiovascular death than men in G2 and G3, which was attributable to the higher incidence of cancer death and pneumonia death in men than in women. Although NYHA functional class III-IV, chronic kidney disease, cancer, LVEF, and BNP had significant impacts on all-cause death in all groups, their impacts were less evident in G3 as compared with G1.

Conclusions: The elderly HF patients, as compared with younger HF patients, were characterized by more severe clinical background, increased proportion of non-cardiovascular death and worse prognosis with different impacts of prognostic factors across the age groups.

1. Introduction

Along with rapid aging of the society [1] and epidemiologic transition [2], the number of patients with heart failure (HF) has been rapidly increasing worldwide [3–6]. This burden of HF, so-called "HF pandemic", is a serious healthcare concern, particularly in the elderly population, highlighting HF management in the elderly as an emerging problem worldwide [7,8]. In particular, considering the fact that elderly patients with cardiovascular (CV) diseases are likely to have non-cardiac prognostic factors, including anemia, malnutrition, frailty, sarcopenia, chronic kidney disease, chronic obstructive pulmonary disease, and cancers, targeted treatment strategies specific for the elderly need to be developed [9–12].

However, to date, evidence of HF in the elderly is limited, [11,12] partly because most of the randomized clinical trials for HF have been designed to exclude the elderly. From this viewpoint, it is clinically important to examine the characteristics, management, outcomes, and prognostic factors in the elderly HF patients from the observational studies, in which consecutive HF patients are enrolled regardless of age. In the present study, we thus aimed to examine the differences in the characteristics and prognostic factors among the age groups, using the database of our large-scale cohort study for HF, the Chronic Heart Failure Analysis and

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Registry in the Tohoku District (CHART)-2 study (N = 10,219) [13–20].

2. Methods

2.1. The CHART-2 study

The CHART-2 Study is a large-scale prospective observational multicenter cohort study, as previously reported in detail (NCT00418041) [13–20]. Briefly, patients aged ≥ 20 years with either coronary artery disease (Stage A, N = 868), asymptomatic structural heart disease (Stage B, N = 4475), or a current or past history of symptomatic HF (Stage C/D, N = 4876) were enrolled between October 2006 and March 2010 [13]. The diagnosis of HF was made by attending cardiologists based on the criteria of the Framingham Heart Study [21] and HF Stages were defined according to the ACCF/AHA guidelines [22]. All information on more than 300 items, including medical history, laboratory data and echocardiography data, were obtained at the time of enrollment and annually thereafter. The CHART-2 Study was approved by the ethics committees in the 24 participating hospitals and a written informed consent was obtained from each patient.

2.2. Study design

The present study enrolled 4876 consecutive HF patients in Stage C/D registered in our CHART-2 Study (**Fig. S1**). We divided them into 3 age groups; G1, ≤64 years (N = 1521); G2, 65–74 years (N = 1510); and G3, ≥75 years (N = 1845), who were followed up for a mean period of 6.3 years. The study endpoints included all-cause, CV and NCV death. We examined clinical characteristics, treatments and long-term outcomes among the groups, and compared the prognostic factors for all-cause death, CV death, and non-cardiovascular (NCV) death. CV death included HF death, sudden death, acute myocardial infarction (AMI) death, stroke death and others/unknown, while NCV death cancer death, pneumonia death, other infection death (without pneumonia), external death and others/unknown. The primary etiology of CHF was classified in each patient as ischemic heart disease (IHD) when prior myocardial infarction or coronary artery disease was present. Those without IHD were then classified as having dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), or valvular heart disease (VHD). Diagnosis of DCM and HCM were made by an attending physician(s) at the time of enrollment to the CHART-2 Study. In the present study, VHD was specifically defined as moderate to severe aortic or mitral valvular disease by echocardiography at the time of enrollment with the use of standard criteria [23]. Hypertensive heart disease (HHD) was considered as the primary etiology when a patient did not have IHD, DCM, HCM or VHD, but had a history of hypertension (HT). Anemia was defined according to the World Health Organization (WHO) definition (Hb < 13.0 g/dL in men, <12.0 g/dL in women) [24]. Hypoalbuminemia was defined as < 3.9 g/dL, since survival classification and regression tree (CART) analysis [25] indicated that the cut-off for albumin (Alb) < 3.9 g/dL most effectively partition the mortality risk in the study population.

2.3. Statistical analysis

All continuous variables are shown as mean ± standard deviation (SD) or median (IQR, interquartile rage) as appropriate, and were compared by Welch's *t*-test or Wilcoxon rank sum test for two groups and by analysis of variance (ANOVA) or Kruskal-Wallis test for three groups. Categorical variables are presented as number (%) and were compared by Fisher's exact test. The study endpoints included all-cause, CV and NCV death. We also estimated incidence of CV and NCV death on the basis of 1000 person-years, and were compared by mid-p exact test. To determine the independent predictors of the mortality of HF patients, multivariable Cox proportional hazard regression models were applied in age groups with the following variables; sex, body mass index (BMI), New York Heart Association (NYHA) functional class III-IV, IHD, HT, diabetes mellitus (DM), dyslipidemia, chronic kidney disease (CKD), atrial fibrillation (AF), stroke, hospitalization for HF, cancer, smoking history, systolic blood pressure (BP), diastolic BP, heart rate, LVEF, anemia, hypoalbuminemia, and brain natriuretic peptide (BNP). For all steps, P value < 0.05 and P value for interaction < 0.05 were considered as statistically significant. All statistical analysis was performed by the statistical computing software R version 3.2.4.

3. Results

3.1. Clinical characteristics

In G1, G2 and G3, mean age was 54.3 ± 8.8, 69.9 ± 2.9 and 80.3 ± 4.4 years and women accounted for 22.8%, 30.7% and 40.2%, respectively (Table 1). The proportion of NYHA functional class III-IV and the prevalence of HT, CKD, stroke, and cancer were increased from G1, G2 to G3 (all P < 0.001), while the proportion of BMI and the prevalence of dyslipidemia were decreased (P < 0.001). The prevalence of AF was comparable between G2 and G3, which was higher than G1 (P < 0.001). As for the primary etiology of HF, the prevalence of IHD was comparable between G2 and G3, which was higher than in G1 (P < 0.001). The prevalence of HCM was highest in G2 (P = 0.005). The prevalence of VHD and HHD was increased from G1, G2 to G3 (P < 0.001 and P = 0.026, respectively), while that of DCM was decreased (P < 0.001). Systolic BP was increased, while diastolic BP was decreased from G1, G2 to G3 (both P < 0.001). The echocardiography data showed that G3 patients had most preserved LVEF among the age groups (P < 0.001), while their left ventricular end-diastolic diameter (LVDd) was smallest. Levels of hemoglobin and indicators of nutrition, such as serum albumin, total cholesterol and triglyceride, were decreased from G1, G2 to G3, while BNP levels were increased (all P < 0.001). G3 patients had most decreased estimated glomerular filtration rate (eGFR) among the age groups (P < 0.001). Clinical characteristics for each sex are shown in Table S1. In G3, but not in G1 or G2, women had higher BNP levels and higher prevalence of CKD and prior history of HF hospitalization than men, while men had higher prevalence of cancer history at baseline than women in G2 and G3, but not in G1 (Table S1).

3.2. Medications

Table 1 shows medications in each age groups. Among the age groups, beta-blockers, angiotensin converting enzyme inhibitors (ACEI), and aldosterone antagonists (AA) were most frequently prescribed in G1, while angiotensin Ⅱ receptor blockers (ARB), calcium channel blockers (CCB), and loop diuretics were more frequently prescribed in G3. The prescription rate of statins was comparable between G1 and G2, which was lower in G3 (P < 0.001). **Fig. S2** shows the prescription rates of cardiovascular medications across the 3 age groups by LVEF (≥50% vs. < 50%). Beta-blockers and ACEI were more frequently prescribed in younger HF patients, while CCB in the elderly, regardless of LVEF. Prescription rate of loop diuretics was comparable among the age groups with LVEF < 50%, while it was significantly increased from G1, G2 to G3 in LVEF ≥ 50% group (**Fig. S2**). No sex differences were noted in prescription rates of beta-blockers, ACEI, ARB, or loop

Table 1
Characteristics of Heart Failure Patients in the CHART-2 Study.

	Overall (N = 4876)	G1 (Age ≤ 64) (N = 1521)	G2 (Age 65–74) (N = 1510)	G3 (Age ≥ 75) (N = 1845)	P Value
Age (Years)	69.0 ± 12.3	54.3 ± 8.8	69.9 ± 2.9	80.3 ± 4.4	<0.001
Women, N (%)	1553 (31.8)	347 (22.8)	464 (30.7)	742 (40.2)	<0.001
BMI (kg/m^2)	23.8 ± 3.9	24.6 ± 4.3	23.9 ± 3.6	23.0 ± 3.6	<0.001
NYHA Class III-IV, N (%)	532 (11.0)	110 (7.3)	115 (7.6)	307 (16.7)	<0.001
Etiology of Chronic Heart Failure, N (%)					
IHD	2452 (50.3)	661 (43.5)	801 (53.0)	990 (53.7)	<0.001
DCM	642 (13.2)	339 (22.3)	170 (11.3)	133 (7.2)	<0.001
HCM	137 (2.8)	45 (3.0)	56 (3.7)	36 (2.0)	0.005
VHD	460 (9.4)	77 (5.1)	141 (9.3)	242 (13.1)	<0.001
HHD	928 (19)	262 (17.2)	283 (18.7)	383 (20.8)	0.026
Clinical History, N (%)					
Hypertension	4356 (89.4)	1279 (84.1)	1370 (90.7)	1707 (92.6)	<0.001
Diabetes Mellitus	1926 (39.5)	609 (40.0)	649 (43.0)	668 (36.2)	<0.001
Dyslipidemia	3969 (81.4)	1317 (86.6)	1245 (82.5)	1407 (76.3)	<0.001
Hyperuricemia	2769 (56.8)	915 (60.2)	818 (54.2)	1036 (56.2)	0.002
CKD	2314 (47.7)	446 (29.5)	706 (46.9)	1162 (63.4)	<0.001
Atrial Fibrillation	1983 (40.7)	480 (31.6)	675 (44.7)	828 (44.9)	<0.001
Stroke	987 (20.2)	187 (12.3)	311 (20.6)	489 (26.5)	<0.001
Hospitalization for HF	2590 (53.1)	806 (53.0)	724 (47.9)	1060 (57.5)	<0.001
Cancer	655 (13.4)	77 (5.1)	216 (14.3)	362 (19.6)	<0.001
Smoking	2134 (46.3)	857 (58.7)	628 (44.4)	649 (37.5)	<0.001
PCI	1568 (32.2)	467 (30.7)	507 (33.6)	594 (32.2)	0.238
CABG	440 (9.0)	112 (7.4)	156 (10.3)	172 (9.3)	0.015
Haemodynamics and echocardiography					
Systolic BP (mmHg)	126.2 ± 19.1	123.2 ± 18.8	126.8 ± 18.0	128.1 ± 20.0	<0.001
Diastolic BP (mmHg)	72.2 ± 12.0	74.2 ± 12.1	72.4 ± 11.4	70.3 ± 12.1	<0.001
Heart Rate (bpm)	72.4 ± 14.9	72.1 ± 14.3	72.2 ± 14.9	72.6 ± 15.3	0.588
LVEF (%)	56.6 ± 15.3	54.5 ± 15.6	56.8 ± 15.0	58.4 ± 15.1	<0.001
EF > 50% (HFpEF), N (%)	3193 (65.5)	937 (61.6)	1005 (66.6)	1251 (67.8)	<0.001
LVDd (mm)	52.1 ± 9.2	53.9 ± 9.6	52.0 ± 9.1	50.6 ± 8.7	<0.001
Laboratory Data					
Hemoglobin (g/dL)	13.2 ± 2.0	14.0 ± 1.9	13.3 ± 1.9	12.4 ± 1.8	<0.001
Lymphocyte (%)	29.0 ± 9.2	30.2 ± 9.0	29.6 ± 9.0	27.7 ± 9.3	<0.001
Albumin (g/dL)	4.1 ± 0.5	4.2 ± 0.5	4.1 ± 0.5	3.9 ± 0.5	<0.001
Total Cholesterol (mg/dL)	183.0 ± 36.9	189.1 ± 39.4	181.6 ± 35.6	178.9 ± 35.0	<0.001
LDL Cholesterol (mg/dL)	106.3 ± 31.1	110.1 ± 32.8	104.6 ± 31.1	104.5 ± 29.3	<0.001
HDL Cholesterol (mg/dL)	51.3 ± 15.4	50.9 ± 15.5	51.8 ± 15.9	51.4 ± 14.9	0.349
Triglyceride (mg/dL)	129.1 ± 89.3	155.2 ± 121.8	125.2 ± 70.4	110.5 ± 61.6	<0.001
Uric Acid (mg/dL)	6.2 ± 1.8	6.4 ± 1.7	6.1 ± 1.7	6.2 ± 1.8	<0.001
BUN (mg/dL)	20.0 ± 10.2	17.4 ± 8.7	19.8 ± 9.9	22.3 ± 10.9	<0.001
Creatinine (mg/dL)	1.1 ± 0.8	1.0 ± 0.9	1.1 ± 0.8	1.1 ± 0.7	0.010
eGFR (ml/min/1.73 m^2)	60.7 ± 21.3	69.8 ± 21.5	60.6 ± 19.9	53.2 ± 19.4	<0.001
BNP (pg/mL) (Median, IQR)	104.0 (41.3, 239.0)	63.3 (21.9, 169.0)	93.2 (40.4, 212.0)	157.5 (74.0, 310.0)	<0.001
Medication, N (%)					
Beta-blocker	2399 (49.2)	927 (60.9)	740 (49.0)	732 (39.7)	<0.001
ACEI	2172 (44.5)	767 (50.4)	633 (41.9)	772 (41.8)	<0.001
ARB	1564 (32.1)	412 (27.1)	501 (33.2)	651 (35.3)	<0.001
CCB	1886 (38.7)	464 (30.5)	620 (41.1)	802 (43.5)	<0.001
Loop Diuretic	2497 (51.2)	706 (46.4)	751 (49.7)	1040 (56.4)	<0.001
Aldosterone Antagonist	1202 (24.7)	410 (27.0)	351 (23.2)	441 (23.9)	0.038
Statin	1865 (38.2)	621 (40.8)	614 (40.7)	630 (34.1)	<0.001
Digitalis	1159 (23.8)	330 (21.7)	389 (25.8)	440 (23.8)	0.030
Antiplatelet Agent	2967 (60.8)	871 (57.3)	953 (63.1)	1143 (62.0)	0.002
Mortality (%)					
All-Cause Death					
1-year	4.4	2.2	2.6	7.5	<0.001
3-year	14.1	5.5	9.7	24.8	<0.001
5-year	23.5	9.9	17.3	39.9	<0.001
Overall (Median 6.3-year)	33.2	14.8	27.2	53.3	<0.001
CV Death					
1-year	2.3	1.2	1.8	3.6	<0.001
3-year	6.9	3.4	4.7	11.5	<0.001
5-year	11.2	5.7	8.1	18.2	<0.001
Overall (Median 6.3-year)	15.2	8.3	12.1	23.4	<0.001
NCV Death					
1-year	1.8	0.8	0.8	3.5	<0.001
3-year	5.9	1.6	4.2	10.9	<0.001
5-year	9.8	3.1	7.5	17.3	<0.001
Overall (Median 6.3-year)	13.9	4.6	12.0	23.2	<0.001

Results are expressed as mean ± SD for continuous variables except BNP.
Abbreviations: ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; BMI, body mass index; BNP, B-type natriuretic peptide; BP, blood pressure; BUN, blood urea nitrogen; CABG, coronary artery bypass grafting; CCB, calcium channel blocker; CKD, chronic kidney disease; DCM, dilated cardiomyopathy; eGFR, estimated glomerular filtration rate; HCM, hypertrophic cardiomyopathy; HDL, high-density lipoprotein; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HHD, hypertensive heart disease; IHD, ischemic heart disease; IQR, interquartile range; LDL, low-density lipoprotein; LVDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; VHD, valvular heart disease.

diuretics in LVEF < 50% group, while some sex differences were noted in LVEF ≥ 50% group (**Fig. S3**).

3.3. Mortality and cause of death

During the median 6.3-year follow-up, 152 (10.0%), 272 (18.0%), and 1196 (64.8%) patients died in G1, G2, and G3, respectively, and 1-, 3- and 5-year mortality were all increased from G1, G2 to G3 (all P < 0.001) (Table S2). In G1 and G2, there were no sex differences in 1-, 3- or 5-year mortality. Although 1-year mortality was comparable between the sexes, men had higher 3-year and 5-year mortality than women in G3 (P = 0.032, and P = 0.003 respectively) (Table S3). The proportion of CV death was decreased from G1, G2 to G3, while that of NCV death was increased in both sexes, reflecting more accelerated increase in NCV death compared with CV death (Fig. 1). Incidence of each of CV and NCV deaths significantly increased from G1, G2 to G3, except AMI death and external death in both sexes (Fig. 2). No sex differences were noted in the incidence of each cause of CV death in all age groups. In contrast, among NCV deaths, men had significantly higher incidence of cancer death in G2 and G3 and that of pneumonia death in G3 (P < 0.05) as compared with women (Fig. 2).

3.4. Prognostic factors

Table 2 shows comparison of prognostic relevance of clinical variables on all-cause death among the age groups. Among the variables examined, several factors had significant impact on all-cause death in each age groups, of which some were equally significant across the groups and others not. Among them, we finally observed significant interactions of age groups, in terms of G1 vs. G3, with NYHA functional class III-IV, CKD, cancer, LVEF and BNP, and notably, all their impacts on all-cause death were less evident in G3 than in G1. Notably, all the variables had generally comparable prognostic impacts on all-cause between the sexes (Table S4).

4. Discussion

In the present study, we examined the differences in the characteristics, prognosis and prognostic factors among the age groups with a reference to sex, using the database of a large scale observational study for HF in Japan. The results clearly indicate that the elderly HF patients were characterized by more severe clinical backgrounds and worse prognosis, particularly in men, and that the prognostic factors had often different impacts across the age groups. These results indicate that HF management in the elderly should include multidisciplinary approach to improve mortality.

4.1. Characteristics of the elderly HF patients in Japan

The present study examined 4876 consecutive patients with Stage C/D HF registered in the CHART-2 Study, the largest prospective observational study for HF in Japan (N = 10,219) [13–20]. The Japanese elderly population of the present study was characterized by higher prevalence of women, higher blood pressure, and more preserved LVEF, a consistent findings with those reported from the Western countries [26–28]. Thus, HF in the elderly can be managed on the common basis worldwide, although pharmacological treatment strategies have yet been established for elderly HF patients [29,30].

4.2. Medications for the elderly HF patients in Japan

The Euro Heart Failure Survey (EHFS) II found that octogenarians hospitalized for HF between 2004 and 2005 still had lower prescription rates of RAS inhibitors, beta-blockers, and spironolactone at the time of discharge than younger HF patients, whereas diuretics and CCBs were more commonly prescribed.[26] In contrast, a significant increase in prescription rates of RAS inhibitors, beta-blockers, and aldosterone antagonists at discharge of HF hospitalization was noted in octogenarians from 2000 to 2001 (EHFS I) [31] to 2004–2005 (EHFS II) [26]. In the present study, prescription rates of beta-blockers and ACEI were decreased from G1 to G3 regardless of LVEF, whereas those of ARB, CCB and diuretics were increased, a consistent finding with the EHFS II [26]. It was noted that prescription rates of beta-blockers and ACEI were decreased from G1 to G3 even in LVEF < 50% group in both sexes, underlining the underuse of cardioprotective medications in the elderly population. However, it warrants a caution to simply recommend up-titration of these drugs for the elderly, because there is little evidence for the benefits of these drugs in the elderly HF patients, particularly in those with HFpEF [32]. Furthermore, it is generally

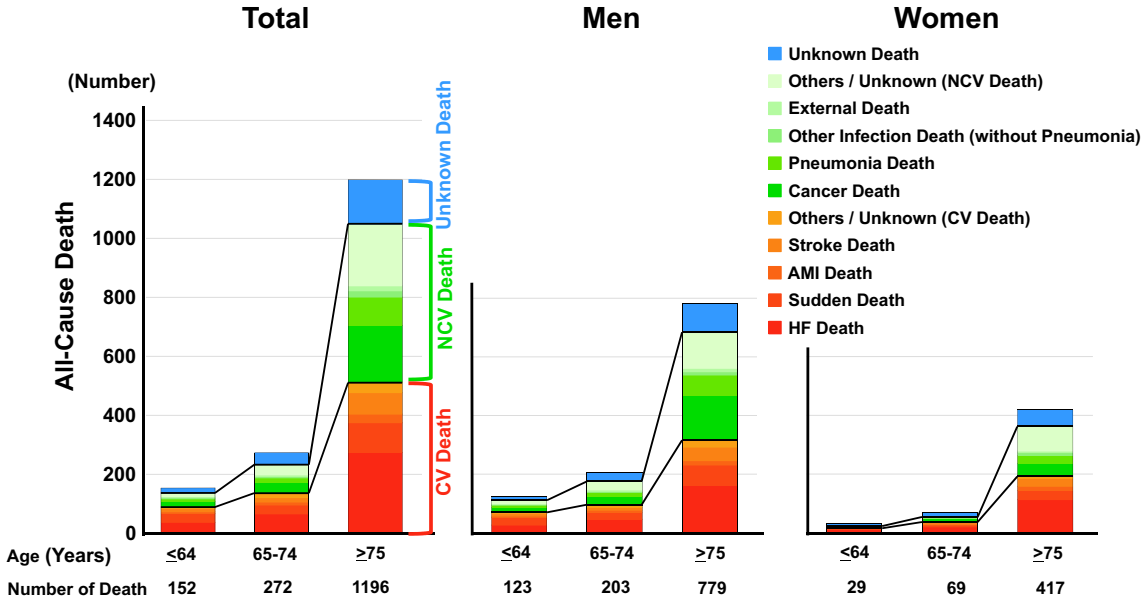

Fig. 1. Causes of Deaths. Abbreviations: AMI, acute myocardial infarction; CV, cardiovascular; HF, heart failure; NCV, non-cardiovascular.

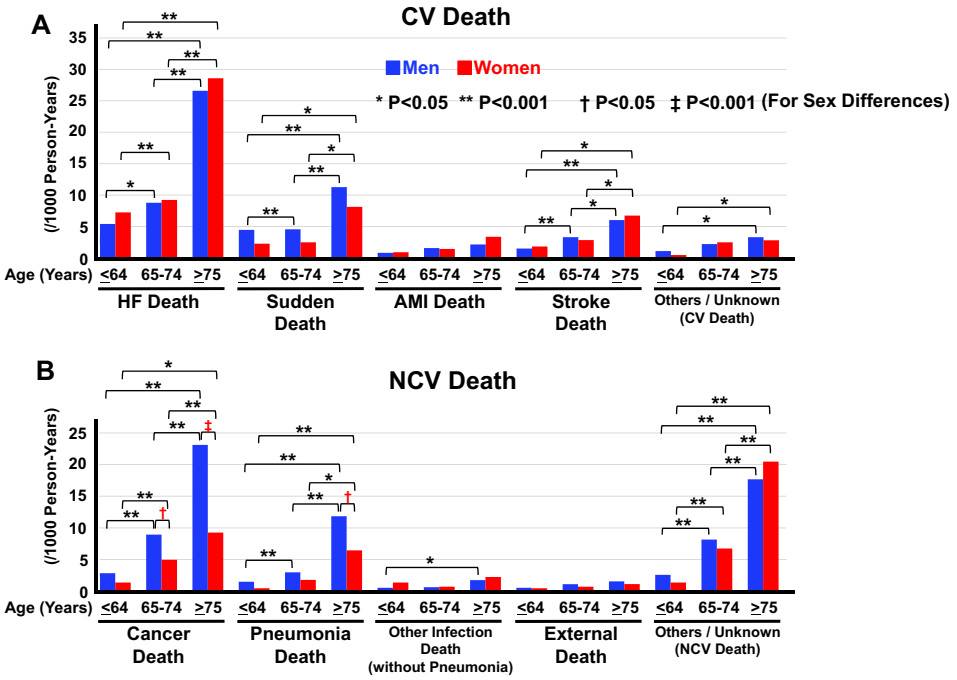

Fig. 2. Mortality by Sex (/1000 Person-Years). (**A**) CV Death, (**B**) NCV Death. Abbreviations: AMI, acute myocardial infarction; CV, cardiovascular; HF, heart failure; NCV, non-cardiovascular.

Table 2
Prognostic Factors for All-Cause Death.

All-Cause Death	G1 (Age ≤ 64) (N = 1521) (Events = 152)			G2 (Age 65–74) (N = 1510) (Events = 272)			G3 (Age ≥ 75) (N = 1844) (Events = 1196)			P. Interaction		
	HR	95% C.I.	P Value	HR	95% C.I.	P Value	HR	95% C.I.	P Value	G1 vs. G3	G1 vs. G2	G2 vs. G3
Sex (Women)	0.82	0.54–1.23	0.327	0.79	0.58–1.08	0.139	0.77	0.64–0.93	0.007	0.590	0.979	0.564
BMI (kg/m^2)	0.99	0.95–1.03	0.713	0.96	0.93–1.00	0.079	0.94	0.92–0.97	<0.001	0.333	0.912	0.337
NYHA Class III-IV	1.99	1.30–3.04	0.001	1.55	1.08–2.23	0.016	1.61	1.32–1.95	<0.001	0.030	0.034	0.824
IHD	1.07	0.74–1.54	0.735	0.99	0.76–1.30	0.962	1.00	0.85–1.19	0.979	0.597	0.687	0.871
Hypertension	0.89	0.58–1.39	0.620	0.88	0.55–1.40	0.585	0.74	0.55–0.99	0.039	0.430	0.980	0.379
Diabetes Mellitus	1.09	0.78–1.53	0.609	1.07	0.84–1.38	0.583	1.13	0.96–1.33	0.154	0.162	0.239	0.815
Dyslipidemia	1.05	0.65–1.71	0.836	0.80	0.58–1.11	0.185	0.77	0.64–0.93	0.006	0.159	0.300	0.510
CKD	1.56	1.12–2.17	0.008	1.43	1.10–1.86	0.007	1.31	1.10–1.56	0.003	0.018	0.097	0.411
Atrial Fibrillation	1.39	1.00–1.93	0.047	1.36	1.04–1.79	0.025	1.15	0.97–1.35	0.110	0.232	0.848	0.404
Stroke	1.72	1.16–2.54	0.007	1.57	1.18–2.09	0.002	1.34	1.12–1.59	0.001	0.149	0.714	0.266
Hospitalization for HF	2.38	1.57–3.59	<0.001	1.11	0.85–1.47	0.448	1.23	1.03–1.47	0.021	<0.001	<0.001	0.887
Cancer	2.12	1.24–3.60	0.006	1.51	1.11–2.05	0.009	1.30	1.08–1.56	0.005	0.084	0.166	0.489
Smoking	1.03	0.73–1.44	0.865	1.15	0.87–1.51	0.331	1.04	0.87–1.24	0.693	0.972	0.601	0.514
Systolic BP (/10 mmHg)	1.21	1.08–1.35	0.001	1.11	1.03–1.21	0.010	1.02	0.97–1.07	0.444	0.993	0.679	0.508
Diastolic BP (/10 mmHg)	0.72	0.61–0.86	<0.001	0.82	0.72–0.94	0.003	0.95	0.88–1.03	0.229	0.050	0.222	0.445
Heart Rate (/10 bpm)	1.03	0.92–1.14	0.644	1.08	1.00–1.17	0.059	1.04	0.99–1.09	0.139	0.926	0.661	0.387
LVEF (/10%)	0.88	0.79–0.97	0.012	0.92	0.84–1.00	0.045	1.02	0.97–1.08	0.468	<0.001	0.048	0.065
Anemia	1.37	0.95–1.98	0.097	1.23	0.94–1.61	0.137	1.45	1.22–1.73	<0.001	0.597	0.160	0.365
Hypoalbuminemia	1.31	0.91–1.87	0.144	1.47	1.09–1.97	0.011	1.42	1.20–1.68	<0.001	0.613	0.462	0.907
BNP (/100 pg/mL)	1.12	1.07–1.17	<0.001	1.08	1.04–1.12	<0.001	1.07	1.04–1.10	<0.001	0.001	0.010	0.490

Abbreviations: BMI, body mass index; BNP, B-type natriuretic peptide; BP, blood pressure; BUN, blood urea nitrogen; C.I., confidence interval; CKD, chronic kidney disease; HF, heart failure; IHD, ischemic heart disease; M, men; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; W, women.

considered that BP should be kept higher in the elderly than in younger patients [33]. Thus, it remains unclear whether or not further reduction of BP with additional use of those drugs could be beneficial in the real world practice for the elderly HF. Further studies are needed to answer this important issue.

4.3. Mortality and cause of death by age

The present study demonstrates that patients in G3 had significantly higher incidence of death, as compared with those in G1 and G2, regardless of sex. Recently, we reported that crude mortality rate in HF patients was similar between both sexes during the median 3.1 year follow-up.[16] In the present study with a longer follow-up period (median 6.3 year), we further confirmed that the incidence of CV death was comparable between both sexes regardless of age, whereas there were sex differences in the incidence of NCV death in the elderly groups, which was mostly attributed to the increased incidence in cancer death and pneumonia death in the elderly men. Although the sex difference in the incidence of death due to pneumonia in the elderly population was unclear, increased incidence of cancer death in men in the elderly HF patients compared to women could be, at least in part, associated with increased prevalence of cancer history at baseline in males in the elderly population. Thus, sex-specific approach

should be established particularly to prevent or reduce NCV death in the elderly HF patients. Considering the controversy on the sex differences in HF, [27,32–36] further studies are needed to establish sex-specific management in the elderly HF.

4.4. Prognostic factors by age

The present study also indicates that prognostic impacts of several factors, including NYHA functional class III-IV, CKD, cancer, LVEF and BNP, significantly differed by age and notably that their impacts were less evident in G3 than in G1. Although the reason for that is unclear, increased number of comorbid prognostic factors could decrease their impact in elderly HF patients. Indeed, it has been reported that physical inactivity, malnutrition, and frailty are other factors related to mortality and morbidity in patients with CV diseases, particularly in the elderly population [17,37–40]. In the present study, multivariable Cox proportional hazard models also showed that low BMI and hypoalbuminemia were associated with poor prognosis in G3. These lines of evidence indicate that elderly patients with HF need more multidisciplinary approach to improve their prognosis.

4.5. Evidence form HF patients in the super-aged society

The present study is one of the first reports, particularly in Asia, to examine the characteristics of the elderly HF patients in terms of clinical profiles and prognostic factors derived from a large-scale cohort [26,31]. Although there has been no consensus, the age of 65 years has been traditionally considered as the conventional threshold for the elderly [9]. However, this cut-off for the definition of the elderly may be outdated in the current era, since the life expectancy has been prolonged in the recent decades and most of the HF patients are now older than this age [41,42]. Thus, in the present study, we set 2 cut-off points (65 and 75 years) and compared the clinical profiles and outcomes among the age groups. As a result, the study subjects were divided into 3 groups with almost comparable number of patients, making the statistical comparisons more appropriate and robust among the age groups. Furthermore, considering the fact that the incidence of HF has been rapidly increasing with poor prognosis in the super-aged society, [4,41] the present findings would be useful to improve current HF management. Indeed, most of the randomized clinical trials for heart failure (HF) were designed to exclude elderly patients. The present findings are clinically important as they were obtained in the large-scale observational study without selection bias.

4.6. Study limitations

Several limitations should be mentioned for the present study. First, since the CHART-2 only enrolled Japanese patients, caution should be taken when generalizing the present findings to other populations. Second, in the present study, the data collected at the time of enrollment were analyzed and we did not take into consideration the possible changes in clinical profiles during the follow-up period. Finally, since the CHART-2 Study is an observational study, there might be unmeasured confounding factors that could influence the results of the present study.

5. Conclusions

The present study demonstrates that elderly HF patients, as compared with younger HF patients, have more severe clinical backgrounds, increased proportion of NCV death, and worse prognosis and that impacts of the prognostic factors differed among the age groups. These results indicate that multidisciplinary management of HF should be established to improve long-term prognosis of elderly HF patients.

CRediT authorship contribution statement

Masayuki Sato: Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Visualization. **Yasuhiko Sakata:** Methodology, Writing - review & editing, Project administration, Conceptualization, Funding acquisition. **Kenjiro Sato:** Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Visualization. **Kotaro Nochioka:** Writing - review & editing. **Masanobu Miura:** Writing - review & editing. **Ruri Abe:** Investigation, Resources, Data curation. **Takuya Oikawa:** Investigation, Resources, Data curation. **Shintaro Kasahara:** Investigation, Resources, Data curation. **Hajime Aoyanagi:** Investigation, Resources, Data curation. **Shinsuke Yamanaka:** Investigation, Resources, Data curation. **Takahide Fujihashi:** Investigation, Resources, Data curation. **Hideka Hayashi:** Investigation, Resources, Data curation. **Takashi Shiroto:** Writing - review & editing. **Koichiro Sugimura:** Writing - review & editing. **Jun Takahashi:** Writing - review & editing. **Satoshi Miyata:** Software, Validation, Formal analysis. **Hiroaki Shimokawa:** Conceptualization, Supervision, Funding acquisition.

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Declaration of competing interest

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Appendix A. Supplementary material

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