

Increased risk of cancer death in patients with chronic heart failure with a special reference to inflammation-A report from the CHART-2 Study

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ABSTRACT

Background: Although several factors, including heart failure (HF) and inflammation, are known to increase the incidence of cancer, it remains unknown whether HF may increase cancer mortality, especially with a reference to inflammation.

Methods and results: We examined 8843 consecutive cardiovascular patients without a prior history of cancer in our CHART-2 Study (mean 68 yrs., female 30.9%). As compared with patients without HF (Stage A/B, N = 4622), those with HF (Stage C/D, N = 4221) were characterized by higher prevalence of diabetes, previous myocardial infarction, atrial fibrillation, and stroke. During the median 6.5-year follow-up (52,675 person-years), 282 cancer deaths occurred. HF patients had significantly higher cancer mortality than those without HF in both the overall (3.7 vs. 2.8%, hazard ratio (HR) 1.42, 95% confidence interval (CI) 1.12–1.79, $P = 0.004$) and the propensity score-matched cohorts (HR 1.46, 95%CI 1.10–1.93, $P = 0.008$), which was confirmed in the competing risk models. The multivariable Cox proportional hazard model in the matched cohort showed that HF was associated with increased cancer mortality in patients with C-reactive protein (CRP) ≥ 2.0 mg/L (HR 1.87, 95%CI 1.18–2.96, $P = 0.008$) at baseline, but not in those with CRP < 2.0 mg/L (HR 0.89, 95%CI 0.54–1.45, $P = 0.64$) (P for interaction = 0.03). Furthermore, temporal changes in CRP levels were associated with cancer death in the overall cohort; HF patients with CRP ≥ 2.0 mg/L at both baseline and 1-year had significantly increased cancer death, while those with CRP ≥ 2.0 mg/L at baseline and < 2.0 mg/L at 1-year not.

Conclusions: These results provide the first evidence that HF is associated with increased cancer death, especially when associated with prolonged inflammation.

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1. Introduction

Reflecting on the rapid aging of the population, the number of patients with heart failure (HF) has been increasing as an epidemic of HF [1–3]. However, recent epidemiologic data remain to be accumulated [4]. Recently, we and others have reported that the proportion of death and hospitalization for non-cardiovascular causes increased by ~30–40% in HF patients [4–6]. Thus, it is important to determine whether HF increases death due to cancer as one of the main causes of non-cardiovascular death, as several studies suggested that HF may increase the incidence of cancer [7–10]. Inflammation is another major

mechanism of non-cardiovascular death. It has been shown that chronic inflammation predisposes individuals to various types of cancer and that underlying infections and inflammatory responses are linked to 15–20% of cancer deaths worldwide [11]. Held et al. recently reported that interleukin (IL)-6, an upstream inflammatory marker, was independently associated with increased risk of cancer death as well as major adverse cardiovascular events in patients with stable coronary artery disease [12]. Furthermore, the CANTOS Study has recently demonstrated that anti-inflammatory therapy with canakinumab, an antibody to IL-1 β , significantly reduced not only the incidence of cardiovascular events but also that of lung cancer and lung cancer mortality in patients with previous myocardial infarction and sustained higher levels of high-sensitivity C-reactive protein (hsCRP) ≥ 2 mg/L [13,14]. This important finding indicates that inflammation plays an important role in developing cancer and cancer death in patients with cardiovascular diseases [13,14]. However, few studies have fully examined a role of association between HF and inflammation on cancer death. In the present study, we

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thus examined whether HF increases cancer death, especially with a reference to inflammation, using the database of our large-scale cohort study for HF, termed as Chronic Heart Failure Registry and Analysis in the Tohoku district-2 (CHART-2) Study [15–17].

2. Methods

2.1. Data source

The CHART-2 Study has previously been described in detail [15–17]. Briefly, the CHART-2 Study is a multicenter, prospective, observational cohort study, designed to identify the characteristics, mortality and prognostic risks of a total of 10,219 patients with a history of HF (Stage C/D; $N = 4876$) and those without HF but at high risk of HF (Stage A/B; $N = 5343$) in Japan. From October 2006 to March 2010, 10,219 consecutive stable patients at outpatients clinics or just before discharge, and older than 20 years were successfully enrolled in the CHART-2 Study, if they had Stage B/C/D HF or significant coronary artery disease (CAD) in Stage A, as defined according to the American College of Cardiology Foundation/American Heart Association guidelines [18]. All patients were enrolled with a written informed consent at outpatient clinics or just before discharge at the Tohoku University Hospital or 23 affiliated hospitals in the Tohoku District, Japan. In the present cohort study, patients who were asymptomatic but who had structural heart disease and/or impaired left ventricular function were categorized as being in Stage B. Stage C was defined as current or past symptoms of HF associated with underlying structural heart disease; and Stage D was defined as refractory HF in which specialized and advanced treatment strategies were indicated. HF was diagnosed by an experienced cardiologist using the criteria of the Framingham Heart Study [19]. There were no exclusion criteria in the CHART-2 study other than age < 20 years. The study protocol was approved by the local ethics committees at each hospital. Baseline and follow-up data, including medical history, laboratory and echocardiography data and clinical outcomes, were collected at the time of enrollment and have been recorded annually thereafter at least once a year by the clinical research coordinators.

2.2. Study design

The study flowchart is shown in eFig. 1. After excluding 1366 patients with past history of cancer and 10 without sufficient data, we finally enrolled 8843 consecutive patients out of 10,219 patients in the CHART-2 Study, consisting of those without HF (Stage A/B; $N = 4622$) and those with HF (Stage C/D; $N = 4221$). In this cohort, we examined the impact of HF on the incidence of cancer death after enrollment. We further compared the incidence of cancer death among 4 subgroups stratified with a cutoff CRP levels ≥ 2.0 mg/L at baseline and at 1-year (eFig. 1).

2.3. Study outcome

The study outcome was cancer death. All clinical events were reviewed and assigned according to consensus of at least 2 independent physicians from the members of the Tohoku Heart Failure Association (Supplementary Appendix) after reviewing case reports, death certificates, and medical records provided by the investigators.

2.4. Statistical analysis

Patient characteristics are described as mean (standard deviation) or median (interquartile range) for continuous variables and as frequency (percentage) for categorical variables. To compare 2 groups, Welch's *t*-test or Wilcoxon rank sum test for continuous

variables and Pearson's chi-squared test for categorical variables were used. To compare the 4 groups, ANOVA test or Kruskal-Wallis test was used for continuous variables as appropriate, and Pearson's chi-squared test was used for categorical variables. To adjust for confounding effects and differences in the patient background between 2 groups (patients without HF vs. those with HF), propensity score (PS) matching method and the inverse probability of treatment weighted (IPTW) using PS was used. A PS was estimated using 13 baseline variables (age, sex, body mass index (BMI), smoking, hypertension, diabetes mellitus, dyslipidemia, stroke, myocardial infarction, angiotensin converting enzyme inhibitor (ACE-I) or angiotensin II receptor blocker (ARB), β -blocker, antiplatelet, and statin). Blood pressure, heart rate, atrial fibrillation, laboratory data such as brain natriuretic peptide (BNP), echocardiography data, diuretics that were likely affected by HF itself, were excluded from variables to estimate PS. Area under the curves to show the performance of the PS was 0.659. All time-to-event outcomes in the overall cohort and PS-matched cohort were assessed with Kaplan-Meier analysis, log-rank tests and Cox proportional hazard models. Cox proportional hazard models were used to estimate hazard ratios (HRs) and their 95% confidence intervals (CIs) of covariates for HF (patients without HF vs. those with HF). To minimize competing risk of non-cancer death, we assessed association of HF and cancer death, using Fine and Gray competing risk regression model with R package "cmprsk" Version 2.2-7 on the total and PS-matched cohorts [20]. Analyses of subgroups defined by age, sex, BMI, smoking, hypertension, diabetes mellitus, myocardial infarction, CRP, ACE-I or ARB, β -blocker, antiplatelet, and statin were performed. To examine the relationship between 1-year transition of CRP and cancer death thereafter, the univariable and the multivariable Cox proportional hazard model were used. All of the potential confounding factors were included in the univariable Cox proportional hazard model analysis. The initial candidates for variable selection were the set of the covariates with P values < 0.1 in the univariable Cox proportional hazard model analysis. To select an optimal subset of the covariates, we adopted a stepwise variable selection procedure. The covariates that may have potentially influenced outcomes included in these analyses included age, sex, BMI, blood pressure, heart rate, New York Heart Association (NYHA) class III or IV (only for patients with HF), smoking, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, stroke, myocardial infarction, left ventricular ejection fraction (LVEF), left ventricular dimension at end-diastole (LVDd), left atrial diameter (LAD), hemoglobin, estimated glomerular filtration rate, low-density lipoprotein cholesterol, BNP, albumin, ACE-I or ARB, β -blocker, diuretic, aldosterone antagonist, antiplatelet, and statin. Statistical computing software, R version 3.4.3, was used for all statistical analysis [21]. $P < 0.05$ and P value for interaction < 0.05 were considered to be statistically significant.

3. Results

3.1. Patient characteristics

In the total cohort, mean age was 68 years and female patients accounted for 30.9%. Baseline patient characteristics of the total and PS-matched groups are shown in Table 1. In the total cohort, there were significant differences in several variables. As compared with the patients without HF, HF patients were characterized by older age, lower BMI, and higher prevalence of women, diabetes mellitus, prior myocardial infarction, and stroke. HF patients were more frequently treated with ACE-I or ARB, β -blocker, and antiplatelet, but less frequently with statin. The prevalence of smoking history and dyslipidemia did not differ between the groups. In the PS-matched cohort,

Table 1
Patients characteristics of the total and PS-matched cohorts.

	Total cohort			PS-matched cohort			
	Without HF ($N = 4622$)	With HF ($N = 4221$)	<i>P</i> value	Without HF ($N = 3064$)	With HF ($N = 3064$)	<i>P</i> value	Standardized difference
Age, mean (SD), y	66.9 (12.2)	68.1 (12.5)	<0.001	67.7 (11.7)	67.6 (12.7)	0.69	−0.010
Female sex, No. (%)	1357 (29.4)	1372 (32.5)	0.002	939 (30.6)	943 (30.8)	0.93	0.003
BMI, mean (SD), kg/m ²	24.3 (3.4)	23.9 (3.9)	<0.001	24.2 (3.3)	24.1 (3.9)	0.63	−0.012
Smoking, No. (%)	2108 (48.2)	1839 (46.1)	0.05	1441 (47.0)	1424 (46.5)	0.68	−0.011
Medical history							
Hypertension, No. (%)	4120 (89.1)	3774 (89.4)	0.71	2753 (89.8)	2763 (90.2)	0.70	0.011
Diabetes mellitus, No. (%)	1572 (34.0)	1658 (43.3)	<0.001	1144 (37.3)	1126 (36.7)	0.65	−0.012
Dyslipidemia, No. (%)	3831 (82.9)	3463 (82.0)	0.31	2535 (82.7)	2531 (82.6)	0.92	−0.003
Myocardial infarction, No. (%)	1290 (27.9)	1442 (34.2)	<0.001	978 (31.9)	980 (32.0)	0.98	0.001
Stroke, No. (%)	839 (18.2)	845 (20.0)	0.03	593 (19.4)	598 (19.5)	0.90	0.004
Medical treatment							
ACE-I or ARB, No. (%)	2708 (58.6)	3059 (72.5)	<0.001	2093 (68.3)	2083 (68.0)	0.81	−0.007
β -blocker, No. (%)	1502 (32.5)	2114 (50.1)	<0.001	1297 (42.3)	1282 (41.8)	0.72	−0.010
Antiplatelet, No. (%)	3308 (71.6)	3397 (80.5)	<0.001	1906 (62.2)	1920 (62.7)	0.73	0.009
Statin, No. (%)	2103 (45.5)	1649 (39.1)	<0.001	1316 (43.0)	1267 (41.4)	0.21	−0.032

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; HF, heart failure; PS, propensity score.

baseline characteristics were generally comparable between the 2 groups, with minimal standardized difference scores in all variables (Table 1).

3.2. Heart failure and cancer death

During the median 6.5 years of follow-up (52,675 person-years), 282 cancer deaths occurred. Fig. 1 shows the Kaplan-Meier curves for the cancer death in the total cohort (log-rank $P = 0.003$) and PS-matched cohort (log-rank $P = 0.008$). The incidence of cancer death was significantly higher in HF patients as compared with patients without HF in both the overall (3.7 vs. 2.8%, HR 1.42, 95% CI 1.12–1.79, $P = 0.004$) and the PS-matched cohorts (HR 1.46, 95% CI 1.10–1.93, $P = 0.008$), which was consistent with the results in the PS stratification model (HR 1.52, 95% CI 1.10–2.10, $P = 0.01$) and by the IPTW method using PS (HR 1.34, 95% CI 1.13–1.60, $P < 0.001$) (eTable 1). Moreover, these results were confirmed by the competing risk model in the total (HR 1.28, 95% CI 1.01–1.62, $P = 0.04$) and the PS-matched cohorts (HR 1.35, 95% CI 1.02–1.78, $P = 0.04$) (eTable 1).

3.3. Subgroup analysis

Fig. 2 shows the results of subgroup analysis in the PS-matched cohort. HF was associated with increased incidence of cancer death in patients without diabetes mellitus (HR 2.10, 95% CI 1.42–3.09, $P < 0.001$) but not in those with diabetes mellitus (HR 0.93, 95% CI 0.61–1.41, $P = 0.72$) (P for interaction 0.005), and in patients with CRP ≥ 2.0 mg/L (HR 1.87, 95% CI 1.18–2.96, $P = 0.008$) but not in those with CRP < 2.0 mg/L (HR 0.89, 95% CI 0.54–1.45, $P = 0.64$) (P for interaction = 0.03) (Fig. 2 and eFig. 2). In contrast, impact of HF on cancer death did not differ significantly in terms of age, sex, BMI, smoking history, prior myocardial infarction, hypertension, and use of ACE-I or ARB, β -blocker, antiplatelet, or statin.

3.4. Prognostic impact of the transition of CRP levels in patients without HF or with HF

Baseline characteristics of 4 groups divided according to the temporal changes in CRP levels are shown in eTables 2 and 3. In the patients without HF, age, sex, BMI, heart rate, smoking history, prevalence of hypertension, diabetes mellitus, myocardial infarction, and atrial fibrillation significant differed among the 4 groups, whereas blood pressure, prevalence of dyslipidemia and stroke were comparable. In the echocardiography data, LVDD values were comparable, while LVEF and LAD were significantly different among the 4 groups. The prescription rates of ACE-I or ARB, β -blocker, aldosterone antagonists, and statin did not differ among the 4 groups, while use of diuretics and antiplatelets differed (eTable 2). In patients with HF, age, BMI, heart rate, NYHA class III or IV, smoking history, prevalence of myocardial infarction, and atrial fibrillation significant differed, whereas the prevalence of female sex, blood pressure, prevalence of hypertension, diabetes mellitus, dyslipidemia and stroke did not differ among the 4 groups. In the echocardiography data, LVEF and LVDD values were comparable among the 4 groups, although LAD was significantly differed. The prescription rates of ACE-I or ARB, β -blocker, aldosterone antagonist, and antiplatelet were comparable, while use of diuretic and statin significantly differed among the 4 groups (eTable 3). Among the patients without HF, there were no differences in the incidence of cancer death among 4 groups according to the transition of CRP levels (eFig. 3). On the other hand, among the patients with HF, as compared with those with baseline CRP < 2.0 mg/L and 1-year CRP < 2.0 mg/L, the incidence of cancer death was significantly higher in those with baseline CRP ≥ 2.0 mg/L and 1-year CRP ≥ 2.0 mg/L (eFig. 3). These results remained after adjustment using multivariable model (Table 2). As compared with non-lung cancer death, the hazard ratio for lung cancer death was higher in patients with persistent elevated CRP levels, regardless of the absence or presence of HF (Table 2). The most common cause of death among cancer deaths was lung cancer, followed by gastric and colorectal cancers in both groups (eTable 4).

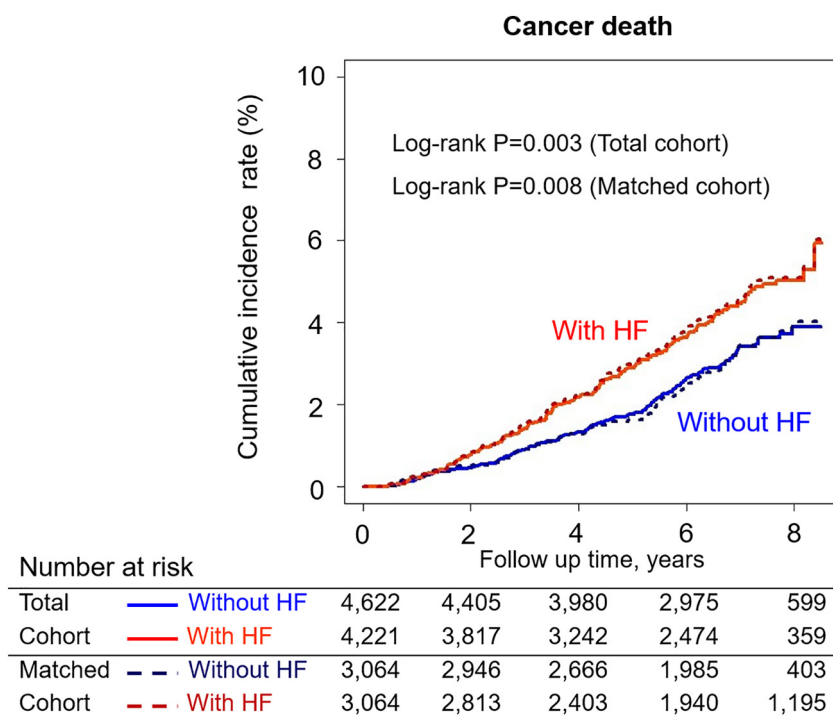


Fig. 1. Kaplan-Meier curves for cancer death in the total and PS-matched cohorts. Abbreviations: HF, heart failure; PS, propensity score.

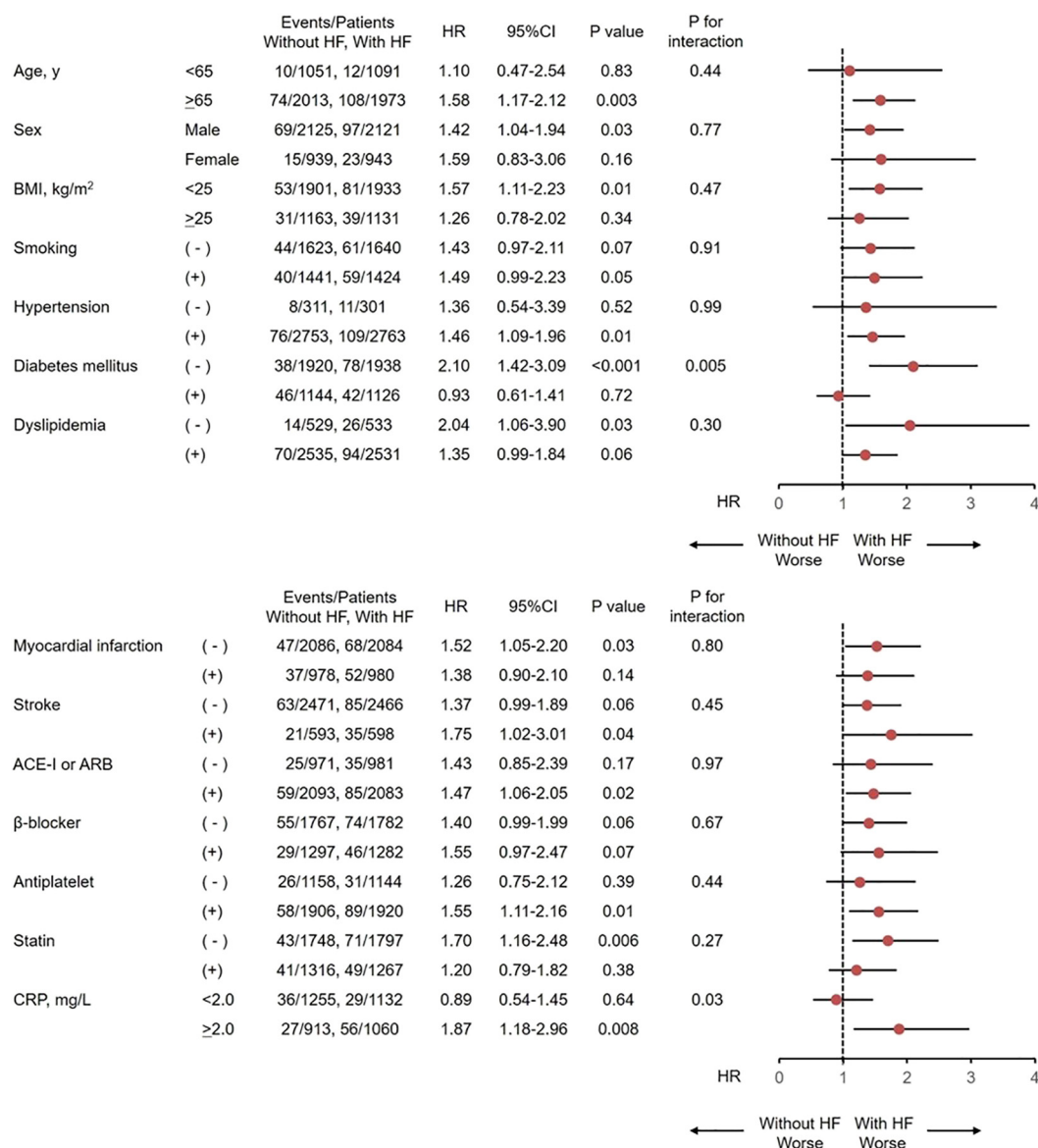


Fig. 2. Impact of HF on cancer death by subgroups (With HF vs. Without HF). Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; HF, heart failure; HR, hazard ratio.

4. Discussion

In the present study, we examined whether HF is a risk of cancer death in our CHART-2 Study, a multicenter, prospective, large observational cohort study in Japan, with state-of the art statistical methods to minimize biases associated with clinical background of HF patients. The results clearly demonstrated that HF was associated with increased cancer death, even after adjusting patient characteristics and competing risks and that persistent inflammation is a key environment to cause cancer death in HF patients.

4.1. Impact of HF on cancer death

To the best of our knowledge, this is the first study to examine whether HF is associated with cancer death. Although it has been reported that HF patients have an increased risk of cancer incidence [7–10], no studies have examined whether HF patients have increased risk of cancer death. In addition, previous studies did not take into account the competing risks adequately. Thus, it is especially important that the present study demonstrated that HF was associated with

increased cancer death after considering the competing risk, namely the risk of non-cancer death, suggesting that prevention of HF may reduce cancer deaths in addition to cardiovascular deaths. This point is of clinical significance, since it has been reported that improvement of cardiovascular prognosis is inevitably associated with increased non-cardiovascular death in HF patients in the last decades [5,6].

4.2. Factors related to cancer mortality in HF patients

It has been reported that cardiovascular medications might influence the risk of cancer death. For example, Rothwell et al. reported that daily aspirin reduced deaths due to several common cancers and risk of cancer metastasis [22–24]. Although controversial, several studies have reported that statin use in patients with cancer was associated with reduced cancer-related mortality [25–30]. SOLVD investigators reported that, as compared with the placebo group, non-fatal cancers of the gastrointestinal tract was more frequently observed in the enalapril group [31]. In addition, Hicks et al. reported that the use of ACE-Is was associated with an increased risk of lung cancer in the population based cohort study [32]. Thus, we employed the PS matching method

Table 2

Impact of temporal changes of CRP levels on cancer death in patients with and without HF in the overall cohort.

Patients without HF		Univariable			Multivariable		
All cancer death #1		HR	95% CI	P value	HR	95% CI	P value
From <2.0 mg/L to <2.0 mg/L		1.00	Reference		1.00	Reference	
From <2.0 mg/L to ≥2.0 mg/L		1.34	0.66–2.74	0.42	0.97	0.42–2.23	0.93
From ≥2.0 mg/L to <2.0 mg/L		0.74	0.36–1.51	0.40	0.50	0.22–1.16	0.11
From ≥2.0 mg/L to ≥2.0 mg/L		1.52	0.84–2.76	0.16	0.98	0.50–1.92	0.95
Lung cancer death #2							
From <2.0 mg/L to <2.0 mg/L		1.00	Reference		1.00	Reference	
From <2.0 mg/L to ≥2.0 mg/L		1.39	0.28–6.08	0.80	0.59	0.07–4.89	0.62
From ≥2.0 mg/L to <2.0 mg/L		1.14	0.28–4.41	0.89	1.03	0.26–4.12	0.97
From ≥2.0 mg/L to ≥2.0 mg/L		3.23	0.93–8.28	0.07	2.30	0.76–6.98	0.14
Non-lung cancer death #3							
From <2.0 mg/L to <2.0 mg/L		1.00	Reference		1.00	Reference	
From <2.0 mg/L to ≥2.0 mg/L		1.33	0.60–2.96	0.48	1.35	0.58–3.17	0.49
From ≥2.0 mg/L to <2.0 mg/L		0.64	0.28–1.48	0.30	0.74	0.31–1.73	0.48
From ≥2.0 mg/L to ≥2.0 mg/L		1.11	0.53–2.32	0.77	1.06	0.50–2.26	0.88
Patients with HF							
All cancer death #4							
From <2.0 mg/L to <2.0 mg/L		1.00	Reference		1.00	Reference	
From <2.0 mg/L to ≥2.0 mg/L		1.53	0.73–3.22	0.26	1.06	0.47–2.38	0.90
From ≥2.0 mg/L to <2.0 mg/L		1.64	0.88–3.03	0.12	1.45	0.76–2.76	0.26
From ≥2.0 mg/L to ≥2.0 mg/L		2.46	1.43–4.21	0.001	1.85	1.05–3.25	0.03
Lung cancer death #5							
From <2.0 mg/L to <2.0 mg/L		1.00	Reference		1.00	Reference	
From <2.0 mg/L to ≥2.0 mg/L		0.89	0.10–8.01	0.79	0.69	0.08–6.23	0.74
From ≥2.0 mg/L to <2.0 mg/L		1.14	0.19–5.77	0.32	1.04	0.19–5.69	0.97
From ≥2.0 mg/L to ≥2.0 mg/L		3.23	1.44–14.63	0.01	2.96	0.91–9.62	0.07
Non-lung cancer death #6							
From <2.0 mg/L to <2.0 mg/L		1.00	Reference		1.00	Reference	
From <2.0 mg/L to ≥2.0 mg/L		1.67	0.75–3.68	0.21	1.50	0.61–3.69	0.37
From ≥2.0 mg/L to <2.0 mg/L		1.76	0.90–3.42	0.10	1.32	0.59–2.95	0.50
From ≥2.0 mg/L to ≥2.0 mg/L		2.01	1.08–3.74	0.03	1.35	0.63–2.88	0.44

#1 Adjusted with age, sex, stroke, hemoglobin, LVDd, and diuretics;

#2 Adjusted with DM, stroke, hemoglobin, and antiplatelet;

#3 Adjusted with age, hemoglobin, diastolic blood pressure, and LVDd;

#4 Adjusted with age, sex, heart rate, dyslipidemia, heart failure admission, and antiplatelet;

#5 Adjusted with age, sex, and heart rate;

#6 Adjusted with age, heart rate, and HbA1c.

Abbreviations: CI, confidence interval; CRP, C-reactive protein; HbA1c, hemoglobinA1c; HF, heart failure; HR, hazard ratio; LVDd, left ventricular dimension at end-diastole.

and IPTW method for statistical analyses in order to minimize the influence of these medications on cancer death, including aspirin, statin, ACE-I or ARB and β -blocker. As a result, even after adjustment for the use of these medications, the present study demonstrated that HF was associated with increased cancer death. The present study also showed that HF was associated with increased cancer death in patients without diabetes mellitus but not in those with diabetes mellitus, while diabetes was not associated with an increased incidence of cancer death among HF patients. Thus, considering that diabetes was associated with an increased incidence of cancer death in patients without HF in the present study, a consistent finding in a previous study [33], risk of cancer death due to diabetes mellitus might have been overwhelmed by the increased risk of cancer death related to HF. Interestingly, in the present study, HF was associated with increased incidence of cancer death in patients with CRP ≥ 2.0 mg/L but not in those with CRP < 2.0 mg/L, indicating that combination of HF and inflammation is important to develop cancer death.

4.3. Inflammation and cancer in HF patients

The detailed mechanisms underlying the association of HF with cancer death are unclear. In the present study, we demonstrated that persistent inflammation is significantly associated with cancer death in HF patients. Although persistent inflammation may not be the cause but the result of subclinical cancer development [11], HF is a significant risk of cancer death. In the present study, persistent inflammation was associated with increased incidence of cancer death in patients with HF, but not in those without HF, even after adjustment of clinical

characteristics in the multivariable Cox analysis. Recently, the CANTOS trial demonstrated that anti-inflammatory therapy with canakinumab, targeting the IL-1 β innate immunity pathway, significantly reduced cardiovascular events, incident cancer and cancer death [13,14]. Several studies reported that activation of IL-1 β stimulates the down-stream IL-6 signaling pathway, which has been associated with the inflammatory response, death from any cause, increased atherosclerosis, and the progression and invasiveness of cancer in patients with coronary artery disease [12–14]. In addition, several studies demonstrated that biomarkers of inflammation, such as tumor necrosis factor- α , IL-6, and CRP, is elevated in patients with HF [34,35] and that these proinflammatory cytokines have been linked to HF severity associated with a poor clinical outcome in HF patients [35–37]. These lines of evidence indicate that HF and cancer may share some molecular pathways in disease development and progression, supporting the hypothesis that combination of inflammation and HF further worsens the long-term prognosis of the patients, including cancer death.

4.4. Inflammation and specific types of cancer death

In the present study, the most common type of cancer death was lung cancer, followed by gastric and colorectal cancers in patients with HF as well as in those without HF. Thus, we may conclude that HF is associated with increased risk of diverse types of cancers. However, in the CANTOS study, it was suggested that inflammation was especially associated with increased risk of lung cancer death in cardiovascular patients, since canakinumab therapy was associated with reduced lung cancer death among myocardial infarction patients

with elevated hsCRP [13,14]. In the present study, the hazard ratio for deaths due to lung cancer was indeed higher than that for non-lung cancer deaths in patients with HF and persistent CRP elevation, although its statistical significance was not examined. Thus, it should be further examined whether persistent inflammation in patients with HF has a significant association with lung cancer death among various types of cancer death.

4.5. Study limitations

Several limitations should be mentioned for the present study. First, since the CHART-2 Study is a prospective observational study in Japan, cautions are needed when generalizing the present findings to other populations in different countries. Second, in the present study, we did not consider the disease severity or duration of HF at the time of enrollment. Third, it should be also noted that several chronic conditions could be a barrier to the receipt of cancer treatments; it is reported that HF, diabetes, and chronic obstructive pulmonary disease patients receive less cancer treatments than non-HF counterparts, eventually facing a higher likelihood of dying [38]. Because the CHART-2 Study did not collect inflammation markers other than CRP, it was difficult to deepen the discussion on prognostic impact of inflammation. Thus, further investigations are warranted to confirm our results. Finally, as a nature of the CHART-2 Study as an observational study, we were unable to rule out the influences of significant confounding factors for cancer death or other biases completely. However, in the present study, we employed the PS matching method and IPTW method using PS as a state-of-the-art statistical analysis to minimize such influences or biases on cancer death.

5. Conclusion

The present results provide the first evidence that HF patients have increased risk of cancer death. Furthermore, persistent inflammation associated with HF may be a key factor to cause cancer death. Further studies are warranted to confirm the effects of inflammation for cancer risk in HF patients.

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Conflicts of interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2019.04.078>.

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