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ORIGINAL ARTICLE

Burden of cardiovascular disease in Japanese cancer patients and survivors: a single cancer-center study in Niigata City

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Abstract

Background Cardiovascular disease (CVD) and cancer are major causes of death in Japan. As most CVDs are chronic and often aggravate, long-term follow-up is necessary. Although some cancer patients and survivors have CVD, its prognostic significance and prevalence are unknown. Therefore, we conducted a retrospective study at our center to determine the prevalence of cancer patients with CVD.

Methods In 2015, our 10-year (2005–2014) cancer registry was summarized. Comorbidities including left ventricular dysfunction, atrial fibrillation (AF), ischemic heart disease, aortic stenosis, venous thromboembolism (VTE), and elevation of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) were examined.

Results In total, 26,235 de novo cancer patients were registered and 16,130 survived until January 1, 2015. The 5-year survival rate was 64.0% for all cancer patients and 44.2% for cancer patients with CVD. Cox proportional hazards analysis adjusting for age, cancer stage, and body mass index revealed that AF [hazard ratio (HR) 1.219, male; $P=0.038$], VTE (HR 1.517, male; $P=0.003$ and HR 2.089, female; $P<0.001$), and NT-proBNP elevation (HR 1.861, female; $P=0.002$) were significantly associated with death. The CVD prevalence among cancer survivors in 2015 was 8.7% vs 3.5% for males vs females. AF was the most common CVD (prevalence: male, 4.0%; female, 1.0%). The prevalence of most CVD in adults increased progressively with age, with male predominance (12.1% for male and 7.5% for female patients in the 80 s age group).

Conclusions One in 10 elderly cancer survivors has serious CVD. AF, VTE, and heart failure were critical comorbidities. Cardiologists and cancer-care providers should recognize CVD presence and monitor patients closely, providing medications or interventions concurrently with cancer therapy.

Keywords Atrial fibrillation · Venous thromboembolism · N-terminal prohormone of brain natriuretic peptide · Heart failure

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Introduction

Cardiovascular disease (CVD) is an epidemic among cancer patients; hypertension, atrial fibrillation (AF), ischemic heart disease (IHD), venous thromboembolism (VTE), left ventricular dysfunction (LVD), and heart failure (HF) are common in cancer patients [1]. Four factors influence the CVD epidemic in cancer patients [2–7]: (1) common risk factors for cancer and CVD, (2) neoplastic effect on the cardiovascular system, (3) cardiovascular toxicities due to chemotherapy and radiotherapy, and (4) increase in the number of survivors.

Cancer and CVD are the two major causes of death in developed countries [2–4]. Aging, smoking, diabetes, obesity, and physical inactivity are risk factors for both cancer

and CVD [3–5]. Cancer patients often have cardiovascular comorbidities, and patients with CVDs often have cancer. Therefore, oncologists often treat cancer patients considering the presence of cardiovascular comorbidities.

Humoral factors or cytokines secreted by tumors often cause hypercoagulability [6]. Moreover, the mass effect and direct compression of the cardiovascular system by tumors cause hemostasis, inducing venous and arterial thromboembolism and resulting in a high incidence of vascular comorbidities in cancer patients [6].

Cancer therapies increase CVD. Antineoplastic agents adversely affect the heart and vessels. Anthracyclines, cyclophosphamide, cisplatin, fluorouracil, trastuzumab, bevacizumab, and lenvatinib are commonly used for cancer therapy. Despite significant advances, toxicities to the cardiovascular system remain [7]. Previously, cardiovascular complications were not prevalent among cancer patients because their lifespan was often too short for complications to manifest. Recently, cancer-patient survivability has increased, with some survivors developing chemotherapy-related cardiovascular dysfunction [1, 6–8].

In 2016, The Japanese Association of Clinical Cancer Centers reported a 58% 10-year survival rate in 35,000 cancer patients diagnosed between 1999 and 2002 in 2016 [8]. CVD is currently a serious problem in cancer patients. Its early identification, prevention, and long-term treatment by cardiologists are necessary; however, information regarding its prevalence is scarce in Japan. Therefore, we conducted a retrospective study at our cancer center to determine the prevalence of cancer patients with CVD.

Patients and methods

Subjects

The Niigata Cancer Center CVD Study is a retrospective single-center registry that enrolled consecutive cancer patients in our facility between January 2005 and December 2014. We focused on LVD, AF, IHD, aortic stenosis (AS), VTE, and significant elevation of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) because they are often associated with cancer and require sustained surveillance and medication. Although hypertension is the most common CVD in cancer and non-cancer patients, it was excluded from our study because its treatment resulted in favorable outcomes.

Definition and diagnosis of CVD

LVD was divided into systolic (LVSD) and diastolic (LVDD) dysfunctions exclusively via echocardiography. LVSD was diagnosed based on a left ventricular ejection fraction (LVEF) $\leq 50\%$, while Doppler (E) and the early diastolic velocity of the mitral valve annulus obtained from tissue Doppler (e') were used for LVDD diagnosis. LVDD was diagnosed based on an LVEF $> 50\%$ and $E/e' > 8$, in addition to, at least, two of the following (after excluding moderate or severe mitral and aortic insufficiency): (1) left atrial enlargement, (2) left ventricular hypertrophy, and (3) AF [9, 10]. AF was diagnosed via 12-lead electrocardiography. IHD was defined based on (1) documented IHD history [myocardial infarction (MI), angina, or prior coronary revascularization]; (2) medication for IHD; or (3) current IHD diagnosed by cardiologists from any cardiac tests or imaging. AS was diagnosed via echocardiography as thickened leaflets with reduced systolic opening associated with an increased velocity across the aortic valve (> 3.0 m/s), as a mean gradient > 25 mmHg, or as an aortic valve area < 1.5 cm^2. Moderate to severe aortic regurgitation was excluded [11]. VTE included proximal deep venous thrombosis (DVT) or pulmonary thromboembolism (PTE) and was diagnosed via contrast-enhanced computed tomography (CT). DVT of the legs was also diagnosed via vascular echocardiography. We included all PTE and central DVT types (superior vena cava, inferior vena cava, subclavian, iliac, femoral, and popliteal DVT) but excluded lower leg DVT. NT-proBNP > 900 pg/mL was diagnosed as a significant elevation in accordance with the statement of the Japanese Heart Failure Society [10, 12]. CVD was defined as any LVSD, LVDD, AF, IHD, AS, VTE, or elevation of NT-proBNP > 900 pg/mL documented at any time during the clinical course. Although some CVDs were controlled and did not meet the aforementioned definition by treatment, treatment and follow-up of those CVDs were continued incessantly. Therefore, in the study, we defined cancer patients diagnosed with CVD, even if diagnosed only once, as cancer patients with CVD regardless of their subsequent conditions.

Cancer database

Our hospital maintains a cancer registry and regularly updates the clinical information and vital statuses of patients. The date of initial diagnosis, clinical and pathological diagnosis, and the date of death were obtained from the registry [13, 14].

Selection of CVD patients

In our hospital, systemic screening was performed before cancer therapy [13, 14]. All patients underwent physical examination, 95% underwent electrocardiography, and 53% underwent chest radiography. If necessary, cancer patients were referred to cardiologists (Y.O., T.T., K.O.), and 23 and 7% of the patients underwent transthoracic echocardiography and vascular ultrasound, respectively. All electrocardiograms

were diagnosed and coded using automatic diagnostic analyzers and checked by cardiologists before being saved in the database. All echocardiography and vascular ultrasound results were verified by four sonographers and two cardiologists (Y.O., T.T.), and their data and reports were saved in the database. Almost all (98%) patients underwent chest, abdomen, or pelvis CT for cancer detection. CT images and the reports by the radiologists were saved in the radiography database, which enabled the systematic extraction of VTE. NT-proBNP levels were measured during screening or HF diagnosis and have been saved since 2008 in the laboratory database. If a patient had multiple imaging or laboratory test data that satisfied our inclusion criteria, only the first image or record was chosen for the analysis. Maximum values of NT-proBNP of each patient were selected for analysis.

Selection of the recruitment period

The 10-year survival of cancer patients was reported as 58% in 2016 by the National Cancer Center Japan [8]. Since a majority of cancer patients survived longer than 10 years, we selected 2005–2014 as our recruitment period. The relationship between the number of enrolled patients and the length of the recruitment period was reported in the Niigata-Sado Heart Failure Study [15]. The number of enrolled patients increased with the extension of the recruitment period. However, the earlier the patients were identified, the more information was lost because of death or missing data. Therefore, we selected the 10-year period. If the same patient was diagnosed with any other cancers two or more times during the recruitment period, only data from the first cancer was considered.

Statistical analysis

Although a large number of cancer patients with LVD, AF, IHD, AS, VTE or NT-proBNP elevation died by the end of 2014, most have survived and required sustained surveillance or medications. To estimate the approximate prevalence of cancer survivors with CVD, the proportion of survivors with CVD in each sex and age group by January 1, 2015, was calculated using the following equation:

$$\text{Number of cancer patients with CVD} / \text{total number of cancer patients} \times 100\,(\%).$$

Categorical variables are presented as numbers and percentages. Proportions were compared using χ^2 or Fisher's exact test. Continuous variables are presented as mean ± standard deviation (SD), or standard error (SE), and were compared using Student's *t* test or Wilcoxon rank-sum test, depending on the variable distribution. A two-tailed significance level of 0.05 was used. Cancer diagnosis-to-event curves were evaluated using the Kaplan–Meier method and differences between cancer with and without each CVD were assessed using a log-rank test. A Cox proportional hazards regression model was used to identify the predictors of death. Univariate analysis was performed for each input variable against a positive death outcome, and all variables with $P \leq 0.1$ were then included in the multivariate forward-stepwise Cox regression model. Data were analyzed with IBM SPSS statistics version 25.0 (Armonk, NY, USA).

Ethical considerations

The study protocol was reviewed and approved by the Niigata Cancer Center ethics committee. The study was approved as a minimal-risk research and informed consent was waived in accordance with the ethical guidelines for epidemiology research in Japan.

Results

Recruitment of cancer patients

From January 2005 through December 2014, 26,235 patients were registered in our hospital (Fig. 1a). The numbers of deceased patients and survivors increased progressively over time. Overall, 8334 patients died, 1771 patients were lost to follow-up, and 16,130 patients survived until January 1, 2015; most were middle- or old-aged patients (Fig. 2a).

Number of cancer patients with any CVD

Among 26,235 patients, 2168 patients were diagnosed with CVD (Fig. 1b). The numbers of deceased patients and survivors also increased progressively over time (Fig. 1b). In total, 1074 patients died, 112 patients were lost to follow-up, and 982 patients survived until January 1, 2015; most were middle- or old-aged patients (Fig. 2b).

Characteristics of cancer patients

Demographics

The majority of patients were males (Table 1) and were significantly older than the female patients ($P < 0.001$).

Sites of cancer and stage in all patients

Among 26,235 patients, 1934 had two or more cancer sites, with male and female patients having 15,949 and 12,402 sites, respectively (Table 1). The top five cancer sites were the lung, stomach, prostate, colon and rectum, and esophagus in male patients and the breast, stomach, lung, uterus,

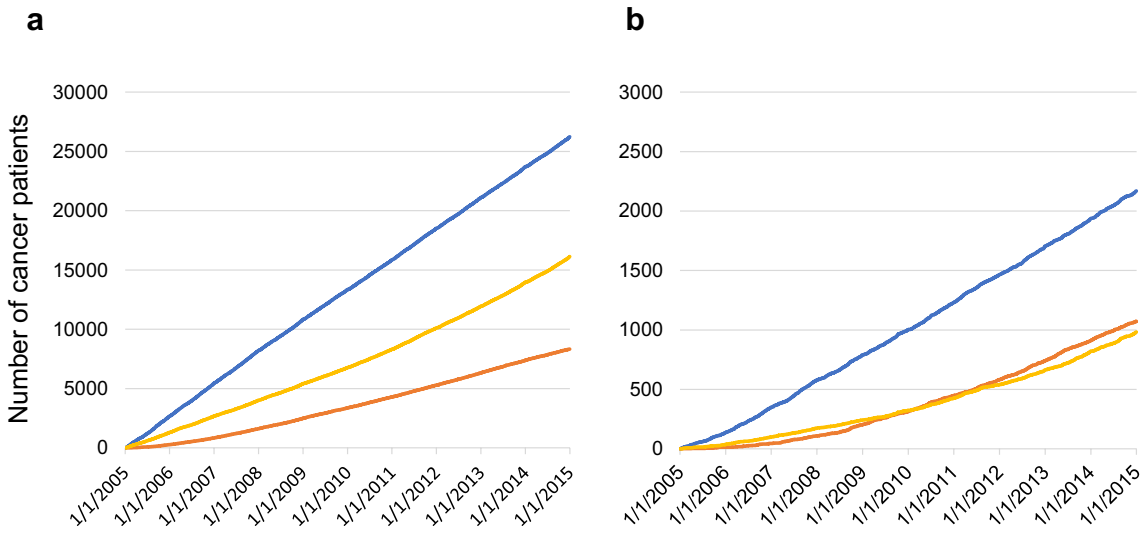


Fig. 1 Cumulative number of patients from January 1, 2005, to January 1, 2015, for all cancer patients (**a**) and for cancer patients with cardiovascular disease (**b**). The blue line represents de novo cancer patients, the yellow line represents survivors, and the orange line represents deceased patients

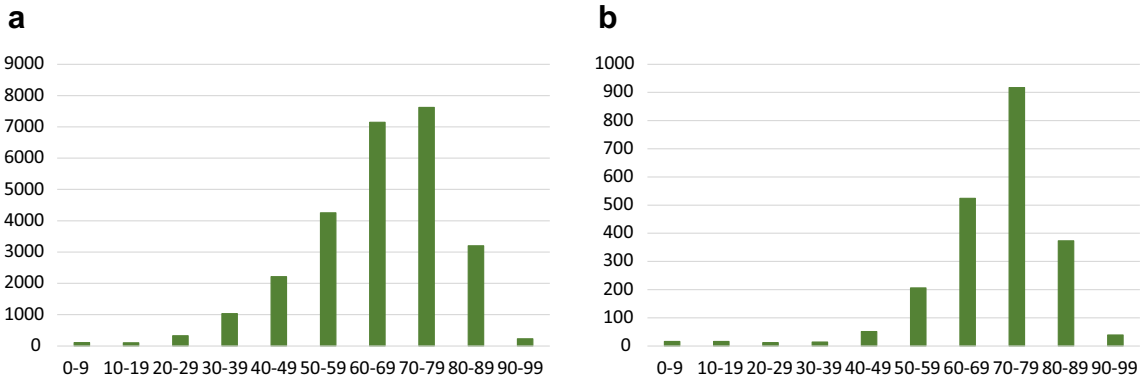


Fig. 2 Distribution of all cancer patients (**a**) and cancer patients with cardiovascular disease (**b**) according to age groups

and colon and rectum in female patients. Cancer sites, including the breast, uterus, ovary, and thyroid, showed female predominance; other sites showed male predominance. Cancer stage was more advanced in male than in female patients ($P < 0.001$).

Comorbidities of CVD

Among all patients, 10.5% of male and 5.6% of female patients had CVD (Table 1). The number of male patients with LVSD, LVDD, AF, IHD, and elevation of NT-proBNP was significantly larger. The occurrence of AS and VTE was similar between the sexes.

Survival outcomes

During the 3.7 ± 2.9 years of follow-up (median 3.0 years), 8334 of all cancer patients died, while 1074 cancer patients with CVD died. The 5-year survival rate was 64.0% for all cancer patients and 44.2% for cancer patients with CVD. Five-year survival rates in each cancer and CVD are shown in Table 3. The survival curves of cancer patients with and without each CVD are shown in Fig. 3. In male patients, significantly worse prognoses were observed in patients with AF, VTE, and elevation of NT-proBNP than in patients without these CVDs, whereas in female patients, significantly worse prognoses were observed in those with all CVD except IHD than in those without those CVDs. Regarding the cause of death, majority of patients died of cancer: 69% of males and 75% of females, respectively (Fig. 4). CVD death was observed in 2.3% of male cancer

Table 1 Characteristics of cancer patients between 2005 and 2014

	Male ($N=14,378$)	Female ($N=11,857$)	P value
Age (years)	67.7 ± 12.6	61.0 ± 15.6	< 0.001
Hight (cm)	164.7 ± 7.0	153.9 ± 6.9	< 0.001
Weight (kg)	61.5 ± 10.6	52.9 ± 9.5	< 0.001
Body mass index (kg/m^2)	22.6 ± 3.3	22.3 ± 3.7	< 0.001
Laboratory data			
Hemoglobin (g/dL)	13.1 ± 2.2	12.3 ± 1.7	< 0.001
Total protein (g/dL)	7.0 ± 0.6	7.0 ± 0.6	0.330
Albumin (g/dL)	3.9 ± 0.6	4.1 ± 0.5	0.001
Total bilirubin (mg/dL)	0.8 ± 0.8	0.8 ± 1.1	0.892
Creatinine (mg/dL)	0.9 ± 0.3	0.7 ± 0.2	< 0.001
Total cholesterol (mg/dL)	180.6 ± 41.0	201.5 ± 40.4	< 0.001
LDL-cholesterol (mg/dL)	107.3 ± 35.0	118.0 ± 28.6	0.099
Site(s) of cancer	15,949 (100)	12,402 (100)	
Oral cavity and pharynx	339 (2.1)	106 (0.9)	< 0.001
Esophagus	1022 (6.4)	174 (1.4)	< 0.001
Stomach	2791 (17.5)	1281 (10.3)	< 0.001
Colon and rectum	1676 (10.5)	1045 (8.4)	< 0.001
Liver	280 (1.8)	99 (0.8)	< 0.001
Gallbladder and bile duct	217 (1.4)	130 (1.0)	0.018
Pancreas	394 (2.5)	269 (2.2)	0.096
Larynx	253 (1.6)	14 (0.1)	< 0.001
Lung	3019 (18.9)	1268 (10.2)	< 0.001
Skin	389 (2.4)	376 (3.0)	< 0.001
Breast	8 (0.1)	3198 (25.8)	< 0.001
Uterus	0 (0.0)	1123 (9.1)	
Ovary	0 (0.0)	443 (3.6)	
Prostate	2237 (14.0)	0 (0.0)	
Urinary bladder	925 (5.8)	240 (1.9)	< 0.001
Kidney and ureter	616 (3.9)	269 (2.2)	< 0.001
Brain	37 (0.2)	40 (0.3)	0.146
Thyroid gland	178 (1.1)	426 (3.4)	< 0.001
Lymphoma	472 (3.0)	387 (3.1)	0.432
Myeloma	104 (0.7)	74 (0.6)	0.558
Leukemia	275 (1.7)	154 (1.2)	< 0.001
Other and unspecified primary sites	717 (4.5)	1286 (10.4)	< 0.001
Cancer stage			
0	699 (4.9)	1433 (12.1)	< 0.001
I	4848 (33.7)	4546 (38.3)	
II	2722 (18.9)	2240 (18.9)	
III	2425 (16.9)	1587 (13.4)	
IV	2824 (19.6)	1353 (11.4)	
Not staged	860 (6.0)	698 (5.9)	
Cardiovascular comorbidities			
Cardiovascular disease	1509 (10.5)	659 (5.6)	< 0.001
Systolic dysfunction	205 (1.4)	77 (0.6)	< 0.001
Diastolic dysfunction	226 (1.6)	113 (1.0)	< 0.001
Atrial fibrillation	709 (4.9)	189 (1.6)	< 0.001
Ischemic heart disease	289 (2.0)	50 (0.4)	< 0.001
Aortic stenosis	51 (0.4)	60 (0.5)	0.060
Venous thromboembolism	259 (1.8)	232 (2.0)	0.356
NT-proBNP > 900 pg/mL	260 (1.8)	162 (1.4)	0.005
NT-proBNP (pg/mL)	1852 ± 162	1439 ± 196	< 0.001

Values are presented as number of subjects and percentage. Age, height, weight, and body mass index are presented as mean ± SD. Height, weight, and body mass index were measured in adult cancer patients. The listed NT-proBNP are presented as mean ± SE. P values indicate differences in the aforementioned variables between men and women

NT-pro BNP N-terminal pro-brain natriuretic peptide

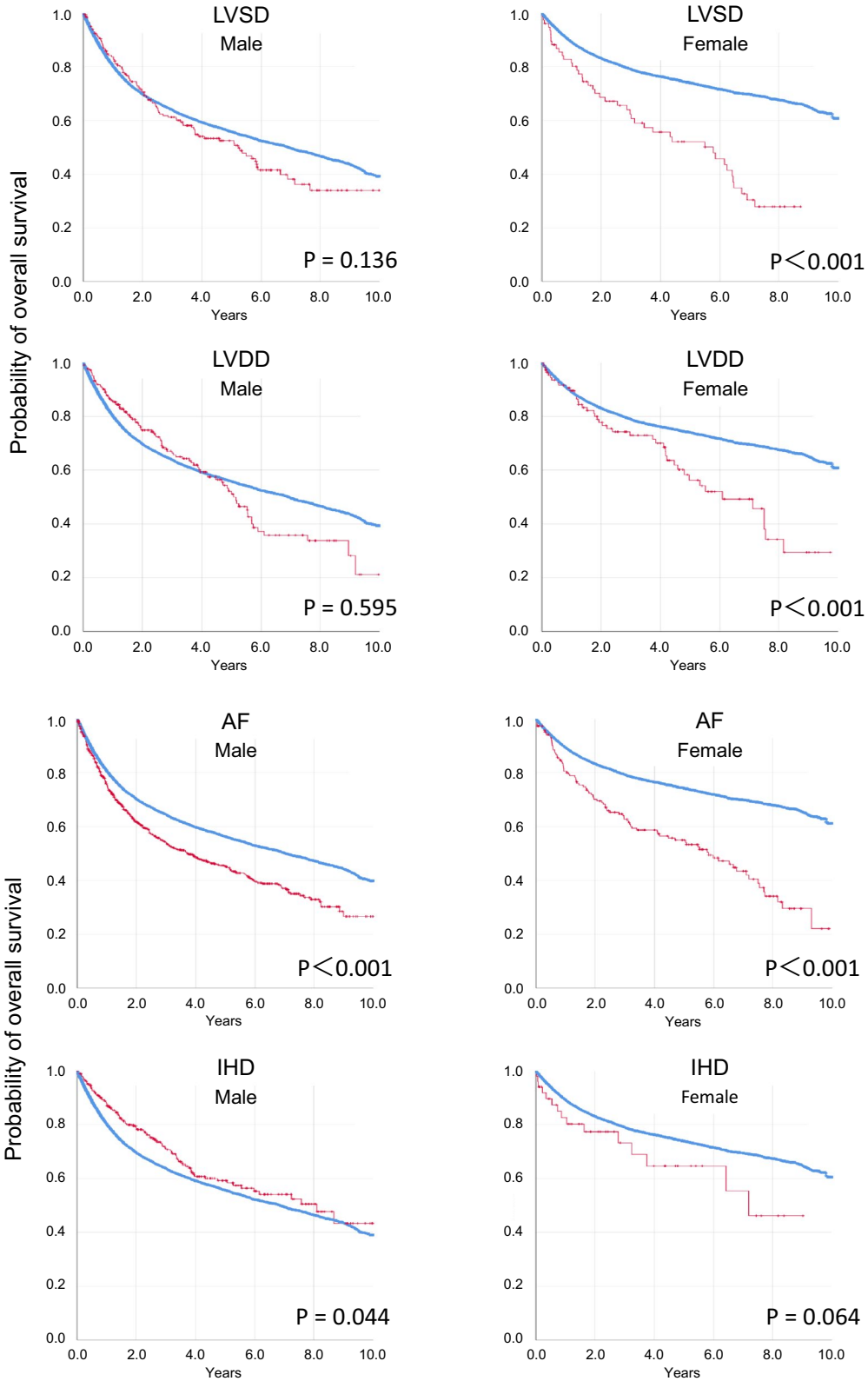


Fig. 3 Kaplan–Meier estimates of overall survival in cancer patients with or without CVD. The blue line represents cancer patients without CVD, and the red line represents cancer patients with CVD. *AF* atrial fibrillation; *AS* aortic stenosis; *CVD* cardiovascular disease; *IHD* ischemic heart disease; *LVDD* left ventricular diastolic dysfunction; *LVSD* left ventricular systolic dysfunction; *NT-proBNP* N-terminal pro-brain natriuretic peptide; *VTE* venous thromboembolism

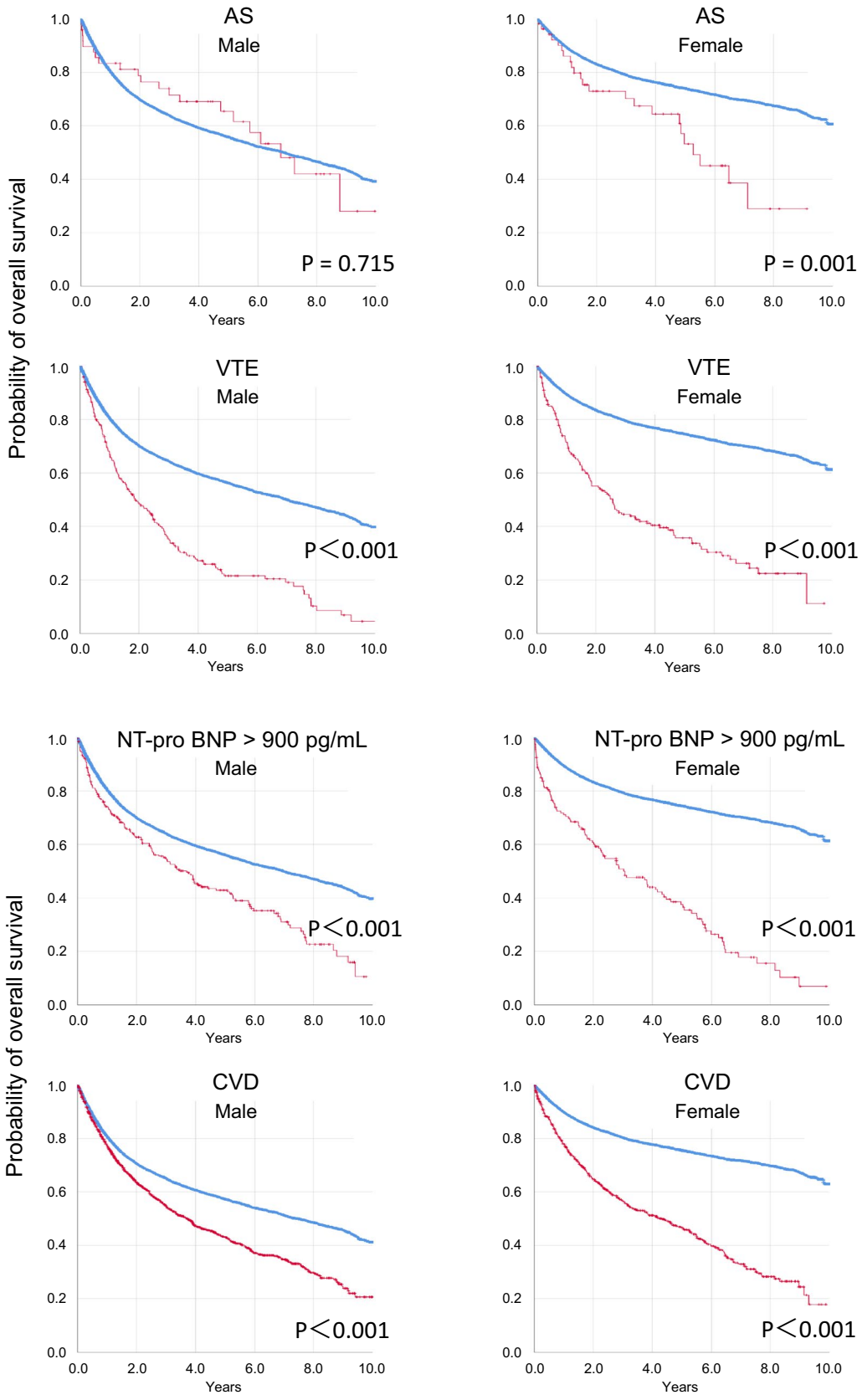


Fig. 3 (continued)

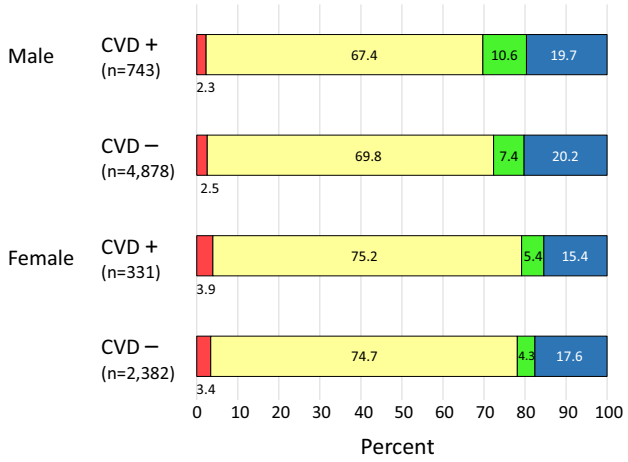


Fig. 4 Proportion of cause of death stratified by sex and cardiovascular disease (CVD) comorbidity. The number shown in each bar represents the proportion (%) of each cause (red, CVD death; yellow, cancer death; green, non-CVD and cancer death; and blue, unknown cause due to unavailable death certificates). CVD + represents cancer patients with CVD, and CVD − represents cancer patients without CVD. Number in (*n*) represents number of deceased patients

patients with CVD and 3.9% of female cancer patients with CVD, respectively.

Predictors of mortality

Older age at cancer diagnosis, lower body mass index, more advanced stage of cancer, and VTE were independently associated with mortality in both sexes (Table 2). Moreover, AF and NT-proBNP elevation were independently associated with mortality in male and female patients, respectively. Cox proportional hazards analysis adjusting for age, cancer stage, and body mass index revealed that AF [hazard ratio (HR) 1.219, 95% confidence interval (CI) 1.011–1.470, males; $P = 0.038$], VTE (HR 1.517, 95% CI 1.154–1.995, males; $P = 0.003$ and HR 2.089, 95% CI 1.568–2.781, females; $P < 0.001$), and NT-proBNP elevation (HR 1.861, 95% CI 1.247–2.778, females; $P = 0.002$) were significantly associated with death.

Sites of cancer and survival rate in survivors by January 1, 2015

Among 16,130 survivors, 1121 survivors had two or more cancer sites (male 8712; female 8539 sites) (Table 3). The top five cancer sites were the prostate, stomach, lung, colon and rectum, and urinary bladder in male patients and the breast, stomach, uterus, lung, and colon and rectum in female patients. The survival rate from cancer diagnosis by January 1, 2015, was higher in female than in male patients (69 and 55%, respectively; $P < 0.001$). Concerning most cancer sites, and compared to male patients, female patients had

Table 2 Variables independently associated with mortality for (a) males and (b) females

	Univariate analysis			Multivariate analysis		
	HR	95% CI of HR	*P* value	HR	95% CI of HR	*P* value
(a)						
Age (per 1 year increase)	1.027	1.025–1.030	< 0.001	1.041	1.036–1.046	< 0.001
Body mass Index (per 1 increase)	0.895	0.882–0.909	< 0.001	0.916	0.902–0.930	< 0.001
Stage (per I stage increase)	1.976	1.928–2.025	< 0.001	1.869	1.796–1.946	< 0.001
Atrial fibrillation	1.405	1.264–1.561	< 0.001	1.219	1.011–1.470	0.038
Ischemic heart disease	0.816	0.669–0.995	0.038			
Venous thrombo -embolism	2.316	1.983–2.705	< 0.001	1.517	1.154–1.995	0.003
NT-proBNP > 900 pg/mL	1.581	1.348–1.853	< 0.001			
(b)						
Age (per 1 year increase)	1.042	1.039–1.045	< 0.001	1.039	1.033–1.044	< 0.001
Body mass Index (per 1 increase)	0.895	0.882–0.909	< 0.001	0.940	0.922–0.959	< 0.001
Stage (per I stage increase)	2.499	2.410–2.591	< 0.001	2.373	2.233–2.521	< 0.001
Systolic dysfunction	2.533	1.896–3.439	< 0.001			
Diastolic dysfunction	1.783	1.324–2.402	< 0.001			
Atrial fibrillation	2.247	1.834–2.754	< 0.001			
Ischemic heart disease	1.608	0.968–2.670	0.067			
Aortic stenosis	2.023	1.342–3.049	0.001			
Venous thrombo-embolism	3.470	2.888–4.170	< 0.001	2.089	1.568–2.781	< 0.001
NT-proBNP > 900 pg/mL	3.684	3.039–4.465	< 0.001	1.861	1.247–2.778	0.002

HR hazard ratio; *CI* confidence interval; *NT-pro BNP* N-terminal pro-brain natriuretic peptide

Table 3 Cancer survivors on January 1, 2015 and their CVD diagnosed by January 1, 2015

	Males ($N=7936$)		Females($N=8194$)		P value
		5-year survival rate		5-year survival rate	
Age (years)	70.2 ± 12.9		63.8 ± 15.0		< 0.001
Site(s) of cancer	8712 (100)		8539 (100)		
Oral cavity and pharynx	138 (1.6)	0.42	56 (0.7)	0.62	0.002
Esophagus	379 (4.4)	0.33	94 (1.1)	0.54	< 0.001
Stomach	1685 (19.3)	0.66	870 (10.2)	0.75	< 0.001
Colon and rectum	1056 (12.1)	0.67	684 (8.0)	0.70	0.086
Liver	69 (0.8)	0.24	23 (0.3)	0.26	0.810
Gallbladder and bile duct	72 (0.8)	0.28	53 (0.6)	0.40	0.442
Pancreas	60 (0.7)	0.07	51 (0.6)	0.08	0.972
Larynx	158 (1.8)	0.75	11 (0.1)	0.90	0.680
Lung	1111 (12.8)	0.31	765 (9.0)	0.56	< 0.001
Skin	279 (3.2)	0.77	256 (3.0)	0.75	0.928
Breast	4 (0.0)	0.86	2699 (31.6)	0.89	0.063
Uterus	0 (0.0)		800 (9.4)	0.78	
Ovary	0 (0.0)		291 (3.4)	0.72	
Prostate	1761 (20.2)	0.82	0 (0.0)		
Urinary bladder	614 (7.0)	0.69	139 (1.6)	0.62	0.074
Kidney and ureter	385 (4.4)	0.61	177 (2.1)	0.68	0.332
Brain	5 (0.1)	0.21	15 (0.2)	0.27	0.034
Thyroid gland	132 (1.5)	0.88	351 (4.1)	0.90	0.159
Lymphoma	255 (2.9)	0.54	247 (2.9)	0.67	0.007
Myeloma	50 (0.6)	0.46	31 (0.4)	0.34	0.096
Leukemia	117 (1.3)	0.43	70 (0.8)	0.45	0.443
Other and unspecified primary sites	382 (4.4)	0.61	856 (10.0)	0.82	< 0.001
Cardiovascular disease	693 (8.7)	0.43	289 (3.5)	0.47	0.676
Systolic dysfunction	104 (1.3)	0.53	32 (0.4)	0.52	0.677
Diastolic dysfunction	125 (1.6)	0.51	65 (0.8)	0.56	0.291
Atrial fibrillation	316 (4.0)	0.45	86 (1.0)	0.55	0.083
Ischemic heart disease	195 (2.5)	0.59	33 (0.4)	0.65	0.931
Aortic stenosis	31 (0.4)	0.65	36 (0.4)	0.53	0.493
Venous thromboembolism	78 (1.0)	0.22	78 (1.0)	0.36	0.025
NT-proBNP > 900 pg/mL	108 (1.4)	0.43	59 (0.7)	0.38	0.090
NT-proBNP (pg/mL)	1355 ± 197		804 ± 130		< 0.001

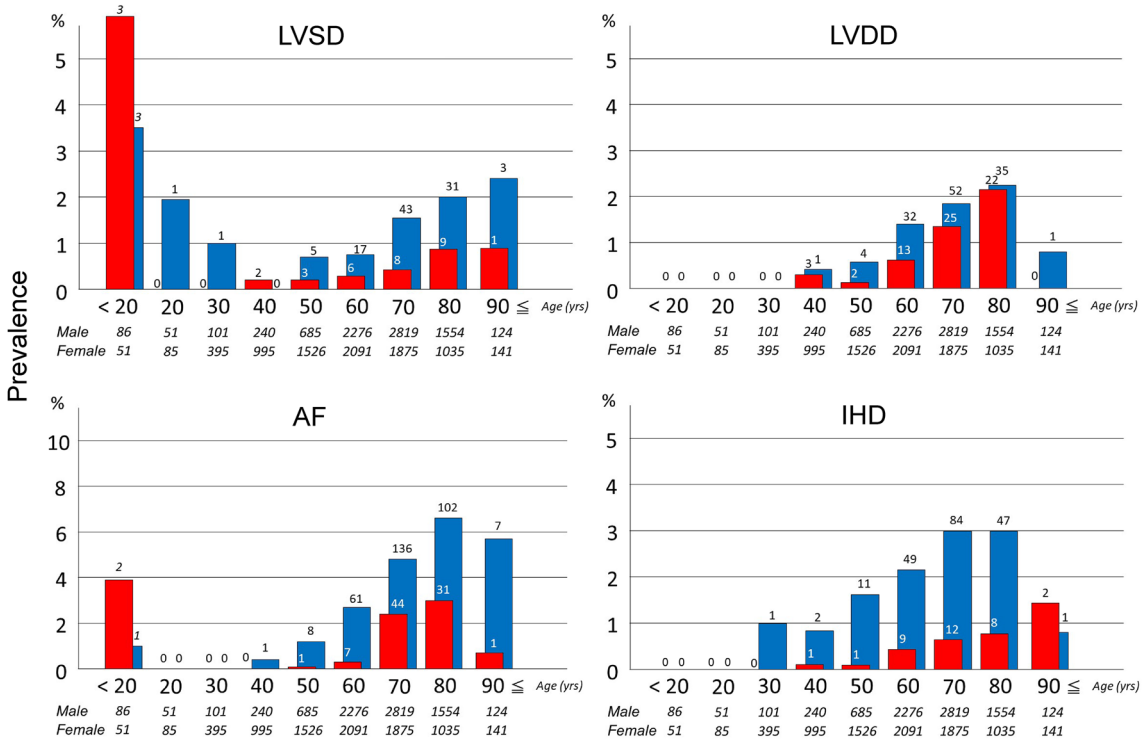
NT-pro BNP N-terminal pro-brain natriuretic peptide

Values are presented as number of subjects and percentage. Age is presented as mean ± SD. NT-proBNP is presented as mean ± SE. 5-year-survival rate was calculated from cancer diagnosis to any event by January 1, 2015, using the Kaplan–Meier method in all cancer patients including survivors of each cancer site. *P* values indicate differences in survival rate between men and women

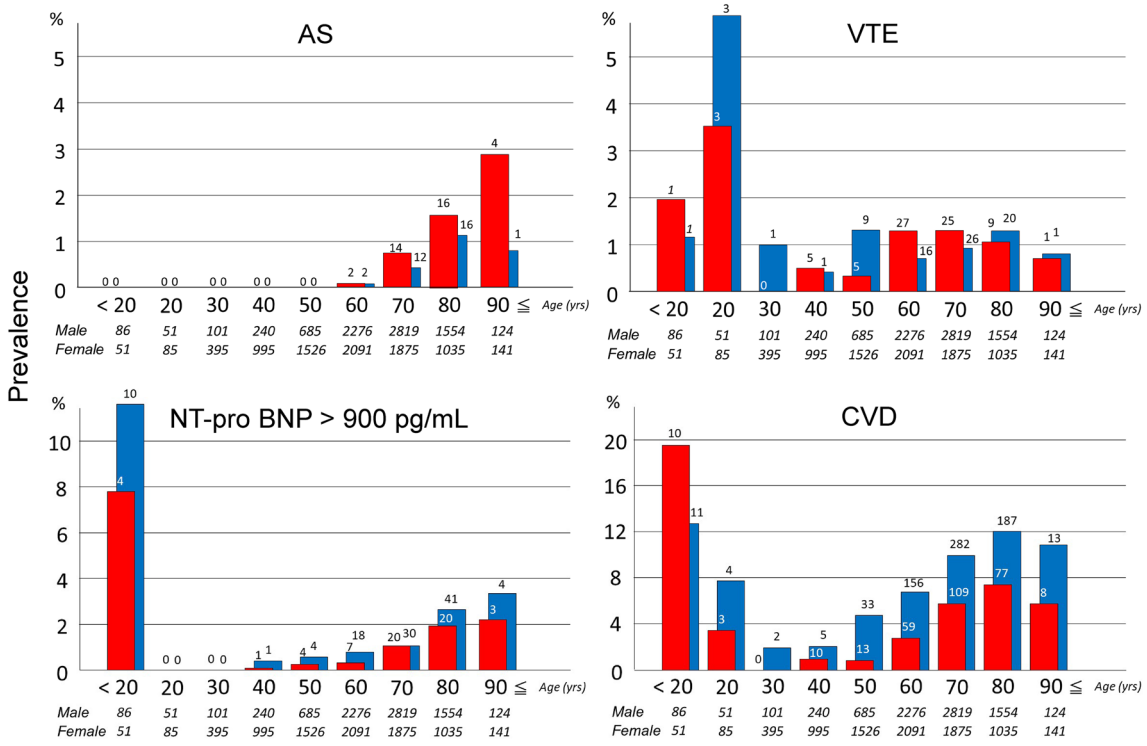
a better survival; however, female patients with CVD did not have a superior survival. Particularly, the survival rate in cancer patients with VTE or NT-proBNP > 900 pg/mL was lower than in those with other CVD in both sexes.

Prevalence of CVD patients among survivors in relation to age and sex

The prevalence of LVSD in adults increased progressively with age, with the prevalence in male patients consistently greater than that in female patients in the same age group (Fig. 5). Similar findings were observed in LVDD, AF, IHD, and NT-proBNP elevation. However, VTE was observed to be almost equal based on age group and sex; AS increased progressively with age and occurred more in female than in male patients. Although the incidence of childhood and adolescent cancers were low, LVSD, VTE, and elevation of NT-proBNP were frequently observed. Generally, CVD increased progressively with age and with male dominance, reaching 12.1% for male survivors and 7.5% for female



Cancer patients stratified by age and gender (n=16,130)



Cancer patients stratified by age and gender (n=16,130)

◂**Fig. 5** The prevalence of cancer patients with cardiovascular disease (CVD) in different age groups. The number shown at the upper end of each bar represents the count of patients with CVD, and the numbers below each age range along the horizontal axis represent the male and female cancer patients for that range. *AF* atrial fibrillation; *AS* aortic stenosis; *CVD* cardiovascular disease *IHD* ischemic heart disease; *LVDD* left ventricular diastolic dysfunction; *LVSD* left ventricular systolic dysfunction; *NT-proBNP* N-terminal pro-brain natriuretic peptide; *VTE* venous thromboembolism

survivors. The prevalence in men (≥ 70 years old) vs women (≥ 70 years old) among survivors (as of January 1, 2015) was as follows: LVSD 1.7% vs 0.6%; LVDD 2.0% vs 1.5%; AF 5.4% vs 2.5%; IHD 2.9% vs 0.7%; AS 0.7% vs 1.1%; VTE 1.0% vs 1.2%; elevation of NT-proBNP 1.7% vs 1.4%, and CVD 10.7% vs 6.4% (data not shown).

Prevalence of CVD patients among survivors in each cancer

The prevalence of CVD was different among cancer sites (Table 4). In men, LVD prevalence was significantly higher in the urinary bladder and myeloma than in other cancer sites. AF prevalence was significantly higher in the liver, pancreas, lung, and urinary bladder than in other cancer sites. VTE prevalence was higher in the esophagus than in other cancer sites. The pancreas has the highest VTE prevalence in cancer sites, but the number of pancreatic cancer was so small that it was not significant ($P = 0.071$). In women, LVD prevalence was significantly higher in myeloma and leukemia than in other cancer sites. AF prevalence was significantly higher in the esophagus, larynx, lung, and lymphoma than in other cancer sites. VTE prevalence was significantly higher in the colon and rectum, uterus, ovary, kidney and ureter, lymphoma, and leukemia than in other cancer sites.

Discussion

Comorbid CVD is a burden on cancer patients [1]. CVD progression often results in acute HF, MI, PTE, stroke, cardiogenic shock, syncope, or arrhythmia, which could prove lethal or lead to serious disability. Therefore, close observation, medications, or interventions are needed concurrently with cancer therapy. However, there is no epidemiological data on the burden of CVD among cancer patients in Japan. We selected seven CVDs that required sustained surveillance or medication, if once diagnosed with these CVDs. Because transient LVD, elevation of NT-proBNP, AF, and proximal VTE were significant predictors of HF, death, stroke, and recurrence of VTE, respectively, these CVD burdens are sustained like chronic disease [10, 11, 14–17, 20, 25–31]. We utilized the nature of these CVDs and counted the prevalence of CVD in January 2015. From this study, we made the following new observations: (1) CVD prevalence in male and female elderly cancer patients reached 12.1 and 7.5%, respectively; (2) there were sex and age differences in the number of cancer patients with CVD; and (3) the prognosis of patients with any CVD was worse than that of patients without CVD; in particular, AF, VTE, and high NT-proBNP were independent predictors of death.

LVD prevalence in our cancer cohort was a slightly higher than those in the Sado Heart Failure study, evaluated in a general hospital cohort in Sado Island [15]. The prevalence of LVSD in our cancer cohort was similar to that in the Sado cohort. However, the prevalence of LVDD in our cancer cohort (1.7% in men and 0.9% in women) was larger than that in the Sado cohort (0.9% in men and 0.5% in women) [16].

Patients with resolved AF were reported to remain at a higher risk of stroke than patients without AF [17]. The risk was increased even in those in whom recurrent AF was not documented [17]. The prevalence of AF in the Japanese general population increases with age and is higher in men than in women [18, 19]. Inoue et al. reported that in patients aged 40 years or more, men had three times (1.35 vs 0.43%) the AF prevalence of women [18]. In our study, however, AF prevalence in those aged 40 years or more was 4.1% for men and 1.1% for women and was higher than in the previous report. Although a precise comparison with the previous report is not feasible because of the different methods of assessment and cohort types (general population vs hospital patients), our cancer patients may have a higher prevalence of AF. Surgery, infection, inflammation, common risk factors between cancer and AF, and cancer-derived factors might trigger AF in cancer patients.

The prevalence of IHD in our patients was not as high as that in Western communities. The prevalence of IHD in the US general population aged 18 years or more was reported to be 5.6% for non-Hispanic whites and 3.3% for Asians [20]. Our Japanese cancer cohort showed a prevalence of 2.5% in men, 0.4% in women, and 1.4% overall; our prevalence was lower than that among Asians in the US. This occurrence is probably due to the much lower incidence of MI in Japan (one-tenth) compared to that in Western countries [21, 22].

AS is the most common valvular heart disease in cancer patients undergoing cancer treatment. Severe AS often causes angina, syncope, HF, or sudden death during cancer therapy [14]. The prevalence in our study, i.e., 0.5% for men and 0.7% for women, in cancer patients over 60 years old, was less than the 3% in the US general population [23]. Sex differences are reported in CVD [24] and male dominance was observed in our cancer patients. Contrary to other CVD, AS was dominant in female patients. Breast and gynecologic oncologists should auscultate the patient's heart for AS, for those aged 70 years or more.

Table 4 Prevalence of each CVD in each cancer site (a) males and (b) females

	Number of patients	LVSD	LVDD	AF	IHD	AS	VTE	NT-proBNP > 900 pg/mL	Any CVD
(a)									
All	7936	1.31	1.58	3.98	2.46	0.39	0.98	1.36	8.73
Oral cavity and pharynx	138	1.45	4.35*	4.35	0.72	0.00	1.45	1.45	10.87
Esophagus	379	1.32	1.32	5.01	5.54	0.00	2.37*	3.17*	15.04*
Stomach	1685	0.95	1.72	3.74	3.20	0.42	0.65	1.31	8.49
Colon and rectum	1056	1.33	2.27	4.07	3.31	0.38	1.33	1.70	9.85
Liver	69	1.45	1.45	11.59*	4.35	1.45	0.00	4.35	14.49
Gallbladder and bile duct	72	0.00	2.78	5.56	1.39	2.78*	1.39	2.78	9.72
Pancreas	60	0.00	5.00*	11.67*	5.00	0.00	3.33	3.33	18.33*
Larynx	158	1.27	1.90	3.16	5.06	0.63	1.27	0.63	10.76
Lung	1111	1.80	1.26	5.31*	3.15	0.45	0.99	1.89	10.53
Skin	279	0.72	0.72	3.94	0.36*	0.36*	0.00	1.43	6.09
Prostate	1761	1.14	0.80*	3.46	1.59*	0.34	0.57*	0.68*	6.87*
Urinary bladder	614	2.44*	3.91*	5.86*	3.26	1.47*	0.65	1.14	12.87*
Kidney and ureter	385	1.30	2.60	4.16	2.86	0.26	1.30	1.30	9.35
Thyroid gland	132	0.76	0.76	2.27	1.52	0.00	1.52	0.00	4.55
Lymphoma	255	1.18	1.96	3.92	2.75	0.00	1.96	1.57	9.80
Myeloma	50	8.00*	6.00*	8.00	4.00	0.00	0.00	8.00*	22.00*
Leukemia	117	5.13*	0.85	1.71	1.71	1.71*	0.00	12.82*	15.38*
Other and unspecified primary sites	382	1.05	0.52	1.05*	1.05*	0.26	2.62*	0.52	4.71*
(b)									
All	8194	0.39	0.79	1.05	0.40	0.44	0.95	0.72	3.53
Oral cavity and pharynx	56	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Esophagus	94	1.06	1.06	5.32*	2.13*	1.06	2.13	1.06	9.57*
Stomach	870	0.11	0.80	0.80	0.23	0.46	0.34*	0.34	2.64
Colon and rectum	684	0.58	1.02	1.61	0.73	0.00	2.49*	1.02	5.99*
Liver	23	0.00	4.35	0.00	0.00	4.35*	0.00	0.00	4.35
Gallbladder and bile duct	53	1.89	1.89	3.77	1.89	0.00	0.00	0.00	3.77
Pancreas	51	0.00	1.96	1.96	1.96	0.00	0.00	1.96	3.92
Larynx	11	0.00	0.00	9.09*	9.09*	0.00	0.00	0.00	18.18*
Lung	765	0.26	0.52	2.09*	0.39	0.78	0.52	0.65	4.18
Skin	256	0.00	0.39	1.56	0.00	2.34*	0.00	0.00	2.34
Breast	2699	0.37	0.82	0.74*	0.30	0.33	0.33*	0.48	2.70*
Uterus	800	0.13	1.38	1.13	0.50	0.13	2.00*	0.75	4.25
Ovary	291	1.03	0.69	1.03	2.06	0.00	3.44*	2.75	8.25*
Urinary bladder	139	0.72	0.72	1.44	0.00	0.72	0.72	0.00	4.32
Kidney and ureter	177	0.56	2.26*	0.56	0.00	1.69*	2.82*	0.56	6.21
Brain	15	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Thyroid gland	351	0.00	0.00	0.57	0.00	0.00	0.00	0.00	0.57*
Lymphoma	247	0.40	1.21	2.83*	0.81	1.62*	3.24*	3.64*	8.10*
Myeloma	31	0.00	9.68*	0.00	0.00	0.00	3.23	6.45*	16.13*
Leukemia	70	5.71	2.86	1.43	0.00	0.00	4.29	7.14	18.57
Other and unspecified primary sites	856	0.23	0.23	0.47	0.12	0.35	0.70	0.23	1.64

Numbers listed below each CVD were prevalence of CVD in each cancer site

Asterisks indicate statistical difference of CVD prevalence between each site and other sites ($P < 0.05$)

AF atrial fibrillation; *AS* aortic stenosis; *CVD* cardiovascular disease *IHD* ischemic heart disease; *LVDD* left ventricular diastolic dysfunction; *LVSD* left ventricular systolic dysfunction; *NT-proBNP* N-terminal pro-brain natriuretic peptide; *VTE* venous thromboembolism

Cancer-associated VTE is a huge burden for cancer patients because VTE is a poor prognostic factor and causes post-thrombotic syndrome [25–28]. The incidence of cancer-associated VTE ranges from 4% to as high as 20% in the US [25, 26]. VTE prevalence in our survivors was 1.1% and was not as high as the prevalence in the US [26]. This low prevalence was consistent with a report by Sakuma et al., who reported lower incidence of PTE (one-eighth) and DVT (one-fourth) in Japan compared with those in Western countries [28]. Contrary to other CVDs listed here, the prevalence of VTE did not increase with age. VTE was an independent predictor of mortality in both sexes in our study. Accordingly, all medical staff should be aware that VTE can occur in every cancer patient regardless of age or sex. Regular follow-up should be considered for secondary prevention.

The measurement of NT-proBNP has diagnostic and prognostic value in non-HF as well as HF [10, 12, 29–31]. B-type natriuretic peptide plasma levels are reported to be stronger predictors of death in women than in men [31]. Oncologists often measure NT-proBNP when they suspect their patients have HF. The optimal cut-off point to distinguish acute HF from other causes is reported to be 900 pg/mL with a 90% sensitivity and 84% specificity [12, 29]. In our study, the number of cancer patients with NT-proBNP > 900 pg/mL increased with age and showed a slight male dominance. The elevation of NT-proBNP was independently associated with mortality in women in our study. We should treat these patients in synergy with oncologists, carefully and continuously.

The CVD prevalence was different among cancer sites. The prevalence of HF-related CVD, such as LVD and elevation of NT-proBNP, was high in hematologic cancer in men and women. In addition to cardiovascular burden due to disease characteristics (e.g., anemia, hyper-viscosity, renal dysfunction, or amyloidosis), cardiovascular toxicities of chemotherapy, and radiotherapy may increase the prevalence. AF prevalence was high in lung cancer in men and women. Anatomical proximity to the atrium, surgery to the pulmonary vein, and cardiovascular toxicities of chemotherapy and radiotherapy may increase the prevalence. VTE prevalence was high in female abdominal cancers and lymphoma. Anatomical proximity to the inferior vena cava and iliac vein, pelvic surgery, cardiovascular toxicities of chemotherapy, long-term catheter placement in the subclavian vain, and hypercoagulability may increase the prevalence in women.

Analysis of the cause of death did not show significant increase in CVD death in cancer patients with CVD (Fig. 4). Lethal CVD (e.g., cardiac arrest, MI, PE, and stroke) during cancer therapy might be counted as CVD death. However, earlier death due to incomplete cancer therapy in cancer patients with CVD might be counted as cancer death even if CVD affected the decision making for cancer therapy. We speculate that more detailed analysis by prospective study aiming at CVD-related death could have clarified the CVD burden in cancer patients.

A number of limitations of this study must also be considered. First, the study was a retrospective and observational study. A prospective study is preferable for the precise assessment of CVD burden on cancer patients. Second, this was a single-center study. Cancer incidence and death rates vary in Japan. For example, stomach cancer is prevalent in prefectures on the side of Sea of Japan. Population demographics, screening behaviors, socioeconomic factors, and environmental exposures by geographic area cause the disparities [32–35]. We could not control the disparities by this single-center study. Niigata Cancer Center Hospital may not be a representative Japanese cancer center. However, our hospital had a sufficient number of cancer cases for each site, and patients were appropriately diagnosed by cardiologists. We believe we qualified for this exploratory study. Third, we may have underestimated the actual prevalence of CVD in cancer patients because of a selection bias arising from the fact that patients with latent CVD in our hospital are not identified because of their non-referral for examinations. Identifying all CVD cases in all cancer patients was not feasible. However, our results showing the lowest prevalence in 2015 were high enough to bring to the attention patients and caregivers.

Cancer survivors with CVD are increasing. One in ten elderly survivors has serious CVD. We recommended behavioral change for cancer patients (e.g., smoking cessation, reducing alcohol intake, reducing sodium intake to appropriate quantity, and maintaining appropriate body weight), use of self-monitoring device for blood pressure, heart rate and heart rhythm, medical check-up for risk assessment of CVD, and adherence to therapy for CVD as well as cancer. We also suggest that healthcare practitioners caring for cancer patients should recognize the presence of CVD, closely monitor patients with CVD markers (e.g., D-dimer, NT-proBNP, LDL-cholesterol, and hemoglobin A1c), and provide medications or interventions concurrently with cancer therapy.

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Compliance with ethical standards

Conflict of interest No author has any conflict of interest.

References

1. Edwards BK, Noone AM, Mariotto AB et al (2014) Annual Report to the Nation on the status of cancer, 1975–2010, featuring prevalence of comorbidity and impact on survival among persons with lung, colorectal, breast, or prostate cancer. Cancer 120:1290–1314
2. Mortality by cause of death (2018) Statistics Bureau, Ministry of internal affairs and communications. http://www.stat.go.jp/data/sekai/0116.htm#c14. Accessed July 2018
3. Eyre H, Kahn R, Robertson RM et al (2004) Preventing cancer, cardiovascular disease, and diabetes: a common agenda for the American Cancer Society, the American Diabetes Association, and the American Heart Association. Circulation 109:3244–3255
4. American Cancer Society Cancer Facts & Figs (2017) American Cancer Society, Atlanta. https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2017.html. Accessed July 2018
5. Goff DC Jr, Lloyd-Jones DM, Bennett G, American College of Cardiology/American Heart Association Task Force on Practice Guidelines et al (2014) 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 129:S74–S75
6. Timp JF, Braekkan SK, Versteeg HH et al (2013) Epidemiology of cancer-associated venous thrombosis. Blood 122:1712–1723
7. Floyd JD, Nguyen DT, Lobins RL et al (2005) Cardiotoxicity of cancer therapy. J Clin Oncol 23:7685–7696
8. Ten years survival of cancer patients in hospital group of Japanese Association of Clinical Cancer Centers (2016) Press release published by National Cancer Center Japan in January 26. https://www.ncc.go.jp/jp/information/pr_release/2016/0120/index.html. Accessed July 2018 **(Japanese)**
9. Paulus WJ, Tschöpe C, Sanderson JE et al (2007) How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J 28:2539–2550
10. Tsutsui H, Isobe M, Ito H, JCS Joint Working Group et al (2017) Guidelines for diagnosis and treatment of acute and chronic heart failure (JCS 2017/JHFS 2017). http://www.j-circ.or.jp/guideline/pdf/JCS2017_tsutsui_h.pdf. Accessed July 2018 **(Japanese)**
11. Okita Y, Okada K, Otsuji Y, JCS Joint Working Group et al (2012) Guidelines for surgical and interventional treatment of valvular heart disease (JCS 2012). http://www.j-circ.or.jp/guideline/pdf/JCS2012_ookita_h.pdf. Accessed January 2018 **(Japanese)**
12. Januzzi JL, van Kimmenade R, Lainchbury J et al (2006) NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study. Eur Heart J 27:330–337
13. Takayama T, Okura Y, Okada Y et al (2015) Characteristics of neoplastic cardiac tamponade and prognosis after pericardio-centesis: a single-center study of 113 consecutive cancer patients. Int J Clin Oncol 20:872–877
14. Okura Y, Ishigaki S, Sakakibara S, et al. (2018) Prognosis of cancer patients with aortic stenosis under optimal cancer therapies and conservative cardiac treatments: a single cancer center study with 92 consecutive patients. Int heart J. https://doi.org/10.1536/ihj.17-320 **(in press)**
15. Okura Y, Ohno Y, Suzuki K et al (2007) Characterization of outpatients with systolic dysfunction in a Japanese community by total enumeration. Circ J 71:1004–1012
16. Okura Y, Ohno Y, Ramadan MM et al (2007) Characterization of outpatients with isolated diastolic dysfunction and evaluation of the burden in a Japanese community: Sado Heart Failure Study. Circ J 71:1013–1021
17. Adderley NJ, Nirantharakumar K, Marshall T (2018) Risk of stroke and transient ischaemic attack in patients with a diagnosis of resolved atrial fibrillation: retrospective cohort studies. BMJ 361:k1717. https://doi.org/10.1136/bmj.k1717
18. Inoue H, Fujiki A, Origasa H et al (2009) Prevalence of atrial fibrillation in the general population of Japan: an analysis based on periodic health examination. Int J Cardiol 137:102–107
19. Akao M, Chun YH, Wada H et al (2013) Current status of clinical background of patients with atrial fibrillation in a community-based survey: the Fushimi AF Registry. J Cardiol 61:260–266
20. Benjamin EJ, Blaha MJ, Chiuve SE, American Heart Association Statistics Committee and Stroke Statistics Subcommittee et al (2017) Heart disease and stroke statistics-2017 update: a report from the American Heart Association. Circulation 135:e146–e603. https://doi.org/10.1161/CIR.0000000000000485
21. Ueshima H, Sekikawa A, Miura K et al (2008) Cardiovascular disease and risk factors in Asia. A selected review. Circulation 118:2702–2709
22. Kitamura A, Sato S, Naito Y et al (2001) Trends in the incidence of cardiovascular diseases and risk factors among urban and rural Japanese males. Nihon Koshu Eisei Zasshi 48:378–394 **(in Japanese)**
23. Osnabrugge RL, Mylotte D, Head SJ et al (2013) Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. J Am Coll Cardiol 62:1002–1012
24. Tei C, Amano K, Ueno K, JCS Joint Working Group et al (2010). guidelines for gender-specific cardiovascular disease (JCS2010). Circ J 74(Suppl. II). http://www.j-circ.or.jp/guideline/pdf/JCS2010tei.h.pdf. Accessed January 2018 **(Japanese)**
25. Lyman GH (2011) Venous thromboembolism in the patient with cancer: focus on burden of disease and benefits of thromboprophylaxis. Cancer 117:1334–1349
26. Chew HK, Wun T, Harvey D et al (2006) Incidence of venous thromboembolism and its effect on survival among patients with common cancers. Arch Intern Med 166:458–464
27. Nakamura M, Miyata T, Ozeki Y et al (2014) Current venous thromboembolism management and outcomes in Japan. Circ J 78:708–717
28. Sakuma M, Nakamura M, Yamada N et al (2009) Venous thromboembolism-deep vein thrombosis with pulmonary embolism, deep vein thrombosis alone, pulmonary embolism alone. Circ J 73:305–309
29. Chen HH, Colucci WS (2017) Natriuretic peptide measurement in non-heart failure settings. https://www.uptodate.com/contents/natriuretic-peptide-measurement-in-non-heart-failure-settings (December 29, 2017)
30. York MK, Gupta DK, Reynolds CF et al (2018) B-type natriuretic peptide levels and mortality in patients with and without heart failure. J Am Coll Cardiol 71:2079–2088
31. Christ M, Laule-Kilian K, Hochholzer W et al (2006) Gender-specific risk stratification with B-type natriuretic peptide levels in patients with acute dyspnea: insights from the B-type natriuretic peptide for acute shortness of breath evaluation study. J Am Coll Cardiol 48:1808–1812
32. Sobue T, Saika K (2015) The 42nd scientific meeting perspectives of internal medicine; considerations to treatment and care of cancer by internists in the era of increasing cancer mortality 2. Fruits of basic research on Cancer; 1) Cancer epidemiology–trends of cancer statistics based on cancer registry]. Nihon Naika Gakkai Zasshi 104:417–425 **(Japanese)**

33. Hori M, Matsuda T, Shibata A et al (2015) Cancer incidence and incidence rates in Japan in 2009: a study of 32 population-based cancer registries for the Monitoring of Cancer Incidence in Japan (MCIJ) project. Jpn J Clin Oncol 45:884–891
34. Cancer mortality in each prefecture in Japan (2018) Cancer registry and statistics. Cancer Information Service, National Cancer Center, Japan. https://ganjoho.jp/reg_stat/statistics /dl/index .html#survival. Accessed July 2018
35. Matsuda A, Katano K (2012) Cancer mortality in each prefecture. In: Sobue T (ed) Gan Toukei Hakusho 2012. Shinohara shuppan shinsha, Tokyo, pp 15–42 **(Japanese)**