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Research article

Prognostic impact of coexisting cardiovascular disease in patients with cancer: A multicenter retrospective cohort study

Yoshihiro Kuwabara *, Toshitaka Morishima, Haruka Kudo, Chaochen Ma, Mizuki Shimadzu Kato, Shihoko Koyama, Kayo Nakata, Takahiro Tabuchi, Isao Miyashiro

Cancer Control Center, Osaka International Cancer Institute, 3-1-69 Otemae, Chuo-ku, Osaka, 541-8567, Japan

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ABSTRACT

Background: The incidence of malignancy and cardiovascular disease (CVD) is increasing worldwide. However, it is not entirely clear how the coexistence of CVD at the time of cancer diagnosis affects the overall survival of patients with cancer.

Methods and results: We used the cancer registries and administrative claims data of patients diagnosed with cancer at 36 designated cancer care hospitals in Osaka, Japan, from 2010 to 2015. The Cox proportional hazard model was used to examine how coexisting CVD (heart failure [HF], ischemic heart disease, peripheral arterial disease, cerebrovascular accidents, and atrial fibrillation) affected overall survival and the impact of HF severity, as documented by the New York Heart Association (NYHA) classification. Of the 131,701 patients with cancer, 9704 had coexisting CVD. The 3-year survival rates for patients with and without coexisting CVD were 62.9 % and 77.6 %, respectively. The adjusted hazard ratio (aHR) for all-cause mortality for coexisting CVD was 1.47 (95 % confidence interval, 1.41–1.52). Among the CVD subtype, patients with coexisting HF had the poorest prognosis. The aHRs in patients with HF by NYHA classification, using the patients without HF as a reference, were as follows: Class I: 1.33 ($p = 0.217$); II: 1.68 ($p < 0.001$); III: 1.54 ($p = 0.011$); IV: 2.47 ($p < 0.001$).

Conclusion: Coexisting CVD and HF severity at cancer diagnosis is associated with survival in patients with cancer.

1. Introduction

Cardiovascular disease (CVD) and cancer are major public health problems [1,2]. With the aging of the population, the incidence of both diseases and the frequency of patients having both comorbidities are increasing. The condition of CVD includes a variety of different diseases such as heart failure (HF), ischemic heart disease (IHD), peripheral arterial disease (PAD), cerebrovascular accident (CVA), and atrial fibrillation (Afib), and the association between each of these diseases and cancer is receiving increasing attention [3–9].

Patients with HF are reported to have a higher risk of cancer development and death than patients without HF [3–6]. Moreover, IHD has been reported to be associated with the risk of developing cancer [4,7]. Patients with PAD have a higher incidence of

* Corresponding author.
E-mail address: ykuwabara72@gmail.com (Y. Kuwabara).

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vascular-related death and a higher incidence of cancer and mortality compared to those without PAD [10,11]. Patients with CVA have also been reported to be at higher risk of developing cancer [12] and a higher mortality rate [13] than patients without CVA. There have also been several reports on the association between Afib and cancer [8,14]. Particularly, Afib was found to be associated with the risk of cancer in a Danish cohort study, with a higher risk of lung and colorectal cancer in men [8].

However, there are no sufficient data on the prognostic impact of CVD present at the time of cancer diagnosis, with consideration of the primary site and stage of cancer. Furthermore, it is unclear whether the New York Heart Association (NYHA) classification [15], which is widely used to assess HF severity, is also useful as a prognostic indicator for patients with both cancer and HF. Assessing a patient's prognostic risk based not only on the site and stage of cancer but also on the presence, type, and severity of coexisting CVD would lead to more accurate and efficient medical care. Therefore, we aimed to examine the impact of coexisting CVD on the overall survival of Japanese patients with cancer. We also examined whether HF severity, as assessed by the NYHA classification, is associated with the prognosis of patients with HF.

2. Materials and methods

2.1. Data source

This multicenter retrospective cohort study used registry data from the Osaka Cancer Registry (OCR) linked to administrative claims data; Information taken from the OCR included cancer diagnosis and survival status of patients residing in Osaka Prefecture, as well as age, sex, type of cancer, date of cancer diagnosis, last follow-up date, date of death, and stage of cancer (i.e., localized, regional to lymph nodes, regional by direct extension, distant) [16–18]. The administrative claims data were based on Japan's Diagnostic Procedure Combination (DPC) per diem payment system, which governs reimbursement from insurance organizations to acute-care hospitals. Data taken from DPCincluded medication and clinical procedure histories [19,20]. The two data sources were collected from 36 designated cancer care hospitals in Osaka with the support of the Council for Coordination of Designated Cancer Care Hospitals in Osaka. These hospitals are medical facilities certified by national and prefectural governments as having a high level of competence, experience, and leadership in cancer treatment. At the time of admission, data such as body height, weight, and diagnostic disease name based on the International Classification of Diseases 10th revision (ICD-10) codes were recorded in the DPC data. NYHA classes were also recorded for some patients for whom an ICD-10 code for HF was recorded in the categories of main diagnosis, most resource-consuming diagnosis, and second most resource-consuming diagnosis in the DPC system. OCR data were then linked to the DPC data and anonymized thereafter in each hospital. Analyses were performed using an anonymized dataset.

2.2. Study participants

The study included patients diagnosed with cancer between 2010 and 2015. Patients with carcinoma in situ, those with multiple cancers diagnosed with a second primary cancer within two months of their first cancer diagnosis, those aged <20 years or >100 years at the time of cancer diagnosis, and death certificate only (DCO) cases at the time of the first cancer diagnosis were excluded.

The presence or absence of CVD was identified using the diagnostic disease code (ICD-10 code) in the DPC data, and patients with coexisting CVD were defined as patients with a CVD disease code recorded before the cancer diagnosis. We extracted HF (I50), ischemic heart disease (IHD, I20–25), peripheral arterial disease (PAD, I70–79), cerebrovascular accident (CVA, I60–69), and atrial fibrillation (Afib, I48) as CVD [13].

Moreover, patients with a confirmed diagnosis of HF at the time of cancer diagnosis and with NYHA classification in the DPC data were selected to examine the association between NYHA class and prognosis.

2.3. Statistical analysis

Baseline characteristics of the two groups of patients were presented as means and standard deviations for continuous variables and as percentages for categorical variables.

CVD impact on the survival of patients with cancer was analyzed by comparing survival at up to 3 years of follow-up in patients with and without CVD at the time of cancer diagnosis. Kaplan–Meier method and log-rank tests were used to compare the overall survival rates for all patients and by cancer site, with and without CVD at the time of cancer diagnosis. Analyses were first applied to all cancers and then replicated to 22 specific cancer sites based on the ICD-10 classification (Because the tables are large and difficult to read, the main table includes data for all patients and the group of patients with coexisting CVD and shows data for the 14 main cancer sites; complete data including the group of patients without coexisting CVD and all 22 cancer sites are shown in the Supplementary Tables).

Next, hazard ratios (HRs) and 95 % confidence intervals (CIs) were calculated using the Cox proportional hazard model adjusted by age categories (20–49, 50–59, 60–69, 70–79, and 80–99 years), sex, first cancer site (analysis for all cancer sites), stage at diagnosis (localized, regional to lymph nodes, regional by direct extension, distant, unknown), and body mass index (BMI) categories (<18.5, 18.5–24.9, ≥ 25.0 kg/m^2, and not measured).

In patient with HF with reported NYHA classification, the correlation between NYHA classification severity and prognosis was also examined using the same Cox proportional hazard model.

Values of two-tailed $p < 0.05$ were considered significant. All analyses were performed using Stata17 (College Station, Texas, USA).

Ethical approval

This study was approved by the Institutional Review Board of the Osaka International Cancer Institute (approval number:1707105108) and was conducted in accordance with the ethical standards of the Declaration of Helsinki. The dataset, which did not contain personally identifiable information, was obtained from the Osaka Cancer Registry and processed independently in accordance with the Act on Promotion of Cancer Registries.

Table 1
Baseline charcteristics of patients diagnosed with cancer by CVD status, Osaka, Japan, 2010–2015.

	Total	no CVD	Any CVD	HF	IHD	PAD	CVA	Afib
n	131,701	121,997	9704	2952	4119	1526	3002	1456
All-cause mortality, n(%)	35,168 (26.7)	31,469 (25.8)	3699 (38.1)	1259 (42.7)	1457 (35.4)	583 (38.2)	1115 (37.1)	553 (38.0)
Male, n(%)	75,853 (57.6)	68,910 (56.5)	6943 (71.6)	1959 (66.4)	3127 (75.9)	1172 (76.8)	2148 (71.6)	1076 (73.9)
Age category, n(%)								
20–49 years	12,103 (9.2)	11,963 (9.8)	140 (1.4)	57 (1.9)	29 (0.7)	28 (1.8)	33 (1.1)	6 (0.4)
50–59 years	14,187 (10.8)	13,878 (11.4)	309 (3.2)	97 (3.3)	111 (2.7)	48 (3.2)	86 (2.9)	32 (2.2)
60–69 years	37,552 (28.5)	35,627 (29.2)	1925 (19.8)	542 (18.4)	857 (20.8)	317 (20.8)	539 (18.0)	258 (17.7)
70–79 years	45,632 (34.7)	41,394 (33.9)	4238 (43.7)	1162 (39.4)	1899 (46.1)	704 (46.1)	1350 (45.0)	653 (44.9)
80–99 years	22,227 (16.9)	19,135 (15.7)	3092 (31.9)	1094 (37.1)	1223 (29.7)	429 (28.1)	994 (33.1)	507 (34.8)
Stage at diagnosis								
Localized	63,227 (48.0)	59,071 (48.4)	4156 (42.8)	1236 (41.9)	1933 (46.9)	713 (46.7)	1259 (41.9)	637 (43.8)
Regional to lymph nodes	13,207 (10.0)	12,398 (10.2)	809 (8.3)	241 (8.2)	365 (8.9)	145 (9.5)	241 (8.0)	123 (8.5)
Regional by direct extension	21,287 (16.2)	19,701 (16.2)	1586 (16.3)	432 (14.6)	685 (16.6)	235 (15.4)	453 (15.1)	258 (17.7)
Distant	25,682 (19.5)	23,399 (19.2)	2283 (23.5)	698 (23.6)	855 (20.8)	329 (21.6)	769 (25.6)	320 (22.0)
Unknown	8298 (6.3)	7428 (6.1)	870 (9.0)	345 (11.7)	281 (6.8)	104 (6.8)	280 (9.3)	118 (8.1)
BMI category								
<18.5	14,330 (10.9)	13,170 (10.8)	1160 (12.0)	397 (13.5)	377 (9.2)	192 (12.6)	386 (12.9)	170 (11.7)
18.5–24.9	72,083 (54.7)	66,218 (54.3)	5865 (60.4)	1746 (59.2)	2572 (62.4)	954 (62.5)	1802 (60.0)	892 (61.3)
≥25.0	24,644 (18.7)	22,443 (18.4)	2201 (22.7)	650 (22.0)	1035 (25.1)	326 (21.4)	610 (20.3)	342 (23.5)
Not measured	20,644 (15.7)	20,166 (16.5)	478 (5.0)	159 (5.4)	135 (3.3)	54 (3.5)	204 (6.8)	52 (3.6)
Site of Cancer based on the ICD-10 codes								
Esophagus (C15)	4112 (3.12)	3900 (3.2)	212 (2.18)	56 (1.9)	79 (1.92)	38 (2.49)	69 (2.3)	42 (2.88)
Stomach (C16)	19,115 (14.51)	17541 (14.38)	1574 (16.22)	468 (15.85)	719 (17.46)	270 (17.69)	502 (16.72)	236 (16.21)
Colorectum (C18–C20)	17,627 (13.38)	16121 (13.21)	1506 (15.52)	489 (16.57)	609 (14.79)	206 (13.5)	488 (16.26)	262 (17.99)
Liver (C22)	7319 (5.56)	6721 (5.51)	598 (6.16)	231 (7.83)	243 (5.9)	93 (6.09)	161 (5.36)	83 (5.7)
Gallbladder (C23–C24)	2722 (2.07)	2392 (1.96)	330 (3.4)	90 (3.05)	137 (3.33)	45 (2.95)	106 (3.53)	50 (3.43)
Pancreas (C25)	5279 (4.01)	4720 (3.87)	559 (5.76)	125 (4.23)	253 (6.14)	80 (5.24)	181 (6.03)	70 (4.81)
Lung (C33–C34)	15,291 (11.61)	13553 (11.11)	1738 (17.91)	518 (17.55)	709 (17.21)	328 (21.49)	545 (18.15)	258 (17.72)
Breast (C50)	12,355 (9.38)	12163 (9.97)	192 (1.98)	64 (2.17)	77 (1.87)	29 (1.9)	62 (2.07)	28 (1.92)
Uterus (C53–C55)	5113 (3.88)	4996 (4.1)	117 (1.21)	44 (1.49)	42 (1.02)	19 (1.25)	31 (1.03)	14 (0.96)
Ovary (C56)	1552 (1.18)	1504 (1.23)	48 (0.49)	15 (0.51)	13 (0.32)	9 (0.59)	16 (0.53)	5 (0.34)
Prostate (C61)	11,833 (8.98)	10999 (9.02)	834 (8.59)	186 (6.3)	398 (9.66)	108 (7.08)	260 (8.66)	145 (9.96)
Thyroid (C73)	2055 (1.56)	1984 (1.63)	71 (0.73)	24 (0.81)	35 (0.85)	11 (0.72)	24 (0.8)	9 (0.62)
Malignant lymphoma (C81–C85, C96)	4735 (3.6)	4364 (3.58)	371 (3.82)	135 (4.57)	155 (3.76)	40 (2.62)	95 (3.16)	46 (3.16)
Multiple myeloma (C88–C90)	871 (0.66)	785 (0.64)	86 (0.89)	49 (1.66)	28 (0.68)	7 (0.46)	16 (0.53)	8 (0.55)
Leukemia (C91–C95)	1832 (1.39)	1659 (1.36)	173 (1.78)	59 (2)	52 (1.26)	22 (1.44)	57 (1.9)	20 (1.37)

Values in parentheses represent column percentanges.
CVD, cardiovascular disease; HF, heart failure; IHD, ishcemic heart disease; PAD, peripheral arterial disease; CVA, cerebravascular accident; BMI, body mass index; ICD-10, International Classification of Diseases 10th revision.

Table 2
Three-year overall survival and 95 % confidence intercal.

	total	Any CVD			HF		IHD		PAD		CVA		Afib	
Site of Cancer based on the ICD-10 codes		No	Yes	p value	Yes	p value	Yes	p value	Yes	p value	Yes	p value	Yes	p value
All cancer site (C00–C96)	76.6 (76.3–76.8)	77.6 (77.4–77.9)	62.9 (61.9–64.0)	<0.001	57.4 (55.5–59.3)	<0.001	66.7 (65.2–68.2)	<0.001	63.4 (60.7–65.9)	<0.001	62.2 (60.3–64.0)	<0.001	62.7 (60.0–65.3)	<0.001
Esophagus (C15)	66.5 (64.9–68)	67.1 (65.5–68.7)	55.9 (48.2–62.9)	<0.001	59.3 (43.9–71.7)	0.434	56.2 (43.6–67.1)	0.053	58.2 (39.5–72.9)	0.352	48.8 (34.3–61.8)	<0.001	43.6 (27.2–58.8)	<0.001
Stomach (C16)	77.7 (77.1–78.3)	78.6 (78.0–79.3)	66.8 (64.2–69.2)	<0.001	64.4 (59.6–68.9)	<0.001	70.6 (66.9–73.9)	<0.001	63.7 (57.3–69.4)	<0.001	62.2 (57.4–66.7)	<0.001	67.7 (60.8–73.6)	<0.001
Colorectum (C18–C20)	82.9 (82.3–83.4)	83.5 (82.9–84.0)	76.4 (74.0–78.6)	<0.001	73.5 (69.1–77.4)	<0.001	80.1 (76.6–83.2)	0.030	75.4 (68.5–81.0)	<0.001	75.9 (71.5–79.6)	<0.001	76.9 (70.9–81.9)	0.004
Liver (C22)	62.7 (61.5–63.9)	63.3 (62.0–64.5)	56.9 (52.5–61.1)	<0.001	54.2 (46.9–61.0)	0.008	59.4 (52.4–65.7)	0.302	57.0 (45.5–67.0)	0.243	53.8 (44.8–62.1)	0.002	60.8 (48.5–71.0)	0.559
Gallbladder (C23–C24)	44.6 (42.5–46.7)	45.6 (43.4–47.9)	38.0 (31.8–44.1)	0.01	36.0 (25.0–47.2)	0.023	40.2 (30.8–49.4)	0.560	43.6 (24.6–61.2)	0.841	44.5 (32.3–55.9)	0.856	34.9 (21.1–49.2)	0.200
Pancreas (C25)	32.5 (31–34)	33.1 (31.5–34.7)	27.4 (22.9–32.1)	<0.001	27.5 (18.8–37.0)	0.183	25.0 (18.6–32.0)	0.014	31.6 (19.9–44.0)	0.865	22.1 (14.4–30.9)	<0.001	23.6 (12.5–36.6)	0.023
Lung (C33–C34)	55.3 (54.4–56.1)	56.6 (55.6–57.5)	44.9 (42.3–47.5)	<0.001	36.5 (31.8–41.1)	<0.001	51.1 (47.0–55.1)	0.003	48.4 (42.3–54.3)	0.013	45.7 (40.9–50.4)	<0.001	43.1 (36.4–49.7)	<0.001
Breast (C50)	95.7 (95.3–96.1)	95.8 (95.4–96.1)	90.8 (85.6–94.2)	<0.001	84.9 (72.9–91.9)	<0.001	94.5 (86.0–97.9)	0.288	85.8 (66.4–94.4)	0.069	91.5 (80.7–96.4)	0.156	96.4 (77.2–99.5)	0.058
Uterus (C53–C55)	89.2 (88.3–90)	89.6 (88.7–90.4)	71.1 (61.5–78.8)	<0.001	54.9 (37.4–69.3)	<0.001	71.8 (54.8–83.4)	0.002	94.7 (68.1–99.2)	0.389	85.2 (65.2–94.2)	0.679	70.7 (39.4–87.9)	0.017
Ovary (C56)	79.9 (77.7–81.9)	80.3 (78.2–82.3)	67.7 (51.5–79.5)	0.026	84.6 (51.2–95.9)	0.693	64.8 (31.0–85.2)	0.229	75.0 (31.5–93.1)	0.390	65.0 (35.1–83.8)	0.213	50.0 (5.8–84.5)	0.049
Prostate (C61)	94.4 (93.9–94.8)	94.7 (94.2–95.1)	90.5 (88.3–92.4)	<0.001	83.8 (77.4–88.5)	<0.001	93.0 (90.0–95.2)	0.174	88.3 (80.3–93.2)	<0.001	90.4 (86.1–93.5)	0.008	89.1 (82.6–93.3)	0.088
Thyroid (C73)	95.2 (94.2–96.1)	95.7 (94.7–96.5)	81.9 (70.2–89.3)	<0.001	86.1 (62.7–95.3)	0.149	87.9 (70.9–95.3)	0.005	90.9 (50.8–98.7)	0.688	77.0 (53.1–89.8)	<0.001	76.2 (33.2–93.5)	0.022
Malignant lymphoma (C81–C85, C96)	77.5 (76.3–78.7)	78.9 (77.6–80.1)	61.9 (56.5–66.8)	<0.001	50.1 (41.0–58.5)	<0.001	59.1 (50.5–66.7)	<0.001	60.8 (43.4–74.3)	0.001	70.4 (59.4–78.9)	0.081	62.3 (45.8–75.0)	<0.001
Multiple myeloma (C88–C90)	70.2 (66.9–73.2)	72.8 (69.4–75.9)	45.6 (33.8–56.7)	<0.001	43.1 (28.1–57.2)	<0.001	44.8 (24.8–62.9)	<0.001	85.7 (33.4–97.9)	0.458	58.3 (28.9–79.1)	0.308	40.0 (6.6–73.4)	0.006
Leukemia (C91–C95)	52.8 (50.3–55.2)	55.0 (52.5–57.5)	29.7 (22.4–37.3)	<0.001	23.7 (13.2–35.8)	<0.001	37.4 (23.3–51.5)	0.002	40.6 (19.7–60.7)	0.281	22.0 (10.7–35.8)	<0.001	20.0 (3.9–45.0)	<0.001

CVD, cardiovascular disease; HF, heart failure; IHD, ishcemic heart disease; PAD, peripheral arterial disease; CVA, cerebravascular accident; ICD-10, International Classification of Diseases 10th revision.

Table 3
Adjusted hazard ratios of coexisting CVDs on 3-year all cause mortality derived from Cox proportional hazard models according to cancer site.

	AnyCVD		HF		IHD		PAD		CVA		Afib	
Site of Cancer based on the ICD-10 codes	aHR (95 % CI)	p value	aHR (95 % CI)	p value	aHR (95 % CI)	p value	aHR (95 % CI)	p value	aHR (95 % CI)	p value	aHR (95 % CI)	p value
All cancer site (C00–C96)	1.47 (1.41–1.52)	<0.001	1.73 (1.63–1.83)	<0.001	1.29 (1.22–1.37)	<0.001	1.37 (1.25–1.50)	<0.001	1.42 (1.33–1.51)	<0.001	1.54 (1.41–1.68)	<0.001
Esophagus (C15)	1.66 (1.32–2.10)	<0.001	1.48 (0.94–2.31)	0.089	1.34 (0.93–1.92)	0.113	2.01 (1.19–3.43)	0.010	1.95 (1.34–2.86)	0.001	2.48 (1.60–3.86)	<0.001
Stomach (C16)	1.76 (1.59–1.94)	<0.001	2.13 (1.81–2.51)	<0.001	1.48 (1.28–1.71)	<0.001	1.89 (1.53–2.33)	<0.001	1.90 (1.62–2.22)	<0.001	1.95 (1.53–2.48)	<0.001
Colorectum (C18–C20)	1.48 (1.31–1.66)	<0.001	1.81 (1.50–2.18)	<0.001	1.28 (1.06–1.55)	0.011	1.65 (1.23–2.22)	<0.001	1.39 (1.14–1.69)	0.001	1.36 (1.03–1.78)	0.027
Liver (C22)	1.20 (1.05–1.38)	0.008	1.40 (1.13–1.72)	0.002	1.08 (0.87–1.34)	0.498	1.09 (0.78–1.51)	0.622	1.16 (0.90–1.50)	0.246	1.12 (0.78–1.62)	0.545
Gallbladder (C23–C24)	1.25 (1.06–1.48)	0.008	1.35 (1.01–1.80)	0.040	1.33 (1.04–1.70)	0.025	1.28 (0.80–2.04)	0.308	0.92 (0.68–1.25)	0.581	1.24 (0.85–1.79)	0.265
Pancreas (C25)	1.19 (1.05–1.34)	0.005	1.13 (0.89–1.43)	0.307	1.21 (1.02–1.43)	0.025	1.02 (0.75–1.38)	0.910	1.22 (1.00–1.50)	0.05	1.41 (1.04–1.91)	0.029
Lung (C33–C34)	1.52 (1.41–1.64)	<0.001	1.81 (1.61–2.04)	<0.001	1.36 (1.21–1.53)	<0.001	1.27 (1.08–1.50)	0.004	1.40 (1.23–1.59)	<0.001	1.67 (1.40–1.99)	<0.001
Breast (C50)	1.12 (0.68–1.84)	0.644	1.65 (0.84–3.26)	0.149	0.89 (0.33–2.39)	0.816	1.71 (0.63–4.58)	0.290	0.79 (0.33–1.93)	0.611	0.46 (0.07–3.30)	0.441
Uterus (C53–C55)	1.64 (1.12–2.41)	0.010	3.43 (2.09–5.61)	<0.001	1.51 (0.81–2.80)	0.192	0.49 (0.07–3.50)	0.479	0.42 (0.15–1.14)	0.087	3.00 (1.11–8.14)	0.031
Ovary (C56)	1.36 (0.78–2.35)	0.280	0.50 (0.12–2.02)	0.328	1.05 (0.39–2.85)	0.923	1.04 (0.26–4.22)	0.954	1.86 (0.75–4.61)	0.181	4.54 (1.11–18.60)	0.035
Prostate (C61)	1.73 (1.35–2.20)	<0.001	2.39 (1.63–3.51)	<0.001	1.28 (0.87–1.89)	0.213	2.24 (1.26–3.98)	0.006	1.67 (1.11–2.51)	0.015	2.28 (1.36–3.81)	0.002
Thyroid (C73)	3.06 (1.62–5.79)	0.001	2.79 (0.86–9.05)	0.087	3.73 (1.33–10.45)	0.012	0.53 (0.07–4.11)	0.545	4.12 (1.63–10.43)	0.003	3.02 (0.71–12.75)	0.133
Malignant lymphoma (C81–C85, C96)	1.38 (1.14–1.67)	0.001	1.82 (1.40–2.36)	<0.001	1.34 (1.03–1.76)	0.030	1.33 (0.80–2.22)	0.272	1.07 (0.72–1.58)	0.738	1.46 (0.89–2.40)	0.134
Multiple myeloma (C88–C90)	2.15 (1.52–3.04)	<0.001	2.43 (1.60–3.68)	<0.001	1.99 (1.15–3.46)	0.015	0.47 (0.06–3.34)	0.447	1.12 (0.50–2.54)	0.783	2.37 (0.87–6.46)	0.092
Leukemia (C91–C95)	1.47 (1.19–1.82)	<0.001	1.55 (1.12–2.13)	0.007	1.00 (0.69–1.47)	0.981	0.98 (0.55–1.73)	0.935	2.06 (1.47–2.87)	<0.001	1.24 (0.70–2.22)	0.460

All models are adjusted for age category, sex, first cancer site (at the time of analysis for all cancer sites), stage at diagnosis and body mass index category. 95 % CI, 95 % confidence interval; HR, hazard ratio.
CVD, cardiovascular disease; HF, heart failure; IHD, ishcemic heart disease; PAD, peripheral arterial disease; CVA, cerebravascular accident; ICD-10, International Classification of Diseases 10th revision.

3. Results

3.1. Participants and baseline characteristics

Of the 155,796 patients diagnosed with cancer between 2010 and 2015, we excluded 18,700 patients with carcinoma in situ, 4657 patients with multiple cancers diagnosed with a second primary cancer within two months of the first cancer diagnosis, 682 patients aged <20 years, 35 patients aged ≥100 years at cancer diagnosis, and 21 DCO cases at the time of their first cancer diagnosis. In total,131,701 patients were included in the analysis, of whom 9704 (7.4 %) had confirmed CVD at the time of cancer diagnosis. Of these, 2952 patients (2.2 %) had confirmed heart failure, 4119 (3.1 %) had IHD, 1526 (1.2 %) had PAD, 3002 (2.3 %) had CVA, and 1456 (1.1 %) had Afib.

Patient characteristics were compared between patients with coexisting CVD at the time of cancer diagnosis and those without CVD (Table 1, Supplementary Table 1). Patients with CVD were older, more likely to be male, and had more advanced cancer at diagnosis than those without CVD. Patients with CVD also tended to have a higher proportion of cancers of the lung, stomach, colon, liver, gallbladder, and pancreas, while relatively fewer cancers of the oral cavity/pharynx, breast, uterus, and ovaries.

Overall survival rate.

For all cancer sites, the patients with any kind of CVD had lower 3-year survival rates than the control group, and the same was true for each CVD subtype. Of these, the group with coexisting HF had the lowest 3-year survival (57.4 %, 95%CI: 55.5–59.3), while the IHD group had a relatively high 3-year survival (66.7, 65.2–68.2). By cancer site, the difference in survival with and without any CVD was particularly pronounced for multiple myeloma (45.6 % for any CVD vs 72.8 % for control), leukemia (29.7 % vs 55.0 %), cancer of the uterus (71.1 % vs 89.6 %), and malignant lymphoma (61.9 % vs 78.9 %). CVD subtypes with the poorest prognosis are HF for cancers of the colorectum, lung, skin, breast, uterus, prostate, bladder, and malignant lymphoma; Afib for cancers of esophagus, gallbladder, larynx, ovary, thyroid, MM, and leukemia; and CVA for cancers of liver, pancreas, and kidney/urinary tract (Table 2, Supplementary

Table 4
Baseline characteristics of patients by NYHA classification, Osaka, Japan, 2010–2015.

	NYHA class				total
	I	II	III	IV	
n (%)	70	153	115	94	432
All-cause mortality, n(%)	21 (30.0)	48 (31.4)	39 (33.9)	45 (47.9)	153 (35.4)
Male, n(%)	51 (72.9)	102 (66.7)	72 (62.6)	60 (63.8)	285 (66.0)
Age category, n(%)					
20–49 years	2 (2.9)	2 (1.3)	0 (0.0)	0 (0.0)	4 (0.9)
50–59 years	6 (8.6)	2 (1.3)	2 (1.7)	1 (1.1)	11 (2.6)
60–69 years	8 (11.4)	24 (15.7)	8 (7.0)	16 (17.0)	56 (13.0)
70–79 years	30 (42.9)	66 (43.1)	49 (42.6)	26 (27.7)	171 (39.6)
80–99 years	24 (34.3)	59 (38.6)	56 (48.7)	51 (54.3)	190 (44.0)
Stage at diagnosis					
Localized	39 (55.7)	81 (52.9)	55 (47.8)	54 (57.5)	229 (53.0)
Regional to lymph nodes	3 (4.3)	13 (8.5)	12 (10.4)	6 (6.4)	34 (7.9)
Regional by direct extension	7 (10.0)	21 (13.7)	16 (13.9)	8 (8.5)	52 (12.0)
Distant	15 (21.4)	28 (18.3)	18 (15.7)	18 (19.2)	79 (18.3)
Unknown	6 (8.6)	10 (6.5)	14 (12.2)	8 (8.5)	38 (8.8)
BMI category					
<18.5	6 (8.6)	21 (13.7)	17 (14.8)	16 (17.0)	60 (13.9)
18.5–24.9	44 (62.9)	98 (64.0)	66 (57.4)	53 (56.4)	261 (60.4)
≥25.0	19 (27.1)	29 (19.0)	27 (23.5)	20 (21.3)	95 (22.0)
Not measured	1 (1.4)	5 (3.3)	5 (4.4)	5 (5.32)	16 (3.7)
Site of Cancer based on the ICD-10 codes					
Esophagus (C15)	1 (1.4)	3 (2.0)	3 (2.6)	0 (0.0)	7 (1.6)
Stomach (C16)	11 (15.7)	32 (20.9)	20 (17.4)	20 (21.3)	83 (19.2)
Colorectum (C18–C20)	15 (21.4)	33 (21.6)	30 (26.1)	20 (21.3)	98 (22.7)
Liver (C22)	9 (12.9)	14 (9.2)	5 (4.4)	10 (10.6)	38 (8.8)
Gallbladder (C23–C24)	1 (1.4)	2 (1.3)	2 (1.7)	2 (2.1)	7 (1.6)
Pancreas (C25)	1 (1.4)	4 (2.6)	3 (2.6)	2 (2.1)	10 (2.3)
Lung (C33–C34)	12 (17.1)	22 (14.4)	15 (13.0)	16 (17.0)	65 (15.1)
Skin (C43–C44)	2 (2.9)	3 (2.0)	2 (1.7)	2 (2.1)	9 (2.1)
Breast (C50)	1 (1.4)	6 (3.9)	2 (1.7)	2 (2.1)	11 (2.6)
Uterus (C53–C55)	1 (1.4)	2 (1.3)	3 (2.6)	2 (2.1)	8 (1.9)
Ovary (C56)	0 (0.0)	0 (0.0)	2 (1.7)	0 (0.0)	2 (0.5)
Prostate (C61)	2 (2.9)	7 (4.6)	7 (6.1)	3 (3.2)	19 (4.4)
Thyroid (C73)	1 (1.4)	0 (0.0)	4 (3.5)	1 (1.1)	6 (1.4)
Malignant lymphoma (C81–C85, C96)	5 (7.1)	3 (2.0)	4 (3.5)	1 (1.1)	13 (3.0)
Multiple myeloma (C88–C90)	1 (1.4)	1 (0.7)	2 (1.7)	2 (2.1)	6 (1.4)
Leukemia (C91–C95)	2 (2.9)	1 (0.7)	1 (0.9)	1 (1.1)	5 (1.2)

Values in parentheses represent column percentanges.
NYHA, New York Heart Association; BMI, body mass index; ICD-10, International Classification of Diseases 10th revision.

Table 2).

HRs adjusted for age group, sex, primary cancer site, cancer progression, and BMI category were 1.47 for patients with any CVD for all cancer sites. For each CVD subtype, the aHR was highest in the patient with HF (1.73), followed by Afib (1.54) and CVA (1.42). By cancer site, the aHR for the patients with any CVD was >2 for thyroid cancer and multiple myeloma. In patients with cancers of the liver, gallbladder, and pancreas, the HR for patients with anyCVD was relatively low. For oral cavity/pharynx, larynx, breast, ovary, and brain/central nervous system, there was no significant association between any CVD and survival, and the same was generally true for each CVD subtype. Patients with cancers of the colorectum, liver, gallbladder, lung, skin, uterus, prostate, bladder, malignant lymphoma, and multiple myeloma had the highest aHR for coexisting HF among CVD subtypes. Patients with cancers of the esophagus and pancreas had the highest aHR for coexisting Afib, and the aHR for coexisting CVA was highest for patients with cancers of kidney/urinary tract, thyroid, and leukemia (Table 3, Supplementary Table 3).

3.2. Association with NYHA classification

The NYHA classification data at the time of cancer diagnosis were recorded for 432 patients with coexisting HF. Patient backgrounds for each group are shown in Table 4. In the analysis using patients without coexisting HF as reference and adjusted for sex, age category, cancer stage, and BMI category, the aHR (95 % CI) for all-cause mortality were 1.33 (0.85–2.08), 1.68 (1.26–2.25), 1.54 (1.10–2.14), 2.47 (1.80–3.38) for NYHA class I, II, III, and IV, respectively (Table 5).

4. Discussion

The key findings of this study are as follows. First, in patients with cancer, CVD comorbidity at the time of cancer diagnosis was associated with poor prognosis. This result will be discussed in detail for each CVD subtype and cancer site. Moreover, HF severity was associated with poor prognosis in patients with cancer with HF.

CVD is a major public health problem with increasing morbidity and mortality worldwide [2]. CVD includes various conditions, and in the general population, each subtype of CVD has a different prognostic impact. Quan et al. compared the CVD subtype using Canadian population data and reported that aHR for 1- year mortality was higher in chronic congestive HF (1.91) than in PAD (1.10), cerebrovascular accident (1.10), or myocardial infarction (0.99) [21]. However, there are few studies on the prognostic impact of CVD and CVD subtypes on patients with cancer.

Using data from the Northern Ireland cancer registry, O'Neill et al. reported a HR of 1.28 (95 % CI: 1.18–1.40) for death in patients with cancer with a history of CVD [22]. Youn et al. examined the impact of CVD subtypes on the prognosis of patients with cancer in a Korean population-based cohort study and found that patients with coexisting HF or stroke had a worse prognosis than those with IHD or PAD [13]. Youn et al. did not adjust for cancer progression, nor did they consider thee coexistence of AFib. In a population-based cohort study, Bertero et al. examined the association between loop diuretic prescription and cancer incidence and mortality in patients with HF and reported that decompensated HF was associated with an increased risk of cancer and cancer-related mortality [23].

A possible mechanism by which coexisting CVD contributes to a poor prognosis in patients with cancer is that CVD promotes cancer progression [24]. In our study, the CVD group also had more advanced-stage cancers. However, the prognosis in patients with coexisting CVD was poor even when adjusted for cancer stage, suggesting that other mechanisms may also be at work. Possible factors other than cancer stage at diagnosis include death from CVD itself [13], risk of postoperative mortality associated with CVD [25], chemotherapy toxicity enhanced by CVD [26], and limited cancer treatment options due to CVD [27].

The impact of coexisting CVD on overall survival varied by cancer site and CVD subtype. The HRs for death for most cancer sites were in the range of 1.2–1.7, with a relatively high HR for thyroid cancer and low HRs for cancers of the liver, gallbladder, and pancreas. This may be partly due to the prognosis of the cancer itself. In cancers with poor prognosis, death due to cancer before coexisting CVD affects prognosis, whereas in cancers with good prognosis, the presence or absence and extent of CVD may strongly affect prognosis. Furthermore, for thyroid cancer, thyroid function abnormalities, which are frequently associated with thyroid cancer, may influence the poor prognosis of patients with CVD [28]. No significant association was found between CVD comorbidity and prognosis in patients with breast cancer, a result that is inconsistent with previous reports [22]. Moreover, anthracyclines and trastuzumab, which are frequently used in breast cancer, are likely to cause cardiac complications and may affect prognosis. One possible interpretation of our results could be related to the fact that older patients with breast cancer have more hormone receptor positive breast cancers than younger patients [29]. Coexistence of CVD is generally more common in older adults than in the young. Patients with breast cancer without CVD are younger and less hormone receptor positive, and therefore use anthracyclines more frequently,

Table 5
Hazard ratios of NYHA classification on 3-year all cause mortality derived from Cox proportional hazard models.

	n	Crude HR (95 % CI)	p value	Adjusted HR (95 % CI)*	p value
nonHF	128,749	ref.		ref.	
NYHA I	70	1.37 (0.87–2.15)	0.168	1.33 (0.85–2.08)	0.217
NYHA II	153	1.65 (1.23–2.20)	0.001	1.68 (1.26–2.25)	<0.001
NYHA III	115	1.76 (1.26–2.45)	0.001	1.54 (1.10–2.14)	0.011
NYHA IV	94	2.65 (1.93–3.62)	<0.001	2.47 (1.80–3.38)	<0.001

*adjusted for age category, sex, first cancer site, stage at diagnosis and body mass index category.

while patients with breast cancer with complications of CVD are relatively older and hormone receptor positive, and therefore use anthracyclines less frequently, which may have influenced the results. Other factors such as the small number of patients with breast cancer with CVD and the influence of unmeasured confounding factors should also be considered in interpreting the results. Similarly, there was no significant association between coexisting CVD and prognosis in patients with cancers of pharyngeal, ovarian, and brain/central nervous system. This also may be partly due to the low number of patients with CVD at these cancer sites. Particularly, the proportion of patients with coexisting CVD was small among cancers of gynecological organs, which may partly be due to the large proportion of women. Differences in the prognostic impact of coexisting CVD by cancer site may be due in part to differences in cancer-specific treatment. For example, cancer treatment with anthracyclines may be reduced or avoided, especially in patients with CVD, because of the potential for cardiotoxicity, and either use at usual dose or avoidance of aggressive therapy may lead to worse prognosis [30]. This may explain why coexistence of CVD is associated with poor prognosis in patients with leukemia, malignant lymphoma, and multiple myeloma, where anthracyclines are frequently used.

When comparing among CVD subtypes, the aHRs are highest in the group with coexisting HF for many cites of cancer, which is similar to the trend seen in patients without cancer. However, for some cancer types, CVD subtypes other than HF are associated with poorer prognosis. For example, in patients with Esophagus and Pancreas cancers, the coexistence of Afib or CVA is associated with poorer prognosis and higher HRs than HF. Cancers of these sites are known to be at high risk for venous thromboembolism [31] and may worsen prognosis by increasing the frequency of thrombotic adverse events in patients with AFib or recurrent CVA in patients with pre-existing CVA. The HR for coexisting CVA is also higher in patients with cancers of the kidney, thyroid, and leukemia. Cancer in these sites has been reported to be strongly associated with the development of hemorrhagic stroke [32], and it may be possible that the frequency of recurrent CVA is increased in patients with a history of CVA.

One of the strengths of this study is that the data were obtained from an Asian population. Although the frequency of CVD and mortality rates differ in Europe, the United States, and Asia [33], we were able to confirm that, as in Caucasians, coexisting CVD is associated with a poor prognosis in Japanese patients with cancer.

The present study had several limitations. First, the coexistence of CVD was determined based on a diagnostic code, and there may have been an omission of patients with CVD. Second, the confounding factors that were not considered in this study require further investigation. For example, the effects of comorbidities other than CVD, lifestyle factors, and environmental factors on survival were not examined in this study. As already mentioned, the lack of association between CVD and prognosis in patients with breast cancer may also be due to unadjusted confounding factors, such as hormone receptor status. Third, although there are various types of heart failure depending on the presence or absence of reduced Ejection Fraction and underlying disease, these classifications were not considered in this analysis. We were also unable to consider changes in NYHA class over time or changes in the pathogenesis of Afib (such as paroxysmal and persistent). Moreover, NYHA classes were recorded only for a subset of patients with ICD-10 code for HF in the categories of main diagnosis, most resource-consuming diagnosis, and second most resource-consuming diagnosis in the DPC system. Therefore, NYHA class data were available for only a small subset of patients with HF, and we must be cautious about in applying our conclusions to the entire population of patients with cancer and HF. Furthermore, treatment for cancer and CVD was not considered, which may have influenced the results. The prognostic impact of early diagnosis and treatment of CVD cannot be determined from the results of this study. The generalizability of our findings may also be limited because the data were collected from designated cancer care hospitals rather than from all hospitals in the region. Finally, the causes of death were not considered. Therefore, the mechanism underlying the increased risk of death due to coexisting CVD remains a topic for future investigation.

In conclusion, this study utilizing the cancer registry and DPC data revealed that coexisting CVD at diagnosis had a negative impact on the prognosis of a variety of cancer types, independently of the cancer stages. In comparisons among CVD subtypes, HF is associated with a particularly poor prognosis for many cancer sites, but for some cancer sites, such as esophageal and pancreatic cancer, the coexistence of Afib or CVA may be associated with a poorer prognosis than HF. The severity of heart failure, as assessed by the NYHA classification, has also been shown to correlate with the prognosis of patients with cancer. Further studies are needed to determine the prognostic impact of CVD screening and treatment in patients with cancer.

Data availability statement

Data supporting the results of this study are available from the corresponding author upon reasonable request. Data are not publicly available due to privacy and ethical regulations.

CRediT authorship contribution statement

Yoshihiro Kuwabara: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Toshitaka Morishima:** Data curation, Methodology, Resources, Validation, Writing – review & editing. **Haruka Kudo:** Formal analysis, Writing – review & editing. **Chaochen Ma:** Validation, Writing – review & editing. **Mizuki Kato:** Data curation, Writing – review & editing. **Shihoko Koyama:** Data curation, Writing – review & editing. **Kayo Nakata:** Conceptualization, Methodology, Writing – review & editing. **Takahiro Tabuchi:** Methodology, Writing – review & editing. **Isao Miyashiro:** Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing

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Appendix A. Supplementary data

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