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ORIGINAL ARTICLE

Clinical evaluation and outcome in heart failure patients receiving chemotherapy with different anti-cancer agents

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Abstract

Background The optimal strategy for modern chemotherapy should be based on a comprehensive approach for cancer patients with cardiovascular diseases. Therefore, cardio-oncology has received increasing attention owing to the cardiotoxic effects of anti-cancer therapies.

Objectives We aimed to evaluate the clinical characteristics and outcomes of patients with heart failure (HF) who received chemotherapy compared with those of a matched cohort with HF who did not receive chemotherapy, using real-world HF data.

Methods This study was based on the Diagnosis Procedure Combination (DPC) database of the Japanese Registry of All Cardiac and Vascular Diseases (JROAD). We identified 1 328 113 patients who were hospitalized for HF between April 2012 and March 2021. The propensity score (PS) was estimated using a logistic regression model, with chemotherapy as the dependent variable, and a clinically score-matched analysis of 11 532 patients with HF with or without chemotherapy. The primary endpoint was readmission.

Results Colon, lung, breast and prostate cancers accounted for >60% of all cancer types. After PS matching, readmission was significantly more frequently observed in patients with chemotherapy than those without [odds ratio (OR), 1.26; 95% confidence interval (CI) 1.17–1.36, $P < 0.01$]. In particular, treatment with epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) (OR, 1.69; 95% CI 1.39–2.07), taxane (OR, 2.95; 95% CI 2.11–4.12), anthracyclines (OR, 1.86; 95% CI 1.19–2.90) and fluorouracil agents (OR, 1.65; 95% CI 1.18–2.30) caused a higher risk of readmission.

Conclusions Medical providers need to monitor and follow-up patients with HF, depending on the characteristics of the anti-cancer agents and types of cancer.

Keywords cardio-oncology; chemotherapy; heart failure; readmission

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Introduction

Heart failure (HF), a clinical syndrome associated with considerable morbidity and mortality, reduced quality of life (QOL) and financial burden, remains a major clinical and public health problem.[1] The common aetiologies are ischaemic heart disease, hypertension, valvular disease and drugs (e.g., anti-cancer agents). The 5 and 10 year survival rates of HF patients are estimated to be 57% and 35%, respectively.[2] Although the majority of patients with HF previously died of cardiovascular (CV) causes, non-CV deaths have been increasing recently, mainly because of an increase in cancer-related deaths.[3]

Over the last few decades, advances in cancer therapy have prolonged the life expectancies of patients diagnosed

with malignancies. Although traditional cytotoxic chemotherapy, molecularly targeted therapy and immunotherapy have improved the survival rates,[4] off-target adverse effects (AEs), such as complications of the CV system, require attention. In particular, immune checkpoint inhibitors (ICIs) lead to acute HF and even death caused by various mechanisms such as myocarditis and arrhythmia.[5] The field of cardio-oncology has received increasing attention because of the problem of cardiotoxic effects of anti-cancer therapies.[6]

The optimal strategy for modern chemotherapy is based on a comprehensive approach for patients in oncology and cardiology. Therefore, medical providers should carefully assess and monitor patients with cancer before, during and after chemotherapy. Currently, the need of the patient is to address any predisposing risk factors, prevent, identify early and properly treat the acute, chronic and late-onset CV toxicity of cancer treatment, and manage and improve the QOL of cancer survivors with CV AEs.[7,8]

Recently, some studies have reported trastuzumab-related cardiotoxicity using claims databases reported from Asia.[9–11] However, the influence of different anti-cancer agents on clinical outcomes in patients with HF is unknown. Therefore, we aimed to investigate the prescription of anti-cancer agents before and after treatment in patients with HF in the Japanese Registry of All Cardiac and Vascular Diseases (JROAD) and evaluate the clinical characteristics and outcomes of patients with HF who received chemotherapy compared with a matched cohort with HF not receiving chemotherapy, using real-world registry data of HF.

Methods

Study population

This study was approved by the Showa University Research Ethics Review Board (approval number: 22-084-B). The study population comprised patients hospitalized from April 2012 to March 2021 as per the JROAD Diagnosis Procedure Combination (DPC) database. The JROAD-DPC is a nationwide registry medical database with information on admission and discharge for CV disease, clinical characteristics and treatment status, patient status and hospital overview. The JROAD-DPC database integrates information from the JROAD-DPC data with analysis datasets covering 11 million cases in 1119 hospitals between April 2012 and March 2021. The identification of HF and cancer was based on the International Classification of Diseases, Tenth Revision (ICD-10) diagnosis codes (Table S1). Data on patient age, sex, main comorbidities at admission, length of hospitalization and treatment content were extracted from the database. We included 1 328 113 patients who were hospitalized for HF (Figure 1), of which 59 229 patients (4.46%) had cancer. We excluded 14 043 patients with unknown outcomes, non-emergency admissions and unknown chemotherapy data. Consequently, 5774 patients who received chemotherapy and 39 412 patients who did not receive chemotherapy were included in the readmission assessment. The chemotherapy group is classified into three groups (oral, transvenous or transarterial, and other) in the DPC database.

We investigated the treatment before hospitalization and at discharge. Anti-cancer agents of chemotherapy included ICIs, human epidermal growth factor receptor 2 (HER2) inhibitors, anti-vascular endothelial growth factor receptor (VEGF) agents, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (EGFR-TKIs), anaplastic lymphoma kinase (ALK) inhibitors, V-Raf murine sarcoma viral oncogene homolog B1 (BRAF) inhibitors, c-ros oncogene 1 (ROS1)/tropomycin receptor kinase (TRK) inhibitors, Janus-activated kinase (JAK) inhibitors, fms-like tyrosine receptor kinase 3 (FLT3) inhibitors, cyclin-dependent kinase 4/6 (CKD4/6) inhibitors, poly-ADP-ribose polymerase (PARP) inhibitors, mammalian target of rapamycin (mTOR) inhibitors, immunomodulatory drugs (IMiDs), proteasome inhibitors, mitogen-activated protein kinase kinase (MEK) inhibitors, fluorouracil agents, anthracyclines, taxanes or alkylating agents (Table S2). In addition, we investigated the use of hormone therapy to treat cancer before hospitalization. Hormone therapy included aromatase inhibitors, anti-oestrogens, anti-androgen, luteinizing hormone-releasing hormone (LHRH) agonists and gonadotropin-releasing hormone (GnRH) antagonists (Table S2).

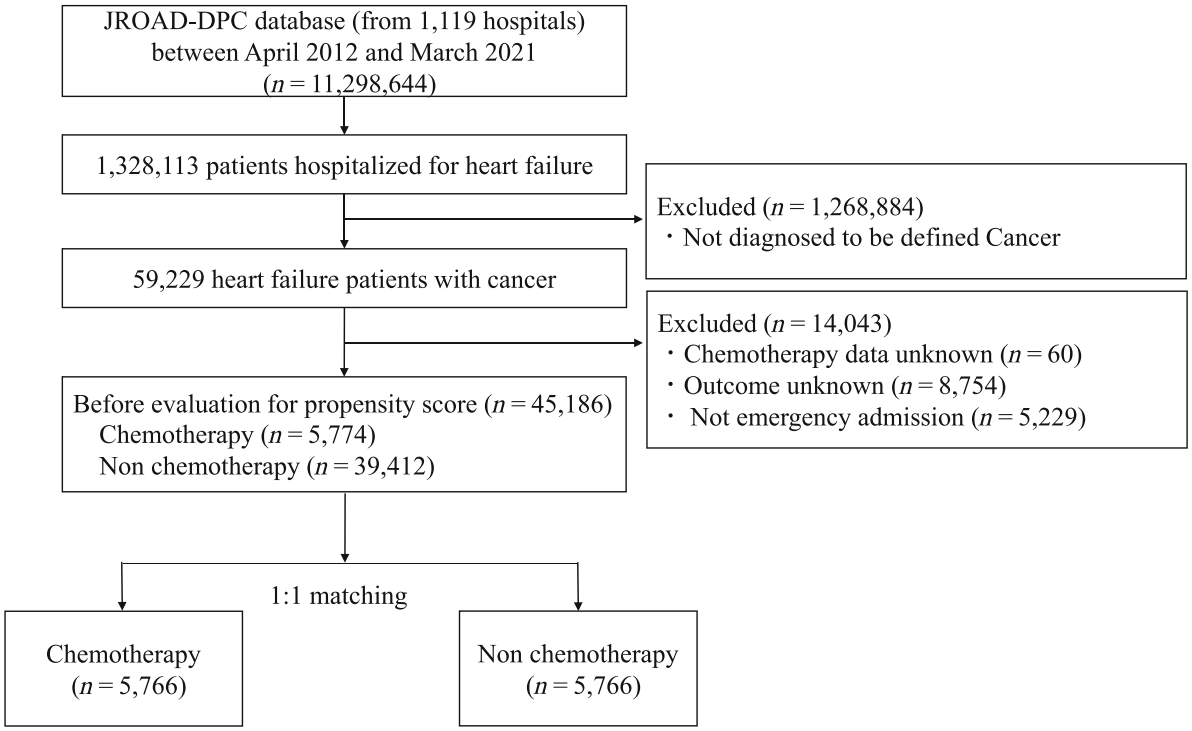
Clinical outcomes

The primary outcome was 1 year of readmission for any cause. We compared the hospital mortality (30 days) between patients with HF who did or did not receive chemotherapy before and after propensity score (PS) matching.

Sample matching

PS matching reduced the confounding effects of differences in patient backgrounds, such as sex and cancer type. After matching the variables, 11 532 patients with HF in the chemotherapy and non-chemotherapy groups were included in the final analyses. The concordance index was 0.85 (Figure S1), and the consistency of the PS densities was confirmed after matching the variables (Figure S2). The balance of each covariate between the two groups before and after matching was evaluated using standardized differences. Match quality was determined using standardized mean differences (SMDs). The absolute value of the standardized differences <0.1 was considered a relatively small imbalance.

Figure 1 Flowchart of this study. We included 1 328 113 patients hospitalized for heart failure. A total of 59 229 patients were diagnosed with cancer. A total of 5774 patients received chemotherapy, while 39 412 patients did not. JROAD-DPC, Japanese Registry of All Cardiac and Vascular Diseases Diagnosis Procedure Combination.



Statistical analysis

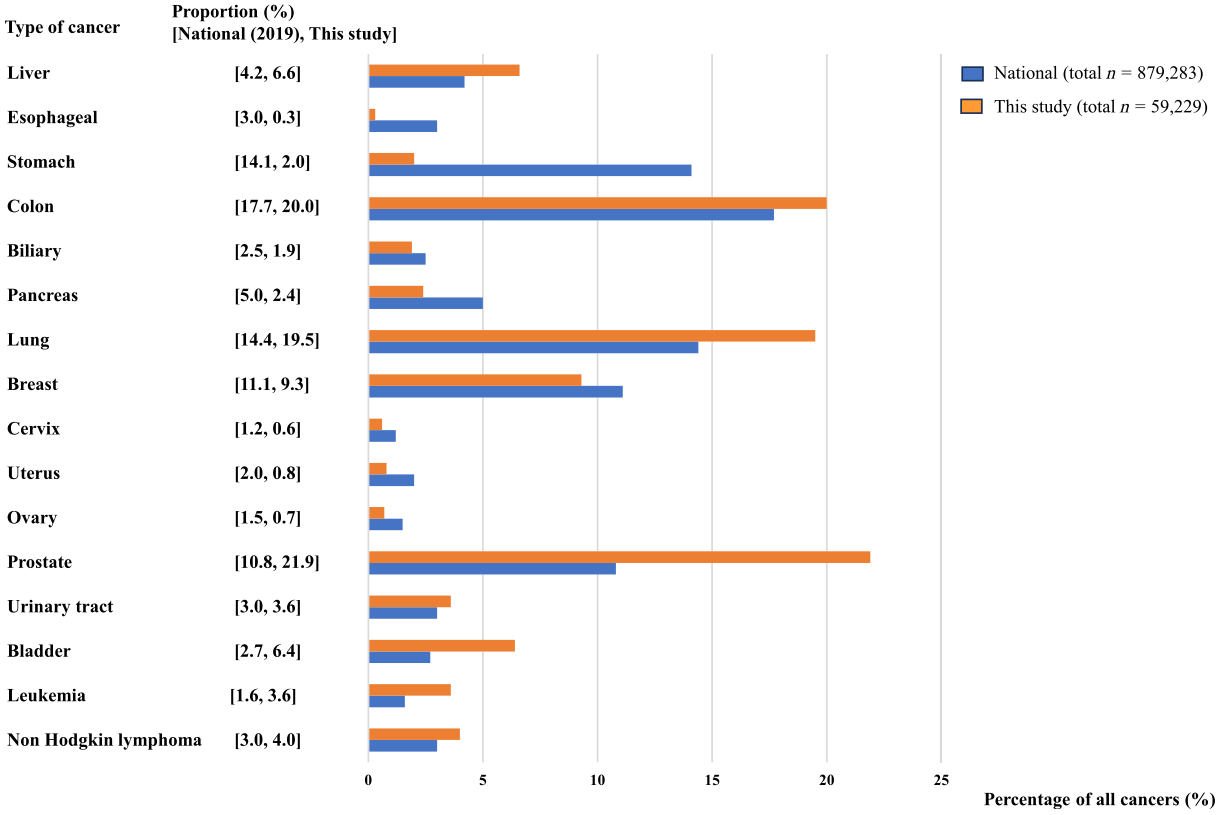
PS was estimated with a logistic regression model, with chemotherapy as the dependent variable and the following 27 clinically relevant covariates: age, sex, hospitalization days, comorbidities (hypertension, diabetes mellitus, dyslipidaemia, stroke, myocardial infarction, peripheral vascular disease, cerebrovascular disease, rheumatic disease, chronic kidney disease, liver failure, chronic obstructive pulmonary disease, dementia and metastatic cancer) and treatment [loop diuretics, thiazide diuretics, tolvaptan, angiotensin-converting enzyme (ACE) inhibitor, angiotensin II receptor blocker (ARB), renin, beta-blocker, αβ-blocker, mineralocorticoid receptor antagonist (MRA), angiotensin receptor–neprilysin inhibitor and sodium–glucose cotransporter 2 inhibitors]. Matching was performed using the nearest neighbour method, with a calliper of width 0.2 standard deviations of the logit of the estimated PS. After matching, we estimated the odds ratio (OR) and 95% confidence interval (CI) for readmission within 1 year. Furthermore, we analysed subgroups according to the type of chemotherapy administered in the PS-matched cohort. The OR for each type of anti-cancer drug was calculated using matched patients who did not receive chemotherapy as the controls. Further, we calculated the readmission rates for the oral, transvenous/transarterial and other groups as classified in the DPC database using Pearson's chi-squared test. All statistical tests were two-sided, and values <0.05 were considered statistically significant. Statistical analyses were performed using JMP Pro Version 16.0 (SAS Institute Inc., Cary, NC, USA), R Version 4.3.2 and RStudio Version 2023.09.1-494.

Results

The proportion of type of cancer in hospitalized patients with HF

We calculated the proportion of each cancer type among patients with HF during the first hospital admission (Figure 2). Colon, lung, breast and prostate cancers accounted for >60% of all cancers. The proportion of prostate cancer, bladder cancer and leukaemia in this study was two times more than national statistics.[12] In contrast, this study's proportion of stomach cancer was seven times less than the national statistics. After PS matching, 62.5% and 19.5% of patients with HF had prostate and breast cancers, respectively.

Figure 2 Proportion of cancer type among patients with heart failure during the first hospital admission and comparison with national statistics. Data are presented as each cancer proportion from the national statistics (%) and this study (%). Colon, lung, breast and prostate cancers accounted for more than 60% of all cancers. The proportions of prostate cancer, bladder cancer and leukaemia were two times higher than the national statistics. However, the proportion of stomach cancer was seven times lower than the national statistics.



The proportion of each anti-cancer agent before hospitalization and at discharge

The proportion of each anti-cancer agent used before hospitalization and at discharge was calculated (Table 1). LHRH agonists, anti-androgens, fluorouracil agents and EGFR-TKIs accounted for more than 50% of the total anti-cancer agents administered before hospitalization. On the other hand, oral anti-cancer agents such as EGFR-TKIs, JAK inhibitors and endocrine therapy were associated with a higher continuation rate than that with injection anti-cancer agents at discharge.

Patient characteristics

We found the patient characteristics before and after PS matching (Table 2). In the group before PS matching (n = 45 186), 64.4% (n = 32 453) were male, with a median age of 82 years (range: 20–106 years). In total, 5774 patients received chemotherapy, and 39 412 did not. Before PS matching, the number of males was higher in the chemotherapy group than in the non-chemotherapy group. Loop diuretics, tolvaptan, ACE inhibitor, ARB, beta-blocker, αβ-blocker and MRA for HF treatment during hospitalization were higher in the group with chemotherapy than without chemotherapy. In addition, the incidences of liver cancer, colon cancer, lung cancer, bladder cancer and non-Hodgkin lymphoma were lower in the chemotherapy group than in the non-chemotherapy group. In contrast, the incidences of breast cancer, prostate cancer and leukaemia were higher in the chemotherapy group than in the non-chemotherapy group. The median length of hospitalization was slightly longer in the chemotherapy group than in the non-chemotherapy group.

After PS matching, 33 654 patients were excluded, and 11 532 patients were included in the analysis. In the matched cohort, there were no significant differences between the groups of patients with and without chemotherapy in terms of age, sex, comorbidities or HF treatment.

Outcomes

After PS matching, HF patients with chemotherapy significantly increased in 1 year of readmission risk compared with

Table 1 The proportion of each anti-cancer agent before hospitalization and discharge.

	Before hospitalization $N = 45\,186$	At discharge $N = 45\,186$
ICIs	187 (0.41)	0
HER2 inhibitors	300 (0.66)	0
Anti-VEGF agents	414 (0.92)	0
EGFR-TKIs	1062 (2.35)	285 (0.63)
ALK inhibitors	21 (0.05)	11 (0.02)
BRAF inhibitors	4 (0.01)	0
ROS1/TRK inhibitors	1 (0.002)	0
FLT3 inhibitors	0	1 (0.002)
JAK inhibitors	21 (0.05)	16 (0.04)
CKD4/6 inhibitors	33 (0.07)	0
PARP inhibitors	1 (0.002)	0
mTOR inhibitors	55 (0.12)	9 (0.02)
IMiDs	25 (0.06)	9 (0.02)
Proteasome inhibitors	16 (0.04)	0
MEK inhibitors	3 (0.01)	0
Fluorouracil agents	803 (1.76)	72 (0.16)
Anthracyclines	279 (0.62)	0
Taxane	542 (1.20)	0
Alkylating agents	573 (1.23)	115 (0.26)
Aromatase inhibitors	996 (2.20)	734 (1.62)
Anti-oestrogens	326 (0.72)	131 (0.29)
Anti-androgens	3213 (7.11)	2224 (4.92)
LHRH agonists	3092 (6.84)	3 (0.01)
GnRH antagonists	373 (0.83)	0

Abbreviations: ALK, anaplastic lymphoma kinase; Anti-VEGF, anti-vascular endothelial growth factor receptor; BRAF, V-Raf murine sarcoma viral oncogene homolog B1; CKD4/6, cyclin-dependent kinase 4/6; EGFR-TKIs, epidermal growth factor receptor tyrosine kinase inhibitors; FLT3, fms-like tyrosine kinase 3; GnRH, gonadotropin-releasing hormone; HER2, human epidermal growth factor receptor 2; ICIs, immune checkpoint inhibitors; IMiDs, immunomodulatory drugs; JAK, Janus-activated kinase; LHRH, luteinizing hormone-releasing hormone; MEK, mitogen-activated protein kinase kinase; mTOR, mammalian target of rapamycin; PARP, poly-ADP-ribose polymerase; ROS1, c-ros oncogene 1; TRK, tropomycin receptor kinase.

matched patients without chemotherapy (OR, 1.26; 95% CI 1.17–1.36, $P < 0.01$) (Figure 3). However, after PS matching, HF patients who received chemotherapy had lower chances of hospital mortality (30 days) than patients without chemotherapy (4.2% vs. 7.7%, $P < 0.01$) (Table 3).

Relation between readmission within 1 year and types of anti-cancer agents

The ORs for the readmission in the case of each anti-cancer agent are shown in Figure 3. Patients treated with EGFR-TKIs, JAK inhibitors, IMiDs, fluorouracil agents, anthracyclines, taxanes and alkylating agents before hospitalization had significantly higher readmission rates than matched patients who did not receive chemotherapy (EGFR-TKIs: OR, 1.69; JAK inhibitors: OR, 4.92; IMiDs: OR, 13.4; fluorouracil agents: OR, 1.65; anthracyclines: OR, 1.86; taxane: OR, 2.95; and alkylating agents: OR, 1.35). In contrast, patients taking anti-VEGF agents, ICIs and HER2 inhibitors before hospitalization showed no significant difference in readmission compared with matched patients who did not receive chemotherapy (anti-VEGF agents: OR, 1.39; ICIs: OR, 1.56; and HER2 inhibitors: OR, 1.39). Patients treated with aromatase inhibitors, anti-androgens, LHRH agonists and GnRH antagonists before hospitalization had significantly higher readmission rates than matched patients who did not receive chemotherapy (aromatase inhibitors: OR, 1.40; anti-androgens: OR, 1.39; LHRH agonists: OR, 1.18; and GnRH antagonists: OR, 2.17). The readmission rates were 2629/4732 (55.6%) for the oral group, 351/612 (57.4%) for the transvenous or transarterial group, and 235/422 (55.7%) for the other group ($P = 0.68$).

Discussion

The main findings of the study were as follows: (1) Prostate and breast cancers were more prevalent among patients with HF after PS matching because prostate and breast cancers have better survival rates compared with other cancers. (2) Patients with HF who received chemotherapy had a significantly higher risk of readmission within 1 year than those who did not receive chemotherapy. However, in the case of hospital mortality, patients who received chemotherapy were at lower risk than patients who did not receive chemotherapy. (3) Patients with HF and cancer who were administered EGFR-TKIs, JAK inhibitors, IMiDs, fluorouracil agents, anthracyclines, taxane or alkylating agents had a significantly higher risk of readmission within 1 year than those who did not receive chemotherapy. (4) Patients with HF and cancer receiving endocrine therapy such as aromatase inhibitors, anti-androgens, LHRH agonists and GnRH antagonists had a significantly higher risk of readmission within 1 year. This study is the first to assess the relationship between chemotherapy and readmission risk in a large-scale cohort of patients with HF.

Patient characteristics and impact of prescription rate of anti-cancer agents before hospitalization and at discharge

The median age was higher than that of the general HF population in this study, and patients with HF and cancer were more likely to have prostate and breast cancers after PS matching. This higher likelihood of having prostate and breast cancers is because of their better prognosis and survival compared with other cancers. The prescription rates of anti-cancer agents before hospitalization were high for EGFR-TKIs, fluorouracil agents, alkylating agents, taxanes and endocrine therapies. The type of cancer, including prostate, colon, lung and breast cancers, and its treatment influenced the results. On the other hand, at discharge, the continuation rates of oral anti-cancer agents were high regarding EGFR-TKIs and endocrine therapies, while injection anti-cancer agents were

Table 2 Baseline characteristics before and after propensity score matching.

	Non-matching				Matching			
	All	Chemotherapy	Non-chemotherapy		All	Chemotherapy	Non-chemotherapy	
	(*n* = 45 186)	(*n* = 5774)	(*n* = 39 412)	SMD	(*n* = 11 532)	(*n* = 5766)	(*n* = 5766)	SMD
Age (years), mean ± SD	81.1 ± 9.5	81.8 ± 8.5	81.0 ± 9.7	0.08	81.7 ± 9.1	81.8 ± 8.5	81.6 ± 9.6	0.02
Median (min–max)	83 (20–106)	83 (27–103)	83 (20–106)		83 (25–103)	83 (27–103)	83 (25–103)	
Male sex (%)	32 453 (64.4)	4243 (73.5)	274 758 (62.8)	0.23	8491 (73.6)	4235 (73.5)	4256 (73.8)	0.01
Comorbidities (%)								
Hypertension	20 320 (45.0)	2694 (46.7)	17 626 (44.7)	0.04	5367 (46.5)	2692 (46.7)	2675 (46.4)	0.01
Diabetes mellitus	11 471 (25.4)	1511 (26.2)	9960 (25.3)	0.02	3026 (26.2)	1509 (26.2)	1517 (26.3)	<0.01
Dyslipidaemia	6834 (15.1)	967 (16.8)	5867 (14.9)	0.05	1931 (16.7)	967 (16.8)	964 (16.7)	<0.01
Stroke	739 (1.6)	80 (1.4)	659 (1.7)	0.02	151 (1.3)	80 (1.4)	71 (1.2)	0.01
Myocardial infarction	4219 (9.3)	541 (9.4)	3678 (9.3)	<0.01	1074 (9.3)	540 (9.4)	534 (9.3)	<0.01
Peripheral vascular disease	2061 (4.6)	252 (4.4)	1809 (4.6)	0.01	513 (4.4)	251 (4.4)	262 (4.5)	0.01
Cerebrovascular disease	3711 (8.2)	442 (7.7)	3269 (8.3)	0.02	868 (7.5)	441 (7.7)	427 (7.4)	0.01
Chronic kidney disease	7678 (17.0)	1049 (18.2)	6629 (16.8)	0.04	2084 (18.1)	1046 (18.1)	1038 (18.0)	<0.01
Liver failure	148 (0.3)	3 (0.1)	145 (0.4)	0.07	6 (0.05)	3 (0.05)	3 (0.05)	<0.01
Chronic obstructive pulmonary disease	4218 (9.3)	482 (8.4)	3736 (9.5)	0.04	953 (8.3)	482 (8.4)	471 (8.4)	0.01
Rheumatic disease	551 (1.2)	46 (0.8)	505 (1.3)	0.05	81 (0.7)	46 (0.8)	35 (0.6)	0.02
Dementia	3019 (6.7)	372 (6.4)	2647 (6.7)	0.01	712 (6.2)	371 (6.4)	341 (5.9)	0.02
Metastatic cancer	3208 (7.1)	466 (8.1)	2742 (7.0)	0.04	958 (8.3)	464 (8.1)	494 (8.6)	0.02
Type of cancer (%)								
Intestinal	19 (0.04)	2 (0.03)	17 (0.04)	<0.01	4 (0.04)	2 (0.03)	2 (0.03)	<0.01
Liver	2953 (6.5)	82 (1.4)	2871 (7.3)	0.29	169 (1.5)	82 (1.4)	87 (1.5)	0.01
Oesophageal	145 (0.3)	9 (0.2)	136 (0.4)	0.04	22 (0.2)	9 (0.2)	13 (0.2)	0.02
Stomach	949 (2.1)	58 (1.0)	891 (2.3)	0.10	120 (1.0)	58 (1.0)	62 (1.1)	0.01
Colon	9217 (20.4)	160 (2.8)	9057 (23.0)	0.63	287 (2.5)	160 (2.8)	127 (2.2)	0.04
Biliary tract	869 (1.9)	19 (0.3)	850 (2.2)	0.17	39 (0.3)	19 (0.3)	20 (0.4)	<0.01
Pancreatic	1110 (2.5)	38 (0.7)	1072 (2.7)	0.16	84 (0.7)	38 (0.7)	46 (0.8)	0.02
Lung	8952 (19.8)	253 (4.4)	8699 (22.1)	0.54	572 (4.6)	253 (4.4)	274 (4.8)	0.02
Breast	4328 (9.6)	1129 (19.6)	3199 (8.1)	0.34	2255 (19.6)	1129 (19.6)	1126 (19.5)	<0.01
Cervical	275 (0.6)	4 (0.07)	271 (0.7)	0.10	6 (0.05)	4 (0.07)	2 (0.03)	0.02
Uterine body	356 (0.8)	7 (0.1)	349 (0.9)	0.11	17 (0.1)	7 (0.1)	10 (0.2)	0.01
Ovarian	291 (0.6)	2 (0.03)	289 (0.7)	0.11	4 (0.04)	2 (0.03)	2 (0.03)	<0.01
Prostate	10 156 (22.5)	3606 (62.5)	6550 (16.6)	1.06	7202 (62.5)	3598 (62.4)	3604 (62.5)	<0.01
Kidney and urinary tract	1657 (3.7)	79 (1.4)	1578 (4.0)	0.16	158 (1.4)	79 (1.4)	79 (1.4)	<0.01
Bladder	2917 (6.5)	85 (1.5)	2832 (7.2)	0.28	159 (1.4)	85 (1.5)	74 (1.3)	0.02
Leukaemia	1615 (3.6)	473 (8.2)	1142 (2.9)	0.23	936 (8.1)	471 (8.2)	465 (8.1)	0.00
Malignant melanoma	39 (0.09)	3 (0.05)	36 (0.09)	0.02	6 (0.05)	3 (0.05)	3 (0.05)	<0.01
Hodgkin lymphoma	89 (0.2)	1 (0.02)	88 (0.2)	0.06	2 (0.02)	1 (0.02)	1 (0.02)	<0.01
Malignant pleural mesothelioma	135 (0.3)	2 (0.03)	133 (0.3)	0.07	9 (0.08)	2 (0.03)	7 (0.1)	0.03
Hand and neck	165 (0.4)	4 (0.07)	161 (0.4)	0.07	7 (0.06)	4 (0.07)	3 (0.05)	0.01
Neuroblastoma	22 (0.05)	0 (0.0)	22 (0.06)	0.03	3 (0.03)	0 (0.0)	3 (0.05)	0.03
Non-Hodgkin lymphoma	1716 (3.8)	42 (0.7)	1674 (4.3)	0.23	80 (0.7)	42 (0.7)	38 (0.7)	0.01
Treatment (%)								
Diuretics								
Loop diuretics	38 429 (85.1)	5059 (87.6)	33 370 (84.7)	0.08	10 110 (87.7)	5052 (87.6)	5058 (87.7)	<0.01
Thiazide diuretics	3398 (7.5)	494 (8.6)	2904 (7.4)	0.04	968 (8.4)	494 (8.6)	474 (8.2)	0.01
Tolvaptan	15 094 (33.4)	2101 (36.4)	12 993 (33.0)	0.07	4247 (36.8)	2099 (36.4)	2148 (37.3)	0.02

(*Continues*)

Table 2 (continued)

	Non-matching				Matching			
	All	Chemotherapy	Non-chemotherapy	SMD	All	Chemotherapy	Non-chemotherapy	SMD
	(*n* = 45 186)	(*n* = 5774)	(*n* = 39 412)		(*n* = 11 532)	(*n* = 5766)	(*n* = 5766)	
RA	9855 (21.8)	1433 (24.8)	8422 (21.4)	0.08	2872 (24.9)	1430 (24.8)	1442 (25.0)	0.01
ACE inhibitor	13 157 (29.1)	1973 (34.2)	11 184 (28.4)	0.13	3942 (34.2)	1970 (34.2)	1972 (34.2)	<0.01
ARB	27 (0.06)	2 (0.03)	25 (0.06)	0.01	3 (0.03)	2 (0.03)	1 (0.02)	0.01
Renin	14 751 (32.7)	2006 (34.7)	12 745 (32.4)	0.05	4080 (35.4)	2006 (34.8)	2074 (36.0)	0.03
Beta-blocker	10 911 (24.2)	1563 (27.1)	9348 (23.7)	0.08	3124 (27.1)	1560 (27.1)	1564 (27.1)	<0.01
αβ-blocker	19 960 (44.2)	2764 (47.9)	17 196 (43.7)	0.09	5553 (48.2)	2759 (47.9)	2794 (48.5)	0.01
MRA	102 (0.2)	13 (0.2)	89 (0.2)	<0.01	28 (0.2)	13 (0.2)	15 (0.3)	0.01
ARNI	1440 (3.2)	177 (3.1)	1263 (3.2)	0.01	353 (3.1)	177 (3.1)	176 (3.1)	<0.01
SGLT2 inhibitor	24.1 ± 20.5	28.6 ± 23.1	23.5 ± 20.0	0.24	28.0 ± 23.4	28.4 ± 22.5	27.6 ± 24.4	0.04
Hospitalization (days), mean ± SD	18 (1–324)	22 (1–277)	18 (1–324)		21 (1–324)	22 (1–273)	20 (1–3249)	
Median (min–max)								

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; RA, renin–angiotensin; SGLT2, sodium–glucose cotransporter 2; SMD, standardized mean difference.

discontinued. We suggested that injection anti-cancer agents were difficult to be re-administered because they might lead to acute toxicity such as febrile neutropenia (FN), whereas oral anti-cancer agents rarely caused it.

Impact of chemotherapy on HF

After PS matching, readmission within 1 year in patients with HF receiving chemotherapy was significantly higher than that in matched patients who did not receive chemotherapy. Patients with HF are increasing dramatically because of an ageing population.[13] In addition, over the last few decades, there has been a remarkable improvement in the life expectancy of patients diagnosed with malignancies because of advances in cancer therapy. Therefore, patients with HF undergoing chemotherapy may have a high risk of readmission because of complicated long-term care management. In addition, these patients often experience serious AEs during chemotherapy. FN is a commonly encountered medical emergency in patients undergoing chemotherapy, and it needs to be managed in a hospital.[14] Nevertheless, we observed that hospital mortality is lower in patients with HF receiving chemotherapy compared with those who did not receive chemotherapy. The American Society of Clinical Oncology guidelines recommend against the use of chemotherapy in patients with solid tumours who have not benefited from prior treatment and have an Eastern Cooperative Oncology Group performance status score of 3 or more.[15] Therefore, a proportion of non-chemotherapy patients might be included in the best support care (BSC) for patients with HF and cancer.

Impact of anti-cancer agents on readmission

Fluorouracil agents are anti-cancer agents used in treating different types of solid malignancies.[16] Our study included fluorouracil agents mainly for breast, colon and lung cancers. Fluorouracil cardiotoxicity is reversible in most cases, and management includes discontinuation of the drug and use of guideline-directed medical therapy.[17] We observed that patients with HF who received fluorouracil agents before hospitalization were at higher risk of admission than patients with HF who did not receive chemotherapy. Chemotherapy in patients with breast cancer does not include only fluorouracil, but it is mainly combined with anthracycline, such as fluorouracil + epirubicin + cyclophosphamide (FEC) therapy.[18] Although combination with anthracycline may influence the outcome, we cannot discuss the readmission risk of combination chemotherapy in our study.

Anthracyclines are key drugs for adjuvant chemotherapy of breast cancer and are used in the treatment of different types of childhood cancer. However, they cause cardiotoxic effects associated with ventricular dysfunction.[19,20] In our

Figure 3 Odds ratio of 1 year readmission in patients treated with each anti-cancer drug compared with matched patients without chemotherapy. After propensity score matching, patients with heart failure who received chemotherapy such as epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), Janus-activated kinase (JAK) inhibitors, immunomodulatory drugs (IMiDs), fluorouracil agents, anthracyclines, taxanes, alkylating agents and endocrine therapy demonstrated a significant increase in 1 year readmission risk compared with matched patients who did not receive chemotherapy. ALK, anaplastic lymphoma kinase; Anti-VEGF, anti-vascular endothelial growth factor receptor; CI, confidence interval; CKD4/6, cyclin-dependent kinase 4/6; GnRH, gonadotropin-releasing hormone; HER2, human epidermal growth factor receptor 2; ICIs, immune checkpoint inhibitors; LHRH, luteinizing hormone-releasing hormone; mTOR, mammalian target of rapamycin.

	n	Readmission	Odds ratio [95%CI]	*P* value
Chemotherapy	5,766	3,212	1.26 [1.17, 1.36]	<0.01
ICIs	11	7	1.56 [0.46, 5.53]	0.48
HER2 inhibitors	148	90	1.39 [1.00, 1.94]	0.05
Anti-VEGF agents	64	39	1.61 [0.54, 4.81]	0.39
EGFR-TKIs	446	290	1.69 [1.39, 2.07]	<0.01
ALK inhibitors	9	5	1.12 [0.30, 4.16]	0.87
JAK inhibitors	13	11	4.92 [1.09, 22.23]	0.04
CKD4/6 inhibitors	19	8	0.65 [0.26, 1.62]	0.35
mTOR inhibitors	30	21	2.09 [0.96, 4.57]	0.06
IMiDs	16	15	13.44 [1.77, 101.77]	0.01
Proteasome inhibitors	11	9	4.03 [0.87, 18.65]	0.07
Fluorouracil agents	153	99	1.65 [1.18, 2.30]	<0.01
Anthracyclines	89	60	1.86 [1.19, 2.90]	<0.01
Taxane	191	146	2.95 [2.11, 4.12]	<0.01
Alkylating agents	330	198	1.35 [1.08, 1.69]	<0.01
Aromatase inhibitors	679	411	1.40 [1.19, 1.65]	<0.01
Anti-estrogens	190	106	1.13 [0.85, 1.51]	0.41
Anti-androgens	2,477	1,467	1.39 [1.27, 1.52]	<0.01
LHRH agonists	2,235	1,256	1.18 [1.08, 1.30]	<0.01
GnRH antagonists	294	207	2.17 [1.68, 2.79]	<0.01

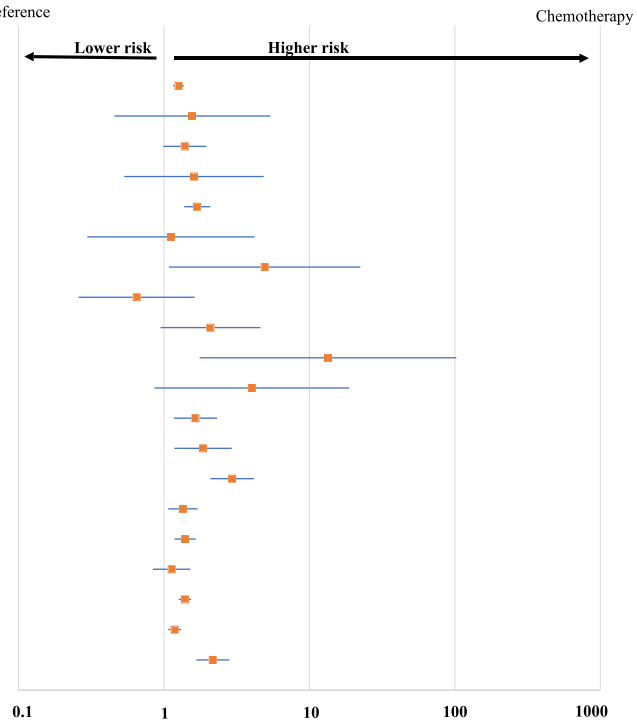


Table 3 In-hospital mortality after propensity score matching.

In-hospital mortality	Chemotherapy (n = 5766)	Non-chemotherapy (n = 5766)	*P* value
Mortality in 30 days, *n* (%)	243 (4.2)	444 (7.7)	<0.01

cohort, anthracyclines were administered mainly to patients with breast cancer. Serial monitoring of left ventricular (LV) ejection fraction (LVEF) while on anthracycline treatment demonstrates a cumulative percentage of significant LV systolic dysfunction of ≥7% at 200 mg/m^2, ≥16% at 400 mg/m^2, ≥20% at 500 mg/m^2 and ≥2% at ≥550 mg/m^2 equivalent dosage.[21] When reduced LVEF develops, an irreversible cardiac injury may have potentially occurred.[22,23] We observed that patients with HF who received anthracyclines before hospitalization were at a higher readmission risk than those who did not receive chemotherapy. Therefore, we need to be careful when managing anthracycline-induced HF.

Taxanes are key drugs for the chemotherapy of advanced cancers, such as breast and prostate cancers. In our study, taxanes were used mainly for breast and prostate cancers. Anti-microtubule agents called taxanes are associated with treatment-induced CV toxicity.[20] For chemotherapy in patients with breast cancer, taxanes are typically combined with anthracyclines, such as docetaxel, after adriamycin + cyclophosphamide (AC) therapy in adjuvant chemotherapy.[18] Although combination with anthracycline may influence the outcome, we cannot discuss the readmission risk of combination chemotherapy in our study.

EGFR inhibitors can be classified into three groups based on the type of cancer for which they are approved: afatinib for the treatment of non-small cell lung cancer, lapatinib for the treatment of breast cancer and vandetanib for the treatment of other types of cancer, such as thyroid cancer.[24,25] The risk of HF is highest in the initial stages of therapy, with 33.8% of patients receiving sorafenib, sunitinib and pazopanib experiencing a cardiac event during treatment for metastatic renal cell carcinoma.[26] In addition, in a meta-analysis of 29 000 patients with cancer, there was a 3.8-fold higher relative risk of hypertension in those treated with a VEGF tyrosine kinase inhibitor (TKI) compared with control subjects.[27] TKI is the main antineoplastic drug involved in developing peripheral artery disease.[28] Our cohort

mainly received EGFR-TKIs for leukaemia and lung cancer. We identified that patients with HF who received EGFR-TKIs before hospitalization had a higher risk of readmission than those who did not receive chemotherapy. As TKIs may continue even after discharge, medical providers must ensure careful monitoring and follow-up.

Myelofibrosis (MF) is a chronic myeloproliferative neoplasm characterized by bone marrow fibrosis, anaemia and splenomegaly. The oral JAK1/JAK2 inhibitor tuxolitinib continues to be the standard of care for high-risk MF. An increased risk of major adverse CV event (MACE) was observed in patients with rheumatoid arthritis receiving tofacitinib compared with those receiving tumour necrosis factor (TNF) blockers.[29] In contrast, a disproportionality analysis using the FDA Adverse Event Reporting System (FAERS) database and the World Health Organization VigiBase database showed no disproportionality for MACE with ruxolitinib.[30] We observed that patients with HF who received JAK inhibitors before hospitalization were at a higher readmission risk than those who did not receive chemotherapy. However, it is unknown whether ruxolitinib, a JAK inhibitor, induces cardiotoxicity.

An increased incidence of stroke has been demonstrated in patients with multiple myeloma (MM) receiving IMiDs such as thalidomide, lenalidomide and pomalidomide.[28] Some of the IMiDs have been associated with cardiotoxicity, in addition to their well-known increased risk of vascular complications, including venous thrombo-embolism, among others.[31] Pharmacovigilance analysis of the FAERS dataset showed that the percentage of cardiac AEs attributable to atrial fibrillation was high in pomalidomide (23.9%) and lenalidomide (18.2%).[32] In addition, MM is indeed a disease prevalent in the elderly population, who inherently carry an increased risk of CV disease solely because of age. Therefore, cardiotoxicity might be influenced not only by drug-induced factors but also by other elements, such as age.

Alkylating agents are key drugs for the chemotherapy of breast cancer, leukaemia and malignant lymphoma. We suggested that patients with HF who received alkylating agents before hospitalization have a higher readmission risk than those who did not receive chemotherapy. While cyclophosphamides are not typically categorized as chemotherapeutic drugs causing CV toxicity,[33] these agents are reported to induce hypertension[34] and may be linked to potentially adverse CV effects, including HF. Moreover, cyclophosphamide is combined with anthracycline, such as AC therapy for breast cancer. Therefore, alkylating agents may have potentially adverse CV effects, but there is also a need to consider confounding factors combined with anthracycline.

Patients with HF who received HER2 inhibitors were not significantly different in terms of readmission from those with HF who did not receive chemotherapy. However, it is recognized that anti-HER2 therapies may lead to LV dilation in up to 15%–20% of patients. LV function surveillance is recommended before and every 3 months during HER2-targeted therapy treatment.[33] A previous study reported that HER2 inhibitor-induced cardiotoxicity was at least partly reversible in more than two thirds of the cases.[35] Although HER2 inhibitors might have less influence on readmission because of the recovery of cardiac function by temporary discontinuation, LV function surveillance is needed to continue, based on guidelines.

Patients with HF who received ICIs, anti-VEGF agents, ALK inhibitors, CKD4/6 inhibitors, mTOR inhibitors and proteasome inhibitors were not significantly different in the case of readmission from those in patients with HF who did not receive chemotherapy. We acknowledge that the use of these agents was limited in our study. Moreover, although anti-VEGF agents induce cardiotoxicity,[33] their effects may vary depending on the type of cancer and the prescribed dosage for the specific indication.

Impact of endocrine therapy on readmission

We observed that patients with HF receiving endocrine therapy have increased readmission rates compared with their counterparts not receiving chemotherapy. Prostate and breast cancers have a high 5 year survival rate in Japan and worldwide at 99.1% and 92.3%, respectively.[12] However, endocrine therapies such as aromatase inhibitors, anti-androgens, LHRH agonists and GnRH antagonists require prolonged administration.[36] These agents induce hypertension[37] and are associated with potentially adverse CV effects, including HF. Recently, a study reported that aromatase inhibitors were associated with a higher risk of CV events.[38] Therefore, long-term endocrine therapy may be more difficult to manage in patients with HF. Medical providers need to be more careful regarding high-risk elderly patients with HF who are predicted to have cardiotoxicity. The European Society of Cardiology suggests that baseline clinical CV assessment, physical examination and electrocardiogram (ECG) are recommended in all cancer patients scheduled for cardiotoxic therapies.[33] Additional investigations, such as the monitoring of brain natriuretic peptide (BNP) levels, may be considered for the early detection of cardiotoxicity during endocrine therapy for patients with prostate and breast cancers.

Limitations

This study, which was based on ICD-10 codes, has several limitations. First, we only analysed hospitalized patients with HF in the database, which may have resulted in a selection bias. Second, although we excluded patients with planned hospitalization, 1 year readmission for any cause was the outcome. We needed to consider readmission due to other

causes such as CV events, because chemotherapy requires readmission for either receiving the next cycle of chemotherapy or dealing with side effects such as myelosuppression and infection. However, more than 80% of patients receive outpatient chemotherapy instead of inpatient chemotherapy at the DPC institutions in Japan.[39] In addition, adverse events in patients with cancer undergoing chemotherapy in Japan are managed better with various initiatives.[40,41] Emergency hospitalization rate in patients undergoing chemotherapy was 0.6% at the National Cancer Center Hospital East in Japan.[42] Some research suggested that outpatient care for low-risk FN emergency patients could be provided safely and effectively.[43,44] In our study, the readmission rate for the three groups (oral, transvenous or transarterial, and other) after PS matching was similar. Acutely toxic chemotherapy is typically discontinued during hospitalization, while oral anti-cancer drugs and hormone therapy are often continued, suggesting that hospitalization due to side effects of chemotherapy might be rare. However, we need to consider the detailed reasons for readmission in future studies, as adverse events such as FN caused by chemotherapy pose significant concerns. Third, regarding the diagnosis of HF, we could not classify ejection fraction (EF), such as reduced or preserved EF due to a lack of real-world clinical and DPC data, and we did not know the details of HF, such as BNP and causes. However, we considered that PS matching could reduce the confounding effects of differences in therapies in patients with HF, and there was similarity regarding severity including, to some extent, EF. Fourth, we could not identify the number of patients who showed signs of HF but without the need for hospitalization. However, in Japan's universal healthcare system, very few patients with severe HF symptoms or HF that is judged by a physician to require hospitalization stay home for socioeconomic reasons. Conversely, patients who enter palliative care because of cancer may choose to remain in hospice or at home rather than be readmitted. Fifth, regarding chemotherapy, it is unclear how many people who did not receive chemotherapy account for BSC and treatments other than chemotherapy. Sixth, our results might limit the effectiveness of observations made in relation to other healthcare systems, ethnic groups and different cancer disease management due to the database created in Japan. Although we could not solve those limitations in this database, we suggest that our study might be a meaningful first-stage report that would enable future development of research combining real-world clinical data with DPC data.

Conclusions

Patients with HF who received chemotherapy such as EGFR-TKIs, JAK inhibitors, IMiDs, fluorouracil agents, anthracyclines, taxanes, alkylating agents or endocrine therapy had a significantly higher risk of readmission within 1 year than those who did not receive chemotherapy. Medical providers need to monitor and follow-up patients with HF depending on the characteristics of the anti-cancer agents and types of cancer. In addition, close collaboration among oncologists, cardiologists and healthcare professionals will ensure the delivery of optimal care for patients with HF undergoing chemotherapy.

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Conflict of interest statement

Tomiko Sunaga received personal fees from the Academic Subcommittee on Health Care and Pharmaceutical Sciences. Yoshitaka Iso received speaker fees from Novartis, Bayer, Toa Eiyo, Tsumura, Daiichi Sankyo, AstraZeneca and Viatris and received a joint research grant from NTT Communications. Mio Ebato received speaker fees from Novartis, Otsuka, Sanofi, Pfizer, Ono, Bayer, Sumitomo Pharma, AstraZeneca, Boehringer Ingelheim and Kowa and has received scholarship funds from Pfizer. Tsutomu Toshida received speaker fees from Daiichi Sankyo and Toa Eiyo. Shuichi Nawata received speaker fees from Pfizer, Daiichi Sankyo, Chugai, Bristol Myers Squibb and Qol and also received consulting fees from Afrac and payment for manuscript writing from Lilly. Hiroshi Suzuki received speaker fees from Novartis and Otsuka, scholarship funds from Abbott and Daiichi Sankyo, and a joint research grant from Abbott. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. The Department of Hospital Pharmaceutics, School of Pharmacy, Showa University, received a contract for research from Ono Pharmaceutical Co., Ltd.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Receiver operating characteristic curve and concordance index.

Figure S2. Comparison the consistency of propensity score densities before and after matching.

Table S1. International Classification of Disease, Tenth Revision (ICD-10) diagnosis codes of heart failure and cancer.

Table S2. Defined type of anti-cancer agents.

References

1. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: a comprehensive and updated review of epidemiology. *Cardiovasc Res* 2023;**118**:3272-3287. doi:10.1093/cvr/cvac013
2. Jones N, Roalfe A, Adoki I, Hobbs FDR, Taylor CJ. Survival of patients with chronic heart failure in the community: a systematic review and meta-analysis. *Eur J Heart Fail* 2019;**21**:1306-1325. doi:10.1002/ejhf.1594
3. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, *et al*. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for Cancer Treatments and Cardiovascular Toxicity of the European Society of Cardiology (ESC). *Eur Heart J* 2016;**37**:2768-2801. doi:10.1093/eurheartj/ehw211
4. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin* 2019;**69**:7-34. doi:10.3322/caac.21551
5. Dolladille C, Akroun J, Morice PM, Dompmartin A, Ezine E, Sassier M, *et al*. Cardiovascular immunotoxicities associated with immune checkpoint inhibitors: a safety meta-analysis. *Eur Heart J* 2021;**42**:4964-4977. doi:10.1093/eurheartj/ehab618
6. Moliner P, Lupón J, de Antonio M, Domingo M, Santiago-Vacas E, Zamora E, *et al*. Trends in modes of death in heart failure over the last two decades: less sudden death but cancer deaths on the rise. *Eur J Heart Fail* 2019;**21**:1259-1266. doi:10.1002/ejhf.1569
7. Adhikari BB, Shi S, Dimond EP, Shelburne N, Desvigne-Nickens P, Minasian LM. Spectrum of National Institutes of Health-funded research in cardio-oncology: a basic, clinical, and observational science perspective. *Heart Fail Clin* 2022;**18**:515-528. doi:10.1016/j.hfc.2022.01.001
8. Leong DP, Lenihan DJ. Clinical practice guidelines in cardio-oncology. *Heart Fail Clin* 2022;**18**:489-501. doi:10.1016/j.hfc.2022.02.002
9. Wu WC, Huang CC, Tsai YF, Lin YS, Feng CJ, Chen YJ, *et al*. The association of trastuzumab with atrial fibrillation and heart failure in breast cancer patients in routine clinical practice: a population-based propensity score matching and competing risk model analysis. *Breast Cancer Res Treat* 2023;**198**:112-122. doi:10.1007/s10549-022-06753-7
10. Ohtsu H, Shimomura A, Miyazaki S, Yonemoto N, Ueda S, Shimizu C, *et al*. Cardiotoxicity of adjuvant chemotherapy with trastuzumab: a Japanese claim-based data analysis. *Open Heart* 2022;**9**:e002053. doi:10.1136/openhrt-2022-002053
11. Chien HC, Yang YHK, Bai JP. Trastuzumab-related cardiotoxic effects in Taiwanese women: a nationwide cohort study. *JAMA Oncol* 2016;**2**:1317-1325. doi:10.1001/jamaoncol.2016.1269
12. Cancer statistics in Japan—2021. https://ganjoho.jp/public/qa_links/report/statistics/2021_en.html (2021). Accessed 6 Nov 2023.
13. Shimokawa H, Miura M, Nochioka K, Sakata Y. Heart failure as a general pandemic in Asia. *Eur J Heart Fail* 2015;**17**:884-892. doi:10.1002/ejhf.319
14. Gould Rothberg BE, Quest TE, Yeung SJ, Pelosof LC, Gerber DE, Seltzer JA, *et al*. Oncologic emergencies and urgencies: a comprehensive review. *CA Cancer J Clin* 2022;**72**:570-593. doi:10.3322/caac.21727
15. Schnipper LE, Smith TJ, Raghavan D, Blayney DW, Ganz PA, Mulvey TM, *et al*. American Society of Clinical Oncology identifies five key opportunities to improve care and reduce costs: the top five list for oncology. *J Clin Oncol* 2012;**30**:1715-1724. doi:10.1200/JCO.2012.42.8375
16. Mishra T, Shokr M, Ahmed A, Afonso L. Acute reversible left ventricular systolic dysfunction associated with 5-fluorouracil therapy: a rare and increasingly recognised cardiotoxicity of a commonly used drug. *BMJ Case Rep* 2019;**12**:e230499. doi:10.1136/bcr-2019-230499
17. Saif MW, Shah MM, Shah AR. Fluoropyrimidine-associated cardiotoxicity: revisited. *Expert Opin Drug Saf* 2009;**8**:191-202. doi:10.1517/14740330902733961
18. Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio IT, *et al*. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2019;**30**:1194-1220. doi:10.1093/annonc/mdz173
19. Cheuk DK, Sieswerda E, van Dalen EC, Postma A, Kremer LC. Medical interventions for treating anthracycline-induced symptomatic and asymptomatic cardiotoxicity during and after treatment for childhood cancer. *Cochrane Database Syst Rev* 2016;**2016**:CD008011. doi:10.1002/14651858.CD008011.pub3
20. Albini A, Pennesi G, Donatelli F, Cammarota R, de Flora S, Noonan DM. Cardiotoxicity of anticancer drugs: the need for cardio-oncology and cardio-oncological prevention. *J Natl Cancer Inst* 2010;**102**:14-25. doi:10.1093/jnci/djp440
21. Curigliano G, Lenihan D, Fradley M, Ganatra S, Barac A, Blaes A, *et al*. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. *Ann Oncol* 2020;**31**:171-190. doi:10.1016/j.annonc.2019.10.023
22. Jensen BV, Skovsgaard T, Nielsen SL. Functional monitoring of anthracycline cardiotoxicity: a prospective, blinded, long-term observational study of outcome in 120 patients. *Ann Oncol* 2002;**13**:699-709. doi:10.1093/annonc/mdf132
23. Lipshultz SE, Colan SD, Gelber RD, Perez-Atayde AR, Sallan SE, Sanders SP. Late cardiac effects of doxorubicin therapy for acute lymphoblastic leukemia in childhood. *N Engl Med* 1991;**324**:808-815. doi:10.1056/NEJM199103213241205
24. Uribe ML, Marrocco I, Yarden Y. EGFR in cancer: signaling mechanisms, drugs, and acquired resistance. *Cancers (Basel)* 2021;**13**:2748. doi:10.3390/cancers13112748
25. Abourehab MAS, Alqahtani AM, Youssif BGM, Gouda AM. Globally approved EGFR inhibitors: insights into their syntheses, target kinases, biological activities, receptor interactions, and metabolism. *Molecules* 2021;**26**:6677. doi:10.3390/molecules26216677

26. Schmidinger M, Zielinski CC, Vogl UM, Bojic A, Bojic M, Schukro C, *et al*. Cardiac toxicity of sunitinib and sorafenib in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2008;**26**:5204-5212. doi:10.1200/JCO.2007.15.6331
27. Totzeck M, Mincu RI, Mrotzek S, Schadendorf D, Rassaf T. Cardiovascular diseases in patients receiving small molecules with anti-vascular endothelial growth factor activity: a meta-analysis of approximately 29,000 cancer patients. *Eur J Prev Cardiol* 2018;**25**:482-494. doi:10.1177/2047487318755193
28. Zito C, Manganaro R, Carerj S, Antonini-Canterin F, Benedetto F. Peripheral artery disease and stroke. *J Cardiovasc Echogr* 2020;**30**:S17-S25. doi:10.4103/jcecho.jcecho_4_19
29. Ytterberg SR, Bhatt DL, Mikuls TR, Koch GG, Fleischmann R, Rivas JL, *et al*. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. *N Engl J Med* 2022;**38**:316-326. doi:10.1056/NEJMoa2109927
30. Verstovsek S, Mesa RA, Livingston RA, Hu W, Mascarenhas J. Ten years of treatment with ruxolitinib for myelofibrosis: a review of safety. *J Hematol Oncol* 2023;**16**:82. doi:10.1186/s13045-023-01471-z
31. Cheikh JE, Moukalled N, Malard F, Bazarbachi A, Mohty M. Cardiac toxicities in multiple myeloma: an updated and a deeper look into the effect of different medications and novel therapies. *Blood Cancer J* 2023;**13**:83. doi:10.1038/s41408-023-00849-z
32. Ahmad J, Thurlapati A, Thotamgari S, Grewal US, Sheth AR, Gupta D, *et al*. Anti-cancer drugs associated atrial fibrillation—an analysis of real-world pharmacovigilance data. *Front Cardiovasc Med* 2022;**9**:739044. doi:10.3389/fcvm.2022.739044
33. Lyon AR, Fernández TL, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J, *et al*. 2022 ESC guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J* 2022;**43**:4229-4361. doi:10.1093/eurheartj/ehac244
34. Chung R, Tyebally S, Chen D, Kapil V, Walker JM, Addison D, *et al*. Hypertensive cardiotoxicity in cancer treatment—systematic analysis of adjunct, conventional chemotherapy, and novel therapies—epidemiology, incidence, and pathophysiology. *J Clin Med* 2020;**9**:3346. doi:10.3390/jcm9103346
35. Bouwer N, Steenbruggen TG, Rier HN, Kitzen JJEM, Smorenburg CH, van Bekkum ML, *et al*. The effect of trastuzumab on cardiac function in patients with HER2-positive metastatic breast cancer and reduced baseline left ventricular ejection fraction. *Int J Cancer* 2022;**151**:616-622. doi:10.1002/ijc.34024
36. Burstein HJ, Lacchetti C, Anderson H, Buchholz TA, Davidson NE, Gelmon KA, *et al*. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: ASCO clinical practice guideline focused update. *J Clin Oncol* 2019;**37**:423-438. doi:10.1200/JCO.18.01160
37. Cohen JB, Brown NJ, Brown SA, Dent S, van Dorst DCH, Herrmann SM, *et al*. Cancer therapy-related hypertension: a scientific statement from the American Heart Association. *Hypertension* 2023;**80**:e46-e57. doi:10.1161/HYP.0000000000000224
38. Boszkiewicz K, Piwowar A, Petryszyn P. Aromatase inhibitors and risk of metabolic and cardiovascular adverse effects in breast cancer patients—a systematic review and meta-analysis. *J Clin Med* 2022;**11**:3133. doi:10.3390/jcm11113133
39. Ministry of Health, Labour and Welfare of Japan. About policy. https://www.mhlw.go.jp/content/12404000/001145874.pdf. Accessed 7 Jul 2024
40. Suzuki H, Suzuki S, Kamata H, Sugama Y, Demachi K, Ikegawa K, *et al*. Impact of pharmacy collaborating services in an outpatient clinic on improving adverse drug reactions in outpatient cancer chemotherapy. *J Oncol Pharm Pract* 2019;**25**:1558-1563. doi:10.1177/1078155218798138
41. Ueda R, Tanda M, Ito T, Enomoto A, Iida M, Mizuta N, *et al*. Evaluation of the collaboration system between community pharmacies and hospital for the management of oral anti-cancer therapy using information sharing tools and team-based learning. *Iryoyakugaku* 2020;**46**:681-691. doi:10.5649/jjphcs.46.681
42. Diagnosis and treatment performance, research performance, and clinical indicators. Medical safety indicators. https://www.ncc.go.jp/jp/ncce/about/achievement/index.html. Accessed 7 Jul 2024
43. Marshall W, Campbell G, Knight T, Al-Sayed T, Cooksley T. Emergency ambulatory management of low-risk febrile neutropenia: Multinational Association for Supportive Care in Cancer fits—real-world experience from a UK cancer center. *J Emerg Med* 2020;**58**:444-448. doi:10.1016/j.jemermed.2019.09.032
44. Heo S, Jeon K, Park B, Ko RE, Kim T, Hwang SY, *et al*. Clinical factors predicting return emergency department visits in chemotherapy-induced febrile neutropenia patients. *Am J Emerg Med* 2023;**67**:90-96. doi:10.1016/j.ajem.2023.02.012