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Original Article

Prevalence, clinical characteristics, and impact of active cancer in patients with acute myocardial infarction: data from an all-comer registry

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ABSTRACT

Background: Although a history of cancer is a poor prognostic factor in patients with acute myocardial infarction (AMI), the clinical importance of coexisting active cancer remains unclear.
Methods: In this single-center retrospective study, we reviewed an AMI registry and assessed the prevalence and predictors of active cancer, 1-year incidence of cardiac death or major bleeding events (defined as a Bleeding Academy Research Consortium type 3 or 5), and the impact of coexisting active cancer on clinical outcomes. Active cancer was defined as either an already-diagnosed or undiagnosed occult cancer.
Results: Between January 2012 and December 2017, 1140 AMI patients (median age, 69 years; male, 76.0%) were enrolled. Active and historical cancers were diagnosed in 63 patients (5.5%) and 50 patients (4.4%), respectively. The most common location was the urinary tract (n=21). In the Kaplan-Meier analysis, the active cancer group had a higher incidence of 1-year cardiac death (17.5% vs. 5.3%, $p < 0.001$) and major bleeding events (19.0% vs. 5.6%, $p < 0.001$) than the non-cancer group. In the multivariate Cox proportional hazards regression models, active cancer was an independent predictor of both cardiac death and major bleeding at 1 year. Specifically, gastrointestinal tract and advanced-stage cancers had the poorest outcomes. Compared to the non-cancer group, the 1-year major bleeding rate was higher for all cancer types and stages. In contrast, early-stage cancers had a weaker impact on the 1-year cardiac mortality compared to advanced-stage cancers. Similarly, cardiac death during 1-year also occurred less frequently in occult cancers than in already-known cancers.
Conclusions: In patients with AMI, coexisting active cancer was rare, but it significantly impacted cardiac death and major bleeding events.

Introduction

Cancer and cardiovascular diseases are the leading causes of death worldwide. These diseases often coexist because they share various risk factors, both classical (such as tobacco smoking, obesity, and diabetes) [1] and novel (such as inflammation and genetic characteristics) [2,3]. Patients with cardiovascular disease and cancer have higher cardiovascular mortality than the non-cancer population [4-6]. In this regard, the interest in cardio-oncology as a subspecialty has been continuously growing, highlighting the need for epidemiological investigations addressing cancer-related cardiovascular disease and the impact of coexisting cancer on cardiovascular outcomes.

According to previous studies, patients with acute myocardial infarction (AMI) and coexisting cancer are rare and have an increased risk of death and bleeding complications [7-10]. However, selection bias might have occurred in two of these studies [7,9] due to the exclusion of patients who did not undergo percuta-

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neous coronary intervention (PCI), died during hospitalization, and did not have a primary diagnosis of AMI. Furthermore, the remaining studies only assessed the previous history of cancer but not active cancer. As a result, the prevalence and clinical impact of active cancer in patients with AMI remain unestablished. In this all-comer registry study, we aimed to investigate the prevalence, clinical characteristics, and clinical outcomes of AMI in patients with active cancer in a real-world setting.

Methods

Study population and data collection

We retrospectively reviewed an all-comer database that included 1140 consecutive AMI patients admitted to the Iwate Medical University Hospital between January 2012 and December 2017. The demographic, clinical, laboratory, and imaging data were collected from medical records.

AMI was diagnosed in accordance with the Third Universal Definition of Myocardial Infarction [11]. Based on the applicable guidelines during the study period [12,13], patients received dual antiplatelet therapy (DAPT) at the standard dose used in Japan (aspirin 81–200 mg/day with clopidogrel 75 mg/day or aspirin 81–200 mg/day with prasugrel 3.75 mg/day), administered at the discretion of the attending physician. Following drug-eluting stent implantation, DAPT was taken for 12 months in patients with ST-elevation myocardial infarction (STEMI) and at least 6 months in those with non-ST-elevation MI (NSTEMI).

Active cancer was defined as an already-diagnosed cancer or undiagnosed "occult" cancer that was diagnosed or suspected during the first hospitalization. In this study, patients with a history of cancer who had undergone curative surgical treatment and completed chemoradiation therapy were categorized into the historical cancer group, while patients without active cancer or cancer history were categorized into the non-cancer group. In addition, early- and advanced-staged cancer were defined based on the presence or absence of metastasis (or organ infiltration in the case of leukemia). In terms of the clinical background, hypertension was defined as a blood pressure greater than 140/90 mmHg or the use of antihypertensive medication. Dyslipidemia was defined as triglyceride >150 mg/dL, low-density lipoprotein cholesterol >140 mg/dL, high-density lipoprotein cholesterol <40 mg/dL, or the use of antidyslipidemic agents. Diabetes mellitus was defined as fasting plasma glucose $\geq$ 126 mg/dL, random plasma glucose $\geq$ 200 mg/dL, HbA1c $\geq$ 6.5%, or receiving medical treatment for diabetes mellitus. Renal deficiency was defined as an estimated glomerular filtration rate of < 60 mL/min/1.73 m^2.

The study protocol was developed on the basis of the code of the Ethics Committee of Iwate Medical University (MH2019-094) and implemented in accordance with the Declaration of Helsinki. Although comprehensive informed consent was obtained from each patient at the time of admission, additional informed consent for this study was obtained through an opt-out format on the website (https://iwate-heart.jp/public_information/).

Clinical outcomes

The primary endpoint was cardiac death. The secondary endpoints were major bleeding events (defined as a Bleeding Academic Research Consortium type 3 or 5 bleeding) [14], non-cardiac death, any bleeding events, minor bleeding events (defined as Bleeding Academic Research Consortium type 1 or 2 bleeding), spontaneous MI, and ischemic stroke. The clinical outcomes were diagnosed based on the standardized definitions by the Academic Research Consortium [15]. All 1-year clinical events were confirmed by medical records or by telephone. The cause of death was determined by a case conference held with all the members of our division.

Statistical analysis

All data are presented as the median (1st–3rd quartile) or number (percentage). The categorical data were compared between groups were using the chi-square contingency test or Fisher's exact test, as appropriate. The medians were compared between groups using the Mann-Whitney U test. A receiver operating characteristic curve analysis was performed to establish the cut-off values of the predictive factors.

Regarding the incidence of the primary and secondary clinical outcomes, the active cancer group and historical cancer group were compared with the non-cancer group. One-year cumulative outcomes were estimated using the Kaplan-Meier method and compared using the log-rank test. A Cox proportional hazards regression model was used to evaluate the predictors of each endpoint in the clinical outcome of AMI patients. Statistically significant variables in the univariate analysis were included in the multivariate analysis to evaluate the independent predictors. These clinical variables were selected based on the Coronary Revascularization Demonstrating Outcome Study in Kyoto's thrombotic and bleeding risk scores and the Japanese criteria for high bleeding risk [16,17]. Differences were considered significant at $p < 0.05$. All statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (version 21.0; SPSS, Chicago, IL, USA).

Results

Prevalence and type of active cancer

Overall, 5.5% (n=63) of all AMI patients had coexisting active cancer, and 4.4% (n=50) were in the historical cancer group. Early- and advanced-stage cancers were observed in 35 (3.1%) and 28 (2.5%) patients, respectively (Supplemental Table 1). In addition, already-known cancers accounted for 82% (n=52) of all cancers; only 18% (n=11) of all cancers were occult. Focusing on the relationship between cancer stage and diagnosis, early-stage cancer was found in 48.1% (n=25) of already-known cancers and 90.9% (n=10) of occult cancers (Supplemental Table 1).

Urinary cancers (including prostate, urinary tract, and bladder cancers) were the most common (n=21), followed by gastrointestinal (GI) tract (n=14; including gastric, colon, hepatobiliary, and pancreas) and lung cancers (n=11). Head and neck (n=6), hematological (n=4), unknown primary (n=3), gynecological (n=2), breast (n=1), and sarcomatous (n=1) cancers were categorized as "other cancers."

Six cases of primary tumors or metastases were incidentally found on computed tomography (CT) scans performed for aortic aneurysm or arteriosclerosis obliterans, while two cases of lung cancer were detected on chest X-ray scans performed on admission. Two cases of bladder cancers were diagnosed due to hematuria, and one case of colon cancer was diagnosed due to anemia.

Baseline characteristics

Table 1 shows a comparison of the baseline characteristics of the non-cancer and active cancer groups. Compared to the non-cancer group, the active cancer group had an older age (68 vs. 75 years, $p < 0.001$), lower body mass index (24.1 vs. 23.6, $p = 0.04$), higher prevalence of renal deficiency (12.4 vs. 22.2%, $p = 0.03$), lower prevalence of dyslipidemia (51.8 vs. 38.1%, $p = 0.02$), lower low-density lipoprotein cholesterol (113 vs. 101 mg/dL, $p < 0.01$) and hemoglobin levels (13.5 vs. 12.4 g/dL, $p < 0.001$), and lower (< 40%) ejection fraction (53 vs. 50 %, $p = 0.02$). Specifically, the

Table 1
Baseline characteristics

	Non-cancer group (n=1027)	Active cancer group (n=63)	Historical cancer group (n=50)	Non vs. Active *p*-value	Non vs. Historical *p*-value
Age, years	68 (59 - 78)	75 (69 – 81)	76 (67 – 82)	<0.001	<0.001
Male gender	779 (75.8)	51 (81.0)	36 (72.0)	0.36	0.54
BMI, kg/m²	24.1 (21.9 – 26.8)	23.6 (21.0 – 25.6)	22.4 (19.9 – 25.5)	0.04	0.005
Hypertension	709 (69.0)	40 (63.5)	39 (78.0)	0.38	0.22
Dyslipidemia	532 (51.8)	24 (38.1)	18 (36.0)	0.02	0.02
Diabetes Mellitus	365 (35.6)	24 (38.1)	20 (40.0)	0.87	0.57
Current smoker	350 (34.1)	15 (23.8)	11 (22.0)	0.13	0.07
History of PCI	98 (9.5)	5 (7.9)	8 (16.0)	0.67	0.12
History of CABG	21 (2.0)	2 (3.2)	1 (2.0)	0.39	0.72
History of Stroke	93 (9.1)	11 (17.5)	2 (4.0)	0.06	0.17
STEMI	543 (52.9)	36 (57.1)	27 (54.0)	0.32	0.66
Killip class 3 or 4	140 (13.6)	13 (20.6)	8 (16.0)	0.11	0.65
CPA on arrival	53 (5.2)	3 (4.8)	2 (4.0)	0.60	0.51
IABP use	112 (10.9)	7 (11.1)	3 (6.0)	0.85	0.31
VA-ECMO use	20 (1.9)	1 (1.6)	0 (0.0)	0.67	0.40
Hb, mg/dl	13.5 (12.2 – 14.8)	12.4 (11.0 – 14.0)	12.9 (11.2 – 14.4)	<0.001	0.04
Plt, x10⁴ /μg	21.6 (17.8 – 25.9)	22.0 (17.7 – 27.7)	20.1 (17.6 – 25.7)	0.56	0.40
Renal deficiency	127 (12.4)	14 (22.2)	8 (16.0)	0.03	0.51
LDL-C, mg/dL	113 (90 – 138)	101 (74 – 128)	101 (84 – 129)	0.01	0.08
HDL-C, mg/dL	45 (38 – 54)	43 (33 – 51)	46 (41 – 58)	0.08	0.10
TG, mg/dl	101 (69 – 155)	93 (68 - 131)	88 (64 – 122)	0.26	0.17
HbA1c, %	5.8 (5.4 – 6.4)	5.9 (5.5 – 6.3)	5.9 (5.5 – 6.5)	0.35	0.07
BNP, pg/mL	113 (42 – 317)	263 (39 – 654)	208 (79 – 360)	<0.001	0.02
EF <40%, %	53 (44 - 60)	49 (39 - 56)	51 (43 - 59)	0.02	0.40
Max CK, IU/L	1259 (341 – 3103)	847 (235 – 2752)	914(393 – 3258)	0.25	0.89

Data are presented as median (1st quartile-3rd quartile), or n (%).
BMI, body mass index; BNP, brain natriuretic peptide; CABG, coronary artery bypass grafting; CK, creatine phosphokinase; CPA, cardiopulmonary arrest; EF, ejection fraction; Hb, hemoglobin; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; IABP, intra-aortic balloon pumping; LDL-C, low-density lipoprotein cholesterol; PCI, percutaneous coronary intervention; Plt, platelet counts; STEMI, ST-segment elevation myocardial infarction; TG, triglyceride; VA-ECMO, venoarterial extracorporeal membrane oxygenation.

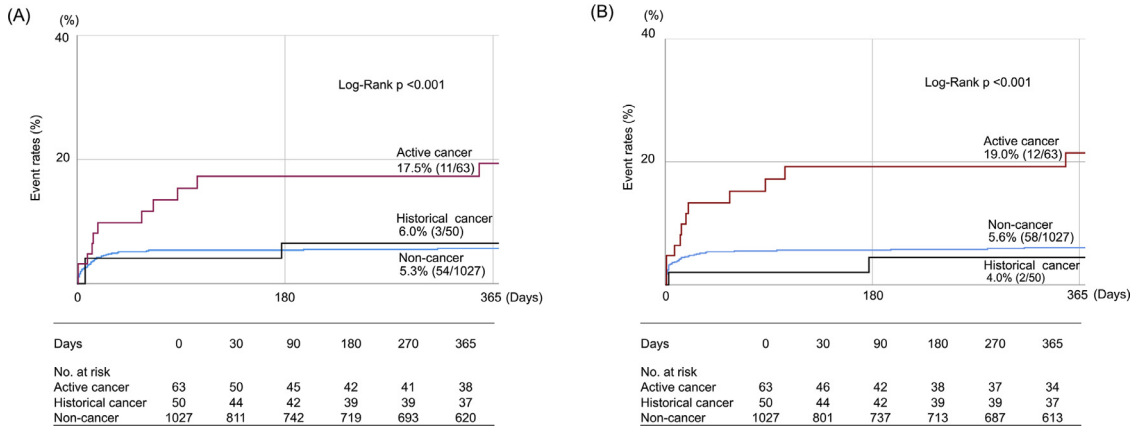


Fig. 1. One-year Kaplan-Meier curves for survival from cardiovascular death (A) and major bleeding (B).
The active cancer group experienced significantly more cardiac deaths than the non-cancer and historical cancer groups. These events occurred mostly during the first 180 days of myocardial infarction. Patients with cancer suffered significantly more episodes of major bleeding than those without active cancer. The increase in bleeding rate parallels that in cardiac death rate.

prevalence of active cancer was relatively high (> 7.0%) in the patients aged ≥ 65 years (Online Fig. 1).

The angiographic features and medications used at discharge are shown in Table 2. There was no difference in the angiographic findings or revascularization strategies between the two groups. However, compared to the non-cancer group, beta-blockers and statins were used less frequently in the active cancer group. Because four patients with active cancer underwent a non-stent procedure (thrombus aspiration and/or ballooning) and nine patients who underwent major bleeding events had DAPT de-escalation before discharge, the use of DAPT at discharge in the active cancer group was also less frequent than in the non-cancer group. Both groups received oral anticoagulants and acid-suppressive drugs (proton pump inhibitor or histamine-2 receptor blockers) at a similar rate. Notably, in the patients with major bleeding events, the usage rate of DAPT at the time of bleeding was significantly lower than that in patients without major bleeding events (56.9% vs. 76.7%, respectively; p < 0.001).

One-year clinical outcomes

In the complete cohort, cardiac death and major bleeding occurred in 68 (6.0%) and 72 patients (6.3%), respectively, during the 1-year follow-up period (details of major bleeding events are shown in Supplemental Table 2). Notably, 95.6% (n=65) of the patients who died of cardiac causes experienced major bleeding events.

Table 2
Angiographic findings and medications at discharge.

	Non-cancer group (n=1027)	Active cancer group (n=63)	Historical cancer group (n=50)	Non vs. Active *p*-value	Non vs. Historical *p*-value
Angiographic findings					
LM lesion	91 (8.9)	6 (9.5)	4 (2.0)	0.77	0.62
Multi-vessel disease	571 (55.6)	32 (50.8)	28 (56.0)	0.79	0.67
Urgent PCI	810 (78.9)	49 (77.8)	39 (78.0)	0.84	0.88
Urgent + elective PCI	862 (84.0)	52 (82.5)	42 (84.0)	0.77	0.99
Urgent CABG	85 (8.3)	3 (4.8)	6 (12.0)	0.31	0.25
Femoral approach	185 (18.0)	10 (15.9)	7 (14.0)	0.67	0.47
Medications at discharge					
ACEi or ARB	615 (59.9)	30 (47.6)	35 (70.0)	0.06	0.15
Beta blocker	562 (54.7)	22 (34.9)	23 (46.0)	0.002	0.23
Statin	824 (80.2)	40 (63.5)	39 (78.0)	0.001	0.67
DAPT	806 (78.5)	37 (58.7)	38 (76.0)	0.005	0.63
OAC	102 (9.9)	8 (12.7)	4 (8.0)	0.83	0.46
PPI or H_2 blocker	873 (85.0)	49 (77.8)	41 (82.0)	0.19	0.70

Data presented as n (%)
ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CABG, coronary artery bypass grafting; DAPT, dual antiplatelet therapies; H_2 blocker, histamine-2 receptor blockers; LM, left main; OAC, oral anticoagulants; PCI, percutaneous coronary intervention; PPI, proton pump inhibitors.

Table 3
One-year clinical outcomes in acute myocardial infarction patients with and without active cancer.

	Non-cancer group (n=1027)	Active cancer group (n=63)	Historical cancer group (n=50)	Non vs. Active *p*-value	Non vs. Historical *p*-value
All cause death	77 (7.5)	17 (27.0)	3 (6.0)	<0.001	0.48
Cardiac death	54 (5.3)	11 (17.5)	3 (6.0)	<0.001	0.50
Non-cardiac death	23 (2.2)	6 (9.5)	0 (0.0)	0.005	0.33
Any bleeding events	114 (11.1)	22 (34.9)	5 (10.0)	<0.001	0.81
Major bleeding events	58 (5.6)	12 (19.0)	2 (4.0)	<0.001	0.46
Minor bleeding events	56 (5.5)	10 (15.9)	3 (6.0)	0.003	0.53
Spontaneous MI	20 (1.9)	5 (7.9)	0 (0.0)	0.01	0.38
Ischemic stroke	20 (1.9)	3 (4.8)	1 (2.0)	0.14	0.64

Data presented as n (%).
Major bleeding event was defined as BARC type 3 or 5 bleeding.
Minor bleeding event was defined as BARC type 1 or 2 bleeding.
BARC, Bleeding Academic Research Consortium; MI, myocardial infarction.

Table 4
Cox proportional hazards regression model for cardiac death.

	Univariate			Multivariate		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age	1.07	1.04 – 1.09	<0.001	1.04	1.01 – 1.07	0.005
Male gender	1.82	1.09 – 3.02	0.02	2.17	1.14 – 4.15	0.02
BMI, kg/m^2	0.85	0.85 – 0.97	0.005	0.98	0.91 – 1.05	0.50
Hb, mg/dl	0.82	0.74 – 0.92	<0.001	1.03	0.88 – 1.20	0.74
eGFR, mL/min/1.73m^2	0.97	0.96 – 0.98	<0.001	0.98	0.97 – 0.99	0.002
STEMI	1.71	1.11 – 2.65	0.02	2.18	1.34 – 3.55	0.002
Killip class 3 or 4	15.64	9.18 – 26.65	<0.001	7.74	4.37 – 13.70	<0.001
Active cancer	3.32	1.74 – 6.34	<0.001	2.39	1.18 – 4.85	0.02

BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HR, hazard ratio; STEMI, ST-segment elevation myocardial infarction.

The patients with active cancer had significantly higher rates of cardiac death (5.3% vs. 17.5%; $p < 0.001$) and major bleeding events during the first year (5.6% vs. 19.0%; $p < 0.001$) than the patients without active cancer (Table 3). In the patients with active cancer, most cardiac deaths and major bleeding events occurred within 2 months of AMI onset (Fig. 1). Regarding the causes of cardiac death in this subgroup, eight were due to heart failure or sudden ventricular arrhythmia following AMI, two due to free wall rupture caused by delayed hospital arrival, and one due to out-of-hospital cardiac arrest (104 days after AMI onset). Notably, 82% (9/11) of these patients developed major bleeding events. Three patients refused aggressive or life-prolonging treatments because of their adverse cancer prognosis. In the present study, there was no significant difference in the cardiac death and major bleeding rates between the non-cancer and historical cancer groups (Table 3).

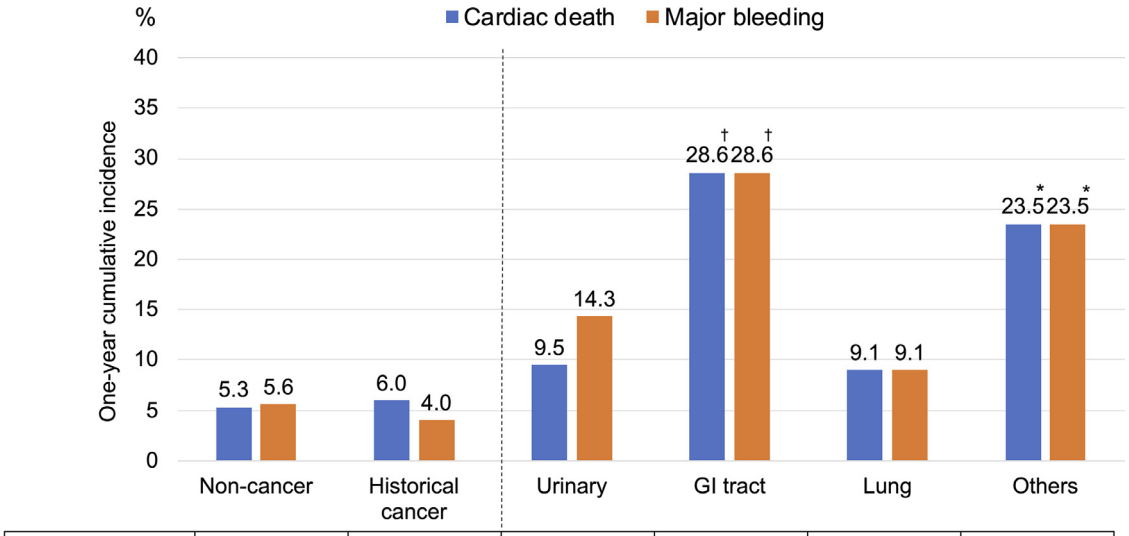
Impact of active cancer on 1-year AMI outcomes

Well-known cardiovascular risk factors and the presence of cancer were included in the univariate and multivariate Cox proportional hazards regression models to investigate their association with the 1-year clinical outcomes. Active cancer was an independent predictor of 1-year cardiac death, similar to advanced age, male sex, estimated glomerular filtration rate, STEMI, and Killip class III or IV (Table 4). In addition, advanced age, estimated

Table 5
Cox proportional hazards regression model for major bleeding events.

	Univariate			Multivariate		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age	1.07	1.04 – 1.09	<0.001	1.04	1.01 – 1.07	0.003
Male gender	1.62	0.98 – 2.66	0.06	N/A	N/A	N/A
BMI, kg/m^2	0.92	0.87 – 0.99	0.02	1.00	0.93 – 1.07	0.90
Hb, mg/dl	0.79	0.71 – 0.88	<0.001	0.89	0.77 – 1.02	0.10
Plt, x10^4 /μg	1.00	0.97 – 1.03	0.78	N/A	N/A	N/A
eGFR, mL/min/1.73m^2	0.97	0.96 – 0.98	<0.001	0.99	0.98 – 1.00	0.046
STEMI	1.55	1.03 – 2.33	0.04	1.79	1.15 – 2.80	0.010
Killip class 3 or 4	13.33	8.09 – 21.97	<0.001	6.61	3.82 – 11.38	<0.001
Triple therapy	0.30	0.04 – 2.18	0.24	N/A	N/A	N/A
Femoral approach	3.38	2.10 – 5.44	<0.001	1.61	0.95 – 2.74	0.08
Active cancer	3.47	1.86 – 6.46	<0.001	2.08	1.08 – 4.02	0.03

Triple treatment was defined as oral anticoagulant therapy with dual antiplatelet therapy.
BMI, body mass index; CI, confidence interval; N/A, not applicable; Hb, hemoglobin; eGFR, estimated glomerular filtration rate; HR, hazard ratio; Plt, platelet counts; STEMI, ST-segment elevation myocardial infarction.



Case number	1027	50	21	14	11	17
Number of cardiac death	54	3	2	4	1	4
Number of major bleeding	58	2	3	4	1	4

Fig. 2. One-year clinical outcome risk according to each cancer type.
* $p < 0.05$ vs. non-cancer group, † $p < 0.01$. vs. non-cancer group
GI = gastrointestinal

glomerular filtration rate, STEMI, Killip class III or IV, and active cancer were predictors of major bleeding at 1 year (Table 5).

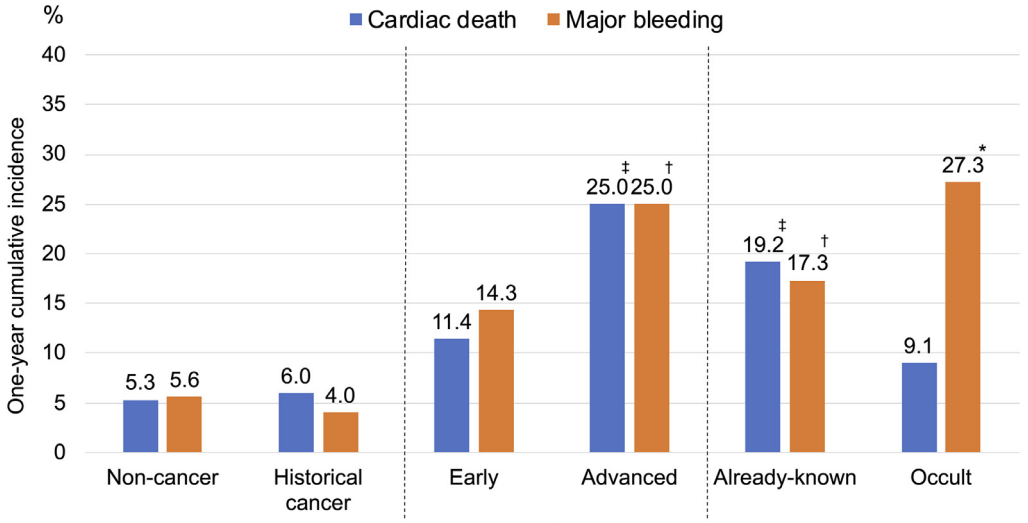
Differences in clinical outcomes according to cancer site, stage, or diagnosis status

The GI tract and other cancers had the highest risk of cardiac death and major bleeding (Fig. 2 and Supplemental Table 3). Conversely, urinary and lung cancers had relatively low incidences of either cardiac death or major bleeding. Advanced-stage and already-known cancers had a higher risk of cardiac death than early-stage and occult cancers, respectively (Fig. 3 and Supplemental Table 3). Patients with occult cancers were associated with a higher risk of major bleeding than those with non-cancer AMI. During the follow-up period, 85.7% (n=30) of patients with early-stage cancer underwent a standard cancer treatment after AMI, 8.6% (n=3) of them did not undergo cancer treatment because of frailty, and 5.7% (n=2) of them could not recall whether they underwent cancer treatment or not.

Discussion

Using data from the all-comer AMI registry, the present study assessed the prevalence, clinical characteristics, predictors, and clinical outcomes of active cancer in AMI patients. The main findings were as follows: (1) the overall prevalence of active cancer in AMI patients was 5.5%, and the most common type was urinary (especially prostate); (2) the risk of major bleeding was higher in the patients with active cancer than in those without; (3) active cancer was an independent predictor of cardiac death and major bleeding at 1 year, similar to well-known risk factors of poor outcomes in AMI; (4) between non-cancer and historical cancer groups, there was little difference in either 1-year cardiac mortality or major bleeding event rate; and (5) patients with GI tract, advanced-stage, and already-known cancers had a higher 1-year risk of cardiac death than the patients without cancer.

During the study period, the age-adjusted incidence of cancer among the general Japanese population was 0.4% per year [18]. Considering that cardiovascular disease and cancer share common



Case number	1027	50	35	28	52	11
Number of cardiac death	54	3	4	7	10	1
Number of major bleeding	58	2	5	7	9	3

Fig. 3. One-year clinical outcome risk according to cancer stage and diagnosis status.
* $p < 0.05$ vs. non-cancer group, † $p < 0.005$ vs. non-cancer group, ‡$p < 0.001$ vs. non-cancer group

risk factors [1], it was expected that the cancer incidence would be higher in AMI patients than in the general population. A previous study involving the American population showed that active cancer was present in 2.8% of patients with AMI [9]. In addition, another international study using a PCI registry showed that active cancer was present in 6.4% of patients with acute coronary syndromes [7]. Thus, the prevalence of coexisting active cancer might be a single-digit rate and almost similar among all AMI cohorts, despite national and racial differences in the incidence of cancer and AMI.

Our results were in accordance with those of a PCI registry [19], which showed that coexisting active cancer has a strong impact on the 1-year cardiac mortality of AMI patients. There may be several reasons for this finding because both AMI and cancer are common diseases among people of advanced age and may sometimes develop various complications. As evidenced by the Global Registry of Acute Coronary Events score [20], age is one of the strongest predictors of in-hospital death in patients with acute coronary syndromes. Considering the close relationship between age and active cancer, one of the main reasons for the above might be that, in our cohort, AMI patients with active cancer were older than those without cancer.

A second explanation for the higher cardiac mortality observed in the patients with active cancer may be that major bleeding events result in unstable hemodynamics and heart failure. In our study, the Kaplan-Meier curves showed that cardiac death and major bleeding events increased in parallel at a very similar rate. In this regard, previous studies have revealed that major bleeding events were associated with increased mortality in patients with acute coronary syndrome [21,22]. As for the third reason, patients with active cancer may have received suboptimal cardiovascular treatments. Similar to our findings, other studies have shown that patients with active cancer were likely to receive fewer medications for secondary prevention than non-cancer patients [4,7,8,23], probably because they (or their families) refused aggressive treatments due to the severity of the disease.

Contrary to the present study, the definition of active cancer in both the consensus document from the Academic Research Consortium for High Bleeding Risk and the updated Japan Cancer Society guidelines included either cancer with ongoing treatment or historical cancer that was diagnosed within 12 months [17,24]. However, it was questionable whether patients who had recently completed cancer treatment were at risk for major bleeding events when starting antiplatelet therapy. In the present study, both the historical cancer and non-cancer groups similarly showed relatively low incidences of major bleeding events. In addition, according to a retrospective study on patients with GI bleeding secondary to anticoagulation therapy for atrial fibrillation, the early restarting of anticoagulants (7 days after discontinuation) was not related to the recurrence of GI bleeding [25]. Thus, while the bleeding risk of antithrombotic treatment following recent cancer surgery has never been established, a recent history of cancer treatment may not be related to major bleeding in AMI patients who will start antithrombotic agents.

Previous studies have demonstrated that patients with active cancer or cancer history who underwent PCI had a higher rate of major bleeding than non-cancer patients [7,16,23,26]. In accordance with our results, a nationwide study reported that colon cancer was associated with a higher bleeding risk than prostate, breast, or lung cancer [9,27]. Thus, cancers of the GI tract may confer one of the highest bleeding risks for patients with AMI. Recently, the Cardiovascular Outcomes for People Using Anticoagulation Strategies trial, which assessed the efficacy of rivaroxaban for the secondary prevention of cardiovascular disease, showed that major bleeding events, especially GI bleeding, were related to new cancer diagnosis [28]. Although the use of antithrombotic agents in our study differed from that in the mentioned trial, these findings suggest that major bleeding during antithrombotic therapy may be a sign of occult cancer, especially of the GI tract.

An important finding of the present study was that occult cancer was found in approximately 1% of AMI cases, and 90% of these were early-stage cancers. Most of these malignancies were detected incidentally during routine imaging examinations performed for other reasons. According to another retrospective study, the incidence of occult cancer was 3.8% in patients with severe aortic stenosis who underwent CT scans to assess their suitability for

transcatheter valve replacement [29]. Because of the possibility of cancer, physicians treating AMI patients should make a special effort to detect suspicious and unexplained signs in routine laboratory examinations and CT scans performed for nonmalignant diseases during the first hospitalization.

Clinical implications

The present study demonstrated that elderly AMI patients had an elevated risk of active cancer compared to the younger patients with AMI. This group of patients may benefit from cancer screening and close surveillance for bleeding events, especially when they present with concurrent anemia or a poor nutritional state. In Japanese patients undergoing PCI, a recent history of cancer (within 12 months) was associated with a high risk of bleeding [17,24]. Therefore, the current guidelines from the Japan Cancer Society recommend a very short (1 to 3 months) DAPT duration in AMI patients with high bleeding risk who receive a drug-eluting stent [17]. As shown above, most major bleeding events in patients with active cancer occurred within the first 2 months of AMI onset. In addition, the present study demonstrated that cardiac mortality in the patients with occult cancer was lower than that in those with major bleeding events. Based on previous research and the results of our study, a 1-month DAPT would be reasonable for AMI patients with active cancers and a relatively high risk of major bleeding compared to the risk of cardiac death.

Limitations

The present study had several important limitations. First, because this was a single-center retrospective study, its findings might not be generalizable to other regions or countries. Second, the sample size was relatively small. We were unable to perform subgroup analysis for all cancers because active cancer occurred only in 63 patients, some types of cancers were missing, and cancer status (i.e., early or terminal) was very heterogeneous in each cancer type. A large-scale cohort study should be performed to confirm the impact of active cancer in patients with AMI. Third, the AMI patients in this study received $>$ 6 months of DAPT, which might have significantly increased the risk of bleeding. With shorter DAPTs, the impact of active cancer on bleeding events might have been different. Fourth, because the strategy of cancer screening was not defined in advance, the incidence of active cancer might vary according to the physician or institution. Simple in-hospital screening tools, such as immunochemical fecal occult blood tests, might help in deciding when to discontinue DAPT after coronary stenting. It might also increase the detection of active cancer among elderly patients [26,30].

Conclusions

In AMI patients, coexisting active cancer is rare, but elderly AMI patients had a higher prevalence of active cancer than younger AMI patients. In addition, AMI patients with active cancer had a higher risk of cardiac death and major bleeding events than those without active cancer. Because differences in cardiac mortality and major bleeding event rates were observed between each cancer type, stage, and diagnosis status, the treatment of AMI should be individualized according to the cancer type and/or stage.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2021.04.004.

References

[1] Koene RJ, Prizment AE, Blaes A, Konety SH. Shared risk factors in cardiovascular disease and cancer. Circulation 2016;133:1104–14.
[2] Ridker PM, MacFadyen JG, Thuren T, Everett BM, Libby P, Glynn RJ. Effect of interleukin-1β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial. Lancet 2017;390:1833–42.
[3] Campia U, Moslehi JJ, Amiri-Kordestani L, Barac A, Beckman JA, Chism DD, et al. Cardio-oncology: vascular and metabolic perspectives: a scientific statement from the American Heart Association. Circulation 2019;139:e579–602.
[4] Hess CN, Roe MT, Clare RM, Chiswell K, Kelly J, Tcheng JE, et al. Relationship between cancer and cardiovascular outcomes following percutaneous coronary intervention. J Am Heart Assoc 2015;4.
[5] Gong IY, Yan AT, Ko DT, Earle CC, Cheung WY, Peacock S, et al. Temporal changes in treatments and outcomes after acute myocardial infarction among cancer survivors and patients without cancer, 1995 to 2013. Cancer 2018;124:1269–78.
[6] Fang F, Fall K, Mittleman MA, Sparén P, Ye W, Adami HO, et al. Suicide and cardiovascular death after a cancer diagnosis. N Engl J Med 2012;366:1310–18.
[7] Iannaccone M, D'Ascenzo F, Vadala P, Wilton SB, Noussan P, Colombo F, et al. Prevalence and outcome of patients with cancer and acute coronary syndrome undergoing percutaneous coronary intervention: a BleeMACS substudy. Eur Heart J Acute Cardiovasc Care 2018;7:631–8.
[8] Itzhaki Ben Zadok O, Hasdai D, Gottlieb S, Porter A, Beigel R, Shimony A, et al. Characteristics and outcomes of patients with cancer presenting with acute myocardial infarction. Coron Artery Dis 2019;30:332–8.
[9] Bharadwaj A, Potts J, Mohamed MO, Parwani P, Swamy P, Lopez-Mattei JC, et al. Acute myocardial infarction treatments and outcomes in 6.5 million patients with a current or historical diagnosis of cancer in the USA. Eur Heart J 2020;41:2183–93.
[10] Velders MA, Hagström E, James SK. Temporal trends in the prevalence of cancer and its impact on outcome in patients with first myocardial infarction: a nationwide study. J Am Heart Assoc 2020;9:e014383.
[11] Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. Circulation 2012;126:2020–35.
[12] JCS. Guidelines for management of acute coronary syndrome without persistent ST Segment Elevation. (in Japanese), https://www.j-circ.or.jp/old/guideline/pdf/JCS2012_kimura_h;2012.pdf.
[13] JCS. Guidelines for the management of patients with ST-elevation acute myocardial infarction (in Japanese), https://www.j-circ.or.jp/old/guideline/pdf/JCS2013_kimur_h.pdf; 2013.
[14] Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123:2736–47.
[15] Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.
[16] Natsuaki M, Morimoto T, Yamaji K, Watanabe H, Yoshikawa Y, Shiomi H, et al. Prediction of thrombotic and bleeding events after percutaneous coronary intervention: CREDO-Kyoto thrombotic and bleeding risk scores. J Am Heart Assoc 2018;7:e008708.

[17] JCS. Guidelines focused update on antithrombotic therapy in patients with coronary artery disease (in Japanese), https://www.j-circ.or.jp/cms/wp-content/uploads/2020/04/JCS2020_; 2020.
[18] Hori M, Matsuda T, Shibata A, Katanoda K, Sobue T, Nishimoto H. 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 2015;45:884–91.
[19] Tabata N, Sueta D, Yamamoto E, Takashio S, Arima Y, Araki S, et al. Outcome of current and history of cancer on the risk of cardiovascular events following percutaneous coronary intervention: a Kumamoto University Malignancy and Atherosclerosis (KUMA) study. Eur Heart J Qual Care Clin Outcomes 2018;4:290–300.
[20] Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, et al. Predictors of hospital mortality in the global registry of acute coronary events. Arch Intern Med 2003;163:2345–53.
[21] Eikelboom JW, Mehta SR, Anand SS, Xie C, Fox KA, Yusuf S. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. Circulation 2006;114:774–82.
[22] Suh JW, Mehran R, Claessen BE, Xu K, Baber U, Dangas G, et al. Impact of in-hospital major bleeding on late clinical outcomes after primary percutaneous coronary intervention in acute myocardial infarction the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial. J Am Coll Cardiol 2011;58:1750–6.
[23] Nakatsuma K, Shiomi H, Morimoto T, Watanabe H, Nakagawa Y, Furukawa Y, et al. Influence of a history of cancer on long-term cardiovascular outcomes after coronary stent implantation (an Observation from Coronary Revascularization Demonstrating Outcome Study-Kyoto Registry Cohort-2). Eur Heart J Qual Care Clin Outcomes 2018;4:200–7.
[24] Urban P, Mehran R, Colleran R, Angiolillo DJ, Byrne RA, Capodanno D, et al. Defining high bleeding risk in patients undergoing percutaneous coronary intervention. Circulation 2019;140:240–61.
[25] Qureshi W, Mittal C, Patsias I, Garikapati K, Kuchipudi A, Cheema G, et al. Restarting anticoagulation and outcomes after major gastrointestinal bleeding in atrial fibrillation. Am J Cardiol 2014;113:662–8.
[26] Kanenawa K, Yamaji K, Morinaga T, Hiromasa T, Hayashi M, Hiramori S, et al. Clinical outcomes after percutaneous coronary intervention in patients with cancer. Circ J 2021. https://www.jstage.jst.go.jp/article/circj/advpub/0/advpub_CJ-20-1119/_article in press.
[27] Potts JE, Iliescu CA, Lopez Mattei JC, Martinez SC, Holmvang L, Ludman P, et al. Percutaneous coronary intervention in cancer patients: a report of the prevalence and outcomes in the United States. Eur Heart J 2019;40:1790–800.
[28] Eikelboom JW, Connolly SJ, Bosch J, Shestakovska O, Aboyans V, Alings M, et al. Bleeding and new cancer diagnosis in patients with atherosclerosis. Circulation 2019;140:1451–9.
[29] Gufler H, Schulze CG, Wagner S. Incidental findings in computed tomographic angiography for planning percutaneous aortic valve replacement: advanced age, increased cancer prevalence? Acta Radiol 2014;55:420–6.
[30] Ikeda K, Koyama T, Ishida M, Okawa M, Oguma Y, Terata Y, et al. Immunochemical fecal occult blood tests predict dual antiplatelet therapy discontinuation after coronary stenting. Intern Med 2014;53:375–81.