Impact of active and historical cancer on short- and long-term outcomes in patients with acute myocardial infarction

（担癌状態と癌既往が急性心筋梗塞後の短期および長期予後に与える影響）

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千葉大学大学院医学薬学府

先端医学薬学専攻

（主任：小林欣夫教授）

松本　忠浩

Abstract

Patients with cancer have an increased risk of cardiovascular events including myocardial infarction (MI) and *vice versa*, and are at high risks of ischemic and bleeding events after MI. However, short- and long-term clinical outcomes in patients with acute MI based on cancer status are not fully understood. This bi-center registry included 903 patients with acute MI undergoing primary percutaneous coronary intervention in a contemporary setting. Patients were divided into active cancer, a history of cancer, and no cancer according to the status of malignancy. Major adverse cardiovascular events (MACE), a composite of all-cause death, recurrent MI, and stroke, and major bleedings were evaluated. Of 903 patients, 49 (5.4%) and 65 (7.2%) had active cancer and a history of cancer, and 87 (9.6%) patients died during the hospitalization. In-hospital MACE was not significantly different among the 3 groups (16.3% vs. 10.8% vs. 10.9%, p=0.48), while the rate of major bleeding events during the index hospitalization was significantly higher in patients with active cancer than their counterpart (20.4% vs. 6.2% vs. 5.8%, p=0.002). After discharge, patients with active cancer had an increased risk of MACE and major bleedings compared to those with a history of cancer and no cancer during the mean follow-up period of 853 days. In conclusions, active cancer rather than a history of cancer and no cancer had significant impact on in-hospital bleeding events, and MACE and major bleedings after discharge in patients with acute MI undergoing primary percutaneous coronary intervention.

Key words: myocardial infarction; percutaneous coronary intervention; cancer; outcome.

Introduction

Cardiovascular disease and cancer are the leading causes of mortality worldwide, especially in developed countries.[1] Patients with cancer have an increased risk of cardiovascular events and *vice versa*, owing to shared lifestyles, risk factors, and toxicities of cancer treatment.[2-5] Numerous previous studies have demonstrated that patients with current or historical diagnosis of cancer are at higher risks of ischemic and bleeding events during the index hospitalization or up to 1 year after acute myocardial infarction (MI), while long-term data are scarce.[6-9] In addition, it is well known that patients with acute MI and cancer are less likely to receive optimal medical therapy and primary percutaneous coronary intervention (PCI).[7,10,11] Although a consensus statement recommends the consideration of percutaneous revascularization in cancer patients with contemporary PCI technologies,[12] optimal procedures (e.g. new-generation drug-eluting stents and intracoronary imaging) are unlikely to be performed at the time of primary PCI.[6, 7] Thus, the impact of cancer on clinical outcomes in acute MI in current practice remains unclear. The present study aimed to evaluate short- and long-term ischemic and bleeding events in a contemporary cohort of patients with acute MI undergoing primary PCI based on cancer status.

Methods

Between January 2012 and December 2018, a total of 942 patients with acute MI undergoing primary PCI at 2 tertiary centers, Chiba University Hospital and Eastern Chiba Medical Center, were retrospectively enrolled. Acute MI including ST-segment elevation and non ST-segment elevation MI was defined based on the fourth universal definition of MI.[13] All patients underwent primary PCI per local standard practice. Patients received dual antiplatelet therapy before or at the time of PCI, and intracoronary imaging and contemporary drug-eluting stents were used in most cases.[14-18] We excluded duplicated patients (n=31) and cases with

failed PCI (n=4) and no stent implantation (n=4). Written informed consent for examination was obtained from all patients, and informed consent for the present study was obtained in the form of opt-out. This study was approved by the ethical committee of Chiba University and Eastern Chiba Medical Center.

Based on the status of malignancy, patients were divided into 3 groups: active cancer, a history of cancer, and no cancer. Patients who were planned for undergoing cancer surgery, were receiving anticancer drug(s) and/or radiotherapy, and had recurrent, metastatic, and/or inoperable cancer were defined as having active cancer. Types of cancer included colon and rectum, stomach and esophagus, lung, hepatobiliary pancreas, prostate and testes, bladder, oral cavity and pharynx, kidney, breast, uterus and ovary, blood, and skin and soft tissue.

Follow-up data were obtained from medical records at Chiba University Hospital and Eastern Chiba Medical Center. The primary endpoint of the present study included major adverse cardiovascular events (MACE), a composite of all-cause death, recurrent MI, and stroke, adjudicated with the Academic Research Consortium-2 consensus document, and major bleeding events (Bleeding Academic Research Consortium type 3 or 5), during the index hospitalization for acute MI and after discharge.[19,20] In clinical events after discharge, cardiovascular death and rehospitalization for heart failure were also determined.[19] Major bleeding events were further divided into vascular, gastrointestinal, intracranial, pericardium, and other bleedings.

Statistical analyses were conducted using JMP Pro 15.0.0 (SAS Institute, Cary, USA). Data are expressed as mean ± standard deviation or frequency (%). Continuous variables were compared using analysis of variance. Categorical variables were compared with Fisher's exact test. Event-free survival was estimated with the Kaplan-Meier method and was compared using the log-rank test. Univariable analyses were performed to identify factors associated with MACE and bleeding events. Associated factors with $p < 0.05$ on univariable analyses were

included into multivariable analysis with age and sex (irrespective of p values on univariable analyses). Logistic regression analysis and a Cox proportional-hazards model were used to estimate adjusted odds and hazard ratios with 95% confidence intervals. A value of $p < 0.05$ was considered statistically significant.

Results

Of 903 patients, 49 (5.4%) and 65 (7.2%) had active cancer and a history of cancer, and 87 (9.6%) patients died during the hospitalization. Types of cancer were displayed in Figure S1. Patients with cancer were older and had lower body mass index and hemoglobin levels (Table 1). In-hospital MACE was not significantly different among the 3 groups, while the rates of major bleedings and recurrent MI were significantly higher in patients with active cancer than their counterpart (Table 2). All patients with active cancer who died during the hospitalization (n=6) had metastasis, half of whom experienced major bleeding events. In patients with active cancer (n=49), 3 had in-hospital bleeding events associated with cancer; bleedings from operation region (n=2) and disseminated intravascular coagulation by cancer (n=1). Patients who experienced in-hospital major bleeding events had higher subsequent MACE than their counterpart (56.7% vs. 8.0%, $p<0.001$). Cancer type was not significantly associated with in-hospital mortality (Figure S1). Types of major bleedings during the index hospitalization and after discharge were shown in Figure 1.

Among 816 patients who survived to discharge, 72 had no follow-up information after discharge. Of 744 patients, 48 (6.5%) died, and 88 (11.8%) and 25 (3.4%) had MACE and major bleeding events during the mean follow-up period of 853 days (Table 3). At discharge, patients with active cancer were less likely to receive β-blocker and angiotensin-converting-enzyme inhibitor or angiotensin II receptor blocker (Table S1). Patients with active cancer had increased risks of MACE and major bleedings after discharge compared to those with a history of cancer

and no cancer (Figure 2 and 3). The rates of cardiovascular and non-cardiovascular death were higher in patients with active cancer (Table 3). At 1 year after discharge, patients with active cancer and a history of cancer experienced major bleedings in 12.0% and 4.3%. Gastrointestinal tract was the most common etiology of major bleedings after discharge (Figure 1). Multivariable analysis showed that active and/or metastatic cancer had impact on MACE and major bleeding events both during the index hospitalization for acute MI and after discharge (Table S2-5).

Discussion

In the present bi-center registry, 5.4% and 7.2% of patients with acute MI undergoing primary PCI had active and a history of cancer. The status of cancer was not significantly associated with in-hospital MACE, but patients with active cancer had a 3-fold higher rate of major bleedings during the hospitalization than those without. After discharge, patients with active cancer had increased risks of MACE and major bleedings. Multivariable analysis indicated that active cancer including metastatic cancer was significantly associated with both ischemic and bleeding events during the hospitalization and after discharge in patients with acute MI.

Patients with cancer are known to have an increased risk of ischemic events. A large-scale registry in the US including over 6.5 million patients with acute MI showed that active and a history of cancer was observed in 2.8% and 6.2%,[8] which is in line with our results. In this US registry, patients with active cancer but historical cancer had higher rates of in-hospital MACE and bleeding events, and the presence of metastatic cancer was significantly associated with worse clinical outcomes.[8] The present study did not show the direct relation of active cancer and in-hospital MACE probably because of limited sample size, while some signals including an increased risk of recurrent in-hospital MI in patients with active cancer (Table 2)

and metastatic cancer as an independent predictor of MACE during hospitalization (Table S2) may be reasonable. It should be also noted that in the US registry, only 27.1% of patients with active cancer underwent PCI, as often seen in clinical practice.[8] In terms of long-term data, previous investigations have reported outcomes mostly up to 1 year following MI.[6,7,21] Several previous studies including patients with cancer undergoing PCI for stable coronary artery disease and acute MI showed that the presence of cancer was associated with increased risks of both ischemic and bleeding events during a follow-up period for up to 5 years.[22,23] However, long-term data on cancer are lacking especially in patients with acute MI undergoing primary PCI, even though a consensus statement recommends the consideration of revascularization and a recent registry data indicated a survival benefit of primary PCI in patients with cancer presenting with acute MI.[9,12] In the current study, patients with active cancer resulted in a higher risk of MACE after discharge in this specific population during long-term follow-up beyond 1 year (Table 3 and S4).

Numerous previous studies have demonstrated that patients with cancer who underwent PCI are at higher risks of bleeding events during the short- and long-term follow-up.[7,8,23,24] The present study also demonstrated that active cancer had significant impact on short- and long-term bleeding events in patients with acute MI (Figure 2 and Table S5). Recently, the Academic Research Consortium defined active cancer as one of the major criteria for a bleeding risk after PCI, which is considered to confer a Bleeding Academic Research Consortium type 3 or 5 bleeding risk of ≥4% at 1 year.[25] Subsequently, several studies showed that the presence of active cancer resulted in the rate of major bleedings of 4.6% to 12.0% at 1 year after PCI.[24,26-30] In the present study, the major bleeding event rate at 1 year (only after discharge) was high (12.0%), presumably because of a different population (i.e. acute MI) and potent antithrombotic therapy (i.e. dual antiplatelet therapy in 90% in the active cancer group). It is well known that patients with acute MI and cancer are less likely to receive optimal medical

therapy,[7,10,11] probably because of asthenia, fatigue, and frailty.[8] While patients with active cancer in the present study were highly adherent to antiplatelet therapy and statin, β-blocker and angiotensin-converting-enzyme inhibitor or angiotensin II receptor blocker were still underused. The underuse of guideline-recommended medical therapy was possibly associated with higher rates of MACE and cardiovascular death after discharge in this study. On the other hand, patients with active cancer had an increased risk of major bleeding evens. Thus, therapeutic strategies to prevent bleedings (e.g. short-term dual antiplatelet therapy and proton pump inhibitor) may be also needed. In patients with active cancer as a vulnerable subset of acute MI, tailored medical therapy should be considered to reduce both ischemic and bleeding events.

The present study has several limitations. This study was conducted in a retrospective fashion. The overall sample size was modest, resulting in small number of events, and subgroups of cancer was underpowered. Although we performed multivariable analyses, unadjusted and unmeasured factors were possible. The present study focused on the prognostic impact of cancer in patients who underwent primary PCI, and no data were available on patients who did not undergo reperfusion therapies. Follow-up information on medications is lacking.

In conclusion, active cancer rather than a history of cancer and no cancer was associated with increased risks of in-hospital bleeding events, and MACE and major bleedings after discharge in patients with acute MI undergoing primary PCI.

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Table 1. Baseline patient characteristics

Variable	Active cancer (n=49)	History of cancer (n=65)	No cancer (n=789)	P value
Age (years)	69.6±8.9	74.5±8.5	66.0±12.3	<0.001
Men	37 (76%)	48 (74%)	614 (78%)	0.66
Body mass index (kg/m^2)	23.3±3.8	22.7±3.4	24.3±3.7	<0.001
Hypertension	34 (69%)	45 (69%)	527 (67%)	0.90
Diabetes mellitus	15 (31%)	27 (42%)	297 (38%)	0.49
Dyslipidemia	24 (49%)	35 (53.9%)	490 (62%)	0.10
Current smoker	9 (18%)	16 (25%)	285 (36%)	0.008
Prior myocardial infarction	5 (10%)	4 (6%)	45 (6%)	0.35
eGFR (ml/min/1.73 m^2)	63.4±25.2	61.2±26.3	67.4±22.5	0.10
Hemoglobin (g/dl)	11.7±2.5	13.1±2.3	14.0±2.1	<0.001
LVEF (%)	47.4±15.5	46.7±13.0	47.6±13.2	0.87
Killip class on admission				0.95
I	30 (61%)	43 (66%)	525 (67%)	
II	5 (10%)	5 (8%)	64 (8%)	
III	4 (8%)	5 (8%)	48 (6%)	
IV	10 (20%)	12 (18%)	152 (19%)	
Type of myocardial infarction				0.34
STEMI	29 (59%)	46 (71%)	542 (69%)	
NSTEMI	20 (41%)	19 (29%)	247 (31%)	

eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; NSTEMI = non ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction.

Table 2. In-hospital clinical outcomes

Variable	Active cancer (n=49)	History of cancer (n=65)	No cancer (n=789)	P value
MACE	8 (16.3%)	7 (10.8%)	86 (10.9%)	0.48
All-cause death	6 (12.2%)	7 (10.8%)	74 (9.4%)	0.62
Recurrent MI	2 (4.1%)	1 (1.5%)	5 (0.6%)	0.04
Stroke	3 (6.1%)	1 (1.5%)	14 (1.8%)	0.12
Major bleeding events	10 (20.4%)	4 (6.2%)	46 (5.8%)	0.002

MACE = major adverse cardiovascular events; MI = myocardial infarction.

Table 3. Clinical events after discharge

Variable	Active cancer (n=40)	History of cancer (n=53)	No cancer (n=651)	P value
MACE	14 (35.0%)	8 (15.1%)	66 (10.1%)	<0.001
All-cause death	14 (35.0%)	5 (9.4%)	29 (4.5%)	<0.001
Recurrent MI	0 (0.0%)	2 (3.8%)	28 (4.3%)	0.56
Stroke	2 (5.0%)	1 (1.9%)	18 (2.8%)	0.50
CV death	8 (20.0%)	3 (5.7%)	17 (2.6%)	<0.001
Non-CV death	6 (15.0%)	2 (3.8%)	12 (1.8%)	<0.001
HF hospitalization	2 (5.0%)	6 (11.3%)	34 (5.2%)	0.20
Major bleeding events	4 (10.0%)	2 (3.8%)	19 (2.9%)	0.054

CV = cardiovascular; HF = heart failure; MACE = major adverse cardiovascular events; MI = myocardial infarction.

Table S1. Characteristics of patients who survived to discharge

Variable	Active cancer (n=40)	History of cancer (n=53)	No cancer (n=651)	P value
Age (years)	69.7±9.0	73.7±7.9	65.3±12.0	<0.001
Men	32 (80%)	38 (72%)	509 (78%)	0.52
Body mass index (kg/m^2)	23.4±3.9	23.0±3.1	24.4±3.6	0.006
Hypertension	27 (68%)	41 (77%)	441 (68%)	0.36
Diabetes mellitus	12 (30%)	24 (45%)	234 (36%)	0.27
Dyslipidemia	21 (53%)	31 (58%)	433 (67%)	0.11
Type of myocardial infraction				0.29
STEMI	22 (55%)	35 (66%)	438 (67%)	
NSTEMI	18 (45%)	18 (34%)	213 (33%)	
Medication at discharge				
Antiplatelet therapy				0.47
DAPT	36 (90%)	49 (92%)	610 (94%)	
SAPT	3 (8%)	4 (8%)	35 (5%)	
None	1 (3%)	0 (0%)	6 (1%)	
OAC	3 (8%)	7 (13%)	66 (10%)	0.67
β-blocker	24 (60%)	38 (72%)	506 (78%)	0.04
ACE-I or ARB	24 (60%)	48 (91%)	572 (88%)	<0.001
Statin	35 (88%)	47 (89%)	601 (92%)	0.29
MRA	7 (18%)	10 (19%)	101 (16%)	0.72
Diuretic	11 (28%)	12 (23%)	119 (18%)	0.25

Patients who died during the index hospitalization were excluded. ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; DAPT = dual antiplatelet therapy; MRA = mineralocorticoid receptor antagonist; NSTEMI = non ST-segment elevation myocardial infarction; OAC = oral anticoagulation; SAPT = single antiplatelet therapy; STEMI = ST-segment elevation myocardial infarction.

Table S2. Factors associated with in-hospital MACE

Variable	Univariable		Multivariable	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (years)	1.02 (1.01-1.04)	0.01	1.05 (1.02-1.08)	0.001
Men	1.21 (0.72-2.02)	0.53	1.45 (0.73-2.91)	0.28
Body mass index (kg/m^2)	0.96 (0.90-1.02)	0.20		
Killip IV	17.03 (10.56-27.49)	<0.001	6.64 (3.66-12.01)	<0.001
LVEF (%)	0.90 (0.88-0.92)	<0.001	0.93 (0.91-0.95)	<0.001
Hypertension	0.60 (0.39-0.91)	0.02	0.58 (0.33-1.04)	0.07
Diabetes mellitus	1.45 (0.96-2.21)	0.08		
Dyslipidemia	0.34 (0.22-0.53)	<0.001	0.84 (0.48-1.46)	0.54
Active cancer	1.60 (0.73-3.51)	0.24		
Metastatic cancer	3.10 (1.19-8.12)	0.03	3.97 (1.18-13.36)	0.02
STEMI	1.24 (0.78-1.96)	0.43		

CI = confidence interval; OR = odds ratio; MACE = major adverse cardiovascular events; LVEF = left ventricular ejection fraction; STEMI = ST-segment elevation myocardial infarction.

Table S3. Factors associated with in-hospital bleeding events

Variable	Univariable		Multivariable	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (years)	1.34 (0.30-5.95)	0.70	1.00 (0.97-1.03)	0.86
Men	0.79 (0.44-1.43)	0.43	0.63 (0.29-1.35)	0.24
Body mass index (kg/m^2)	0.91 (0.84-0.99)	0.03	0.92 (0.84-1.02)	0.10
Killip IV	13.75 (7.61-24.84)	<0.001	5.81 (2.78-12.12)	<0.001
LVEF (%)	0.92 (0.90-0.93)	<0.001	0.94 (0.92-0.96)	<0.001
Hypertension	0.72 (0.42-1.23)	0.26		
Diabetes mellitus	1.04 (0.60-1.78)	0.89		
Dyslipidemia	0.54 (0.32-0.91)	0.03	1.12 (0.58-2.17)	0.74
Active cancer	4.12 (1.95-8.74)	0.001	6.49 (1.84-22.89)	0.004
Metastatic cancer	4.42 (1.57-12.42)	0.01	0.79 (0.13-4.65)	0.80
STEMI	1.42 (0.78-2.59)	0.31		

CI = confidence interval; OR = odds ratio; LVEF = left ventricular ejection fraction; STEMI = ST-segment elevation myocardial infarction.

Table S4. Factors associated with MACE after discharge

Variable	Univariable		Multivariable	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)	1.02 (1.00-1.03)	0.11	1.01 (0.99-1.02)	0.24
Men	0.74 (0.46-1.18)	0.20	0.74 (0.45-1.21)	0.24
Body mass index (kg/m^2)	0.96 (0.90-1.02)	0.21		
Killip IV	1.21 (0.66-2.23)	0.54		
LVEF (%)	0.99 (0.98-1.01)	0.39		
Hypertension	2.73 (1.52-4.93)	0.001	2.62 (1.44-4.75)	0.001
Diabetes mellitus	1.15 (0.75-1.76)	0.53		
Dyslipidemia	0.67 (0.44-1.03)	0.07		
Active cancer	3.49 (1.97-6.19)	<0.001	2.43 (1.18-5.02)	0.02
Metastatic cancer	5.38 (2.34-12.38)	<0.001	2.59 (0.90-7.46)	0.08
STEMI	1.09 (0.70-1.70)	0.71		

CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiovascular events; LVEF = left ventricular ejection fraction; STEMI = ST-segment elevation myocardial infarction.

Table S5. Factors associated with bleeding events after discharge

Variable	Univariable		Multivariable	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)	1.03 (1.00-1.07)	0.07	1.02 (0.99-1.07)	0.20
Men	0.49 (0.21-1.10)	0.08	0.55 (0.24-1.28)	0.17
Body mass index (kg/m^2)	1.04 (0.93-1.15)	0.93		
Killip IV	1.56 (0.54-4.55)	0.42		
LVEF (%)	1.01 (0.97-1.04)	0.73		
Hypertension	3.29 (0.98-11.01)	0.053		
Diabetes mellitus	1.59 (0.72-3.48)	0.25		
Dyslipidemia	0.53 (0.24-1.16)	0.11		
Active cancer	3.73 (1.28-10.87)	0.02	3.38 (1.15-9.95)	0.03
Metastatic cancer	NA	NA		
STEMI	1.27 (0.57-2.83)	0.56		

CI = confidence interval; HR = hazard ratio; LVEF = left ventricular ejection fraction; NA = not applicable; STEMI = ST-segment elevation myocardial infarction.

Figure 1. Types of major bleeding events during the hospitalization and after discharge

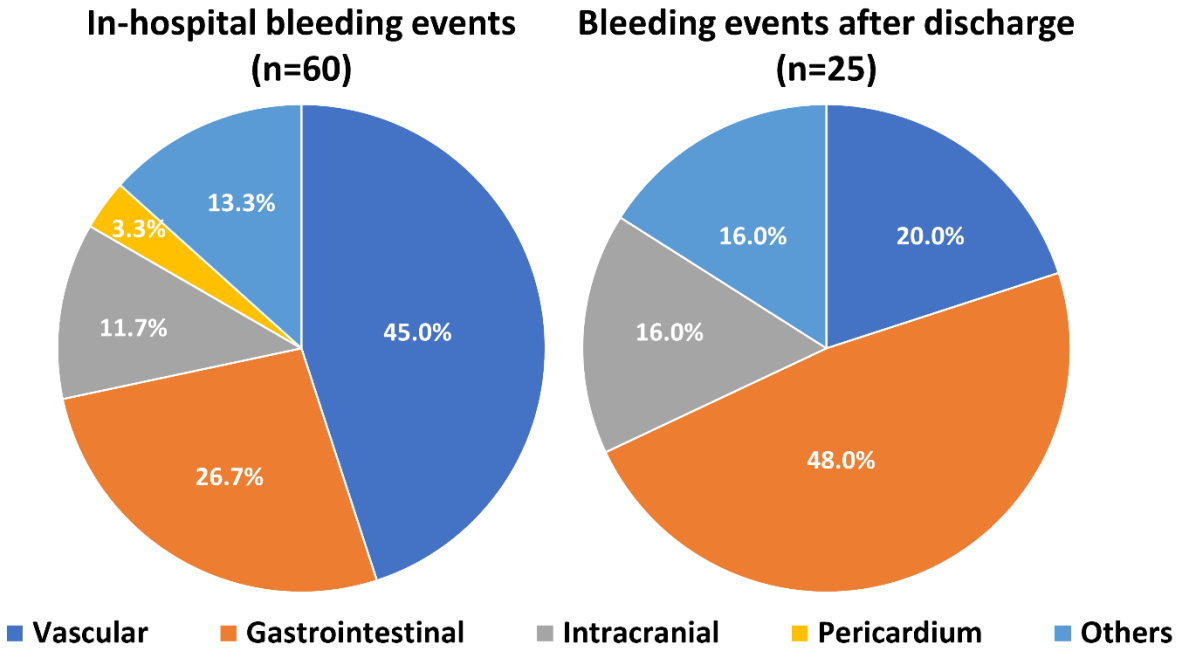
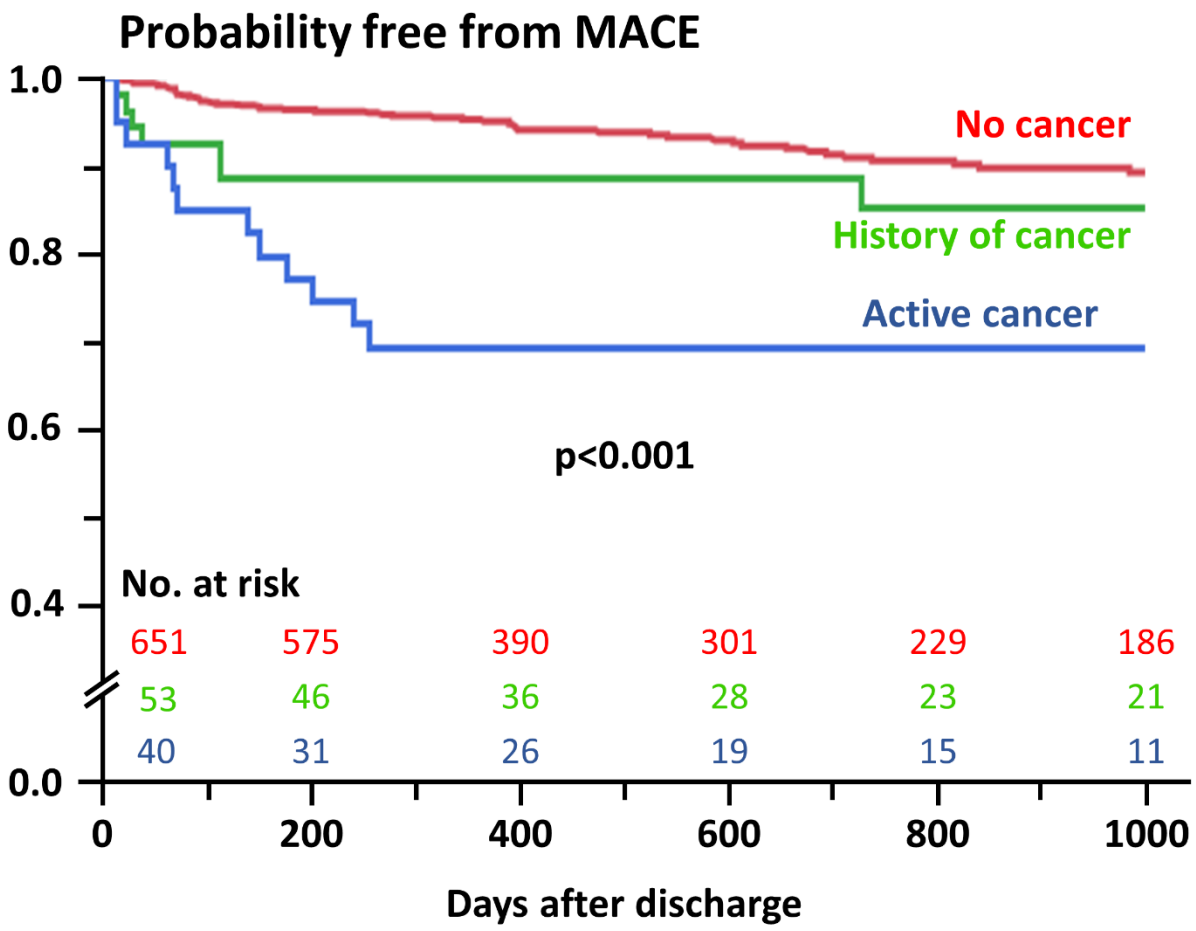


Figure 2 Probability free from MACE after discharge across status of cancer



MACE = major adverse cardiovascular events.

Figure 3. Probability free from major bleedings after discharge across status of cancer

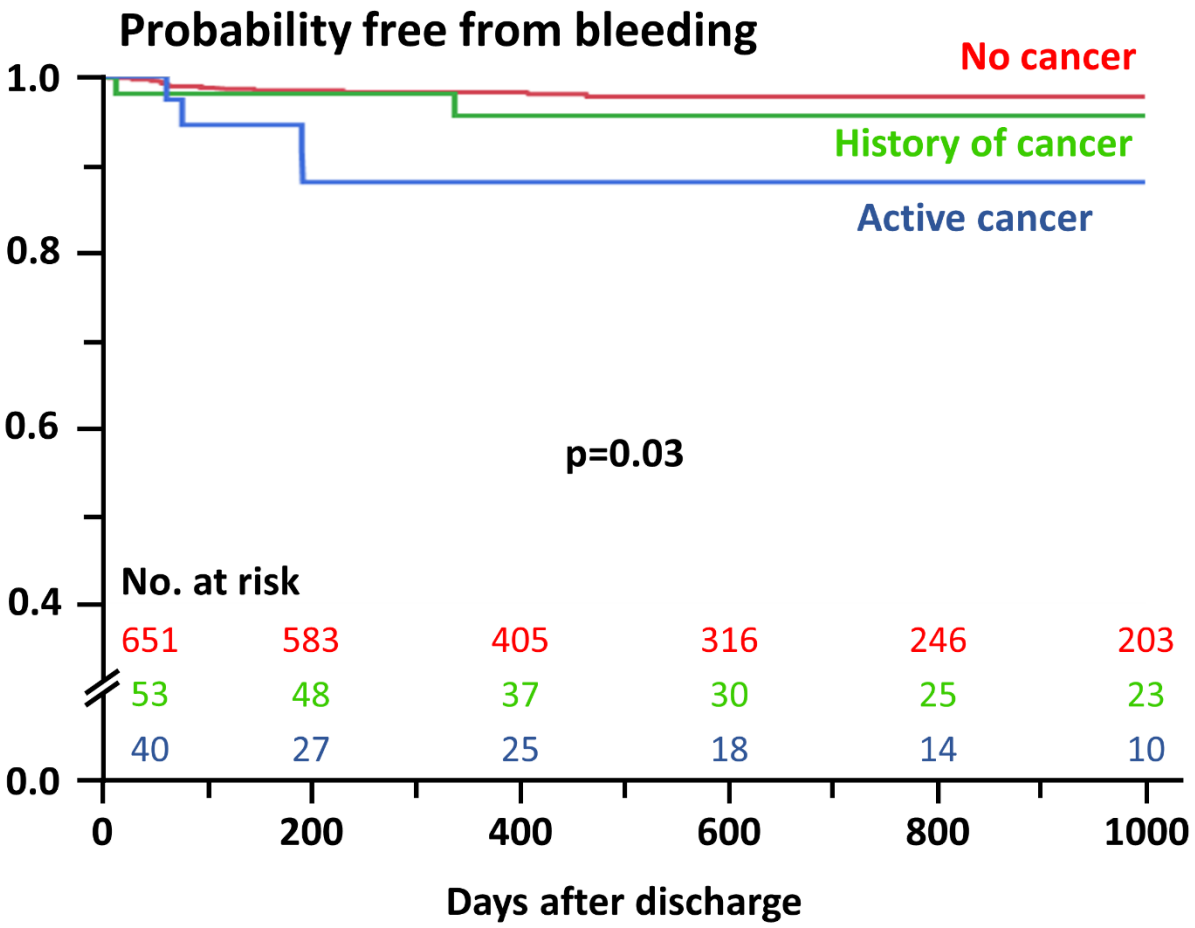
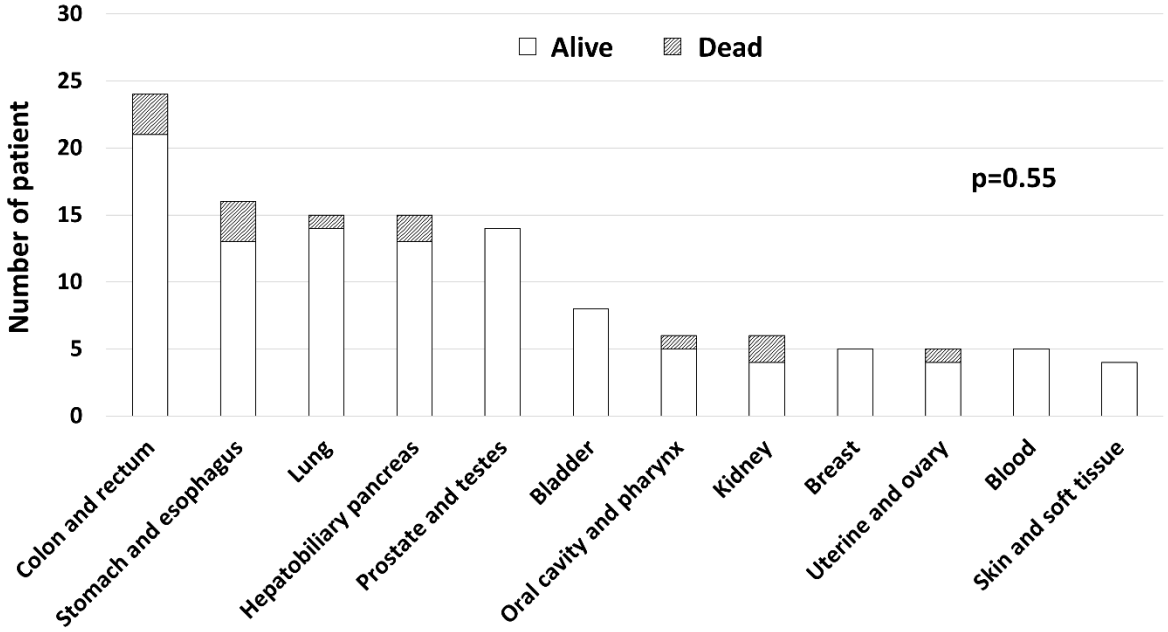


Figure S1. Types of cancer in patients with active and a history of cancer with in-hospital survival data



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