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ORIGINAL RESEARCH

Acute Hospital Mortality of Venous Thromboembolism in Patients With Cancer From Registry Data

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BACKGROUND: The prognosis of patients with cancer-venous thromboembolism (VTE) is not well known because of a lack of registry data. Moreover, there is also no knowledge on how specific types are related to prognosis. We sought to evaluate the clinical characteristics and outcomes of patients with cancer-associated VTE, compared with a matched cohort without cancer using real-world registry data of VTE.

METHODS AND RESULTS: This study was based on the Diagnosis Procedure Combination database in the JROAD-DPC (Japanese Registry of All Cardiac and Vascular Diseases and the Diagnosis Procedure Combination). Of 5 106 151 total patients included in JROAD-DPC, we identified 49 580 patients who were first hospitalized with VTE from April 2012 to March 2017. Propensity score was estimated with a logistic regression model, with cancer as the dependent variable and 18 clinically relevant covariates. After propensity matching, there were 25 148 patients with VTE with or without cancer. On propensity score-matched analysis with 25 148 patients with VTE, patients with cancer had higher total in-hospital mortality within 7 days (1.3% versus 1.1%, odds ratio [OR], 1.66; 95% CI, 1.31–2.11; $P<0.0001$), 14 days (2.5% versus 1.5%, OR, 2.07; 95% CI, 1.72–2.49; $P<0.0001$), and 30 days (4.8% versus 2.0%, OR, 2.85; 95% CI, 2.45–3.31; $P<0.0001$). On analysis for each type of cancer, in-hospital mortality in 11 types of cancer was significantly high, especially pancreas (OR, 12.96; 95% CI, 6.41–26.20), biliary tract (OR, 8.67; 95% CI, 3.00–25.03), and liver (OR, 7.31; 95% CI, 3.05–17.50).

CONCLUSIONS: Patients with cancer had a higher in-hospital acute mortality for VTE than those without cancer, especially in pancreatic, biliary tract, and liver cancers.

Key Words: cardio-oncology ■ mortality ■ venous thromboembolism

Venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis, is a major cause of death in patients with cancer.[1] It is also well known that cancer is a strong risk factor for the development of VTE. Patients with cancer are reported to have a 4 to 8 times higher incidence compared with patients without cancer.[2–4] In addition, several metabolic factors, including a trend toward a diet rich in meat and fat, decline in physical activity, and increasing incidence of obesity, continue to increase the risk of developing VTE.[5] Thus, an optimal management strategy for patients with VTE and cancer is a major need in daily clinical practice.

To understand current issues and improve patient care and prognosis, data on current real-world clinical outcomes in patients with cancer-associated VTE are important. Despite several guideline recommendations about VTE, there is still a lack of robust data on these

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CLINICAL PERSPECTIVE

What Is New?

- On propensity matched analysis with 25 148 patients with venous thromboembolism, patients with cancer had higher total in-hospital mortality within 14 days and within 30 days.
- On analysis for each type of cancer, in-hospital mortality in 11 types of cancer was significantly high, especially pancreas (odds ratio [OR], 13.48; 95% CI, 6.74–26.96), biliary tract (OR, 9.12; 95% CI, 3.17–26.24), and liver (OR, 7.96; 95% CI, 3.20–19.82).

What Are the Clinical Implications?

- The knowledge from a high-risk cohort of venous thromboembolism with specific cancers may be useful for the management of patient care and prevention of venous thromboembolism.

Nonstandard Abbreviations and Acronyms

PS	propensity score

patients for their prognosis.[6] Malignancies of the brain, stomach, pancreas, lungs, uterus, and ovaries were well known to be associated with high incidence rate of VTE.[7,8] Not only is VTE considered an independent negative prognostic factor, but the resulting reduction in quality of life can delay cancer treatment, lead to more frequent and prolonged hospitalizations, and result in higher treatment costs. Some previous reports for prognosis have focused on the presence of cancers, but few studies have examined the prognosis on the individual cancer types during hospitalization.[9,10] Therefore, we sought to evaluate the clinical characteristics and outcomes of patients with cancer-associated VTE compared with the matched cohort without cancer using a real-world registry data of VTE. Our hypothesis was that cancer type is associated with an increased short-term risk of death (mortality within 7, 14, or 30 days) during hospitalizations in patients with VTE.

METHODS

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the Japanese Circulation Society via e-mail (j-circdb@ml.ncvc.go.jp).

Study Population

The study population was composed of hospitalized patients from April 2012 to March 2017 in the JROAD-DPC (Japanese Registry of All Cardiac and Vascular Diseases and the Diagnosis Procedure Combination) database. JROAD-DPC is a nationwide registry, a medical database with information on admission and discharge for cardiovascular diseases, clinical examinations and treatment status, patient status, and hospital overview. The JROAD-DPC database integrates the information composed by JROAD-DPC data, with analysis data sets covering 5.1 million cases in 1022 hospitals between April 2012 and March 2017. The identification of VTE and cancer was based on the *International Classification of Diseases, Tenth Revision* (*ICD-10*) diagnosis codes related to PE (I26.0, I26.9); deep vein thrombosis (I80.0, I80.1, I80.2, I80.3, I80.9, I82.2, I82.3, I82.9, O22.2, O22.3, O22.9, O87.0, O87.1, O87.9); cancer of esophagus (C15), stomach (C16), colon (C18–20), liver (C22), biliary tract (C23–24), pancreas (C25), lung (C34), breast (C50), cervix (C53), uterine body (C54), ovary (C56), prostate (C61), kidney and urinary tract (C64–66, 68), and bladder (C67); and leukemia (C91–95). Patient age and sex, main diagnosis, comorbidity at admission, length of hospitalization, and treatment content were extracted from the database. We included 54 976 patients hospitalized with VTE (Figure 1). Diagnosis of VTE was defined as the main diagnosis, admission-precipitating diagnosis,

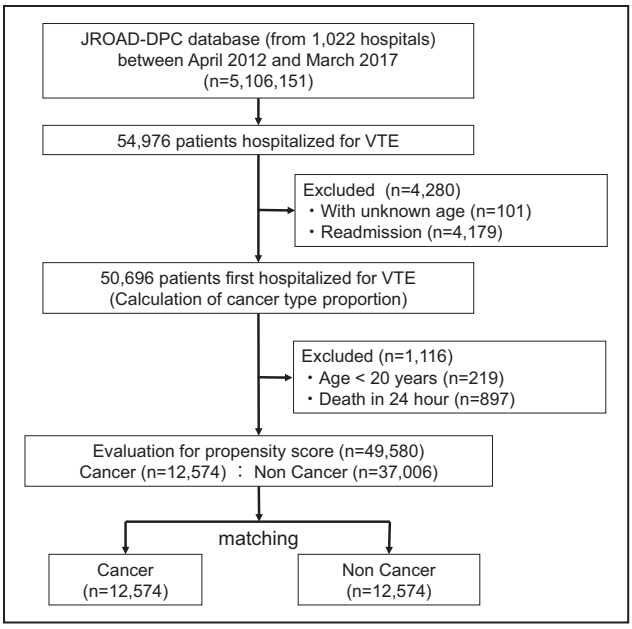


Figure 1. Flowchart of this study.
JROAD-DPC indicates The Japanese Registry of All Cardiac and Vascular Diseases and the Diagnosis Procedure Combination; and VTE, venous thromboembolism.

or most resource-consuming diagnosis. Medical resources were determined by the cost of examinations and treatments during hospitalization. Most resource-consuming diagnosis was defined by the doctor's discretion based on medical resources and the main diagnosis disease. After excluding patients with unknown age or patients who were readmitted (readmission for VTE was defined as the first readmission after discharge from the initial hospitalization), 12 685 patients (25.0%) of 50 696 patients had cancer. To confirm that the stratification of cancer types did not deviate from the national statistics and to identify which cancer types were more frequently hospitalized for VTE in Japan, we calculated cancer type proportion of 12 685 patients with cancer and compared it with national statistics. Subsequently, we excluded 219 patients aged <20 years and 897 who died within 24 hours after admission. Patients who died within 24 hours after admission were excluded because their medical histories were not properly interviewed, and JROAD-DPC data may have been omitted. As a result, 12 574 patients with cancer and 37 006 patients without cancer were included to assess hospital mortality. The Institutional Review Board of the Tokushima University Hospital approved the study protocol (no. 3503) and waived the requirement for individual informed consent because information specific to individuals is not included.

Clinical Outcomes

The main outcome was in-hospital mortality death ≤7, 14, and 30 days after admission, because acute and subacute mortality are mainly related to VTE in this cohort. Total number of deaths after admission was assessed as secondary outcomes. Patients were censored upon discharge and were not followed beyond that point.

Sample Matching

Propensity score (PS) matching was used to reduce confounding effects related to differences in patient background. After matching, 12 574 patients each in the cancer and noncancer groups were included in the final analysis. Concordance index was 0.64 and the consistency of PS densities was matched after matching (Figure S1). The balance of each covariate before and after the matching between the 2 groups was evaluated by standardized differences. Absolute value of standardized differences <10% was considered to be a relatively small imbalance.

Patient and Public Involvement Statement

Neither patients nor the public were involved in the design, conduct, reporting, or dissemination of our research.

Statistical Analysis

The Shapiro-Wilk test was used to assess the normal distribution of continuous data. Continuous variables are expressed as mean±SD for parameters with normal distribution, as median (interquartile range) for parameters with skewed distribution, and categorical variables as proportion (%). PS was estimated with a logistic regression model, with cancer as the dependent variable and the following 18 clinically relevant covariates: age, sex, hypertension, diabetes mellitus, dyslipidemia, congestive heart failure, myocardial infarction, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, rheumatic disease, moderate-severe chronic kidney disease, moderate-severe liver failure, PE, dementia, and use of intra-aortic balloon pumping, percutaneous cardiopulmonary support, and catecholamine for treatment. These covariates were chosen for their potential association with reference to risk factor of thromboembolism and mortality.[11–13] Matching was performed with greedy-matching algorithm (ratio=1:1 without replacement), with a caliper of width 0.2 SDs of the logit of the estimated PS. After matching, we estimated the odds ratio (OR) and 95% CI with cancer for in-hospital mortality (total, within 7 days, 14 days, and 30 days) by matched logistic regression analysis adjusted for hospitalization days. To confirm that the results were similar, we used inverse probability treatment weighting with a logistic regression model adjusted for hospitalization days in the full sample before matching. We assigned patients with cancer a weight of 1÷PS and patients without cancer a weight of 1÷(1–PS). We also analyzed subgroups by type of cancer in the PS-matched cohort. The OR for each type of cancer was calculated using matched patients without cancer as controls. In-hospital mortality was assessed using Kaplan-Meier method and compared between patients with and without cancer using log-rank test. All statistical tests were 2-sided and *P* values <0.05 were considered statistically significant. Statistical analysis was performed using SAS version 9.4 and JMP 14.0 (SAS Institute Inc., Cary, NC).

RESULTS

Patient Characteristics

In the group before PS matching (n=49 580), a total of 40.3% (n=19 995) of this group were male, with a median age of 72 years (range: 60–81 years) and 51.2% (n=25 385) had PE. In patients without cancer, there was a significantly larger prevalence of hypertension, dyslipidemia, cerebrovascular disease, congestive heart failure, rheumatic diseases, and dementia than in patients with cancer. The distribution of other comorbidities was similar by cancer status. We calculated the proportion

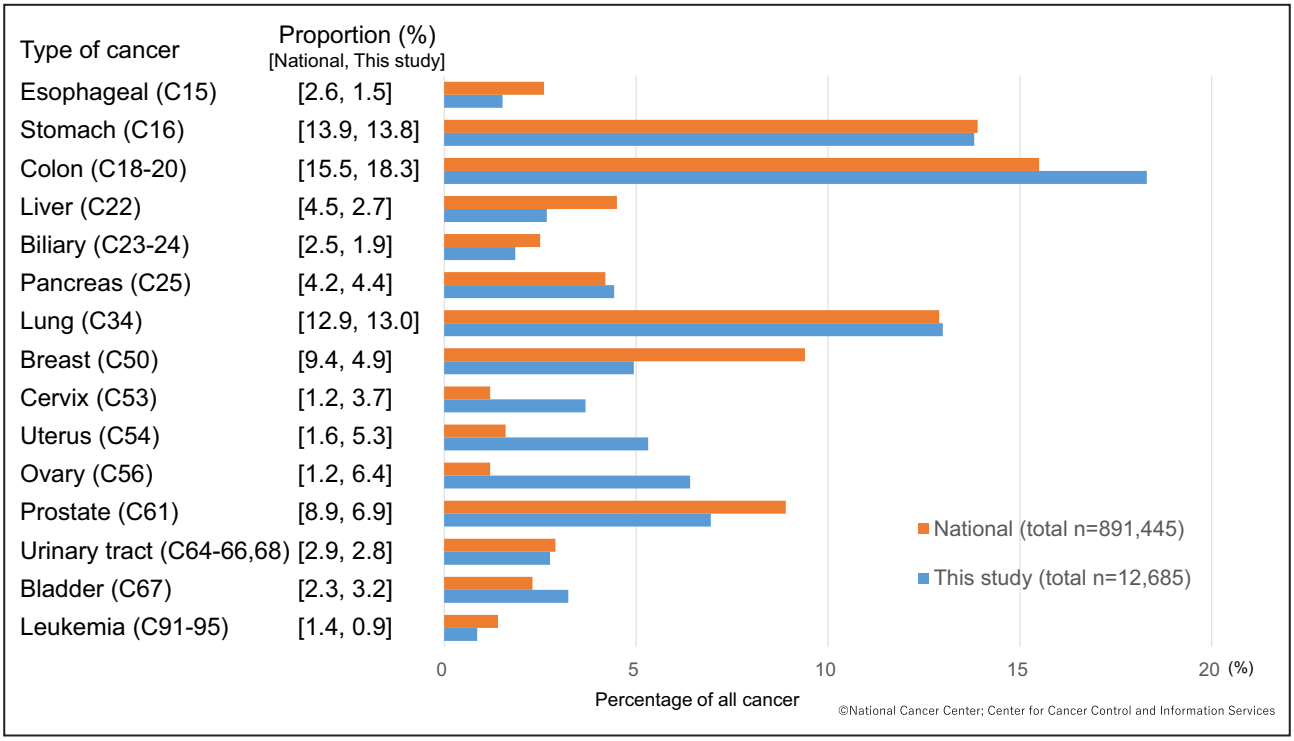


Figure 2. Proportion of cancer type of first hospitalized patients with VTE and comparison with national statistics.
Data are presented as [each cancer proportion of national statistics (%) and this study (%)]. VTE indicates venous thromboembolism.

of each type of cancer from patients before second exclusion (Figure 2). Gastric, colon, and lung cancers accounted for more than 40% of the total cancer type, which was equivalent to the national statistics. On the other hand, the proportion of cancer of cervix, uterine body, and ovary in this study were 3 to 5 times higher than the national statistics. After PS matching, 24 432 patients were excluded and 25 148 patients were included in the analysis. In the matched cohort, there were no differences between groups of patients with cancer versus noncancer for age, sex, comorbidities, PE, intra-aortic balloon pumping, percutaneous cardiopulmonary support, and catecholamine treatment (Table 1). Median hospitalization length was slightly longer in the group with cancer than noncancer (16 days versus 14 days, standard difference=19.5). The median length of hospitalization was relatively long in this cohort because we selected patients with poorer conditions, not those in outpatient care.

Outcomes

Patients with VTE and cancer had significantly higher in-hospital mortality at 7, 14, and 30 days postadmission compared with those without cancer (Table 2). The OR after matching was higher than before matching in all periods. Because all patients with cancer were matched, the change in OR depended on the change in mortality of patients without cancer after matching. Kaplan–Meier curves of in-hospital mortality after matching were shown in Figure 3. In this analysis, patients with cancer had a significantly higher mortality than those without cancer (P<0.001). In inverse probability treatment weighting with logistic regression model, in-hospital mortality within 7 days (OR, 1.29; 95% CI, 1.15–1.45), within 14 days (OR, 1.71; 95% CI, 1.57–1.87), and within 30 days (OR, 2.22; 95% CI, 2.07–2.38) were significantly higher in patients with cancer (Table 2).

Prognostic Impact by Cancer Types

For hospitalization mortality of each cancer type, forest plots of ORs are shown in Figure 4. Patients with stomach, colon, liver, biliary tract, pancreas, lung, breast, cervix, uterine body, ovary, or bladder cancers had significantly higher in-hospital mortality than matched patients without cancer. Mortality in pancreatic cancer was especially high, followed by biliary tract and liver cancer. Patients with esophageal cancer, prostate cancer, kidney and urinary tract cancer, or leukemia had no significant difference in in-hospital mortality compared with matched patients without cancer.

DISCUSSION

The main findings of the study were (1) among patients hospitalized with cancer and VTE, gastric, colon, and lung cancers accounted for more than 40% of the total cancer type, which was equivalent to the national

Table 1. Baseline Characteristics Before and After Propensity Score Matching

	Nonmatching				Matching		
	All	Cancer	Noncancer	Std. diff	Cancer	Noncancer	Std. diff
	(n=49 580)	(n=12 574)	(n=37 006)		(n=12 574)	(n=12 574)	
Age, y	72 (60–81)	70 (61–79)	73 (59–81)	−2.0	70 (61–79)	70 (60–79)	0.7
Male sex, %	40.3	42.4	39.6	5.6	42.4	42.4	<0.1
Pulmonary embolism, %	51.2	51.3	51.2	0.2	51.3	51.7	−0.8
Comorbidities, %							
Hypertension	28.9	23.1	30.8	−17.5	23.1	23.2	−0.1
Diabetes mellitus	13.5	13.3	13.5	−0.8	13.3	13.3	−0.2
Dyslipidemia	14.0	9.0	15.7	−20.4	9.0	9.0	<0.1
Stroke	5.8	4.2	6.4	−9.6	4.2	4.1	0.6
Congestive heart failure	15.3	11.2	16.7	−16.0	11.2	11.2	<0.1
Myocardial infarction	1.4	0.9	1.6	−6.8	0.9	0.9	0.2
Peripheral vascular disease	2.7	1.6	3.1	−9.7	1.6	1.5	0.6
Chronic kidney disease	2.9	2.1	3.2	−6.4	2.1	2.2	−0.6
Liver failure	0.1	0.2	0.1	2.0	0.2	0.2	1.2
Chronic obstructive pulmonary disease	4.7	4.7	4.7	0.3	4.7	4.6	0.6
Rheumatic diseases	3.2	1.9	3.7	−10.8	1.9	1.9	0.1
Dementia	4.7	2.6	5.4	−14.7	2.6	2.5	0.1
Treatment, %							
Warfarin	54.9	55.1	54.9	0.6	55.1	55.1	0.1
Direct oral anticoagulants	32.1	33.0	31.8	2.7	33.0	32.7	0.7
Heparin	80.1	82.1	79.4	6.9	82.1	79.4	6.9
Catecholamines	5.7	5.2	5.9	−3.2	5.2	4.7	2.0
Intra-aortic balloon pumping	0.4	0.2	0.5	−4.4	0.2	0.2	0.7
Percutaneous cardiopulmonary system	1.3	0.8	1.5	−7.0	0.8	0.8	−0.6
Inferior vena cava filter	27.3	30.3	26.3	9.0	30.3	26.8	7.7
Chemotherapy	3.3	13.0	NA	NA	13.0	NA	NA
Hospitalization (d)	16 (10–24)	16 (10–26)	15 (9–22)	14.0	16 (10–26)	14 (9–21)	19.5

Data are presented as percentage of patients or median (interquartile range). A standardized difference of <10% suggests adequate balance. NA indicates not applicable; and Std. diff, standardization difference.

statistics; (2) patients with VTE and cancer had significantly higher acute hospital mortality (within 7, 14, and 30 days of hospitalization); and (3) patients with pancreatic cancer had especially high in-hospital mortality, followed by those with biliary tract and liver cancer. To the best of our knowledge, this is the first report assessing the relationship between cancer and acute mortality during hospitalization in a large-scale cohort of VTE.

Impact of Cancer on VTE

After matching, mortality within 7, 14, and 30 days of hospitalization in patients with VTE and cancer were higher than patients without cancer. As shown in Table 2, patients with VTE who did not have cancer before PS matching had a higher mortality rate than after matching. Providers should not underestimate the mortality associated with VTE in patients without cancer.

Patients with cancer are more likely to have acute thrombotic events because of changes in the coagulation and fibrinolytic systems.[14] The cause is thought to be that tissue factor, mucin, and cytokines derived from cancer cells activate the coagulation system and contribute to the development of thrombosis.[15,16] Because of these mechanisms, patients with cancer

Table 2. In-Hospital Mortality for Propensity Score Matching and IPTW

In-Hospital Mortality	Nonmatching				Matching				IPTW	
	Cancer (n=12 574)	Noncancer (n=37 006)	OR (95% CI)	*P* Value	Cancer (n=12 574)	Noncancer (n=12 574)	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
7 d, %	1.3	1.4	1.17 (0.97–1.41)	0.1046	1.3	1.1	1.66 (1.31–2.11)	<0.0001	1.29 (1.15–1.45)	<0.0001
14 d, %	2.5	2.0	1.52 (1.32–1.74)	<0.0001	2.5	1.5	2.07 (1.72–2.49)	<0.0001	1.71 (1.57–1.87)	<0.0001
30 d, %	4.8	2.6	2.08 (1.87–2.31)	<0.0001	4.8	2.0	2.85 (2.45–3.31)	<0.0001	2.22 (2.07–2.38)	<0.0001
Total, %	7.3	3.2	2.37 (2.16–2.59)	<0.0001	7.3	2.4	3.08 (2.70–3.52)	<0.0001	2.45 (2.30–2.61)	<0.0001

Data given as proportion. IPTW indicates inverse probability treatment weighting; and OR, odds ratio.

have 4 to 8 times higher risk of VTE incidence than patients without cancer.[2–4] Therefore, thromboembolism is the second leading cause of death in outpatient cancer cases.[1] Based on our results, VTE had a high mortality rate at short term. Early detection and treatment of deep vein thrombosis in patients with cancer may improve patient prognosis.

Cancer and Bleeding Risk

Patients with cancer often develop cachexia and weight loss.[17] In addition, chemotherapy, sepsis, tumor lysis syndrome, and contrast agent nephropathy can cause acute renal failure in patients with cancer.[18] For treatment of VTE in cancer cases, low molecular weight heparin and direct oral anticoagulants are recommended by the European Society of Cardiology and American Society of Clinical Oncology[19,20], but these drugs may be difficult to control owing to low body weight and renal failure and may increase the risk of bleeding. In addition, chemotherapy occasionally causes anemia and thrombocytopenia.[21,22] Therefore, it is also reported that anticoagulant therapy for cancer-related VTE had 6 times higher risk of bleeding than noncancer VTE. It is necessary to consider the bleeding risk and prognosis for each case.[23]

Differences of Incidence and Prognosis by Cancer Types

Compared with national statistics on cancer incidence, hospitalized patients with VTE and cancer tended to have a higher percentage of gynecological malignancies. Gynecological cancers are thought to cause thromboembolic events because of surgery (pelvic visceral resection, inguinal lymphadenectomy) and venous congestion for tumors or enlarged lymph nodes.[24] Also, gynecological cancer has a 5-year survival rate of more than 60% to 80%.[25] Thus, our VTE cohort may also include many patients with high VTE risk and high survival rate from cancer (eg, gynecological cancers).

From our data, the ORs of mortality for pancreatic, biliary tract, and liver cancers were higher than the other cancers. We consider the following as causes. First, liver and biliary tract cancers often cause hepatic dysfunction. Anticoagulants for VTE, warfarin and several direct oral anticoagulants, are metabolized in the liver. Hepatic dysfunction may lead to unstable anticoagulant effects and affect the prognosis.[26] Patients with liver cancer may have underlying cirrhosis. Esophageal varices increase the risk of bleeding from anticoagulation therapy.[27] After patients develop VTE 30-day mortality rates are twice as high for patients with cirrhosis.[28] Second, pancreatic cancer and ovarian cancer are mucin-producing tumors. Mucin causes platelet aggregation, probably increasing the risk of thromboembolism.[29,30]

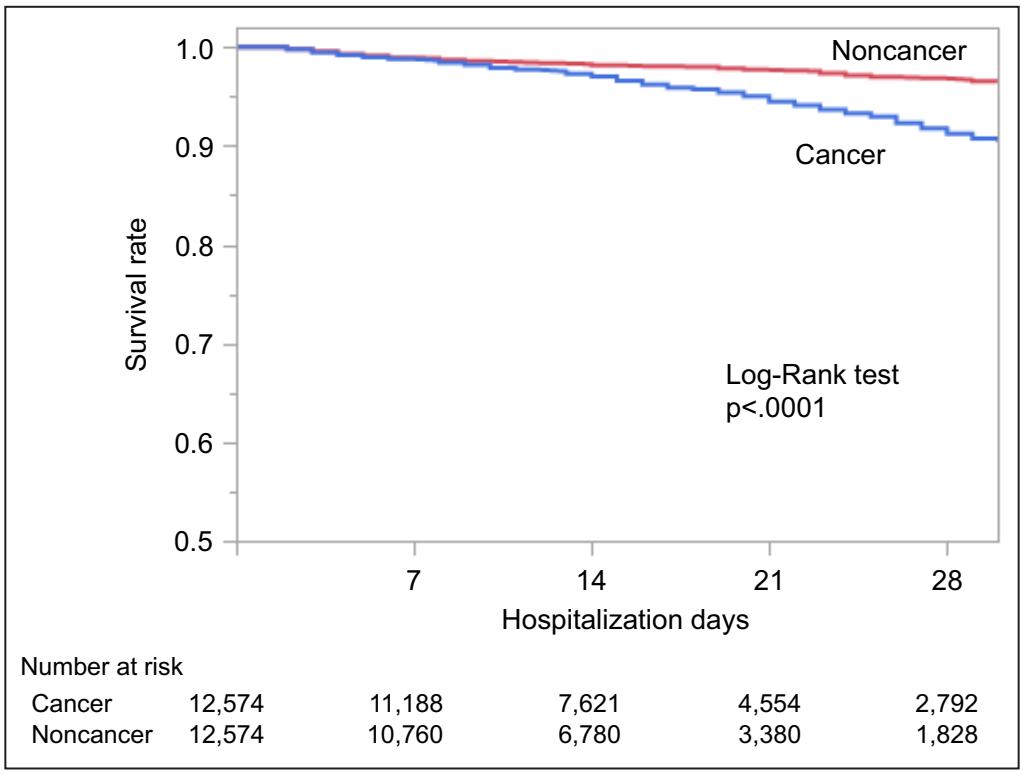


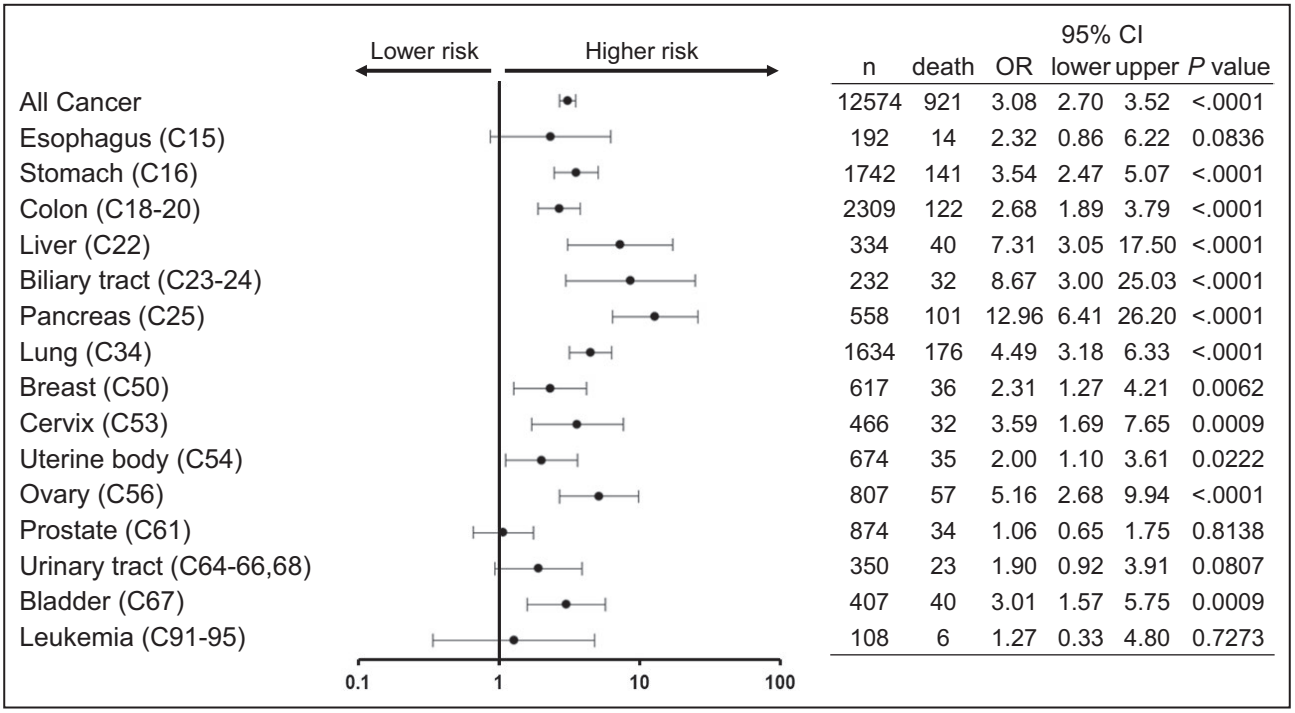
Figure 3. Kaplan-Meier curves of in-hospital mortality and hospitalization days compared between patients with and without cancer.

Clinical Implication

Although cancer is associated with a high incidence of VTE and there are many guidelines/recommendations about VTE, the prognosis of patients with cancer-VTE is not well known because of a lack of registry data. Moreover, there is also no knowledge on which type of cancer is related to worse prognosis. According to our results, patients with VTE and cancer had a high acute hospital mortality, and patients with VTE and pancreatic, biliary tract, or liver cancer seemed to be at the highest risk of in-hospital mortality compared with matched patients with VTE without cancer. It has been reported that low molecular weight heparin is effective in preventing thrombi formation in patients at high risk of VTE.[31,32] Recently, some studies have focused on the effectiveness of direct oral anticoagulants use in these patients,[33] perhaps providing us with another means of treatment. We believe that knowledge from a high-risk cohort of VTE with specific cancers may be useful for the management of patient care.

Limitations

The study based on *ICD* codes has several limitations. First, we analyzed only hospitalized patients with VTE in the database, which may lead to a selection bias. Even if the patients had developed VTE during cancer hospitalization (patients had anticancer drugs or surgery), these patients were not included as the most resource-consuming diagnosis in such cases would be registered as "cancer." When the most resource-consuming diagnosis is cancer, cancer itself may have a strong impact on mortality. Thus, we did not pick up these patients in this analysis. Second, the database has no information on echocardiography, laboratory data (D-dimer), or radiation therapy to assess the prognosis of VTE. Third, the accuracy of the diagnosis is not perfect, because these are less validated in the JROAD-DPC database compared with planned prospective studies. However, the original JROAD-DPC data set has been validated[34] and we believed that consistency is relatively high for the data set. Fourth, it is unknown whether patients diagnosed with cancer had already finished cancer treatment. Fifth, PS matching reports the potential differences between groups but is never perfect. Despite the application of PS matching to the comparator group of patients, this nonrandomized observational study could still be subject to hidden biases related to patient selection, because of unknown unadjusted differences. To overcome this issue, we used circulatory assist devices and catecholamine medication as markers of VTE severity. All-cause mortality was used



	n	death	OR	95% CI lower	95% CI upper	*P* value
All Cancer	12574	921	3.08	2.70	3.52	<.0001
Esophagus (C15)	192	14	2.32	0.86	6.22	0.0836
Stomach (C16)	1742	141	3.54	2.47	5.07	<.0001
Colon (C18-20)	2309	122	2.68	1.89	3.79	<.0001
Liver (C22)	334	40	7.31	3.05	17.50	<.0001
Biliary tract (C23-24)	232	32	8.67	3.00	25.03	<.0001
Pancreas (C25)	558	101	12.96	6.41	26.20	<.0001
Lung (C34)	1634	176	4.49	3.18	6.33	<.0001
Breast (C50)	617	36	2.31	1.27	4.21	0.0062
Cervix (C53)	466	32	3.59	1.69	7.65	0.0009
Uterine body (C54)	674	35	2.00	1.10	3.61	0.0222
Ovary (C56)	807	57	5.16	2.68	9.94	<.0001
Prostate (C61)	874	34	1.06	0.65	1.75	0.8138
Urinary tract (C64-66,68)	350	23	1.90	0.92	3.91	0.0807
Bladder (C67)	407	40	3.01	1.57	5.75	0.0009
Leukemia (C91-95)	108	6	1.27	0.33	4.80	0.7273

Figure 4. Odds ratio (OR) of in-hospital mortality in patients with each cancer compared with matched patients without cancer.
Dots and lines indicate OR and 95% CI, respectively.

as the primary end point in our patient population. We found a high prevalence of PE in patients who died within 7 days (92.9%), 14 days (89.7%), and 30 days (84.0%) in this study. Thus, the most likely cause of acute death in our patient population is PE, although deaths from other diseases were unable to be completely excluded.

Although discerning how the presence of cancer is associated with risk of sudden death, major adverse cardiac events, major bleeding, or cancer death would be of important interest, determining the definitive cause of death by death certificates can be difficult in such a very high-risk population and can pose a source of bias. The patients in this study are mostly Japanese. Results may differ because of racial/ethnic differences compared with other countries. This study included only patients hospitalized for VTE because we focused on the high-risk group to clarify the relationship between VTE and cancer. Our results are unable to be applied to the outcome of outpatients. Considering these limitations, a prospective study involving a large number of patients with VTE should also be performed in other countries.

CONCLUSIONS

Patients with cancer had a higher acute mortality during hospitalization for VTE than patients without cancer, especially in pancreatic, biliary tract, and liver cancers.

ARTICLE INFORMATION

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Author contributions: Kusunose conceived the idea for this study. Okushi and Okayama conducted the data analyses. The initial draft of the article was produced by Kusunose and Okushi. All authors were involved in interpreting the results and writing the article. All authors read and approved the final article.

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Disclosures

None.

Supplementary Material

Figure S1

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SUPPLEMENTAL MATERIAL

Figure S1. a: Receiver operating characteristic curve and concordance index. b: comparison the consistency of propensity score densities before and after matching.