Analysis of thromboembolism and prognosis in metastatic pancreatic cancer from the Tokushukai REAl-world data project

RAI SHIMOYAMA[1], YOSHINORI IMAMURA[2-4], KIYOAKI URYU[5], TAKAHIRO MASE[6], MEGU OHTAKI[7], KEIKO OHTANI[7], MEGUMI SHIRAGAMI[8], YOSHIAKI FUJIMURA[8], MAKI HAYASHI[9], NOBUAKI SHINOZAKI[1] and HIRONOBU MINAMI[4,10]

[1]Department of General Surgery, Shonan Kamakura General Hospital, Kamakura, Kanagawa 247-8533, Japan; [2]Cancer Care Promotion Center, University of Fukui Hospital, Eiheiji, Fukui 910-1193, Japan; [3]Department of Hematology and Oncology, University of Fukui Hospital, Eiheiji, Fukui 910-1193, Japan; [4]Department of Medical Oncology and Hematology, Kobe University Graduate School of Medicine, Kobe, Hyogo 650-0017, Japan; [5]Department of Medical Oncology, Yao Tokushukai General Hospital, Yao, Osaka 581-0011, Japan; [6]Department of Breast Surgery, Ogaki Tokushukai Hospital, Ogaki, Gifu 503-0015, Japan; [7]deCult Co., Ltd., Hatsukaichi, Hiroshima 739-0413, Japan; [8]Tokushukai Information System Inc., Osaka 530-0001, Japan; [9]Mirai Iryo Research Center Inc., Tokyo 102-0074, Japan; [10]Cancer Center, Kobe University Hospital, Kobe, Hyogo 650-0017, Japan

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Abstract. Cancer-associated thromboembolism (CAT), including venous thromboembolism (VTE) and arterial thromboembolism (ATE), is a frequent complication of advanced pancreatic cancer. However, reports on its incidence and clinical outcomes, especially on ATE, are limited. The present study aimed to investigate the incidence of CAT and its effects on overall survival in patients with metastatic pancreatic cancer. As part of the Tokushukai REAl-world data project in Japan, 846 eligible patients with metastatic pancreatic cancer treated with first-line chemotherapy were identified between April 2010 and March 2020. Using diagnosis procedure combination data from these patients, the present study investigated the incidence of VTE, ATE and cerebral and gastrointestinal bleeding requiring hospitalization. Blood laboratory data were collected within 14 days of the start of first-line treatment, and Khorana scores were calculated. The associations between CAT complications and comorbidities, concomitant medications and prognosis were examined. Among the 846 patients, 21 (2.5) and 70 (8.3%) had VTE and ATE, respectively (including five with overlapping VTE and ATE). CAT-positive patients had a significantly higher rate of gastrointestinal bleeding events compared with CAT-negative patients [13 of 86 (15.2%) vs. 46 of 760 (6.1%); P=0.01]. CAT-positive patients had a poorer prognosis [hazard ratio (HR), 1.28; 95% confidence interval (CI), 1.01-1.62] compared with CAT-negative patients, even after adjusting for background factors (HR, 1.20; 95% CI, 0.95-1.52). Cox regression analyses showed that higher Khorana scores were associated with significantly worse prognosis. This real-world data demonstrated that the incidence rate of CAT in patients with metastatic pancreatic cancer was 10.2%, and no statistically significant differences were observed, although there was a trend toward an adverse prognosis. The Khorana score may also be useful for predicting prognosis, even in the absence of CAT. This study was registered in the UMIN Clinical Trial Registry (http://www.umin.ac.jp/ctr/index.htm; clinical trial no. UMIN000050590).

Correspondence to: Dr Yoshinori Imamura, Cancer Care Promotion Center, University of Fukui Hospital, 23-3 Matsuoka-Shimoaizuki, Yoshida, Eiheiji, Fukui 910-1193, Japan
E-mail: yimamura@u-fukui.ac.jp

Abbreviations: AIC, Akaike information criterion; ATE, arterial thromboembolism; BMI, body mass index; CAT, cancer-associated thromboembolism; CIs, confidence intervals; DOACs, direct-acting oral anticoagulants; DPC, Diagnosis Procedure Combination; DVT, deep venous thrombosis; HRs, hazard ratios; LMWH, low-molecular-weight heparin; OS, overall survival; PAD, peripheral arterial disease; PE, pulmonary embolism; PS, performance status; VTE, venous thromboembolism

Key words: cancer-associated thromboembolism, metastatic pancreatic cancer, real-world data, Tokushukai REAl-world Data project, venous thromboembolism

Introduction

The association between cancer and thrombosis was first reported in 1865 by Trousseau in his book 'Clinique Medicale de l'Hotel-Dieu de Paris' as 'Phlegmatia Alba Dolens' (1,2). In 1977, Sack *et al* reported that the Trousseau syndrome was a chronic disseminated intravascular coagulation associated with cancer (3). In recent years, the risk of thromboembolism, including venous thromboembolism (VTE) and arterial thromboembolism (ATE), has increased in patients with cancer (4). Cancer-associated thrombosis is a major cause of morbidity and mortality in cancer patients.

Thromboembolism can occur at any stage of cancer and often complicates the course of the disease and treatment. The exact incidence of VTE, including deep venous thrombosis (DVT) and pulmonary embolism (PE), in patients with cancer remains under investigated. In total, 50% of autopsy cases in patients with cancer have VTE (5); however, the incidence rate of clinically significant VTE ranges from 0.4-43% (6-8), with 3.5-9% of VTE cases resulting in death (9,10). However, there are few reports on the incidence of ATE, including acute coronary syndrome, ischemic stroke, and peripheral arterial disease (PAD). It has an incidence rate of 4.7% and a 2.2-fold incidence risk compared with patients without cancer (11,12). In addition, it is known that patients with cancer-associated thrombosis also have a 2.2-fold increased risk of bleeding (13). This increased risk in cancer patients requires careful monitoring, and appropriate management of thromboembolic events is necessary to improve their overall prognosis and quality of life.

Pancreatic cancer has one of the poorest prognoses, with a remarkably low 5-year survival rate of approximately 10% in both Japan and the United States. It is the fourth leading cause of cancer-related deaths (14,15). Most recently, we reported the outcomes of 846 patients treated with first-line chemotherapy for metastatic pancreatic cancer in a real-world setting (16). Pancreatic cancer also has a higher incidence of VTE than other cancers (17); however, data on ATE are scarce despite the presence of shared risk factors, such as smoking, obesity, and diabetes mellitus. Understanding the interplay between pancreatic cancer and thromboembolism, particularly ATE, could lead to more effective prevention and management strategies.

In this study, we aimed to examine the incidence of cancer-associated thromboembolism (CAT), its prognosis background factors affecting survival and the prognostic utility of the Khorana score in predicting outcomes in patients with metastatic pancreatic cancer treated with chemotherapy using the aforementioned dataset. This study allows us to provide new information on the clinical effects of cancer-associated ATE and VTE.

Materials and methods

The Tokushukai REAl-world Data project is a large-scale, retrospective cohort study that includes hospitals from the Tokushukai Medical Group across Japan. Comprehensive details regarding the study are outlined in a separate protocol article (18). The project was developed in compliance with Japanese ethical guidelines for medical and biological research involving human subjects (19) and adheres to the principles of the Declaration of Helsinki. The study was approved by the Ethics Committee of the Tokushukai Group in April 2020 (approval no. TGE01427-024). Patients were informed via an opt-out method. Additionally, the study was registered with the UMIN Clinical Trial Registry (http://www.umin.ac.jp/ctr/index.htm) under the registration no. UMIN000050590 in March 2023.

Objective patients. We assessed patients with pathologically or radiologically confirmed metastatic pancreatic cancer who received first-line chemotherapy from April 1, 2010, to March 31, 2020, at the Tokushukai Medical Group hospitals, comprising 46 hospitals with 14,829 beds. They operate under a unified medical record system (e-Karte and Newtons2, Software Service Inc.) and a chemotherapy protocol system (srvApmDrop, Software Service Inc.).

All patients were administered first-line treatments, which included gemcitabine, S-1, a combination of gemcitabine and S-1, a combination of gemcitabine and nab-paclitaxel, or a regimen of fluorouracil, folinic acid, oxaliplatin, and irinotecan (FOLFIRINOX). The study covered a range of pathological diagnoses such as adenocarcinoma, adenosquamous carcinoma, and other carcinomas/malignant neoplasms. However, patients diagnosed with acinar and neuroendocrine carcinoma were excluded from the study. Other significant exclusion criteria were the presence of active concurrent cancers, an inadequate treatment history, and missing essential patient data, including body weight and height. Patients with an insufficient treatment history (e.g., those who received cancer treatment outside of the Tokushukai Medical Group hospitals or lacked detailed treatment information) were excluded from this study.

Data collection. We assessed eligible patients identified through electronic medical records. Patient information including age, sex, height, weight, body surface area, body mass index (BMI), most recent survival data, survival outcomes, diagnosis from medical receipts, and hospital classification (government-designated cancer hospital, prefectural designated cooperative cancer hospital, or non-designated general hospital) was extracted. Data related to chemotherapy regimens, including start and end dates of treatment and performance status (PS), were obtained from the chemotherapy protocol system. Prescription information for oral medications (antiplatelets, anticoagulants, antihypertensive medications, diabetes medications, statins) was extracted from the electronic medical record's commercial information for medications prescribed within 30 days before and after the cancer diagnosis. Blood laboratory data within 14 days of treatment were also extracted from the electronic medical record. Data from the linked cancer registry, encompassing diagnostic details (such as site, pathology, and stage), treatment specifics (including surgery, endoscopic procedures, radiotherapy, and chemotherapy), and prognosis data (final survival confirmation date, date of death, and cause of death), were obtained from the National Cancer Registry Data in Japan (20). The date of the last confirmed survival was extracted from both the cancer registry and electronic medical record data, and the later date was used. The incidence of VTE (DVT and PE) (21), ATE (acute coronary syndrome, ischemic stroke, and PAD) (22-24), bleeding complications (subarachnoid, intracranial, epidural, cerebral, and upper and lower gastrointestinal bleeding) (25), and comorbidity (diabetes mellitus, hypertension, hyperlipidemia, and chronic renal failure) (26), coded by the International Classification of Diseases 10th Revision, were extracted from the Diagnosis Procedure Combination (DPC), as listed in Table I. The DPC is diagnosis group classification system in Japan, linked to the comprehensive payment system for medical fees. To analyze secular trends and ensure nearly equal distribution of patients, the study period was divided into three intervals: Period A (2010-2013), Period B (2014-2016), and

Table I. International Classification of Diseases, 10th revision codes.

Category	Disease	Code
Venous thromboembolism (24)	Deep vein thrombosis	I80.1, I80.2, I80.3, I80.8, I80.9, I82.8, I82.9, O22.3, O22.9, O87.1
	Pulmonary embolism	I26.0, I26.9
Arterial thromboembolism (25-27)	Acute coronary syndrome	I20.0, I21.x-I22.x
	Cerebrovascular accident	G45.x, I63.x-I64.x
	Peripheral arterial disease	I70.0, I70.20-25, I70.29, I70.9
Major bleeding (28)	Subarachnoid hemorrhage	I60.x
	Intracranial hemorrhage	I61.x
	Subdural hemorrhage	I62.x
	Upper gastrointestinal bleeding	I85.0, K22.1, K22.6, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K31.80, K63.80, K92.0, K92.1, K92.2
	Lower gastrointestinal bleeding	K55.2, K51, K57, K62.5, K92.0, K92.1, K92.2
Preexisting condition (29)	Diabetes mellitus	E10.x-E14.x
	Hypertension	I10.x-I13.x, I15.x
	Dyslipidemia	E78.x

Period C (2017-2020). In Japan, FOLFIRINOX were approved in period A, gemcitabine plus nab-paclitaxel received approval in period B, and nal-irinotecan received approval in period C.

The Khorana score was calculated from the blood collection data. The Khorana score, which consists of five clinical and pre-chemotherapy laboratory parameters, primary tumor site (+1 or 2 points), platelet count of ≥350x10^9/l (+1 point), hemoglobin concentration of ≤100 g/l or use of erythropoiesis-stimulating agents (+1 point), leukocyte count of ≥11x10^9/l (+1 point), and a BMI of ≥35 kg/m^2 (+1 point), predicts VTE development (27,28). For pancreatic cancer, the minimum score is 2. The score increases according to other parameters.

Statistical analyses. The primary endpoint of this study was overall survival (OS), defined as the duration from the start date of the initial palliative chemotherapy to the date of death or the last confirmation of survival.

Basic statistics were calculated to summarize the distribution of variables related to patient background factors, complications, other prognostic factors, and primary endpoints. These statistics included absolute and relative frequencies for categorical variables, quartiles, maximum and minimum values, means and standard deviations for continuous variables, and quartiles and relative frequencies for discrete variables. The study period spanned from April 1, 2010, to March 31, 2020. The time variable was defined as the number of days from the start date of the first-line chemotherapy treatment to the date of death. Censored cases included patients who were alive at the end of the study or those who dropped out for any reason. Fisher's exact tests were used in these between-group comparisons.

For each prognostic score, Kaplan-Meier curves (univariate analysis) for the occurrence of events associated with the study endpoint (OS) were obtained and log-rank tests were performed.

Additionally, several hierarchical predictive models were developed by integrating explanatory variables anticipated to impact the evaluated endpoints. Both single- and multi-tiered proportional hazard models were established using each predictive model. Stratified and conventional Cox multiple regression analyses were performed. Conventional Cox regression was used when the proportional hazards assumption was valid; otherwise, stratified Cox regression was employed.

The Akaike information criterion (AIC), based on partial likelihood, was utilized to identify the optimal model in this study. When the number of eligible cases varied between models, the average AIC per case was used. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for each category of prognostic factors related to OS identified in the optimal model. The effects of these prognostic factors were assessed using likelihood tests, with associated p-values provided for each factor.

All analyses were performed using R, version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were two-sided, with significance set at $P<0.05$.

Results

A total of 846 eligible patients were analyzed (16). With a median follow-up of 5.4 months (95% confidence interval [CI], 4.8-6.0), 86 (10.2%) of them had any form of CAT requiring hospitalization, comprising 21 patients with VTE (2.5%) and 70 patients with ATE (8.3%) (including five patients with overlapping VTE and ATE). The patient backgrounds for both groups are shown in Table II. There were no differences in patient backgrounds, including Khorana scores, between the CAT-positive and CAT-negative patients.

Patient comorbidities, concomitant medications before and during first-line treatment, and first-line systemic therapy

Table II. Patients' medical and demographic characteristics.

Characteristics	CAT(-) (n=760), n %	CAT(+) (n=86), n %	P-value
Age			
Median	70	72	0.26
Quantile (Min, Q1, Q2, Q3, Max)	(36, 64, 70, 76, 90)	(47, 68, 72, 77, 84)	
≥75	232 (30.5)	34 (39.5)	
Sex			
Male	451 (59.3)	52 (60.5)	0.91
Female	309 (40.7)	34 (39.5)	
Performance status			
0	210 (27.6)	22 (25.6)	0.84
1	260 (34.2)	30 (34.9)	
≥2	46 (6.1)	7 (8.1)	
Not available	244 (32.1)	27 (31.4)	
BMI			
Median	19.7	20.3	0.55
Quantile (Min, Q1, Q2, Q3, Max)	(11.2, 17.4, 19.7, 21.9, 35.4)	(13.6, 17.3, 20.3, 22.0, 34.3)	
≥25	64 (8.4)	9 (10.5)	
Smoking status			
Current or former (Brinkman index >0)	197 (28.3)	20 (23.3)	0.44
Never smoked (Brinkman index=0)	500 (71.3)	62 (72.1)	
Not available	63 (8.4)	4 (4.7)	
Pathological confirmation			
Yes	666 (87.6)	79 (91.9)	0.20
Adenocarcinoma	382 (50.3)	36 (41.9)	
Adenosquamous carcinoma	6 (0.8)	1 (1.2)	
Carcinoma/malignant neoplasm	278 (36.6)	42 (48.3)	
No (radiological diagnosis only)	94 (12.4)	7 (8.1)	
Primary disease site			
Pancreas head	318 (41.8)	41 (47.7)	0.37
Pancreas body	215 (28.3)	17 (19.8)	
Pancreas tail	196 (25.8)	24 (27.9)	
Whole/not evaluable	31 (4.1)	4 (4.7)	
Previous procedures			
Surgery	115 (15.1)	8 (9.3)	0.77
Endoscopic procedure	40 (5.3)	4 (4.7)	
Radiotherapy	43 (5.7)	4 (4.7)	
Study period			
Period A (2010-2013)	240 (31.6)	28 (32.6)	0.22
Period B (2014-2016)	232 (30.5)	19 (22.1)	
Period C (2017-2020)	288 (37.9)	39 (45.3)	
Hospital scale (no. of registered patients)			
High volume (n≥50)	454 (59.7)	55 (64.0)	0.49
Low volume (n<50)	306 (40.3)	31 (36.0)	
Hospital type			
Government-designated cancer hospital	192 (25.3)	26 (30.2)	0.61
Prefectural designated cooperative cancer hospital	286 (37.6)	30 (34.6)	
General hospital	282 (37.1)	30 (34.6)	
Platelet count			
Median, $x10^9$/l	22	20.4	0.45
Quantile, $x10^9$/l	(4.4, 17.1, 22.0, 28.5, 71.3)	(6.5, 16.0, 20.4, 27.9, 63.0)	
≥350, $x10^9$/l	82 (10.8)	6 (7.0)	

Table II. Continued.

Characteristics	CAT(-) (n=760), n %	CAT(+) (n=86), n %	P-value
Hemoglobin			
Median, gl	12.2	11.8	1.00
Quantile, g/l	(7.2, 10.9, 12.2, 13.3, 18.4)	(8.6, 10.7, 11.8, 12.7, 16.1)	
<100 g/l	75 (9.9)	8 (9.3)	
White blood cell count			
Median, $x10^9$/l	6.8	71	0.17
Quantile, $x10^9$/l	(19, 53, 68, 88, 290)	(27, 56, 71, 92.7, 195)	
>$11x10^9$/l	87 (11.4)	15 (17.4)	
Khorana score			
2	502 (71.6)	57 (65.1)	0.50
3	155 (22.1)	20 (23.3)	
4	42 (6.0)	3 (3.5)	
5	2 (0.3)	1 (1.2)	
6	0 (0.0)	0 (0.0)	
Not available	59 (7.8)	5 (5.8)	

CAT, cancer-associated thromboembolism; BMI, body mass index.

regimens are shown in Table III. Dyslipidemia was observed significantly more frequently in CAT-positive patients than in CAT-negative patients. Patients in the CAT-positive group used significantly more antiplatelet and anticoagulant medications than those in the CAT-negative group. Additionally, CAT-positive patients had a significantly higher rate of gastrointestinal bleeding events than CAT-negative patients [13 of 86 (15.2%) vs. 46 of 760 (6.1%), P=0.01]. The detailed thromboembolic and bleeding incidences are shown in Table IV.

We derived crude Kaplan-Meier curves and adjusted results for 'age,' 'sex,' 'BMI,' 'study period,' and 'PS,' which were correlated with prognosis in our previous analyses (16). The Kaplan-Meier curves of OS with and without CAT are shown in Fig. 1. CAT-positive patients had a poor prognosis than those without CAT in the crude data (HR, 1.28; 95% CI, 1.01-1.62; P=0.044), and this trend persisted even after adjusting for background factors (HR, 1.20; 95% CI, 0.94-1.52; P=0.131). Prognostic analysis based on the presence of VTE and ATE was also performed. However, no statistically significant difference was found between the two groups, although there was a trend toward a poorer prognosis in positive cases than in negative cases (Fig. 2). Kaplan-Meier curves of OS with and without antiplatelet or anticoagulant use are shown in Fig. 3. Patients taking anticoagulants or antiplatelets also had a poorer prognosis than those not taking these medications (HR, 1.22; 95% CI, 1.01-1.48; P=0.036).

The Kaplan-Meier curves for OS based on the Khorana score are shown in Figs. 4 and 5. The Khorana score was significantly associated with poor prognosis (P<0.001), with higher scores indicating a poorer prognosis. Although the Khorana score was not associated with OS in the CAT-positive group, it was a prognostic factor in the CAT-negative group (P<0.001).

Discussion

This real-world study revealed that the incidence rate of CAT in patients with treatment-naive metastatic pancreatic cancer was sufficiently high to be clinically alarming (10.2%). In addition, a trend toward a poorer prognosis and higher risk of gastrointestinal bleeding events in CAT-positive patients than in CAT-negative patients was observed. A higher Khorana score did not predict CAT events but had prognostic value in our cohort.

As noted in the Introduction section, the frequency of clinically significant VTE ranges from 0.4-43% (6-8), which is a significantly wide range. In a multicenter prospective cohort study conducted in Japan, VTE was reported in 5.9% of the patients (asymptomatic, 5.5%; symptomatic, 0.3%) (17). A retrospective study on VTE in patients with pancreatic cancer in Japan reported a prevalence of 7.2% (29). Similarly, an Italian and a German database study reported 26.0% (30) and 26.4%, respectively (31).

The incidence rate of VTE reported in this study (2.5%) was significantly low compared with those of previous studies. As the data in this study were based on DPC, only VTE requiring hospitalization was extracted, and asymptomatic VTE identified by ultrasonography or computed tomography imaging was not included, as in other studies based on chart reviews. This may explain the lower incidence of VTE in our study than that in previous studies. In fact, the largest Japanese cohort study on symptomatic VTE in metastatic pancreatic cancer reported a 1-year cumulative incidence rate of only 1.4%, which is comparable to our incidence rate (32).

The incidence rate of ATE (8.3%) in this study was higher than that in previous studies. Although there are fewer reports of ATE compared to VTE, the incidence rate of ATE in cancer patients is 4.7-5.9% (33,34); in patients with pancreatic cancer, the reported rate is 2.8-5.0% (35,36). A retrospective study

Table III. Comorbidities, concomitant medications and first-line systemic therapy.

Characteristics	CAT(-) (n=760), n (%)	CAT(+) (n=86), n (%)	P-value
Pre-existing condition			
Diabetes mellitus	249 (32.8)	39 (45.3)	0.18
Hypertension	290 (38.2)	41 (47.7)	0.3
Dyslipidemia	145 (19.1)	36 (41.9)	<0.001
Chronic kidney disease	122 (16.1)	19 (22.1)	0.24
Concomitant medication			
Antidiabetics	205 (27.0)	31 (36.0)	0.19
Antihypertensive	279 (36.7)	49 (57.0)	0.03
Statins	78 (10.3)	25 (29.1)	<0.001
Antiplatelets	51 (6.7)	35 (40.7)	<0.001
Aspirin	8 (5.0)	25 (29.1)	<0.001
Thienopyridine	13 (1.7)	16 (18.6)	<0.001
Others	11 (1.5)	10 (11.6)	<0.001
Anticoagulants	113 (14.9)	38 (44.2)	<0.001
Warfarin	14 (1.8)	9 (10.5)	<0.001
Direct oral anticoagulants	7 (0.9)	11 (12.8)	<0.001
Heparin[a]	101 (13.3)	28 (32.6)	<0.001
Others	1 (0.1)	4 (4.7)	<0.001
First-line systemic therapy			
Gemcitabine alone	269 (35.4)	35 (40.7)	0.9
S-1 alone	178 (23.4)	20 (23.3)	
Gemcitabine+S-1	59 (7.8)	8 (9.3)	
Gemcitabine + nab-paclitaxel	209 (27.5)	23 (26.7)	
FOLFIRINOX	45 (5.9)	7 (8.1)	

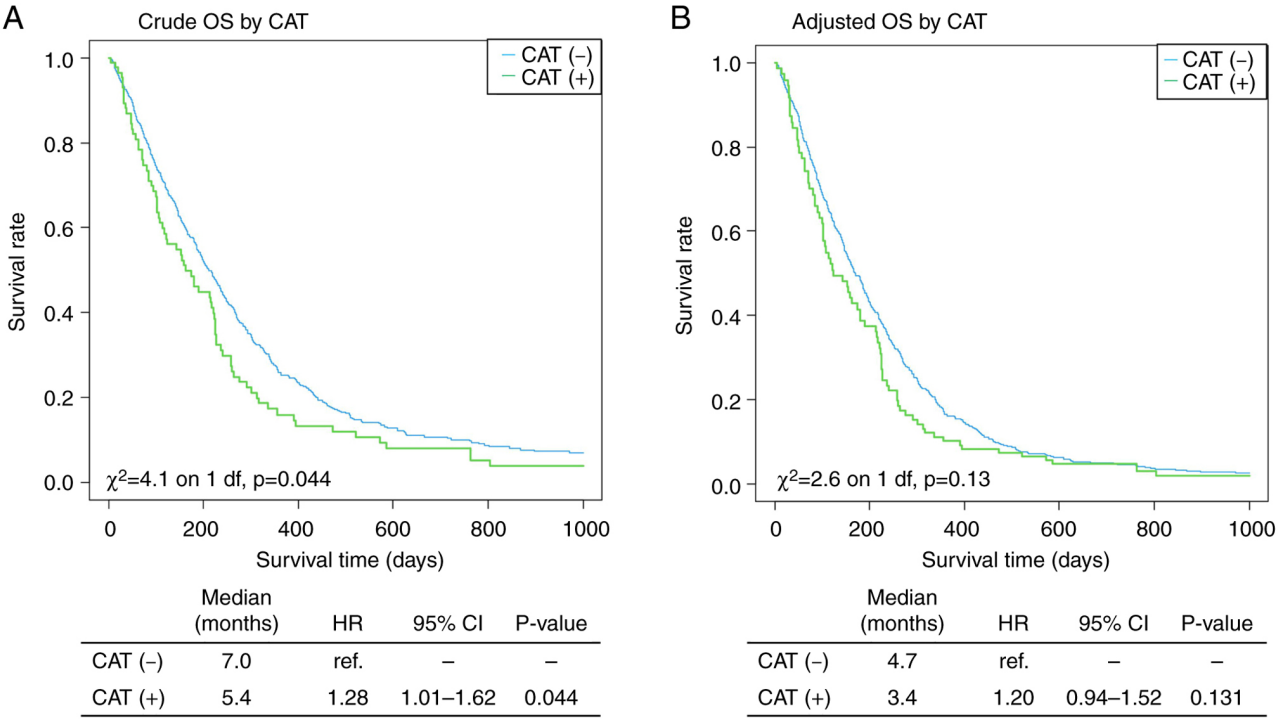
[a]Since low-molecular-weight heparin is not reimbursed, unfractionated heparin is essentially the only type available in Japan. CAT, cancer-associated thromboembolism; FOLFIRINOX, leucovorin calcium (folinic acid), fluorouracil, irinotecan hydrochloride, and oxaliplatin.

Table IV. Incidences of thromboembolism and bleeding events.

Characteristics	CAT^- (n=760), n (%)	CAT^+ (n=86), n (%)[a]	P-value
Thrombotic events (%, CAT^+/total)			
Venous thromboembolism		21 (24.4/2.5)	
Deep venous thrombosis		16 (18.6/1.9)	
Pulmonary embolism		8 (9.3/0.9)	
Arterial thromboembolism		70 (81.4/8.3)	
Acute coronary syndrome		24 (27.9/2.8)	
Ischemic stroke		39 (45.3/4.6)	
Peripheral arterial disease		12 (13.9/1.4)	
Bleeding events			
Cerebral bleeding	7 (0.9)	1 (1.1)	0.58
Gastrointestinal bleeding	46 (6.1)	13 (15.2)	0.01

[a]Percentages of the CAT-positive group are shown on the left with the denominator as the CAT-positive group and on the right with the denominator in all cases. CAT, cancer-associated thromboembolism.

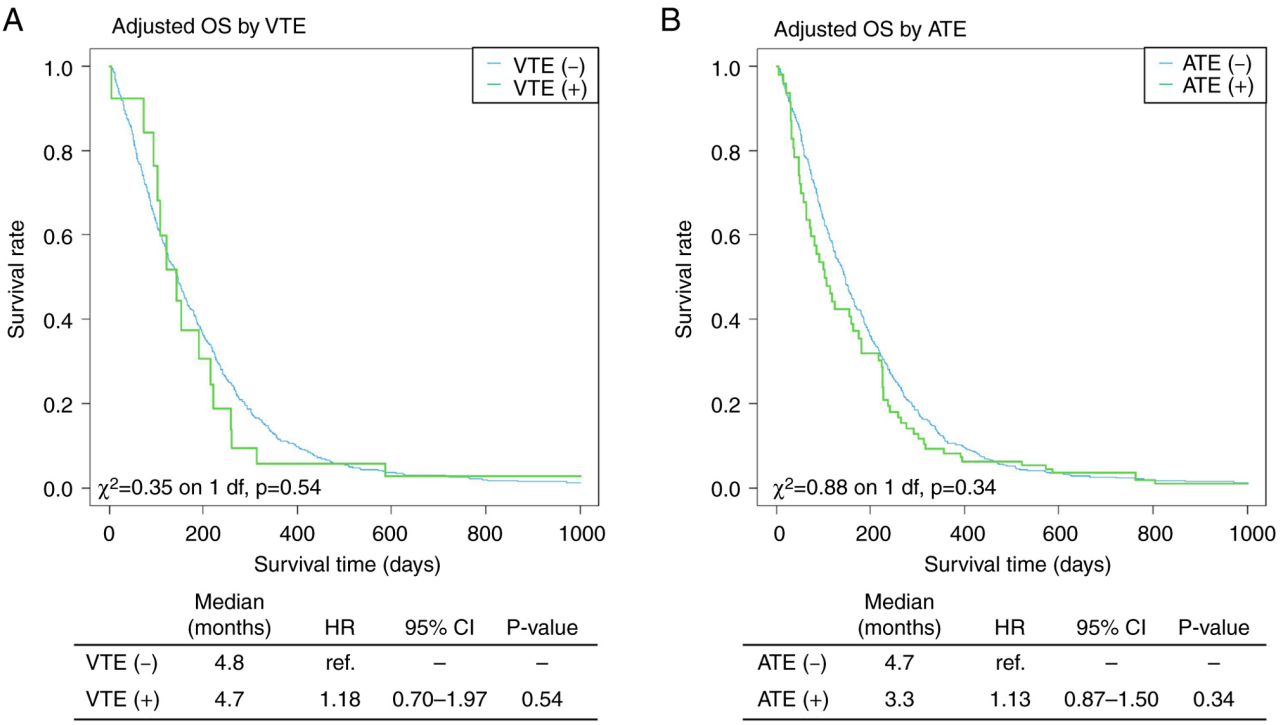
of thromboembolism in patients with gastric and colorectal cancer in Japan reported that ATE was found in 12.9% of patients (37). The incidence rate of PAD is reported much less frequently. A case report of PAD in a patient with pancreatic cancer described an incidence rate of 0.65% (38). However, a previous study reported that 11.5% of hospitalized patients



	Median (months)	HR	95% CI	P-value
CAT (−)	7.0	ref.	–	–
CAT (+)	5.4	1.28	1.01–1.62	0.044

	Median (months)	HR	95% CI	P-value
CAT (−)	4.7	ref.	–	–
CAT (+)	3.4	1.20	0.94–1.52	0.131

Figure 1. Kaplan-Meier curves of OS with or without cancer-associated thromboembolism. (A) Crude and (B) adjusted. OS, overall survival; CAT, cancer-associated thromboembolism; HR, hazard ratio; CI, confidence interval.



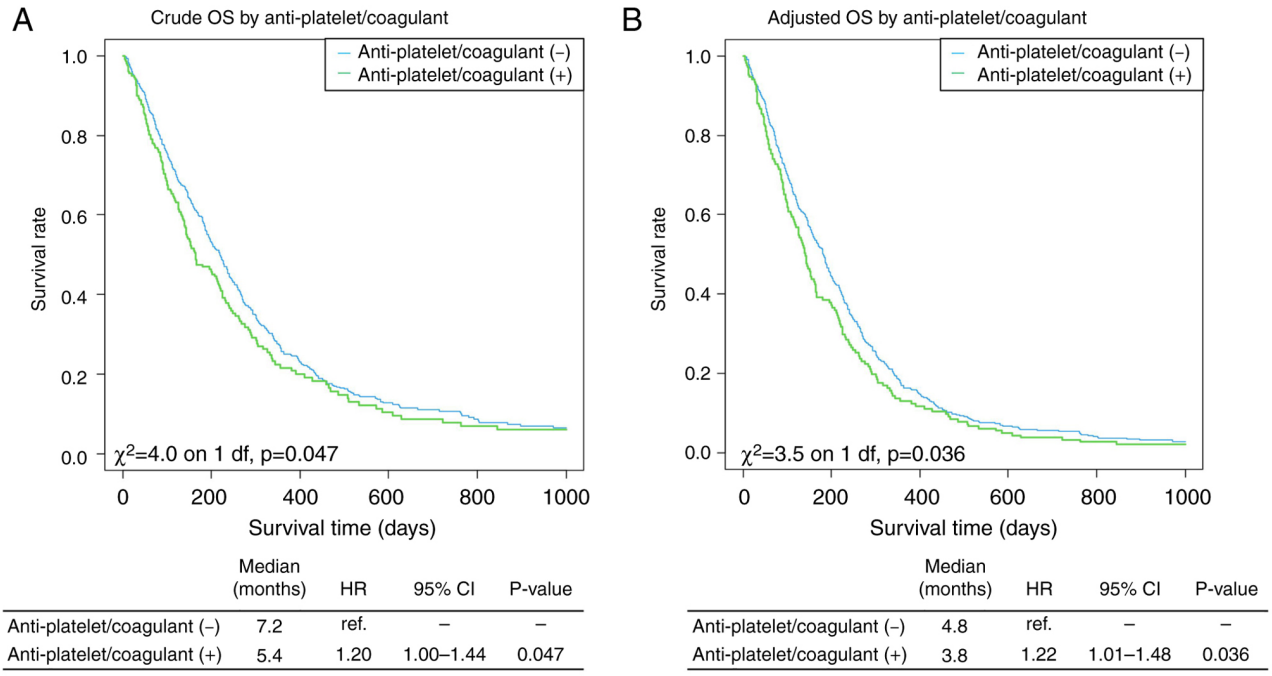
	Median (months)	HR	95% CI	P-value
VTE (−)	4.8	ref.	–	–
VTE (+)	4.7	1.18	0.70–1.97	0.54

	Median (months)	HR	95% CI	P-value
ATE (−)	4.7	ref.	–	–
ATE (+)	3.3	1.13	0.87–1.50	0.34

Figure 2. Kaplan-Meier curves of adjusted OS with or without (A) VTE and (B) ATE. OS, overall survival; CAT, cancer-associated thromboembolism; HR, hazard ratio; CI, confidence interval; VTE, venous thromboembolism; ATE, arterial thromboembolism.

with PAD had concurrent cancer (39). Therefore, future studies should elucidate the incidence of PAD. Additionally, the clinical significance of the incidence rates of acute coronary syndrome (2.8%) and ischemic stroke (4.6%) warrants further investigation.

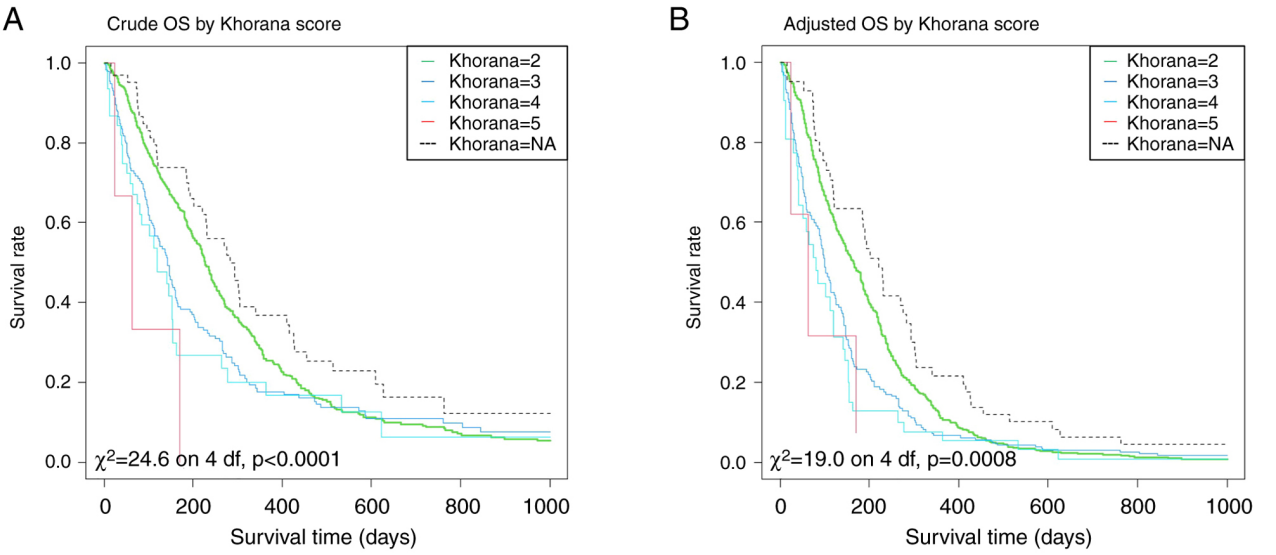
Several reports have reported that CAT is associated with a poor prognosis in patients with cancer, and this trend was also observed in the present dataset. In the short term, VTE is an independent prognostic factor for death in patients with cancer receiving chemotherapy, with a remarkably high HR of 6.58 (4.50



	Median (months)	HR	95% CI	P-value
Anti-platelet/coagulant (–)	7.2	ref.	–	–
Anti-platelet/coagulant (+)	5.4	1.20	1.00–1.44	0.047

	Median (months)	HR	95% CI	P-value
Anti-platelet/coagulant (–)	4.8	ref.	–	–
Anti-platelet/coagulant (+)	3.8	1.22	1.01–1.48	0.036

Figure 3. Kaplan-Meier curves of OS with or without antiplatelets/anticoagulants. (A) Crude and (B) adjusted. OS, overall survival; HR, hazard ratio; CI, confidence interval.

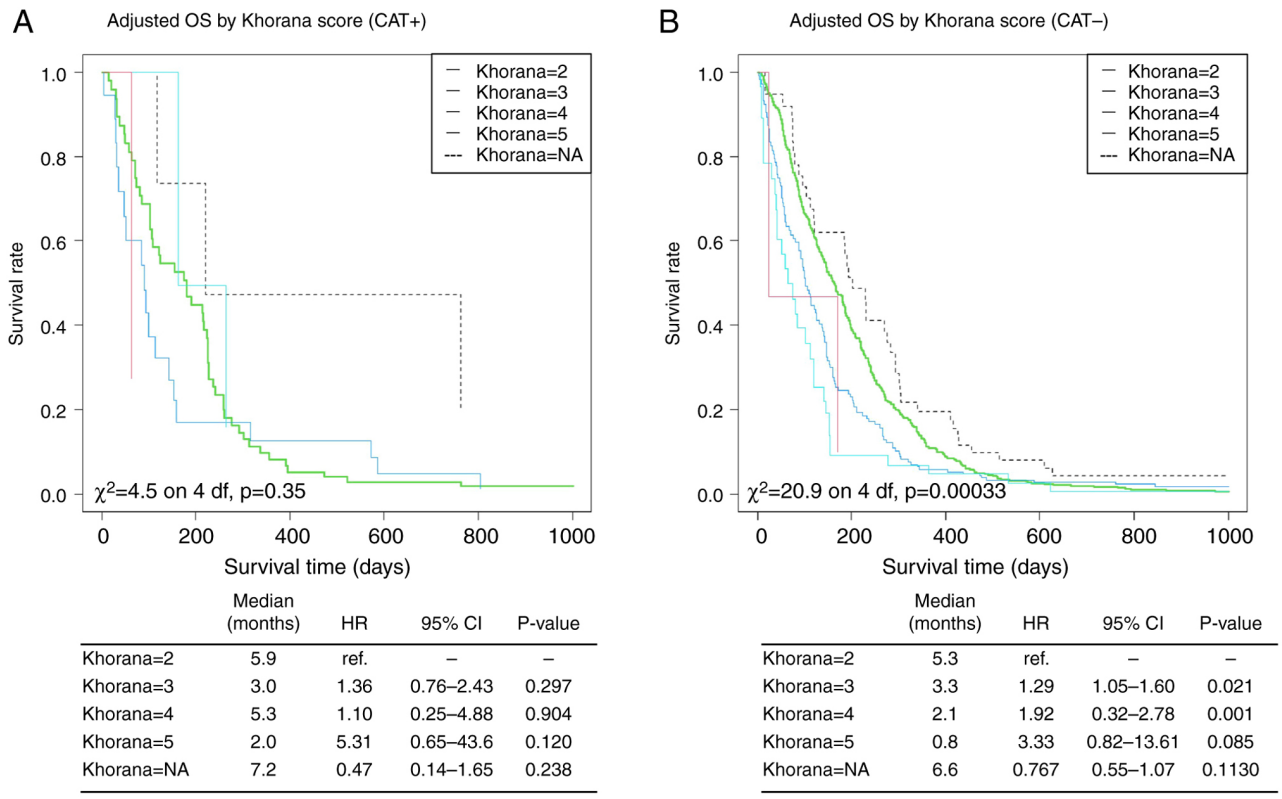


	Median (months)	HR	95% CI	P-value
Khorana=2	7.4	ref.	–	–
Khorana=3	4.7	1.32	1.09–1.60	0.005
Khorana=4	3.9	1.59	1.12–2.25	0.010
Khorana=5	2.0	4.10	1.31–12.80	0.015
Khorana=NA	9.3	0.76	0.56–1.04	0.089

	Median (months)	HR	95% CI	P-value
Khorana=2	5.4	ref.	–	–
Khorana=3	3.3	1.29	1.07–1.58	0.012
Khorana=4	2.6	1.74	1.21–2.47	0.002
Khorana=5	2.0	3.72	1.16–11.54	0.025
Khorana=NA	7.2	0.73	0.54–1.01	0.053

Figure 4. Kaplan-Meier curves of overall survival according to the Khorana score. (A) Crude and (B) adjusted. OS, overall survival; HR, hazard ratio; CI, confidence interval.

after adjustment for background factors) (10). Inpatient mortality rates for patients hospitalized with VTE were higher at 7, 14, and 30 days in analyses of patient groups adjusted for background factors by propensity score matching and were particularly high for pancreatic, liver, and biliary tract cancers (40). Retrospective studies of patients with pancreatic cancer have also demonstrated that patients with VTE have shorter progression-free survival and OS, with HRs of 2.02 and 2.42, respectively (31). Similarly, ATE is associated with poor prognosis (41) and is independently associated with poor prognosis for OS (33).



	Median (months)	HR	95% CI	P-value
Khorana=2	5.9	ref.	–	–
Khorana=3	3.0	1.36	0.76–2.43	0.297
Khorana=4	5.3	1.10	0.25–4.88	0.904
Khorana=5	2.0	5.31	0.65–43.6	0.120
Khorana=NA	7.2	0.47	0.14–1.65	0.238

	Median (months)	HR	95% CI	P-value
Khorana=2	5.3	ref.	–	–
Khorana=3	3.3	1.29	1.05–1.60	0.021
Khorana=4	2.1	1.92	0.32–2.78	0.001
Khorana=5	0.8	3.33	0.82–13.61	0.085
Khorana=NA	6.6	0.767	0.55–1.07	0.1130

Figure 5. Kaplan-Meier curves of adjusted overall survival according to the Khorana score. (A) CAT$^-$ and (B) CAT$^+$. OS, overall survival; HR, hazard ratio; CI, confidence interval.

In terms of patient background, our results demonstrated a significant association between CAT onset and dyslipidemia. Dyslipidemia is associated with hypercoagulability, endothelial dysfunction, and increased platelet aggregation. A meta-analysis showed that high triglyceride and low high-density lipoprotein cholesterol levels were significantly associated with VTE (42). Additionally, the CAT-positive group was administered significantly more antiplatelet and anticoagulant drugs than the CAT-negative group. In the overall population, patients receiving antiplatelet and anticoagulant medications have a poorer prognosis than those not receiving these medications, which may be associated with a poorer prognosis in the CAT-positive group than in the CAT-negative group. In this study, patients with CAT had a higher risk of bleeding than those without. This may reflect the fact that antiplatelet and anticoagulant agents are used in patients with CAT (13).

Patients with cancer with VTE have a poor prognosis, and the risk of death is 2.20 times higher than that in patients without VTE (11). The Khorana score was originally developed as a predictive model for chemotherapy-related thrombosis (11,27), and several studies have validated its effectiveness in predicting VTE in cancer (28,43,44). In addition, a cohort study demonstrated that the Khorana score had a negative prognostic value in patients with resectable pancreatic cancer (45). Similarly, the Khorana score had a strong negative prognostic value in our patients with metastatic pancreatic cancer. Notably, this predictive significance remained consistent, even among patients classified as CAT-negative. The Khorana score was originally developed to estimate the risk of VTE in outpatients undergoing chemotherapy and is not intended for patients with CAT requiring hospitalization, which is the subject of this study. However, the factors composing the Khorana score, which include elevated platelets, leukocytosis, and anemia, may reflect an association with the presence of cancer cachexia, a condition commonly observed in pancreatic cancer (46,47). Therefore, it is not surprising that the study found the Khorana score may be effective in predicting the prognosis of metastatic pancreatic cancer. Calculation of the Khorana score is straightforward, suggesting its potential application as a prognostic marker in routine clinical practice.

A clinical practice guideline was published in 2009 for CAT with detailed recommendations for diagnosis, treatment, and prevention (48). Since the publication of the European Society for Medical Oncology guideline in 2011 (49), similar guidelines have subsequently been published and updated by several academic societies (50-52). The most current guidelines are the updated guidelines of the American Society of Clinical Oncology and European Society of Medical Oncology (53,54). Most guidelines recommend direct-acting oral anticoagulants (DOACs), low-molecular-weight heparin (LMWH) or unfractionated heparin for treatment induction, DOACs or LMWH for maintenance of VTE, and antiplatelets with or without anticoagulants for ATE. In addition, the guidelines recommend the use of LMWH for VTE prevention. In the present study, the CAT-positive group received both anticoagulants and antiplatelet agents. The frequent use of these drugs in the CAT group suggests that these guidelines are reflected in daily clinical practice; however, LWMH has not been approved for VTE in Japan. It is therefore believed

that cases in which LMWH is administered prophylactically are almost nonexistent, and that virtually all of the heparin found in this study was unfractionated heparin.

The present study had some limitations. First, the incidence of CAT and bleeding events may have been underestimated because our dataset was based on the DPC data. Virtually, only symptomatic cases requiring hospitalization were recorded, while asymptomatic cases and complications treated on an outpatient basis were not counted. Additionally, fatal cases in the emergency department that were not admitted to our hospitals were not included. Furthermore, the cause of death cannot be accurately determined due to lack of data, making it impossible to determine if the cause was cancer, CAT, bleeding, etc. Second, VTE and ATE were integrated into the analysis. Although VTE and ATE should have been separately analyzed, the small number of cases and overlapping cases made this difficult; therefore, they were integrated and analyzed. Finally, the precise timing and intended use of prescription oral medications remain uncertain because this study only recorded whether each medication had been prescribed at any point during the study period, without details on usage patterns. Therefore, it is difficult to distinguish from these data whether the dose administered was prophylactic or therapeutic against thrombosis or other conditions, including whether the medication was administered before or after the onset of CAT. Patients who started antithrombotic therapy before the onset of CAT might have a higher risk of CAT recurrence, while their survival rates may be higher because they are already receiving treatment. This survivor bias could lead to an overestimation of the efficacy of antithrombotic therapy. Therefore, care should be taken when interpreting the findings in connection with prescription. Acknowledging these limitations, the strength of this study lies in the notable incidence of CAT, particularly ATE, in patients with metastatic pancreatic cancer treated with first-line chemotherapy.

In conclusion, our real-world data demonstrated that the incidence rate of CAT in patients with metastatic pancreatic cancer was 10.2%. This clinically alarmingly high incidence rate was not dependent on chemotherapy. At the same time, gastrointestinal bleeding occurred more frequently in CAT-positive patients than in CAT-negative patients. Additionally, patients with CAT exhibited a trend towards a less favorable prognosis compared to those without CAT. Moreover, the Khorana score may be useful in predicting prognosis, even without CAT development. Further analyses should be performed after accumulating a significant number of cases, including metastatic pancreatic cancer and other cancer types.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

RS, YI, and MO made significant contributions to the study design and conception. RS, YF, MS, and MH were responsible for data acquisition. YF and MS confirm the authenticity of all the raw data. RS and YI interpreted the data and drafted the manuscript. KU, TM, KO, NS, and HM provided valuable advice on the research design and contributed to the critical interpretation of the study findings. NS and HM thoroughly reviewed and approved the final version of the manuscript. All authors have read and endorsed the final version of the manuscript.

Ethics approval and consent to participate

The project followed the ethical guidelines for medical and biological research involving human subjects in Japan, in accordance with the principles set forth in The Declaration of Helsinki. Approval for the study was obtained from the Ethics Committee of the Tokushukai Group in April 2020 (approval no. TGE01427-024), and the study was registered in the UMIN Clinical Trial Registry under the registration no. UMIN000050590. Patients were informed about the study using opt-out methods, and all patients chose to participate; none declined participation.

Patient consent for publication

Patient consent for publication was obtained through opt-out methods.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

The authors used chatGPT 3.5 and DeepL as AI tools during the preparation of this study to improve the English translation, readability of the manuscript, and language. The authors have revised and edited the content generated by the AI tools as needed and have undertaken English language editing. The authors take full responsibility for the final content of this manuscript.

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