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ORIGINAL RESEARCH

Factors Associated and Survival Outcomes Among Japanese Patients with Solid Cancer Who Developed Deep Vein Thrombosis (DVT)

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Objective: Deep vein thrombosis (DVT) is a common and serious complication in patients with cancer. We retrospectively analyzed patients newly diagnosed with solid cancers in a Japanese cohort.

Patients or Materials: We retrospectively reviewed the medical records (2013–2020) of Japanese patients with solid cancers who were suspected of having DVT and were diagnosed and treated at Ehime University Hospital. Controls were patients with solid cancers in whom DVT was suspected on physical examination and/or laboratory testing but subsequently ruled out by definitive imaging. Candidate risk and prognostic variables were extracted from electronic medical records. This was a single-center cohort study.

Results: Among the initial 1399 patients, 224 with DVT and 560 without DVT (as controls) were included in the final analysis after excluding those with incomplete medical records, missing diagnostic tests, or unclear medical histories. The median overall survival (OS) period was 5.87 years for patients with DVT and 6.81 years for patients without DVT (p=0.0014). Anemia (Hb <11 g/dl) and thrombocytopenia (Plt <15 x 104 / μL) were found to be strong risk factors related to an increased incidence of DVT. Female cancer patients with DVT had a significantly worse outcome than those without DVT (p=0.028). Analysis of OS in patients with DVT associated with gynecological cancers following treatment with three different direct oral anticoagulants (DOACs; edoxaban, rivaroxaban, and apixaban) indicated that those treated with apixaban had a significantly worse outcome than those treated with the others (p=0.019) in this Japanese cohort.

Conclusion: Japanese patients with solid cancers, particularly those with gynecologic cancers, tend to have poorer outcomes when DVT co-occurs with anemia and low platelet counts. In addition, the choice of DOAC for DVT treatment may be associated with differences in prognosis. These exploratory findings require more detailed, adjusted analyses and confirmation using other datasets or populations.

Keywords: cancer patient, deep vein thrombosis, DVT, prognostic factor, direct oral anticoagulant, DOAC

Introduction

Venous thromboembolism (VTE) – primarily including deep vein thrombosis (DVT), pulmonary embolism (PE), and mesenteric venous thrombosis (MVT)[1] – occurs in over 20% of cancer patients,[2] and has been identified as the second most common cause of death among such patients after the malignancy itself. VTE also leads to increased morbidity, including the need for anticoagulation therapy, delays in chemotherapy administration, a higher risk of fatal bleeding and infarction, and ultimately a reduced quality of life (QOL).[3,4] Recently, two major models have been employed for prediction of VTE in daily practice: the Wells score[5] and the Khorana score (KRS).[6] The KRS in particular is widely used, and has been reported to be superior to the Wells score for detection of asymptomatic VTE in cancer patients.[7] The KRS assesses the risk of developing VTE based on information such as the cancer site (especially cancers located in

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abdominal organs), blood parameters (white blood cell, red blood cell, and platelet counts), and body mass index (BMI). However, this scoring system has been based predominantly on Western data, raising uncertainties about its ability to predict VTE risk among individuals of Asian descent. For example, in Western populations, a BMI of 35 or higher is considered a high-risk factor according to the KRS.

In contrast, in the Japanese population (a representative Asian population), as a BMI of 25 or higher is considered to indicate obesity, the BMI distribution differs significantly.[8] Furthermore, genetic and ethnic differences may also influence treatment response and safety profiles to anticoagulants. Therefore, studies focusing specifically on Japanese patients are expected to provide crucial insights for developing treatment strategies optimized for this population.

In recent years, direct oral anticoagulants (DOACs) have been recommended as the first-line agents for anticoagulant therapy in VTE from the acute to the chronic phase, replacing warfarin. Compared with warfarin,[9] DOACs do not require dose adjustment or regular PT-INR monitoring and are associated with a lower risk of intracranial hemorrhage; therefore, they are preferred in eligible patients.[10] On the other hand, in real-world clinical practice, many questions remain regarding how best to differentiate among individual DOACs and the specific clinical significance and optimal use of each agent.[11]

The primary objective of this study was to characterize risk factors for VTE, with a focus on DVT, among Japanese patients newly diagnosed with cancer. The Secondary endpoints were (1) to delineate differences in the incidence and outcomes of DVT between gynecologic and gastrointestinal cancers, both of which are categorized as high risk by KRS, and (2) to evaluate VTE treatment with DOACs in Japanese patients.

Materials and Methods

Studied Patients and Exclusion Criteria

This retrospective, single-center cohort study reviewed electronic medical records from the Cancer Registry at Ehime University Hospital for all patients aged 18 years or older who were newly diagnosed with solid cancers and had diagnosed or clinically suspected DVT between January 1, 2013, and December 31, 2020. Inclusion criteria were: (1) pathologically confirmed cancer (surgical histopathology or aspiration cytology) and (2) receipt of any first-line anticancer treatment at Ehime University Hospital. Exclusion criteria were: (1) more than one primary cancer; (2) awaiting first-line treatment for another cancer; and (3) prescription of medication for VTE prior to the cancer diagnosis. All cases in the present study were classified according to the Multiple Primary and Histology Coding Rules for the National Program of Cancer Registries in Japan, which is a nationally registered database for cancer patients and the treatments they receive[12] ensuring #1 standardized identification criteria for multiple primary cancers, #2 consistent recording of histology based on the WHO classification and ICD-O-3, #3 standardization and comparability of cancer registration systems at the national level, and #4 accumulation of high-quality data for use in epidemiological research and formulation of cancer control policies.

Analysis of Cancer Patients and Their Survival in Relation to Prognostic Factors

For analysis of prognostic factors, the survival time of the study patients was investigated from the date of enrollment for any treatment in 2013 to the date of the last follow-up (at the end of 2023) or date of death. However, this included some patients who had requested hospital transfers for further treatment after first-line treatment (hospital-change cases). Clinical variables were prespecified a priori based on the KRS and prior studies. From the electronic medical records, we extracted: demographics (age, sex, body mass index [BMI]); clinical characteristics (primary tumor site, cancer stage, ECOG performance status [0–1 vs ≥2]); investigations (ISO 15189-compliant assays: hemoglobin, platelet count, and coagulation parameters [PT-INR, APTT]); treatment (direct oral anticoagulant [DOAC] use, agent, and treatment duration); and outcomes (overall survival). Although the KRS includes leukocytosis as a component of venous thromboembolism (VTE) risk, white blood cell (WBC) values varied widely with disease and clinical status (eg, postoperative period, intercurrent infection) and were not informative in our analyses – an effect particularly pronounced during the COVID-19 pandemic. Therefore, we excluded WBC from the present analysis.

The disease stage in each patient was based on the AJCC Cancer Staging System 8th edition. In cases complicated by DVT, the presence of thrombus was confirmed by lower extremity vein ultrasonography (compression ultrasonography) or contrast-enhanced CT, based on an independent, blinded review by two radiologists. Cancer patients with suspected DVT upon physical and hematological examination on admission, but without confirmed DVT complications after several examinations such as ultrasonography and contrast-enhanced CT scan, were defined as controls (patients without DVT). For the present analysis, we did not consider the treatment details for various cancers. At the outset, in this control setting, we hypothesized that the development of DVT in cancer patients would be associated with poorer clinical outcomes. To rigorously test this hypothesis, it was essential to establish a control group comprising cancer patients without DVT or other risk factors such as intravenous devices, congenital thrombophilia, or other venous compression syndromes. However, the selection of an appropriate control cohort posed a significant methodological challenge, as inclusion of all cancer patients without DVT as controls would have introduced substantial heterogeneity, particularly due to overrepresentation of early-stage cancer cases in this group.[13] Given that DVT is observed more frequently in patients with advanced malignancies, such an approach would risk confounding the association between DVT and prognosis through inadvertent comparison of patients at different stages of cancer progression. Therefore, to mitigate this bias, we defined the control group as cancer patients in whom DVT had been clinically suspected (based on standard pre-procedural laboratory tests, such as the D-dimer test, and the attending physician's clinical impression) but subsequently excluded by definitive imaging studies. We considered this population to be an appropriate control because these individuals shared similar clinical contexts and baseline characteristics with those definitively diagnosed as having DVT. Moreover, since imaging is considered the gold standard for diagnosis of DVT, we focused exclusively on radiologically confirmed cases to ensure diagnostic accuracy and minimize misclassification. Controls were patients in whom DVT was clinically suspected but ruled out by definitive imaging; potential confounding, including disease stage, was addressed using multivariable adjustment. This control selection strategy was designed to minimize confounding by disease stage and to more accurately define the prognostic impact of DVT in cancer patients.

Selecting appropriate controls was critical. Using all cancer patients without DVT would have introduced heterogeneity (eg, overrepresentation of early-stage disease) and risked confounding the DVT-prognosis association.[13] Therefore, we defined controls as patients in whom DVT was clinically suspected but subsequently ruled out by definitive imaging (duplex ultrasonography and/or contrast-enhanced CT). This approach aligned baseline clinical context with the DVT cohort and, by relying on the imaging gold standard, minimized diagnostic misclassification. Controls were patients in whom DVT was clinically suspected but ruled out by definitive imaging; potential confounding, including disease stage, was addressed using multivariable adjustment.

After examination of the hospital medical records and, when necessary, collection of further information by contact with patients or their families, overall survival (OS) curves were calculated for each prognostic group according to the Kaplan-Meier method and analyzed using the log-rank univariate test. All-cause mortality was used as the endpoint for statistical analysis. Fisher's exact test and chi-squared test were performed to detect significant differences among the groups at $P < 0.05$. Prognostic factors were subjected to univariate and multivariate analyses using Cox's proportional hazard model. All statistical analyses were performed using the SAS software package version 9.4 (SAS Institute Inc., Cary, NC, USA).

DOACs (Rivaroxaban, Edoxaban, and Apixaban) Treatments

Edoxaban was given once daily at 60 mg, reduced to 30 mg once daily in patients with creatinine clearance 15–50 mL/min or body weight ≤60 kg. It was not used in patients with severe renal impairment or mechanical heart valves. Rivaroxaban was given mainly once daily at 20 mg, reduced to 15 mg once daily in patients with moderate renal impairment. It was used cautiously or avoided in patients with severe renal or significant hepatic impairment, or with mechanical heart valves. Apixaban was given at 5 mg twice daily, reduced to 2.5 mg twice daily in patients meeting at least two of the following: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL.

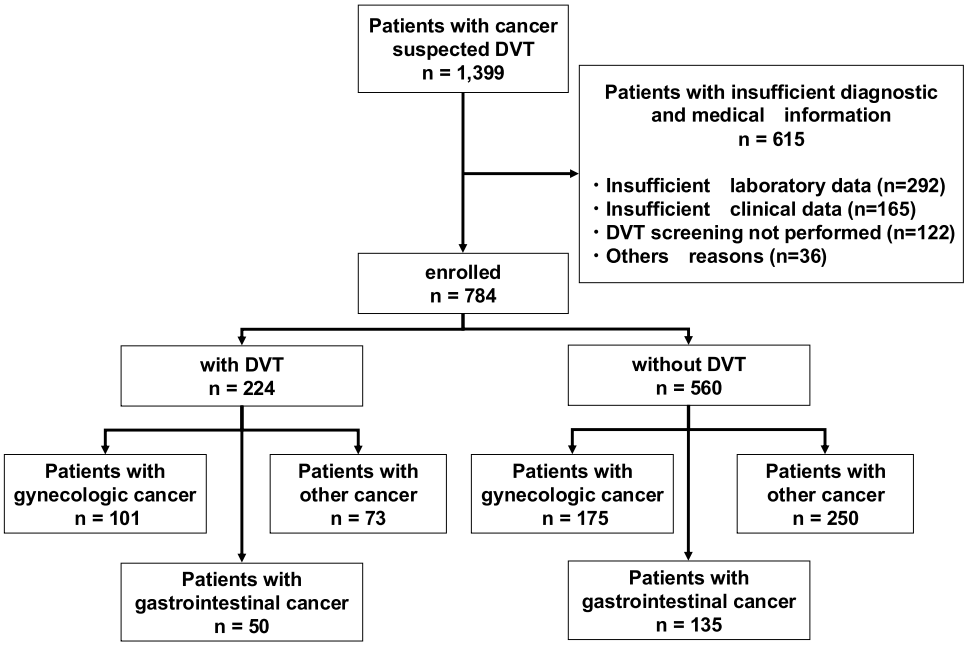

Figure 1 Flow diagram of the selection procedure for patients with or without DVT. "Patients with insufficient diagnostic and medical information (n=615)" refers to patients with incomplete medical records, missing diagnostic tests, and unclear medical histories, making pathological diagnosis and clinical staging difficult.

Ethical Considerations

This study was approved by the Ethics Committee for Clinical Studies at Ehime University Graduate School of Medicine (study IRB; Ehime 2109016), and carried out in accordance with the ethical standards of the 1995 Declaration of Helsinki (as revised in Brazil 2013). Informed consent was by the opt-out principle; we disclosed information about the study on the associated website (https://www.m.ehime-u.ac.jp/school/clinical.oncology/?page_id=1487) and provided patients an opportunity to decline to participate in the study.

Results

Patient Demographics

Of the 1399 patients screened (Figure 1), 784 met eligibility criteria and were included in the analysis; 224 (28.6%) had DVT and 560 (71.4%) did not. The cohort comprised 478 women; 276 patients had gynecologic cancers and 185 had gastrointestinal cancers. Baseline characteristics are summarized in Table 1. In univariate comparisons, patients with DVT were more often female and more likely to have gynecologic cancers, presented with more advanced disease and poorer ECOG performance status, and had higher rates of anemia (Hb <11 g/dL) and thrombocytopenia (Plt <15 × 10^4/μL) than those without DVT. Serum creatinine levels were lower in the DVT group, whereas BMI did not differ meaningfully between groups (Table 1). In multivariable models, advanced stage, lower serum creatinine, anemia, and thrombocytopenia were independently associated with DVT (Table 2). Kaplan–Meier analysis showed shorter overall

Table 1 Cancer Types and Patient Characteristics

		With DVT	(%)	Without DVT	(%)	Total
Sex	Male	59	26.3	247	44.1	306
	Female	165	73.7	313	55.9	478
Age	Mean	67.7		66.2		
	Median (range)	70 (20–95)		68 (13–93)		

(*Continued*)

Table 1 (Continued).

		With DVT	(%)	Without DVT	(%)	Total
ECOG-PS	0	99	44.2	399	71.3	498
	1	99	44.2	110	19.6	209
	2	15	6.7	26	4.6	41
	3	8	3.6	23	4.1	31
	4	3	1.3	2	0.4	5
Stage	I	62	27.7	248	44.3	310
	II	35	15.6	104	18.6	139
	III	55	24.6	108	19.3	163
	IV	72	32.1	100	17.9	172
Primary	Oral	4	1.8	11	2.0	15
	Parotid/submandibular gland	0	0.0	2	0.4	2
	Pharynx/larynx	5	2.2	11	2.0	16
	Esophagus	3	1.3	8	1.4	11
	Stomach	13	5.8	19	3.4	32
	Small intestine	0	0.0	2	0.4	2
	Colon/anus	23	10.3	71	12.7	94
	Liver	5	2.2	23	4.1	28
	Gall bladder/pancreas	9	4.0	20	3.6	29
	Lung/pleura/heart	20	8.9	36	6.4	56
	Bone/soft tissue	5	2.2	9	1.6	14
	Skin	1	0.4	20	3.6	21
	Peritoneum	3	1.3	3	0.5	6
	Breast	8	3.6	26	4.6	34
	Genital area	4	1.8	6	1.1	10
	Cervix	29	12.9	46	8.2	75
	Uterine	35	15.6	62	11.1	97
	Ovary	37	16.5	67	12.0	104
	Penis/testis	2	0.9	2	0.4	4
	Prostate	7	3.1	62	11.1	69
	Kidney/ureter	4	1.8	34	6.1	38
	Bladder	4	1.8	15	2.7	19
	Thyroid	2	0.9	5	0.9	7
	Adrenal gland	1	0.4	0	0.0	1

Abbreviation: ECOG-PS, Eastern Cooperative Oncology Group Performance Status.

Table 2 Analysis of Risk Factors for DVT in Patients with Cancer; (A) Univariate, (B) Multivariate

(A) Cancer patient with DVT (n=224) vs without DVT (n=560)		
	Odds-ratio (95% CI)	**P-value**
Sex (female vs male)	2.19 (1.62–3.00)	<0.001
BMI	0.99 (0.97–1.01)	0.387
Age	1.01 (1.00–1.02)	0.038
Stage (3,4 vs 1,2)	2.30 (1.68–3.15)	<0.001
ECOG-PS (2,3,4 vs 0.1)	1.14 (0.73–1.75)	0.550
Anemia (Hb < 11 g/dL)	4.24 (3.14–5.75)	<0.001
Thrombocytopenia (Plt < 15 ×10^4/μL)	2.09 (1.44–3.03)	<0.001
PT-INR	0.75 (0.34–1.06)	0.150
APTT	1.01 (0.97–1.04)	0.734
BUN	1.00 (0.98–1.02)	0.904
Creatinine	0.74 (0.51–0.97)	0.019
(B) Cancer patient with DVT (n=224) vs without DVT (n=560)		
	Odds-ratio (95% CI)	**P-value**
Sex (female vs male)	1.62 (1.02–2.61)	0.041
BMI	1.00 (0.96–1.02)	0.772
Age	1.02 (1.00–1.04)	0.015
Stage (3,4 vs 1,2)	1.80 (1.19–2.71)	0.005
ECOG-PS (2,3,4 vs 0.1)	1.50 (0.77–2.88)	0.229
Anemia (Hb < 11 g/dL)	3.63 (2.35–5.63)	<0.001
Thrombocytopenia (Plt < 15 ×10^4/μL)	3.17 (1.74–5.77)	<0.001
PT-INR	0.62 (0.14–1.37)	0.394
APTT	0.98 (0.94–1.03)	0.450
BUN	1.01 (0.97–1.05)	0.551
Creatinine	0.50 (0.22–0.94)	0.023

Notes: Sex, Stage, ECOG-PS, Anemia, and Thrombocytopenia were compared between the two groups, and all other variables were analyzed as continuous variables. In the original KRS (6), thrombocytopenia and anemia were defined using cut off values of a platelet count of 350,000/μL and a hemoglobin level of 10 g/dL, respectively. However, these thresholds did not correspond to the median values of platelet count or hemoglobin. Therefore, in this Japanese cohort study, thrombocytopenia was defined as a platelet count < 150,000/μL and anemia as a hemoglobin level < 11 g/dL, based on the median values of platelet count and hemoglobin. Other continuous variables were initially examined both as continuous terms and as categorical variables. For the final models Cut points were selected a priori based on a combination of clinical relevance.

Abbreviations: ECOG-PS, Eastern Cooperative Oncology Group Performance Status; BMI, body mass index; Hb, hemoglobin; Plt, Platelet; BUN, blood urea nitrogen.

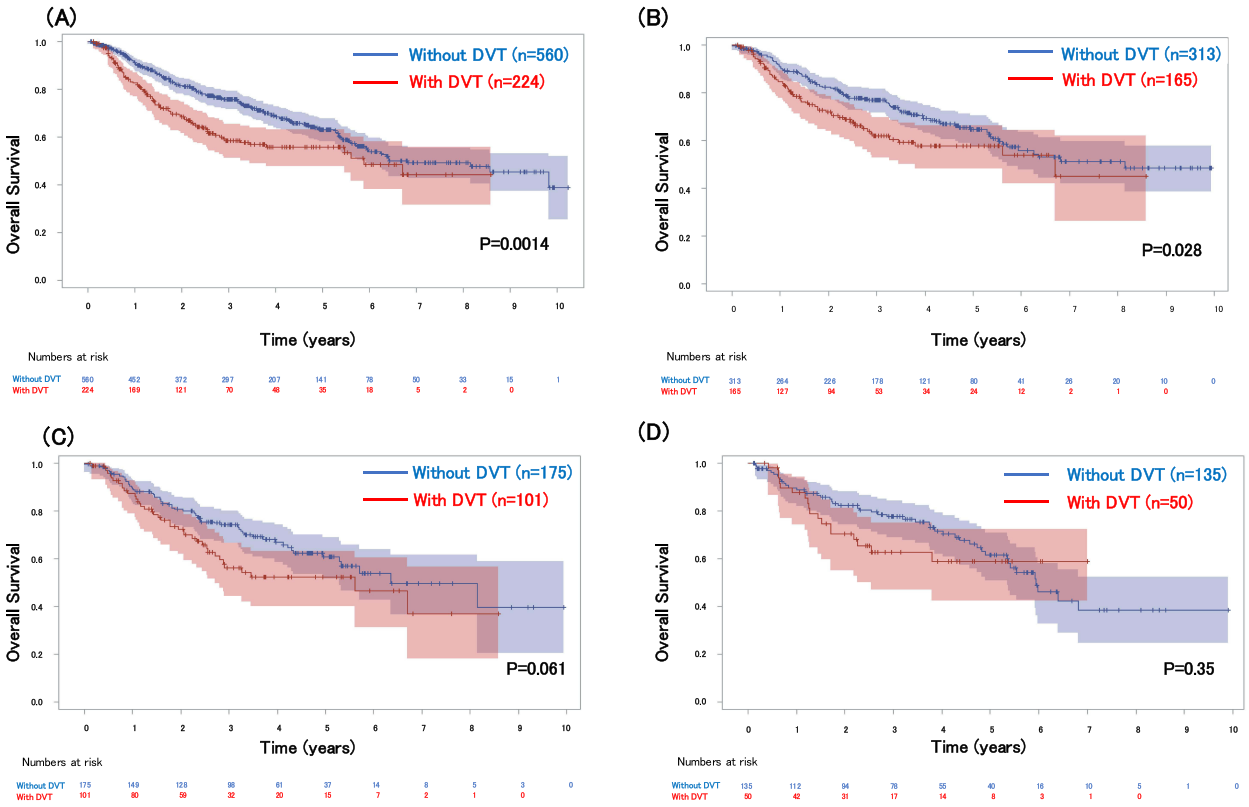

Figure 2 Overall survival of patients with or without DVT; (**A**) all patients (median follow up: 2.9 years), (**B**) female patients (median follow up: 3.0 years), (**C**) patients with gynecological cancer (median follow up: 2.9 years), (**D**) patients with gastrointestinal cancer (median follow up: 3.1 years).

survival in patients with DVT than in those without DVT (p=0.0014; Figure 2A), with this association particularly evident among women (p=0.028; Figure 2B) and among patients with gynecologic cancers (Figure 2C). Additional analyses focusing on female patients and those with gynecologic cancers are presented in Table 3; in these subgroups, older age, poorer performance status, anemia, and thrombocytopenia were associated with higher DVT risk.

Analysis of Outcome in Patients with or without DVT and Risk Factors for DVT

We performed Kaplan–Meier analyses to estimate overall survival (OS) in patients with and without DVT. Figure 2 presents OS curves for four groups: the overall cohort (A; n=784), women (B; n=478), patients with gynecologic cancers (C; n=276), and patients with gastrointestinal cancers (D; n=185). Table 2 summarizes multivariable models evaluating risk factors for DVT. Variables entered into the multivariable model were those significant in univariate analyses (p<0.05) together with prespecified covariates based on the KRS. Across groups, patients with DVT at the time of cancer diagnosis had shorter OS than those without DVT, with the difference particularly marked among women and among patients with gynecologic cancers. In adjusted analyses, advanced stage, lower serum creatinine, anemia (Hb <11 g/dL), and thrombocytopenia (Plt <15 × 10^4/μL) were independently associated with DVT (Table 2). Table 3 presents subgroup analyses in women and in patients with gynecologic cancers, in which older age, poorer ECOG performance status, anemia, and thrombocytopenia were associated with higher DVT risk. BMI was not associated with DVT in this Japanese cohort.

Impact of DVT Treatment with Oral Anticoagulants on Patient Outcome

Recently in Japan, three direct oral anticoagulants (DOACs), rivaroxaban, edoxaban, and apixaban, were introduced into clinical practice in 2012 and were approved for the treatment of DVT in 2015. DOACs are now an integral part of prophylaxis, treatment, and prognosis for cancer-associated DVT. In the present analysis, cancer patients with DVT were also treated with DOACs at the discretion of the attending physician. DOAC treatment was generally continued until

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Table 3 Multivariate Analysis of Prognostic Factors Among Female Patients with or without DVT; (A) Female Patients, (B) Patients with Gynecological Cancer

(A) Female cancer patients with DVT (n=165) vs without DVT (n=313)		
	Odds-ratio (95% CI)	**P-value**
Primary (gynecologic cancer vs other cancer)	2.91 (1.78–4.85)	<0.001
Age	1.07 (1.05–1.10)	<0.001
BMI	0.99 (0.95–1.02)	0.613
Stage (3,4 vs 1,2)	1.86 (1.17–2.98)	0.009
ECOG-PS (2,3,4 vs 0.1)	1.68 (0.81–3.50)	0.166
Anemia (Hb < 11 g/dL)	3.44 (2.11–5.67)	<0.001
Thrombocytopenia (Plt < 15 ×10^4/μL)	1.74 (0.99–3.06)	0.053
BUN	1.04 (1.01–1.08)	0.025
Creatinine	1.10 (0.69–1.68)	0.659
(B) Gynecologic cancer patients with DVT (n=101) vs without DVT (n=175)		
	Odds-ratio (95% CI)	**P-value**
Age	1.03 (1.01–1.06)	0.005
BMI	0.99 (0.94–1.02)	0.665
Stage (3,4 vs 1,2)	1.74 (0.98–3.10)	0.055
ECOG-PS (2,3,4 vs 0.1)	3.31 (1.34–8.52)	0.010
Anemia (Hb < 11 g/dL)	2.92 (1.62–5.30)	<0.001
Thrombocytopenia (Plt < 15 ×10^4/μL)	7.68 (2.94–22.93)	<0.001
BUN	0.99 (0.94–1.05)	0.762
Creatinine	0.93 (0.31–1.87)	0.866

Notes: Primary, Stage, ECOG-PS, Anemia, and Thrombocytopenia were compared between the two groups, and all other variables were analyzed as continuous variables. In the original KRS (6), thrombocytopenia and anemia were defined using cut off values of a platelet count of 350,000/μL and a hemoglobin level of 10 g/dL, respectively. However, these thresholds did not correspond to the median values of platelet count or hemoglobin. Therefore, in this Japanese cohort study, thrombocytopenia was defined as a platelet count < 150,000/μL and anemia as a hemoglobin level < 11 g/dL, based on the median values of platelet count and hemoglobin. Other continuous variables were initially examined both as continuous terms and as categorical variables. For the final models Cut points were selected a priori based on a combination of clinical relevance.

Abbreviations: ECOG-PS: Eastern Cooperative Oncology Group Performance Status, BMI: body mass index, Hb: hemoglobin, Plt: Platelet, BUN: blood urea nitrogen.

completion of the patient's cancer therapy, although in some cases administration was extended beyond the treatment period if DVT persisted. These treatment decisions were based on the findings of CT and ultrasound examinations. On the basis of these findings and the cancer types and patient characteristics in our cohort (Table 4), DOAC-associated patient mortality was then examined. As shown in Figure 3A and B, this revealed that the cancer patients treated with apixaban showed slightly higher mortality than those treated with the other agents. This tendency was likewise observed among female cancer patients (Figure 4A), and was particularly pronounced for patients with gynecological cancers (Figure 4B).

The higher mortality observed with apixaban in the unadjusted analysis may reflect residual confounding and patient selection (eg, preferential use in frailer or higher-risk patients). In addition, even after adjustment for baseline

Table 4 Cancer Types and Patient Characteristics Based on the Type of Treatment for DVT; Patient Characteristics and Cancer Types

		Apixaban	(%)	Rivaroxaban	(%)	Edoxaban	(%)	Total
Sex	Male	8	29.6	9	22.0	17	21.5	34
	Female	19	70.4	32	78.0	62	78.5	113
Age	Mean	65.9		67.1		66.7		
	Median (range)	66 (38–83)		71 (38–88)		69 (20–89)		
ECOG-PS	0	13	48.1	21	51.2	30	38.0	64
	1	11	40.7	15	36.6	36	45.6	62
	2	1	3.7	3	7.3	7	8.9	11
	3	2	7.4	1	2.4	4	5.1	7
	4	0	0.0	1	2.4	2	2.5	3
Stage	I	1	3.7	6	14.6	21	26.6	28
	II	5	18.5	5	12.2	10	12.7	20
	III	10	37.0	14	34.1	18	22.8	42
	IV	11	40.7	16	39.0	30	38.0	57
Primary	Oral	0	0.0	1	2.4	1	1.3	2
	Pharynx/larynx	0	0.0	1	2.4	1	1.3	2
	Esophagus	2	7.4	0	0.0	0	0.0	2
	Stomach	2	7.4	2	4.9	3	3.8	7
	Colon/anus	1	3.7	5	12.2	6	7.6	12
	Liver	1	3.7	0	0.0	3	3.8	4
	Gall bladder/pancreas	1	3.7	2	4.9	4	5.1	7
	Lung/pleura/heart	1	3.7	3	7.3	8	10.1	12
	Bone/soft tissue	0	0.0	0	0.0	5	6.3	5
	Peritoneum	0	0.0	2	4.9	1	1.3	3
	Breast	1	3.7	1	2.4	3	3.8	5
	Genital area	1	3.7	0	0.0	2	2.5	3
	Cervix	5	18.5	5	12.2	10	12.7	20
	Uterine	5	18.5	5	12.2	13	16.5	23
	Ovary	5	18.5	9	22.0	15	19.0	29
	Penis/testis	0	0.0	1	2.4	0	0.0	1
	Prostate	0	0.0	3	7.3	0	0.0	3
	Kidney/ureter	0	0.0	0	0.0	1	1.3	1
	Bladder	1	3.7	1	2.4	2	2.5	4
	Thyroid	1	3.7	0	0.0	1	1.3	2

Abbreviation: ECOG-PS, Eastern Cooperative Oncology Group Performance Status.

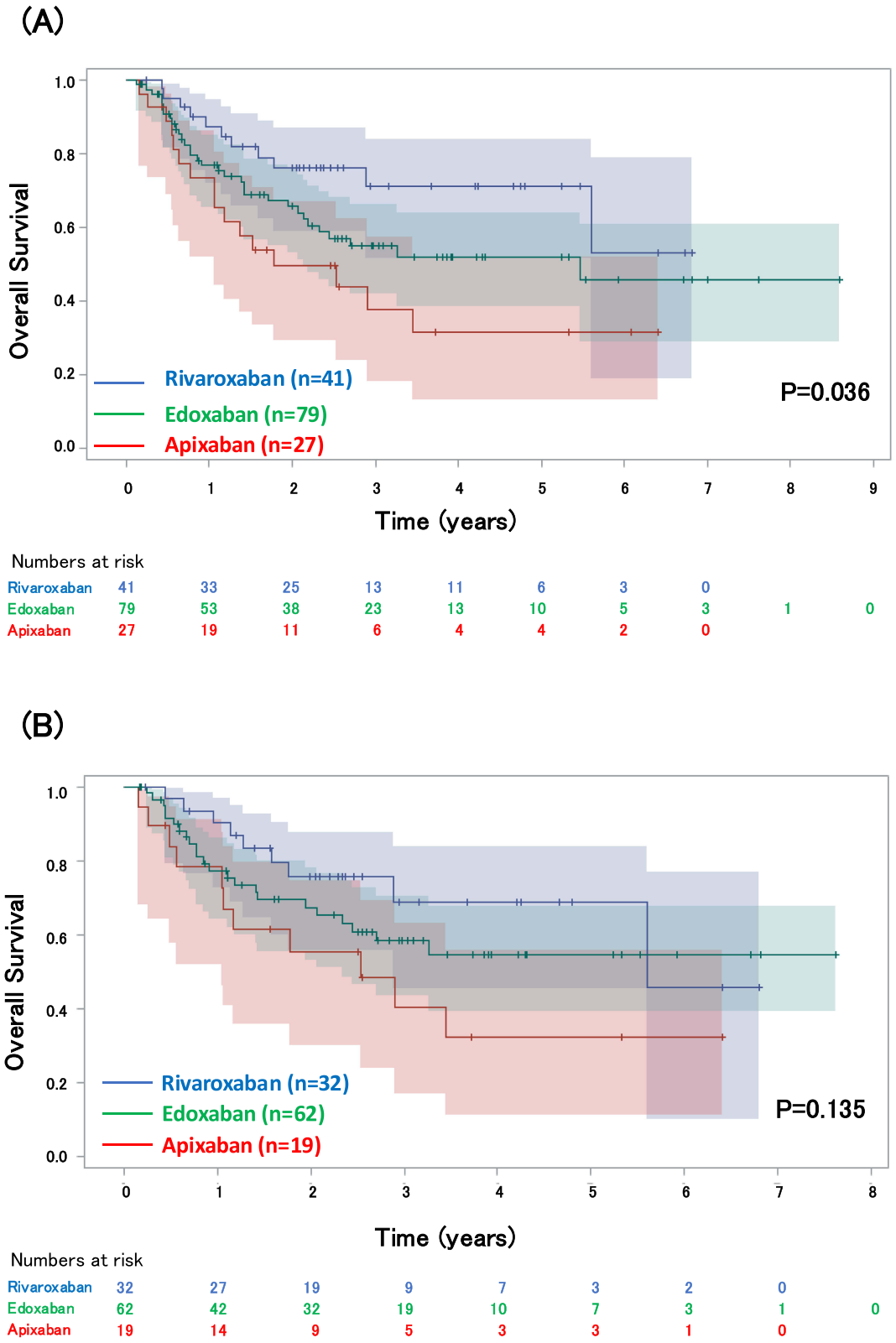

Figure 3 Overall survival based on the type of treatment for DVT; (**A**) all patients (Median follow up: 2.1 years), (**B**) female patients (Median follow up: 2.2 years). Data on dosing, route of administration, median treatment duration, and the number of major bleeding events were not collected in the DOAC table, and the relative performance of each DOAC was assessed solely on the basis of patient survival outcomes.

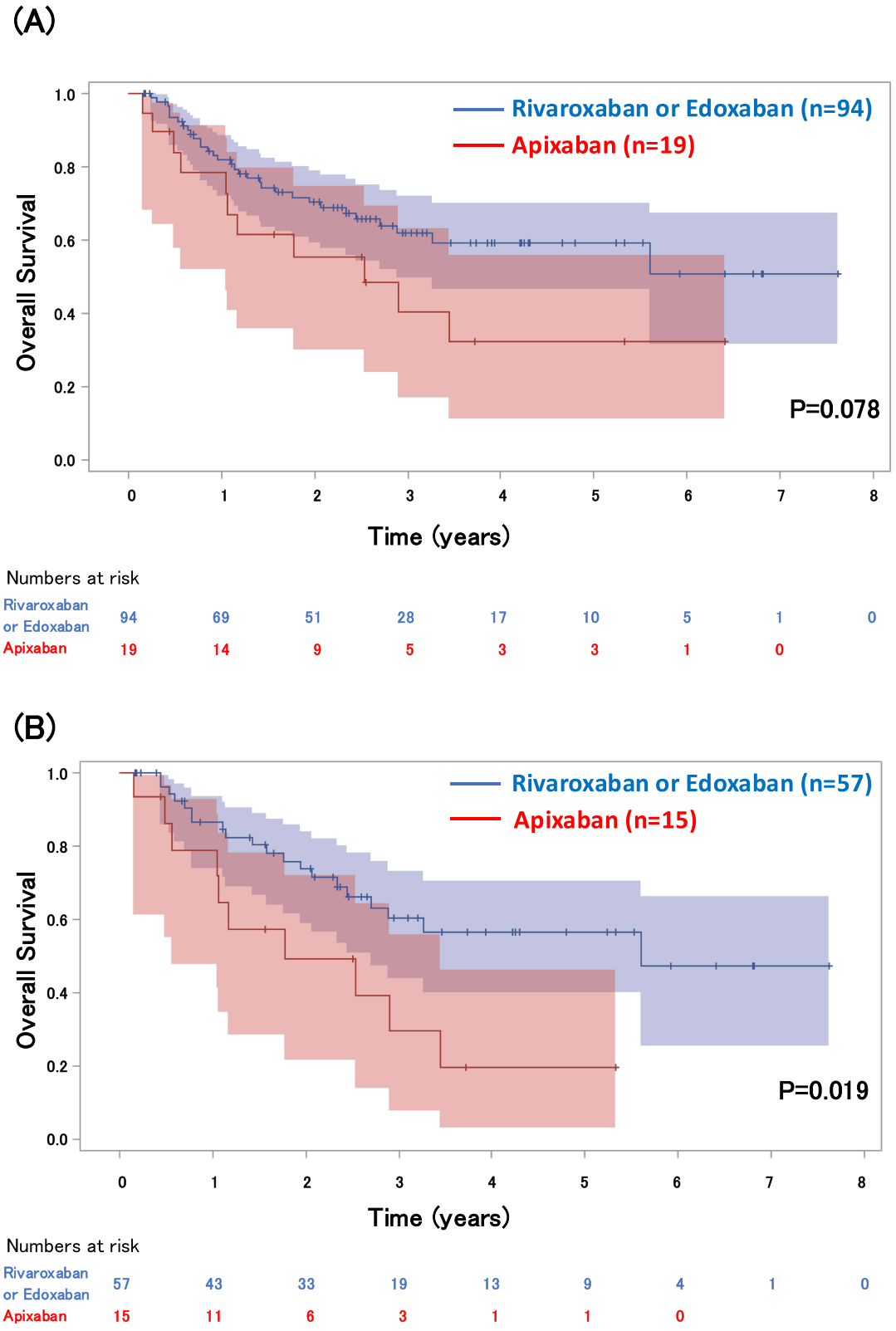

Figure 4 Overall survival based on the type of treatment for DVT (apixaban versus others); (**A**) female patients (Median follow up: 2.2 years), (**B**) patients with gynecological cancer (Median follow up: 2.2 years). Data on dosing, route of administration, median treatment duration, and the number of major bleeding events were not collected in the DOAC table, and the relative performance of each DOAC was assessed solely on the basis of patient survival outcomes.

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characteristics (and considering bleeding and recurrence outcomes), the mortality difference should be interpreted with caution and does not establish a causal relationship.

Discussion

Although this was a single-center study, our analysis included 784 cancer patients and the data revealed that the incidence of DVT was significantly higher in patients with gynecological cancers, as well as in those with hematological abnormalities: specifically, a hemoglobin level below 11 g/dL or a platelet count below $15 \times 10^4/\mu L$. These findings are novel, and suggest that the primary tumor site and anemia are significant risk factors for DVT, being consistent with the findings based on the KRS. Conversely, BMI, another risk factor identified on the basis of the KRS, was found not to be a significant risk factor in the present Japanese cohort.

It is well established that intra-abdominal cancers and patient obesity contribute to deep venous stasis, thereby increasing the risk of DVT. Additionally, anemia exacerbates hypoxia and circulatory failure in peripheral tissues, leading to endothelial damage and an increased tendency for coagulation due to endothelium-derived coagulation factors.[14,15] Furthermore, in cancer patients, platelet activation, rather than quantitative abnormalities, has been implicated in increased coagulability,[16] with consequent platelet consumption and reduction reflecting a higher risk of DVT.[17] Our present findings suggest that risk factors similar to those on which the KRS is based, in conjunction with a reduced platelet count, were significant contributors to DVT in this cohort. Moreover, DVT was significantly more prevalent among patients who received radiotherapy during post-treatment follow-up (data not shown), potentially due to vascular endothelial damage.[18] The absence of obesity as a risk factor for DVT in our cohort may be attributed to the lower prevalence of obesity in the general Japanese population, in comparison to Western populations. In addition, recent nationwide studies have shown that, without pretreatment screening, asymptomatic DVT in cancer patients is often overlooked, leading to underestimation of its true incidence.[17,19]

Our comparison between patients with and without DVT showed that the former had poorer outcomes across all cancer types. This finding suggests that, beyond the direct impact of DVT on life expectancy, complications arising from DVT and its treatment may adversely affect the management of the underlying malignancy. However, differences in patient demographics, such as sex ratio, age, and disease stage, between the DVT and control groups may have introduced variability into the prognostic analysis. To address this, we conducted an additional analysis focusing on female patients with gynecological cancers, as per the KRS guidelines. This analysis revealed a more pronounced negative impact of DVT on life expectancy among women with cancer, particularly gynecological cancers (Figure 2C). This aligns with previous studies,[20–22] which have reported that thrombotic complications worsen patient outcome. These results are noteworthy, as they indicate that the presence of DVT not only significantly influences the prognosis of patients with gynecological cancers but may also affect the course of treatment for the tumor itself. One plausible example of this is a reduction in the intensity of anti-tumor therapy due to DVT complications. For instance, bevacizumab, an anti-vascular endothelial growth factor (VEGF) antibody commonly used for patients with gynecological tumors, has a well-documented profile of adverse effects, including an increased risk of thrombosis and bleeding due to vascular endothelial damage. This may limit its use in patients with DVT. Additionally, DVT-related complications may contribute to anemia and thrombocytopenia, potentially compromising the maintenance of therapeutic intensity. These issues are particularly relevant for colorectal cancer, for which bevacizumab is frequently administered. Unfortunately, the present study did not undertake a detailed assessment of DVT complications in relation to the types of anticancer treatment.

Recent randomized Phase III trials comparing DOACs with low-molecular-weight heparin, which is traditionally considered safe, effective, and associated with a lower recurrence rate for treating VTE in cancer patients, have demonstrated that DOACs are not inferior in terms of treatment efficacy and recurrence rate.[23] In addition, trials comparing individual DOACs with vitamin K antagonists (VKAs) for the treatment of VTE have shown that DOACs are not inferior in terms of efficacy and recurrence rate.[24–27] Consequently, VTE treatment has shifted from VKAs to DOACs in view of their efficacy, standardized dosing, reduced requirement for monitoring, less frequent follow-up, and fewer interactions with food or drugs.[28]

In the present study, we also examined the impact of each DOAC on patient outcome. Interestingly, while the type of DOAC employed affected outcome across all cancer types (Figure 3A), apixaban in particular was associated with a poorer outcome, especially in patients with gynecological cancer (Figure 4B). Although DOACs are generally associated with fewer drug-drug interactions, the potential for antitumor medications affecting CYP3A4 enzymes or P-glycoprotein to alter the blood concentrations of DOACs, and thus their anticoagulant effects,[29,30] warrants consideration. Recently, DOACs have been evaluated for their use in cancer patients. For examples, apixaban has been deemed the most effective and safest treatment for DVT in cancer patients in a systematic review.[31] In contrast, a study using a small number of patients has indicated that edoxaban might be a viable treatment option for gynecological cancer, because as multiple cycles of taxane-based chemotherapy were shown not to significantly alter edoxaban trough blood concentrations or the area under the curve (AUC).[32] In addition, to a retrospective study about the clinical safety of edoxaban,[33] increased risk of bleeding in the use of rivaroxaban or apixaban for patients with gynecological cancer has been reported.[34,35] At present, interactions between DOACs and antitumor treatments, such as alterations of the blood concentration levels, remain inadequately studied. As a twice-daily apixaban dosing regimen may negatively impact treatment compliance for both VTE and cancer, selection of an appropriate DOAC for each type of cancer warrants further investigation.

This study suggests that in patients with solid tumors, especially gynecologic cancers, concurrent anemia and thrombocytopenia may be associated with poorer prognosis. In exploratory analyses, overall survival appeared to differ according to the type of DOAC used for DVT treatment, but this may largely reflect confounding by indication and should be interpreted with caution. The study is limited by its single-center, retrospective design, potential selection bias, and the lack of systematic evaluation of cancer therapies and drug–drug interactions with DOACs. Prospective, multicenter studies in Asian populations are needed to adjust more precisely for cancer stage and treatment, assess hemoglobin and platelet counts, and evaluate bleeding and VTE recurrence, as well as pharmacologic interactions.

Conclusions

In Japanese solid cancers, especially gynecologic cancers, DVT with anemia/thrombocytopenia predicts poorer survival, DOAC effects should need validation.

Data Sharing Statement

Data supporting Figures 1–4 and Tables 1–4 are not publicly available in order to protect patient privacy.

Ethical Approval and Consent to Participate

This study was approved by the Ethics Committee for Clinical Studies at Ehime University Graduate School of Medicine (study IRB; Ehime 2109016), and carried out in accordance with the ethical standards of the 1995 Declaration of Helsinki (as revised in Brazil 2013). Informed consent was by the opt-out principle; we disclosed information about the study on the associated website (https://www.m.ehime-u.ac.jp/school/clinical.oncology/?page_id=1487) and provided patients an opportunity to decline to participate in the study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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