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ORIGINAL RESEARCH

Arterial Thromboembolism in Japanese Patients With Cancer

Incidence, Predictors, and Survival Impact

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ABSTRACT

BACKGROUND Thromboembolism is a significant complication for patients with cancer, leading to treatment interruptions and poor outcomes.

OBJECTIVES The aim of this study was to investigate the incidence of arterial thromboembolism (ATE) within cancer populations, identify the predictors of ATE, and determine its survival impact.

METHODS A retrospective multicenter study was performed using data from the Osaka Cancer Registry linked with administrative data from 2010 to 2015. Patients were monitored for 5 years after cancer diagnosis, and ATE incidence was calculated with death as a competing risk. Fine and Gray competing risk regression models and Cox proportional hazards models were used to evaluate the predictors of ATE and the survival impact. Restricted mean survival time (RMST) was used to assess whether antithrombotic therapy after ATE contributed to improved survival.

RESULTS The cohort comprised 97,448 patients with cancer (42.3% women, median age 70 years). ATE incidence displayed an annual increase, peaking 1 year after cancer diagnosis (1-, 2-, 3-, 4-, and 5-year cumulative incidences were 1.29%, 1.77%, 2.05%, 2.22%, and 2.32%, respectively). Male sex, advanced age, advanced cancer stage, and hematologic malignancies correlated with a high risk for ATE. Patients with ATE had a 2-fold increased risk for mortality compared with those without ATE. The 90-day and 1-year RMST differences for those on antithrombotic therapy were 13.3 days (95% CI: 10.4-16.2 days; $P < 0.001$) and 57.8 days (95% CI: 43.1-72.5 days; $P < 0.001$), favoring the antithrombotic therapy group. The RMST differences varied by cancer stage.

CONCLUSIONS The risk for ATE varies according to sex, age, and cancer progression and type. Antithrombotic therapy after ATE is associated with improved survival among patients with cancer. (J Am Coll Cardiol CardioOnc 2024;6:283–297)

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ABBREVIATIONS AND ACRONYMS

ATE = arterial thromboembolism

BMI = body mass index

DPC = Diagnosis Procedure Combination

IPTW = inverse probability of treatment weighting

OCR = Osaka Cancer Registry

RMST = restricted mean survival time

SHR = subdistribution HR

VTE = venous thromboembolism

There is growing concern regarding thromboembolic complications in patients with cancer, driven by factors such as improved patient survival, the adoption of more thrombogenic cancer treatments, the widespread use of central catheters, and an increased awareness of cancer-associated thrombosis.[1] The effective management of thromboembolism is crucial for both physicians and patients, as it can potentially interrupt essential cancer treatments and worsen overall outcomes.[1]

Venous thromboembolism (VTE) is a frequent occurrence in patients with cancer, with an incidence ranging from 4 to 9 times higher than that in the general population.[2-4] Approximately 15% of patients with cancer experience VTE during the course of their illness.[5] Regarding arterial thrombosis, previous studies have indicated an increased risk for arterial thromboembolism (ATE) in patients with cancer,[6-12] with a cumulative incidence rate ranging from 1.1% to 6.5% in the first year after cancer diagnosis.[9-12] Notably, the risk is particularly high immediately after cancer diagnosis.[9-11] Additionally, advanced stages of cancer and atrial fibrillation contribute to an increased risk for ATE in patients with cancer.[8,10,12] Although studies of ATE in cancer have been reported in Europe,[6-9] the United States,[10,11] and the Middle East,[12] comparable data for Asian populations remain scarce.

Clinical guidelines recommend anticoagulant treatment for patients with cancer who develop VTE;[13] however, the effectiveness of antithrombotic therapy after ATE remains unknown. In the general population, antithrombotic agents are widely used to prevent and treat ATE, such as ischemic stroke and myocardial infarction.[14,15] For patients with cancer, it is essential to assess the impact of antithrombotic therapy after ATE on survival, especially in advanced cancers for which the benefit of antithrombotic agents may be limited because of the increased risk for bleeding complications and short life expectancy.[13] Currently, there are insufficient data available to determine how antithrombotic therapy after ATE affects survival in patients with cancer.

The aim of this study was to investigate the incidence of ATE in patients with cancer, using cancer registry data from designated cancer care hospitals in Osaka, Japan. We analyzed the predictors of ATE and assessed their survival impact. Furthermore, we examined whether antithrombotic therapy after ATE was associated with improved prognosis of patients with cancer.

METHODS

STANDARD PROTOCOL APPROVALS, REGISTRATIONS, AND PATIENT CONSENT. This study complied with the principles of the Declaration of Helsinki, and approval was obtained from the Institutional Review Board of Osaka University Hospital (approval number 22485). Because of the retrospective nature of the study and the availability of an opt-out opportunity on the institutional website, the requirement to obtain written informed consent was waived.

DATA SOURCES. We performed a retrospective multicenter cohort study involving patients with cancer, using data from the Osaka Cancer Registry (OCR) registered between January 2010 and December 2015. Established in 1962, the OCR is one of the largest population-based cancer registries in Japan, encompassing more than 8 million residents in Osaka Prefecture.[16] Cancer-specific information was collected from the OCR. Comorbidities and medication data for the study cohort were obtained from the Diagnosis Procedure Combination (DPC) data of designated cancer care hospitals. The DPC system comprises a case-mix patient classification system providing clinical information and medical procedures.[17] Introduced by the Japanese government in 2003 for acute care hospitals,[17] the DPC system records diagnoses using International Classification of Diseases-10th Edition codes; accuracy is reported elsewhere.[18] By integrating the OCR and DPC data, we constructed the OCR-DPC database for research purposes.[19] The creation of the OCR-DPC database was a collaborative effort with the Council for Coordination of Designated Cancer Care Hospitals in Osaka. The data for this study were collected from 36 hospitals and involved more than 50% of patients with cancer in Osaka Prefecture. Supplemental Tables 1 and 2 contain all codes for disease diagnoses and medications used in this study.

CLINICAL VARIABLES. The following data were obtained from the OCR-DPC database: sex, age at cancer diagnosis, body mass index (BMI), cancer type, stage at cancer diagnosis, cancer treatment (cancer surgery, chemotherapy, and radiotherapy), smoking history, and comorbidities (hypertension, dyslipidemia, diabetes mellitus, atrial fibrillation, heart failure, chronic obstructive pulmonary disease, chronic kidney disease, liver disease, previous ATE, and previous VTE). Information on previous antithrombotic medications and ATE after cancer diagnosis was also included. Age at cancer diagnosis was grouped into 3 categories: <65, 65 to 74, and ≥75 years. BMI was divided into 3 groups in accordance with the World

Health Organization criteria: <18.5, 18.5 to 25, and ≥25 kg/m^2.[20] Stage at cancer diagnosis was classified into 5 categories: 1) localized (cancer limited to the organ where it originated, with no sign of spread); 2) regional (lymph node metastasis [cancer spread to regional lymph nodes] or infiltration to adjacent organs [cancer spread to nearby tissues or organs]); 3) distant metastasis (cancer metastasized to distant parts of the body); 4) not applicable (the extent of leukemia and multiple myeloma is registered as "not applicable" in the Japanese cancer registry); and 5) unknown (insufficient information to determine the stage or data not available). Patients with intraepithelial cancer were excluded from the study population.

In the OCR, cancer treatment refers to the first treatment administered for a diagnosed cancer, continuing until the completion of the treatment plan. For hematologic malignancies, initial therapy refers to all therapies used until induction of initial remission.

FOLLOW-UP DURATION AND OUTCOMES. Patients were monitored for 5 years after cancer diagnosis. During the observation period, data on ATE and deaths were collected. Patients who had received second cancer diagnoses or were lost to follow-up were censored at that time. ATE was defined as a composite outcome comprising ischemic stroke, myocardial infarction, and peripheral arterial occlusion,[8,9] in accordance with the International Classification of Diseases-10th Edition codes (details are provided in Supplemental Table 2). Transient ischemic attack was excluded from the definition of ATE because of its limited accuracy in disease identification. Death was defined as mortality resulting from any cause.

STATISTICAL ANALYSIS. Baseline characteristics were summarized as median (Q1-Q3) for continuous variables and as count (percentage) for categorical variables. To compare groups, the Mann-Whitney *U*, Kruskal-Wallis, or chi-square test was used. The cumulative incidence of ATE during the 5-year period after cancer diagnosis was determined using Gray's method,[21] considering death as a competing risk. Incidence rates were calculated by sex, age at cancer diagnosis, stage at cancer diagnosis, and solid tumors or hematologic malignancies. The rates were also calculated for specific outcomes, including ischemic stroke, myocardial infarction, and peripheral arterial occlusion.

Next, we used the Fine and Gray competing risk regression models[22] to estimate the subdistribution HRs (SHRs) and their corresponding 95% CIs. The aim of the analysis was to identify predictors of ATE after cancer diagnosis, with death treated as a competing risk event. The following variables were considered potential confounders in multivariable model: sex, age at cancer diagnosis, BMI, smoking history, comorbidities (hypertension, dyslipidemia, diabetes mellitus, arterial fibrillation, heart failure, chronic obstructive pulmonary disease, renal disease, liver disease, previous ATE, and previous VTE), antithrombotic medication before ATE, stage at cancer diagnosis, and cancer treatment.

Furthermore, the HR and 95% CI for ATE in predicting mortality among patients with cancer were evaluated. ATE events were treated as time-dependent variables for survival analysis. To ensure the validity of the analysis, the assumption of

TABLE 1 Baseline Patient Characteristics (n = 97,448)

Women	42.3 (41,184)
Age, y	70 (62-76)
<65 y	32.4 (31,625)
≥65 and <75 y	36.0 (35,088)
≥75 y	31.5 (30,735)
Body mass index[a]	22.1 (19.7-24.5)
<18.5 kg/m^2	14.5 (13,926)
≥18.5 and <25 kg/m^2	64.1 (61,374)
≥25 kg/m^2	21.4 (20,455)
Vascular risks and comorbidities	
Smoking history	39.5 (38,466)
Hypertension	16.7 (16,313)
Dyslipidemia	7.0 (6,863)
Diabetes mellitus	12.5 (12,161)
Atrial fibrillation	2.4 (2,322)
Heart failure	2.3 (2,263)
Chronic obstructive pulmonary disease	3.3 (3,223)
Chronic kidney disease	1.9 (1,887)
Liver disease	2.8 (2,714)
Previous arterial thromboembolism	1.4 (1,335)
Previous venous thromboembolism	2.0 (1,903)
Previous antithrombotic medications	
Previous antiplatelet medications	4.9 (4,823)
Previous anticoagulant medications	7.7 (7,541)
Cancer stage	
Localized	48.1 (46,896)
Regional	26.8 (26,096)
Distant	19.1 (18,568)
Not applicable[b]	2.8 (2,756)
Unknown	3.2 (3,132)
Cancer treatment	
Cancer surgery	63.9 (62,228)
Chemotherapy	40.0 (38,994)
Radiotherapy	13.5 (13,201)

Values are % (n) or median (Q1-Q3). [a]Body mass index data were missing data for 1.7% of the cases (n = 1,693). No missing values were observed for the other variables. [b]The extent of leukemia and multiple myeloma is registered as "not applicable" in the Japanese cancer registry.

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TABLE 2 Cumulative Incidence (95% CI) of Arterial Thromboembolism by Years After Cancer Diagnosis

	Time After Cancer Diagnosis					
	6 mo	1 y	2 y	3 y	4 y	5 y
All (n = 97,448)	0.93 (0.87-1.00)	1.29 (1.22-1.36)	1.77 (1.69-1.86)	2.05 (1.97-2.15)	2.22 (2.13-2.32)	2.32 (2.23-2.42)
Sex						
Female (n = 41,184)	0.75 (0.67-0.83)	1.02 (0.92-1.12)	1.36 (1.25-1.47)	1.57 (1.46-1.70)	1.70 (1.57-1.83)	1.75 (1.63-1.88)
Male (n = 56,264)	1.07 (0.99-1.16)	1.49 (1.40-1.60)	2.08 (1.96-2.20)	2.41 (2.29-2.54)	2.61 (2.48-2.75)	2.75 (2.61-2.89)
Age at cancer diagnosis						
<65 y (n = 31,625)	0.46 (0.69-0.54)	0.65 (0.56-0.74)	0.85 (0.76-0.96)	1.00 (0.90-1.12)	1.08 (0.97-1.20)	1.17 (1.05-1.30)
≥65 and <75 y (n = 35,088)	1.06 (0.96-1.17)	1.41 (1.29-1.54)	1.97 (1.82-2.12)	2.29 (2.14-2.46)	2.46 (2.30-2.63)	2.56 (2.40-2.74)
≥75 y (n = 30,735)	1.28 (1.16-1.41)	1.82 (1.68-1.98)	2.51 (2.34-2.69)	2.88 (2.70-3.08)	3.15 (2.95-3.35)	3.27 (3.06-3.48)
Stage at cancer diagnosis						
Localized (n = 46,896)	0.70 (0.62-0.78)	0.98 (0.89-1.07)	1.42 (1.31-1.53)	1.71 (1.59-1.83)	1.93 (1.81-2.06)	2.02 (1.89-2.16)
Regional (n = 26,096)	0.88 (0.77-0.99)	1.22 (1.09-1.36)	1.74 (1.59-1.91)	2.04 (1.88-2.22)	2.19 (2.02-2.38)	2.34 (2.15-2.53)
Distant (n = 18,568)	1.45 (1.28-1.63)	1.93 (1.74-2.14)	2.42 (2.21-2.65)	2.62 (2.40-2.86)	2.67 (2.45-2.92)	2.74 (2.50-2.98)
Not applicable[a] (n = 2,756)	1.53 (1.12-2.04)	2.23 (1.72-2.83)	2.98 (2.39-3.67)	3.45 (2.81-4.18)	3.57 (2.92-4.32)	3.69 (3.01-4.45)
Unknown (n = 3,132)	1.38 (1.02-1.84)	1.98 (1.53-2.52)	2.40 (1.90-2.99)	2.76 (2.22-3.40)	2.97 (2.40-3.62)	3.09 (2.50-3.77)
Cancer type						
Solid (n = 91,369)	0.91 (0.85-0.97)	1.26 (1.19-1.33)	1.73 (1.64-1.81)	2.00 (1.91-2.10)	2.17 (2.08-2.27)	2.27 (2.17-2.37)
Hematologic (n = 6,079)	1.32 (1.06-1.63)	1.82 (1.51-2.18)	2.47 (2.10-2.88)	2.82 (2.42-3.26)	2.93 (2.52-3.38)	3.13 (2.70-3.60)

[a]The extent of leukemia and multiple myeloma is registered as "not applicable" in the Japanese cancer registry.

proportional hazards was tested using Schoenfeld residuals, as well as visual inspection of a log-log plot.

Finally, we selected the patients who experienced ATE and performed a subgroup analysis to assess the prognostic impact of antithrombotic medications after ATE. Data on the prescription of antithrombotic drugs after ATE were extracted for this subgroup analysis, and patients were categorized into 2 groups on the basis of antithrombotic therapy: with or without. The index date of follow-up was defined as the date of ATE onset, and the end date of follow-up was death, loss to follow-up, or the end of the follow-up period, whichever occurred first.

We used Kaplan-Meier curves to present the survival data. To control for confounding due to imbalances of prognostic factors between the antithrombotic and nonantithrombotic therapy groups, we used the Kaplan-Meier method with inverse probability of treatment weighting (IPTW) by propensity score. Baseline characteristics before and after matching were evaluated using the standardized mean difference. Additionally, the restricted mean survival time (RMST) was calculated to evaluate between-group differences.[23] RMST was estimated 90 days and 1 year after the onset of ATE.

Statistical analysis was performed using R software. The level of significance was set at $P < 0.05$, and all tests were 2-sided.

DATA AVAILABILITY. The data supporting the findings of this study are available from the corresponding author upon reasonable request.

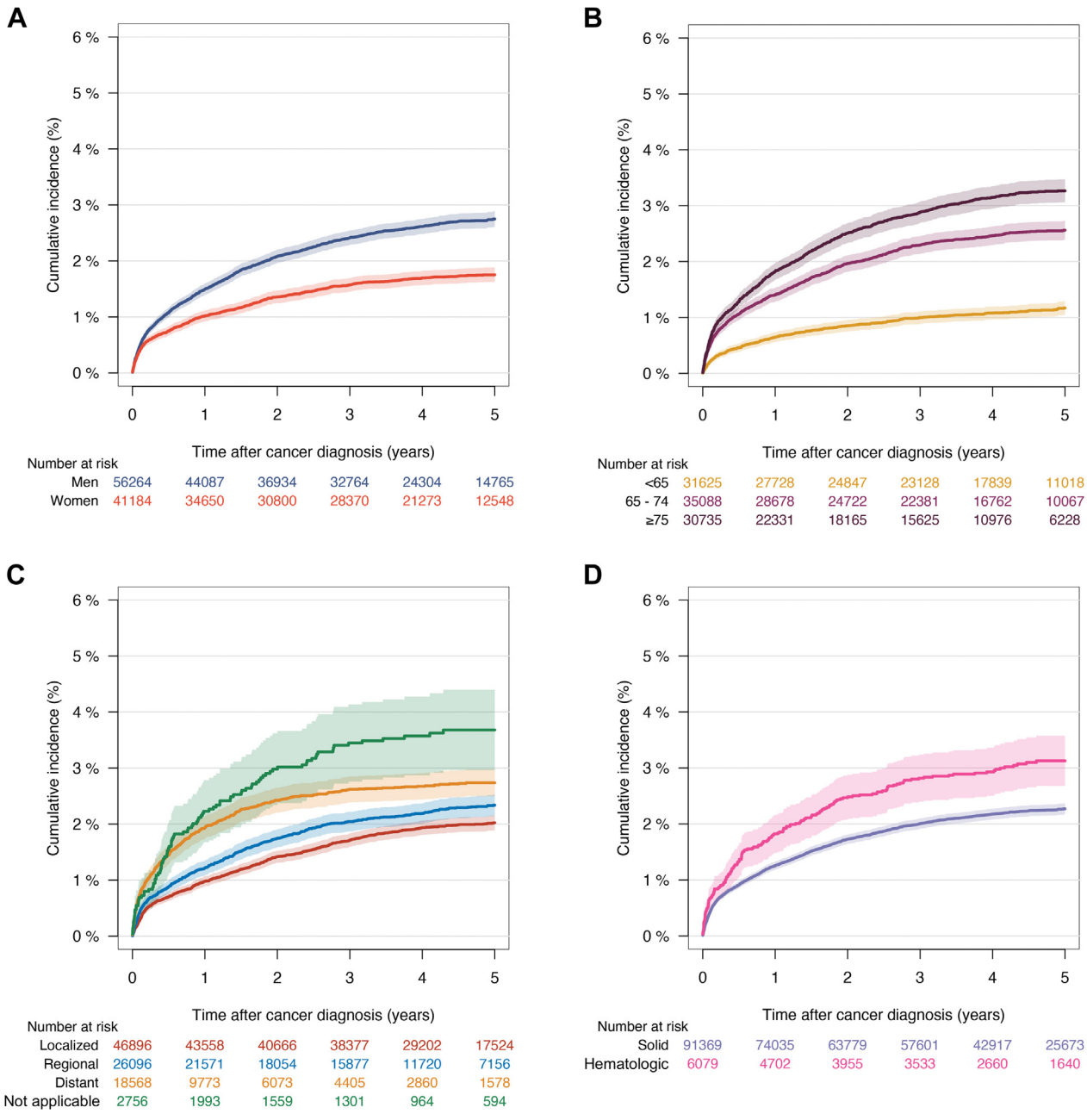
RESULTS

STUDY POPULATION. Data for 97,448 patients with cancer were included for analysis. Table 1 presents the baseline characteristics of the study cohort: 42.3% were women, and the median age was 70 years (Q1-Q3: 62-76 years). Among the patients, more than one-half (64.1%) had BMIs of 18.5 to 25 kg/m^2, 39.5% had smoking histories, and hypertension (16.7%) was the most common comorbidity. Antiplatelet and anticoagulant medications were prescribed to 4.9% and 7.7% of patients, respectively. Localized cancer was the most prevalent stage at cancer diagnosis (48.1%), followed by regional (26.8%), distant (19.1%), unknown (3.2%), and not applicable (2.8%).

CUMULATIVE INCIDENCE OF ATE. The median follow-up time was 3.85 years (Q1-Q3: 1.43-5.00 years), during which time 2,159 patients experienced ATE. Table 2 presents the temporal trends and the breakdown of cumulative ATE incidence after cancer diagnosis. Figure 1 illustrates the cumulative incidence of ATE, stratified by sex, age at cancer diagnosis, stage at cancer diagnosis, and cancer type (solid tumors or hematologic malignancies).

As shown in Table 2, the incidence was clearly high during the first year after cancer diagnosis (1.29%), accounting for more than one-half of the overall 5-year incidence rate (2.32%). ATE was most prevalent in men, older patients with cancer, and those with advanced cancer stages. Hematologic

FIGURE 1 **Cumulative Incidence of Arterial Thromboembolism**

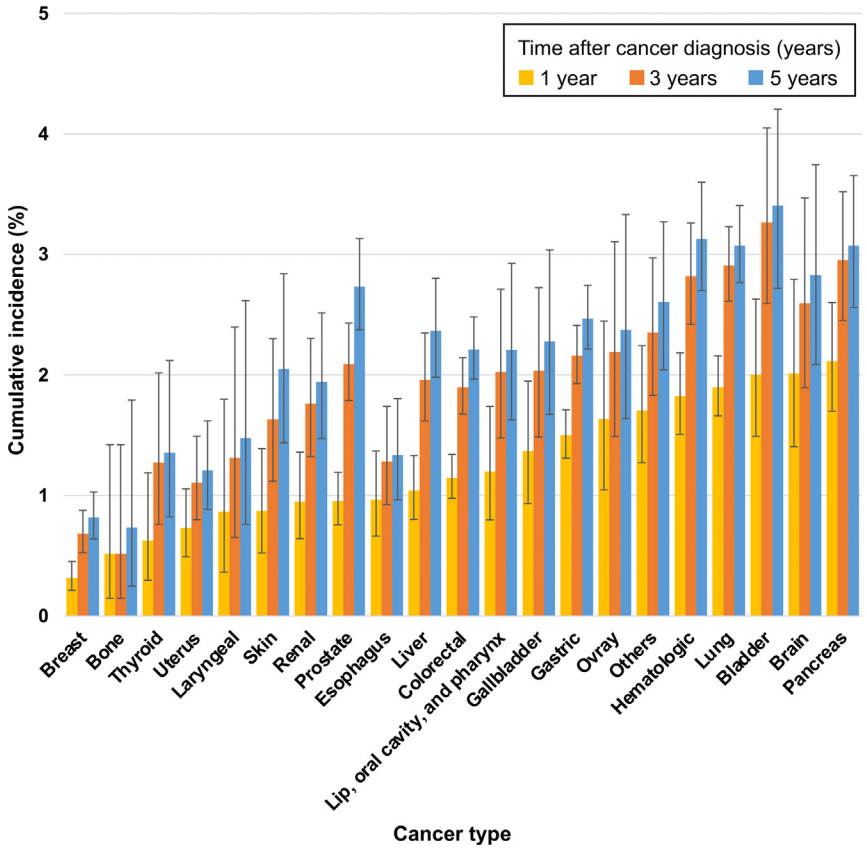


The vertical axis indicates the cumulative incidence rate, and the horizontal axis indicates the number of years after cancer diagnosis. The cumulative incidence of arterial thromboembolism is illustrated by sex (A), age at cancer diagnosis (B), stage at cancer diagnosis (C), and solid tumors and hematologic malignancies (D).

malignancies were associated with a significantly higher ATE incidence than solid tumors.

Baseline comparisons in the analysis of ATE incidence (**Table 2**, **Figure 1**) are presented in Supplemental Tables 3 to 6. Male patients were older and had a higher prevalence of vascular risk factors, comorbidities, and more distant metastases than female patients (Supplemental Table 3). Older patients at cancer diagnosis frequently presented with vascular risk factors and comorbidities and received

FIGURE 2 Incidence of Arterial Thromboembolism by Cancer Type and Years After Cancer Diagnosis



The vertical axis indicates the cumulative incidence of arterial thromboembolism with 95% CIs, and the horizontal axis indicates the cancer type. Different time periods after diagnosis (<1, 1-3, and 3-5 years) are shown in different colors. Within 1 year after cancer diagnosis, the cumulative incidence of arterial thromboembolism was highest for pancreatic cancer (2.1%) and lowest for breast cancer (0.3%). Within 5 years after cancer diagnosis, the cumulative incidence was highest for bladder cancer (3.4%) and lowest for bone tumors (0.7%).

antithrombotic medications (Supplemental Table 4). Significant differences were observed across all variables except hypertension, diabetes mellitus, and previous ATE when considering the stage at cancer diagnosis (Supplemental Table 5). In examining different cancer types, patients with hematologic malignancies were younger and had a higher frequency of heart failure and chronic kidney disease than those with solid tumors (Supplemental Table 6). For other vascular risks and comorbidities, either no significant differences or fewer comorbidities were observed in hematologic malignancies compared with solid tumors. Furthermore, approximately one-half of all lymphomas (hematologic malignancies with stage classification) were classified as advanced at cancer diagnosis.

The cumulative incidence of ischemic stroke, myocardial infarction, and peripheral arterial occlusion is shown in Supplemental Tables 7 to 9 and Supplemental Figures 1 to 3. Within the cohort, ischemic stroke was the most prevalent type (71.6%) of ATE. Male sex, advanced cancer, and hematologic malignancies were commonly associated with ATE across all 3 types. Ischemic stroke and myocardial infarction showed a similar tendency, with older age being associated with these conditions, whereas patients in the 65- to 74-year age range had the highest incidence of peripheral artery occlusion. When comparing patients who developed ischemic stroke with those who developed myocardial infarction or peripheral artery occlusion, a significantly higher prevalence of atrial fibrillation was observed in the

ischemic stroke group than in the nonischemic stroke group.

CUMULATIVE INCIDENCE OF ATE BY CANCER TYPE AND YEARS AFTER CANCER DIAGNOSIS. Figure 2 shows the cumulative incidence of ATE by cancer type and years after cancer diagnosis, with detailed data available in Supplemental Table 10. In the first year after cancer diagnosis, pancreatic cancer (2.1%) exhibited the highest incidence of ATE, followed by brain tumors (2.0%), bladder cancer (2.0%), lung cancer (1.9%), and hematologic malignancies (1.8%). During the 5 years after cancer diagnosis, bladder cancer had the highest incidence of ATE (3.4%), followed by hematologic malignancies (3.1%), lung cancer (3.1%), pancreatic cancer (3.1%), and brain tumors (2.8%). Notably, although pancreatic cancer had the highest incidence of ATE within 1 year after cancer diagnosis, its incidence ranked fourth over the 5-year period. Supplemental Tables 11 to 13 present the cumulative incidence of ischemic stroke, myocardial infarction, and peripheral arterial occlusion by cancer type and time after cancer diagnosis.

PREDICTORS OF ATE AND THE EFFECT OF ATE ON SURVIVAL. Table 3 shows the predictors of ATE in the cohort. Patients aged ≥75 years had an approximately 1.9 times higher SHR compared with those aged <65 years. Additionally, men had an approximately 1.2 times higher risk than women. Notably, patients with obesity had a lower risk for ATE than those who were underweight. Among vascular risks and comorbidities, atrial fibrillation exhibited the strongest association with ATE (SHR: 3.34; 95% CI: 2.88-3.88; $P < 0.001$), whereas liver disease was not a predictor of ATE. Patients prescribed antithrombotic medications before ATE diagnosis had a higher risk for ATE than those who were not. Regarding stage at cancer diagnosis, a notable increase in risk was observed in advanced stages compared with early stages.

Table 4 shows the predictors of mortality among patients with cancer, analyzed with ATE as a time-dependent variable. ATE was associated with an increased risk for mortality after adjusting for all potential confounders (HR: 2.02; 95% CI: 1.86-2.20; $P < 0.001$).

PROGNOSIS OF CANCER PATIENTS AFTER ATE. After identifying 2,159 cases of ATE during the study period, we focused on this subgroup of patients and investigated their prognosis. Survival outcomes of the patients after ATE were analyzed on the basis of antithrombotic therapy (with or without) and cancer stage.

The median duration of antithrombotic therapy was 108 days (Q1-Q3: 29-426 days). Overall, the 90-day and 1-year RMSTs were 81 and 281 days for patients with antithrombotic therapy, compared with 68 and 224 days for those without antithrombotic therapy, respectively. The 90-day and 1-year RMST differences were 13.3 days (95% CI: 10.4-16.2 days; $P < 0.001$) and 57.8 days (95% CI: 43.1-72.5 days; $P < 0.001$), favoring the antithrombotic therapy group.

Figure 3 presents the Kaplan-Meier survival curves by solid tumors and hematologic malignancies. Baseline characteristics before and after IPTW adjustment are shown in Supplemental Tables 14 and 15. Both unadjusted 90-day and 1-year RMST favored the antithrombotic therapy group for both solid tumors and hematologic malignancies.

TABLE 3 Predictors of Arterial Thromboembolism Among Patients With Cancer

	Unadjusted SHR (95% CI)	Adjusted SHR (95% CI)
Age at cancer diagnosis		
<65 y	Reference	Reference
≥65 and <75 y	2.26 (1.99-2.55)	1.67 (1.47-1.90)
≥75 y	2.89 (2.56-3.26)	1.89 (1.66-2.16)
Sex		
Male	1.56 (1.43-1.71)	1.25 (1.13-1.38)
Body mass index[a]		
<18.5 kg/m^2	Reference	Reference
≥18.5 and <25 kg/m^2	0.77 (0.69-0.86)	0.71 (0.63-0.79)
≥25 kg/m^2	0.73 (0.63-0.83)	0.60 (0.52-0.69)
Vascular risks and comorbidities		
Smoking	1.24 (1.14-1.35)	1.09 (0.99-1.20)
Hypertension	2.97 (2.72-3.24)	1.76 (1.59-1.94)
Dyslipidemia	3.75 (3.38-4.15)	2.35 (2.09-2.63)
Diabetes mellitus	2.53 (2.30-2.78)	1.63 (1.47-1.81)
Atrial fibrillation	5.73 (5.03-6.53)	3.34 (2.88-3.88)
Heart failure	4.03 (3.46-4.69)	2.09 (1.77-2.46)
Chronic obstructive pulmonary disease	1.72 (1.43-2.07)	1.39 (1.15-1.68)
Renal disease	3.82 (3.24-4.52)	2.06 (1.73-2.46)
Liver disease	0.86 (0.66-1.13)	0.88 (0.67-1.16)
Previous arterial thromboembolism	4.13 (3.43-4.99)	2.41 (1.97-2.94)
Previous venous thromboembolism	1.59 (1.24-2.03)	1.80 (1.40-2.31)
Previous antithrombotic medications		
Previous antiplatelets	3.20 (2.83-3.61)	1.41 (1.22-1.64)
Previous anticoagulants	2.45 (2.19-2.75)	1.16 (1.01-1.33)
Cancer stage		
Localized	Reference	Reference
Regional	1.15 (1.04-1.28)	1.17 (1.04-1.31)
Distant	1.39 (1.25-1.56)	1.30 (1.14-1.49)
Not applicable[b]	1.87 (1.52-2.30)	1.58 (1.25-2.00)
Unknown	1.56 (1.25-1.93)	1.45 (1.15-1.83)
Cancer treatment		
Cancer surgery	0.72 (0.66-0.78)	0.91 (0.82-1.02)
Chemotherapy	1.00 (0.92-1.09)	1.06 (0.96-1.18)
Radiotherapy	0.82 (0.71-0.93)	0.91 (0.79-1.04)

Variables controlled in the calculation of adjusted SHR included all the factors listed in Table 3. [a]Body mass index data were missing data for 1.7% of the cases (n = 1,693). No missing values were observed for the other variables. Given the low rate, missing data were imputed using mean substitution. [b]The extent of leukemia and multiple myeloma is registered as "not applicable" in the Japanese cancer registry.

SHR = subdistribution hazard ratio.

TABLE 4 Predictors of Mortality Among Patients With Cancer

	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Atrial thromboembolism	2.93 (2.74-3.14)	2.02 (1.86-2.20)
Age at cancer diagnosis		
<65 y	Reference	Reference
≥65 and <75 y	1.44 (1.40-1.48)	1.39 (1.35-1.43)
≥75 y	2.29 (2.23-2.35)	2.28 (2.21-2.35)
Sex		
Male	1.42 (1.39-1.45)	1.21 (1.18-1.24)
Body mass index[a]		
<18.5 kg/m^2	Reference	Reference
≥18.5 and <25 kg/m^2	0.58 (0.56-0.59)	0.65 (0.63-0.67)
≥25 kg/m^2	0.42 (0.40-0.43)	0.53 (0.51-0.55)
Vascular risks and comorbidities		
Smoking	1.19 (1.16-1.21)	1.06 (1.03-1.09)
Hypertension	1.20 (1.17-1.24)	1.05 (1.02-1.08)
Dyslipidemia	0.95 (0.91-0.99)	0.82 (0.78-0.85)
Diabetes mellitus	1.31 (1.27-1.35)	1.17 (1.13-1.21)
Atrial fibrillation	1.38 (1.29-1.47)	1.14 (1.06-1.23)
Heart failure	1.62 (1.52-1.72)	1.19 (1.11-1.27)
Chronic obstructive pulmonary disease	1.72 (1.64-1.81)	1.28 (1.21-1.35)
Renal disease	1.73 (1.63-1.85)	1.48 (1.37-1.59)
Liver disease	1.55 (1.47-1.64)	1.77 (1.66-1.88)
Previous arterial thromboembolism	1.34 (1.23-1.46)	1.07 (0.98-1.18)
Previous venous thromboembolism	1.05 (0.97-1.13)	1.04 (0.96-1.12)
Previous antithrombotic medications		
Previous antiplatelets	1.56 (1.50-1.63)	1.18 (1.12-1.25)
Previous anticoagulants	1.44 (1.39-1.49)	1.16 (1.11-1.21)
Cancer stage		
Localized	Reference	Reference
Regional	2.89 (2.80-2.97)	2.89 (2.80-2.98)
Distant	9.33 (9.07-9.60)	6.86 (6.62-7.12)
Not applicable[b]	4.53 (4.27-4.80)	2.79 (2.62-2.98)
Unknown	6.23 (5.90-6.58)	4.08 (3.85-4.32)
Cancer treatment		
Cancer surgery	0.27 (0.27-0.28)	0.54 (0.52-0.55)
Chemotherapy	2.05 (2.01-2.09)	1.06 (1.03-1.09)
Radiotherapy	1.09 (1.05-1.12)	0.96 (0.93-0.99)

Variables controlled in the calculation of adjusted HR included all the factors listed in Table 4. [a]Body mass index data were missing for 1.7% of the cases (n = 1,693). No missing values were observed for the other variables. Given the low rate, missing data were imputed using mean substitution. [b]The extent of leukemia and multiple myeloma is registered as "not applicable" in the Japanese cancer registry.

The results remained significant after analysis using IPTW-adjusted RMST.

Figure 4 illustrates Kaplan-Meier survival curves for patients with solid tumors, comparing those who received antithrombotic therapy after ATE and those who did not. Baseline characteristics before and after IPTW adjustment are shown in Supplemental Tables 16 to 18. In the unadjusted survival analysis, the 90-day and 1-year RMST differences significantly favored the antithrombotic therapy group for all stages. Following IPTW adjustment, significant differences were observed in the 90-day RMST for all cancer stages. Regarding the 1-year RMST, a significant difference was found in patients with regional cancer, whereas no significance was observed in patients with localized or distant metastatic cancer. Analyses by antithrombotic agents are presented in Supplemental Figures 4 and 5.

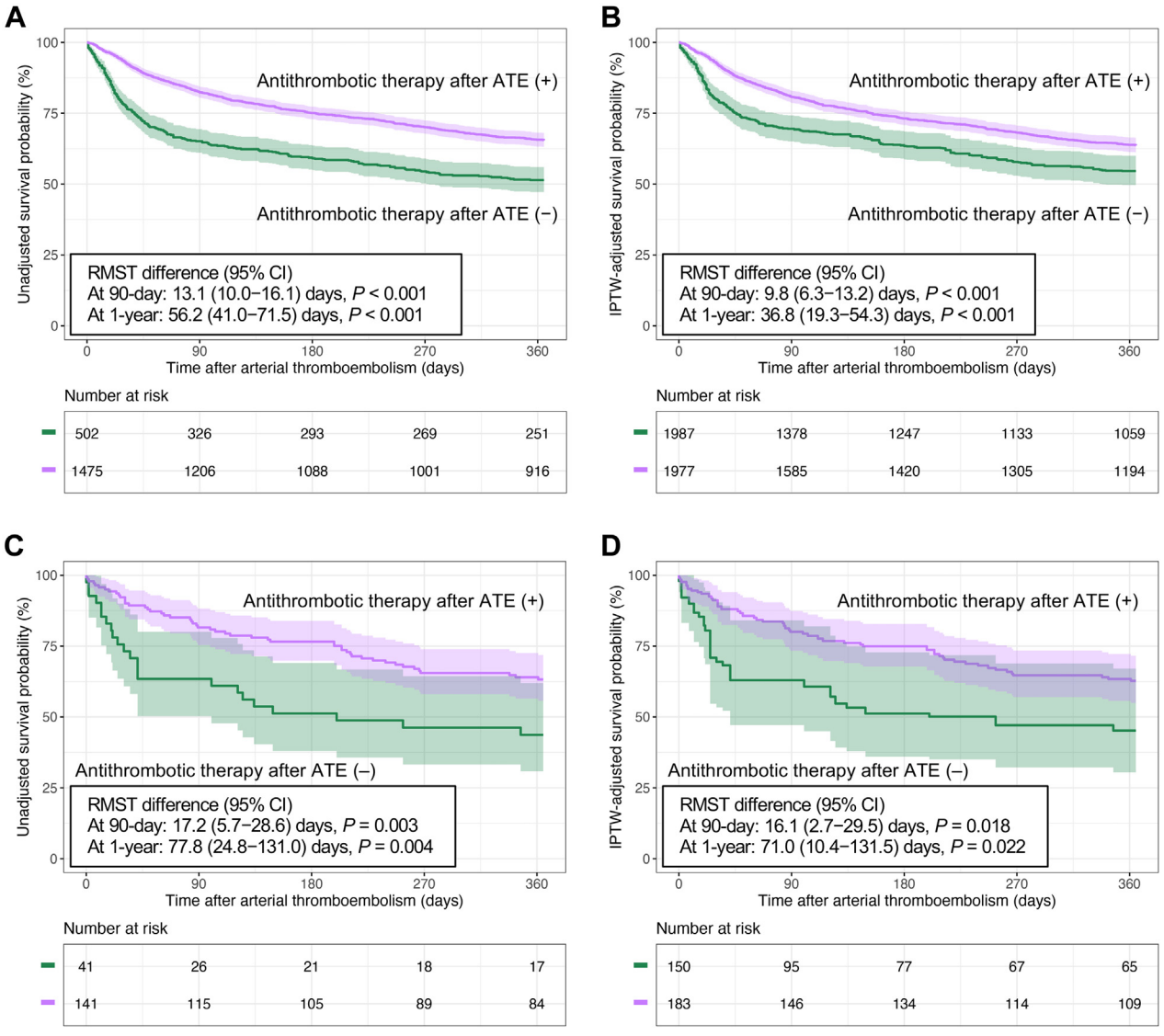
DISCUSSION

In this study, we investigated the incidence of ATE and its impact on survival over a 5-year period after cancer diagnosis. The incidence was notably high immediately after cancer diagnosis, being most frequently observed in men and in patients with advanced age, advanced cancer stages, and hematologic malignancies. Patients with ATE experienced a 2-fold increased risk for mortality compared with those without ATE. Moreover, patients who received antithrombotic therapy after ATE had a better prognosis than those who did not. These results offer novel insights into ATE incidence in an Asian population and shed light on the effects of antithrombotic therapy after ATE (**Central Illustration**).

Patients with cancer have an increased risk for ATE immediately after cancer diagnosis,[6-12] consistent with our findings. Regarding the cumulative incidence of ATE within the first year after cancer diagnosis, Navi et al[10] reported an incidence of 6.5% in an analysis of data taken from Medicare and the Surveillance, Epidemiology, and End Results program. Feldman et al,[11] analyzing data from the Memorial Sloan Kettering Cancer Center, reported an incidence of 1.9%. Mulder et al[8] showed an incidence of 2.1% using data from the Danish cancer registry, and Leader et al,[12] using insurance data from Israel, reported an incidence of 1.1%. In our study, the cumulative incidence of ATE within the first year after cancer diagnosis was 1.3%. It is worth noting that a higher incidence was reported in the Navi et al[10] study compared with our reports and others.[8,9,11,12] This difference may be attributed to specific patient characteristics in Navi et al's[10] study, such as the advanced age of the study participants (≥66 years) and the high prevalence of hypertension or atrial fibrillation (present in more than 60% of the patients).

The incidence of ATE in different groups revealed interesting findings. When stratified by sex and age at cancer diagnosis, the group with the highest incidence of ATE had a greater proportion of conventional vascular risks. However, this trend did not consistently hold when the analysis was stratified by cancer progression or by solid tumors and hematologic malignancies. Notably, the ATE incidence was higher in the hematologic malignancies group than the solid tumors group, although

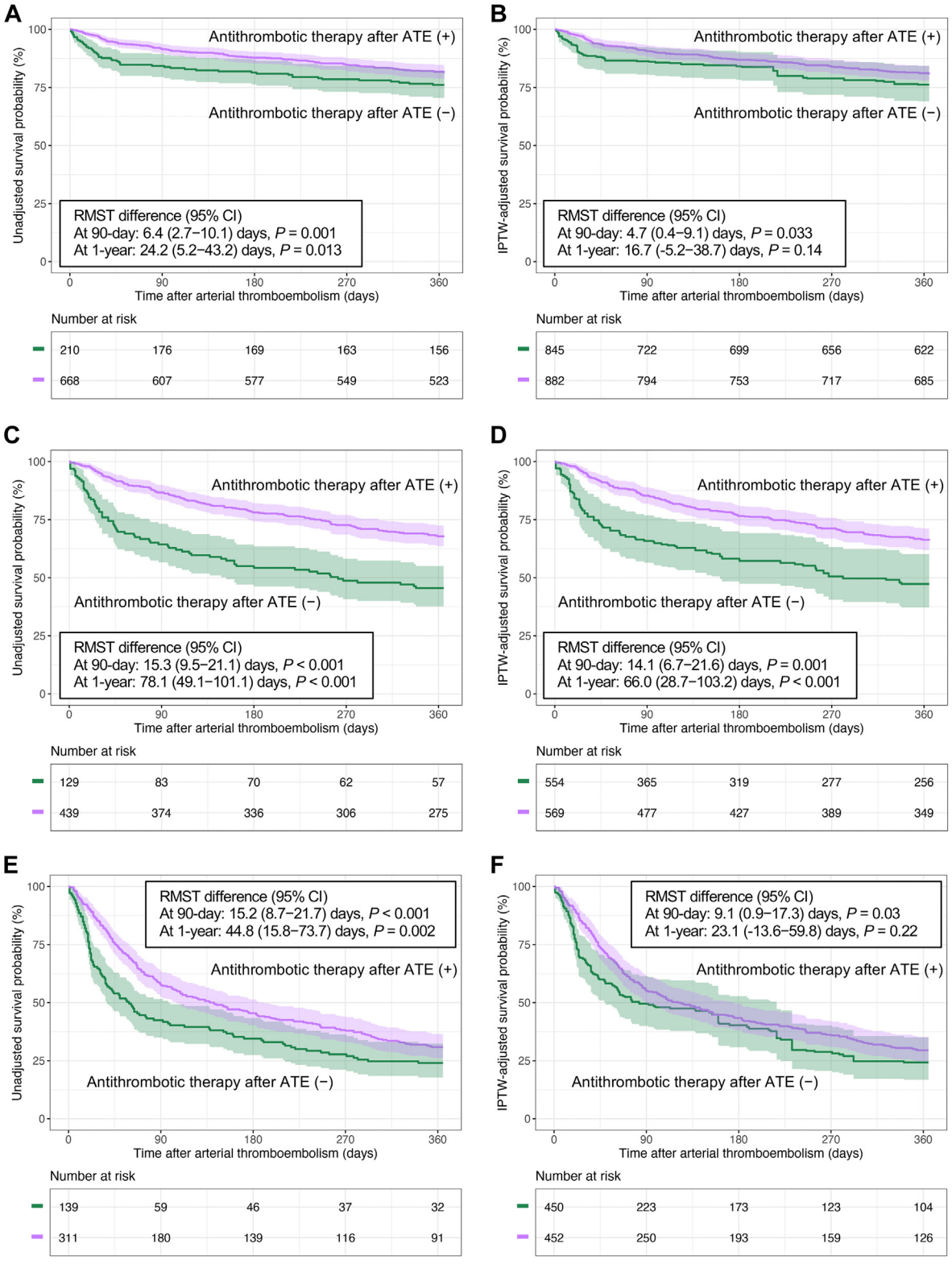
FIGURE 3 **Kaplan-Meier Curves After Arterial Thromboembolism in Solid Tumors and Hematologic Malignancies**



(A) Unadjusted and (B) inverse probability of treatment weighting (IPTW)-adjusted survival probabilities for patients with solid tumors. Adjustments were made for the following factors: age at cancer diagnosis, sex, body mass index, hypertension, dyslipidemia, diabetes mellitus, smoking, atrial fibrillation, heart failure, chronic obstructive pulmonary disease, chronic kidney disease, liver disease, previous arterial thromboembolism (ATE), previous venous thromboembolism (VTE), previous antiplatelet therapy, previous anticoagulant therapy, cancer type, cancer stage, cancer surgery, chemotherapy, and radiotherapy. (C) Unadjusted and (D) IPTW-adjusted survival probabilities for patients with hematologic malignancies. Adjustments were made for the following factors: age at cancer diagnosis, sex, body mass index, hypertension, dyslipidemia, diabetes mellitus, smoking, atrial fibrillation, heart failure, chronic obstructive pulmonary disease, chronic kidney disease, liver disease, previous ATE, previous VTE, previous antiplatelet therapy, previous anticoagulant therapy, cancer stage, cancer surgery, chemotherapy, and radiotherapy. There were significant differences between the groups for 90-day and 1-year restricted mean survival time (RMST) after ATE.

patients in the former group were younger and had a lower prevalence of vascular risk factors, such as hypertension, dyslipidemia, and diabetes mellitus. Hematologic abnormalities increased the risk for ATE in conditions such as multiple myeloma and acute leukemia.[24,25] Mutations associated with clonal hematopoiesis of indeterminate potential were associated with elevated cardiovascular events in patients with acute myeloid leukemia.[26] These findings emphasize the possible relationship between blood coagulation abnormalities and genetic mutations.

FIGURE 4 Kaplan-Meier Curves in Solid Cancer After Arterial Thromboembolism



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We found that ischemic stroke accounted for a substantial majority (71.6%) of ATE cases among patients with cancer (Supplemental Table 7, Supplemental Figure 1). The imbalanced proportion may be attributable in part to thrombosis associated with atrial fibrillation. Another noteworthy finding was the prevalence of ischemic stroke, myocardial infarction, and peripheral arterial disease in men, as well as in patients with advanced cancer and hematologic malignancies (Supplemental Tables 7 to 9). These findings suggest a common pathophysiology of these ATEs among patients with cancer. Currently, the pathophysiology of ATE in patients with cancer is unclear. Nevertheless, it is plausible that a combination of conventional vascular risk factors and coagulation abnormalities derived from cancer contributes to the development of ATEs. Further studies are needed to clarify the pathophysiological mechanisms underlying ATE among patients with cancer.

The survival analysis involving the 2,159 patients with ATE yielded 2 important findings. First, patients who did not receive antithrombotic drugs after ATE had a high mortality rate immediately after the events. This can be attributed to the high immediate recurrence of ATE,[27] resulting in a fatal outcome within a short period. However, it is important to acknowledge that our study had a retrospective design, and there is a possibility that antithrombotic drugs were not administered to patients with severe ATE who were expected to have a poorer prognosis. Second, patients who received antithrombotic therapy after ATE did not demonstrate a worse medium- to long-term prognosis than those who did not receive this therapy. Although there is ample evidence supporting the use of anticoagulation therapy in patients who develop VTE,[28,29] survival data for antithrombotic therapy after ATE are limited.

Given the high risk for bleeding events in patients with cancer, concerns arise regarding the potential increase in bleeding-related mortality and shortened survival associated with the use of antithrombotic agents.[30,31] The findings of the present study provide valuable insights into the prescription of antithrombotic drugs after ATE. Our previous prospective multicenter observational study, the SCAN (Ischemic Stroke in Patients With Cancer and Neoplasia) study, was focused on 1-year outcomes in patients with acute stroke with active cancer.[32] The results showed that the use of antithrombotic drugs after ischemic stroke was associated with a lower recurrence rate of stroke and did not increase the risk for bleeding complications.[32] Therefore, there appears to be a potential benefit in administering antithrombotic drugs after ATE in patients with cancer over the medium to long term.

When examining the types of antithrombotic drugs, patients receiving antiplatelet agents exhibited a better prognosis than those who receiving other drugs (Supplemental Figures 4 and 5). Given the retrospective nature of this observational study, determining the appropriateness of specific therapeutic drugs proved challenging. Further studies are necessary to evaluate the optimal antithrombotic agents, ATE recurrence, and major bleeding, to provide a more comprehensive understanding of this topic.

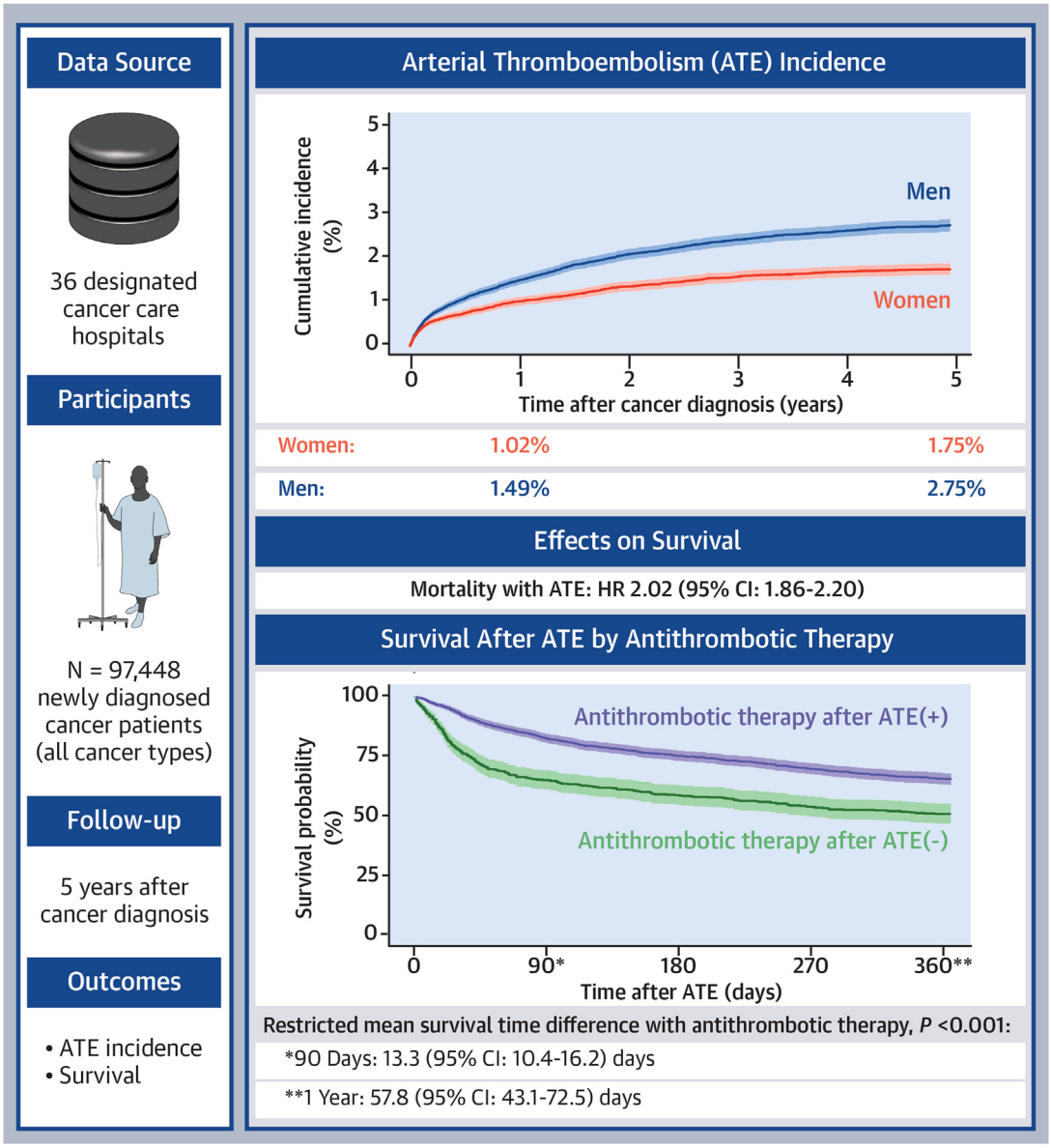
Notably, the ATE incidence varied on the basis of cancer type and the number of years after cancer diagnosis. For example, pancreatic cancer was associated with a higher incidence of ATE shortly after cancer diagnosis, with a relatively low increase over 3 years. This might be attributable to the elevated short-term risk for ATE associated with pancreatic cancer[10] coupled with its high mortality rate, resulting in relatively small long-term increases in ATE incidence. In contrast, prostate cancer demonstrated fewer ATE events early after diagnosis, but the incidence significantly increased over 3 years. Notably, patients with prostate cancer faced an elevated risk for ATE 4 years after cancer diagnosis.[33] This heightened risk may be linked to metabolic syndrome–related side effects of hormone therapy used in prostate cancer treatment, potentially associated with an increased cardiovascular risk.[34]

In this study, the use of antithrombotic medications before ATE was associated with an increased

FIGURE 4 Continued

(A) Unadjusted and (B) IPTW-adjusted survival probabilities for patients with localized cancer. (C) Unadjusted and (D) IPTW-adjusted survival probabilities for patients with regional cancer. (E) Unadjusted and (F) IPTW-adjusted survival probabilities for patients with distant cancer. Adjustments were made for the following factors: age at cancer diagnosis, sex, body mass index, hypertension, dyslipidemia, diabetes mellitus, smoking, atrial fibrillation, heart failure, chronic obstructive pulmonary disease, chronic kidney disease, liver disease, previous ATE, previous VTE, previous antiplatelet therapy, previous anticoagulant therapy, cancer surgery, chemotherapy, and radiotherapy. In the unadjusted survival analysis, significant differences were observed between the groups for 90-day and 1-year RMST after ATE. Following IPTW adjustment, significant differences were observed for 90-day RMST for all cancer stages. Regarding 1-year RMST, significant differences were observed in patients with regional cancer but not in those with localized or distant metastatic cancer. Notably, survival was better in the antithrombotic therapy group than that in the non-antithrombotic therapy group across all cancer stages. Abbreviations as in **Figure 3**.

CENTRAL ILLUSTRATION **Incidence and Survival Impact of Arterial Thromboembolism in Patients With Cancer**



Gon Y, et al. J Am Coll Cardiol CardioOnc. 2024;6(2):283-297.

Arterial thromboembolism (ATE) incidence among patients with cancer differed significantly by sex. Patients with ATE had a 2-fold increased risk for mortality compared with those without ATE, after accounting for potential confounding factors. In the subgroup analysis of individuals who experienced ATE, patients who received antithrombotic therapy after ATE had a better prognosis than those who did not receive this therapy.

risk for both ATE and mortality, even after adjusting for confounding factors. This correlation aligns with findings from a recent Danish cohort, in which patients receiving systemic anticoagulation therapy before ATE had an increased risk for developing ATE compared with those without this therapy (HR: 1.23; 95% CI: 1.11-1.36).[8] This observed association might have been attributed to the presence of comorbidities

that necessitated the prescription of antithrombotic drugs before ATE. In other words, the use of antithrombotic medications before ATE did not inherently increase the risk for ATE; rather, the increased risk was linked to the underlying comorbidities that necessitated their use. This issue was also emphasized by Feldman et al.[11] The finding that antithrombotic medication before ATE was associated with an increased mortality risk may appear contradictory to the favorable outcome associated with antithrombotic therapy after ATE. The contrast is likely explained by the difference between antithrombotic agents used for thromboprophylaxis and those prescribed for acute ATE treatment.

Chemotherapy did not show an increased risk for ATE compared with no chemotherapy in our analysis. This finding aligns with the results of the previous study, which indicated that anticancer agents did not elevate the risk for ischemic stroke occurrence.[35] As discussed in that study, the association is likely more related to patients undergoing anticancer treatment having advanced cancer stages, potentially contributing to an increased risk for thromboembolic events. However, it should be noted that some anticancer agents have vascular toxicity.[36] In the study by Mulder et al,[8] chemotherapy was associated with an elevated ATE risk. Further research is warranted to determine the potential contribution of anticancer agents to the risk for ATE.

STUDY LIMITATIONS. This study's strength lies in its extensive investigation of ATE incidence in patients with cancer over a 5-year period using OCR data in Japan. However, several limitations merit consideration. First, this study obtained information on ATE events from administrative data in designated cancer care hospitals. Data were not collected for cases in which patients were not admitted to a designated cancer care hospital, potentially resulting in uncollected event data. Second, despite validating the disease codes, there remains a possibility of misclassification. Third, we did not investigate ATE recurrence or major hemorrhagic complications. Fourth, in our study, information about death was recorded, and the specific causes of death remain unidentified. Fifth, we performed survival analysis after ATE, incorporating IPTW for antithrombotic therapy. However, certain clinical variables, such as atrial fibrillation in the patients with hematologic malignancies, remained imbalanced. This imbalance may be attributed to substantial variability in background characteristics among patients with hematologic malignancies. It is important to consider this aspect when interpreting the results of our study. Finally, differences in antithrombotic therapy practices between Japan and Western countries should be acknowledged. For example, regarding ischemic stroke, the most common subtype of ATE in this study, dual antiplatelet therapy (aspirin and dipyridamole), is recommended for secondary prevention in Western countries,[14] but the effectiveness of this therapy has not been demonstrated in the Japanese population.[37] Therefore, it is crucial to recognize the existing differences in antithrombotic therapy approaches.

CONCLUSIONS

The incidence of ATE in the Asian population in this study aligns with findings from previous studies. The risk for ATE varies considerably on the basis of sex, age at cancer diagnosis, cancer progression, and cancer type. Of note is the higher incidence of ATE associated with hematologic malignancies compared with solid tumors, despite fewer classical vascular risk factors in the former. Patients who received antithrombotic therapy after ATE demonstrated better survival than those who did not. This suggests that concerns about using antithrombotic agents after ATE to avoid bleeding complications among patients with cancer may be unnecessary. These findings provide valuable insights into the understanding of ATE among patients with cancer and may carry implications for their management and care.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The incidence of ATE was greatest immediately after cancer diagnosis, being most frequently observed in men and in patients with advanced age, advanced cancer stages, and hematologic malignancies. Patients with ATE experienced a 2-fold increased risk for mortality compared with those without ATE. Patients who received antithrombotic therapy after ATE had a better prognosis than those who did not.

TRANSLATIONAL OUTLOOK: The improved survival observed in patients with cancer suggests a potential benefit in administering antithrombotic drugs after ATE in patients with cancer over the medium to long term. Further research is needed to assess the therapeutic utility of antithrombotic agents in patients with cancer who experience ATE, focusing on aspects such as ATE recurrence and bleeding complications.

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KEY WORDS advanced age, antithrombotic therapy, hematologic malignancies, Kaplan-Meier curve, risk

APPENDIX For supplemental tables and figures, please see the online version of this paper.