Cancer-related thrombosis: impact of biological sex on the risk of rethrombosis and bleeding

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Abstract

Patients with cancer have a higher risk of re-thrombosis and bleeding secondary to anticoagulant treatment than have individuals without cancer. Given the lack of specific clinical trials, the decision regarding the optimal duration of treatment must consider multiple factors, including sex. The current study used data from the international, prospective TESEO Registry that includes consecutive patients diagnosed with cancer-associated thrombosis. Between July 2018 and December 2022, 2,823 patients were included in the TESEO Registry, 1,351 (48%) of whom were female. The most common venous thromboembolic event (VTE) in both sexes was pulmonary embolism, with an incidence of 58.0% among men and 54.3% in women (*P*=0.045). After a median follow-up of 6.9 months (interquartile range, 1.9-14.4), the re-thrombosis rate at the end of follow-up was 10.0% in males and 15.0% in females (*P*=0.14). The location of the primary tumor in the gastrointestinal tract was associated with a greater risk of re-thrombosis, whereas sex had no significant impact. Men had twice as many major bleeds. Additional risk factors for major bleeding included situations of risk due to tumor site or thrombocytopenia, as well as the presence of active tumor bleeding at the time of VTE diagnosis. Overall survival was longer among women. Given the higher incidence of major bleeding among men, sex should be deemed a relevant factor when deciding the duration of anticoagulant treatment in cancer patients.

Introduction

The interrelationship between cancer and venous thromboembolic events (VTE) stands out given its two-way nature, revealing a significant increase in the risk of thrombotic complications in cancer patients, which can be as much as nine times that of the general population.[1] The frequency of VTE among these patients is modulated by a series

of factors that include the type and stage of the cancer, the presence and extent of metastasis, the treatment received, as well as the specific demographic and clinical characteristics of the patient, such as age and existing comorbidities. Despite this, there is a paucity of information regarding the incidence of VTE broken down by sex among patients with cancer.

Individuals with cancer not only face an up to 3-fold risk of re-thrombosis compared to those without cancer, but also exhibit a greater risk of bleeding during anticoagulant treatment.[2] Clinical guidelines recommend maintaining anticoagulant therapy for at least 6 months, basing the decision to extend this period on an individualized assessment that considers the balance between the risk of re-thrombosis and that of bleeding for each person.[3-6] Some factors, such as the presence of an active tumor and ongoing oncological treatment, are acknowledged as increasing the risk of re-thrombosis, whereas the presence of renal failure, advanced age, thrombocytopenia, or certain tumor sites appear to elevate the risk of bleeding during anticoagulant therapy.

As for the influence of sex on the risk of re-thrombosis and bleeding, the data are contradictory. Studies in general populations reveal a greater risk of VTE recurrence in men *versus* women,[7-11] whereas several studies conducted in subjects with cancer have failed to detect significant differences in the incidence of thrombotic recurrence based on sex.[12-15] As for the risk of bleeding in anticoagulated cancer patients due to cancer-associated thrombosis, while some publications evidence no significant sex-related differences,[12,16] others suggest a higher incidence of bleeding among males.[13,17,18]

We have performed this study in an attempt to shed light on the impact of sex on the risk of re-thrombosis and bleeding in cancer patients, taking into account the possible influence of other factors, such as the primary tumor site and certain cancer treatments.

Methods

Study design

TESEO is an observational, non-intervention, prospective, longitudinal registry promoted by the Spanish Society of Medical Oncology (SEOM, for its acronym in Spanish), in which 52 Spanish and two Portuguese centers participate. This registry consecutively includes patients diagnosed with cancer-associated thrombosis, both incidental and symptomatic, confirmed by imaging studies (Doppler ultrasound, computed tomography angiography scans, scheduled computed tomography to assess tumor response, etc.). The participants are followed up until their demise. Subjects with superficial venous thrombosis, as well as those in whom the VTE appears more than 1 month prior to the diagnosis of cancer or more than 1 month after concluding adjuvant cancer treatment are excluded.[19,20]

The study was conducted in compliance with current safety legislation established in Spanish Organic Law 3/2018 and EU Regulation 2016/679 of the European Parliament and of the Council on the Protection of Personal Data. It was approved by the Research Ethics Committees of all the autonomous communities and participating centers, and it was classified as a prospective, post-marketing surveillance study by the Spanish Agency of Drugs and Medical Devices (*Agencia Española de Medicamentos y Productos Sanitarios,* AEMPS). Written informed consent was obtained from all patients before their enrollment in the study.

Study objectives and variables

The main objective of the study was to evaluate the impact of sex on the incidence of re-thrombosis and major bleeding in the TESEO Registry population. Re-thrombosis was defined as the appearance of a second thrombotic event following proper management of the index VTE or progression of the previous episode despite appropriate anticoagulant therapy. Bleeding severity was graded as per the International Society of Thrombosis and Hemostasis (ISTH) criteria as minor, clinically relevant, or major.[21]

Secondary objectives included analyzing the type of VTE, the type of anticoagulant therapy administered, as well as survival and cause of death. Overall survival was defined as the time between the diagnosis of the VTE until the patient's demise from any cause.

Patients' demographic variables were collected (age, sex, comorbidity, etc.). Clinical and molecular characteristics of the neoplasms (such as the site of the primary tumor, stage, histological type, location of metastasis, bleeding risk) were recorded, along with the cancer treatment administered, the characteristics of the VTE and its treatment, as well as the evolution of the cancer-associated thrombosis (re-thrombosis, bleeding, and death).

Statistical analysis

The continuous variables are presented as medians and interquartile ranges (IQR), while the categorical variables are expressed as absolute and relative frequencies. The statistical comparisons were performed by means of the χ^2 test (or Fisher exact test when needed) for the categorical variables and the Welch two-sample *t* test for continuous variables.

We used Fine-Gray proportional subdistributions hazards models to identify predictors of re-thrombosis and major bleeding, both within 6 months after the initial VTE and throughout the follow-up, with death as a competing risk. Survival rates were calculated by means of the Kaplan-Meier estimator. Log-rank tests were applied to compare survival rates based on sex and type of VTE.

All statistical analyses were performed with the R v4.3.2 software package. Statistically significant differences were considered to be present when the *P* value was <0.05.

Results

Demographic and clinical profiles of patients and characteristics of the venous thromboembolic events

Between July 2018 and December 2022, 2,866 patients were included in the TESEO Registry. Of them, 43 were excluded from analysis because of the lack of essential clinical information in the database. Finally, 2,823 subjects were considered for this analysis, of whom 1,351 (48%) were women. The most common tumor sites among females were breast (20.9%), lung (16.5%), and colorectal (16.5%), whereas the leading tumor locations in males were lung (27.6%), colorectal (21.7%), and pancreatic-biliary (12.7%). Table 1 illustrates that arterial hypertension, dyslipidemia,

Table 1. Clinical characteristics of the patients and risk factors for venous thromboembolic events.

Characteristics	Overall N=2,823	Male N=1,472	Female N=1,351	*P**
Age in years, mean ± SD	64.9±11.4	65.2±10.9	64.6±11.8	0.139
Race, N (%) Caucasian Other	 2,768 (98.1) 55 (1.9)	 1,446 (98.2) 26 (1.8)	 1,322 (97.9) 29 (2.1)	 0.266
Chronic arterial hypertension, N (%)	1,192 (42.3)	652 (44.4)	540 (40.0)	0.018
Dyslipidemia, N (%)	1,015 (36.0)	561 (38.2)	454 (33.6)	0.011
Body mass index >30, N (%)	586 (21.2)	260 (18.1)	326 (24.5)	<0.001
Performance status, ECOG score, N (%) 0-1 ≥ 2	 2,043 (72.4) 780 (27.6)	 1,092 (74.2) 380 (25.8)	 951 (70.4) 400 (29.6)	0.024
Smoking status, N (%) Active smoker Ex-smoker Never smoker	 448 (17.2) 1,095 (41.9) 1,068 (40.9)	 273 (19.9) 777 (56.7) 321 (23.4)	 175 (14.1) 318 (25.6) 747 (60.2)	<0.001
History of inherited thrombophilia, N (%)	15 (0.5)	4 (0.3)	11 (0.8)	0.048
Immobilization, N (%)	211 (7.6)	122 (8.3)	141 (10.4)	0.052
Central venous catheter, N (%)	673 (24.0)	312 (21.4)	361 (27.0)	<0.001
Previous VTE, N (%)	211 (7.6)	110 (7,6)	101 (7.6)	0.98
TNM stage, N (%) I II III IV	 79 (2.8) 200 (7.1) 534 (18.9) 2,010 (71.2)	 28 (1.9) 84 (5.7) 269 (18.3) 1,091 (74.1)	 51 (3.8) 116 (8.6) 265 (19.6) 919 (68.0)	<0.001
Primary tumor location, N (%) Lung Colorectal Pancreas and bile duct Breast Gynecological Bladder Central nervous system Prostate Head and neck Esophagus/stomach Kidney Melanoma Testicular Hematologic Other	 629 (22.3) 543 (19.2) 358 (12.6) 291 (10.3) 200 (7.1) 103 (3.6) 73 (2.6) 62 (2.2) 59 (2.1) 49 (1.7) 47 (1.7) 23 (0.8) 21 (0.7) 18 (0.6) 349 (12.4)	 406 (27.6) 320 (21.7) 187 (12.7) 9 (0.6) - 81 (5.5) 50 (3.4) 62 (4.2) 50 (3.4) 42 (2.9) 32 (2.2) 17 (1.2) 21 (1.4) 7 (0.5) 187 (12.7)	 223 (16.5) 223 (16.5) 169 (12.5) 282 (20.9) 200 (14.8) 22 (1.6) 23 (1.7) - 9 (0.7) 7 (0.5) 15 (1.1) 6 (0.4) - 11 (0.8) 161 (11.9)	 <0.001 <0.001 0.876 <0.001 - <0.001 <0.005 - <0.001 <0.001 0.027 <0.036 - 0.259 0.525
Recent major surgery (30 days), N (%)	63 (2.2)	26 (1.8)	37 (2.7)	0.081
Active tumor disease, N (%)	2,393 (84.8)	1,278 (86.8)	1,115 (82.5)	0.002
Prior anticoagulant therapy, N (%)	87 (3.1)	67 (4.5)	20 (1.5)	<0.001

*Welch two-sample *t* test; Pearson χ^2 test; Fisher exact test. SD: standard deviation: ECOG: Eastern Cooperative Oncology Group; VTE: venous thromboembolic event; TNM: tumor, node, metastasis.

and smoking were more prevalent among men, while women exhibited a higher incidence of obesity and worse functional status. The men had more advanced tumor stages and greater presence of active tumor at the time of diagnosis of the VTE compared to the women. No pregnancies were reported in the women at the time of VTE diagnosis. When diagnosed with VTE, 27.0% of the females had a central venous catheter VTE (71% Port-a-Cath, 28% peripherally inserted central catheter) compared to 21.4% of the males (66% Port-a-Cath, 32% peripherally inserted central catheter); this difference was statistically significant (*P*=0.003).

In both men and women, the most common VTE was pulmonary embolism (PE) (58.0% and 54.3%, respectively; *P*=0.045), followed by deep vein thrombosis (DVT) (37.9% *vs.* 40.6%; *P*=0.136), with more than 9% of the subjects presenting simultaneously with PE and DVT in both groups. No significant differences were found between sexes with respect to the incidence of splanchnic thrombosis; nevertheless, central catheter-associated thromboses were significantly more frequent in women (Table 2). PE severity, incidence of bilateral PE (46.5% and 49.2%, respectively; *P*=0.299), location (central: 31.3% *vs.* 32.4%; peripheral: 42.6% *vs.* 44.0%; both: 26.1% *vs.* 23.6%), and the presence of right ventricular dysfunction (9.1% compared to 10.6%; *P*=0.329) revealed no significant differences across the sexes. Almost half (47%) of the individuals with PE were incidental cases at the time of diagnosis, with no differences based on sex.

Most of VTE were treated with low molecular weight heparin both in the initial phase (first 5-10 days), 90% of the cases, as well as during maintenance (95%); again, with no differences noted based on sex. Only 55 patients received long-term treatment with direct oral anticoagulants and a mere 14 were treated with vitamin K antagonists (Table 3). The choice of antithrombotic therapy was uninfluenced by the person's sex. The median duration of anticoagulant treatment was 5.0 months in men (IQR, 1.5-11.0) and 5.6 months in women (IQR, 1.8-11.7).

Analysis of re-thrombosis and bleeding

With a median follow-up of 6.1 months (IQR, 1.8-14.3) among males and 7.4 months (IQR, 2.1-16.7) among women, the incidence of re-thrombosis was 6.5% (7.1% in men and 5.8% in women; *P*=0.178). As evidenced in Table 4, no significant differences were observed in the cumulative incidence of re-thrombosis between men and women. Of the 103 men with re-thrombosis, 51 (49.5%) had PE (with 3 cases of simultaneous DVT), compared to 32 of the 78 women (41.0%); this difference failed to achieve statistical significance (*P*=0.256). DVT was the second most frequent location of recurrence (28.1% in males *vs.* 32.1% in women; *P*=0.571), followed by splanchnic thrombosis (8.7% *vs.* 11.5%; *P*=0.533) and catheter-associated thrombosis (6.8% *vs.* 7.7%; *P*=0.817). Of the 181 re-thromboses, most occurred in subjects with digestive tumors (36 colorectal, 3 esophageal, 11 gastric, and 37 biliary/pancreatic), followed by lung carcinoma (40 cases) and breast cancer (18 cases). Eighty percent of the re-thromboses (N=145) occurred in subjects with adenocarcinomas in contrast to 6.6% in those with squamous cell carcinoma, and 2.2% in patients with small cell carcinoma. Forty-one percent of the cases (N=74) had discontinued anticoagulant therapy prior to re-thrombosis for different reasons, including the end of scheduled treatment (N=36), bleeding (N=10), patients' decision (N=9), palliative management (N=6), and other reasons (N=13).

The univariate analysis evidenced that being <70 years of age increased the risk of re-thrombosis by 6 months after VTE diagnosis. When evaluating the risk of re-thrombosis at the end of follow-up, primary tumor location in the digestive tract was identified as the only independent risk factor (subdistribution hazard ratio [HR]=1.87; 95% confidence interval [CI]: 1.21-2.89), whereas sex did not have a significant impact on this risk (*Online Supplementary Table S1*).

As shown in Table 4, the incidence of any kind of bleeding and the incidence of major bleeding were significantly higher in males. The adjusted multivariate analysis (*On-*

Table 2. Type of thrombotic event by sex.

Type of event	Overall N=2,823	Male N=1,472	Female N=1,351	*P**
Type of VTE, N (%)				
PE	1,588 (56.2)	855 (58.0)	733 (54.3)	0.045
DVT	1,107 (39.2)	558 (37.9)	549 (40.6)	0.136
DVT and/ or PE	2,433 (86.2)	1,272 (86.4)	1,161 (85.9)	0.714
Simultaneous PE + DVT	262 (9.3)	141 (9.5)	121 (8.9)	0.573
Splanchnic thrombosis	207 (7.3)	125 (8.5)	82 (6.1)	0.343
Catheter-associated thrombosis	277 (9.8)	121 (8.2)	156 (11.7)	0.003
VTE diagnostic type, N (%)				0.143
Unsuspected/incidental	1,380 (48.9)	739 (50.2)	641 (47.5)	
Suspected	1,441 (51.1)	732 (49.8)	709 (52.5)	

*Welch two-sample *t* test; Pearson χ^2 test; Fisher exact test. VTE: venous thromboembolic event; PE: pulmonary embolism; DVT: deep vein thrombosis.

line Supplementary Table S2) evidenced that being male doubled the risk of major bleeding at the end follow-up (subdistribution HR=2.34; 95% CI: 1.36-4.04; *P*=0.002), but not at 6 months of VTE diagnosis (subdistribution HR=1.85; 95% CI: 0.87-3.94; *P*=0.11). Other factors associated with higher risk of major bleeding at the end of follow-up were the presence of a situation of risk for bleeding (due to tumor location and/or presence of thrombocytopenia)

Table 3. Anticoagulant therapy by sex.

Anticoagulant therapy	Male N=1,472	Female N=1,351
Initial therapy, N (%)		
Low-molecular weight heparin	1,324 (89.9)	1,216 (90.0)
Unfractionated heparin	90 (6.1)	83 (6.1)
Direct oral anticoagulant	13 (0.9	19 (1.4)
No therapy	43 (2.9)	31 (2.3)
Unknown	2 (0.1)	2 (0.2)
Long-term therapy, N (%)		
Low-molecular weight heparin	1,392 (94.5)	1,284 (95.0)
Direct oral anticoagulant	26 (1.8)	29 (2.3)
Vitamin K antagonist	9 (0.6)	5 (0.3)
No therapy	43 (3.0)	31 (2.3)
Unknown	2 (0.1)	2 (0.1)
Duration of anticoagulation in months		
Mean ± SD	8.0 ± 9.0	8.8 ± 9.7
Median (IQR)	5.0 (1.5-11.0)	5.6 (1.9-11.7)
Anticoagulation discontinuation, N (%)	293 (20.5)	288 (21.9)
Causes of discontinuation, N (%)		
Treatment complete	123 (42.0)	157 (54.5)
Patient's decision	14 (4.8)	14 (4.9)
Bleeding	58 (19.8)	31 (10.8)
Other complications	13 (4.4)	15 (5.2)
Palliative care	67 (22.9)	51 (17.7)
Other	18 (6.1)	20 (6.9)

SD: standard deviation; IQR: interquartile range.

Table 4. Clinical outcome by sex.

Clinical outcome	Male N=1,472	Female N=1,351	*P**
Recurrent VTE, % (95% CI)			0.14
Cumulative incidence at 6 months	4.5 (3.5-5.7)	2.8 (2.0-3.9)	
Cumulative incidence at 12 months	6.7 (5.4-8.2)	4.9 (3.8-6.3)	
Cumulative incidence at the end of follow up	10.0 (8.1-12.0)	15.0 (4.8-32.0)	
Any bleeding, % (95% CI)			0.009
Cumulative incidence at 6 months	9.7 (8.2-11.0)	7.3 (5.9-8.8)	
Cumulative incidence at 12 months	12.0 (9.9-13.0)	8.8 (7.2-10.0)	
Cumulative incidence at the end of follow up	15.0 (13.0-17.0)	12.0 (9.3-15.0)	
Major bleeding, % (95% CI)			0.026
Cumulative incidence at 6 months	1.8 (1.2-2.7)	0.7 (0.3-1.3)	
Cumulative incidence at 12 months	2.7 (1.9-3.7)	1.4 (0.8-2.2)	
Cumulative incidence at the end of follow up	12.0 (4.8.23.0)	6.0 (3.2-9.9)	
Death, N (%)	805 (55.2)	691 (51.5)	0.046
Cause of death, N (%)			0.971
Cancer	612 (76.0)	527 (76.3)	
Mixed causes, VTE probably involved	98 (12.1)	80 (11.6)	
Infection	40 (5.0)	36 (5.2)	
VTE	12 (1.5)	12 (1.7)	
Fatal bleeding	11 (1.4)	13 (1.9)	
Other, VTE probably not involved	32 (4.0)	23 (3.3)	

*Gray test; Pearson χ^2 test. VTE: venous thromboembolic event; 95% CI: 95% confidence interval.

and the existence of tumor bleeding at the time of VTE diagnosis (*Online Supplementary Table S2*). Tumor stage, age, thrombocytopenia, use of anti-angiogenic therapies, and glomerular filtration rate <60 mL/min (none of the 31 patients with glomerular filtration <30 mL/min had major bleeding) did not increase the risk of major bleeding (*Online Supplementary Table S2*). Of the 77 individuals with major bleeding, most had digestive tumors (17 colorectal, 4 esophageal, 6 gastric, 7 biliary/ pancreatic, and 2 gastrointestinal stromal tumors), followed by carcinoma of the breast (11 cases), lung (9 cases), and urological tumors (5 cases). The location of the primary tumor in the breast was also associated with a higher risk of major bleeding at the end of follow-up in the multivariate analysis (subdistribution HR=2.75; 95% CI: 1.18-6.38; *P*=0.019). No significant differences were noted (*P*=0.563) regarding the median number of days between VTE diagnosis and bleeding among males (53 days; IQR, 18.0-163.5) or women (72 days; IQR, 16.8-175.5). There were 13 cases of fatal bleeding among the women, mostly in patients with colorectal (N=4), pulmonary (N=2), and ovarian (N=2) carcinoma, and 11 cases among men, predominantly in those with digestive (N=4), pulmonary (N=2), and urological (N=2) tumors.

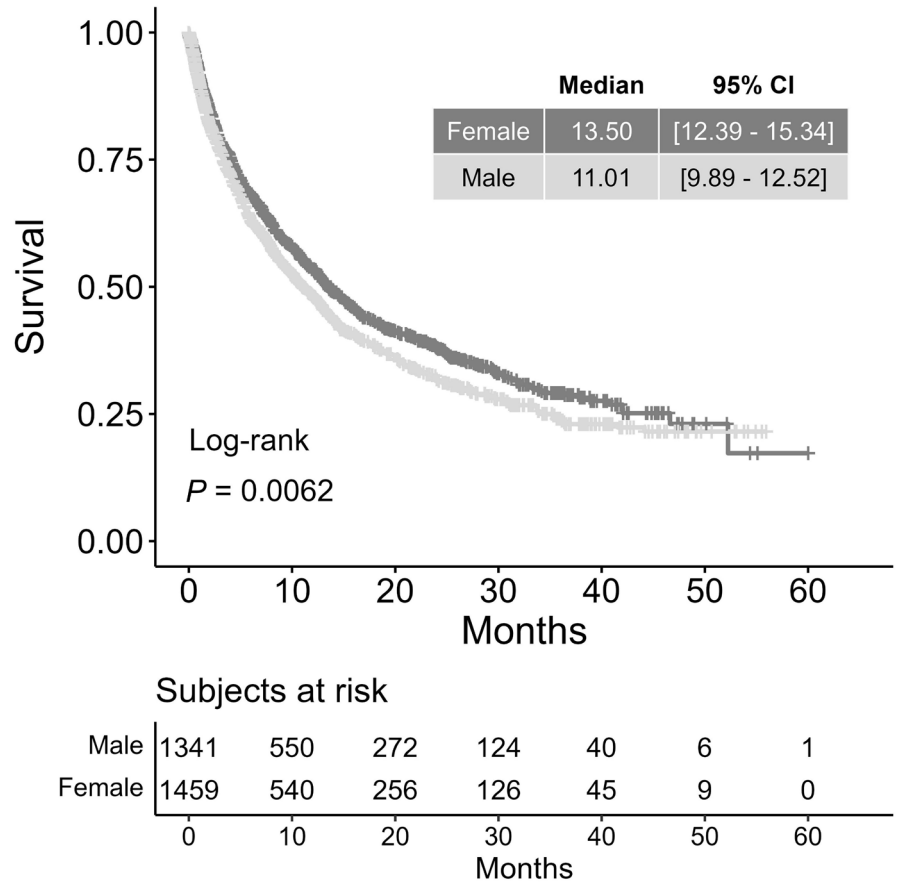

Figure 1. Survival by sex. 95% CI: 95% confidence interval.

Analysis of survival

At the time of analysis, mortality was slightly greater among males than females, with 55.2% and 51.5% of the participants having died, respectively. The median overall survival was 11.0 months for men (95% CI: 9.9-12.5) in contrast to 13.5 months for women (95% CI: 12.4-15.3), revealing a significant advantage for females (*P*=0.0062) (Figure 1). The leading cause of death was tumor progression, present in 76% of all cases, with no differences across sexes (Table 4). Survival was greater in patients who developed catheter-associated thrombosis with respect to other forms of VTE, in both sexes (Figure 2).

Discussion

The association between thrombosis and cancer has been widely acknowledged and, while more clinical trials are being conducted that evaluate anticoagulant treatments in this population in particular, the optimal duration of anticoagulant therapy in the oncological patient has yet to be fully elucidated. This dilemma is due to the more than well-known increased risk of re-thrombosis in these patients, together with an added bleeding risk attributable to the tumors and cancer treatments.

In this context, evidence from real-life data in ample populations and, in particular, prospective series, has begun to play a critical role with the real-world evidence emerging as a possible answer to the questions as yet unresolved by clinical trials. In fact, international regulatory agencies are beginning to use this real-world evidence for various purposes.

In recent years, several real-life registries of patients with thrombosis have been consolidated, notably the RIETE (the Spanish acronym for the Computerized Registry of Thrombo-Embolic Disease), an international registry that collects consecutive cases of acute VTE. Although the RIETE covers a broader population, it includes an important segment of oncological patients that has yielded interesting information concerning the evolution of cancer-associated thrombosis. Several of the RIETE publications have examined the impact of sex on re-thrombosis and bleeding, focusing exclusively on subjects with symptomatic PE and DVT.[12,13,22] In contrast, the TESEO Registry covers any type of VTE, including incidental and symptomatic events, in patients with cancer.

Our findings failed to reveal sizable differences in the incidence of DVT as the first event based on sex, although it did show a slightly higher incidence of PE among males. Nonetheless, the incidence of central catheter-associated thrombosis was significantly greater in women, possible given that these devices are used more in this sex. Although women with breast cancer have typically exhibited a low risk of thrombosis, the surge in the use of catheters in this group has brought with it more VTE in recent years. Of the 277 catheter-associated thromboses, 26.0% (N=72) occurred in patients with colorectal carcinoma, with breast cancer (22.4%, N=62) being the second tumor most frequently associated with this kind of VTE.

Some studies indicate that PE may be more serious in women than in men, with a higher incidence of centrally located embolisms, massive PE, and secondary right ven-

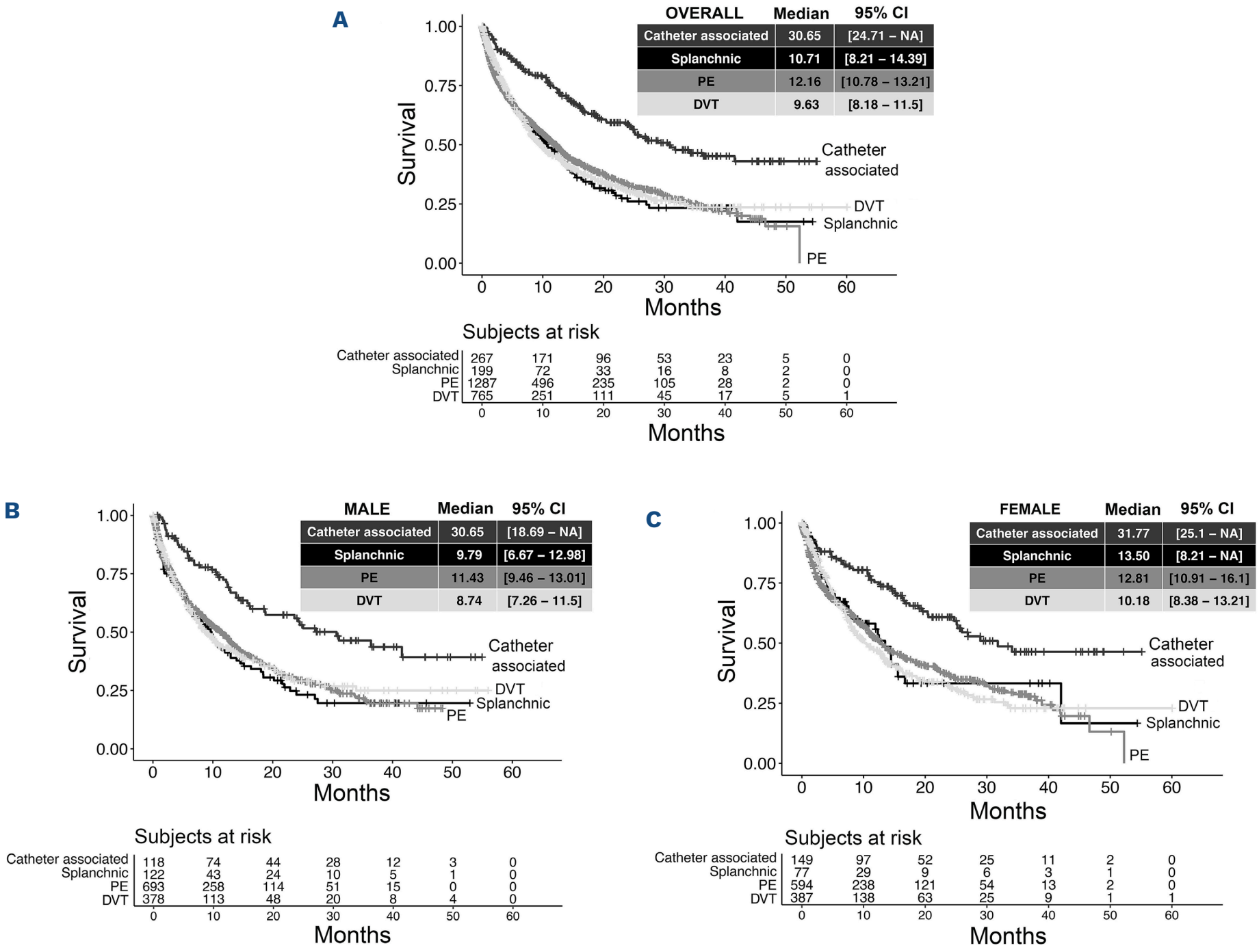

Figure 2. Survival by type of venous thromboembolic event. (A) Kaplan-Meier curve comparing survival from time of cancer diagnosis to demise according to type of venous thromboembolic event (VTE) (all patients, excluding patients with simultaneous VTE). (B) Kaplan-Meier curve comparing survival from time of cancer diagnosis to demise according to type of VTE (male, excluding patients with simultaneous VTE). (C) Kaplan-Meier curve comparing survival from time of cancer diagnosis to demise according to type of VTE (female, excluding patients with simultaneous VTE). 95% CI: 95% confidence interval; NA: not available; PE: pulmonary embolism; DVT: deep vein thrombosis.

tricle dysfunction.[13,23,24] These findings were not confirmed by our study in which we found no significant differences in terms of the extension of the PE, presence of symptoms, or cardiac dysfunction.

Several studies in populations that are not exclusively oncological have identified a higher risk of re-thrombosis among males with respect to women, although the specific causes of this difference are complex and probably multifactorial.[7-11] It has been suggested that a significant proportion of initial VTE in females develop in relation to exposure to hormonal factors and that the risk of recurrence decreases when these factors are eliminated, such as when contraceptive treatments are discontinued. In our study, no association was found between sex and the risk of re-thrombosis. Research carried out in the cancer population has also detected that the risk of recurrence does not vary significantly according to sex.[12,13,15] Nevertheless, it did confirm that the presence of digestive primary tumors markedly increments the risk of re-thrombosis. This endorses earlier studies concerning the higher incidence of VTE recurrence in individuals with gastrointestinal tumors than in those with primary tumors in other sites.[14,25] Unlike other studies, our analysis did not detect a significant difference in the risk of re-thrombosis depending on the tumor stage,[14,15,26] or between incidental and suspected thrombotic events, with 7% of recurrences in the former compared to 6% in the latter.[15,27] The absence of an increased risk of re-thrombosis in patients with stage IV

disease in our univariate and multivariate analyses may be due to the adjustment for death as a competing risk in the Fine-Gray model. By accounting for death as a competing event, the association between stage IV disease and re-thrombosis may be attenuated. However, when we applied the Cox proportional hazards model, which does not consider competing risks, stage IV disease was associated with a higher risk of re-thrombosis (*Online Supplementary Table S3*)

Our study stands out in that it reveals a greater incidence of bleeding in men than in women, a finding that diverges from that of some studies performed in non-exclusively oncological populations that point toward a higher risk of bleeding among females during anticoagulant therapy.[28-30] Nevertheless, research focused on cancer patients reflects results similar to ours.[13,17,31] In the general population, uterine bleeding, common in women of reproductive age, is a typical cause of bleeding.[32,33] Nonetheless, it is important to bear in mind that, in subjects with cancer, most VTE in females are diagnosed in menopause, whether physiological (78% of women in our series were more than 55 years of age) or induced by cancer treatments. Martin-Martos *et al.* observed a lower risk of fatal bleeding in women with cancer than in men included in the RIETE (relative risk=0.69; 95% CI: 0.47-0.99), as well as a trend toward a lower incidence of major bleeding that failed to achieve statistical significance.[13] A specific sub-analysis within the TICAT study of patients treated with low molecular weight heparin for at least 12 months demonstrated a greater risk of clinically relevant bleeding in males (HR=2.97; 95% CI: 1.01-8.1).[17] In contrast, in individuals who were anticoagulated for reasons other than VTE, Raposeiras *et al*. found a lower incidence of bleeding in women and a higher incidence of bleeding in individuals with active cancer in a population of more than 1,100 cancer patients anticoagulated due to atrial fibrillation.[31]

In our series, more than 90% of the subjects were treated with low molecular weight heparin both during the initial phase, as well as during maintenance, an approach that differs from that observed in RIETE studies, in which a considerable proportion of cases (40% of patients in the study by Martin Martos *et al.*[13]) received treatment with antivitamin K, probably because recruitment for the said registry began in 2001. The limited use of direct oral anticoagulants in our population is worthy of note and is attributable to the lack of financial coverage for this indication in Spain. Consequently, in light of the fact that direct oral anticoagulant and antivitamin K use was practically anecdotal in our study, the type of anticoagulant therapy was not included as a bleeding risk factor in the analysis. Apropos of bleeding risk by sex in patients with cancer receiving direct oral anticoagulants, Bosch *et al.* examined gastrointestinal bleeding risk factors in subjects with gastrointestinal tumors who received edoxaban in the Hokusai VTE Cancer study.[18] They found a higher proportion of males in the group with bleeding than in the control group (79% *vs.* 64%; *P*=0.27).

Our study demonstrates the evolution of a sizable cohort of subjects with cancer-associated thrombosis treated in daily clinical practice, outside the controlled conditions of a clinical trial. Be that as it may, it presents limitations inherent to observational studies. To begin with, as with other studies based on real-life registries, the incidence of VTE recurrence may be underestimated because of the lack of radiological testing to confirm VTE recurrences if the result will not entail a change in therapeutic attitude. Secondly, the impact of direct oral anticoagulants on the risk of recurrence or bleeding cannot be determined because of the paucity of patients who received them in our series. Third, subjects were classified according to their biological sex, without factoring in their sexual orientation. On the other hand, the representation of hematologic tumors is limited (only 18 cases), a reflection of the scant participation of hematologists in the registry. Despite these limitations, our research provides valuable insights into an area with little clinical evidence. It guides professionals regarding which patients might benefit from prolonged anticoagulation beyond 6 months, inasmuch as the mean duration of anticoagulant therapy in our study exceeded 8 months. Subjects with digestive or pulmonary tumors, and metastatic spread[14,15,25,26] are at greater risk of VTE recurrence, which suggests that they might be eligible to maintain anticoagulation, as long as the risk of bleeding is carefully considered. This risk appears to be greater in individuals with tumors who had already exhibited bleeding at the time of VTE diagnosis, in those with tumors at high risk of bleeding given their location (infiltration of digestive, bronchial, or vesical mucosa) or in the presence of thrombocytopenia, and in males. It is worth noting a higher than expected incidence of major bleeding in women with breast cancer in our study, indicating that the benefit of maintaining prolonged anticoagulation may be lower in this group.

In short, given the absence of clinical trials to inform decision-making, the decision as to whether to extend anticoagulation or not must be made on a case-by-case basis, bearing in mind all the possible factors that increase the risk of re-thrombosis and bleeding, including biological sex as one such relevant factor.

Disclosures

No conflicts of interest to disclose.

Contributions

SGA conceptualized the study, interpreted the data and wrote the manuscript. AJMM, PJF, AC-B, EMdC, PPS and JML designed the study, contributed essential material and revised the manuscript. FN analyzed results and created figures. All authors contributed essential material and approved the final manuscript.

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Data-sharing statement

Data are available upon request to the corresponding author.

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