

Cancer-associated venous thromboembolism and its impact on survival in the ONCOTHROMB12-01 cohort study

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ABSTRACT

Cancer patients are at increased risk of venous thromboembolism (VTE), representing one of the main causes of death. In this paper, we used the ONCOTHROMB12-01 study cohort for the analysis of 18-month overall survival (OS) and cancer-associated venous thrombosis (CAT) cumulative incidence. The OS is described for patients with and without CAT across age, sex, cancer type, stage and presence of recurrent VTE using the Kaplan-Meier method and log-rank test. Moreover, a Cox regression model with stepwise feature selection is trained to identify predictors of prognosis. Results show an 18-month CAT cumulative incidence of 16.5 % (CI 13.1–21.0 %) and a median OS for patients with CAT of 9.1 months (CI 5.9–12.5). Furthermore, CAT is associated with shorter survival in lung, colorectal and pancreatic cancer in advanced stages, regardless of age and sex; VTE recurrence also reduces survival significantly. The model found ECOG performance status of 2, cancer type, metastatic stage, VTE, mucinous histology and complete tumor resection as meaningful predictors; the latter being the only protective factor. In conclusion, the diagnosis of CAT has a profound impact on OS in the ONCOTHROMB12-01 study regardless of the clinical characteristics of patients.

1. Introduction

Cancer is one of the most concerning global health problems, affecting 20 million people and causing 9.7 million deaths in 2022 [1]. Similarly, venous thromboembolism (VTE), which manifests mainly as

deep vein thrombosis (DVT) or pulmonary thromboembolism (PE), is also a highly prevalent and potentially fatal disease [2]. For over a century, the connection between these two illnesses has been acknowledged, currently referred to as cancer-associated thrombosis (CAT), although the interplay between malignancy and hemostasis

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remains poorly understood [3]. In this paper, we use the abbreviation CAT to refer specifically to cancer-associated venous thrombosis. It is estimated that up to 20 % of VTE are associated with cancer [4] and cancer patients have a ninefold increased VTE risk when compared with the general population [5]. In fact, CAT is one of the main causes of death in oncology [6].

Several large studies have reported a negative impact of CAT on patient's survival. For example, the analysis of a large Danish population-based cohort showed that cancer patients with VTE presented decreased 1-year survival rate compared to cancer patients without VTE [7]. Also, patients with VTE had their short- and long-term survival reduced at various points in time along 5 years [8]. Similarly, data from the Californian Cancer Registry revealed that the diagnosis of VTE was a significant predictor of lower survival for the next 2 years across different cancer types in models adjusted by age, ethnicity and stage [9]. A long-term survival analysis from the case-control MEGA study revealed that patients with some type of malignancy and VTE had the highest risk of death [10]. In 2023, an analysis of a Scandinavian population-based cohort determined that cancer patients with VTE had an increased 3.4-fold risk of death compared to cancer patients without thrombosis and 25-fold risk compared to disease-free individuals [11].

A concerning fact is that CAT incidence is increasing over time—it has been found that individuals diagnosed with cancer between 2014 and 2017 were in higher risk of venous thrombosis than those between 2005 and 2007 [12]. Besides, the life expectancy of cancer patients has increased in recent decades, partly due to new anti-cancer therapies and early diagnosis [13]. Therefore, it is safe to assume that the burden of CAT will only become greater, especially for patients with good prognosis.

Most venous thrombosis research has traditionally concentrated on symptomatic DVTs and PEs. Although incidental VTEs and other thrombotic events—such as visceral, catheter-related and superficial vein thromboses—are relatively common in cancer patients [13], their impact on prognosis has been less thoroughly explored. Some studies hint at the significance of unprovoked VTEs, but sample size is limited [14,15], and evidence remains scarce. This highlights an overall gap in understanding the broader spectrum of VTE in oncology populations.

In the present article, we utilize the prospective, multi-centric ONCOTHROMB12-01 study cohort to explore how venous thrombosis affects overall survival, including a broader definition of venous thrombosis events as well as incidentally diagnosed thromboses, to provide a more complete picture of its prognostic implications.

2. Materials and methods

2.1. Study design and participants

The ONCOTHROMB12-01 study ([ClinicalTrial.gov](https://clinicaltrials.gov/ct2/show/study/NCT03114618) ID: NCT03114618) is an observational, prospective non interventional and multicenter cohort study conducted across 8 hospitals in Spain between March 2013 and November 2016 that recruited 416 pancreatic, esophagus, gastric, non-small cell lung (NSCLC) and colorectal cancer patients naïve for systemic chemotherapy that were going to receive treatment in an outpatient setting. All enrolled patients were required to sign off the informed consent and all their information was anonymized. The study protocol was approved by the participant hospitals' Ethics Committees. The follow-up period for the entire cohort was 18 months, with interim analysis at 6, 12, and 18 months. The inclusion and exclusion criteria are summarized in [Table S1](#). A total of 26 patients were excluded for the analysis due to the following reasons: (a) not eligible according to the inclusion/exclusion criteria ($n = 19$, 73 %); (b) premature discontinuation from study ($n = 2$, 7.7 %); (3) not enough data for analysis ($n = 5$, 19.3 %). Thus, the final database for survival analysis contains 390 patients.

2.2. Data collection and data set characteristics

At the baseline visit, demographic data, prior medical history—including arterial thromboembolism (ATE) and VTE—, family history of VTE and tumor-related data were recorded. A blood sample was taken for the testing of required lab parameters and genetic profiling.

Concomitant VTE episodes that led to the diagnosis of cancer or VTE identified by imaging while performing tumor staging were also recorded and considered as CAT. In our study we approached a wider definition for VTE events that included non-classic venous thrombosis events that were categorized into deep venous thrombosis (DVT), pulmonary thromboembolism (PE), catheter-related thrombosis (CRT), superficial venous thrombosis (SVT), and visceral thrombosis (VT). Additionally, both incidental and symptomatic VTEs are reported.

2.3. Data pre-processing

Features with little information (e.g. those with small variance or more than 50 % of missing data) were removed from the data set. Levels of categorical variables with few observations were grouped into a single level to reduce data sparsity and thus increase statistical power. Multiple Imputation by Chained Equations (MICE) was chosen as the best approach to deal with missing data, as supported by [16–19].

2.4. Data analysis

Kaplan-Meier method was applied to estimate survival functions and obtain median overall survival (OS) and 18-month OS rate. Differences in survival between patients' groups were tested with log-rank tests. Kaplan-Meier curves were plotted to depict 18-months OS and median OS.

Gray's test is used to estimate CAT cumulative incidence while accounting for the competing risks between death and CAT [20]. Importantly, CAT events that happened before cancer diagnosis were left out to properly estimate it.

Survival analysis was conducted for the outcome 'death'. Survival time was computed between the date of cancer diagnosis and the end-point date (considered as either death, patient's withdrawal from the study, lost to follow-up or last study visit). Patients who did not experience the outcome of interest were right-censored.

Cox Proportional Hazards (CPH) regression with stepwise feature selection was used to model time until event and, more importantly, find the most influential factors and quantify their individual effects as a hazard ratio (HR). Specifically, we considered that cause-specific hazard regression is better suited for such purpose than Fine-Gray sub-distribution hazard models in spite of the competing risks setting [21].

The whole data set is partitioned into training and test set using an 80/20 split, and 10-fold cross-validation is applied on the training set. In each fold, stepwise feature selection is applied during the model's fitting using the Akaike's Information Criterion (AIC). Furthermore, the number of times a variable is selected during cross-validation is recorded and the most frequent ones are used to train the final model. This model is evaluated in terms of concordance index (C-index) during cross-validation and on the test set.

Time-varying covariates were treated accordingly [16]. Plus, covariates with low variance, found to be multicollinear or affected by confounding effects were excluded after careful inspection. The proportional hazards assumption of all CPH models was tested by inspecting the correlation between the scaled Schoenfeld residuals and time. Covariates that violated this assumption were either included as stratification variables or removed altogether.

Additionally, a Lasso CPH model is trained following the same schema as described above to validate the final stepwise CPH model, given that Lasso regularization often results in more robust models. More detailed information can be found in [Supplementary Material \(Tables S6 and S7\)](#).

Fisher's exact tests were performed to find associations between categorical variables. Continuous variables were compared between groups using the *t*-test or Mann-Whitney-Wilcoxon test. A *p*-value < 0.05 was set as threshold for statistical significance and confidence intervals (CI) were calculated with a confidence level of 95 %. Finally, categorical variables are described in terms of absolute and relative frequencies, and continuous variables as their median and interquartile range.

2.5. Software used

All statistical analyses were done using R (version 4.4.1). Database management was done using the 'an9elproject' (version 0.9.0) and 'an9elversions' package (0.3.0). Imputation was done using the 'mice' package (version 3.16.0). Packages 'arsenal' (version 3.6.3) and 'ggstatsplot' (version 0.12.4) were used during exploratory data analysis. Log-rank tests, formatting of the dataset to fit time-varying covariates, CPH regression models and the test of proportional hazards assumption were done using the 'survival' package (version 3.5–3). Kaplan-Meier curves were plotted with 'survminer' (version 0.4.9) and 'ggfortify' (version 0.4.14). Stepwise feature selection CPH regression models were trained using the 'StepReg' package (version 1.4.4). Finally, the calculation of the VTE cumulative incidence was done using the package 'tidycmprsk' (version 1.0.0).

3. Results

3.1. Clinical data

Demographic and clinical characteristics of the cohort are shown in [Table 1](#). Briefly, patients had a median age of 64 years old (interquartile range [IQR] = [57–72]). Almost two thirds were male (65.6 %), and the rest were female (34.4 %). The predominant ethnicity was Caucasian (97 %). The most common type of cancer was colorectal (41 %); other types were non-small cell lung cancer (NSCLC) (21.5 %), pancreatic (18.5 %), gastric (14.1 %) and esophageal (3.6 %) cancer.

Among all these variables, ECOG performance status, personal history of VTE, cancer type, stage, having had the tumor surgically removed and implantation of a central venous catheter (CVC) are significantly associated with CAT. Within the group of patients under antiaggregant treatment at the beginning of the study, we observe a lower proportion of patients that developed VTE compared to those that did not (9.1 % vs 17.2 %; *p*-value = 0.06). On another hand, known risk factors such as BMI over 25 kg/m², previous ATE and family history of VTE, as well as comorbidities such as arterial hypertension, diabetes mellitus, dyslipidemia, etc., were not found to be statistically associated with CAT. Moreover, KRS is not statistically linked to CAT in our cohort.

3.2. Venous thrombosis events

A total of 88 patients suffered one or more VTEs, which represents 22.6 % of the cohort. Interestingly, VTE was diagnosed concomitantly with the neoplasm for 30 patients, which makes up for 33 % of patients suffering CAT. On the other hand, a total of 11 patients (12.4 % of patients suffering CAT) showed VTE recurrences. Within this subgroup, 10 patients experienced one recurrence, and 1 patient had two recurrences.

The 12-month cumulative incidence of VTE in the ONCOTHROMB12-01 cohort is 14.8 % (CI 10.8–19.5 %) and the 18-month cumulative incidence is 18.1 % (CI 13.7–22.3 %). Similar cumulative incidences are found for colorectal, lung and esophago-gastric cancer, with the exception of pancreatic cancer which presents 12- and 18-month CAT cumulative incidences twice as large as the former ones ([Table 2](#)). Notably, the cumulative incidence curve ([Fig. 1](#)) increases rather slowly during the first 3 months, and then drastically from the third month until the sixth month. From this point onwards, the growth becomes steady.

Regarding types of VTE according to location, most patients

presented visceral thrombosis (VT) (*n* = 26, 29.5 %), followed by PE (*n* = 23, 26.1 %), DVT (*n* = 12, 13.6 %), DVT & PE (*n* = 6, 6.8 %), catheter-related thrombosis (CRT) (*n* = 5, 5.7 %), DVT & VT (*n* = 5, 5.7 %), PE & VT (*n* = 4, 4.5 %), DVT & CRT (*n* = 3, 3.4 %), DVT & PE & VT (*n* = 2, 2.3 %), superficial vein thrombosis (SVT) (*n* = 1, 1.1 %), and DVT & PE & SVT (*n* = 1, 1.1 %) ([Table S6](#), [Table S7](#)).

[Fig. 2](#) depicts the relative frequency of incidental and symptomatic VTE episodes by cancer type. Out of the 120 VTE events observed in this study, 59.7 % of them were incidental (*n* = 71) and 40.3 % were symptomatic (*n* = 48) (one proportion Z-test *p*-value = 0.03). For both colorectal (66.7 % symptomatic vs 33.3 % incidental VTEs; one proportion Z-test *p*-value = 0.05) and pancreatic cancer patients (68.6 % symptomatic vs 31.4 % incidental VTEs; *p*-value = 0.007), the proportion of incidental VTE is significantly higher. In contrast, for NSCLC patients, symptomatic VTEs are more frequent (73.3 % symptomatic vs 26.7 % incidental VTEs; *p*-value = 0.07). Esophago-gastric cancer patients do not show significant differences in the amount of incidental and symptomatic VTEs either (52.9 % symptomatic vs 47.1 % incidental VTEs; *p*-value = 0.81).

3.3. Survival analysis

At the end of the study, 149 patients had died, and 241 patients did not experience death and were right-censored. Overall survival (OS) estimate at 18 months for all patients was 63.4 % (CI 58.7–68.5 %). The median survival time cannot be computed since at no time point does half of the cohort die ([Fig. S2](#)).

However, it is important to note that 71 % (CI 65.6–76.3 %) of the patients that did not suffered CAT remained alive after 18 months since cancer diagnosis, in contrast with the patients that suffered CAT, of whom only 28.8 % (CI 20–41 %) were alive after this period (log-rank test *p*-value < 0.001) ([Table 3](#)). Patients that suffered CAT showed a median survival time of 9.1 months (CI 5.9–12.5) after 18 months, but this measure could not be computed for the group without CAT ([Table 3](#), [Fig. 3](#)).

The impact of CAT in a patient's survival was significant regardless of stratification by age, sex, cancer type (except for esophago-gastric cancer); and stages III and IV ([Table 3](#)). Survival curves for each subgroup are depicted in [Supplementary Material \(Figs. S1, S2, S3, S4\)](#).

In addition, to analyze whether CAT recurrence is associated with shorter OS time, a log-rank test comparing three groups of patients — cancer patients with no CAT, patients that suffered CAT once and patients that had CAT recurrence — was performed. [Table 4](#) shows that patients with CAT recurrence had a median OS of 9.7 months (95 % CI 8.4-NA), in contrast to patients that suffered only one episode of CAT, who presented a median OS of 18 months (95 % CI 12.3-NA); this difference is statistically significant (*p*-value < 0.0001). Cancer patients with no CAT do not reach the median OS during the study. It is important to note that only 18.2 % (95 % CI 5.2–63.7 %) of the patients with CAT recurrence survived after 18 months, while 18-month OS rate was of 46.5 % (CI 36.4–59.4 %) and 69.4 % (95 % CI 64.3–75 %) for patients suffered only one episode of CAT or no CAT at all, respectively ([Table 4](#)).

In addition, survival curves for these three groups of patients are shown in [Fig. 4](#).

In order to identify factors predictive of mortality, a stepwise CPH regression model was trained applying 10-fold cross-validation (mean C-index during cross-validation = 0.8606; C-index on test set = 0.8973). The selected features are presented in [Table 5](#). Factors influencing mortality in the ONCOTHROMB12-01 cohort resulting from 10-fold stepwise CPH model (listed from highest to lowest HR).

An ECOG performance status of 2 is the most influential factor of overall survival in our cohort, increasing 4 times the risk of death.

As expected, certain types of cancer are associated with lesser survival to varying degrees. Esophago-gastric cancer and non-small cell lung cancer increase almost 2-fold the risk of death in comparison with colorectal cancer; while pancreatic cancer increases it 3-fold, which is in

Table 1
Study population characteristics.

Variable		Patients that suffered VTE n (%) 88 (22.6 %)	Patients that did not suffer VTE n (%) 302 (77.4 %)	All patients n (%) 390 (100 %)	p-value
Demographic characteristics					
Age in years (median & interquartile range [IQR])		65 [55–73]	64 [58–71]	64 [57–72]	0.963
Gender	Male	53 (60.2 %)	203 (67.2 %)	256 (65.6 %)	0.224
	Female	35 (39.8 %)	99 (32.8 %)	134 (34.4 %)	
Ethnicity	Caucasian	87 (98.9 %)	291 (96.4 %)	378 (96.9 %)	0.675
	Latin-American	1 (1.1 %)	3 (3 %)	4 (2.6 %)	
	African	0 (0 %)	1 (0.3 %)	1 (0.3 %)	
	Sephardic Jew	0 (0 %)	1 (0.3 %)	1 (0.3 %)	
BMI category	Underweight	3 (3.4 %)	11 (3.6 %)	14 (3.6 %)	0.986
	Normal	43 (48.9 %)	152 (50.3 %)	195 (50 %)	
	Overweight	30 (34.1 %)	102 (33.8 %)	132 (33.8 %)	
	Obese	12 (13.6 %)	37 (12.3 %)	49 (12.6 %)	
Performance Status (ECOG scale)	0	24 (27.3 %)	121 (40.1 %)	145 (37.2 %)	0.046
	1	52 (59.1 %)	152 (50.3 %)	204 (52.3 %)	
	2	11 (12.5 %)	22 (7.3 %)	33 (8.4 %)	
	Unknown	1 (1.1 %)	7 (2.3 %)	8 (2.1 %)	
Medical History					
Number of comorbidities	0	28 (31.8 %)	94 (31.1 %)	122 (31.3 %)	0.992
	1	27 (30.7 %)	114 (31.1 %)	147 (31 %)	
	2+	33 (37.5 %)	114 (37.8 %)	147 (37.7 %)	
Arterial hypertension	Yes	39 (44.3 %)	134 (44.4 %)	173 (44.4 %)	0.993
	No	49 (55.7 %)	168 (55.6 %)	217 (55.6 %)	
Diabetes mellitus	Yes	13 (14.8 %)	61 (20.2 %)	74 (19 %)	0.253
	No	75 (85.2 %)	241 (79.8 %)	316 (81 %)	
Dyslipidemia	Yes	37 (42.0 %)	98 (32.5 %)	135 (34.6 %)	0.096
	No	51 (58.0 %)	204 (67.5 %)	255 (65.4 %)	
Tobacco use	Active smoker	25 (28.4 %)	62 (20.8 %)	115 (29.5 %)	0.184
	Former smoker	35 (39.8 %)	87 (50.0 %)	122 (31.3 %)	
	Never	28 (31.8 %)	4 (29.2 %)	32 (8.2 %)	
	Unknown	0 (0 %)	1 (1.3 %)	1 (1 %)	
COPD	Yes	8 (9.1 %)	46 (15.3 %)	54 (13.8 %)	0.139
	No	80 (90.9 %)	255 (84.4 %)	335 (85.9 %)	
	Unknown	0 (0 %)	1 (0.3 %)	1 (0.3 %)	
Chronic heart failure	Yes	1 (1.1 %)	9 (3 %)	10 (2.6 %)	0.336
	No	87 (98.9 %)	293 (97 %)	380 (97.4 %)	
Renal insufficiency	Yes	5 (5.7 %)	13 (4.3 %)	18 (4.6 %)	0.588
	No	83 (94.3 %)	289 (95.7 %)	372 (95.4 %)	
Hormonal therapy	Yes	1 (1.1 %)	4 (1.3 %)	5 (1.3 %)	0.890
	No	87 (98.9 %)	298 (98.7 %)	385 (98.7 %)	
Antiaggregant intake	Yes	8 (9.1 %)	52 (17.2 %)	60 (15.4 %)	0.063
	No	80 (90.1 %)	250 (82.8 %)	330 (84.6 %)	
Thromboembolic disease					
Previous VTE	Yes	6 (6.8 %)	6 (2 %)	12 (3.1 %)	0.0210
	No	82 (93.2 %)	296 (98 %)	378 (96.9 %)	
Previous ATE	Yes	6 (6.8 %)	36 (11.9 %)	47 (12.1 %)	0.174
	No	82 (93.2 %)	266 (88.1 %)	343 (87.9 %)	
Family history of VTE	Yes	7 (8.0 %)	11 (3.6 %)	18 (4.6 %)	0.090
	No	81 (92.0 %)	291 (96.4 %)	355 (91 %)	
Khorana risk score	Low risk	19 (21.6 %)	89 (29.6 %)	108 (27.7 %)	0.157
	Intermediate risk	47 (53.4 %)	52 (53.2 %)	99 (25.3 %)	
	High risk	22 (25.0 %)	1 (17.3 %)	23 (18.9 %)	
	Unknown	0 (0 %)	1 (0.3 %)	1 (0.3 %)	
Tumor characteristics					
Cancer type	Colorectal	28 (31.85 %)	134 (44.4 %)	162 (41.5 %)	<0.001
	NSCLC	15 (17.0 %)	39 (23.8 %)	54 (22.3 %)	
	Pancreatic	10 (37.5 %)	45 (12.9 %)	55 (18.5 %)	
	Gastric	2 (11.4 %)	12 (14.9 %)	14 (14.1 %)	
TNM Stage	Esophageal	2 (2.3 %)	12 (4.0 %)	14 (3.6 %)	0.005
	I + II	11 (12.5 %)	60 (19.9 %)	71 (18.1 %)	
	III	23 (26.1 %)	126 (38.4 %)	149 (35.7 %)	
	IV	54 (61.4 %)	126 (41.7 %)	180 (46.2 %)	
Histological grade	Well differentiated	10 (11.4 %)	37 (12.3 %)	47 (12.1 %)	0.735
	Moderately differentiated	28 (31.8 %)	78 (41.7 %)	106 (27.3 %)	
	Poorly differentiated	22 (25.0 %)	61 (25.8 %)	83 (25.6 %)	
	Unknown	28 (31.8 %)	126 (41.7 %)	154 (39.5 %)	
Tumor surgically removed	Yes	18 (20.5 %)	99 (32.8 %)	117 (30 %)	0.026
	No	70 (79.5 %)	203 (67.2 %)	273 (70 %)	
Central venous catheter	Yes	42 (47.7 %)	105 (34.8 %)	147 (37.7 %)	0.029
	No	46 (52.3 %)	196 (64.9 %)	242 (62.1 %)	
	Unknown	0 (0 %)	1 (0.3 %)	1 (0.3 %)	

Abbreviations: BMI, Body Mass Index; ECOG, Eastern Cooperative Oncology Group; COPD, Chronic Obstructive Pulmonary Disease; ATE, arterial thromboembolism; NSCLC, Non-Small Cell Lung Cancer; CVC, Central Venous Catheter. More information can be found in the [Supplementary Material \(Table S2\)](#).

Table 2
CAT cumulative incidence for ONCOTHROMB12-01 cohort and stratified by cancer type.

	CAT cumulative incidence & 95 % CI	
	12-month	18-month
All cancer types	14.8 % (10.8–19.5 %)	18.1 % (13.7–22.3 %)
Colorectal cancer	12.8 % (7.3–18.1 %)	14.5 % (8.52–20.03 %)
NSCLC	14.2 % (6.0–21.8 %)	18.2 % (8.4–26.9 %)
Esophago-gastric cancer	14.2 % (CI 4.3–23.1 %)	17.7 % (5.7–28.1 %)
Pancreatic cancer	28.3 % (CI 13.8–40.4 %)	35.9 % (18.4–49.6 %)

Abbreviations: CAT, cancer-associated venous thrombosis; NSCLC, Non-Small Cell Lung Cancer.

accordance with its aggressiveness. Similarly, patients in stage IV also have an almost 3-fold increased risk of dying compared to patients in earlier and locally advanced stages (I-III).

Naturally, VTE is identified as an important factor in mortality prediction. Patients suffering from VTE have a 2-fold increased risk of dying compared to patients with no VTE.

Interestingly, mucinous histology is selected during the training of the model as an important predictor, although it is close to being a statistically significant associated risk factor.

Last but not least, the single protective factor found is undergoing complete resection of the tumor, which decreases risk of death in 72 %.

4. Discussion

Cancer-associated venous thromboembolism poses a significant challenge for cancer patients. In the present work, we leveraged the data from the ONCOTHROMB12-01 cohort to calculate CAT incidence, describe the characteristics of venous thrombosis events, estimate its effect on mortality, and inspect risk and protective factors of overall survival through the creation of predictive models. Importantly, our analysis incorporated incidental and non-classic venous thromboembolic events, which are frequently underrepresented in existing studies, providing a more comprehensive understanding of the VTE burden in this population.

Our cohort is mainly comprised by Caucasian individuals with a

mean age of 64 years old, where women represent a third of the subjects. The cancer types represented are digestive cancers (colorectal, pancreatic, esophageal and gastric) and non-small cell lung cancer, and most individuals are in locally advanced and metastatic stages. Over half of the patients have an ECOG performance status of 1, and two thirds present one or more comorbidities.

Almost one quarter of our cohort suffered CAT, either shortly before the beginning of the study or during the observation period. Within this group, 34 % of patients had VTE concomitant to cancer diagnosis, and 13 % suffered VTE recurrence.

The estimated CAT cumulative incidence at 12 months is 14.0 % (CI 12.0–19.5 %), which is in agreement with some large cohorts that also gather high VTE risk cancer types [12,22]. Unsurprisingly, pancreatic cancer stands out amongst the other types in terms of CAT cumulative incidence (28.3 %, CI 13.8–40.4 %). The steepest rise of the CAT cumulative incidence curve is found between the 3rd and 6th month. However, literature establishes that most VTEs frequently happen within the first 6 months after the first clinical manifestations of cancer [23]. This discrepancy could be explained due to the high proportion of patients for whom CAT was diagnosed concomitantly with cancer, who were excluded from this estimation. From the 6th month onwards, the curve increases rather slowly, but new VTEs are still diagnosed. This underscores the importance of proper thromboprophylaxis after this period in high-risk patients, in consonance with current clinical guidelines, that recommend extended treatment based on maintaining benefit-risk balance [24].

Approximately 60 % of all VTEs were incidental, and 42 % of them were non-classic VTEs (VTs, CRTs, SVTs). This supports the belief that unprovoked venous thrombosis could be a reliable sign of occult malignancy [25,26].

Regarding survival, our findings further confirm the association between CAT and poor prognosis. Only 30 % of patients with CAT were alive after 18 months of follow-up, in contrast with 70 % of patients that did not suffer CAT and remained alive. For instance, the 1-year survival rate of cancer patients with VTE in a Danish cohort is 12 % vs 36 % for patients without VTE [7]. Likewise, CAT is significantly associated with decreased OS after stratifying for age group and sex; the same is true for patients with colorectal, NSCLC and pancreatic cancer, and patients in locally advanced and metastatic stages. Moreover, patients that

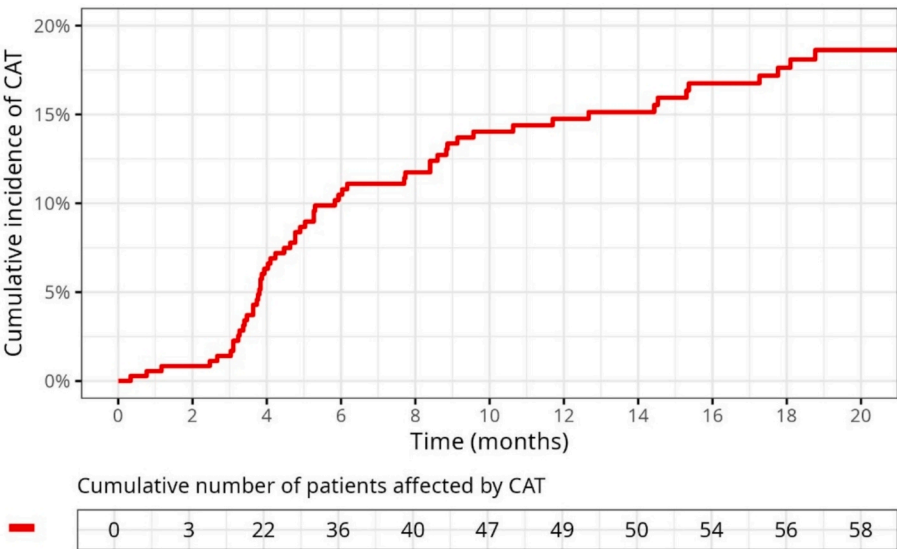


Fig. 1. Cumulative incidence of VTE for 18 months adjusted by competing risk with death (VTE events concomitant to cancer diagnosis are excluded).

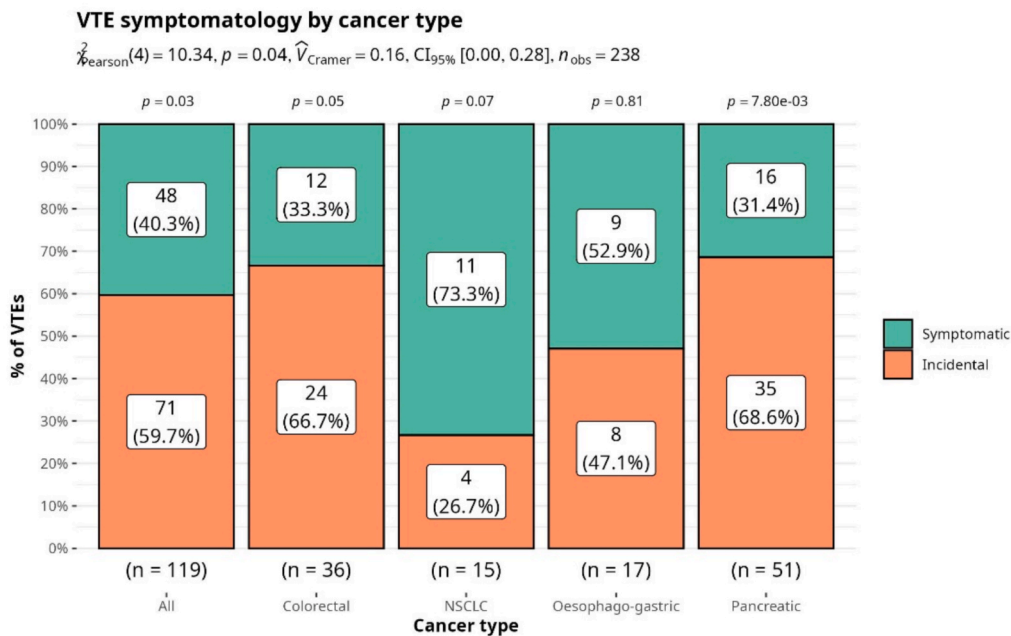


Fig. 2. Type of VTE events (incidental/symptomatic) according to cancer type. A more in-depth description of the VTE events can be found in the [Supplementary Material](#).

Table 3
Median OS (months) and OS at 18 months for all patients and for patients according to age group, gender, primary tumor and TNM stage.

Cohort groups		Median OS (months) and 95 % CI		18-month OS rate (%) and 95 % CI		Log-rank test p-value
		Patients with CAT	Patients w/o CAT	Patients with CAT	Patients w/o CAT	
All patients		9.1 [5.9–12.5]	NR	28.8 % [20–41 %]	71 % [66.1–76.3 %]	<0.0001
Age group	<65 years old≥65 years old	10.4 [8.4–16.7]7.1 [2.7–14]	NR	30.7 % [19–49.7 %]27 % [16–45.4 %]	70.1 % [63.3–77.6 %]72 % [65–79.7 %]	<0.001<0.0001
Gender	Male	8.4 [3.4–14]	NR	25.4 % [15.5–41.6 %]	67.6 % [61.4–74.5 %]	<0.0001
	Female	10.7 [5.2-NA]		34 % [20.2–56.8 %]	77.4 % [69.8–85.8 %]	<0.0001
Cancer type	Colorectal	9.4 [2.5-NA]	NR	43.5 % [22.7–83.3 %]	88 % [82.7–93.5 %]	<0.05
	NSCLC	9.2 [5.9–16.7]		10.8 % [2.7–43.1 %]	59 % [48.3–71.8 %]	<0.01
	Esophago-gastric	18.5 [8.4-NA]		51.9 % [29.1–92.5 %]	56.2 % [44.1–71.8 %]	0.40
	Pancreatic	5.9 [3.6–10.4]		12.7 % [5.3–30.7 %]	54.1 % [41–71.7 %]	<0.0001
pTNM stage	I-II	NR	NR	87.5 % [67.3–100 %]	92 % [85.2–99 %]	0.38
	III	24 [12.3-NA]	NR	52.7 % [34.6–80.2 %]	84 % [77.6–91 %]	<0.05
	IV	6.5 [3.8–10.4]	15.8 [12.7-NA]	17.2 % [9.7–30.4 %]	48 % [40–57.8 %]	<0.0001

Abbreviations: OS, overall survival; CI, confidence interval; CAT, cancer-associated thrombosis; NSCLC, non-small cell lung carcinoma; NR, not reached; NA, not available.

experienced recurrent VTE showed a significantly shorter OS when compared to those that suffered VTE but no recurrences. Only 18 % of patients with VTE recurrence were alive after 18 months, whilst 46.5 % with VTE but no recurrence lived.

We trained a CPH regression model with automated feature selection, resulting in a model whose C-index on test set was 0.8973. Within the set of predictors, we found death risk factors well established in literature, such as an ECOG performance status of 2; pancreatic, NSCLC and esophago-gastric cancer; and stage IV [27,28].

Also, VTE is selected as an important predictor, and its effect on mortality is on par with that of metastatic disease. It has been found that the presence of malignancy favors thrombosis, and vice versa [329].

Mucinous adenocarcinomas are less frequent than other histology types and it is linked to worsened prognosis in lung and digestive system cancers [30–32]. In fact, mucins are suspected to play a role both in cancer progression [33,34] and cancer-associated venous thrombosis [3]. Therefore, this feature being picked up by our model as a poor survival predictor is of interest, despite the fact that statistical significance is not reached.

Complete resection of the tumor is considered a protective factor, which makes sense considering that patients that undergo this procedure have a localized tumor that is not yet widely spread. Furthermore, the removal of solid tumors might help prevent a prothrombotic state [3].

Not only does VTE affect survival, but also the quality of life. The diagnosis of VTE usually leads to hospitalization, and postponement of surgery and systemic therapy. All these mishaps worsen patients' outcomes [13]. Our findings reinforce VTE as an independent predictor of mortality across tumor types and stages, as seen in our survival model. While thromboprophylaxis cannot be used to treat cancer itself, it can reduce complications that disrupt or delay anti-cancer therapies. Despite this, outpatient thromboprophylaxis is rarely used by medical oncologists. Currently, the main international clinical guidelines suggest outpatient thromboprophylaxis for patients at high risk of VTE based on validated risk assessment models; the most well-known example is the Khorana Risk Score [13,35]. Several risk assessment tools based on clinical data have been developed [36,37]; although their performances in independent cohorts is a subject of debate [38,39]. Further research is

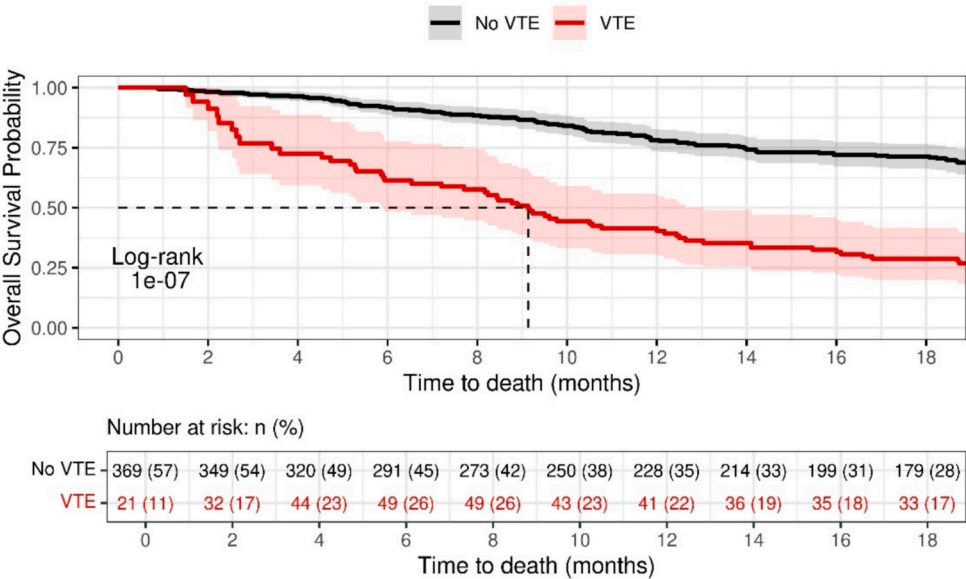


Fig. 3. Kaplan-Meier curves for patients that suffered CAT vs those who did not (including recurrences).

Table 4
Median OS (months) and OS at 18 months for all patients and for patients according to CAT occurrence.

Cohort subgroups	Median OS (months) and 95 % CI	18-month OS rate (%) and 95 % CI	Log-rank test p-value
No CAT (n = 302)	NR	69.4 % [64.3–75 %]	<0.0001
CAT w/o recurrence (n = 77)	16 [12.3-NA]	46.5 % [36.4–59.4 %]	
CAT recurrence (n = 11)	9.7 [8.4-NA]	18.2 % [5.2–63.7 %]	

Abbreviations: OS, overall survival; CI, confidence interval; CAT, cancer-associated thrombosis; NR, not reached.

needed to improve said tools and thus help clinicians in making management decisions that enhance the survival prognosis and well-being of cancer patients.

One of the main strengths of our work relies on the study design. This

is one of the few prospective studies with 18 months of follow-up for the research of the relationship between cancer and venous thrombosis. The inclusion of digestive and lung cancer patients enabled us to observe a higher number of VTEs, thus increasing power to detect associations. Also, periodical monitoring allowed us to account for non-classic and incidental thromboses, preventing us from underestimating the real incidence and effects of VTE. Apart from that, our approach to survival analysis draws upon Machine Learning methodologies—i.e. dataset partitioning, k-fold cross-validation and feature selection—which alleviates spurious effects that might affect variable selection and prevents model overfitting. Thus, we were able to inspect the importance of features from both a statistical and predictive point of view.

We are aware of the limitations of our study. Firstly, the number of patients recruited is modest, and the population sample is limited to mainly Caucasian individuals with five types of cancer, mostly at advanced stages. Caution should be exercised when extrapolating the results shown here to populations of different characteristics. In addition, information related to bleeding events, and cause of death are not accounted for in the ONCOTHROMB12-01 cohort, hindering us from delivering a more comprehensive analysis on cancer-related and VTE-

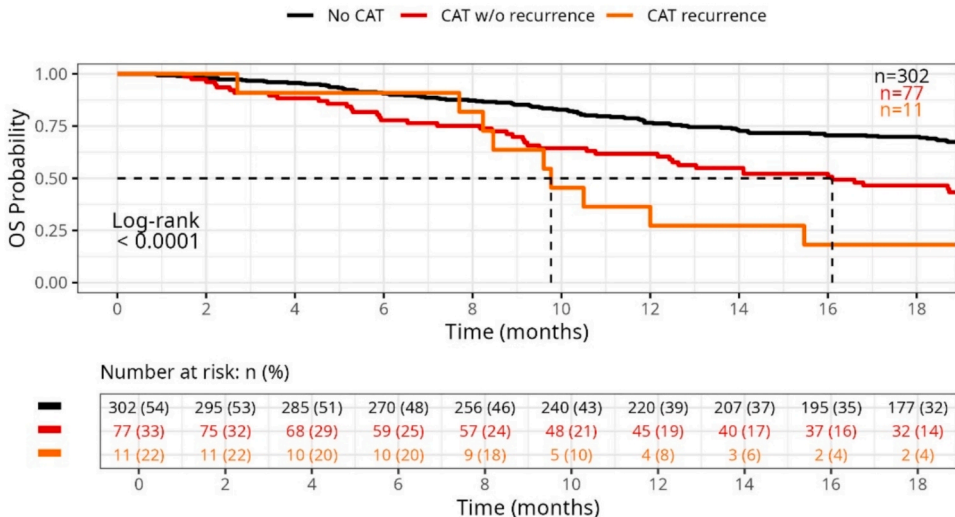


Fig. 4. Kaplan-Meier curves for patients without CAT vs those with CAT but no recurrences vs those with CAT recurrences.

Table 5

Factors influencing mortality in the ONCOTHROMB12-01 cohort resulting from 10-fold stepwise CPH model (listed from highest to lowest HR).

Covariate	HR (95 % CI)	p-value
ECOG performance status = 2	4.19 [2.38–7.37]	<0.001
Cancer type		
Colorectal	–	–
NSCLC	1.91 [1.13–3.24]	0.016
Esophago-gastric	1.86 [1.07–3.23]	0.028
Pancreatic	3.09 [1.81–5.26]	<0.001
Stage IV	2.74 [1.81–5.26]	<0.001
VTE	2.08 [1.39–3.11]	<0.001
Mucinous histology	1.40 [0.94–2.10]	0.10
Tumor surgically removed	0.28 [0.14–0.56]	<0.001

Abbreviations: HR, hazard ratio; CI, confidence interval; NSCLC, non-small cell lung carcinoma; VTE, venous thromboembolism.

related mortality.

We envision several promising avenues for future research. To this end, we will leverage the ONCOTHROMB02 cohort—a recent dataset that not only broadens the population sample but also encompasses new clinical features (i.e. hematological parameters, systemic anti-tumor therapies, antithrombotic treatments), as well as genetic information. Our primary focus will be on the discovery of CAT biomarkers and the development of risk assessment models using Machine Learning. First, we aim to evaluate the predictive capability of potential CAT biomarkers, specifically blood D-dimer levels and single nucleotide polymorphisms (SNPs) linked to this disease. Furthermore, we will examine how systemic anti-cancer therapies, along with antithrombotic treatments administered to patients, contribute to the overall risk of developing CAT.

5. Conclusions

In this study, we analyzed data from the ONCOTHROMB12-01 cohort to assess the incidence and prognostic relevance of cancer-associated venous thrombosis. We used a broad definition of VTE that includes incidental and non-classic events to ensure a more accurate estimation of its true clinical burden. Our results confirm that VTE significantly affects overall survival, independent of cancer type, stage or patient demographics, and VTE recurrences are associated with even worse outcomes. Our survival model, developed using Cox Proportional Hazards regression with automated feature selection, identified VTE as a strong, independent predictor of mortality. Given our results, we emphasize the importance of adequate thromboprophylaxis to prevent VTE and subsequent medical complications. Future efforts should aim to improve prognostic and VTE-risk stratification tools.

Data availability

The data presented in this study are available on request from the corresponding author with approval of the Ethics Committee and the Innovation Unit of Institut de Recerca Sant Pau (IR Sant Pau), Sant Quintí 77–79, 08041 Barcelona, Spain due to legal and ethical reasons.

Informed consent and patient details

Informed consent was obtained from all subjects involved in the study. The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Boards of all participant hospitals (protocol code ONCOTHROMB12-01 approved in March of 2013).

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT in order to improve English sentences. After using these tools, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

CRediT authorship contribution statement

Bárbara Lobato-Delgado: Writing – original draft, Investigation, Formal analysis. **Magdalena Ruiz:** Writing – original draft, Formal analysis. **Carne Font:** Resources, Methodology. **Vanessa Pachón:** Methodology, Investigation. **Victoria Castellón:** Methodology, Investigation. **Virginia Martínez-Marín:** Methodology, Investigation. **Mercedes Salgado:** Resources, Methodology. **Eva Martínez:** Methodology, Investigation. **Julia Calzas:** Methodology, Investigation. **Laura Ortega:** Methodology, Investigation, Formal analysis. **Ana Rupérez:** Methodology, Investigation. **Oriol Pujol:** Methodology, Formal analysis. **José Manuel Soria:** Writing – original draft, Supervision, Funding acquisition. **Andrés Muñoz:** Writing – original draft, Methodology, Investigation, Funding acquisition.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Andres Munoz reports financial support was provided by Spanish Society of Medical Oncology. Andres Munoz reports financial support was provided by Spanish Society of Thrombosis and Haemostasis. Jose Manuel Soria reports financial support was provided by Asociacion ActivaTT por la Salud. Jose Manuel Soria reports financial support was provided by IMPACT. Jose Manuel Soria reports financial support was provided by Center for Biomedical Research in Network on Rare Diseases. Jose Manuel Soria reports financial support was provided by Government of Catalonia. Jose Manuel Soria reports a relationship with Asociación ActivaTT por la Salud that includes: board membership. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. . Supplementary materials

A repository with the code for all analyses can be found in https://github.com/BarbaraLobatoDelgado/oncothromb1_survival_analysis.

Appendix B. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijc.2025.101754>.

[org/10.1016/j.ijcha.2025.101754](https://doi.org/10.1016/j.ijcha.2025.101754).

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Glossary

AIC: Akaike Information Criterion
 ATE: arterial thromboembolism
 BMI: body mass index
 CAT: cancer-associated venous thrombosis
 CI: confidence interval
 COPD: chronic obstructive pulmonary disease
 CPH: Cox Proportional Hazards
 CRT: catheter-related thrombosis
 CVC: central venous catheter
 DVT: deep venous thrombosis
 ECOG: Eastern Cooperative Oncology Group
 HR: hazard ratio
 KRS: Khorana Risk Score
 NA: not available
 NR: not reached
 NSCLC: non-small cell lung cancer
 OS: overall survival
 PE: pulmonary embolism
 SVT: superficial venous thrombosis
 VT: visceral thrombosis

VTE: venous thromboembolism