Multistate Models: Accurate and Dynamic Methods to Improve Predictions of Thrombotic Risk in Patients with Cancer

Alberto Carmona-Bayonas[1] Paula Jimenez-Fonseca[2] Marcelo Garrido[3] Ana Custodio[4] Raquel Hernandez[5] Alejandra Lacalle[6] Juana María Cano[7] Gema Aguado[8] Eva Martínez de Castro[9] Felipe Alvarez Manceñido[10] Ismael Macias[11] Laura Visa[12] Marta Martín Richard[13] Monserrat Mangas[14] Manuel Sánchez Cánovas[1] Federico Longo[15] Leticia Iglesias Rey[16] Nieves Martínez Lago[17] Alfonso Martín Carnicero[18] Ana Sánchez[19] Aitor Azkárate[20] María Luisa Limón[21] Carolina Hernández Pérez[22] Avinash Ramchandani[23] Paola Pimentel[24] Paula Cerdá[25] Raquel Serrano[26] Aitziber Gil-Negrete[27] Miguel Marín[28] Alicia Hurtado[29] Rodrigo Sánchez Bayona[30] Javier Gallego[31]

[1] Hematology and Medical Oncology Department, Hospital General Universitario Morales Meseguer, University of Murcia, IMIB, Murcia, Spain
[2] Medical Oncology Department, Hospital Universitario Central de Asturias, Oviedo, Spain
[3] Medical Oncology Department, Pontificia Universidad Católica de Chile, Santiago de Chile, Chile
[4] Medical Oncology Department, Hospital Universitario La Paz, Madrid, Spain
[5] Medical Oncology Department, Hospital Universitario de Canarias, Tenerife, Spain
[6] Medical Oncology Department, Complejo Hospitalario de Navarra, Pamplona, Spain
[7] Medical Oncology Department, Hospital General Universitario de Ciudad Real, Ciudad Real, Spain
[8] Medical Oncology Department, Hospital Universitario Gregorio Marañon, Madrid, Spain
[9] Medical Oncology Department, Hospital Universitario Marqués de Valdecilla, Santander, Spain
[10] Pharmacy Department, Hospital Universitario Central de Asturias, Oviedo, Spain
[11] Medical Oncology Department, Hospital Universitario Parc Tauli, Sabadell, Spain
[12] Medical Oncology Department, Hospital Universitario El Mar, Barcelona, Spain
[13] Medical Oncology Department, Hospital Universitario Santa Creu i Sant Pau, Barcelona, Spain
[14] Medical Oncology Department, Hospital Galdakao-Usansolo, Galdakao-Usansolo, Spain,
[15] Medical Oncology Department, Hospital Universitario Ramón y Cajal, Madrid, Spain
[16] Medical Oncology Department, Complejo Hospitalario de Orense, Orense, Spain
[17] Medical Oncology Department, Complejo Hospitalario Universitario de A Coruña, La Coruña, Spain
[18] Medical Oncology Department, Hospital San Pedro, Logroño, Spain
[19] Medical Oncology Department, Hospital Universitario Doce de Octubre, Madrid, Spain
[20] Medical Oncology Department, Hospital Universitario Son Espases, Mallorca, Spain
[21] Medical Oncology Department, Hospital Universitario Virgen del Rocío, Sevilla, Spain
[22] Medical Oncology Department, Hospital Universitario Nuestra Señora de la Candelaria, Tenerife, Spain
[23] Medical Oncology Department, Hospital Universitario Insular de Gran Canaria, Las Palmas de Gran Canaria, Spain
[24] Medical Oncology Department, Hospital Santa Lucia, Cartagena, Spain
[25] Medical Oncology Department, Centro Médico Teknon, Barcelona, Spain
[26] Medical Oncology Department, Hospital Universitario Reina Sofía, Córdoba, Spain
[27] Medical Oncology Department, Hospital Universitario Donostia, San Sebastián, Spain
[28] Medical Oncology Department, Hospital Universitario Virgen de la Arrixaca, Murcia, Spain
[29] Medical Oncology Department, Hospital Universitario Fundación Alcorcón, Madrid, Spain
[30] Medical Oncology Department, Clínica Universidad de Navarra, Pamplona, Spain
[31] Medical Oncology Department, Hospital General Universitario de Elche, Elche, Spain

Address for correspondence Alberto Carmona-Bayonas, MD, PhD, Hospital Universitario Morales Meseguer, Calle Marqués de los Vélez s/n, Murcia, Spain (e-mail: alberto.carmonabayonas@gmail.com).

Thromb Haemost

received
April 13, 2019
accepted after revision
June 21, 2019

DOI https://doi.org/10.1055/s-0039-1694012.
ISSN 0340-6245.

Abstract

Research into cancer-associated thrombosis (CAT) entails managing dynamic data that pose an analytical challenge. Thus, methods that assume proportional hazards to investigate prognosis entail a risk of misinterpreting or overlooking key traits or time-varying effects. We examined the AGAMENON registry, which collects data from 2,129 patients with advanced gastric cancer. An accelerated failure time (AFT) multistate model and flexible competing risks regression were used to scrutinize the time-varying effect of CAT, as well as to estimate how covariates dynamically predict cumulative incidence. The AFT model revealed that thrombosis shortened progression-free survival and overall survival with adjusted time ratios of 0.72 and 0.56, respectively. Nevertheless, its prognostic effect was nonproportional and disappeared over time if the subject managed to survive long enough. CAT that occurred later had a more pronounced prognostic effect. In the flexible competing risks model, multiple covariates were seen to have significant time-varying effects on the cumulative incidence of CAT (Khorana score, secondary thromboprophylaxis, high tumor burden, and cisplatin-containing regimen), whereas other predictors exerted a constant effect (signet ring cells and primary thromboprophylaxis). The model that assumes proportional hazards was incapable of capturing the effect of these covariates and predicted the cumulative incidence in a biased way. This study evinces that flexible and multistate models are a useful and innovative method to describe the dynamic effect of variables associated with CAT and should be more widely used.

Keywords

- cancer
- thrombosis
- time-varying effects
- multistate models
- flexible models

Introduction

Recent decades have witnessed greater knowledge about cancer-associated thrombosis (CAT). Nevertheless, highly relevant issues concerning the causes, dynamic effects, and variable prognosis of thrombosis have yet to be fully clarified.[1] These patients' "life stories" are often complex and their risk factors interweave time-dependent stochastic events (e.g., admissions, toxicities, surgeries, etc.) and reciprocal interactions between clinical and biological factors.[2,3] This complexity poses a challenge for the statistical analysis of CAT.[4]

The two main aims in clinical research into CAT are to understand how it affects prognosis and to identify the most significant predictors. However, these analyses entail some specific difficulties. First, the Cox model, widely used for analyzing survival data, assumes proportional hazards (the hazard ratio [HR] must be constant with time),[5] yet this assumption is often not fulfilled in series with longer follow-up times.[6] This is relevant, because if we are to glean information about long-term survivors, we must understand that the prognostic impact of thrombosis is attenuated over time.[7] Nevertheless, for all intents and purposes, the specific literature all but fails to reflect this information.[8] In light of this, accelerated failure time (AFT) models, a kind of parametric model that assumes that the effect of a covariate is to accelerate or to decelerate the course of the disease, might be more suitable in dynamic clinical settings.

Moreover, most experts consider that thrombotic risk varies over the natural evolution of cancer; consequently, some key predictors do not exert a constant effect.[9] To model cumulative incidence of thrombosis, the Fine-Gray subdistribution hazard regression (FGR) is commonly used, although it fails to capture how the predictors' behavior changes with time.[4,10,11] Consequently, since the proportional hazards assumption may, again, not hold and the interest lies in absolute effects, flexible competing risks models (sensitive to competing events, yet flexible enough to deal with time-varying dynamics of covariate effects) are needed.[12,13]

Second, CAT is a time-dependent variable. More often than not, thrombosis does not occur at baseline, but during the course of the disease.[14] If thrombosis is evaluated as a fixed variable, an error known as "immortal time bias" emerges, which continues to be common in the literature.[15,16] Multistate models are one of the most appealing solutions, as their architecture makes it possible to demarcate periods with and without thrombosis, as well as to address other common problems (e.g., competing risks).[17] Posch et al have demonstrated that multistate models are useful for integrally dissecting the process of CAT.[18] More recently, multistate models based on AFT models have been proposed as a flexible solution to incorporate these time-varying effects.[19] Despite its potential benefit, this methodology has scantly been explored in CAT.

For a proof of concept, our group hypothesized that a registry of advanced gastric cancer (AGC) might be especially useful to test these methods, since the cumulative incidence of venous thromboembolic events (VTE) ranges between 9 and 24%,[20,21] having a marked prognostic effect.[8,22] The AGAMENON AGC registry has guided us previously in several aspects of this disease.[23–29] Here, we have set out to assess whether flexible modeling strategies are superior to non-flexible methods for correctly capturing and interpreting the most important features of CAT.

Methods

Patients and Study Design

Participants are from the AGAMENON AGC registry in which 32 Spanish hospitals and 1 Chilean center participated. Its design, characteristics, and quality of the information have been reported previously.[23–29] The evaluation of thrombotic risk was a prespecified aim. Data are managed electronically via a Web site (www.agamenonstudy.com) that controls for lost data, inconsistencies, and errors in real time, and double-checks the study's selected endpoints (events, thrombosis, and dates), with telephone and online monitoring (P.J.F.).

Eligibility criteria include being > 18 years of age, with a histologically confirmed diagnosis of adenocarcinoma of the stomach, gastroesophageal junction, or distal esophagus. All the tumors must present metastasis or be locally advanced and unresectable, and subjects must have been treated with at least one cycle of polychemotherapy, with regimens deemed acceptable by guidelines.

The main event of interest is the appearance of incidental or symptomatic CAT during first-line chemotherapy (superficial thrombophlebitis was ruled out). Diagnosis must have been made by means of imaging techniques (computerized tomography [CT] initially indicated to evaluate tumor response, Doppler ultrasound, CT pulmonary angiography, etc., as per each center's clinical practice).

Other endpoints were overall survival (OS) and progression-free survival (PFS) defined as the survival times between treatment initiation and tumor progression or all-cause mortality, censoring patients lost to follow-up, venous thrombotic recurrence, and bleeding. ►**Supplementary Material A** (available in the online version) presents the full list of variables and definitions used as CAT predictors or survival endpoints.

The objective of the present study is to evaluate whether fully parametric multistate survival models and flexible competing risk regressions are capable of providing useful information regarding CAT.

The study was approved by a multicenter research ethics committee and by the Spanish Agency for Medicines and Medical Devices (AEMPS). All patients still alive at the time of data collection provided signed, informed consent.

Multistate Models

Multistate models are useful for depicting complex event history data. It is a statistical framework in which the events and their connections are named "states" and "transitions," respectively. States without transitions, such as demise, are known as absorbing states, whereas the rest are considered transitory states. The simplest multistate models include competing risks analysis (the presence of more than one absorbing state) and the illness-death model (defined as the presence of a transitory state, such as CAT, and an absorbing state).[30] Thus, the causes of thrombogenesis and the effect of CAT can be modeled simultaneously. The so-called Markov property implies that the future course depends on the current state, but not on the previous history. In CAT and cancer studies, an alternative must be considered according to which the hazard of a transition (e.g., toward the endpoint "death") would go on to depend on the time it took for CAT to occur. This extension has been named the state-arrival extended semi-Markov[31] and is particularly attractive in hemostasis to assess whether the effect of early CAT is equivalent to that of late thrombosis. The appearance of intermediate events determines the possibility of using two different timescales, from onset or from CAT. Given that thrombosis and demise are a function of time from the onset of cancer, a "clock forward" timescale is used, in which time flows from the beginning and never stops moving forward.[17,31] The "clock reset" formulation, from the time of thrombosis, can likewise be contemplated in this stratum. The multistate model adopted in this study is illustrated in ►**Supplementary Fig. S1** (available in the online version). Finally, the time-dependent effect of VTE on OS cannot be disregarded[32]; a parametric AFT model has been used that assumes that the effect of covariates either accelerates or decelerates the course of the disease and does not require the hazards to be proportional.[19] The most intuitive way of expressing the coefficients of the AFT model is exponentiated (time ratios [TRs]); thus, the regression coefficient of a binary predictor such as CAT equal to log(0.5) means that the median OS (mOS) is halved in the presence of the thrombotic event. Key characteristics of the models used have been summarized in ►**Table 1**.

Statistics

A fully parametric AFT model has been implemented to estimate the effect of VTE on prognosis.[19] This formulation allows both time-dependent variables and time-varying effects to be included into the framework of a multistate model.[19,33] AFT models from several distribution families incorporating covariates were fitted to model time to event (PFS and OS). The Akaike information criterion and the Bayesian information criterion were used to compare models (►**Supplementary Material C**, available in the online version). The log-logistic distribution was then selected, given that it was the one that best suited the data. No data-driven method, such as univariate screening or stepwise regressions, was applied to select eligible predictors.[34] VTE was entered as a time-dependent covariate. Landmark analysis was used to evaluate the impact of VTE on survival.[35]

The Aalen–Johansen estimator was then applied to obtain the cumulative incidence of CAT without covariates. The cumulative incidence function of thrombosis was modeled by flexible competing risks regression (direct binomial regression applying the cloglog link).[12] This approach enables the covariate effects on the cumulative incidence curve to be estimated in competing risk scenarios. The resulting model allows some effects to be time-variant (dynamic) and others to be constant over time. Two tests were performed to evaluate whether the effects were significantly time-varying (Kolmogorov–Smirnov and Cramer–von Mises tests).[12] We also applied FGR, as comparison. The analyses were executed with R version 3.5.1,[36] including the mstate, timereg, and flexsurv packages.[12,37,38] The R code is reflected in ►**Supplementary Material B** (available in the online version).

Table 1 Summary of the models' key characteristics

	Cox proportional hazards models	Accelerated failure time (AFT)	Fine–Gray subdistribution hazard model	Direct binomial regression
Estimations of the model	Adjusted HRs	Adjusted TRs	sHRs	Cumulative subhazard ratios
Interpretation of the coefficients	- HR = 1 indicates no association between the covariate and the cause-specific hazard function - HR > 1 means that an increase in the value of the covariate is associated with a greater hazard rate - HR < 1 means that an increase in the value of the covariate is associated with a reduced hazard rate	- TR = 1 indicates no association between the covariate and survival time - TR > 1 means that an increase in the value of the covariate is associated with longer survival - TR < 1 means that an increase in the value of the covariate is associated with shorter survival	- sHR = 1 indicates no association between the covariate and the cumulative incidence function - sHR > 1 means that an increase in the value of the covariate increases the risk - sHR < 1 means the opposite	In constant effect variables, the interpretation is identical to the previous case. The model adds a function with a direct link on the CIF for time-varying covariates
Example of interpretation for a binary predictor	HR = 0.5, the rate of events is half at any given point in time in the presence of the variable	TR = 0.5, the median time-to-event is halved in the presence of the predictor	The exact numerical interpretation is not direct	The exact numerical interpretation is not direct
Assumption of proportional hazards	Yes	No	Yes	No
Possibility of analyzing dynamic variables	Dynamic variables, e.g., covariates that change over time, can be incorporated using extensions of the Cox model	Yes	No	Yes
Competing events	Competing events can be addressed in a Cox model by fitting cause-specific hazards for each type of event	Not in its basic formulation, although extensions have been reported that make it possible to adapt the analysis	Yes	Yes
Time-dependent variables	Yes	Yes	No	No

Abbreviations: CIF, cumulative incidence function; HR, hazard ratio; sHRs, subdistribution hazard ratios; TR, time ratio.

Results

Database Description

The registry contained 2,129 patients at the time of analysis. There were 211 thromboses during first-line chemotherapy with a cumulative incidence at 3 and 6 months of 5.7% (95% confidence interval [CI], 4.8–6.7%) and 8.2% (95% CI, 7.1–9.5%), respectively (►**Supplementary Fig. S2**, available in the online version). These CAT events occurred after a median of 2.4 months (range, 0–23). Patients' baseline characteristics are recorded in ►**Table 2**. A history of thrombosis prior to first-line chemotherapy was also reported in 133 patients (see time distribution in ►**Supplementary Fig. S3**, available in the online version). Detection was incidental in 46%. The most common locations of thrombosis were lung (48%), lower limb (24%), splanchnic (8%), and catheter (7%). Thromboses were treated with low molecular weight heparin, at full (91%), low (5%), or prophylactic dosages (3%), or with direct oral anticoagulants (1%). The cumulative incidence of venous rethrombosis and major bleeding at 6 months was 4.4% (95% CI, 2.3–8.3%) and 5.7% (95% CI, 3.3–10.0%), respectively. In the complete cohort, median PFS and mOS were 6.05 (95% CI, 5.82–6.31) and 10.4 (95% CI, 9.9–10.9) months, respectively. Thrombosis was the direct cause of death in 15 cases.

Dynamic Effect of VTE

In the log-logistic AFT models, the development of CAT shortened PFS and OS with adjusted TR of 0.72 (95% CI, 0.49–1.06) and 0.56 (95% CI, 0.43–0.74), respectively (►**Table 3**). The formulation through HRs was not suitable, since the effect of CAT faded over time (►**Fig. 1** and ►**Supplementary Fig. S4**, available in the online version). The log-logistic model showed

Table 2 Patients' baseline characteristics

Characteristics	All patients, $n = 2{,}135$, %
Sex, male	1,511 (71)
Age, median (range)	64 (20–89)
Albumin, < 3.5 g/dL	510 (24)
ECOG-PS, ≥ 2	278 (13)
Primary tumor site	
Distal esophagus	164 (8)
Gastroesophageal junction	264 (12)
Stomach	1,707 (80)
Stage at diagnosis, metastatic	2,017 (94)
Surgery of primary tumor	615 (29)
Chemotherapy	
Oxaliplatin	1,236 (58)
Anthracycline	454 (21)
Cisplatin	719 (34)
Docetaxel	266 (12)
Irinotecan	42 (2)
Other	132 (6)
Lauren classification, diffuse subtype	932 (44)
Histological grade	
Grade 1	205 (10)
Grade 2	606 (28)
Grade 3	873 (41)
Not available	451 (21)
Presence of signet ring cells	638 (30)
Site of metastases	
Liver	799 (37)
Peritoneum	926 (43)
Ascites	504 (24)
Bone	202 (9)
Lung	274 (19)
Prior use of anticoagulant for	
No	1,779 (83)
Primary thromboprophylaxis	56 (3)
Atrial fibrillation	95 (4)
Thrombosis before cancer diagnosis	11 (1)
Thrombosis prior to beginning chemotherapy	48 (2)
Not available	135 (6.3)
History of tumor hemorrhage (≤ 1 month before the first-line chemotherapy)	
No	1,351 (63)
Iron deficiency anemia without evidence of bleeding	507 (24)
Tumor hemorrhage requiring transfusion	223 (10)
Tumor hemorrhage with history of hemodynamic instability	36 (2)
Not available	18 (1)

Abbreviation: ECOG-PS, Eastern Cooperative Oncology Group performance status.

adequate goodness-of-fit (►**Supplementary Fig. S5**, available in the online version). After adjusting for confounding factors, CAT that took place later were seen to exert a more powerful prognostic effect (TR 0.69 and 0.93 on progression and demise, respectively, for each month it took the thrombosis to occur). Kaplan–Meier curves to represent the long-term effects of early or late VTEs conditional on surviving at least 6 months are depicted in ►**Fig. 2**. Median PFS and mOS from the time of CAT were 1.21 (95% CI, 3.05–5.16) and 3.91 months (95% CI, 3.05–5.16), respectively.

Flexible Modeling of VTE Predictors

It is clear in the flexible competing risks model that four covariates (Khorana score, secondary prevention of venous thromboembolism, high tumor burden, and cisplatin-containing regimen; see ►**Fig. 3**) have significant time-varying effects ($p < 0.05$). As for the Khorana score, or the high tumor load, the association with VTE is more intense at the beginning, but rapidly abates after 2 to 3 months of follow-up. In the case of cisplatin, the effect is also early, with a cumulative late component in individuals with chronic vascular disease aged ≥ 60 years. For secondary thromboprophylaxis, there is an initial increased risk of thrombotic recurrence, with subsequent, long-term protection. In contrast, the significant predictors with a constant effect were signet ring cells (cumulative sub-HR [csHR], 1.47; 95% CI, 1.06–2.05) and primary thromboprophylaxis (csHR, 0.43; 95% CI, 0.18–0.99) (►**Table 4**). For comparison sake, ►**Supplementary Material D** (available in the online version) displays FGR, which assumes proportional hazards, thereby verifying that it fails to detect the significant effect of two of the four dynamic covariates ("cisplatin" and "secondary thromboprophylaxis"). Finally, we compared the FGR predictions with those of the dynamic model, by means of three patient profiles (see ►**Fig. 4** footnote). For each, predictions have been stratified according to having received primary thromboprophylaxis or not. ►**Fig. 4A** and **B** illustrate that FGR underestimates the cumulative incidence in those profiles in which there is a predominance of time-varying covariates having a late effect (e.g., cisplatin-containing regimens in elderly patients with cardiovascular disease). In contrast, FGR overestimates thrombotic risk when dynamic covariates with an early effect predominate (e.g., Khorana score, cisplatin, or high tumor burden) (►**Fig. 4C** and **D**).

Discussion

In this study, we have applied a flexible multistate model as an innovative method[38] to comprehensively dissect CAT predictive factors and their influence on survival endpoints. This work shows that mortality in an illness-death model, in which thrombosis represents a transient state, can depend on when the event occurs, and that the time-dependent effect cannot be overlooked, as doing so would fail to reflect the reality of its impact. Furthermore, this methodology makes it possible to explore the dynamic effects of variables, yielding additional insights into cancer patients' hypercoagulability.

The use of flexible modeling or time-to-event analysis is not yet routine in the field of thrombosis, even with censored data

Table 3 Accelerated failure time models (for PFS and OS)

	PFS		OS	
Parameter	**Estimate (SE)**	**TR (95% CI)**	**Estimate (SE)**	**TR (95% CI)**
Shape	1.981 (0.037)	NA	1.947 (0.039)	NA
Scale	8.481 (0.712)	NA	17.80 (15.015)	NA
VTE (time-varying)	−0.323 (0.195)	0.723 (0.493–1.061)	−0.564 (0.138)	0.568 (0.433–0.745)
Neutrophil–lymphocyte ratio (continuous)	−0.031 (0.004)	0.968 (0.959–0.978)	−0.041 (0.005)	0.959 (0.949–0.968)
Cisplatin-containing regimen	−0.030 (0.041)	0.969 (0.894–1.051)	−0.015 (0.042)	0.984 (0.905–1.069)
Albumin, < 3.5 gr/dL	0.048 (0.047)	1.049 (0.955–1.152)	0.113 (0.049)	1.120 (1.016–1.234)
Ascites	−0.140 (0.048)	0.868 (0.790–0.954)	−0.148 (0.049)	0.862 (0.781–0.950)
Grade 1, vs. other	−0.164 (0.068)	0.848 (0.742–0.969)	−0.272 (0.070)	0.761 (0.662–0.873)
HER2 positive treated with trastuzumab	0.417 (0.055)	1.518 (1.362–1.691)	−0.015 (0.057)	0.984 (0.905–1.069)
High tumor load[a]	−0.263 (0.051)	0.768 (0.695–0.849)	−0.315 (0.052)	0.729 (0.657–0.808)
Months to VTE	−0.359 (0.155)	0.698 (0.514–0.947)	−0.071 (0.052)	0.931 (0.840–1.031)
ECOG-PS, ≥ 2	−0.372 (0.059)	0.688 (0.612–0.774)	−0.501 (0.061)	0.605 (0.536–0.682)
Bone metastases	−0.246 (0.065)	0.781 (0.687–0.889)	−0.264 (0.067)	0.767 (0.672–0.877)
Tumor with signet ring cells	−0.017 (0.044)	0.982 (0.899–1.072)	−0.081 (0.046)	0.921 (0.842–1.009)

Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status scale; HER2, human epidermal growth factor receptor 2; NA, not available; OS, overall survival; PFS, progression-free survival; SE, standard error; TR, time ratio; VTE, venous thromboembolic disease.
Notes: Months to thrombosis are computed from the start of chemotherapy. Estimates are from log-logistic parametric models for PFS and OS; scale and shape are the parameters of these models.
[a]High tumor burden was defined as the presence of ≥ 3 metastatic sites or tumor occupying ≥ 25% of the liver.

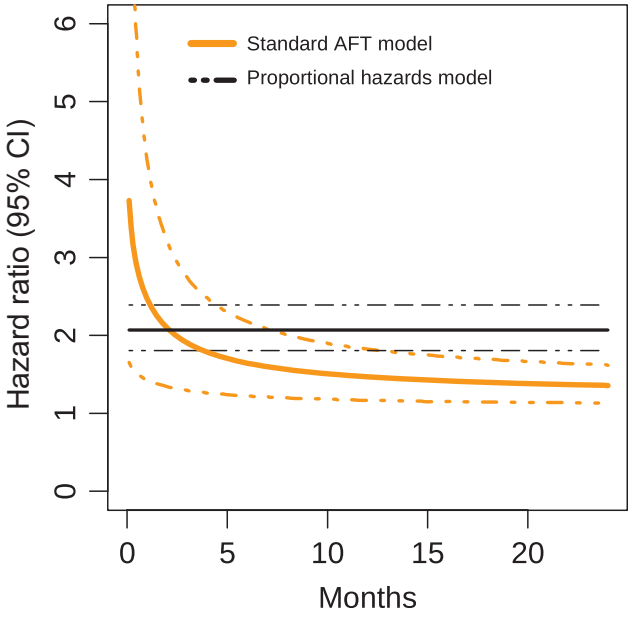

Fig. 1 Time-varying effect of thrombosis on overall survival. AFT, accelerated failure time model; CI, confidence interval; VTE, venous thromboembolism. Note: Hazard ratios are multivariable adjusted and estimated from multistate model (AFT) with generalized gamma distribution or through a hazard ratio formulation assuming proportional hazards.

or variable follow-up times,[39] which can also cause competing risks[14,40,41] and immortal time bias[16,42] to be missed. Insofar as considering dynamic effects is concerned, few studies have taken them into account explicitly[32]; others address the problem indirectly, limiting analyses to arbitrarily early periods,[5,43] and most do not contemplate them at all.[4] Thus, studies coincide in that thrombosis has a constant, negative effect when, in fact, the effect gradually disappears and is residual after 5 to 6 months.

To implement flexible modeling, we have turned to a multistate model that enables complicated life stories to be portrayed with time-dependent events as transitions between states.[31] Within this framework, the AFT model offers the advantages of being robust and easy to interpret,[38] as well as the ability to incorporate nonproportional data, molding the basic shapes of the hazard function.[44] With this method, we have found that CAT heralds progressive disease at first-line chemotherapy and is associated with shortened mOS. Moreover, the state arrival-extended semi-Markov model[31] enabled the differential effect of early or late CAT to be gauged, such that the later the thrombosis, the more intense its effect. Despite the fact that the study was not specifically designed to evaluate the different physiopathology of CAT based on time of occurrence, the data point toward late thromboses being associated with hypercoagulability due to tumor progression and they might have worse prognosis for this reason. On the other hand, early thromboses are related to cisplatin's early thrombogenic effect or with the presence of an initial proinflammatory state, partially captured by the Khorana score. This differential impact depending on its time of appearance is consistent with a prior result observed by Posch et al.[18]

The development of cost-effective thromboprophylaxis strategies calls for the pursuit of reliable thrombotic risk predictors, which is proving to be especially complex in oncology patients.[45] FGR is one of the most popular methods

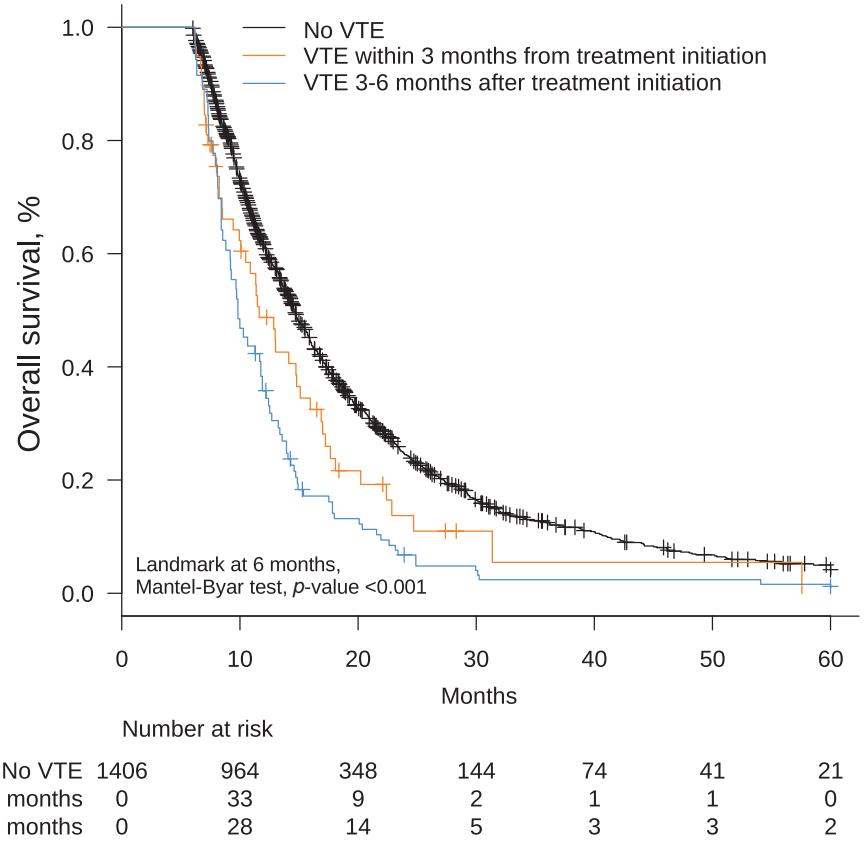

Fig. 2 Kaplan–Meier curves for conditional overall survival from 6-month landmark time, according to the appearance of thrombosis. Patients have been stratified according to development of VTE before 3 months from treatment initiation (orange), between 3 and 6 months (blue), or the nonoccurrence of thrombosis. The plot compares the long-term effects of VTE conditional on surviving at least 6 months. The landmark approach has been used[35]; only patients surviving the first 6 months are included. VTE, venous thromboembolic events.

to model thrombotic risk in the presence of competing events; however, this model is only capable of assuming a constant effect of the predictors.[10,46] Methods have been developed recently to verify whether the assumption of proportional hazards in this model is valid[12]; this is relevant, given that thrombotic risk varies over the natural course of cancer. Here, we have explored the existence of these hypothetical time-varying effects by means of a direct binomial model.[12] The procedure has been able to reveal the complexity of the relations between covariates, so that certain important features of the model, such as the use of cisplatin or secondary thromboprophylaxis, would have been misinterpreted or overlooked if they had been mistakenly assumed to have static effects. On the other hand, the consideration of a flexible competing risks model makes better calibrated predictions possible. As example, the Khorana score is associated with thrombotic risk, but the effect is essentially restricted to early time points, rapidly disappearing as the proinflammatory state that underpins the prediction changes. This dynamic effect is not surprising because, in fact, thrombotic events predicted by the Khorana score occurred after a median of 2.5 months.[39] Being aware of the time-varying effect of the Khorana score not only sheds light on its nature, but also facilitates the possible correspondence between its predictive categories and possible treatment applications, since, based on the dynamic associations, thromboprophylaxis could be prescribed early, late, or of varying duration. The same concept has been seen to apply to other covariates; for instance, tumor burden, which presumably varies over the natural history of the cancer, impacting survival. Similarly, it is interesting that cisplatin-containing regimens have an early prothrombotic effect, which is important to know so as to determine the best thromboprophylaxis strategy. However, in contrast, it must be remembered that using cisplatin in the elderly with prior vascular comorbidity can have an accumulative component that must be factored in. Likewise, in the case of secondary prophylaxis (anticoagulant therapy for a thrombotic event before chemotherapy), a biphasic effect has been observed, with an initial risk of thrombosis, but a protective effect over the longer term. Thus, these time profiles are projected in the prediction of the cumulative incidence in a variable way. In those patients with predominantly early-acting dynamic predictors (e.g., the Khorana index), FGR overestimates thrombotic risk. In contrast, it underestimates risk when the predominant effects act later.

As regards generalizability, one of the key aspects is that the database used, the AGAMENON registry, contains a single kind of tumor. However, we hypothesized that AGC was an ideal model to conduct a simplified appraisal of some of the complexities of paraneoplastic thrombosis, as proof of concept. First, AGC is a relatively common neoplasm, with a

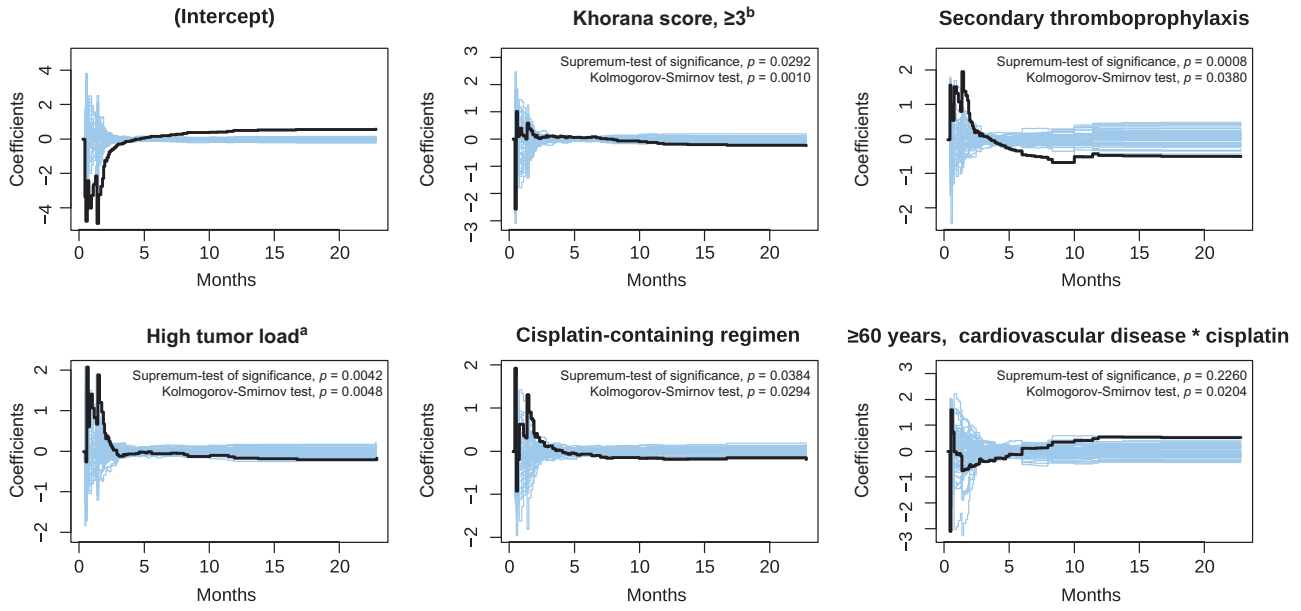

Fig. 3 Time-varying estimates for significant cancer-associated thrombosis (CAT) predictors. The estimates come from a flexible competing risks model. The covariates described by a constant effect are shown in ►**Table 3**. The observed estimates are shown by a black line; the blue lines represent simulations of coefficients based on 500 resamples. The Kolmogorov–Smirnov test evaluates whether predictors have time-varying effect, or the null hypothesis of proportional hazards can be accepted, while the supremum test of significance evaluates the association with thrombotic risk. As a summary of the output, it is appreciated that Khorana, secondary thromboprophylaxis, high tumor burden, and cisplatin-containing regimens have a clearly dynamic effect, not compatible with the Fine–Gray model. [a]High tumor burden was defined as the presence of ≥3 metastatic sites or tumor occupying ≥25% of the liver. [b]The Khorana score was evaluated in a modified way, given that the registry considers prechemotherapy platelet count ≥450 × 10^9/L (+1 point).

Table 4 Flexible competing risk regression (for thrombotic risk)

Covariate	Coefficient	csHR	95% CI	*p*-Value
HER2-positive treated with trastuzumab	0.1550	1.17	0.77–1.78	0.4720
Tumor with signet ring cells	0.3850	1.47	1.06–2.05	**0.0229**
ECOG-PS, ≥ 2	–0.0548	0.95	0.59–1.51	0.8190
Surgery on primary tumor (baseline)	–0.0407	0.96	0.66–1.40	0.8310
Bone metastases	0.1520	1.16	0.72–1.88	0.5350
Use of anticoagulant therapy[a]				
Primary prophylaxis	–0.8500	0.43	0.18–0.99	**0.0490**
≥ 60 years of age, with chronic cardiovascular disease[b]	–0.0923	0.91	0.49–1.70	0.7720

Abbreviations: CI, confidence interval; csHR, cumulative subhazard ratio; HER2, human epidermal growth factor receptor 2; ECOG PS, Eastern Cooperative Oncology Group performance status scale; VTE, venous thromboembolic disease.
Notes: The estimates come from a direct multivariate binomial model, with cloglog link. The parametric part (constant effects of the model) is represented here, while the dynamic covariates of this model are shown in ►**Fig. 2**.
[a]Primary thromboprophylaxis included those who received low molecular weight heparin for the prevention of VTE, but also those subjects who were anticoagulated for atrial fibrillation.
[b]Chronic vascular disease includes chronic heart disease, peripheral vascular disease, and prior cerebrovascular disease.

high cumulative incidence of VTE (9–24%).[20,21,47] Different studies have reported that thrombosis has a negative prognostic effect in AGC.[8,22,47,48] Moreover, several characteristics simplify CAT modeling in this registry by attenuating the most pronounced oscillations of thrombotic risk, such as the relatively homogenous clinical course of AGC,[30] similar chemotherapy treatments, and limited histopathological varieties. The thrombotic risk associated with signet ring cell tumors, cisplatin-containing regimens, and high tumor burden reported here is compatible with data from the literature.[47,49–51] Thus, it is interesting that primary thromboprophylaxis was associated with a reduction of thrombotic risk (csHR, 0.43; 95% CI, 0.18–0.99; $p = 0.049$), similar to the estimated magnitude for ambulatory cancer patients.[52]

Our study has several limitations that should be taken into account. The most evident one is the registry's retrospective nature, with the limited accuracy this involves. Second, the study of CAT was a predetermined aim of the registry, but data collection focused on the events that took place during first-line treatment. This may complicate the estimation of

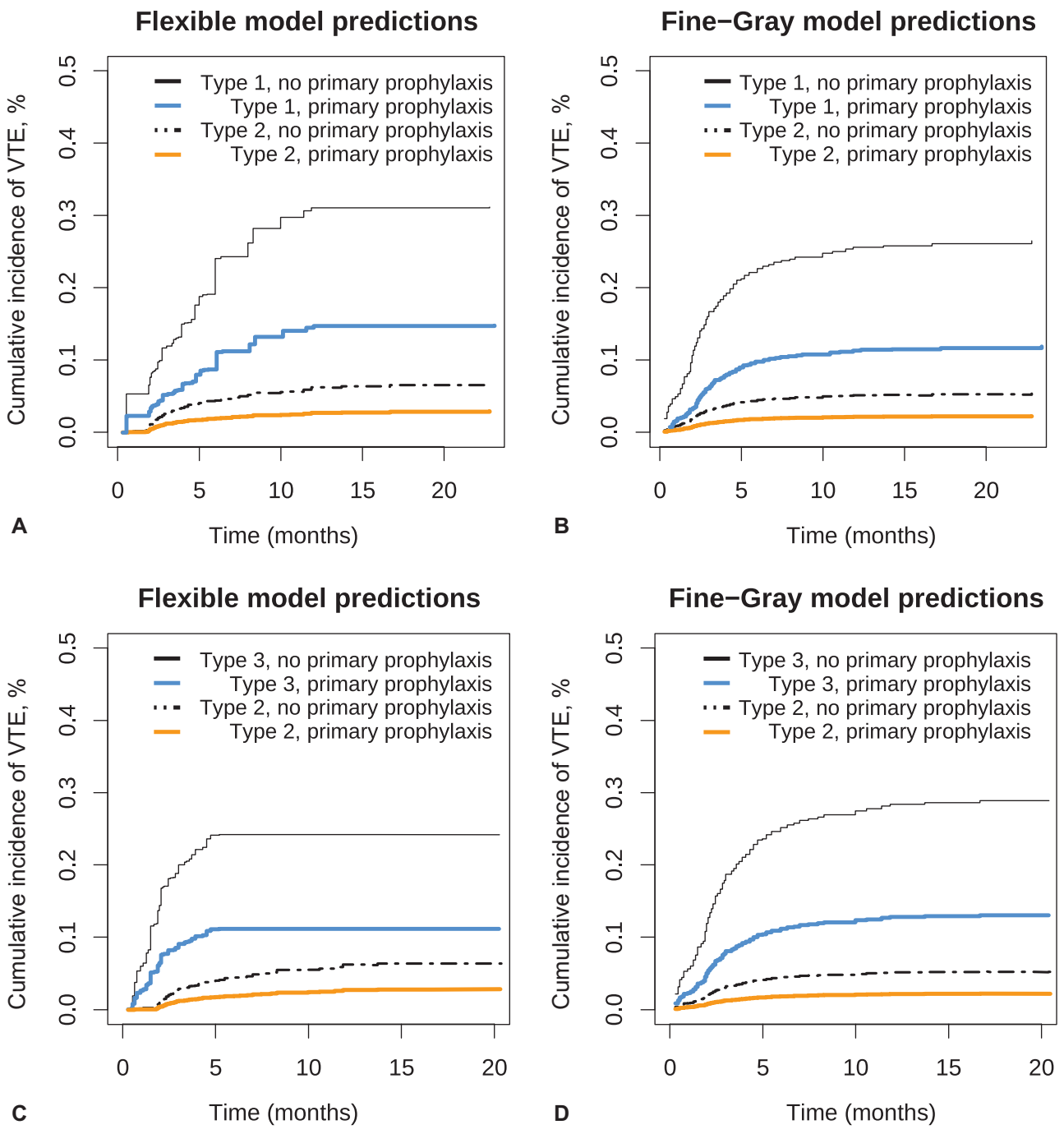

Fig. 4 Predictions of cumulative incidence function using a flexible competing risks model (**A** and **C**) or assuming proportional hazards (**B** and **D**) for three patient profiles. The graphs represent three patients' profiles, type 1 is an elderly person with chronic vascular comorbidity, who has a tumor with signet ring cells, high tumor burden, treated with cisplatin, who presents a Khorana 3. Type 2 has none of these features. Type 3 is similar to type 1, but has no vascular comorbidity. Predictions are stratified according to the use of primary thromboprophylaxis. Abbreviation: VTE, venous thromboembolism.

the individual effect of several covariates on thrombotic risk, in light of the presence of thrombotic events prior to first-line.

In conclusion, while the use of this method is still uncommon in hemostasis, our data demonstrate that flexible multistate analyses are promising analytical techniques that should be extended to CAT studies, given that time-dependent effects should not be discounted. This framework would make it possible to perform adaptable, multiple endpoint evaluations under the same umbrella, providing contextually rich and realistic descriptions of interactions and of these patients' clinical evolution. The study supports that the innovative integration of time-varying effects analysis within the theoretical framework of the multistate

model can aid in selecting patients for thromboprophylactic strategies.

What is known about this topic?

- The "life histories" of oncology patients with venous thromboembolic events (VTE) are complex and most develop multiple time-dependent risk factors that exert a dynamic effect.
- Multistate models provide rich descriptive insights in the process of cancer-associated VTE for both estimation and prediction.
- Survival is growing in these patients, which implies that the hazards of progression or death will not be proportional to the effect of VTE in most studies.

What does this paper add?

- Time-varying effects should not be overlooked when analyzing cancer-associated VTE, so flexible analyses, within the framework of multistate models, are promising methods by which to assess cancer-associated VTE.
- VTE shortens progression-free and overall survival, depending on the effect of the time at which thrombosis occurs.
- The multistate model makes it possible to globally dissect the leading risk factors and the impact of VTE in this population.

Ethical Approval

All procedures followed were in accordance with the ethical standards of the (institutional and national) committee responsible for human experimentation and with the Helsinki Declaration of 1964 and later versions. Informed consent was obtained from all patients before they were included in the study.

Funding

None.

Conflict of Interest

None declared.

Acknowledgments

The authors thank Priscilla Chase Duran for editing the manuscript. They also thank Natalia Cateriano, Miguel Vaquero, and IRICOM S.A. for supporting the registry Web site. The authors also thank Chris Jackson for his help in interpreting flexible models.

References

1 Jimenez-Fonseca P, Carmona-Bayonas A, Calderon C, et al. FOTROCAN Delphi consensus statement regarding the prevention and treatment of cancer-associated thrombosis in areas of uncertainty and low quality of evidence. Clin Transl Oncol 2017;19(08): 997–1009
2 Falanga A, Marchetti M, Vignoli A. Coagulation and cancer: biological and clinical aspects. J Thromb Haemost 2013;11(02): 223–233
3 Ay C, Dunkler D, Marosi C, et al. Prediction of venous thromboembolism in cancer patients. Blood 2010;116(24):5377–5382
4 Carmona-Bayonas A, Jimenez-Fonseca P, Fernández-Somoano A, et al. Top ten errors of statistical analysis in observational studies for cancer research. Clin Transl Oncol 2018;20(08):954–965
5 Chew HK, Wun T, Harvey D, Zhou H, White RH. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. Arch Intern Med 2006;166(04):458–464
6 Brand JS, Hedayati E, Bhoo-Pathy N, et al. Time-dependent risk and predictors of venous thromboembolism in breast cancer patients: a population-based cohort study. Cancer 2017;123(03):468–475
7 Khan UT, Walker AJ, Baig S, Card TR, Kirwan CC, Grainge MJ. Venous thromboembolism and mortality in breast cancer: cohort study with systematic review and meta-analysis. BMC Cancer 2017;17(01):747
8 Sørensen HT, Mellemkjaer L, Olsen JH, Baron JA. Prognosis of cancers associated with venous thromboembolism. N Engl J Med 2000;343(25):1846–1850
9 Lyman GH, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol [Internet] 2013;31:2189–204
10 Ay C, Posch F, Kaider A, Zielinski C, Pabinger I. Estimating risk of venous thromboembolism in patients with cancer in the presence of competing mortality. J Thromb Haemost 2015;13(03):390–397
11 Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. Circulation 2016;133 (06):601–609
12 Scheike TH, Zhang M-J. Analyzing competing risk data using the R timereg package. J Stat Softw NIH Public Access; 2011:38
13 Martinussen T, Scheike TH. Dynamic Regression Models for Survival Data. Berlin, Germany: Springer Science & Business Media; 2007
14 Blix K, Gran OV, Severinsen MT, et al. Impact of time since diagnosis and mortality rate on cancer-associated venous thromboembolism: the Scandinavian Thrombosis and Cancer (STAC) cohort. J Thromb Haemost 2018;16(07):1327–1335
15 Suissa S. Immortal time bias in pharmaco-epidemiology. Am J Epidemiol 2008;167(04):492–499
16 Metcalf RL, Fry DJ, Swindell R, et al. Thrombosis in ovarian cancer: a case control study. Br J Cancer 2014;110(05):1118–1124
17 Geskus RB. Data Analysis with Competing Risks and Intermediate States. Boca Raton, FL: Chapman and Hall/CRC Press; 2015
18 Posch F, Riedl J, Reitter E-M, et al. Hypercoagulabilty, venous thromboembolism, and death in patients with cancer. A multistate model. Thromb Haemost 2016;115(04):817–826
19 Crowther MJ, Lambert PC. Parametric multistate survival models: flexible modelling allowing transition-specific distributions with application to estimating clinically useful measures of effect differences. Stat Med 2017;36(29):4719–4742
20 Marshall-Webb M, Bright T, Price T, Thompson SK, Watson DI. Venous thromboembolism in patients with esophageal or gastric cancer undergoing neoadjuvant chemotherapy. Dis Esophagus 2017;30(02):1–7
21 Larsen AC, Dabrowski T, Frøkjær JB, et al. Prevalence of venous thromboembolism at diagnosis of upper gastrointestinal cancer. Br J Surg 2014;101(03):246–253
22 Tetzlaff ED, Correa AM, Komaki R, et al. Significance of thromboembolic phenomena occurring before and during chemoradiotherapy for localized carcinoma of the esophagus and gastroesophageal junction. Dis Esophagus 2008;21(07):575–581

23 Carmona-Bayonas A, Jiménez-Fonseca P, Custodio A, et al. Anthracycline-based triplets do not improve the efficacy of platinum-fluoropyrimidine doublets in first-line treatment of advanced gastric cancer: real-world data from the AGAMEMON National Cancer Registry. Gastric Cancer 2018;21(01):96–105
24 Carmona-Bayonas A, Jiménez-Fonseca P, Lorenzo MLS, et al. On the effect of triplet or doublet chemotherapy in advanced gastric cancer: results from a national cancer registry. J Natl Compr Canc Netw 2016;14(11):1379–1388
25 Custodio A, Carmona-Bayonas A, Jiménez-Fonseca P, et al. Nomogram-based prediction of survival in patients with advanced oesophagogastric adenocarcinoma receiving first-line chemotherapy: a multicenter prospective study in the era of trastuzumab. Br J Cancer 2017;116(12):1526–1535
26 Carmona-Bayonas A, Jiménez-Fonseca P, Echavarria I, et al; AGAMENON Study Group. Surgery for metastases for esophageal-gastric cancer in the real world: data from the AGAMENON national registry. Eur J Surg Oncol 2018;44(08):1191–1198
27 Jiménez Fonseca P, Carmona-Bayonas A, Hernández R, et al. Lauren subtypes of advanced gastric cancer influence survival and response to chemotherapy: real-world data from the AGAMENON National Cancer Registry. Br J Cancer [Internet] 2017;117 (06):775–782
28 Visa L, Jiménez-Fonseca P, Martínez EA, et al; AGAMENON Study Group. Efficacy and safety of chemotherapy in older versus non-older patients with advanced gastric cancer: a real-world data, non-inferiority analysis. J Geriatr Oncol 2018;9(03):254–264
29 Jiménez-Fonseca P, Carmona-Bayonas A, Sánchez Lorenzo ML, et al. Prognostic significance of performing universal HER2 testing in cases of advanced gastric cancer. Gastric Cancer 2017;20(03):465–474
30 Meira-Machado L, de Uña-Alvarez J, Cadarso-Suárez C, Andersen PK. Multi-state models for the analysis of time-to-event data. Stat Methods Med Res 2009;18(02):195–222
31 Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med 2007;26(11):2389–2430
32 Brand JS, Hedayati E, Humphreys K, et al. Chemotherapy, genetic susceptibility, and risk of venous thromboembolism in breast cancer patients. Clin Cancer Res 2016;22(21):5249–5255
33 Therneau T, Crowson C, Atkinson E. Using time dependent covariates and time dependent coefficients in the cox model. Survival Vignettes. Available at: https://cran.r-project.org/web/packages/survival/vignettes/timedep.pdf. Accessed July 27, 2019
34 Harrell F. Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis. 2nd ed. New York: Springer; 2015
35 Dafni U. Landmark analysis at the 25-year landmark point. Circ Cardiovasc Qual Outcomes 2011;4(03):363–371
36 R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria; 2019. Available at: https://www.R-project.org/. Accessed
37 de Wreede LC, Fiocco M, Putter H. The mstate package for estimation and prediction in non- and semi-parametric multi-state and competing risks models. Comput Methods Programs Biomed 2010;99(03):261–274
38 Jackson CH. flexsurv: a platform for parametric survival modeling in R. J Stat Softw; 2016;70:pii: i08
39 Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood 2008;111(10):4902–4907
40 Parpia S, Julian JA, Thabane L, Lee AY, Rickles FR, Levine MN. Competing events in patients with malignant disease who are at risk for recurrent venous thromboembolism. Contemp Clin Trials 2011;32(06):829–833
41 Prandoni P, Lensing AW, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood 2002;100(10):3484–3488
42 Muriel A, Jiménez D, Aujesky D, et al; RIETE Investigators. Survival effects of inferior vena cava filter in patients with acute symptomatic venous thromboembolism and a significant bleeding risk. J Am Coll Cardiol 2014;63(16):1675–1683
43 Font C, Carmona-Bayonas A, Beato C, et al. Clinical features and short-term outcomes of cancer patients with suspected and unsuspected pulmonary embolism: the EPIPHANY study. Eur Respir J 2017;49(01):pii:1600282
44 Prentice RL. A log gamma model and its maximum likelihood estimation. Biometrika Oxford Univ Press 1974;61:539–544
45 van Es N, Di Nisio M, Cesarman G, et al. Comparison of risk prediction scores for venous thromboembolism in cancer patients: a prospective cohort study. Haematologica 2017;102 (09):1494–1501
46 Campigotto F, Neuberg D, Zwicker JI. Accounting for death as a competing risk in cancer-associated thrombosis studies. Thromb Res 2012;129(Suppl 1):S85–S87
47 Lee KW, Bang SM, Kim S, et al. The incidence, risk factors and prognostic implications of venous thromboembolism in patients with gastric cancer. J Thromb Haemost 2010;8(03):540–547
48 Siewert JR, Böttcher K, Roder JD, et al. Venous thromboembolism in patients receiving perioperative chemotherapy for esophagogastric cancer. Br J Surg Wiley Online Library 1993;80:1015–1018
49 Starling N, Rao S, Cunningham D, et al. Thromboembolism in patients with advanced gastroesophageal cancer treated with anthracycline, platinum, and fluoropyrimidine combination chemotherapy: a report from the UK National Cancer Research Institute Upper Gastrointestinal Clinical Studies Group. J Clin Oncol 2009;27(23):3786–3793
50 Bosch DJ, Van Dalfsen QA, Mul VEM, Hospers GA, Plukker JT. Increased risk of thromboembolism in esophageal cancer patients treated with neoadjuvant chemoradiotherapy. Am J Surg 2014; 208(02):215–221
51 Kang MJ, Ryoo B-Y, Ryu M-H, et al. Venous thromboembolism (VTE) in patients with advanced gastric cancer: an Asian experience. Eur J Cancer 2012;48(04):492–500
52 Di Nisio M, Porreca E, Otten H-M, Rutjes AW. Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy. Cochrane Database Syst Rev 2014; (08):CD008500

Supplementary Material A Variables and endpoints

Variables	Definitions
Definition of venous thromboembolic event (VTE) endpoint	VTE included all thrombosis grade $\geq$2 according to the Common Terminology Criteria for Adverse Events (CTCAE) classification v3.0 (56), regardless of whether the diagnosis was incidental or symptomatic. This definition excludes superficial thrombophlebitis (grade 1). The registry recorded only those thromboses that occurred during first-line chemotherapy. The reason for choosing this target was the initial intention of developing a practical predictive model for thrombotic risk in patients receiving ambulatory chemotherapy (e.g., in whom thromboprophylaxis might be useful). There are no data available for thrombosis beyond first-line chemotherapy. Diagnosis was made by means of objective imaging techniques (CT to assess antitumor response, Doppler ultrasound, etc.) depending on each center's clinical practice. Images were not subject to control by a centralized radiology team. Thrombotic events taking place prior to initiating chemotherapy were deemed history of prior VTE and were analyzed as such separately. Successive thromboses were recorded in this registry as thrombotic recurrences.
Overall survival (OS) and progression-free survival (PFS)	OS and PFS were defined as the time between treatment initiation (first-line chemotherapy for advanced disease) and tumor progression or all-cause mortality, censoring patients lost to follow-up.
Selection of variables	To create the predictive model, we contemplated 38 clinical and histopathological covariates with a plausible relation with thrombotic risk in earlier studies. Among them are (1) patient-related factors, such as demographic data, Eastern Cooperative Oncology Group Performance Status (ECOG-PS) scale, number of chronic comorbidities according to the Charlson comorbidity index (57); laboratory parameters including platelet or leukocyte count; modified Khorana score (dichotomizing thrombocytosis at $>$ 450,000/μL) and tumor-dependent characteristics (liver tumor load, number of metastatic sites, location of metastasis, or histopathological traits).
High tumor load	High tumor load was defined as the presence $\geq$ 3 metastatic sites or tumor occupying $\geq$ 25% of the liver.
Khorana risk score	This score was applied in a modified way insofar as the AGAMENON registry considered a pre-chemotherapy platelet count $\geq 450 \times 10^9$/L (+1 point). The remaining variables were scored as per the model's original description (Khorana et al, Blood 111:4902–4907, 2008): BMI $\geq$ 35 kg/m^2 (+1), prechemotherapy leukocyte count $> 11 \times 10^9$/L (+1), hemoglobin level $<$ 10 g/dL or using red blood cells growth factors (+1), gastric cancer (+2). The original description defines the high-risk group as those patients having $\geq$ 3 points, with a VTE rate of 6.7–7% at 2.5 months.
ECOG PS	The ECOG-PS is based on 5 grades, from 0 to 5, with 0 denoting perfect health and 5 indicating death. The purpose of this scale is to assess how the disease affects patients' daily living abilities.
Metastatic sites (organs involved)	This variable is defined as the number of organs involved, not the number of metastases. Distant lymph node regions (cervical, thoracic, abdominal, peritoneal, retroperitoneal, inguinal, etc.) should be considered independently. The primary tumor is not counted.
Signet ring cell adenocarcinoma	This definition was considered in this study if the tumor exhibited evidence of signet ring cells, regardless of the percentage.
Histological grade	Grade denotes the degree of differentiation of cancer cells that correlates with the aggressiveness of the tumor. Pathologic grade classifies gastric cancer into 1 of 3 categories: well- (G1), moderately- (G2), or poorly-differentiated (G3).
NLR ratio	Neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the absolute neutrophil count by the number of lymphocytes in a peripheral blood sample.
HER2-positive treated tumor	HER2-positive tumor (defined as 3+ immunohistochemical staining (IHC) or 2+ IHC with fluorescence in situ hybridization positivity) undergoing first-line trastuzumab with polychemotherapy.
Major bleeding	Major bleeding is defined as episodes in a critical location (intracranial, intraspinal, intraocular, retroperitoneal, or pericardial) associated with death; bleeding with hemoglobin levels of $>$ 2 g/dL, or bleeding requiring two units of packed red blood cells.
Venous rethrombosis	Rethrombosis was defined as a second thrombotic event after proper anticoagulant treatment of the previous event.
Primary thromboprophylaxis	In this study, primary thromboprophylaxis included those who received low molecular weight heparin for the prevention of VTE, but also those subjects who were anticoagulated for atrial fibrillation.
Secondary thromboprophylaxis	In this study, secondary thromboprophylaxis is one in which patients with paraneoplastic thrombosis initiated anticoagulant therapy before the first cycle of chemotherapy for advanced disease, and maintained it during the course of treatment.

Supplementary Material C Comparison of parametric models. The Akaike information criterion (AIC) and Bayesian information criterion (BIC) are measures of goodness-of-fit. Lower values indicate a better fit.

Model	AIC	BIC
Log-logistic	12174.26	12254.39
Generalized F	12175.42	12266.99
Generalized gamma	12202.47	12288.32
Log-normal	12222.72	12302.84
Gamma	12296.59	12376.72
Weibull	12366.06	12446.18

Supplementary Material D Fine and Gray competing risk regression (for thrombotic risk)

Covariate	Coefficient	Robust SE	95% CI	*p*-Value
HER2-positive treated with trastuzumab	0.1920	0.211	–0.2220 to 0.6060	0.3620
Tumor with signet ring cells	0.3980	0.167	0.0707 to 0.7250	0.0173
ECOG-PS, ≥ 2	–0.0163	0.233	–0.4730 to 0.4400	0.9440
Khorana score, ≥ 3 Ψ	0.3760	0.162	0.0585 to 0.6940	0.0201
Surgery on primary tumor (baseline)	–0.0247	0.191	–0.3990 to 0.3500	0.8970
Bone metastases	0.1810	0.243	–0.2950 to 0.6570	0.4570
Use of anticoagulant therapy ‡ Primary prophylaxis Secondary prophylaxis	–0.8910 0.4350	0.442 0.432	–1.7600 to –0.0247 –0.4120 to 1.2800	0.0437 0.3130
High tumor load §	0.3890	0.166	0.0636 to 0.7140	0.0193
Cisplatin-containing regimen	0.3090	0.175	–0.0340 to 0.6520	0.0775
≥ 60 years of age, with chronic cardiovascular disease*	–0.0505	0.318	–0.6740 to 0.5730	0.8740
≥ 60 years of age, with chronic cardiovascular disease* Cisplatin-containing regimen (interaction)	0.3170	0.456	–0.5770 to 1.2100	0.4870

ΨThe Khorana score was evaluated in a modified way since the registry considers the pre-chemotherapy platelet count $\geq 450 \times 10^9$/L.
‡Primary thromboprophylaxis included those subjects who received low molecular weight heparin for the prevention of cancer-associated thrombosis, but also subjects anticoagulated by atrial fibrillation. Secondary thromboprophylaxis included those individuals anticoagulated by paraneoplastic thrombosis prior to either first-line chemotherapy or diagnosis.
*Chronic cardiovascular disease includes chronic heart disease, peripheral vascular disease, and previous cerebrovascular disease.