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Original article

A snapshot of cancer-associated thromboembolic disease in 2018–2019: First data from the TESEO prospective registry

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ABSTRACT

Background: The ever-growing complexity of cancer-associated thrombosis (CAT), with new antineoplastic drugs and anticoagulants, distinctive characteristics, and decisions with low levels of evidence, justifies this registry.

Method: TESEO is a prospective registry promoted by the Spanish Society of Medical Oncology to which 34 centers contribute cases. It seeks to provide an epidemiological description of CAT in Spain.

Results: Participants (N = 939) with CAT diagnosed between July 2018 and December 2019 were recruited. Most subjects had advanced colon (21.4%), non-small cell lung (19.2%), and breast (11.1%) cancers, treated with dual-agent chemotherapy (28.4%), monochemotherapy (14.4%), or immune checkpoint inhibitors (3.6%). Half (51%) were unsuspected events, albeit only 57.1% were truly asymptomatic. Pulmonary embolism (PE) was recorded in 571 (58.3%); in 120/571 (21.0%), there was a concurrent deep venous thromboembolism (VTE). Most initially received low molecular weight heparin (89.7%). Suspected and unsuspected VTE had an OS rate of 9.9 (95% CI, 7.3-non-computable) and 14.4 months (95% CI, 12.6-non-computable) ($p = 0.00038$). Six-month survival was 80.9%, 55.9%, and 55.5% for unsuspected PE, unsuspected PE admitted for another reason, and suspected PE, respectively ($p < 0.0001$). The 12-month cumulative incidence of venous rethrombosis was 7.1% (95% CI, 4.7-10.2) in stage IV vs 3.0% (95% CI, 0.9-7.1) in stages I-III. The 12-month cumulative incidence of major/clinically relevant bleeding was 9.6% (95% CI, 6.1-14.0) in the presence of risk factors.

Conclusion: CAT continues to be a relevant problem in the era of immunotherapy and targeted therapies. The initial TESEO data highlight the evolution of CAT, with new agents and thrombotic risk factors.

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1. Introduction

Venous thromboembolism (VTE) is a common cause of morbidity and mortality among patients with cancer [1]. Both pathologies interrelate at a deep biological level with numerous interactions between key elements of the hemostatic system and cancer cell programs [2]. Cancer-associated thrombosis (CAT) falls within a panorama of growing complexity in oncology, with the appearance of new anticoagulant therapies, emerging molecular data [3], and new antineoplastic treatments associated with thrombotic risk. Most targeted therapies that have proven benefit in recent clinical trials, such as CDK4/6 inhibitors, immune checkpoint inhibitors, or antiangiogenics, are linked to increased risk of VTE [4–6]. Managing CAT is challenging, given the higher risk of rethrombosis and severe bleeding with anticoagulant treatment [7]. Moreover, people with cancer exhibit numerous specific characteristics, such as the use of chemotherapy, hormone therapy, or targeted therapies with specific mechanisms of action and toxicities, increased incidental thrombosis, and chronic comorbidities (hepatic, renal, thrombocytopenia, etc.) that add an extra layer of complication to decision-making.

Despite the multiple clinical practice guidelines regarding the prevention and management of CAT, numerous critical decisions about anticoagulant therapy, primary thromboprophylaxis, or management of special cases continue to be made with low levels of evidence [8]. The problem is exacerbated, in light of the high percentage of these patients who will not be eligible or will be under-represented in clinical trials, given the complexity of their clinical situation [9].

The Spanish Society of Medical Oncology's (SEOM) registry of thrombosis and embolism [TESEO] was born in 2018 to detect emerging epidemiological trends in CAT and to analyze outcomes in real-world clinical practice of cases that run the gamut from ordinary to the most highly complex and exceptional (e.g., those with high risk of bleeding, incidental episodes, etc.). With these premises, we present the first data coming out of the TESEO registry (NCT03855592) that provide a prospective snapshot of CAT (2018-2019).

2. Method

2.1. Patients and study design

TESEO is a prospective registry under the auspices and management of SEOM with the collaboration of 34 Spanish hospitals that recruit consecutive cases of CAT [10].

Eligibility criteria consist of individuals ≥18 years of age with cancer, with a VTE event confirmed by objective imaging technique (Doppler ultrasound, CT angiography scans, high probability scintigraphy, CT scheduled to assess tumor response or for other reasons, etc.). In the case of multiple episodes, only the first event is recorded as the index event. Exclusion criteria include superficial thrombophlebitis and the appearance of VTE >1 month prior to their cancer diagnosis or >1 month after completing adjuvant therapy.

The TESEO database is managed via a web platform consisting of filters and a system of queries to assure the reliability, structure, and temporal relation of events and outcomes, and to minimize missing values and inconsistences. The registry monitors cases remotely and online. The study was approved by a multicenter Research Ethics Committee of all the Autonomous Communities and participating centers and was classified as a post-marketing, prospective, follow-up study by the Spanish Agency of Medicines and Medical Devices. All participants still alive at the time of data collection signed written informed consent forms. Informed consent was allowed to be exempt for those patients who died very suddenly after their VTE diagnosis so as to avoid biasing the database.

2.2. Variables and objectives

The aim of this study is to provide an epidemiological description of CAT in Spain. The study variables included clinical and molecular characteristics of the neoplasms, VTE-associated variables, prognostic evaluation of the episodes, and anticoagulant therapy. The study endpoints comprise overall survival, 15-day complication rate, venous rethrombosis, and bleeding. Overall survival (OS) was defined as the time since development of VTE and all-cause mortality, bearing in mind the right-censored nature of the data. Lacking autopsy, the investigators attributed cause of death on the basis of clinical record review and findings on complementary testing.

Death was ascribed exclusively to VTE when there was a direct nexus of causality through a series of events related to the physiopathology of the VTE, such as shock or respiratory failure, and no suspicion of cancer-related mechanisms. This definition is consistent with previous definitions put forth by our group [11]. Mixed cause mortality was defined as the presence of a temporal association between demise and VTE, although multiple intercurrent conditions (e.g., infections or tumor progression) could plausibly have played a more relevant role in patient demise than VTE. Death was deemed unrelated to VTE if there was no clear temporal relation or concatenation of events.

Concurrent diagnosis encompasses those thromboses detected between one month prior to and one week subsequent to the diagnosis of cancer. Rethrombosis was defined as the appearance of a second thrombotic event following proper management of the index VTE or progression of the previous episode despite appropriate anticoagulant therapy. Bleeding severity was graded as per the International Society of Thrombosis and Hemostasis (ISTH) criteria as minor, clinically relevant, or major [12]. Another outcome measure was the occurrence of a serious medical condition between imaging-based VTE diagnosis and 15 days later, following the same criterion as in previous studies [1]. Ambulatory management was defined as discharge <24 hours after arrival at the hospital; early discharge was defined as release within 24-72 hours.

2.3. Statistical methods

Survival was estimated using the Kaplan-Meier method. Survival functions were compared by log-rank tests. The Aalen–Johansen estimator was used to obtain the cumulative incidence function for rethrombosis and bleeding, in the presence of death as a competing event. A multivariable Cox proportional hazards model was used to estimate the effect of the type of VTE on survival. The time pattern of the appearance of thrombosis was visually assessed by means of probability density graphs. Comparisons between proportions were made by $\chi 2$-tests. These descriptive analyses were executed using R version 3.5.1 [13], including the survival, dplyr, tidyr, and ggplot2 packages [14,15].

3. Results

3.1. Patients and oncological context

At the time of analysis, 939 patients diagnosed with VTE between July 2018 and December 2019 had been recruited. The baseline characteristics of these individuals are summarized in Table 1. The most common tumors were high incidence ones: colorectal (n = 201, 21.4%), non-small cell lung (n = 181, 19.2%), and breast (n = 105, 11.1%), followed by of other neoplasms associated with high thrombotic risk (pancreas, stomach, ovary, etc.) (see detailed list in A.1).

Most had an active tumor or stage IV (n = 672, 71.5%) at the time of the event and only a minority were receiving adjuvant (n = 104, 11.0%) or neoadjuvant (n = 52, 5.5%) therapy. However, distribution based on TNM stage varied significantly according to tumor type, with stage IV in 48.6%, 71.6%, and 80.1%, in breast, colorectal, and non-small cell lung

Table 1
Baseline characteristics of patients and thrombotic episodes. Abbreviations: EGFR, Epidermal Growth Factor Receptor; DVT, Deep venous thrombosis; PE, pulmonary embolism; NCI-CTC, National Cancer Institute Common Toxicity Criteria.

Baseline characteristics	N (%)
Age (median, range)	65 (25-92)
Sex, male	477 (50.8)
Most common tumors	
Colorectum	201 (21.4)
Lung - Non-small cell	181 (19.2)
Breast	105 (11.1)
Pancreas	77 (8.2)
Stomach	55 (5.8)
Ovarian	33 (3.5)
Bladder	28 (2.9)
Endometrial	25 (2.6)
Bile duct/gallbladder	24 (2.5)
Esophagus	21 (2.2)
Brain	18 (1.9)
Prostate	15 (1.6)
Other/Unknown	192 (20.4)
TNM stage, IV	672 (71.5)
Histology, adenocarcinoma	663 (70.6)
Tumor biomarkers	213 (22.6)
Oncological treatment	
Dual-agent chemotherapy	279 (29.7)
Single-agent chemotherapy	141 (15.0)
Immunotherapy	36 (3.8)
Triple-agent chemotherapy	34 (3.6)
Dual-agent with antiangiogenic	32 (3.4)
Dual-agent with antiEGFR	22 (2.3)
Antiangiogenic	18 (1.9)
Others	377 (40.1)
Type of detection	
Suspected	453 (48.2)
Unsuspected	473 (50.3)
Unknown	13 (1.3)
Type of thromboembolism	
DVT	368 (39.1)
PE + without DVT	451 (48.0)
PE + DVT	120 (12.8)
Severity, NCI-CTC criteria	
Grade 1	-
Grade 2	404 (43.0)
Grade 3	491 (52.2)
Grade 4	27 (2.8)
Grade 5	4 (0.4)
Unknown	13 (1.3)
Unresected primary tumor in mucosa	508 (54.1)
Total	939 (100)

Abbreviations: EGFR, Epidermal Growth Factor Receptor; DVT, Deep venous thrombosis; PE, pulmonary embolism; NCI-CTC, National Cancer Institute Common toxicity Criteria.

cancer, respectively ($\chi 2$ test, $p < 0.0001$) (A.2). The majority of thromboses (n = 663, 70.6%) occurred in subjects with adenocarcinoma histologic subtype cancers. Tumors were biologically heterogenous with known molecular alterations in 22.6% (n = 213), the most common ones being KRAS mutation (n = 64), HER2 overexpression (n = 31), and BRAF mutation (see breakdown in A.3). The antineoplastic regimens most often associated with VTE were chemotherapy doublets (n = 279, 29.7%), monochemotherapy (n = 141, 15%), followed by immune checkpoint inhibitors (n = 36, 3.8%), and triple agent chemotherapy. The most widely used schedules are detailed in the A.4. Strikingly, despite dual-agent chemotherapy being the most common type of therapy, targeted agents as a whole, account for up to 20.0%, making it the second strategy most frequently associated with thrombosis in this series.

Fig. 1A illustrates the time pattern of the appearance of VTE by stage; events tended to be early in localized stages with reactivations during relapse, and a longer tail of events in stage IV. Thus, the median time to thrombosis since cancer diagnosis ranged from 3.8 months (95% confidence interval (CI), 0.8-202) for stage I to 10 months (95% CI, 0-163) in stage IV. These patterns are also reflected in the distribution by tumor type (Fig. 1B). Of these episodes, 8.1% (n = 76) were detected concurrently with the diagnosis of cancer.

3.2. VTE-associated variables

Half (50.3%, n = 473) of the VTE in this registry were unsuspected (Table 1). Nonetheless, only 57.1% (n = 270) of the unsuspected VTE were truly asymptomatic. By large, the main source of symptoms was the VTE itself (n = 412, 43.8%), followed by the tumor (n = 167, 17.7%) and toxicity related to antineoplastic therapies (n = 20, 2.1%) (see Annex 5). Most events were grade 2 (n = 406, 43.2%) or 3 (n = 491, 52.2%), with few grade 4 (n = 27, 2.8%) (NCI-CTC). Pulmonary embolism (PE) was recorded in 571 individuals (60.8%); deep venous thrombosis (DVT) was concurrent with PE in 120/571 (21.0%), while in 451/571 (79%), PE was not accompanied by DVT. PE was more frequent in patients receiving antiangiogenic drugs (73.9% vs 57.1%, $\chi 2$-test, $p = 0.017$). As for DVT (n = 488, including DVT with or without concurrent PE, see Table 1), the most frequent sites were the femoral vein (n = 92, 18.8%), catheter-related (n = 62, 12.7%), popliteal vein (n = 55, 11.2%), and portal vein (n = 34, 6.9%) (see most common sites in Fig. 2).

In part, VTE location depended on the type of neoplasm. For instance, thrombosis of the portal vein or its tributaries, predominantly affected colorectal (n = 21, 33.3%), pancreatic (n = 17, 26.9%), hepatocellular (n = 7, 11.1%), and biliary (n = 5, 7.9%) tumors (A.6). By comparison, catheter-related VTE developed more often in the scenario of colorectal (n = 23, 28.7%), breast (n = 19, 23.7%), and gastric (n = 14, 17.5%) cancer (A.7). The A.8 includes a heat-map with these data.

3.3. Approach and treatment

Table 2 summarizes both treatment and type of approach to CAT. Most of the subjects initially received low molecular weight heparin (LMWH) (n = 826, 87.9%). Other alternatives were less common, such as starting with non-fractionated heparin (n = 54, 5.7%); beginning with LMWH for 2-5 days followed by vitamin K antagonists (VKA) (n = 8, 0.8%); initial LMWH followed by direct oral anticoagulants (DOAC) (n = 8, 0.8%), and DOAC (n = 6, 0.6%). Among the cases treated with LMWH, the most common treatment was enoxaparin, followed by bemiparin and tinzaparin (Table 2).

Most received weight-adjusted LMWH (96.3%), although in some cases lower doses were administered due to prior bleeding (0.5%), bleeding risk (1.2%), renal failure (0.9%), thrombopenia (0.5%), or prophylactic doses (0.5%). At the time of analysis, 60.8% maintained anticoagulant therapy; the most common reasons for termination were having administered for the scheduled duration (40.7%), bleeding (23.8%), palliative treatment (15.1%), patient's decision (7.1%), other complications (6.2%), and other reasons (7.1%). In individuals who have completed treatment, the median duration was 4.2 months (95% CI, 0.1-11.3).

Place of treatment is reported in Table 2. Most were treated in their homes (44.9%), during usual hospital admission (38%), or with early discharge (10.4%). The following are among the most common reasons for in-hospital management: the person was hospitalized for another reason, acute respiratory failure, other non-VTE related medical reasons, safety concerns, cancer evaluation, hemodynamic instability, hospital logistics, and the need for oxygen therapy. In contrast, reasons linked to bleeding risk, such as active hemorrhage, perception of high risk of bleeding, thrombopenia $< 50000/mm3$, were less prevalent (Table 2, A.9).

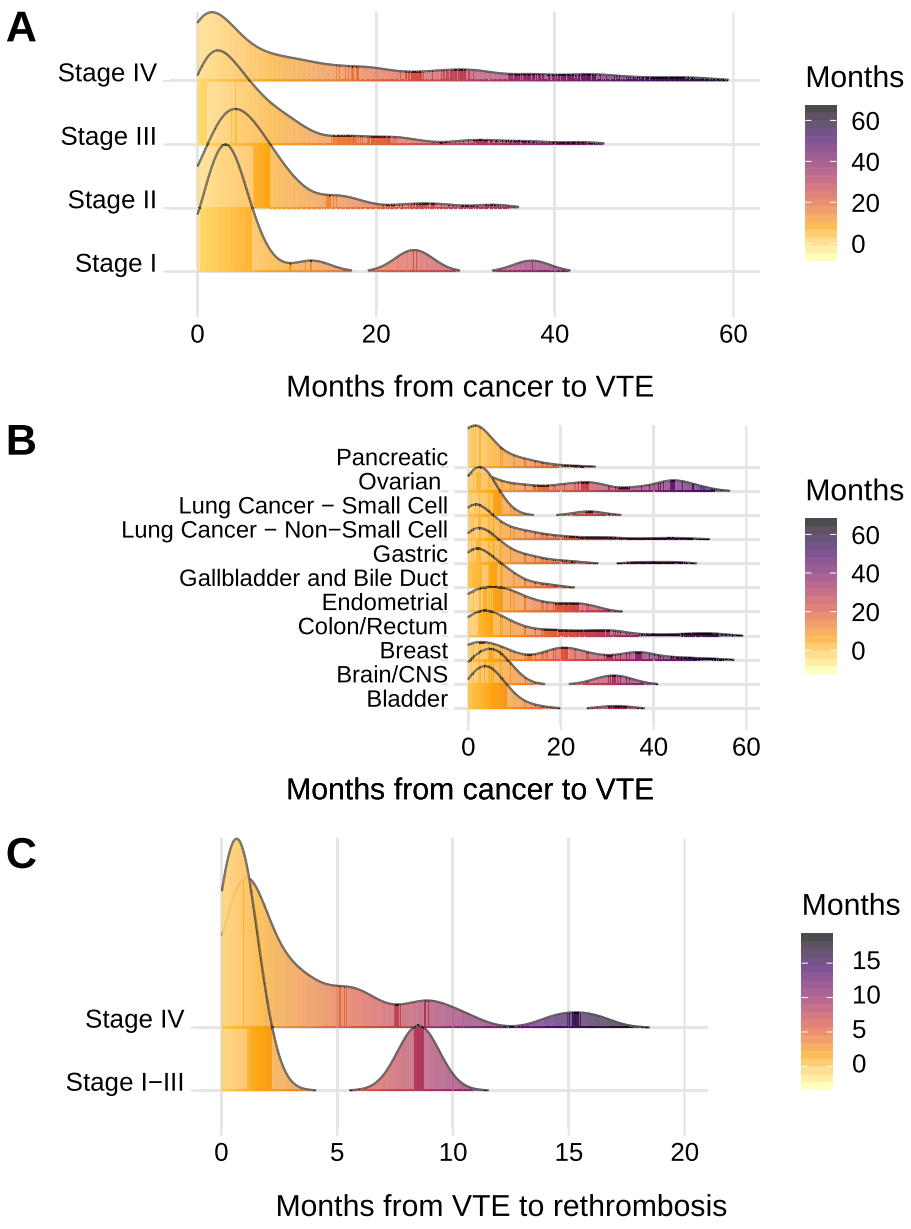

Fig. 1. Time of appearance of thrombosis and rethrombosis (probability density). (A) Time to thrombosis based on stage; (B) Time to thrombosis based on cancer site; (C) time to rethrombosis based on stage. Abbreviations: CNS, central nervous system; VTE, venous thromboembolism. Note: the area under the density curve represents all the events in each group

3.4. Complications and general outcomes

At the time of analysis, survival data were available for 905 (96.3%) cases, with a median follow-up in living patients of 5.7 months (95% CI, 5.2-6.3), having recorded 270 deaths. Table 3 displays the summary of the main outcomes. The most common causes of death were the cancer itself (n = 197, 73%), mixed-cause death with VTE possibly involved (n = 44, 16.3%), infection (n = 9, 3.3%), VTE (n = 9, 3.3%), bleeding (n = 6, 2.2%), and other comorbidities (n = 5, 1.8%) (A.10).

Suspected and unsuspected VTE had median OS rates of 9.9 months (95% CI, 7.3-NR) and 14.4 months (95% CI, 12.6-NA) (log-rank test, p = 0.00038) (Fig. 3A). In the multivariable Cox proportional hazards model, the diagnosis of suspected (as opposed to unsuspected) VTE increased mortality with a hazard ratio of 1.57 (95% CI, 1.21-2.04), p = 0.0005. Unsuspected PE had a better prognosis than suspected PE; 6-month OS rates of 80.9% (95% CI, 75.1-87.2), 55.9% (95% CI, 43.8-71.5), and 55.5% (95% CI, 48.2-64.7), for unsuspected PE with outpatient management, unsuspected PE hospitalized for a different medical reason, and suspected PE, respectively (log-rank test, p < 0.0001) (Fig. 3B).

The cumulative incidence of venous rethrombosis at 12 months was 7.1% (95% CI, 4.7-10.2) in stage IV cancers vs 3.0% (95% CI, 0.9-7.1) in non-metastatic tumors (Fig. 4A). All these episodes occurred after adequate treatment of the index VTE. Most of these patients with venous rethrombosis continued to receive active treatment at the time of relapse, the most common of which were: the same therapy as in the index VTE (n = 13, 34.2%), successive line (n = 9, 23.6%), non-systemic therapy (n = 3, 7.8%), treatment within a clinical trial (n = 3, 7.8%), palliative care (n = 6, 15.7%), and others (n = 4, 10.5%). Tumors having the highest rate of rethrombosis were non-small cell lung (n = 11), colorectal (n = 9), and pancreatic (n = 8) cancers. Median time to rethrombosis was 1.7 months (95% CI, 0.9-3.8). Nevertheless, time to venous rethrombosis varied depending on stage (Fig. 1C). Thus, the median time to rethrombosis was 0.8 months (95% CI, 0.3-7.7) in stages I-III, with upturns at the time of relapse, vs 2.0 months (95% CI, 0.3-14.9) in stage IV.

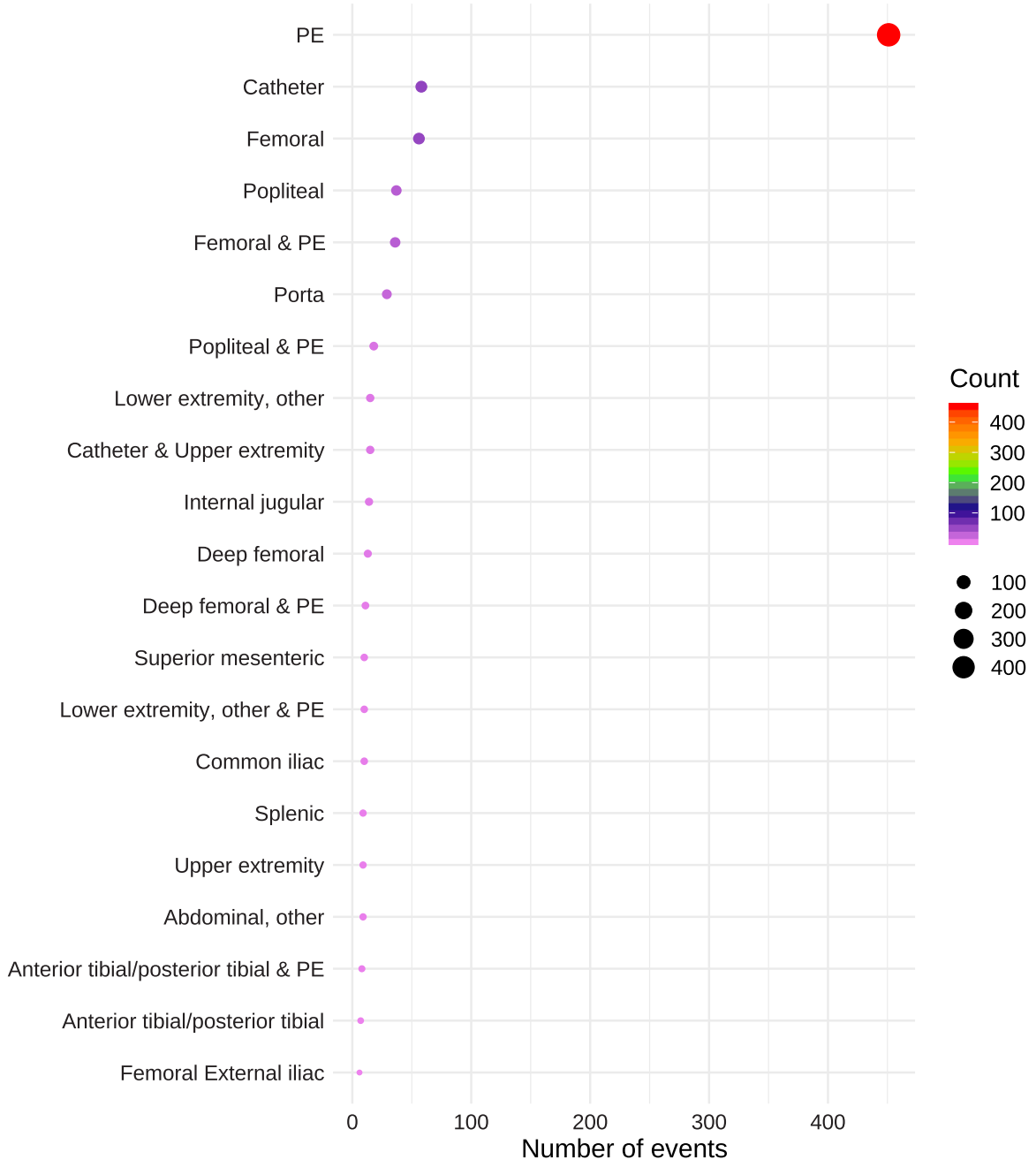

Fig. 2. Site of VTE. In this case, only localizations with >5 events have been represented (the complete graph can be found in the Annex). The analysis allows for the presence of multiple localizations. Abbreviations: PE, pulmonary embolism; VTE, venous thromboembolism.

Venous rethrombosis affected antineoplastic therapy, with only 50% (n = 19) of the patients capable of maintaining the same anticancer schedule, versus 26.3% (n = 10) who moved on to palliative care, 10.5% (n = 4) who kept it, although in modified form, and 13.1% (n = 5) who had to change the line of systemic treatment.

Rethrombosis was similar in suspected or unsuspected VTE. Similarly, no differences were observed in the case of subsegmental PE (A.11). In this registry, there is no statistical evidence that the proportion of venous rethrombosis differs among subjects with subsegmental PE (5.2%; 95% CI 0.9-19.0) compared to other PE (3.3%; 95% CI, 2.0-5.3).

Finally, the 12-month cumulative incidence of major or clinically relevant bleeding was 9.6% (95% CI, 6.1-14.0) in individuals with some risk factor, vs 6.3% (95% CI 4.2-9.2) without risk factors for bleeding (Fig. 4B). The A.12 & 13 displays these data broken down by tumor, intensity of bleeding, and risk factors.

As for those individuals with clinically relevant or major bleeding, 34.6% (n = 18) were still receiving the same line of anticancer treatment; 26.9% (n = 14) were receiving successive lines; 23% (n = 12) were not receiving any treatment, and the remainder were receiving trial therapy (5.7%, n = 3), or unknown (n = 5, 9.6%). Of them, 24 individuals (2.5%, 95% CI, 1.6-3.8) had major bleeding. The sites involved in major bleeding were the gastrointestinal tract (n = 5, 20.8%), central nervous system (n = 4, 16.4%), gastrointestinal anastomosis (n = 2, 8.3%), genitourinary tract (n = 2, 8.3%), other (n = 8, 33.3%), and unknown (n = 3, 12.5%).

4. Discussion

This analysis describes the situation of CAT during the 2018-2019

Table 2
Treatment & approach. Abbreviations: LMWH, low molecular weight heparin; UFH, unfractionated heparin; VKA, vitamin K antagonist; DOAC, direct oral anticoagulant drug.

Variable	N (%)
Anticoagulant therapy	
LMWH	826 (87.9)
Initial UFH followed by LMWH	54 (5.7)
No therapy (palliative care or contraindications)	18 (1.9)
Initial LMWH for 2-5 days followed by VKA	8 (0.8)
Initial LMWH followed by DOAC	8 (0.8)
DOACs	6 (0.6)
Not available	19 (2.0)
Type of LMWH	
Enoxaparin	384 (40.8)
Bemiparin	254 (27.0)
Tinzaparin	196 (20.8)
Enoxaparin biosimilar	31 (3.3)
Dalterparin	17 (1.8)
Nadroparin	7 (0.7)
Other	7 (0.7)
Not available	43 (4.5)
Site of management	
Ambulatory care	422 (44.9)
Normal hospital admission	357 (38.0)
Early discharge	98 (10.4)
Intensive care unit	24 (2.5)
Home hospitalization	15 (1.6)
Ambulatory palliative care	4 (0.4)
Not available	19 (2.0)
Reasons for admission	
Already admitted due to other reasons	105 (27.5)
Acute respiratory failure	66 (17.3)
Other medical reasons	52 (13.6)
Safety concerns	48 (12.6)
Cancer assessment	30 (7.8)
Hemodynamic instability	23 (6.0)
Hospital service logistics	22 (5.7)
Need for oxygen therapy	19 (4.9)
Pre-existing comorbidities	5 (1.3)
Bleeding	4 (1.0)
High risk of bleeding	2 (0.5)
Low platelet count <50,000/mm3	2 (0.5)
Impossible to monitor case	1 (0.2)
Lack of social support	1 (0.2)
Other problems for home care	1 (0.2)

Abbreviations: LMWH, low molecular weight heparin; UFH, unfractionated heparin; VKA, vitamin K antagonist; DOAC, direct oral anticoagulant drug.

Table 3
Outcomes. Abbreviations: CI, confidence interval.

Variable	Estimates, % (95% CI)
Venous rethrombosis (overall)	
3 months	2.9 (1.8-4.3)
6 months	3.8 (2.5-5.4)
12 months	6.0 (4.1-8.5)
Venous rethrombosis (stage IV)	
3 months	3.3 (2.0-5.1)
6 months	4.6 (3.0-6.7)
12 months	7.1 (4.7-10.2)
Bleeding (clinically relevant + major)	
3 months	5.0 (3.6-6.8)
6 months	6.4 (4.7-8-4)
12 months	7.4 (5.4-9.8)
Bleeding (clinically relevant + major) in patients with any risk factor	
3 months	7.1 (4.4-10.6)
6 months	8.8 (5.6-12.9)
12 months	9.6 (6.1-14.0)
Overall survival	
3 months	79.0 (76.1-82.1)
6 months	68.6 (65.1-72.4)
12 months	52.7 (47.8-58.1)

Abbreviations: CI, confidence interval.

period, based on the initial data from the SEOM's registry of thrombosis, TESEO. The reason for undertaking this project has been the perception that cancer treatment is developing at breakneck speed, with transformations that force us to reassess aspects having to do with support [16], re-think the thrombotic risk of new survivors [17], as well as the effect new antitumor drugs have on hemostasis [4–6]. Added to that is the well-known greater complexity of managing VTE in patients with cancer [7] and the low level of evidence with which to confront any number of general or unique VTE-related situations (e.g., managing subjects with thrombopenia, with antiangiogenics, etc.) on a daily basis [8]. In addition, the intention of a prospective thrombosis registry is to contribute epidemiological and descriptive data that validate assumptions derived from clinical trials and facilitate the transference of inferences to daily work [18]. Regular reevaluation may reveal elements to be considered. For example, colorectal, lung and breast are the three most common cancers in TESEO, which is similar to earlier series [1,11]. The epidemiological profile of these tumors, most of them adenocarcinomas, would account for the predominance of this histology in the registry. Nevertheless, the abundance of adenocarcinomas might also be due in part to this histology's greater thrombogenicity associated with specific mechanisms [19]. Nevertheless, the percentage of genitourinary tumors, in particular, prostate cancer, is appreciably lower with respect to historical series [7,20]. One plausible hypothesis to confirm is whether the new prostate cancer therapies (e.g., enzalutamide, abiraterone, etc.) have contributed to decreasing associated thrombotic risk. The epidemiological data from TESEO also help to interpret other data from the literature. For instance, Mahé *et al.* have recently reported that there are significant differences in the clinical course of VTE depending on the type of cancer, with progressively growing rates of rethrombosis in breast, colorectal, and lung neoplasms [21]. Another possible reading in light of our data is that the incremental percentage of rethrombosis in these tumors is simply linked to the progressively increased frequency of advanced disease. All of this points to the need to conduct contextually rich evaluations of the clinical scenario of cancer. The clinical background is that thrombotic risk is a dynamic phenomenon that varies over time and gradually lessens in localized tumors [22,23]. Therefore, comparing thrombotic risk of patients with different tumors, without disaggregating for stage or context, or assuming that the thrombotic risk is constant, fails to enable robust conclusions to be made. For example, the DACUS trial examined prolonging anticoagulant therapy in subjects with active cancer and residual VTE [24]. However, 78% of the individuals with 'active' cancer in this trial had no metastasis, hindering the extrapolation of data to the context of advanced tumors, which is the most common.

The timing of the appearance of events is another aspect of interest when designing possible thromboprophylactic strategies that cover the periods of greatest risk. Essentially, in TESEO most of the events are seen to be early, although probability density curves point toward a dynamic relation with relapses or progressions, as well as slightly dissimilar patterns in different tumors. The data indicate the need to evaluate thrombotic risk longitudinally, updated as per the clinical situation. In this way, ovarian or breast cancer have a clinical course that alternates remissions and relapses, unlike the more homogenous evolution followed by pancreatic cancer, which impacts the incidence of CAT.

The link between thrombosis and specific treatment strategies is another aspect to be taken into account. The TESEO database strongly suggests that an increasing number of patients were receiving targeted molecular therapies, such as immune checkpoint inhibitors, antiangiogenics, or antiEGFR treatments, instead of a single cytotoxic chemotherapy when the thrombosis developed. All of them have an emerging rationale that endorses the contribution of these new agents targeting thrombotic risk, through novel biological mechanisms. Nevertheless, the data gleaned from clinical trials generally capture thrombotic risk as toxicity and details as to the impact of the

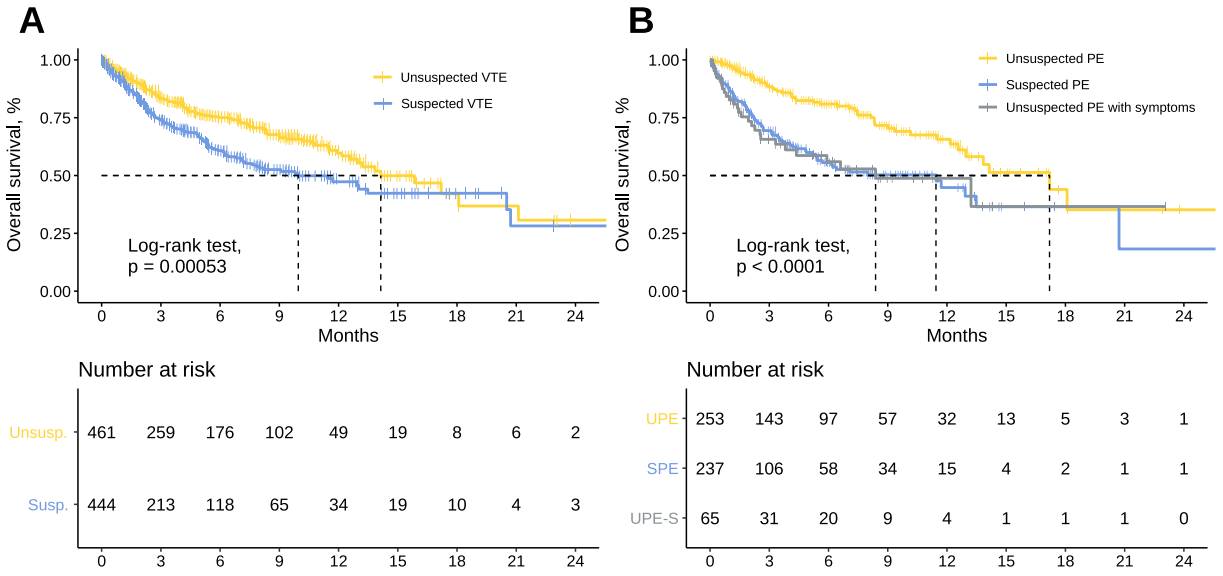

Fig. 3. Survival end points. (A) overall survival based on type of detection (complete series); (B) overall survival of patients with PE in suspected, unsuspected asymptomatic, and unsuspected symptomatic episodes. Abbreviations: PE, pulmonary embolism; VTE, venous thromboembolism.

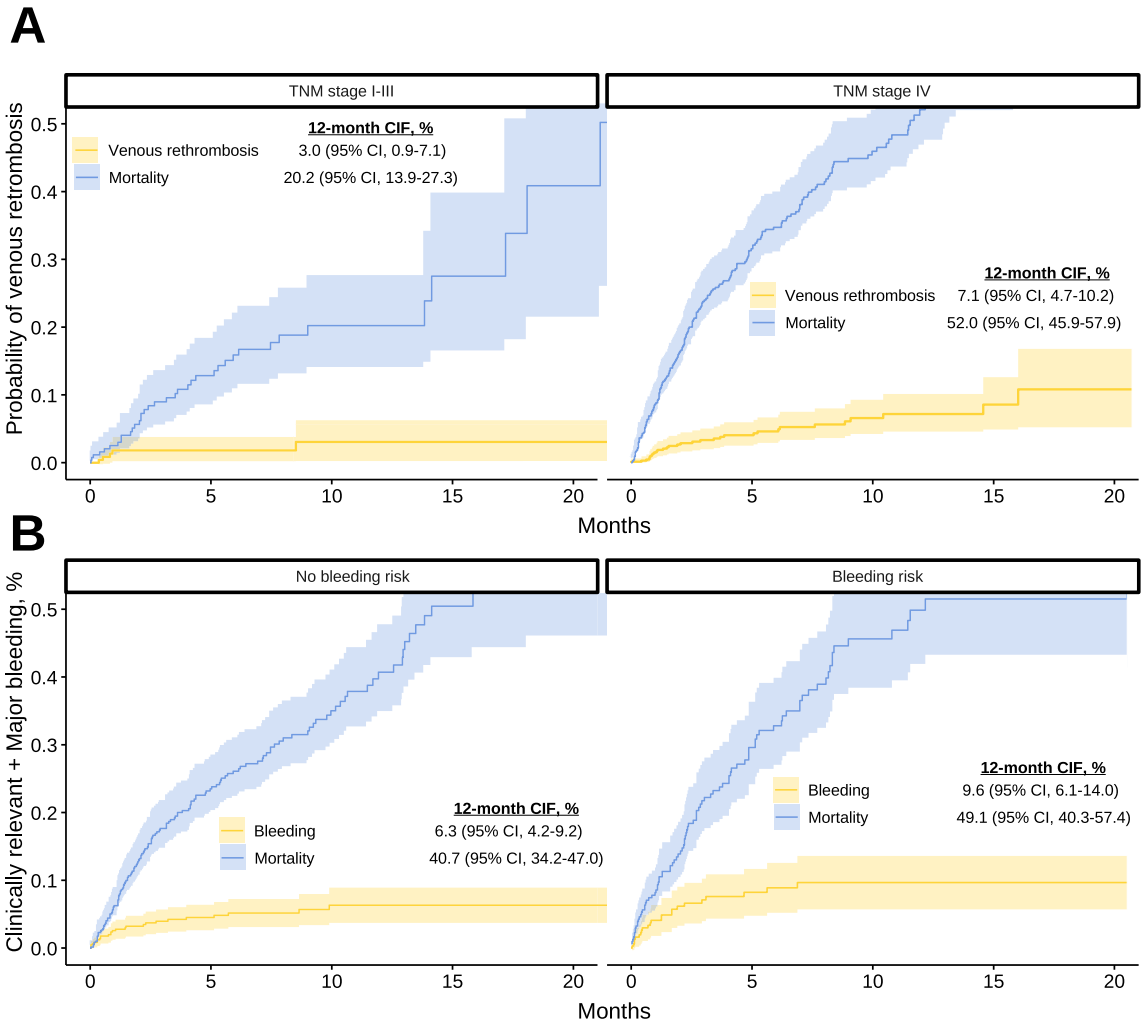

Fig. 4. Venous rethrombosis and major or clinically relevant bleeding. (A) venous rethrombosis and mortality by stage; (B) major or clinically relevant bleeding based on the presence of risk factors for hemorrhage (some factor vs no factors). Abbreviations: CIF, cumulative incidence function; CI, confidence interval.

thrombotic disease on the antineoplastic treatment and the evolution of the cancer are often lacking [25]. The reader must not lose sight of the fact that the heterogeneity of drugs and mechanisms in play hinder detailed analysis of these effects. The finding warns of how important it is to monitor the thrombotic risk of these agents through post-marketing studies, as well as to elucidate the impact thrombosis has on subsequent cancer management. Consequently, clinicians should consider thrombotic risk when choosing treatments that include these agents [4–6,26] and, in turn, a real-world database is an ideal instrument with which to address these issues.

As for the clinical characteristics of VTE, it is worth pointing out that more than half of the events are unsuspected, in line with the literature [27]. Moreover, PE occurs in 58.3%, although one of every four PE develops in individuals with a concurrent DVT. One interesting hypothesis highlighted by the data and subject to subsequent confirmation, is that the use of antiangiogenics might be connected to an increase in the proportion of PE. If confirmed, a possible explanation would be defective vascular repair in people receiving antiangiogenics [28].

In this registry, incidental or unsuspected events represent approximately half of the diagnoses of cancer-associated thrombosis. This trend is similar to that of other contemporary series [29–31], which presumably reflects the increased use of high-resolution CTs to assess tumor response [32]. As for the prognosis of unsuspected PE, our results are compatible with the prospective data yielded by the EPIPHANY study, that proved the influence of clinical severity, and the diagnostic scenario on short-term mortality [33]. The results of the TESEO registry confirm the better long-term prognosis of unsuspected, truly asymptomatic PE, with survival data that are comparable to other series in the literature [34–36].

Insofar as outcomes are concerned, the detection of venous rethrombosis is generally uncommon, in line with the rest of the literature [37]. However, thrombotic risk depends on the stage, with a twofold risk in advanced cancer. Rethrombosis tends to be early, albeit caution must be exercised when generalizing because it is conditioned by stage. The number one risk factor for bleeding is the presence of unresected tumors in the mucosa. In contrast, one peculiar finding is that other risk factors for hemorrhage, such as thrombopenia or kidney failure, are extremely uncommon. Furthermore, the cumulative incidence curves stratified by the presence or absence of risk factors reveal only a slight increase in the risk of major or clinically relevant hemorrhage in these patients, possibly due to pragmatic changes in anticoagulant therapy or because some individuals with primary cancer are finally able to undergo surgery.

The main limitation of this study is that follow-up is still relatively short. However, the rate of rethrombosis in advanced stages is consistent with reports in the literature. Given the relatively low frequency, the sample does not yet make it possible to model the risk of hemorrhage/ rethrombosis or its dynamic evaluation. Another outstanding aspect is that controls without thrombosis are not currently recorded. We therefore cannot directly infer the thrombotic risk of certain factors. The reader should also be aware that the results reflect the dissimilar management of CAT at the participating centers, including current patterns of anticoagulant use. Therefore, the low frequency with which DOACs are used as an alternative to LMWH is largely due to the regulatory context in Spain that have limited access to these treatments [38]. Given that DOACs are anticipated to be introduced gradually [39], the immediate future will witness a disparity of strategies, thereby complicating decision-making based on the profiles of both patients and their tumors. The impact of this on daily clinical practice will be both gradual and dissimilar, and will be ascertained through registries of real-world data.

In short, with this study, the authors have sought to present a snapshot of CAT in the era of immunotherapy and targeted therapies. One of the most intriguing lessons is the need to adequately note the stage, oncological context, anticancer treatment, and point in time properly to comprehend the clinical course of events. In conclusion, CAT continues to be a clearly polymorphic entity that calls for meticulous statistical analysis, given that it occurs in an ever-changing clinical scenario, in which there are new factors and new sources of risk of rethrombosis and bleeding, as well as competing events.

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Research involving human participants

All procedures followed are in accordance with the ethical standards of the committee in charge of human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

Informed consent or a substitute for it was obtained from all patients before they were included in the study.

CRediT authorship contribution statement

Alberto Carmona-Bayonas: Formal analysis, Writing - original draft, Writing - review & editing. **David Gómez:** Formal analysis, Writing - original draft, Writing - review & editing. **Eva Martínez de Castro:** Formal analysis, Writing - original draft, Writing - review & editing. **Pedro Pérez Segura:** Formal analysis, Writing - original draft, Writing - review & editing. **José Muñoz Langa:** Formal analysis, Writing - original draft, Writing - review & editing. **Paula Jimenez-Fonseca:** Formal analysis, Writing - original draft, Writing - review & editing. **Manuel Sánchez Cánovas:** Formal analysis, Writing - original draft, Writing - review & editing. **Laura Ortega Moran:** Formal analysis, Writing - original draft, Writing - review & editing. **Ignacio García Escobar:** Formal analysis, Writing - original draft, Writing - review & editing. **Ana Belén Rupérez Blanco:** Formal analysis, Writing - original draft, Writing - review & editing. **Isaura Fernández Pérez:** Formal analysis, Writing - original draft, Writing - review & editing. **Purificación Martínez de Prado:** Formal analysis, Writing - original draft, Writing - review & editing. **Rut Porta i Balanyà:** Formal analysis, Writing - original draft, Writing - review & editing. **Teresa Quintanar Verduguez:** Formal analysis, Writing - original draft, Writing - review & editing. **Álvaro Rodríguez-Lescure:** Formal analysis, Writing - original draft, Writing - review & editing. **Andrés Muñoz:** Formal analysis, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2020.05.031.

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