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Original article

Incidence, risk factors, and evolution of venous thromboembolic events in patients diagnosed with pancreatic carcinoma and treated with chemotherapy on an outpatient basis

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ABSTRACT

Background: Pancreatic carcinoma is one of the tumors associated with a higher risk for thromboembolic events, with incidence rates ranging from 5% to 41% in previous retrospective series.

Patients and methods: We conducted a retrospective study in eleven Spanish hospitals that included 666 patients diagnosed with pancreatic carcinoma (any stage) between 2008 and 2011 and treated with chemotherapy. The main objective was to evaluate the incidence of venous thromboembolic events (VTE) in this population, as well as potential risk factors for thrombosis. The impact of VTE on mortality was also assessed.

Results: With a median follow-up of 9.3 months, the incidence of VTE was 22.1%; 52% were diagnosed incidentally. Our study was unable to confirm the ability of the Khorana score to discriminate between patients in the intermediate or high risk category for thrombosis. The presence of VTE proved to be an independent prognostic factor associated with increased risk of death (HR 2.39, 95% CI 1.96–2.92). Symptomatic events correlated with higher mortality than asymptomatic events (HR 1.72; 95% CI, 1.21–2.45; $p = 0.002$), but incidental VTE, including visceral vein thrombosis (VVT), negatively affected survival compared to patients without VTE. Subjects who developed VTE within the first 3 months of diagnosis of pancreatic carcinoma had lower survival rates than those with VTE after 3 months (HR 1.92, 95% CI 1.30–2.84; $p<0.001$).

Conclusions: Pancreatic carcinoma is associated with a high incidence of VTE, which, when present, correlates with worse survival, even when thrombosis is incidental. Early onset VTE has a particularly negative impact.

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1. Introduction

Venous thromboembolic disease is considered one of the leading causes of morbi-mortality [1,2]. in oncological patients. Cancer multiplies the risk of thromboembolic events 6- or 7-fold compared to the general population without cancer [3,4], and this risk is greater in certain tumor sites and in people receiving chemotherapy. The incidence of VTE in individuals with pancreatic cancer is high, although it varies widely in the literature [5–23] due, in part, to the differences in the populations studied. In fact, several publications report incidence rates exceeding 30% [11,12,14,15,20]. Data regarding the impact of these events on survival are contradictory [7,11–13,17–19,23].

Chemotherapy has been identified as an independent risk factor for VTE and most chemotherapy treatments are administered on an outpatient basis. A risk model to identify individuals at high risk of developing symptomatic VTE among those receiving chemotherapy on an outpatient basis was validated a decade ago by Khorana et al. [24]. The Khorana score stratifies patients into three risk categories depending on the primary tumor site, prechemotherapy blood cell count (leukocytes, platelets, and hemoglobin), and body mass index (BMI). One of the advantages of this model is that it can be easily calculated in routine clinical practice. Furthermore, it has proven to be predictive of mortality and progression-free survival in cancer patients [25]. However, several observational studies conducted in different tumors [26–30], including pancreatic carcinoma [14–20], have failed to confirm the predictive value of the Khorana score to assess the risk of thrombosis.

Although most VTE occur within the first few months of tumor diagnosis, they can appear at any time in the course of the disease. It has recently been suggested that early VTE prognosticates worse survival, not only in pancreatic cancer [8,18,21,23], but in other tumors as well [31].

Therefore, we conducted a retrospective study to establish the incidence of VTE in subjects diagnosed with pancreatic carcinoma and undergoing outpatient chemotherapy at 11 hospitals belonging to the Thrombosis and Cancer Section of the Spanish Society of Medical Oncology (SEOM, for its acronym in Spanish). Simultaneously, we examined the relationship between the Khorana score and the occurrence of thrombosis in this population, as well as the frequency and evolution of incidental events in our series, and the possible impact of early thrombosis on patient survival.

2. Material and method

2.1. Patients

Consecutive adult patients diagnosed with histologically and/or cytologically confirmed exocrine pancreatic carcinoma (all stages) between January 1, 2008 and December 31, 2011 receiving outpatient chemotherapy at eleven hospitals belonging to the Thrombosis and Cancer Section of SEOM were included. The last follow-up visit was in July 2016. Cases of pancreatic neuroendocrine tumors were excluded. The inclusion of patients who were receiving anticoagulant treatment at diagnosis of pancreatic carcinoma for other reasons was allowed.

Medical records and radiological test reports (computed tomography, magnetic resonance imaging, and ultrasound) of all individuals admitted were retrospectively reviewed. Laboratory data were collected from the blood tests immediately prior to initiating chemotherapy to calculate the Khorana score.

The primary end point was to evaluate the incidence of VTE in our population. To this end, we included any VTE, either symptomatic or incidental, that was identified following diagnosis of pancreatic carcinoma or in the three months immediately preceding. Diagnoses of pulmonary embolism (PE), deep vein thrombosis (DVT), and all locations of visceral venous thrombosis (VVT) were included. This "extended" definition of VTE is based on the rationale that incidental thromboses and VVT would behave similarly to symptomatic events, in addition to having analogous pathophysiology. Moreover, this "extended" definition has been used in similar, recently published studies [7,11,14,15,17–22]. Catheter-associated thromboses were analyzed as DVT.

Arterial thromboembolic events were not recorded in our series.

2.2. Statistical analysis

Continuous variables are presented as medians and interquartile ranges and categorical variables as absolute and relative frequencies. Statistical comparisons were performed using the χ^2 test (or Fisher's exact test when necessary) for categorical variables and the Mann–Whitney–Wilcoxon test for continuous variables.

Time to VTE was defined as the time from histological diagnosis of pancreatic cancer to VTE diagnosis. Early thrombosis was defined as occurring within the first three months after diagnosis of the pancreatic tumor.

A univariate logistic regression model was used to explore the risk factors associated with VTE; once identified, a multivariate model was constructed to globally explain the variables involved in development of VTE. Factors with $p \leq 0.25$ by univariate analysis were further analyzed in a multivariate analysis.

Overall survival (OS) was defined as the time from diagnosis of pancreatic carcinoma to all-cause mortality. Patients who presented VTE before diagnosis of the tumor were not included in the survival analysis. The risk of the presence of VTE and other variables potentially implicated in survival was assessed through a Cox proportional hazards model in which VTE was analyzed as a time-dependent variable. In the case of stratified analyses, median survival was computed using Kaplan-Meier curves, together with hazard ratios (HR) associated with each subgroup compared to the subgroup without a diagnosis of VTE.

Statistical analyses were performed using the statistical software package R v 4.1.1. Statistical significance was established when the p value was $\leq$0.05.

3. Results

The study sample consisted of 666 patients who met the inclusion criteria and were included in the analyses. Table 1 reflects the clinical characteristics of the study population.

With a median follow-up of 9.3 months (range 0.4–72.0 months), 147 patients developed VTE, representing 22.1% of the total population. In 20, more than one VTE was diagnosed simultaneously (by and large, PE and DVT). The type of VTE is displayed in Table 2. Fifty-two percent of the VTE (77 of the 147 cases) were incidental findings during the extension study following diagnosis of the tumor (35 subjects) or in radiological examinations during follow-up. In 20 individuals, the VTE was diagnosed in the 3 months prior to the diagnosis of pancreatic carcinoma (16 in the month previous). The diagnosis of VTE led to the diagnosis of pancreatic cancer in 15 participants. Sixty-two patients were receiving anticoagulant treatment at diagnosis of pancreatic carcinoma (37 acenocoumarol, 12 LMWH at therapeutic doses, 9 LMWH at prophylactic doses and 4 unknown), 10 of whom developed VTE. Table 3

At the time of VTE diagnosis, 70% of the sample presented distant metastases and 24%, locally advanced disease. Only 9 cases occurred in patients with localized cancer, 4 of whom following complete resection of the tumor, with a median of 2.9 months (range 0.2–4.1 months) since surgery. Two thirds of all VTE occurred in the first 6 months subsequent to the diagnosis of pancreatic cancer. Median time to VTE appearance was 2.93 months (IQR 0.30–8.38). Once those individuals who had presented the event in the 3 months prior to cancer diagnosis were excluded (n = 20), the cumulative incidence of VTE at 3, 6, and 12 months was 1.6% (95% CI 0.8%−2.9%), 8.2% (95% CI 6.0%−10.7%), and 15.6% (95% CI 12.4%−19.1%), respectively.

The Khorana score for 30 participants was unknown, given that their body mass index (BMI) had not been recorded in their medical history.

Table 1
Study population characteristics.

	N	Overall, $N = 666$[1]	Patients with VTE No, $N = 519$ (78%)[1]	Yes, $N = 147$ (22%)[1]	p-value[2]
Sex	666				**0.003**
Male		384 (57.7%)	315 (60.7%)	69 (46.9%)	
Female		282 (42.3%)	204 (39.3%)	78 (53.1%)	
Age	666	65 [57–72]	65 [58–72]	64 [55–72]	0.10
BMI	645				**0.033**
Underweight (<18.5)		40 (6.2%)	29 (5.8%)	11 (7.6%)	
Normal (18.5–24.9)		381 (59.0%)	298 (59.5%)	83 (57.6%)	
Overweight (25–29.9)		161 (25.0%)	133 (26.5%)	28 (19.5%)	
Obese (>30)		63 (9.8%)	41 (8.2%)	22 (15.3%)	
Tumor site	649				**<0.001**
Head		398 (61.3%)	327 (64.7%)	71 (49.3%)	
Body		86 (13.3%)	55 (10.9%)	31 (21.5%)	
Tail		84 (12.9%)	55 (10.9%)	29 (20.2%)	
Overlapping		81 (12.5%)	68 (13.5%)	13 (9.0%)	
Stage	665				**0.004**
Localized		76 (11.4%)	67 (12.9%)	9 (6.1%)	
Locally advanced		198 (29.8%)	163 (31.5%)	35 (23.8%)	
Metastatic		391 (58.8%)	288 (55.6%)	103 (70.1%)	
ECOG	650				>0.9
ECOG 0–1		500 (76.9%)	389 (77.0%)	111 (76.6%)	
ECOG ≥ 2		150 (23.1%)	116 (23.0%)	34 (23.4%)	
Previous VTE	666				0.3
No		644 (96.7%)	504 (97.1%)	140 (95.2%)	
Yes		22 (3.3%)	15 (2.9%)	7 (4.8%)	
Catheter	665				**<0.001**
No		526 (79.1%)	425 (82.0%)	101 (68.7%)	
Yes		139 (20.9%)	93 (18.0%)	46 (31.3%)	
Gemcitabine	573				0.614
No		42 (7.3%)	36 (7.6%)	6 (6.1%)	
Yes		531 (92.7%)	439 (92.4%)	92 (93.9%)	
Capecitabine	572				0.671
No		447	372	75	
Yes		125	102	23	
Erlotinib	573				0.505
No		429	350	69	
Yes		154	125	29	
Oxaliplatin	573				**0.039**
No		368	314	54	
Yes		205	161	44	
5FU	573				**0.047**
No		478	403	75	
Yes		95	72	23	
Irinotecan	573				0.088
No		508	426	82	
Yes		65	49	16	
Other chemotherapy	573				0.369
No		501	418	83	
Yes		72	55	15	
Follow up	666	9.3 [4.7–17.0]	9.2 [4.6–17.4]	9.4 [4.9–16.3]	0.8

[1] Median [IQR]; n (%).
[2] Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test.

Excluding the 44 subject who presented VTE prior to the start of chemotherapy, 372 (63%) were included in the intermediate risk category and 220, in the high risk category (3 points: 153 patients; 4 points: 48 subjects; 5 points: 19 participants). The incidence of VTE in the Khorana score-based intermediate and high risk categories was 15.6% (58/372) and 18.6% (41/220), respectively, though these differences were not significant ($p = 0.3$). Moreover, no significant differences were detected when comparing VTE incidence across individuals with a Khorana score of 2–3 versus 4–5 (16.8% vs 16.4%, $p > 0.9$).

The results of the univariate and multivariate analyses to evaluate the prognostic factors associated with a greater risk of developing VTE are illustrated in Table 4. In the multivariate analysis, being female and the presence of a central catheter were significantly associated with a greater risk of developing VTE.Thirteen of the 147 patients (8.8%) developed recurrence of the VTE during follow up (4 PE, 2 DVT, 2 VVT, 3 other events, and 2 exhibited several simultaneous events). Twelve of the 13 recurrences occurred in the first 6 months following diagnosis of the first thrombotic event. The antithrombotic treatment at the time of recurrence was not recorded.

Median survival since diagnosis of pancreatic cancer was 5.2 months (95% CI 4.3–6.0 months) for subjects diagnosed with VTE as opposed to 11.9 months (95% CI 10.5–13.5 months) for those who did not exhibit the event ($p < 0.001$) (Fig. 1a). To assess the impact VTE had on OS, Cox proportional risks models were performed using VTE as the time-dependent covariable. The multivariate analysis (Table 5) identified VTE as an independent poor prognostic factor that doubled the risk of death in cases with VTE versus those without (HR 1.94, 95% CI 1.57–2.40; $p < 0.001$). Similarly, poor functional status (ECOG Performance Status ≥ 2), male sex, older age and locally advanced or metastatic disease at diagnosis of pancreatic carcinoma were associated with worse overall survival. At the time of data analysis, 128 of the VTE patients had died. Most of the deaths were secondary to oncological disease, although 8 of them were a consequence of VTE and in 3 cases the cause of death was unknown.

Table 2
VTE characteristics.

VTE characteristics	$N = 147$[1]
Type	
VVT (portal, SMV …)	49 (33.3%)
DVT	45 (30.6%)
PE	25 (17.0%)
Simultaneous events	20 (13.6%)
Another type of VTE	8 (5.4%)
Detection of VTE	
Asymptomatic / incidental	77 (52.4%)
Symptomatic	70 (47.6%)

[1]n (%).
Abbreviations: VVT: visceral venous thrombosis; SMV: superior mesenteric vein;.
DVT: deep vein thrombosis; PE: pulmonary thrombosis; VTE: venous thrombotic event.

Table 3
Comparative of Khorana score and VTE.

	Khorana Score Intermediate risk, $N = 372$ (63%)[1]	High risk, $N = 220$ (37%)[1]	p-value[2]
VTE			0.3
No	314 (84.4%)	179 (81.4%)	
Yes	58 (15.6%)	41 (18.6%)	

[1] n (%).
[2] Pearson's Chi-squared test.

3.1. Stratified analysis

3.1.1. Analysis of visceral thromboses vs. PE/ DVT

Forty-nine participants (7.4% of total population) developed only VVT. Median survival was 5.9 months (95% CI 4.3–12.2 months) for individuals with VVT, significantly lower than those without VTE (HR 1.57; 95% CI 1.14–2.17; $p = 0.006$). As Fig. 1b shows, for patients with PE (HR 4.03; 95% CI 2.90–5.59; $p < 0.001$) or DVT (HR 2.38; 95% CI 1.70–3.32) median overall survival was also inferior to that of patients without VTE. Prognosis was significantly worse for subjects who exhibited PE relative to those who only had VVT (HR 2.56; 95% CI, 1.64–3.98, $p < 0.001$) or DVT (HR 1.69; 95% CI 1.08–2.65; $p = 0.021$). A non-significant trend for longer survival was observed for patients with VVT compared to those with DVT (HR 0.66; 95% CI 0.42–1.03: $p = 0.07$).

3.1.2. Analysis of incidental versus symptomatic events

Of the 25 individuals who presented PE, 15 (60%) such events were incidental findings in asymptomatic patients. In contrast, 90% of the DVT were symptomatic. All the VVT were diagnosed incidentally. As Fig. 1c illustrates, the risk of death was significantly greater for both individuals with incidental (HR 1.90; 95% CI 1.47–2.47; $p < 0.001$) and symptomatic (HR 3.28; 95% CI 2.51–4.30; $p < 0.001$) VTE relative to those without VTE. Median OS rates were 5.8 months (95% CI 4.0–10.2 months) and 5.1 months (95% CI 4.1–6.1 months) for subjects with incidental and symptomatic VTE, respectively. In contrast, the risk of death was significantly higher for those with symptomatic VTE versus incidental events (HR 1.72, 95% CI 1.21–2.45; $p = 0.002$).

3.1.3. Analysis of early events

Participants with a history of VTE prior to their cancer diagnosis were excluded from this analysis. There were 54 cases of VTE in the 3 months after tumor diagnosis. Early appearance of thrombosis was associated with worse prognosis (Fig. 1d), with a median survival of 5.9 months (95% CI 4.8–9.5) for individuals with early thrombosis compared to 10.8 months for the rest (HR 1.52, 95% CI 1.12–2.08; $p < 0.001$). These differences were also observed (HR 1.92 95% CI 1.30–2.84; $p < 0.001$) when we compared OS of subjects who presented VTE in the first 3 months with those who developed VTE more than 3 months after cancer diagnosis (median 14.1 months; 95% CI 12.7–17.4).

4. Discussion

Studies published to date report VTE incidence rates in patients with pancreatic cancer that vary between 5% and 41% [5–23] and even higher if autopsy series are analyzed. This great variability is due, in part, to racial differences, given the well-known lower incidence of VTE in Asian populations [5–7,23], and partially, to the inclusion of heterogeneous patient groups in the series (some studies included only cases of locally advanced or metastatic disease [8,14,15,17,18,21,23]; others, such as ours, also admitted individuals with localized disease [6,11–13,16,19,20,22]). In contrast, some studies include only cases treated with chemotherapy [6–8,14,17,18], while others admit patients with or without specific cancer treatment. Finally, when comparing incidence rates across studies, the definition of VTE in each must be evaluated, bearing in mind whether or not VVT, incidental events, arterial thromboses, etc. are analyzed. Our series, one of the most extensive published to date, examines individuals with pancreatic cancer treated with outpatient chemotherapy in daily clinical practice and confirms the elevated incidence of VTE in this population (22.1%), similar to reports in recent studies [11,12,17–19,21,22]. The main objective of the study was to analyze the incidence of VTE in this population, as well as to evaluate the factors associated with a higher risk of thrombosis and its impact on patient survival.

Our study was unable to confirm the Khorana score's capacity to discriminate between intermediate or high risk. The incidence of VTE was 18.6% and 15.6% in high risk and intermediate risk, respectively, very much in line with the findings of the recently published BACAP-VTE study [19]. These findings can be explained by the fact that incidental events, very common in our series, were not assessed in the study by Khorana et al. One study conducted in patients with pancreatic carcinoma, presented as an abstract [32], revealed that the Khorana score was useful only in predicting symptomatic VTE, but that its value to prognosticate incidental events and VVT was less clear. Furthermore, we must point out that fewer than 2% of the participants in the cohorts to develop and validate the Khorana score had a diagnosis of pancreatic carcinoma. Several studies similar to ours have likewise failed to demonstrate the merit of the Khorana score to predict risk of thrombosis in patients with pancreatic cancer [14–20]. Nevertheless, in the publication by Barrau et al. [21], individuals with pancreatic carcinoma and a Khorana score ≥ 4 had twice the risk of VTE than those scoring 2–3 (HR=1.96,95% CI 1.05–3.65; $p = 0.03$), differences that were not detected in our study. Recently, van Es et al. have published a meta-analysis of individual data from participants in seven randomized clinical trials of thromboprophylaxis [33]. In this meta-analysis, a Khorana score indicating high risk correlated significantly with the appearance of VTE in subjects with pancreatic cancer (odds ratio [OR], 2.2; 95% CI, 1.02–4.9), but not in the other solid tumors examined. The recent publication by Godinho et al. [20] that evaluated 165 cases of pancreatic cancer suggests that the ONKOTEV score is significantly better suited to predict VTE than the Khorana score, albeit in their analysis only 66% of the study populations received chemotherapy. The ONKOTEV score looks at four risk variables: Khorana score ≥ 3, prior history of VTE, metastatic disease, and compression of vascular structures by the tumor [34]. Unfortunately, we did not contemplate this last variable in our series; hence, we were unable to assess the predictive value of ONKOTEV in our patients.

Regarding the use of chemotherapy, we must point out that the cytostatics received by the patient throughout their oncological disease were collected, but we do not know which ones the patient was receiving at the time of thrombosis. In the univariate analysis, patients who received oxaliplatin or 5FU had a higher risk of thrombosis, which is

Table 4
Risk factors for VTE. Univariate and multivariate analysis.

	Univariate			Multivariate		
	OR[1]	95% CI[1]	p-value	OR[1]	95% CI[1]	*p*-value
Sex						
Male	—	—		—	—	
Female	1.75	1.21, 2.53	**0.003**	2.09	(1.30, 3.39)	**0.003**
Age (years)						
<= 65 years	—	—				
> 65 years	0.88	0.61, 1.27	0.5			
BMI						
< 25	—	—				
≥ 25	1.00	0.67, 1.47	> 0.9			
ECOG						
ECOG 0–1	—	—				
ECOG ≥ 2	1.03	0.66, 1.58	>0.9			
Stage						
Localized	—	—				
Locally advanced	1.60	0.76, 3.70	0.2			
Metastatic	2.66	1.34, 5.90	**0.009**			
Tumor site						
Head	—	—		—	—	
Body	2.60	1.55, 4.31	**<0.001**	1,69	0.85, 3.23	0,122
Tail	2.43	1.44, 4.06	**<0.001**	1,75	0.86, 3.41	0,109
Overlapping	0.88	0.44, 1.63	0.4	0,6	0.24, 1.35	0,252
Catheter						
No	—	—		—	—	
Yes	2.08	1.37, 3.14	**<0.001**	1,8	1.03, 3.11	**0,036**
Previous VTE						
No	—	—				
Yes	1.68	0.63–4.07	0.3			
Gemcitabine						
No	—	—				
Yes	1.26	0.55, 3.40	0.6			
Capecitabine						
No	—	—				
Yes	1.12	0.66, 1.85	0.7			
Erlotinib						
No						
Yes	1.18	0.72, 1.88	0.5			
Oxaliplatin						
No	—	—			—	—
Yes	1.59	1.02 2.47	**0.04**	1,56	0.93, 2.61	0,087
5FU						
No	—	—				
Yes	1.71	0.99, 2.88	**0.047**			
Irinotecan						
No				—	—	
Yes	1.70	0.90, 3.07	0.09			
Other chemotherapy						
No	—	—				
Yes	1.33	0.68, 2.41	0.4			
Khorana						
Intermediate risk	—	—				
High risk	1.24	0.79, 1.92	0.3			

[1] OR=Odds Ratio, CI=Confidence Interval.

possibly related to the more frequent use of central catheters in these patients (41% and 72% of patients who received oxaliplatin and 5FU respectively, compared to 10% of those who do not receive either drug). The fact that catheter-associated thromboses were analyzed as DVT in our series may represent a limitation in the interpretation of the results.

The studies that have probed the impact of thrombosis on survival in these patients yield dissimilar results; whereas some studies find a negative impact on survival [8,11–13,17,19], others evince no significant differences [5,6,17,18,20–23]. Our results illustrate that the presence of VTE is associated with shorter OS in individuals with pancreatic cancer. The fact that VTE was associated with poor prognosis, even after adjusting for stage, could be related to a higher tumor burden in patients who developed thrombosis, compared to patients of the same stage who did not. VTE may identify a more aggressive disease, or cancer phenotype, which could be associated with a higher risk of death.

Consistent with other studies [13,15–17,19], more than half of the VTE in our series were diagnosed incidentally on routine radiological scans and these asymptomatic events were associated with a better prognosis than symptomatic events, despite having a lower survival rate than subjects without VTE (HR 1.90; 95% CI 1.47–2.47). In a population of pancreatic cancer, Lee et al. [6] found that symptomatic VTE correlated with a worse prognosis than incidental ones (HR 1.87; 95% CI 1.26–2.78; $p = 0.0002$) and that PE/ DVT events were also linked with a worse prognosis than VVT (HR 1.53; 95% CI 1.02–2.20; $p = 0.022$), consistent with our findings. Nevertheless, other studies in pancreatic cancer have not found differences in survival between symptomatic and incidental events [7,11,15,17,19]. Further, a high percentage of the thromboses that occur in individuals with pancreatic carcinoma are located at the spleno-portal axis and most of these events are diagnosed incidentally. Management of these VVT and their impact on mortality in the context of pancreatic cancer have yet to be ascertained, although a recent publication [35] demonstrates that the presence of splanchnic thrombosis in patients with advanced pancreatic cancer negatively affects survival, in keeping with findings previously published by Søgaard

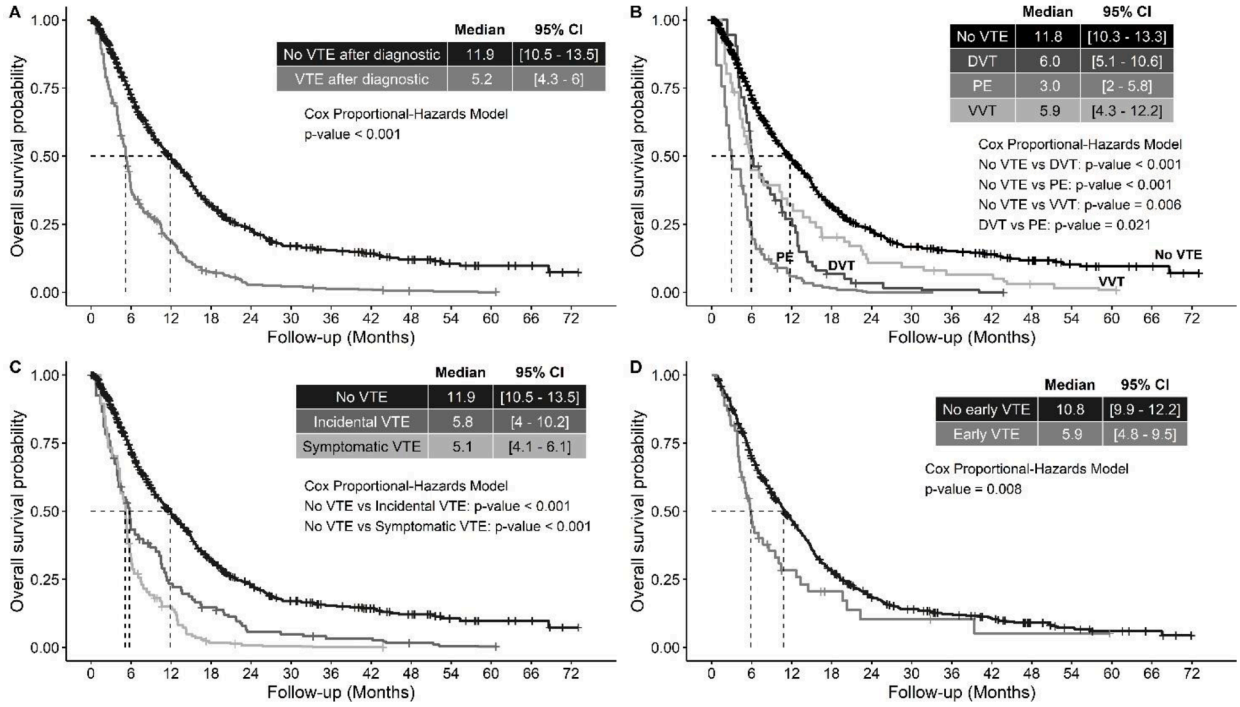

Fig. 1. Fig. 1A: Kaplan-Meier curve comparing survival from time of cancer diagnosis to demise with and without VTE. Fig. 1B: Kaplan-Meier curve comparing survival from time of cancer diagnosis to demise among patients without VTE, those with VVT, DVT and PE. Fig. 1C: Kaplan-Meier curve comparing survival from time of cancer diagnosis to demise among patients without VTE, those with incidental VTE, and those with symptomatic VTE. Fig. 1D: Kaplan-Meier curves comparing survival from time of cancer diagnosis to demise among between "Early VTE" (< 3 months) and "Non-early VTE".

et al. [36] Treating these VVT in daily clinical practice entails a complex decision that must factor in the risk of bleeding in relation to the benefit of anticoagulant treatment, as stated in the publication by Mier-Hicks et al. [37] in which 8% of the subjects with pancreatic cancer and VVT included in the study, exhibited bleeding complications secondary to anticoagulation, despite the fact that almost one fourth of the patients did not receive anticoagulant therapy. There again, the publication by Afzal et al. [35] revealed that, despite the negative effect of VVT on survival, anticoagulant therapy did not significantly improve prognosis and, in contrast, almost tripled the risk of bleeding.

It has been well established that VTE in pancreatic cancer is a time-dependent event, which has led recent studies to examine whether the timing of the VTE impacts survival. While the definition of early thrombosis varies from one study to another [18,21,23], all reveal that early thrombosis following diagnosis is predictive of worse survival. The recent work by Barrau et al. [21] found that individuals who developed VTE in the first 3 months following inclusion in the study had a median OS that was significantly lower than the rest (8 months vs. 14 months; HR 2.62; $p = 0.002$), comparable to our study.

This work has certain limitations, the main ones having to do with its retrospective analyses. The Khorana score, one of the main variables to be analyzed, could not be ascertained in 30 of the patients included as some data were not available in the clinical history. The antithrombotic treatment administered following the first VTE was not recorded. This information would have been relevant to assess observed recurrences, as well as if they occurred in properly anticoagulated subjects, which is important considering that some authors suggest reducing the dose of anticoagulant treatment (>90% of recurrences occurred in the first 6 months after VTE). Likewise, we are unaware of how the VVT (all of which were incidental) were managed and the treatment of which may or may not have affected OS. On the other hand, the fact that this is a multicenter study has enabled us to analyze a large number of patients, although we have also found that the frequency of VVT has been considerably lower in some centers than in others, leading us to think that the interobserver variability of the radiologists across the different centers may have influenced the results, probably underestimating the true incidence of VTE.

The high incidence of VTE observed in our study warrants an evaluation of the possibility of thromboprophylaxis in this subgroup of patients, especially in the first 6 months after the diagnosis of pancreatic carcinoma, when up to two thirds of thrombotic events occur. Four randomized clinical trials have been published in recent years that examined the role of LMWH thromboprophylaxis in cancer patients undergoing outpatient chemotherapy. Two of these studies were conducted in a heterogeneous population of cancer patients, including patients with pancreatic cancer (PROTECHT and SAVE ONCO) [38,39], and another two were performed specifically in pancreatic carcinoma (FRAGEM and CONKO 004) [40,41]. All these studies confirm a significant reduction of the incidence of VTE, albeit without affecting OS. More recently, two clinical trials (AVERT and CASSINI) [42,43] have appraised the possible benefit of new direct oral anticoagulants (DOACs) in thromboprophylaxis in oncology patients and with Khorana scores ≥2. In the AVERT trial [42], in which 14% of the study population had pancreatic cancer, apixaban significantly decreased the incidence of VTE during the study's follow-up period. Rivaroxaban failed to demonstrate a significant reduction of the incidence of VTE or death due to VTE during the 180-day period (primary end point) in the CASSINI study [41], despite being associated with a lower incidence of VTE during the intervention period. The results of a pre-specified sub--analysis of patients with pancreatic cancer ($n = 273$, 32.6% of the total) included in the CASSINI study has recently been published, yielding results that were consistent with findings in the overall population [44]. The basic concern regarding the use of thromboprophylaxis in this population is the risk of bleeding. Clinical guidelines coincide in that thromboprophylaxis should not be routinely administered to cancer patients who are initiating chemotherapy, but rather suggest that its use be contemplated in individuals with an intermediate-high risk (Khorana score ≥ 2), as long as there is no significant risk of bleeding [45–47]. Guidelines deem LMWH, apixaban, or rivaroxaban to be suitable in this context.

Table 5
Risk factors for death. Univariate and multivariate analysis.

	Univariate			Multivariate		
	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value
VTE	2.39	1.96, 2.92	**<0.001**	1.94	1.57, 2.40	**<0.001**
Sex						
Male	—	—		—	—	
Female	0.90	0.76, 1.07	0.2	0.81	0.68, 0.97	**0.022**
Age (years)						
≤ 65 years	—	—		—	—	
> 65 years	1.26	1.06, 1.48	**0.008**	1.21	1.01, 1.44	**0.036**
BMI						
< 25	—	—				
≥ 25	1.04	0.87, 1.24	0.7			
ECOG						
ECOG 0–1	—	—		—	—	
ECOG ≥ 2	2.33	1.91, 2.84	**<0.001**	2.06	1.67, 2.53	**<0.001**
Stage						
Localized	—	—		—	—	
Locally advanced	2.25	1.60, 3.18	**<0.001**	1.91	1.32, 2.76	**<0.001**
Metastatic	4.92	3.54, 6.84	**<0.001**	3.91	2.74, 5.59	**<0.001**
Tumor site						
Head	—	—		—	—	
Body	1.48	1.15, 1.91	**0.002**			
Tail	1.55	1.20, 2.01	**<0.001**			
Overlapping	1.23	0.95, 1.58	0.12			
Khorana						
Intermediate risk	—	—				
High risk	1.03	0.86, 1.23	0.8			

[1] HR=Hazard Ratio, CI=Confidence Interval.

In conclusion, VTE is a common complication in individuals with pancreatic cancer that affects survival, even when the events are incidental, which justifies probing the use of thromboprophylaxis in this population.

Ethical statements

The study was approved by the Ethics Committee of Hospital General Universitario Gregorio Marañón. Informed consent was not requested as it is not required for this type of study.

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