

# Early Venous Thromboembolism Is A Strong Prognostic Factor In Patients With Advanced Pancreatic Ductal Adenocarcinoma

**Mathilde Barrau**

CHU Saint-Étienne: Centre Hospitalier Universitaire de Saint-Etienne

**Khawla Maoui**

CHU Saint-Étienne: Centre Hospitalier Universitaire de Saint-Etienne

**Bertrand Le Roy**

CHU Saint-Étienne: Centre Hospitalier Universitaire de Saint-Etienne

**Xavier Roblin**

CHU Saint-Étienne: Centre Hospitalier Universitaire de Saint-Etienne

**Patrick Mismetti**

CHU Saint-Étienne: Centre Hospitalier Universitaire de Saint-Etienne

**Jean-Marc Phelip**

CHU Saint-Étienne: Centre Hospitalier Universitaire de Saint-Etienne

**Nicolas WILLIET** (✉ [nwilliet@yahoo.fr](mailto:nwilliet@yahoo.fr))

CHU Saint-Étienne: Centre Hospitalier Universitaire de Saint-Etienne <https://orcid.org/0000-0002-7296-5464>

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# Abstract

## Background

There is still controversial data regarding prognostic value of Venous ThromboEmbolic (VTE) in advanced Pancreatic Ductal AdenoCarcinoma (PDAC) and thromboprophylaxis is poorly prescribed despite international recommendations.

## Methods

Medical charts of patients consecutively treated for advanced PDAC from 2010 to 2019 were retrospectively reviewed. Progression-free survival (PFS) and overall survival (OS) were estimated using Kaplan-Meier method. Prognostic Factors were identified using a multivariate Cox's proportional hazard model. Early VTE was defined as VTE occurring within the third months from PDAC diagnosis.

## Results

A total of 174 patients were included (median age: 67 years; males: 55.2%; performance status (PS) 0-1: 88.5%) with metastatic disease in 74.7%. At baseline, Khorana score was high ( $\geq 3$ ) in the vast majority of cases (93.7%). The cumulative incidences of VTE were 12.4% (95% CI: 7.3-17.2) at 3 months, 20.4% (95% CI: 13.9-26.4) at 6 months and 28.1% (95% CI: 20.0-35.3) at 12 months. Early VTE was associated with shorter PFS (3.8 months vs. 7.1 months; HR=2.02; 95%CI: 1.21-3.37; p=0.006) and shorter OS (8.0 months vs. 14.1 months; HR=2.42; 95%CI: 1.37-4.30; p=0.002) compared to the remnant patients, independently of the other prognostic factors including PS, liver metastases, carcinomatosis, and chemotherapy regimen.

## Conclusion

Early VTE is a strong prognostic factor in advanced PDAC and occurs in about 1 in 10 patients.

## Introduction

The risk of Venous ThromboEmbolic (VTE) is increased in cancer patients due to a prothrombotic and proangiogenic state involving numerous mechanisms such as tumor overexpression of tissue factor (Khorana and Fine 2004). Chemotherapy, distant metastases and the primary site of cancer are additional risk factors for VTE (Blom et al. 2006).

Pancreatic ductal adenocarcinoma (PDAC) is among the most common malignancies associated with this risk (Blom et al. 2006). In the majority of PDAC cohorts, the prevalence of VTE ranges from 10–30% (Epstein et al. 2012; Lee et al. 2016; Frere et al. 2019). However, VTE can occur at various times of the disease. Hence, the cumulative incidence of VTE appears more informative but has been less frequently reported in the literature (Lee et al. 2016; Gade et al. 2017; Chen et al. 2018; Frere et al. 2019; Godinho et al. 2020; van Es et al. 2020).

The Khorana score was developed and validated in 2008 (Khorana et al. 2008) as a predictive model for chemotherapy-associated thrombosis. This score takes into account the primary site of cancer, prechemotherapy platelets count, hemoglobin level, use of erythropoiesis-stimulating agents, leucocytes count, and body mass index (BMI) (Khorana et al. 2008). According to this, all patients with PDAC have a Khorana score of at least 2 points (moderate risk) and a significant proportion of them have a high risk (score  $\geq 3$ ) and should undergo primary thromboprophylaxis as recommended since 2013 with a Grade 1B evidence level.

However, the benefit of thromboprophylaxis in these patients continues to be under-recognized worldwide. Indeed, except for the perioperative setting and for hospitalized patients, ambulatory thromboprophylaxis remains underused because of high rates of VTE recurrence, and potential bleeding complications during VTE treatment (Key et al. 2020). Due to their short life expectancy, there has been no strong evidence that inhibition of the coagulation cascade improves survival in patients with advanced PDAC (Frere et al. 2019). Moreover, there are still controversial data regarding the prognostic value of VTE in PDAC (Mandalà et al. 2007; Epstein et al. 2012; Lee et al. 2016; Chen et al. 2018; Frere et al. 2019). Given VTE is a time-dependent factor there is growing evidence that early-VTE predicts survivals (Mandalà et al. 2007; Chen et al. 2018; Kim et al. 2018). Therefore this retrospective cohort study was conducted to assess the impact of early VTE on survivals.

## Methods

### Study design and objectives

All consecutive patients treated for PDAC from 2010 to 2019 at the University Hospital of Saint-Etienne (France) were reviewed. Until June 2018, patients were identified by using the International Classifications of Diseases (CIM10). Their data were collected from their electronic charts in agreement with the Declaration of Helsinki. The Ethics Committee of Hospital Saint Etienne approved the study protocol (IRBN632017/CHUSTE). From June 2018 to June 2019, this retrospective cohort was pooled to a prospective cohort, observational and carried-out in the same centre (IRBN362018/CHUSTE).

The primary objective of this study was to assess the prognostic value of VTE and early VTE in advanced PDAC. Secondary objective was to report the cumulative incidence of VTE in patients with advanced PDAC. Inclusion criteria were patients with advanced PDAC at baseline (locally advanced or metastatic disease) or in recurrence in case of tumor previously resected.

### Data collection and definitions

Patient data collection included demographic characteristics (age, sex, body mass index [BMI]), comorbidities (diabetes, tobacco consumption), the performance status (PS) by the Eastern Cooperative Oncology Group Performance Status Scale (ECOG-PS) and nutritional status (albumin level).

Regarding cancer disease, the following data were collected: primary tumor location, disease stage (locally advanced, metastatic or in recurrence), CA 19 – 9 at baseline, and first-line chemotherapy regimen. Baseline was defined as the time of diagnosis for advanced disease or as the time of recurrence for tumors which were previously resected.

Progression-free survival (PFS) was defined from the date of baseline to disease-progression (according to Response Evaluation Criteria in Solid Tumors (RECIST v1) criteria), or to date of death or loss to follow-up. Overall survival (OS) was defined from the date of baseline to death or loss to follow-up.

Regarding VTE events, the following data were collected: date of VTE occurrence, location of the thrombosis (visceral, extra-visceral), symptomatic or asymptomatic feature, treatment, duration and response to the treatment. Time-to-progression and Time-to-death were defined from the date of VTE occurrence to the date of disease progression or death, respectively, or loss to follow-up. Early VTE was defined as the occurrence of VTE within the third months from baseline.

## Statistical analysis

Survivals (PFS, OS) and time from VTE to event (progression, death) were estimated using Kaplan Meier Method. Prognostic factors were identified using Cox's proportional hazards regression. Multivariate analyses were performed either by stepwise method or by selecting variables according their corresponding p value ( $\leq 0.05$ ) in univariate analyse. For each continuous variable, cut-offs used to evaluate the prognosis were in accordance with the literature (e.g.: BMI  $\geq 25$  or  $30\text{kg}/\text{m}^2$ , platelets count  $\geq 350 \times 10^9/\text{L}$ , leucocytes count  $\geq 11 \times 10^9/\text{L}$ , hemoglobin  $< 100\text{g}/\text{L}$ ). The cumulative incidence of VTE was estimated by using the inverse Kaplan Meier method.

Quantitative variables were reported as median with corresponding interquartile range and were compared by Wilcoxon test. Qualitative variables were reported as numbers and percentages and compared using chi2 or fisher test. All statistical analyses were performed using R® version 3.2.2 (R project, Auckland, New Zealand).

## Results

### Whole study population

A total of 174 patients matching with inclusion criteria were identified. Patients and disease characteristics were reported in Table 1, as well as corresponding data for the group of patients who experienced VTE during follow-up (n = 46) and data for those who did not (n = 128). Forty six patients (26.4%) had at least one VTE event during follow-up. There was no statistically significant difference between the two groups regarding their main characteristics. The median age was 67 years [60–75] with a sex ratio close to 1. At time of diagnosis, most patients (88.5%) had an ECOG-PS of 0–1, about 1/3 (32.8%) had diabetes and 37.4% had history of tobacco consumption. At baseline, median of albumin was 32.6 g/L [27.2–37.9].

Table 1 Baseline characteristics of the population study

<b>Variables</b>	<b>Population Study (n = 174 )</b>	<b>No VTE during follow-up (n = 128 )</b>	<b>VTE during follow-up (n = 46 )</b>	<b>P value</b>
Age, mean [IQR]	67 [60–75]	68 [61–75]	65 [57.5–73]	0.302
Sex Male	96 ( 55.2 %)	71 ( 55.5 %)	25 ( 54.3 %)	1
History of Tobacco	65 ( 37.4 %)	51 ( 39.8 %)	14 ( 30.4 %)	0.37
Diabetes	57 ( 32.8 %)	41 ( 32 %)	16 ( 34.8 %)	0.734
Diabetes duration (years) mean [IQR]	6.4 [0.5–9]	6.3 [0.5–10.2]	7.1 [2.2–7.6]	0.982
Body mass index mean [IQR]	24 [21–27.8]	24 [21–27]	25 [22–29]	0.052
Performance status				
ECOG-0	61 ( 35.1 %)	42 ( 32.8 %)	19 ( 41.3 %)	0.397
ECOG-1	93 ( 53.4 %)	71 ( 55.5 %)	22 ( 47.8 %)	
ECOG-2	20 ( 11.5 %)	15 ( 11.7 %)	5 ( 10.9 %)	
CA19.9_C1	353.5 [87.5–2761]	283 [65–1329]	648 [184.5–4576]	0.133
missing data	44 (25.3%)	34 (26.6%)	10 (21.7%)	-
CRPa.C1	17 [7–43.5]	16.5 [7–40.8]	19.5 [9–51.5]	0.364
missing data	28 (16.1%)	22 (17.2%)	6 (13%)	-
AlbumineC1	32.6 [27.2–37.9]	33 [29–37]	32 [25–38]	0.766
Missing data	52 (29.9%)	43 (33.6%)	9 (19.6%)	-
Leucocytes count $\geq 11 \times 10^9/L$	34 ( 21.4 %)	21 ( 18.3 %)	13 ( 29.5 %)	0.18
Hemoglobin $\leq 100g/L$	19 ( 11.9 %)	10 ( 8.7 %)	9 ( 20.5 %)	0.08
Platelets count $\geq 350 \times 10^9/L$	25 ( 15.7 %)	18 ( 15.7 %)	7 ( 15.9 %)	1
Khorana Score	3 [3–4]	3 [3–3]	3 [3–4]	0.114
$\geq 3$	149 ( 93.7 %)	108 ( 93.9 %)	41 ( 93.2 %)	1
$\geq 4$	44 ( 27.7 %)	27 ( 23.5 %)	17 ( 38.6 %)	0.09
missing data	15 (8.6%)	13 (10.2%)	2 (4.3%)	-

<b>Variables</b>	<b>Population Study (n = 174 )</b>	<b>No VTE during follow-up (n = 128 )</b>	<b>VTE during follow-up (n = 46 )</b>	<b>P value</b>
Disease stage				
<i>Non-metastatic</i>	44 ( 25.3 %)	31 ( 24.2 %)	13 ( 28.3 %)	0.59
<i>Metastatic</i>	130 ( 74.7 %)	97 ( 75.8 %)	33 ( 71.7 %)	0.59
Prior surgery	30 ( 17.2 %)	24 ( 18.8 %)	6 ( 13 %)	0.50
Location of primary tumor				
<i>Head</i>	93 ( 53.4 %)	73 ( 57 %)	20 ( 43.5 %)	0.634
<i>Body</i>	29 ( 16.7 %)	19 ( 14.8 %)	10 ( 21.7 %)	
<i>Tail</i>	27 ( 15.5 %)	21 ( 16.4 %)	6 ( 13 %)	
missing data	25 ( 14.4 %)	15 ( 11.7 %)	10 ( 21.7 %)	
Metastases sites				
<i>Liver</i>	78 ( 44.8 %)	60 ( 46.9 %)	18 ( 39.1 %)	0.366
<i>Lung</i>	20 ( 11.5 %)	16 ( 12.5 %)	4 ( 8.7 %)	0.489
<i>Bone</i>	6 ( 3.4 %)	6 ( 4.7 %)	0 ( 0 %)	0.34
<i>Carcinomatosis</i>	33 ( 19.1 %)	22 ( 17.3 %)	11 ( 23.9 %)	0.45
<i>Number of sites</i>	1 [0–1]	1 [0–1]	1 [0–1]	0.603
Chemotherapy regimen				
<i>5FU-based</i>	92 ( 52.9 %)	68 ( 53.1 %)	24 ( 52.2 %)	1
<i>Gemcitabine-based</i>	82 ( 47.1 %)	60 ( 46.9 %)	22 ( 47.8 %)	
<i>Intensive</i>	106 ( 60.9 %)	78 ( 60.9 %)	28 ( 60.9 %)	0.87
<i>Doublet 5FU-based</i>	12 ( 6.9 %)	8 ( 6.2 %)	4 ( 8.7 %)	
<i>Gemcitabine only</i>	56 ( 32.2 %)	42 ( 32.8 %)	14 ( 30.4 %)	
<i>Notes. ECOG: Eastern Cooperative Oncology Group; 5FU: fluoropyrimidine; VTE: Venous thromboembolism</i>				

About half of patients had a primary tumor located in the head of the pancreas and metastatic disease in 74.7% (17.2% after prior surgery of the primitive tumor). At baseline, median CA19.9 was 353.5 UI/L [87.5–2761], and 17 mg/L [7.0–43.5] for CRP. About 2/3 of patients received intensive chemotherapy (FOLFIRINOX or Gemcitabine/Nab-Paclitaxel). About 1/3 were treated with Gemcitabine only. The

Khorana score at baseline was similar between patients who experience VTE vs. those who did not (median: 3 [3–4]) despite a statistical trend for patients with score  $\geq 4$  in VTE group (38.6% vs. 23.5%;  $p = 0.11$ ).

## Incidence of Venous ThromboEmbolism

During a median follow-up of 9.3 months [5.1–16.7], 46 patients (26.4%) experienced VTE. In the whole study population, the cumulative incidence of VTE was 12.4% (95% CI: 7.3–17.2) at 3 months, 20.4% (95% CI: 13.9–26.4) at 6 months, and 28.1% (95% CI: 20.0–35.3) at 12 months (Fig. 1A). Patients with Khorana score  $\geq 4$  had a doubled risk of VTE (HR = 1.96; 95%CI: 1.05–3.65; Log-rank  $p = 0.03$ ) with the following corresponding cumulative incidences: 21.0% (95%CI: 7.8–32.4) at 3 months, 36.3% (95%CI: 18.6–50.2) at 6 months and 40.9% (95%CI: 21.3–55.5) at 12 months (Fig. 1B).

Among patients who experienced VTE, 15.2% (95%CI: 4.2–25) had it at baseline, 45.7% (95%CI: 29.2–58.3) within three months and more than  $\sim 2/3$  (71.7%; 95%CI: 55.2–82.2) within six months.

## Clinical presentation and treatment of venous thromboembolism events

Of the 46 patients who experienced VTE during follow-up, the majority of VTE was symptomatic (78.3%) and extra-abdominal (76.1%) including pulmonary embolism in 30.4%. Most of them were treated with Low Molecular Weight Heparins (LMWHs) (69.6%). Vitamin K antagonists (VKA) (4.3%), direct oral anticoagulants (DOAC) (2.1%), and unfractionated heparin (2.1%) were rarely used and 17.4% of patients did not received specific treatment for VTE. One patient (2.1%) underwent vena cava filter. Under anticoagulant agents, VTE was considered as progressive (locally, or by the occurrence of a second TVE site), stable or reduced in 17.4%, 67.4% and 13%, respectively. Second-line anticoagulation strategy was dominated by an increase of LMWH dose ( $n = 4$ ), or maintenance the same strategy ( $n = 4$ ). Bleeding complication was observed in 15.2% with 1 related death (2.2%) by digestive hemorrhage.

## Survivals

In the whole study population the median PFS was 9.3 months (95%CI: 5.1–16.7). In univariate analysis, VTE occurrence during follow-up was not predictive of progression ( $p = 0.18$ ). In contrast, there was a correlation between time from cancer diagnosis to VTE and PFS ( $p = 0.006$ ; HR = 0.89). Patients who experienced early VTE (within three months) were associated with shorter PFS than the others: 3.8 months (95%CI: 2.7–10.1) vs. 7.1 months (95%CI: 6.2–8.4), respectively (HR = 2.02; 95%CI: 1.21–3.37;  $p = 0.006$ ) (Fig. 2A). After multivariate analysis (Table 2), early VTE remained predictor of PFS, independently to other prognostic factors such as ECOG-PS  $> 1$  ( $p < 0.01$ ; HR = 2.60; 95%CI: 1.49–4.52), BMI  $\geq 25$  ( $p = 0.002$ ; HR = 0.57; 95%CI: 0.4–0.82), liver metastasis ( $p = 0.003$ ; HR = 1.71; 95%CI: 1.20–2.45), carcinomatosis ( $p = 0.03$ ; HR = 1.60; 95%CI: 1.04–2.46), and chemotherapy regimen (Gemcitabine-based vs. fluoropyrimidine-based:  $p = 0.06$ ; HR = 1.45; 95%CI: 0.98–2.15).

Table 2 Prognostic factors for progression-free survival

	Univariate analyses		Multivariate analyses	
	p value	HR [95%CI]	p value	HR [95%CI]
Age	0.12	1.01 [1–1.03]		
Age > 75 years	0.11	1.37 [0.93–2.03]	0.69	0.91 [0.58–1.43]
Sex : Male vs Female	0.65	0.93 [0.67–1.28]		
Tobacco vs No Tobacco	0.24	1.22 [0.87–1.7]		
Diabetes vs No Diabetes	0.79	1.05 [0.74–1.49]		
Body mass index (BMI)	0.09	0.97 [0.93–1.01]		
BMI $\geq$ 25	0.01	0.64 [0.46–0.9]	0.002	0.57 [0.4–0.82]
Performance Status: ECOG 2 vs 0–1	< 0.001	2.78 [1.69–4.57]	< 0.001	2.6 [1.49–4.52]
Time from cancer diagnostic to VTE (months)	0.006	0.89 [0.86–0.91]		
<b>Early VTE vs No Early VTE</b>	<b>0.01</b>	<b>2.02 [1.21–3.37]</b>	<b>0.037</b>	<b>1.8 [1.04–3.12]</b>
Stage : Metastatic vs Locally Advanced	0.06	1.42 [0.98–2.06]		
No prior surgery vs prior surgery	0.24	1.33 [0.83–2.14]		
Primitive Tumor location				
<i>head vs body</i>	0.6	0.89 [0.57–1.39]		
<i>tail vs body</i>	0.37	1.28 [0.74–2.21]		
Liver metastases	0.035	1.42 [1.03–1.97]	0.003	1.71 [1.2–2.45]
Lung metastases	0.91	1.03 [0.62–1.71]		
Bone metastases	0.67	0.82 [0.34–2.01]		

	Univariate analyses		Multivariate analyses	
Carcinomatosis	0.005	1.77 [1.18–2.64]	0.032	1.6 [1.04–2.46]
Gemcitabine-based vs 5FU-based CT regimen	0.012	1.53 [1.1–2.12]	0.06	1.45 [0.98–2.15]
Doublet chemotherapy vs intensive CT regimen	0.73	1.12 [0.6–2.1]		
Gemcitabine alone vs intensive CT regimen	0.015	1.55 [1.09–2.21]		
<i>Notes. ECOG: Eastern Cooperative Oncology Group; 5FU: fluoropyrimidine; VTE: Venous thromboembolism</i>				

In the whole study population the median OS was 13.3 months (95%CI: 10.6–16.7). In univariate analysis, VTE occurrence during follow-up was not predictive of death ( $p = 0.97$ ). In contrast, there was a correlation between time from cancer diagnosis to VTE and OS ( $p < 0.001$ ; HR = 0.88). Patients who experienced early VTE were associated with shorter OS than the others: 8.0 months (95%CI: 4.7-NA) vs. 14.1 months (95%CI: 11.1–17.4) respectively (HR = 2.42; 95%CI: 1.37–4.30;  $p = 0.002$ ) (Fig. 2B). The other prognostic factors for OS were reported in Table 3. Early VTE remained predictor of OS ( $p = 0.02$ ; HR = 2.05) independently to PS-2 vs PS-1-2 ( $p < 0.01$ ; HR = 2.43), liver metastasis ( $p = 0.02$ ; HR = 1.64), carcinomatosis ( $p = 0.05$ ; HR = 1.64), chemotherapy regimen ( $p = 0.18$ ) and age > 75years ( $p = 0.6$ ).

Table 3 Prognostic factors for overall survival

	Univariate analyses		Multivariate analyses	
	p value	HR [95%CI]	p value	HR [95%CI]
Age	0.17	1.02 [0.99–1.04]		
Age > 75 years	0.02	1.66 [1.07–2.59]	0.6	1.15 [0.69–1.91]
Sex : Male vs Female	0.3	0.82 [0.56–1.19]		
Tobacco vs No Tobacco	0.64	1.1 [0.75–1.61]		
Diabetes vs No Diabetes	0.69	0.92 [0.61–1.39]		
Body mass index (BMI)	0.23	0.97 [0.93–1.02]		
BMI $\geq$ 25	0.3	0.82 [0.56–1.2]		
Performance Status: ECOG 2 vs 0–1	< 0.001	2.66 [1.55–4.56]	0.004	2.43 [1.34–4.4]
Time from cancer diagnostic to VTE (months)	< 0.0001	0.88 [0.86–0.9]		
<b>Early VTE vs No Early VTE</b>	<b>&lt; 0.001</b>	<b>2.42 [1.37–4.3]</b>	<b>0.023</b>	<b>2.05 [1.1–3.82]</b>
Stage : Metastatic vs Locally Advanced	0.24	1.29 [0.84–1.96]		
No prior surgery vs prior surgery	0.5	0.85 [0.52–1.38]		
Primitive Tumor location				
<i>head vs body</i>	0.52	1.21 [0.68–2.16]		
<i>tail vs body</i>	0.22	1.54 [0.78–3.06]		
Liver metastases	0.17	1.31 [0.89–1.93]	0.023	1.64 [1.07–2.52]
Lung metastases	0.59	0.85 [0.47–1.55]		
Bone metastases	0.33	0.61 [0.22–1.65]		

	Univariate analyses		Multivariate analyses	
Carcinomatosis	0.07	1.55 [0.96–2.48]	0.05	1.64 [1–2.71]
Gemcitabine-based vs 5FU-based CT regimen	0.01	1.65 [1.13–2.41]	0.18	1.37 [0.86–2.18]
Doublet chemotherapy vs intensive CT regimen	0.1	1.72 [0.9–3.28]		
Gemcitabine alone vs intensive CT regimen	0.004	1.83 [1.22–2.76]		
<i>Notes. CT : chemotherapy ; ECOG: Eastern Cooperative Oncology Group; 5FU: fluoropyrimidine; ; Intensive CT : Folfirinox or Gemcitabine/Nab-Paclitaxel ; VTE: Venous thromboembolism</i>				

## Time from venous thromboembolism to progression or death

The median time from VTE to progression was 1.6 months (95%CI: 0.0-2.8) (**Supplementary Fig. 1**), which means that half of patients who had VTE experienced disease progression at the same time. Half of the remnant patients had disease progression about 3 months after the occurrence of VTE.

The median time from VTE to death was 5.8 months (95%CI: 2.9–8.4) (**Supplementary Fig. 2**), but there was any difference between patients with abdominal thrombosis (n = 11) compared to those who had extra-abdominal thrombosis (n = 35; p = 0.01), or regarding the symptomatic feature of the VTE event (p = 0.85).

## Discussion

The present study confirms the high risk of VTE in patients with advanced PDAC since about ¼ to ⅓ of them experienced such event during follow-up. Other large cohorts had previously reported such outcomes (Lee et al. 2016; Gade et al. 2017; Chen et al. 2018; Frere et al. 2019). Thereby, the interest of thromboprophylaxis is revived for all patients with advanced PDAC as recommended since 2013 (Farge et al. 2013; Frere et al. 2019; Key et al. 2020).

However, VTE is a time dependent factor and only early VTE, defined by the occurrence of VTE within the three months from advanced PDAC diagnosis, seems prognostic in this study which involves about 1 in 10 patients. Most studies have reported VTE without taking into account its time dependent nature (Oh et al. 2008; Shaib et al. 2010; Kruger et al. 2017; Godinho et al. 2020). Only few recent studies evaluated VTE either by considering VTE as time-dependent factor in Cox model (Frere et al. 2019), or by evaluating the binary factor early VTE as this one (Mandalà et al. 2007; Chen et al. 2018; Kim et al. 2018).

This study is one of rare that reported time from VTE to disease progression or death. Hence we showed that VTE seems in relation with tumor aggressiveness (median time to progression: 1.6 months; median time to death: 5.8 months) which raises the question about impact of anticoagulation therapy on survival. Moreover, 17.4% of patients treated for VTE experienced an extension of their thrombosis under anticoagulation and 67.4% had stability in the present study. Seven patients (15.2%) had bleeding complication including one (2.2%) death by digestive hemorrhage. There has been no strong evidence that thromboprophylaxis improves survival outcomes in advanced PDAC. In vitro, anticoagulation agents might have an anti-tumor effect by inhibiting metastatic spreading process. Most of randomized clinical trials that evaluated impact of anticoagulant agents on survival included all kind of primary cancers (Kakkar et al. 2004; Klerk et al. 2005). Conclusions were controversial regarding the role of anticoagulation in the improvement of survivals, and outcomes in subgroup of patients with PDAC should be interpreted with cautious (Frere et al. 2019). Corresponding data with DOAC are very scarce (Frere et al. 2019). Overall, anticoagulant use is recommended to reduce the risk of VTE (Maraveyas et al. 2012; Pelzer et al. 2015; Frere et al. 2019; Key et al. 2020) but not to improve survival in patients with cancer without VTE (van Doormaal et al. 2011). For this last reason, thromboprophylaxis is rarely prescribed for ambulatory patients in our center.

The present study is not designed to assess impact of thromboprophylaxis on survival but underlines the importance to identify patients who will experience early VTE. By definition, all patients with pancreatic cancer have a Khorana score at least 2 and the vast majority of them have a score at 3 such in this cohort. Hence, the Khorana score does not allow the identification of patients who will truly experience early VTE. Thereby, if primary thromboprophylaxis is done, most of patients are overtreated with potential risk of anticoagulation-related complication. Other score should be developed to improve the identification of these patients or those who did not experience VTE within the three following months.

The ONKOTEV score is another emerging reference to predict VTE (Godinho et al. 2020). To calculate the ONKOTEV score, vascular/lymphatic compression and previous history of VTE must be known. Hence, this score is not used in clinical practice due to its complexity, which supports the interest of the development of new score more feasible and reproducible.

In conclusion, VTE occurred in about ¼ to 1/3 of patients with advanced PDAC. Early VTE, defined by VTE occurrence within three months from advanced PDAC diagnostic, appears prognostic in this study which supports guidelines. However, failing to apply recommendations for primary thromboprophylaxis, further score should be developed to identify better patients who are at very high-risk for early VTE, or those who will not experience such event. Such score could avoid overtreatment of the majority of patients (9/10).

## Abbreviations

BMI	Body mass index
CI	Confidence interval
CRP	C-Reactive protein
DOAC	Directoral anticoagulant
ECOG	Eastern Cooperative Oncology Group
LMWHs	Low Molecular Weight Heparins
NPV	Negative predictive value
OS	Overall survival
PDAC	Pancreatic ductal adenocarcinoma
PFS	Progression-free survival
PPV	Positive predictive value
PS	Performance status
RECIST	Response Evaluation Criteria in Solid Tumors
ROC	Receiver operating characteristic
Se	Sensibility
Sp	Specificity
VTE	Venous thromboembolism

## Declarations

**Funding:** None

**Conflicts of interest:** None

**Data availability statement:** Research data are available from Dr Nicolas Williet

**Code availability:** please contact Dr Nicolas Williet

**Authors' contributions.** MB: data collection, drafting the manuscript; KM/MF: data collection; BLR/XR/PM/JMP: interpretation of data and critical review of the manuscript; NW: conception of the study, study supervision, statistical analyses, interpretation of data, drafting the manuscript;

**Ethic approval:** IRBN632017/CHUSTE & IRBN362018/CHUSTE

**Consent to participate:** patients deaths but they were informed that such retrospective studies are frequently performed in our institution

Consent for publication: idem. And I declare that all co-authors are consent for the publication of this article

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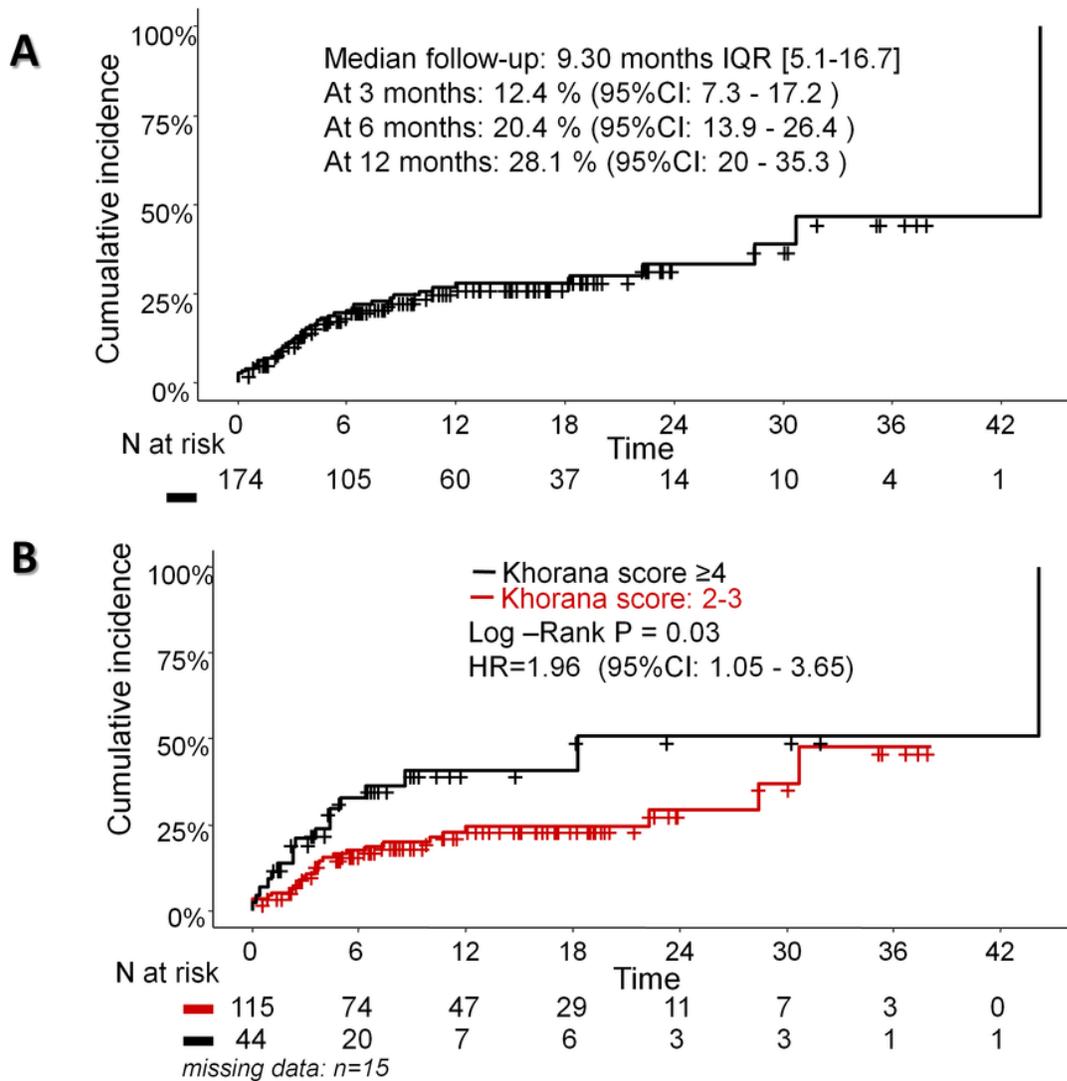
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## Supplemental Data

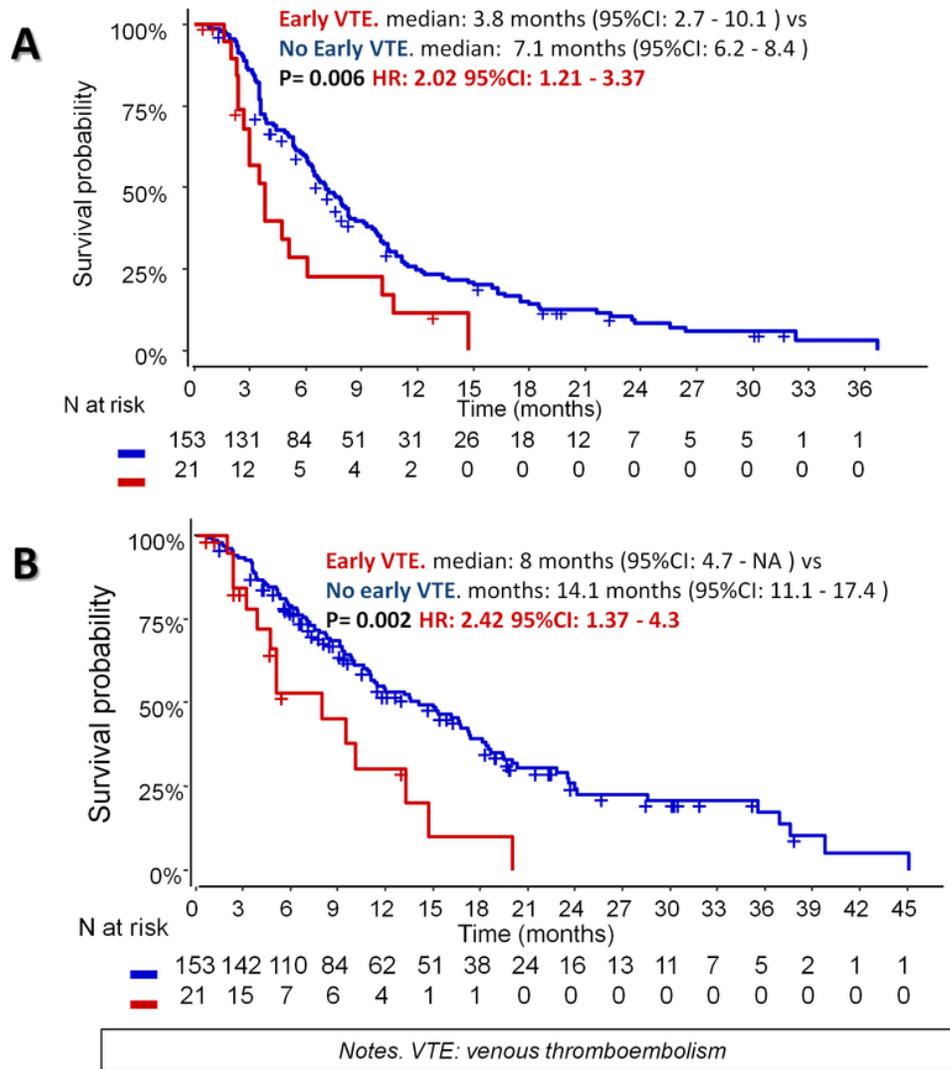
Supplementary Figures 1 and 2 not available with this version

## Figures



**Figure 1**

Cumulative incidence of venous thromboembolism A) in the whole population study B) according to a high Khorana score.



**Figure 2**

Impact of early venous thromboembolism on A) Progression-free survival B) overall survival.