Clinical characteristics and 3-month outcomes in cancer patients with incidental *versus* clinically suspected and confirmed pulmonary embolism

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In cancer patients with incidental pulmonary embolism the risk of venous thromboembolism recurrences or major bleeding are similar, with a lower mortality https://bit.ly/36AVqSy

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Abstract

Background Current guidelines suggest treating cancer patients with incidental pulmonary embolism (PE) similarly to those with clinically suspected and confirmed PE. However, the natural history of these presentations has not been thoroughly compared.

Methods We used the data from the RIETE (Registro Informatizado de Enfermedad TromboEmbólica) registry to compare the 3-month outcomes in patients with active cancer and incidental PE *versus* those with clinically suspected and confirmed PE. The primary outcome was 90-day all-cause mortality. Secondary outcomes were PE-related mortality, symptomatic PE recurrences and major bleeding.

Results From July 2012 to January 2019, 946 cancer patients with incidental asymptomatic PE and 2274 with clinically suspected and confirmed PE were enrolled. Most patients (95% *versus* 90%) received low-molecular-weight heparin therapy. During the first 90 days, 598 patients died, including 42 from PE. Patients with incidental PE had a lower all-cause mortality rate than those with suspected and confirmed PE (11% *versus* 22%; OR 0.43, 95% CI 0.34–0.54). Results were consistent for PE-related mortality (0.3% *versus* 1.7%; OR 0.18, 95% CI 0.06–0.59). Multivariable analysis confirmed that patients with incidental PE were at lower risk of death (adjusted OR 0.43, 95% CI 0.34–0.56). Overall, 29 (0.9%) patients developed symptomatic PE recurrences, and 122 (3.8%) had major bleeding. There were no significant differences in PE recurrences (OR 0.62, 95% CI 0.25–1.54) or major bleeding (OR 0.78, 95% CI 0.51–1.18).

Conclusions Cancer patients with incidental PE had a lower mortality rate than those with clinically suspected and confirmed PE. Further studies are required to validate these findings, and to explore optimal management strategies in these patients.

Introduction

Patients with cancer frequently undergo chest computed tomography (CT) scans to assess the extent of the malignancy, the response to cancer therapy, or to screen for metastases. These tests may lead to the

identification of incidental cases with pulmonary embolism (PE). Furthermore, presence of baseline cardiopulmonary limitations in cancer patients (including pulmonary metastases, pleural or pericardial effusion, chemotherapy-induced or radiation-associated cardiomyopathy and comorbidities, as well as general deconditioning) may mask the development of PE, increasing the possibility that a PE diagnosis is unsuspected, but rather, incidental. With widespread use of CT testing in cancer patients, the detection of incidental PE has become increasingly common [1, 2]. The prevalence of incidental PE in the population of patients with active cancer is reported to range between 1.1% and 5.0% [3–5]. Several guidelines recommend using the same treatment strategy for patients with incidental PE as for those with clinically suspected and confirmed PE [6–8]. However, these recommendations are based mainly on retrospective studies that have reported no significant differences in the rates of recurrent venous thromboembolism (VTE), major bleeding and mortality in patients with incidental *versus* clinically suspected PE. However, most of these studies were small, were under-powered to detect differences on important outcomes, and did not focus on case fatality rates (*i.e.* PE-related mortality) [9–12].

The RIETE (Registro Informatizado de Enfermedad TromboEmbólica) Registry is an ongoing, multicentre, international registry of consecutive patients with objectively confirmed acute VTE (ClinicalTrials.gov identifier NCT02832245) [13]. Data from this registry have been used to evaluate outcomes after acute VTE, such as the frequency of recurrent VTE, bleeding and mortality, and risk factors for these outcomes in cancer-associated VTE [14–18]. The goal of the current study is to compare the clinical characteristics and 3-month outcomes of cancer patients with incidentally found asymptomatic PE *versus* those with clinically suspected and confirmed PE.

Patients and methods

Data source

Details about the methodology of RIETE have been discussed elsewhere [11]. In brief, RIETE is a multicenter prospective registry of consecutive patients with objectively confirmed acute deep vein thrombosis (DVT) or PE with 205 collaborating centres from 27 countries. The protocol for enrolling patients into RIETE has been approved by the ethics committees at the participating sites. All patients provided written or oral consent for participation in the registry, in accordance with local ethics committee requirements. Physicians participating in the RIETE registry made all efforts to enrol consecutive patients.

Inclusion criteria

Incidental PE was defined as PE detected on a CT scan ordered for reasons other than a clinical suspicion of PE [19]. Patients with incidental PE have been incorporated into RIETE since July 2012. Thus, for this study we only included patients who were enrolled in RIETE from July 2012 to January 2019 and grouped them in two subgroups of incidental asymptomatic PE *versus* clinically suspected and confirmed PE. For this study, we only included patients in both subgroups who were diagnosed by contrast-enhanced CT and had no signs or symptoms of DVT concomitantly, to make the comparisons between the two groups more consistent. Active cancer was defined as newly (<3 months before) diagnosed cancer, metastatic cancer or cancer that was being treated (*i.e.* surgery, chemotherapy, radiotherapy, support therapy or combined therapies). CT scan findings were classified as centrally located thrombi (defined as a central or lobar thrombus location) and more peripherally located thrombi (defined as a segmental or subsegmental thrombus location), according to the site reports.

Nomenclature

We used the term incidental because this is the terminology endorsed by the International Society on Thrombosis and Haemostasis [19]. Patients with suspected and confirmed PE were those investigated specifically for PE based on signs and symptoms. Chart reviews of patients with incidentally diagnosed PE suggest that some of them were in fact symptomatic, with symptoms possibly attributed to the underlying cancer or other factors, rather than to PE before the PE diagnosis was made [18, 20]. Thus, we excluded from the analysis all patients who had incidental but symptomatic PE.

Main comparisons and outcomes

We compared the clinical characteristics, treatment and 3-month outcomes of cancer patients with incidental and asymptomatic PE *versus* those with clinically suspected and confirmed PE. The primary outcome was all-cause mortality within the first 90 days. Secondary outcomes were fatal PE, symptomatic PE recurrences and major bleeding. Fatal PE, in the absence of autopsy, was defined as any death appearing within 10 days after symptomatic PE diagnosis (either the index PE or recurrent PE), in the absence of any alternative cause of death. Each episode of clinically suspected recurrent PE was investigated by repeat helical-CT scan. Bleeding complications were classified as “major” if they were overt and required a transfusion of two units of blood or more, or were retroperitoneal, spinal, intracranial, intraocular,

intrapericardial or when they were fatal. Fatal bleeding was defined as any death occurring within 10 days of a major bleeding episode, in the absence of an alternative cause of death.

Baseline variables

The following parameters were routinely recorded in RIETE: demographics, history of chronic heart or lung disease, cancer sites and stage, other risk factors for VTE, laboratory data, treatment received upon VTE diagnosis (drugs, doses and duration) and the clinical outcome during the course of anticoagulant therapy. RIETE, by design, includes follow-up for all (100%) patients for ⩾90 days or until death. Immobilised patients were defined as nonsurgical patients who had been immobilised (*i.e.* total bed rest with bathroom privileges) for ⩾4 days in the 2-month period prior to VTE diagnosis. Surgical patients were defined as those who underwent a major surgical intervention in the 2 months prior to VTE. Recent bleeding was defined as a major bleeding episode <30 days prior to VTE.

Treatment and follow-up

Patients were managed according to the clinical practice of each participating hospital (*i.e.* there was no standardisation of treatment). All patients were followed-up for ⩾3 months, or until death if it occurred earlier. During each visit, any signs or symptoms suggesting symptomatic VTE recurrences or bleeding events were noted. The outcomes were classified as reported by the clinical enrolling site. However, if staff at the RIETE coordinating centre were concerned about background variables (*e.g.* inconceivable values), the site investigators were contacted for clarifications. For uncertain or ambiguous outcome values, the events were reviewed by a central adjudicating committee (<10% of events).

Statistical analysis

We reported continuous data as mean±SEM, or median (interquartile range) if not normally distributed, and categorical data as frequency counts with percentages. We used the t-test and Chi-squared test (or Fisher's exact test where appropriate) to compare continuous or categorical variables. Then, a multivariable analysis was performed through a logistic regression model to identify the predictors for all-cause death within the first 3 months. Covariates entering in the model were selected by a significance level of $p<0.10$ on univariable analysis, or by a well-known association reported in the literature. In addition, the primary end-point was explored in pre-defined subgroups (including males *versus* females, patients aged ⩾75 years *versus* younger patients and patients with *versus* without metastases). Finally, we conducted several sensitivity analyses. First, we performed exploratory factor analysis in order to rule out redundant variables, and to condense many variables into just a few homogenous variables together, thereby reducing the number of variables to be considered. Then, we used a propensity score regression adjustment to compare outcomes for patients with incidental *versus* those with clinically suspected and confirmed PE, with similar baseline demographic and clinical variables. SPSS software (version 20; SPSS, Chicago, IL, USA) and Stata 16.1 (StataCorp, College Station, TX, USA) were used for the statistical management of the data, and a two-sided $p<0.05$ was considered to be statistically significant.

Results

From July 2012 to January 2019, 3324 patients with active cancer and PE were enrolled in RIETE. Of these, 1020 (31%) had incidental PE and 2304 (69%) had clinically suspected and confirmed PE. Among patients with incidental PE, 946 (93%) did not complain of respiratory symptoms, and were included in the study. Most patients in both subgroups (919 and 2274 in the incidental and clinically suspected and confirmed groups, respectively) received anticoagulant therapy, and were included into the current analysis.

Baseline characteristics

Patients with incidental PE were more likely to be male (OR 1.24, 95% CI 1.06–1.44), and slightly younger than those with suspected and confirmed PE (table 1). Only a few patients with incidental PE had tachycardia, tachypnoea, hypotension, hypoxaemia or atrial fibrillation at baseline (table 1). In contrast, nearly all patients with suspected and confirmed PE had a constellation of such symptoms and signs. At baseline, patients with incidental PE were less likely to have chronic lung or heart disease, recent surgery or immobility, leukocytosis, renal insufficiency, abnormal prothrombin time or abnormal fibrinogen levels than those with clinically suspected PE, but were more likely to have anaemia. The anatomical burden of larger branches on CT scan was relatively similar. Among patients who had echocardiographic data available, those with incidental PE had lower pulmonary artery pressure levels or evidence of right ventricle dysfunction. Finally, patients with incidental PE were more likely to have metastases than those with suspected PE (OR 1.94, 95% CI 1.65–2.28), or to have colorectal, pancreatic, gastric cancer or melanoma, but less likely to have breast, prostatic, haematological malignancies or primary brain tumours than those with clinically suspected PE (table 2).

TABLE 1 Clinical characteristics at baseline (and computed tomography (CT) scan findings) in patients with incidental and asymptomatic pulmonary embolism (PE) *versus* those with clinically suspected PE

	Incidental PE	Suspected PE	OR (95% CI)	p-value
Patients	946	2274		
Clinical characteristics				
Male	548 (58)	1197 (53)	1.24 (1.06–1.44)	
Age years	67±11	68±13		0.001
Body weight kg	72±13	74±15		p<0.001
Additional risk factors for VTE				
Surgery	107 (11)	379 (17)	0.64 (0.51–0.80)	
Immobility ⩾4 days	121 (13)	354 (16)	0.80 (0.64–0.99)	
Prior VTE	61 (6.4)	246 (11)	0.57 (0.42–0.76)	
Underlying conditions				
Chronic lung disease	91 (9.6)	394 (17)	0.51 (0.40–0.65)	
Chronic heart disease	29 (3.1)	162 (7.1)	0.41 (0.28–0.62)	
Recent (<30 days) major bleeding	37 (3.9)	75 (3.3)	1.19 (0.80–1.78)	
PE symptoms/signs at baseline				
Dyspnoea	0	1834 (82)		
Chest pain	0	786 (36)		
Syncope	0	281 (13)		
Haemoptysis	0	91 (4.2)		
SBP levels <100 mmHg	48 (5.4)	236 (10)	0.49 (0.36–0.68)	
Heart rate >100 beats·min^{-1}	105 (12)	826 (37)	0.23 (0.19–0.29)	
Respiratory rate >20 breaths·min^{-1} (n=1602)	33 (7.1)	523 (46)	0.09 (0.06–0.13)	
Saturated oxygen levels <90% (n=1353)	11 (5.1)	325 (29)	0.13 (0.07–0.25)	
Atrial fibrillation	17 (1.8)	124 (5.5)	0.32 (0.19–0.53)	
Largest arteries involved on CT scan				
Segmental or subsegmental	348 (37)	781 (34)	1.11 (0.95–1.30)	
Pulmonary or lobar	410 (43)	847 (37)	1.29 (1.10–1.50)	
Not reported	188 (20)	646 (28)	0.63 (0.52–0.75)	
Transthoracic echocardiogram (n=739)				
Mean PAP levels mmHg	37±12	46±16		p<0.001
Right ventricle dysfunction	4 (3.9)	117 (18)	0.18 (0.07–0.50)	
Laboratory data				
Anaemia	592 (63)	1288 (57)	1.28 (1.10–1.50)	
Leukocyte count >11 000 cells·μL^{-1}	184 (19)	754 (33)	0.49 (0.41–0.58)	
Platelet count <100 000 cells·μL^{-1}	36 (3.8)	122 (5.4)	0.70 (0.48–1.02)	
CrCl levels <60 mL·min^{-1}	224 (24)	686 (30)	0.72 (0.60–0.86)	
Abnormal prothrombin time (n=2436)	45 (7.3)	195 (11)	0.66 (0.47–0.92)	
Abnormal fibrinogen levels (n=1639)	200 (43)	591 (50)	0.76 (0.61–0.95)	

Data are presented as n, n (%) or mean±SD, unless otherwise stated. VTE: venous thromboembolism; SBP: systolic blood pressure; PAP: pulmonary artery pressure; CrCl: creatinine clearance.

Treatment

Median duration of anticoagulant therapy was similar in both subgroups (162 *versus* 146 days; p=0.759), as shown in table 3. The majority of patients (95% *versus* 90%) were initially treated with low-molecular-weight heparin (LMWH), but those with incidental PE received lower daily doses (160±43 *versus* 174±42 IU·kg^{-1}·day^{-1}; p<0.001) than those with clinically suspected PE. No patient with incidental PE received thrombolytic therapy, compared to 33 (1.5%) patients with suspected and confirmed PE. For long-term therapy, most patients in both subgroups kept receiving LMWH (90% *versus* 69%), again with lower doses per body weight in those with incidental PE (150±41 *versus* 158±42 IU·kg^{-1}·day^{-1}; p<0.001). A lower proportion of patients with incidental PE switched to vitamin K antagonists (4.5% *versus* 17%; p<0.001).

Outcomes

During the first 3 months of therapy, 598 (19%) patients died (fatal PE 42, fatal bleeding 19), 29 (0.9%) developed recurrent symptomatic PE, 37 (1.1%) had DVT and 122 (3.8%) had major bleeding. Patients with incidental PE had a lower mortality rate than those with suspected and confirmed PE (11% *versus* 22%; OR 0.43, 95% CI 0.34–0.54), as shown in table 4. Results were consistent for PE-related mortality

TABLE 2 Cancer characteristics in patients with incidental and asymptomatic pulmonary embolism (PE) *versus* those with clinically suspected PE

	Incidental PE	Suspected PE	OR (95% CI)
Patients	946	2274	
Time from cancer diagnosis[#] months	5 (2–22)	6 (1–26)	
<3 months	378 (40)	1046 (46)	0.78 (0.67–0.91)
>12 months	293 (31)	739 (32)	0.93 (0.79–1.10)
Metastases			
Yes	663 (70)	1243 (55)	1.94 (1.65–2.28)
Sites of cancer			
Lung	185 (20)	503 (22)	0.86 (0.71–1.03)
Colorectal	224 (24)	304 (13)	2.01 (1.66–2.44)
Breast	76 (8.0)	311 (14)	0.55 (0.42–0.72)
Prostate	34 (3.6)	182 (8.0)	0.43 (0.29–0.62)
Pancreas	68 (7.2)	104 (4.6)	1.62 (1.18–2.22)
Stomach	63 (6.7)	69 (3.0)	2.28 (1.61–3.24)
Hematological	24 (2.5)	106 (4.7)	0.53 (0.34–0.83)
Bladder	33 (3.5)	83 (3.6)	0.95 (0.63–1.44)
Ovary	29 (3.1)	82 (3.6)	0.85 (0.55–1.30)
Uterine	24 (2.5)	81 (3.6)	0.70 (0.44–1.12)
Central nervous system	17 (1.8)	87 (3.8)	0.46 (0.27–0.78)
Kidney	35 (3.7)	65 (2.9)	1.31 (0.86–1.98)
Carcinoma of unknown origin	23 (2.4)	34 (1.5)	1.64 (0.96–2.80)
Oropharynx	16 (1.7)	36 (1.6)	1.07 (0.59–1.94)
Melanoma	27 (2.9)	20 (0.88)	3.31 (1.85–5.93)
Biliary tract	9 (0.95)	38 (1.7)	0.57 (0.27–1.17)
Oesophageal	15 (1.6)	21 (0.92)	1.73 (0.89–3.37)
Liver	5 (0.53)	28 (1.2)	0.43 (0.16–1.11)
Other	39 (4.1)	117 (5.1)	0.79 (0.55–1.15)
Therapy for cancer			
Chemotherapy	514 (57)	939 (46)	1.59 (1.36–1.86)
Radiotherapy	111 (13)	307 (16)	0.79 (0.63–1.00)
Chemo- and radiotherapy	88 (10)	199 (10)	1.00 (0.77–1.30)
Hormonal therapy	60 (7.0)	298 (16)	0.41 (0.31–0.55)
None of the above	337 (37)	803 (39)	0.94 (0.80–1.10)

Data are presented as n, median (interquartile range) or n (%), unless otherwise stated. [#]: nonsignificant.

(0.3% *versus* 1.7%; OR 0.18, 95% CI 0.06–0.59) (figure 1). There were no significant differences between subgroups in the rates of PE recurrences (OR 0.62, 95% CI 0.25–1.54), symptomatic DVT (OR 0.66, 95% CI 0.30–1.45) or major bleeding (OR 0.78, 95% CI 0.51–1.18).

On multivariable analysis, after adjusting for patient's age and sex, additional risk factors for VTE, systolic blood pressure levels and heart rate at baseline, anaemia, renal function, presence of metastases, site of cancer and treatment for cancer, patients with incidental PE had nearly half the risk for all-cause mortality than those with suspected PE (hazard ratio (HR) 0.43, 95% CI 0.34–0.56), as shown in table 5. When we performed exploratory factor analysis adjusted by the same variables that were included into the multivariable analysis, the results mimicked the findings of the primary analysis: the mortality rates in patients with incidental PE were significantly lower than in those with clinically suspected and confirmed PE (HR 0.50, 95% CI 0.39–0.63). Similarly, we found consistent results when using a propensity score regression adjustment (HR 0.50, 95% CI 0.40–0.64). Finally, the analyses by subgroups revealed a higher influence of incidental PE on mortality in males (OR 0.33, 95% CI 0.23–0.47) than in females (OR 0.65, 95% CI 0.43–0.99); in patients aged ⩽75 years (OR 0.36, 95% CI 0.26–0.51) than in those aged >75 years (OR 0.62, 95% CI 0.38–1.00), and in patients without metastases (OR 0.38, 95% CI 0.28–0.51) than in those with metastases (OR 0.92, 95% CI 0.50–1.72).

Discussion

Our findings, obtained from a large series of consecutive patients with active cancer and PE, reveal that nearly a third of PEs were incidental and asymptomatic. In our cohort, patients with incidental PE were more likely to have metastases than those with symptomatic PE and less likely to have chronic lung or

TABLE 3 Treatment strategies in patients with incidental and asymptomatic pulmonary embolism (PE) *versus* those with clinically suspected PE

	Incidental PE	Suspected PE	OR (95% CI)	p-value
Patients	946	2274		
Duration of anticoagulation days				
Mean±SD	247±293	244±336		0.759
Median (IQR)	162 (96–290)	146 (69–291)		
Initial therapy				
Unfractionated heparin	12 (1.3)	124 (5.5)	0.22 (0.12–0.40)	
LMWH	899 (95)	2050 (90)	2.09 (1.51–2.89)	
Mean LMWH dose IU·kg^{-1}·day^{-1}	160±43	174±42		p<0.001
LMWH <100 IU·kg^{-1}·day^{-1}	78 (8.7)	135 (6.6)	1.35 (1.01–1.80)	
Fondaparinux	5 (0.53)	28 (1.2)	0.43 (0.16–1.11)	
DOACs	3 (0.32)	24 (1.1)	0.30 (0.09–0.99)	
Thrombolytics	0	33 (1.5)		
Inferior vena cava filter	39 (4.1)	110 (4.8)	0.85 (0.58–1.23)	
Long-term therapy				
LMWH	854 (90)	1567 (69)	4.19 (3.32–5.29)	
Mean LMWH dose IU·kg^{-1}·day^{-1}	150±41	158±42		p<0.001
LMWH <100 IU·kg^{-1}·day^{-1}	76 (8.9)	130 (8.3)	1.08 (0.80–1.45)	
Vitamin K antagonists	43 (4.5)	395 (17)	0.23 (0.16–0.31)	
DOACs	13 (1.4)	106 (4.7)	0.28 (0.16–0.51)	
Fondaparinux	5 (0.53)	30 (1.3)	0.40 (0.15–1.03)	

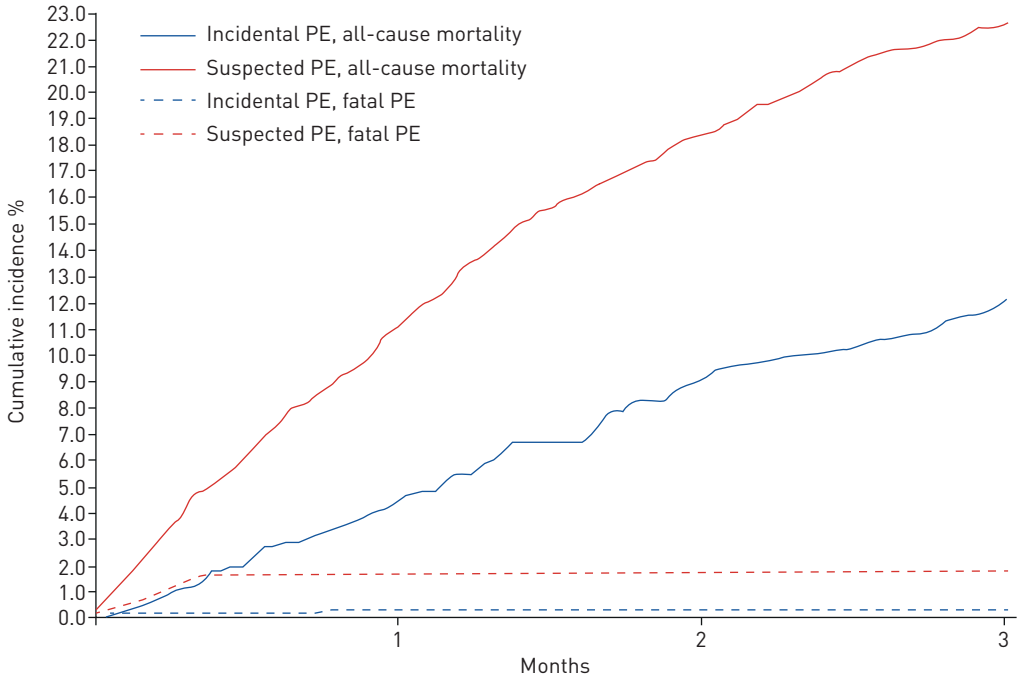
Data are presented as n, mean±SD or n (%), unless otherwise stated. IQR: interquartile range; LMWH: low-molecular-weight heparin; IU: international units; DOACs: direct oral anticoagulants.

heart disease, renal insufficiency or abnormal coagulation tests at baseline. There were only slight differences in the treatment of PE, although 1.5% of patients with symptomatic PE and none with incidental PE received thrombolytics. During the first 3 months of therapy, there were no significant differences in the rates of symptomatic PE recurrences or major bleeding, but the mortality rate was half in patients with

TABLE 4 Clinical outcomes at 90 days in patients with incidental and asymptomatic pulmonary embolism (PE) *versus* those with clinically suspected and confirmed PE

	Incidental PE	Suspected PE	OR (95% CI)
Patients	946	2274	
Symptomatic PE	6 (0.63)	23 (1.0)	0.62 (0.25–1.54)
Deep vein thrombosis	8 (0.85)	29 (1.3)	0.66 (0.30–1.45)
Major bleeding	30 (3.2)	92 (4.0)	0.78 (0.51–1.18)
Sites of major bleeding			
Gastrointestinal	14 (1.5)	37 (1.6)	0.91 (0.49–1.69)
Intracranial	4 (0.42)	13 (0.57)	0.74 (0.24–2.27)
Death	102 (11)	496 (22)	0.43 (0.34–0.54)
Causes of death			
PE	3 (0.32)	39 (1.7)	0.18 (0.06–0.59)
Initial PE	0	36 (1.6)	
Recurrent PE	3 (0.32)	3 (0.13)	2.41 (0.49–11.95)
Respiratory failure	1 (0.11)	24 (1.1)	0.10 (0.01–0.73)
Sudden, unexpected	2 (0.21)	5 (0.22)	0.96 (0.19–4.96)
Bleeding	2 (0.21)	17 (0.75)	0.28 (0.06–1.22)
Disseminated cancer	76 (8.0)	309 (14)	0.56 (0.43–0.72)
Infection	7 (0.74)	17 (0.75)	0.99 (0.41–2.39)
Multiorgan failure	3 (0.32)	13 (0.57)	0.55 (0.16–1.95)
Heart insufficiency	0	8 (0.35)	
Ischaemic stroke	1 (0.11)	4 (0.18)	0.60 (0.07–5.38)
Other/unknown	7 (0.74)	60 (2.6)	0.28 (0.13–0.60)

Data are presented as n or n (%), unless otherwise stated.



		Days				
		2	10	30	60	90
All-cause death	Incidental PE	3 (0.3%)	13 (1.3%)	45 (4.5%)	90 (9.2%)	117 (12%)
	Suspected PE	30 (1.3%)	111 (4.9%)	250 (11%)	405 (18%)	496 (23%)
Fatal PE	Incidental PE	2 (0.2%)	2 (0.2%)	3 (0.3%)	3 (0.3%)	3 (0.3%)
	Suspected PE	11 (0.5%)	36 (1.6%)	38 (1.7%)	38 (1.7%)	39 (1.8%)

FIGURE 1 Cumulative mortality rates during the first 90 days of anticoagulant therapy in patients with incidental *versus* suspected pulmonary embolism (PE).

incidental PE than in those with suspected PE. Patients with incidental PE had a significantly lower mortality due to PE, but also due to respiratory failure and even to disseminated malignancy, than those with symptomatic PE. The results were consistent after adjusting for a number of potential confounders.

The lower rate of all-cause mortality in patients with incidental PE is clinically relevant and deserves further discussion. First, the lower rate of fatal PE in patients with incidental PE could have been expected. Second, we should acknowledge that the lower mortality rate due to disseminated malignancy was unexpected, since patients with incidental PE were more likely to have metastases and less likely to have less aggressive cancers (*i.e.* breast or prostate) than those with suspected PE. On multivariable analysis, we tried to adjust for a number of variables, but patients with cancer may have additional confounders that were not considered in this analysis. For instance, in RIETE there is no information on the duration or the intensity of chemo- and radiotherapy.

The nonsignificant differences in the rates of PE recurrences or major bleeding found also in other studies suggests that patients with incidental PE should be treated as those with suspected PE [6–8, 21]. However, in patients with incidental PE in our cohort the rate of major bleeding was five-fold greater than the rate of symptomatic PE recurrences (30 *versus* six events), as reported earlier [22]. In patients with clinically suspected PE the rate of major bleeding was four-fold greater than the rate of recurrent PE (92 *versus* 23 events), but the mortality rate due to PE was two-fold greater than the mortality for bleeding, particularly during the first days. This was not the case in patients with incidental PE. Further studies are needed to identify which cancer patients with incidental PE are at increased risk of bleeding, and if they could benefit from reduced doses of LMWH (or maybe of shorter durations of therapy). While caution should be exercised in interpretation of the results, our findings may have implications for treatment strategies, including among patients with highest risk of complications from antithrombotic therapy. The optimal management strategy for these patients should be tested in future randomised trials.

TABLE 5 Bivariate and multivariable analysis for all-cause death at 90 days

	Bivariate	Multivariable
Incidental PE	0.45 (0.37–0.56)***	0.43 (0.34–0.56)***
Clinical characteristics		
Body weight ⩾70 kg	0.63 (0.53–0.74) ***	0.75 (0.62–0.91)**
Recent surgery	0.43 (0.31–0.59) ***	0.40 (0.27–0.58) ***
Recent immobility ⩾4 days	1.96 (1.62–2.37) ***	1.48 (1.19–1.83) ***
Chronic lung disease	1.30 (1.06–1.60)*	0.92 (0.72–1.17)
PE signs at baseline		
SBP levels <100 mmHg	1.69 (1.33–2.13) ***	1.49 (1.15–1.94)**
Heart rate >100 beats·min^{-1}	1.88 (1.60–2.21) ***	1.53 (1.27–1.85) ***
Laboratory data		
Anaemia	1.70 (1.43–2.02) ***	1.74 (1.43–2.13) ***
Leukocyte count >11 000 cells·µL^{-1}	2.25 (1.91–2.64) ***	1.71 (1.42–2.05) ***
CrCl levels <30 mL·min^{-1}	2.31 (1.63–3.27) ***	1.78 (1.19–2.65)**
Metastases	3.50 (2.84–4.31) ***	3.30 (2.56–4.26) ***
Sites of cancer		
Lung	Ref.	Ref.
Colorectal	0.32 (0.23–0.44) ***	0.40 (0.28–0.58) ***
Breast	0.30 (0.21–0.43) ***	0.47 (0.30–0.73) ***
Prostate	0.37 (0.24–0.57) ***	0.43 (0.25–0.72)**
Pancreas	1.77 (1.35–2.33) ***	1.94 (1.42–2.66) ***
Hematological	0.44 (0.26–0.73)**	0.52 (0.28–0.96)*
Bladder	0.46 (0.27–0.77)**	0.66 (0.37–1.17)
Ovary	0.62 (0.39–0.99)*	0.72 (0.42–1.23)
Uterine	0.53 (0.31–0.89)*	0.71 (0.40–1.27)
Oropharynx	0.26 (0.10–0.70)**	0.41 (0.13–1.31)
Biliary tract	1.88 (1.18–2.98)**	1.40 (0.85–2.32)
Liver	2.02 (1.21–3.37)**	2.16 (1.23–3.78)**
Therapy for cancer		
Chemotherapy	0.75 (0.62–0.90)**	0.77 (0.62–0.95)*
Radiotherapy	0.82 (0.63–1.07)	0.94 (0.69–1.27)
Hormonal therapy	0.41 (0.29–0.59) ***	0.78 (0.51–1.20)

Variables entered in the multivariable analysis: patient's age, sex, chronic heart or lung disease, additional risk factors for venous thromboembolism, systolic blood pressure (SBP) levels and heart rate at baseline, anaemia, renal function, presence of metastases, site of cancer and treatment for cancer. PE: pulmonary embolism; CrCl: creatinine clearance; Ref.: reference. *: p<0.05; **: p<0.01; ***: p <0.001.

The present study has several limitations. First, RIETE is an observational study (not a randomised trial). Second, treatment was not standardised across sites and unmeasured biases are likely present. However, our results reflect practices from several centres, with widespread clinical and geographical diversity. Third, the use of CT scanning in patients with incidental PE is variable and could have resulted in selection bias. Patients receiving chemotherapy, those with metastases and those with colorectal, stomach or pancreatic cancers are more likely to undergo regular CT scans. In contrast, patients in palliative care, and those without metastases or with breast, prostatic or brain tumours are less likely to be scanned. Fourth, we included the causes of death according to the opinion of the attending physicians, since RIETE, by design, does not entail central end-point adjudication, which may be a potential limitation. In light of this, one of the major outcomes of interest was all-cause death. Reassuringly, results for all-cause mortality and PE-related mortality were directionally and statistically consistent. Finally, variability in the treating physicians' index of suspicion for PE may have influenced whether patients with cancer were referred for radiological studies to rule out PE, even in the presence of symptoms.

In conclusion, cancer patients with incidental PE who were treated with anticoagulation had a more benign clinical course, including lower rates of PE-related mortality and lower rates of all-cause mortality, compared with patients with clinically suspected and confirmed PE. While caution should be exercised in interpretation of the results, our findings may have implication for treatment strategies, including among patients with highest risk of complications from antithrombotic therapy. The optimal management strategy for these patients should be tested in future randomised trials.

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