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Phlébologie ANNALES VASCULAIRES 2022, 75, 1, p. 40-48

Original paper
Article original

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Pulmonary embolism and coexisting deep vein thrombosis: a detrimental association?

Embolie pulmonaire et thrombose veineuse profonde coexistante : une association de mauvais pronostic ?

Cordeanu E.-M., Stephan D.

Abstract

Background: The prognostic significance of coexisting deep vein thrombosis (DVT) in acute pulmonary embolism (PE) is controversial.

This study aimed to provide routine patient care data on the impact of this association on PE severity and 3-months outcomes in a population presenting with symptomatic venous thromboembolism (VTE), from the REMOTEV registry.

Methods and Results: REMOTEV is a prospective, non-interventional study of patients with acute symptomatic VTE, treated with direct oral anticoagulants (DOACs) or standard anticoagulation (vitamin K antagonists (VKA) or parenteral heparin/fondaparinux alone) for at least 3 months.

From November 2013 to May 2018, among 1241 consecutive patients included, 1192 had a follow-up of at least 3 months and, among them, 1037 had PE with (727) or without DVT (310). The median age was 69 (55-80, 25th-75th percentiles).

Patients with PE-associated DVT had more severe forms of PE ($P <$ 0,0001).

However, no difference in all-cause mortality rate (HR 1,36 (CI 95% 0,69 – 2,92)), or in the composite criterion of all-cause mortality and recurrence rate (HR 1,56 (CI 95% 0,83 – 3,10)) was noted at 3 months of follow-up.

Conclusion: In REMOTEV, coexisting DVT was associated with a higher severity of PE, with no impact on short-term prognosis.

Keywords: *venous thromboembolism, DVT, PE, severity.*

Résumé

Contexte : *La signification pronostique de la coexistence d'une thrombose veineuse profonde (TVP) dans l'embolie pulmonaire aiguë (PE) est controversée.*
Cette étude visait à fournir des données de routine dans le cadre des soins sur l'impact de cette association sur la sévérité de l'EP et sur le suivi à 3 mois d'une population présentant des symptômes d'une thrombo-embolie veineuse (VTE), à partir du registre REMOTEV

Méthodes et résultats : *REMOTEV est une étude prospective non interventionnelle, chez des patients présentant une symptomatologie aiguë d'une maladie thromboembolique veineuse (MTEV), traités avec des anticoagulants oraux directs (DOAC) ou par une anticoagulation standard (antagonistes de la vitamine K (AVK)) ou par une héparinothérapie parentérale (Fondaparinux seule) pendant au moins 3 mois.*
De novembre 2013 à mai 2018, parmi 1241 patients inclus consécutivement, 1192 avaient eu un suivi d'au moins 3 mois et parmi eux 1037 avaient une PE avec une TVP (727) ou sans TVP (310). L'âge médian était de 69 ans (55-80 ans, 25^{e} au 75^{e} percentiles).
Les patients atteints de TVP associée à l'EP ont présenté des formes plus graves de PE ($p <$ 0,0001).
Cependant, aucune différence dans le taux de mortalité toutes causes confondues (HR 1,36 (IC 95 % 0,69 – 2,92)), ou dans le critère composite de toutes causes de mortalité et de récidive (HR 1,56 (IC 95 % 0,83 – 3,10)) n'a été notée à 3 mois de suivi.

Conclusion : *Dans le registre REMOTEV, la survenue d'une TVP coexistante à une EP était associée à une sévérité plus élevée de l'EP, mais elle n'a pas d'impact sur le pronostic à court terme.*

Mots-clés : maladie thrombo-embolique veineuse, TVP, PE, sévérité.

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The authors declared no potential conflicts of interest with respect to the research, authorship and publication of this article.

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List of abbreviations

- **AF:** atrial fibrillation
- **CG:** Cockcroft and Gault
- **CI:** confidence interval
- **CKD:** chronic kidney disease
- **CrCl:** creatinine clearance
- **CRNM:** clinically-relevant non-major
- **DOAC(s):** direct oral anticoagulant(s)
- **DVT:** deep vein thrombosis
- **eGFR:** estimated glomerular filtration rate
- **ESC:** European Society of Cardiology
- **FU:** follow-up
- **HR:** hazard ratio
- **INR:** international normalized ratio
- **LMWH:** low molecular weight heparin
- **MDRD:** modification of diet renal disease
- **PE:** pulmonary embolism
- **RCT(s):** randomized clinical trial(s)
- **RV:** right ventricle
- **SD:** standard deviation
- **(s)PESI:** (simplified) Pulmonary embolism severity index
- **IQR:** interquartile range
- **UFH:** unfractioned heparin
- **VKA:** vitamin K antagonist
- **VTE:** venous thromboembolism

Introduction

Pulmonary embolism (PE) is a frequent, potentially fatal condition, with a wide spectrum of clinical features and protean prognosis.

If its discovery on autopsy series ranges from 7 to 30%, symptomatic PE occurs in 1/1000 persons per year [1]. PE is the third cause of cardiovascular death and its early mortality is directly related to initial severity [2, 3].

Early death rate ranges from 0,5% in hemodynamically stable patients to 20% in patients presenting with cardiogenic shock.

In order to detect patients at higher risk of complication during the acute phase, the Pulmonary Embolism Severity Index (PESI) and its simplified version (sPESI) integrating age, comorbidities, blood pressure, heart rate and oxygen saturation have been validated in the estimation of mortality risk at 30 days [4, 5].

In 2014, the European Society of Cardiology (ESC) adopted a 4-level risk classification:

a) high risk in case of haemodynamic instability,
b) intermediate high risk in case of cardiac biomarkers elevation and right ventricular (RV) dysfunction,
c) intermediate low risk in the presence of a sPESI score › 0 and/or positive biomarkers or RV dilation and
d) low risk in the absence of biomarkers elevation or right heart dysfunction or sPESI elevation [6].

PE and deep vein thrombosis (DVT) are two expressions of the same pathology, frequently associated.

Though one third of clinically-overt DVTs are associated with a silent PE it has been shown that isolated DVT has lower complication rates than PE [7-9].

Historically, the reported rates of concomitant presence of DVT in PE are ranging from 10 to 93%, but most recent studies found a coexisting DVT in 56 to 61% of the symptomatic PE cases [10-12].

Whether the association of DVT and PE has a poorer prognosis than isolated PE is not known.

Literature analysis shows opposing data regarding the association of DVT and outcomes such as death and recurrence [13-15].

Our study aimed to assess the correlation between the presence of concomitant DVT and PE severity, as well as 3-months outcomes (recurrence, death) in patients with acute PE.

Thus, we conducted an observational study on a prospective cohort of VTE (REMOTEV registry) in order to advance our understanding of short-term PE outcomes.

Patients and methods

Study design and patient selection

REMOTEV is an ongoing observational, prospective registry enrolling all consecutive patients hospitalized in the Vascular Medicine Unit of Strasbourg University Hospital for acute DVT and/or PE [16-20].

In the present study, we analyzed the clinical characteristics, comorbidity, treatment and events during the first 3 months after VTE diagnosis in PE patients.

Patients were informed about the purpose of the registry and gave an oral consent to their participation according to the requirements of the local Ethics Committee.

Data were recorded in a computerized anonymized form.

Baseline variables

Age, sex, weight, height and comorbidities were collected. Comorbidities included chronic kidney disease (CKD) and active cancer. CKD was evaluated according to the Cockcroft estimated glomerular filtration rate (eGFR).

For patients whose body weight was unknown, the eGFR was calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) equation.

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VTE was classified as provoked or unprovoked depending on the presence or absence of the following associated risk factors: recent surgery, prolonged immobilization (more than 3 days), recent travel (for more than 6 hours), known active cancer, pregnancy or a postpartum setting, estrogen therapy (oral contraception or hormone replacement therapy) [19].

Known active cancer was defined by a recently diagnosed cancer (‹ 6 months), cancer under treatment or metastatic cancer.

Cardiac biomarkers (troponin I, brain natriuretic peptide) and right ventricle parameters, measured by CT-scan or ultra-sound, were recorded.

PE severity was classified according to the 2014 ESC Guidelines for PE management based on the short-term mortality risk (*i.e.* low risk, intermediate low, intermediate high and high risk).

Requirements for VTE diagnosis

The imaging procedures to confirm PE and DVT were validated diagnostic tests [16-18]. The initial PE and/or DVT (index event) was recorded.

PE was confirmed by either computed tomography pulmonary angiogram or ventilation perfusion lung scan.

Patients with symptomatic PE were routinely screened for DVT.

The presence of DVT was assessed by ultrasonography from inferior vena cava to calf veins in both lower limbs.

Treatment regimens

The type, dose, and duration of anticoagulant drug therapy was based on current recommendations [6, 21-23].

Anticoagulation treatment consisted of:
- rivaroxaban (15 mg twice daily for 21 days, followed by 20 mg once a day),
- apixaban (10 mg twice daily for 7 days, followed by 5 mg twice daily),
- unfractionated heparin (UFH),
- low molecular weight heparin (LMWH) or fondaparinux,
- overlapping with and followed by International Normalized Ratio (INR) titrated vitamin K antagonists (VKA) or long-term parenteral anticoagulation including LMWH, or fondaparinux.

Indications for thrombolysis, thromboaspiration or surgical thrombectomy or implantation of an inferior vena cava filter were based on the current guidelines [6, 21, 22].

Follow-up and outcome assessment

For the purpose of this study, the observation period ended 3 months from the date of the index event. All patient data were collected at the initial visit and then via phone interview at 1 month (+/– 5 days) and 3 months (+/– 10 days).

The main evaluation criteria were: major or non-major clinically relevant bleeding, recurrent venous thromboembolism, major adverse cardiovascular events (MACE) and death.

Major and non-major clinically relevant bleeding events were classified according to the International Society on Thrombosis and Haemostasis (ISTH) criteria [24].

Recurrent VTE was considered as the cause of death when other causes were excluded and when PE could not be ruled out.

Death was classified as due to PE, bleeding, cancer, cardiovascular causes (myocardial infarction, stroke, sudden death and heart failure) or other.

The evaluation criteria were adjudicated by senior physicians of the vascular medicine unit.

Statistical analysis

This was a prospective observational study and therefore no formal power calculation was performed.

Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR) depending on the distribution.

The normality of the distribution was assessed graphically and using Shapiro-Wilk test. Categorical variables were presented as numbers of cases (percentages).

Patients were divided according to the presence of concomitant DVT (EP with or without DVT) as well as PE severity (low risk versus intermediate/high risk PE).

The risk of more severe forms of PE (intermediate/high risk) associated with several baseline factors, known to be correlated to PE severity, was assessed by univariate analysis. Risk factors associated with PE severity having a univariate test considered significant were selected as a candidate for the multivariate logistic regression analysis.

We compared the risk of death, major and CRNM bleeding or VTE recurrence between the two groups (PE with DVT *versus* PE without DVT).

A composite factor including the three events was also created.

Results were expressed as hazard ratio (HRs) with 95% confidence intervals (CI). A *P*-value ‹ 0.05 was considered as statistically significant.

The Kaplan-Meier estimator was employed to compute survival curves over the 3-month follow-up (FU). All analyses were performed using R software version 3.2.2 (www.r-project.org).

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Results

Baseline characteristics and deep vein thrombosis prevalence

Between November 1st, 2013 and April 30th, 2018, 1241 patients with VTE were included in the REMOTEV registry and 1192 had a follow-up of at least 3 months **(figure 1)**.

Among them, 1037 had PE with (70.1%) or without DVT (29.9%).

There were 53% of women and the median age was 69 (55-80, 25th-75th percentiles).

For 59% of the patients, the index event was considered unprovoked while 11% had a known active cancer.

Anticoagulant treatment consisted of a direct oral anticoagulant (DOAC) in 73% of the cohort.

Median hospital length of stay was 6 days (5-9: 25th-75th percentiles).

The recommended duration of treatment was 3 months for 9% of patients, 6 months for 46% of patients and without scheduled stop date for 45% patients.

The baseline characteristics of all PE patients are summarized in **table 1** according to the presence of a concomitant DVT or not.

Our further analysis focused on coexisting DVT.

Comparing DVT patients with DVT-free patients, yielded several differences between groups as shown in **table 1**.

DVT and PE severity assessment

When DVT was present, it was proximal in 62% of cases. PE was at low risk for 35,1% of the patients, intermediate low for 38,3%, intermediate high for 24% and high for 2,6% of the cohort.

PE severity was strongly associated to the presence of DVT, $P < 0{,}0001$ in a linear manner **(figure 2)**.

Furthermore, proximal location of DVT was significantly correlated with intermediate/high risk PE ($P < 0{,}01$).

Risk factors associated with PE severity

Univariate and multivariate analyses of factors associated to PE severity are presented in **table 2**.

According to univariate analysis, PE severity (low risk *versus* intermediate/ high risk) was correlated with cancer, age, DVT, female sex, high blood pressure, diabetes, COPD, renal impairment and ischemic heart disease.

As such, a multivariate Cox proportional hazards regression was performed to adjust for those covariates considered significant ($P < 0{,}01$ for univariate analysis) and found a strong correlation with cancer, age, DVT and poor renal function.

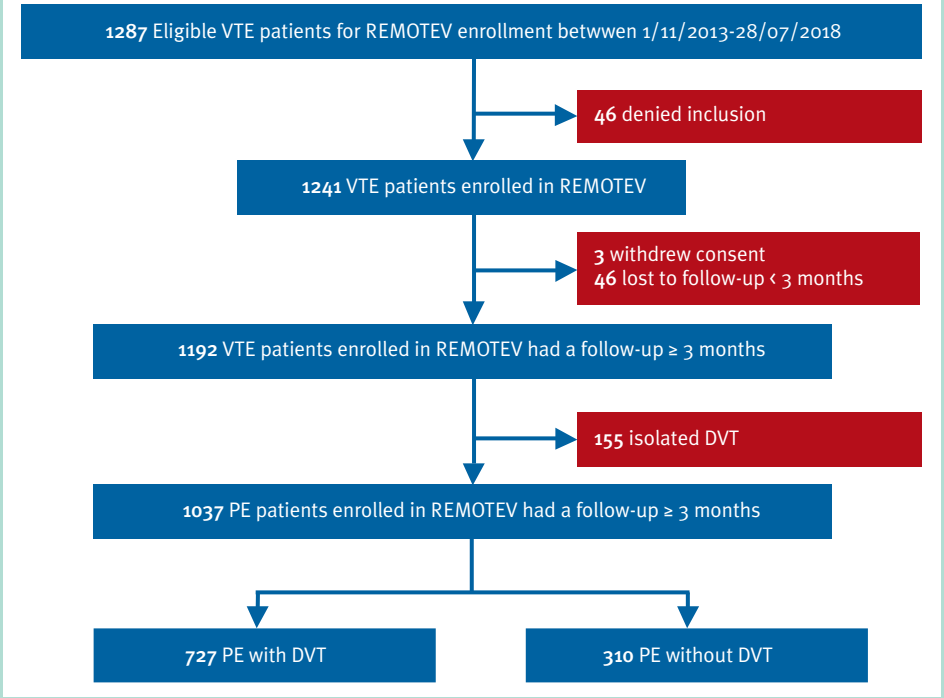


FIGURE 1:
Study Flowchart.

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	Total N (%)/m ± sd/ M (Q1-Q3)	PE with DVT N (%)/m ± sd/ M (Q1-Q3)	PE without DVT N (%)/m ± sd/ M (Q1-Q3)	*P*
N	**1037**	**727 (70,1)**	**310 (29,9)**	
Age (years)	69 (55-80)	71 (57-80)	67 (50-78)	**0.002**
Age ≥ 70 years old	499 (48.1)	368 (50.6)	131 (42.3)	0.008
Male	493 (47.5)	361 (49.7)	132 (42.6)	**0.04**
Weight (kg) N = 1018	77.5 (67-188)	78 (67-167)	77 (68-188)	0.47
Weight ≤ 50 kg	31 (3)	18 (2.5)	13 (4.3)	0.19
BMI (kg/m²) N = 987	27 (24-31)	27 (24-31)	27 (24-31)	0.91
BMI ≥ 30 kg/m²	324 (32.8)	230	94	0.69
eGFR (mL/min/1.73 m²) on admission	85.5 (67.2-104.3)	83 (65.1-100.7)	91.9 (70.8-112.2)	**0.0001**
eGFR ≥ 90	460 (44.4)	294 (40.4)	166 (53.7)	
60 ≤ eGFR < 90	381 (37.8)	285 (39.2)	96 (31.1)	
30 ≤ eGFR < 60	166 (16)	125 (17.2)	41 (13.3)	
eGFR < 30	29 (2.8)	23 (3.2)	6 (1.9)	
CrCl Cockcroft (mL/min) on admission	85.2 (58.7-119.6)	81.7 (55.5-114.1)	90.9 (64.7-128.4)	**0.001**
CrCl < 50 mL/min	177 (17.4)	137 (19.2)	40 (13.2)	**0.02**
Cardiovascular risk factors				
Hypertension	563 (54.3)	418 (57.5)	145 (46.8)	**0.001**
Diabetes	165 (15.9)	115 (15.8)	50 (16.1)	0.97
Dyslipidemia	344 (33.2)	251 (34.5)	93 (30)	0.17
Smoking (history or current)	417 (41.2)	287 (40.3)	130 (43.3)	0.40
Medical history				
Previous thromboembolism	332 (32)	230 (31.6)	102 (33)	0.71
PAD	32 (3.1)	20 (2.8)	12 (3.9)	0.71
CAD	62 (5.9)	41 (5.6)	21 (6.8)	0.57
COPD	56 (5.4)	32 (4.4)	24 (7.7)	**0.04**
Active cancer, total	89 (8.6)	68 (9.4)	21 (6.8)	0.21
Known thrombophilia	41 (3.9)	24 (3.3)	17 (5.5)	0.13
Antithrombotic treatment on admission				
Antiplatelet	202 (19.6)	131 (18.1)	71 (22.9)	0.08
Anticoagulation	66 (6.4)	40 (5.5)	26 (8.4)	0.11
PE severity				
Low risk	364 (35.1)	220 (30.3)	144 (46.5)	**< 0.0001**
Intermediate low	397 (38.3)	279 (38.4)	118 (38.1)	
Intermediate high	249 (24)	202 (27.8)	47 (15.1)	
High risk	27 (2.6)	26 (3.5)	1 (0.3)	
DVT location				
Lower limbs	717 (69.1)	717 (98.6)	–	
Bilateral	127 (12.2)	127 (12.2)	–	
Proximal	454 (43.8)	454 (43.8)	–	
Distal	263 (25.3)	263 (25.3)	–	
Unusual site	25 (2.4)	25 (2.4)	–	
Isolated	10 (1)	10 (1.4)	–	
Type of VTE				
Unprovoked	613 (59.1)	430 (59.1)	183 (59)	1
IVC filter	13 (1.2)	12 (1.6)	1 (0.3)	0.12
PE Thrombolysis/-ectomy/-aspiration	18 (1.7)	17 (2.4)	1 (0.3)	**0.02**
Anticoagulant treatment at discharge				
DOAC	756 (72.9)	528 (72.6)	228 (73.5)	0.81
VKA	135 (13)	92 (12.6)	43 (13.9)	0.66
LMWH/Fondaparinux	145 (14)	106 (14.6)	39 (12.6)	0.44
No anticoagulant	1 (0.1)	1 (1.4)	0	1
Anticoagulant treatment duration				
3 months	93 (8.9)	53 (7.2)	40 (12.9)	**0.007**
6 months	474 (45.7)	342 (47)	132 (42.6)	0.21
Indefinite	469 (45.2)	331 (45.6)	138 (44.5)	0.81

***TABLE 1:** Demographic and clinical characteristics of the study population at baseline and discharge.*

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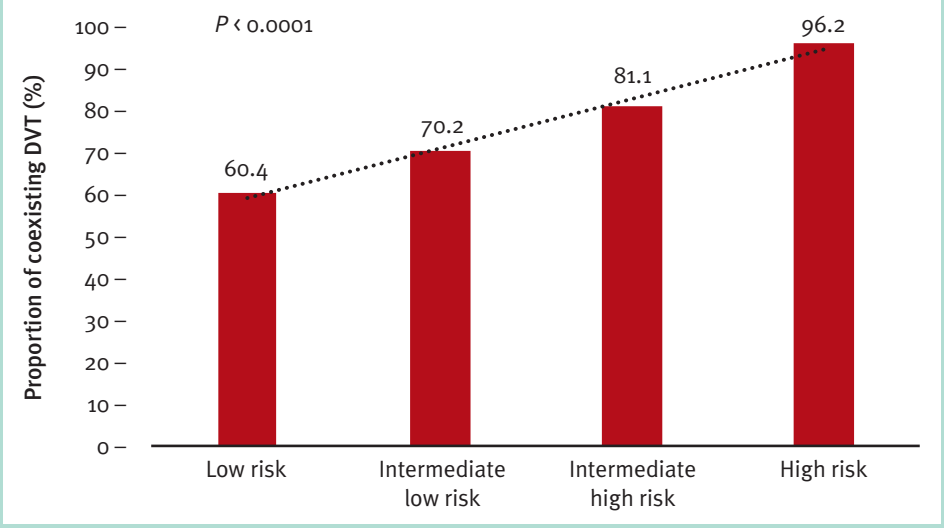


FIGURE 2: Presence of coexisting deep vein thrombosis (%) according to pulmonary embolism severity.

Risk factor	Unadjusted HR (95%CI)	*P* value	Adjusted HR (95% CI)	*P* value
Age > 70 years old	7.02 (5.15-9.65)	< 0.001	4.85 (3.46-6.87)	< 0.001
Female sex	1.47 (1.13-1.92)	< 0.01	1.41 (1.04– 1.91)	< 0.05
High blood pressure	3.42 (2.60-4.52)	< 0.001	1.56 (1.12-2.17)	< 0.01
Diabetes	1.84 (1.24-2.77)	< 0.01	0.95(0.60-1.52)	NS
eGFR < 60 mL/min/1.73 m²	5.35 (3.34-8.95)	< 0.001	2.70 (1.64-4.61)	< 0.001
Cancer	26.82 (7.12-225.30)	< 0.001	30.64 (9.30-189.37)	< 0.001
COPD	3.41 (1.57-8.45)	< 0.001	4.00 (1.82-9.83)	< 0.01
Ischemic heart disease	3.36 (1.62-7.86)	< 0.001	1.50 (0.69-3.56)	NS
Presence of DVT	1.99 (1.50-2.65)	< 0.001	2.03 (1.47-2.82)	< 0.001
Known thrombophilia	0.36 (0.18-0.72)	< 0.01	0.88 (0.42-1.77)	NS

TABLE 2: Univariate and multivariate analysis of baseline risk factors for pulmonary embolism severity.

Concomitant DVT and risk of poor outcomes after a 3-month follow-up

Overall, 36 major bleedings (34 patients), 63 CRNM bleedings (59 patients), 21 thromboembolic recurrences (20 patients) and 50 deaths were recorded over the 3-month FU. Although there was a tendency towards a higher mortality and VTE recurrence risk in patients with DVT, statistical significance was not reached **(table 3)**.

The composite criterion of VTE recurrence and all-cause mortality was more frequent in patients with DVT than without DVT, but the difference was not statistically significant HR 1.56 (CI 95% 0.83-3.10) **(figure 3)**.

Discussion

This was a prospective cohort study assessing PE severity and 3-month outcomes according to the presence of coexisting DVT in a consecutively recruited PE-population from the REMOTEV registry.

Our study showed that, in a real-life setting, the presence of concomitant DVT was significantly associated with more severe forms of PE (intermediate or high risk). Furthermore, when a DVT was present, proximal location was significantly correlated to PE severity.

The secondary study outcome which was a composite of VTE recurrence and overall mortality at 3 months after PE

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Outcome	Total *N*	DVT *N*	DVT-free *N*	HR (CI 95%)	*P*
All-cause death	50	38	12	1.36 (0.69-2.92)	0.42
VTE recurrence	21	15	6	1.28 (0.44-4.55)	0.80
Major bleeding	34	23	11	0.88 (0.40-20.4)	0.70
Clinically relevant non-major bleeding	59	40	19	0.89 (0.49-1.65)	0.66

TABLE 3: *Three-month adverse outcomes according to the presence of coexisting deep vein thrombosis.*

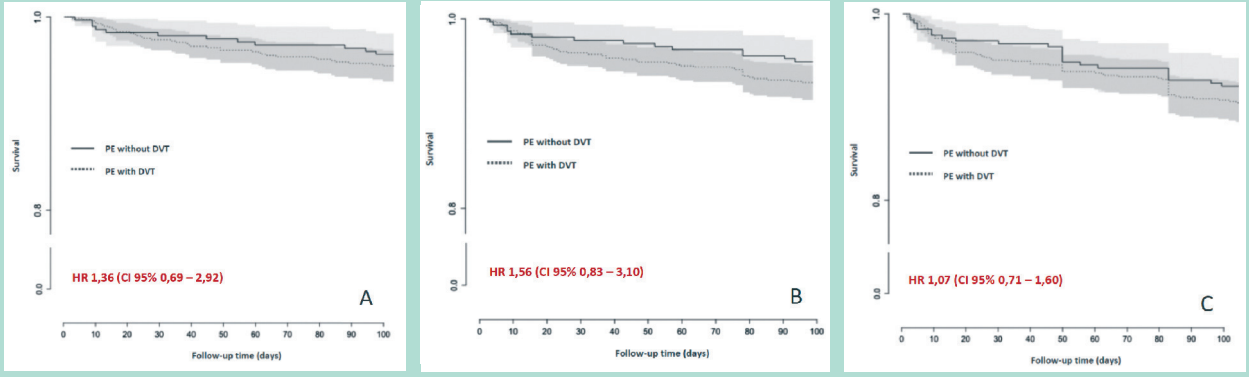


FIGURE 3: *Kaplan-Meier curves of (**A**) all-cause mortality, (**B**) the composite of venous thromboembolism recurrence and all-cause mortality, (**C**) the composite of major and non-major clinically relevant bleeding, venous thromboembolism recurrence and all-cause death.*

diagnosis showed no difference with respect to the presence of DVT.

Several studies showed that short-term outcomes were correlated to PE severity at presentation [25].

As such, an accurate risk stratification is of paramount importance.

We have already shown in a prior study that sPESI, the central piece of the ESC prognostic model, underestimated the severity of PE *id est* one third of low risk PE as defined by a sPESI of 0 had positive cardiac biomarkers or RV dilation [17].

Thus, improving risk stratification may lead to more suitable initial management and better prognosis.

In our study, 14% of patients had a complicated course including VTE recurrence, major or non-major clinically relevant bleeding totalizing 163 adverse events during the 3-month FU. This is the largest prospective cohort analyzing the significance of coexisting DVT in the era of DOACs, but failed to prove any correlation between DVT and PE short-term adverse outcomes.

To date, published studies have design and methodology discrepancies showing conflicting results.

Certain authors have identified a close relationship between coexisting DVT and PE prognosis (all-cause mortality and/or PE-related complications) [10, 13, 26].

Indeed, ICOPER (International Cooperative Pulmonary Embolism Registry) included 2442 patients with PE diagnosed on necropsy, lung scan or pulmonary angiography and showed that DVT presence was inversely correlated to mortality risk (HR 0,5 (CI95% 0,4-0,6)) [13]. *A contrario*, Jimenez *et al.* used a subgroup of the RIETE population including 4476 patients for a validation cohort showing a 1,7-fold risk for all-cause death in patients with concomitant DVT, but their analysis had a retrospective design.

In a meta-analysis of 10 cohorts (8859 patients), Becattini *et al.* found that the presence of a coexisting DVT was associated with higher PE severity and a 90% increase in the risk of 30-days all-cause mortality.

However, 90-days PE-related adverse outcomes (VTE recurrence, PE-related death) were not significantly enhanced.

Nonetheless, this meta-analysis included 10 cohorts of different methodology out of which only 2 studies totalizing 1003 patients had a prospective follow-up of at least 3 months [14, 26].

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Two other studies were published since this meta-analysis [27, 28].

Lee *et al*. analyzed 141 PE-patients but failed to establish any clinical significance of concomitant DVT for PE-related unfavorable outcomes and all-cause mortality [28].

More recently, Quezada *et al*. suggested in an analysis based on the PROTECT study including 848 patients that adding DVT testing to the ESC intermediate risk subpopulation improved the identification of patients with higher risk of complication [27].

One of the strengths of our report is to have systematically and thoroughly searched for DVT in the presence of PE which is not always performed in clinical practice when patients are asymptomatic although more than half of the DVTs associated to PE are known to be asymptomatic [29].

We have thus identified a high proportion of patients with DVT among PE patients (71%) that was similar to the one found by Hirmerova *et al*. and closer to reported rates of venographically-detected DVT (82%) than ultrasound-detectable ones (45-55%) [26, 29]. Distal DVT was present in one third of our population which is similar to the rates found by Hirmerova *et al*. and is in line with the lower risk of PE associated with distal DVTs [29].

The prospective design and high recruitment rate of our study account for some of its other strengths.

However, this study has some limitations related to its monocentric design and, as most registries, suffers from biases related to the absence of randomization.

Conclusion

In conclusion, our results show a strong correlation between DVT and PE severity as defined by the 2014 ESC model.

We therefore believe that including DVT in PE severity assessment might improve risk stratification quality and pertinence with a direct therapeutic incidence.

Thus, patients at higher risk of complication should benefit from more comprehensive in-hospital surveillance and more intensive therapy.

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