Clinical Characteristics and Outcomes of Patients with Clinically Unsuspected Pulmonary Embolism versus Patients with Clinically Suspected Pulmonary Embolism

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Key Words

Unsuspected pulmonary embolism · Suspected pulmonary embolism · Prognosis · Malignancy

Abstract

Background: The routine use of multidetector computed tomography has led to increased detection of unsuspected pulmonary embolism (UPE), with questionable benefit for diagnosis and treatment. **Objective:** The purpose of this work was to compare the clinical characteristics and prognosis of patients with UPE to patients with suspected PE (SPE). **Methods:** We retrospectively reviewed the charts of patients diagnosed with PE in a community-based university hospital between the years 2002 and 2007. UPE was defined as PE detected on CT scans performed for indications other than suspicion of PE. We compared patients with UPE to patients with SPE for differences in clinical features, electrocardiogram, imaging and echocardiographic findings. We also assessed the long-term outcomes using electronic patient records. **Results:** Of 500 patients with PE, 408 had SPE and 92 had UPE. Patients with UPE were similar to patients with SPE regarding age and sex distribution. Malignancy was more prevalent in UPE patients (39 vs. 23%, $p < 0.0068$). UPE pa-

tients had significantly less tachypnea (37 vs. 57%, $p = 0.0005$), dyspnea (47 vs. 87%, $p < 0.0001$), chest pain (19 vs. 42%, $p < 0.0001$) and hypoxemia (36 vs. 55%, $p = 0.0011$). Mortality was higher in UPE patients (70.3 vs. 53%, $p = 0.0029$). The hazard ratio after adjustment for confounders including age, sex and malignancy was 1.546 (95% CI: 1.139–2.099, $p = 0.0052$). **Conclusions:** We suggest that UPE is more prevalent in patients with a malignancy and is associated with higher mortality despite a less severe clinical presentation. UPE may be a marker of poor prognosis.

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Introduction

Pulmonary embolism (PE) is a condition with high morbidity and significant mortality. Traditionally, PE is diagnosed when patients present with suggestive symptoms (e.g. dyspnea, chest pain) and respiratory or cardiac failure [1]. The growing utilization of multidetector computerized tomography (CT) is leading to a change in the

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trends of PE diagnosis, with a higher rate of detection of unsuspected PE (UPE) [2]. The incidence of UPE has been estimated to be in the range of 0.5–5.7% of chest CT scans, depending on the patient population screened: 3.4–5.7% in unselected CT scans [3, 4] and 2.6–4% of cancer patients undergoing staging CT scans for malignancy [5–7]. Incidental detection of PE on chest CT is especially common in peripheral, subsegmental emboli [8]. While the existence of UPE is well recognized, only limited information exists regarding the clinical characteristics of these patients, especially the prevalence of comorbidities, clinical presentation and whether they are asymptomatic or merely unsuspected, and the prognostic implications of this condition [9]. Engelke et al. [10] retrospectively studied the prognosis of patients with UPE who were undiagnosed at the time of the CT scan and hence not treated, and compared it to that of patients with suspected PE (SPE) who were treated with anticoagulation. The two groups did not differ significantly in their 1-year survival rates. These findings cast some doubt on the necessity of treatment of UPE. However, probably based on the paucity of data, guidelines on the treatment of venous thromboembolism currently recommend treating patients with UPE regardless of the clinical presentation [11].

The purpose of our study was to assess the clinical characteristics of patients with UPE as opposed to patients with SPE. A second objective was to compare the outcome with respect to survival, recurrent thromboembolism and bleeding complications associated with therapy.

Methods

We retrospectively reviewed the charts of patients diagnosed with PE at Carmel Medical Center (a community-based university hospital) between 1st January 2002 and 31st December 2007. We excluded patients with nonacute PE (i.e. past history) or patients in whom PE was not confirmed by either CT scans with contrast or ventilation/perfusion scan (V/Q scan) interpreted as having high probability for PE. When patients had two or more episodes of PE, all hospitalizations but the last were excluded in order to assess morbidity after PE.

Demographic data, medical history, smoking status, number of chronic medications (as a sign of comorbidity) and presenting signs and symptoms were collected. A hyperestrogenic state was defined as existence of at least one of the following: use of oral contraceptives, pregnancy or postpartum state (6 weeks after delivery), hormone replacement therapy or hormonal therapy for breast cancer. Patients were included in the UPE group if they were referred for a CT scan for indications other than suspicion of acute PE. Lack of suspicion for PE prior to the CT scan was confirmed by examining clinician notes in the patients' files.

Follow-up data were retrieved from the electronic medical records of patients. This database includes outpatient clinic visits, list of diagnoses and their dates, medication use as well as laboratory and imaging findings. It also includes records from hospitalizations throughout the country [12]. For rehospitalization in our institute, additional data was retrieved from the local electronic medical records.

We assessed quality of treatment with anticoagulants by recording laboratory results of prothrombin international normalized ratio (INR) taken during follow-up. Adequacy of anticoagulation was defined in two ways: (1) patients who either had therapeutic range INR for longer than 6 months, or who were treated with low molecular weight heparin (LMWH) at a dose of 1 mg/kg twice daily, and (2) patients with either therapeutic INR for more than 80% of the follow-up time, or who were treated with LMWH at a dose of 1 mg/kg twice daily. The parameter of 80% of the time was defined in order to assess patients who died after less than 6 months and had adequate treatment during their follow-up. Data on recurrent hospitalizations and emergency room visits were taken from the electronic database. Viability status and date of death were taken from a computerized database.

Statistical Analysis

We performed statistical analysis using SAS 9.2 software. The continuous variables are presented as means and standard deviations. The categorical variables are presented as percentages. Comparison between the two groups was analyzed using a t test as appropriate for the continuous variables. The categorical variables were compared using the χ^2 test.

A logistic model was used to find a set of independently contributory factors for discrimination between the two groups and the relative importance of each factor to this discrimination. The odds ratios with a 95% confidence interval were used in order to present the independent contribution of each factor to the discrimination between the two groups.

We built survival curves for patients with SPE and UPE using product-limit survival estimates and compared these curves by log-rank test for comparison between strata. To find the most independently contributing factors to survival, we used the Cox proportional hazards model. The stepwise method was used to find a set of independently contributing factors, including PE suspicion. For statistical computation and graphics we used SAS 9.2 software (procedures: Univariate, Means, Ttest, Freq, Logist, lifetest, and phreg). The study protocol was approved by the Carmel Medical Center IRB (CMC 0085-08).

Results

Clinical Presentation

We reviewed 1,352 files of patients discharged between the years 2002 and 2007 with a diagnosis of PE. Of these, 725 had a past diagnosis of PE and in 116 PE was not confirmed by imaging. Of the remaining 511 patients who were diagnosed with acute PE, 11 patients had two episodes of PE within the designated time period, and we excluded the first episode. Of the remaining 500 patients

Fig. 1. Flow chart of patients included in the analysis.

(= episodes), PE was suspected in 408 patients, and not suspected in 92 (fig. 1).

There were no significant differences between the two patient groups (UPE vs. SPE) regarding age and sex (table 1). Malignancy was significantly more common in the UPE group (39 vs. 23%, $p = 0.0068$). Other past and present illnesses were equally distributed between the groups. Patients with UPE were significantly less likely to have dyspnea (48 vs. 88%, $p < 0.0001$), chest pain (19.6 vs. 42.3%, $p < 0.0001$), tachypnea (37 vs. 57%, $p = 0.0005$) and hypoxemia (36.1 vs. 55.5%, $p = 0.0011$) than patients with SPE, respectively (table 2). The difference in the prevalence of hemoptysis (2.17 vs. 7.35%, $p = 0.0667$) did not reach statistical significance. Patients with UPE had a higher incidence of pneumonia (16.3 vs. 9.1%, $p = 0.04$) and deep venous thrombosis (DVT; 25 vs. 15.7%, $p = 0.0333$) than patients with SPE.

Ancillary Testing

There was no significant difference between the groups in the prevalence of PE-associated findings on ECGs and chest x-rays. We did not find a difference in the level of the most proximal filling defect on CT scans between patients with SPE and UPE. Echocardiographic data during hospitalization was available for 150 patients,

23 with UPE and 127 with SPE. Echocardiographic findings suggestive of pulmonary hypertension such as RV/RA enlargement, pulmonary hypertension and tricuspid regurgitation occurred with similar prevalence.

We found small but significant differences in laboratory parameters previously associated with morbidity in PE [12, 13]. Patients with UPE had a slightly higher blood creatinine at PE diagnosis (1.16 ± 0.93 vs. 1.017 ± 0.44 , respectively, $p = 0.0341$) and lower hemoglobin (11.7 ± 2.49 vs. 12.3 ± 1.75 , respectively, $p = 0.0089$). Blood sodium and glucose concentrations did not vary significantly between the groups (table 3).

Multivariate Model for Suspicion of PE

We built a multivariate logistic model to find contributing factors differentiating between suspicion and lack of suspicion of PE. We tested the following factors: sex, malignancy, past DVT, thrombophilia, immobilization, recent flight, presence of ischemic heart disease, heart failure, past cerebrovascular accident (CVA), smoking status, hypoestrogenic state, hospitalization department, current DVT, presence of pneumonia, dyspnea at presentation, chest pain, hemoptysis, tachypnea, hypoxemia, respiratory rate, hypocapnea, electrocardiogram (ECG) rhythm disturbances, right axis deviation, presence of

right bundle branch block and S₁Q₃T₃ on the ECG. The variables significantly associated with SPE were the presence of dyspnea (odds ratio 8.26, 95% CI 4.38–15.6), and chest pain (odds ratio 3.15, 95% CI 1.51–6.61) at presentation. The variables associated with UPE were the presence of malignancy (odds ratio for suspicion 0.422, 95% CI 0.226–0.787) and pneumonia (odds ratio 0.339, 95% CI 0.143–0.806). All other factors were found to be not contributory.

Treatment

In our medical center all patients with diagnosed PE are initially treated with LMWH/unfractionated heparin (UFH). Most are concomitantly treated with vitamin K antagonists (VKA) until therapeutic INR is achieved, at which time LMWH/UFH is discontinued and the patient is considered for discharge. Upon discharge, most patients with PE continue treatment with anticoagulants, either VKA or LMWH (table 4). For patients treated with VKA, we tested the adequacy of anticoagulation by looking at INR test results throughout the follow-up period. Time with INR at the recommended therapeutic level for PE (INR = 2–3) [10] was not significantly different between the groups (20.4 and 26.5 months for patients with UPE and SPE, respectively, $p = 0.11$). The two patient groups were similar regarding adequacy of anticoagulation. There were no statistically significant differences in the use of thrombolytic therapy or the placement of IVC filters.

Prognosis

Mean follow-up times in months were 36.0 ± 30 (range 0.5–99) for UPE and 49.8 ± 32.7 (range 0.25–106) for SPE, $p = 0.0007$. During the follow-up period, 70.33% of patients with UPE and 53.22% of patients with SPE died ($p = 0.0029$; table 5) with a 3-year survival rate of 60 and 42% in patients with SPE and UPE, respectively (fig. 2). We performed a Cox proportional hazards model and corrected for important factors that were found to have an effect on survival, including age, sex, presence of malignancy, chest pain, heart rate, hypoxemia, hospitalization department, presence of congestive heart failure (CHF), presence of past CVA and adequacy of anticoagulation. Other factors were noncontributory to the survival difference between the two groups. After correcting for these confounders, UPE was independently associated with higher mortality than SPE, with a hazard ratio of 1.546 (95% CI 1.139–2.099, $p = 0.0052$). Other factors independently associated with mortality in all patients were age, male sex, malignancy, chest pain at presenta-

Table 1. Clinical history of patients with PE

	UPE	SPE	p value
n	92	408	NA
Mean age $\pm$ SD	72 ± 15.8	71 ± 15.8	0.42
Females, %	62	62	0.97
Malignancy	36 (39)	94 (23)	0.0068
Immobilization ^a	52 (56.5)	205 (50.25)	0.157
Flight ^a	1 (1.09)	9 (2.21)	0.49
Thrombophilia	7 (7.6)	21 (3.19)	0.0632
Heart failure	16 (17.4)	77 (18.9)	0.74
Chronic lung disease	5 (5.44)	44 (10.79)	0.417
Past PE	2 (2.2)	20 (4.9)	0.49
Past DVT	7 (7.61)	32 (7.84)	0.96
Ischemic heart disease	25 (27.2)	110 (27.1)	0.99
Past CVA	8 (8.7)	52 (12.75)	0.28
Mean chronic drugs $\pm$ SD ^b	4.75 ± 3.8	5.05 ± 3.4	0.46
Smoking			
No	65 (79)	285 (74)	0.49
Past	8 (10)	56 (15)	
Current	9 (11)	45 (12)	
Hyperestrogenic state ^c	2 (2.17)	41 (7.11)	0.104

Sample size = 500 unless stated otherwise. Values in parentheses are percentages.

^a Within 1 month.

^b Sample size = 497 (91 UPE, 406 SPE).

^c Use of oral contraceptives, pregnancy or the postpartum state (6 weeks after delivery), hormone replacement therapy or treatment with hormonal therapy for breast cancer.

Table 2. Symptoms and signs at presentation

	UPE	SPE	p value
n	92	408	NA
Respiratory rate	18.9 ± 6.5	21.5 ± 7.8	0.0111
O ₂ saturation, %	89.4 ± 6.7	88.0 ± 8.6	0.23
Dyspnea	44 (48)	357 (88)	<0.0001
Chest pain	18 (19.6)	172 (42.3)	<0.0001
Hemoptysis	2 (2.17)	30 (7.35)	0.0667
Tachypnea ^a	34 (37)	233 (57)	0.0005
Hypoxemia ^b	31 (36.1)	224 (55.5)	0.0011
Hypocapnea ^c	29 (70.7)	125 (64.2)	0.416
Leg pain and swelling	30 (13)	136 (15)	0.896
Pneumonia	15 (16.3)	37 (9.07)	0.04
Current DVT	39 (25)	180 (15.7)	0.0333

Values in parentheses are percentages.

^a Respiratory rate >20.

^b O₂ saturation <90% or PO₂ <60 when breathing room air.

^c PCO₂ <35 mm Hg while breathing room air.

Table 3. Ancillary testing in patients with PE

	UPE	SPE	p value
Electrocardiography, n	92	408	NA
Tachycardia (%)	39 (42.4)	186 (45)	0.7
New AF (%)	6 (6.82)	53 (12.9)	0.443
Rt axis deviation (%)	2 (2.38)	16 (4.05)	0.64
RBBB (%)	8 (9.09)	47 (11.66)	0.488
S ₁ Q ₃ T ₃ (%)	11 (12.8)	70 (17.7)	0.272
Laboratory parameters, n	88	408	
Creatinine, mg/dl	1.16 ± 0.93	1.02 ± 0.44	0.0341
Hemoglobin, g/dl	11.7 ± 2.5	12.3 ± 1.8	0.0089
Sodium, mg/dl	136.4 ± 5.4	137.4 ± 3.8	0.0845
Glucose, mg/dl	148 ± 81.5	143 ± 71.3	0.61
CT Imaging, n	92	306	
PE grade, % sub/seg/lob/lung/MPA	5.6/36.1/29.1/27.8/1.39	7.6/49.7/17.8/23.6/1.27	0.144
Bilat./lt./rt., %	50.6/20.9/28.6	57.1/15.3/27.7	0.378
CT or X-ray features			
Pulm. congestion (%)	17 (27.9)	130 (36.9)	0.17
Pleural effusion (%)	39 (42.4)	180 (48.65)	0.598
Lung infiltrate (%)	34 (37)	121 (32)	0.329
Atelectasis (%)	33 (35.9)	131 (35.4)	0.9669
Echocardiography patients, n	23	127	
RA/RV enlargement (%)	3 (13)	10 (7.87)	0.4175
PH (%)	9 (39.13)	47 (36.7)	0.8255
TR (%)	4 (17.39)	37 (29.37)	0.237

New AF = New onset of atrial fibrillation; RBBB = right bundle branch block; PE grade = the highest level artery with filling defect on chest CT; sub = subsegmental; seg = segmental; lob = lobar; lung = right or left pulmonary artery; MPA = main pulmonary artery; PH = pulmonary artery hypertension; TR = tricuspid regurgitation.

Table 4. Treatment of patients with SPE and UPE

	UPE	SPE	p value
n	92	408	NA
Any anticoagulation	81 (89)	398 (97.55)	0.0002
IVC filter	4 (4.35)	20 (4.9)	0.8223
Thrombolysis	0	10 (2.45)	0.13
LMWH ^a	8 (10.53)	19 (5.57)	0.1125
Adequate anticoagulation >6 months ^b	41 (54)	230 (57.8)	0.5414
Adequate anticoagulation >80% of time ^c	40 (50)	168 (42.2)	0.1712
Time with INR 2–3 (n = 410), months	20.36 ± 25.6	26.25 ± 29.6	0.11
Time with INR 2–3/follow-up time (n = 410)	0.57 ± 0.44	0.572 ± 0.418	0.9977

Data are expressed as mean ± SD and values in parentheses are percentages. IVC = Inferior vena cava.

^a Data missing for 83 patients.

^b Patients with therapeutic INR (2–3) for more than 6 months after diagnosis or those treated long-term with LMWH.

^c Patients with therapeutic INR (2–3) for more 80% of the follow-up time or those treated long-term with LMWH.

Fig. 2. Survival after PE diagnosis. Kaplan-Meier survival analysis of patients with SPE vs. UPE. Censoring of data was due to death from any cause.

Table 5. Cox proportional hazards model for survival

Parameter	Hazard ratio	95% hazard ratio confidence limits	
Unexpected	1.546	1.139	2.099
Age	1.060	1.045	1.074
Female sex	0.775	0.601	0.999
Malignancy	2.379	1.441	3.929
No chest pain	1.637	1.235	2.171
Hypoxemia	1.742	1.330	2.280
Medical department	2.326	1.418	3.816
Orthopedic department	4.564	1.657	12.57
Heart rate	1.006	1.001	1.011
CHF	1.508	1.129	2.016
Warfarin >0.8/LMWH	0.730	0.568	0.938

Mortality hazards ratios for selected variables; hospitalization in medical and orthopedic departments is compared to hospitalization in surgical department.

Warfarin >0.8/LMWH = Therapeutic INR for more than 80% of follow-up time or treatment with LMWH; age = parameter estimate for every year of age; heart rate = parameter estimate for every increment of 1 beat per min.

tion, hypoxemia, tachycardia, heart failure and lack of adequate anticoagulation treatment (table 5).

Frequency of other prognostic factors including emergency room visits, bleeding events and recurrent thromboembolic events was not significantly different between

the groups (table 6). However, the rate of recurrent hospitalizations was higher for patients with UPE than SPE (2.51 vs. 1.7 hospitalizations per year of follow-up, respectively, $p = 0.0633$). We also examined the number of chronic drugs as a reflection of the morbidity of the patients. This parameter was significantly different between the two groups of patients: 11.4 versus 6.25 drugs per year of follow-up for patients with UPE versus SPE, respectively ($p = 0.031$).

Discussion

We report our findings in a cohort of 500 hospitalized patients with PE. Ninety-two (18.4%) patients had UPE. The major finding in our study is that patients with UPE have a higher rate of all-cause mortality than patients with SPE. This finding was independent of other confounders such as age, malignancy and adequacy of anticoagulation. This finding contradicts a recent study by den Exter et al. [14] who compared the mortality of oncologic patients with SPE and UPE. The authors reported that survival at 12 months was not significantly different between patients with SPE vs. UPE, with a rate of mortality of 52.9 and 53.3% in incidental and symptomatic patients, respectively. However, patients in the earlier study had advanced cancer, which may explain the poorer survival than in our patient population, and the absence of mortality difference between patients with SPE and UPE. We did not have data regarding causes of death and so we cannot determine whether mortality was associated with the diagnosis of PE or concomitant illnesses. However, we did find a difference in the rate of hospitalizations per year of follow-up which did not reach statistical significance (2.5 vs. 1.7 hospitalizations per year for UPE vs. SPE, respectively, $p = 0.0633$). We also found a significant difference in the rate of chronic drug prescription (11.4 vs. 6.25 drugs per year of follow-up for patients with UPE vs. SPE, respectively, $p = 0.031$). We consider these parameters – the rate of recurrent hospitalizations and the rate of prescription of chronic drugs – as a reflection of the patients' morbidity status, which was higher for patients with UPE than SPE.

UPE could represent either a lack of clinical signs and symptoms ('silent PE') or failure of clinicians to attribute a diagnosis of PE to the patient's condition. We found that patients with SPE had more symptoms and signs compatible with the diagnosis of PE, as evidenced in table 2. However, many patients in the UPE group had symptoms compatible with PE but also with other diagnoses (e.g.

Table 6. Prognosis other than mortality in patients with PE

	UPE	SPE	p value
n	92	408	NA
All-cause mortality, %	70.33	53.22	0.0029
ER visits	4.26 ± 3.95 (3.36)	4.9 ± 4.36 (2.46)	0.3135 (0.11)
Hospitalizations	2.72 ± 2.7 (2.51)	2.9 ± 3.78 (1.70)	0.7 (0.0633)
Bleeding events	0.33 ± 0.66 (0.293)	0.124 ± 1.44 (0.195)	0.6572 (0.3406)
Rec. VTE events	0.1184 ± 0.33 (0.037)	0.124 ± 0.393 (0.045)	0.9 (0.8276)
Chronic drugs at follow-up, n	7.41 ± 4.15 (11.4)	8.0 ± 4.96 (6.25)	0.3514 (0.0310)
CHF at follow-up, %	13.16 (13)	15.01 (13)	0.678 (0.9970)
Newly diagnosed malignancy at follow-up, %	9.21 (9.98)	13.88 (10.51)	0.273 (0.9641)

Data are expressed as mean ± SD, with values per year of follow-up in parentheses. Rec. VTE = Thromboembolic events during follow-up.

pneumonia). While our findings support the definition of UPE as less symptomatic PE, we cannot exclude the possibility that UPE represent a heterogeneous population of patients with silent PE and patients with symptomatic PE in whom the diagnosis of PE was not considered due to concomitant diagnoses (e.g. pneumonia) with overlapping clinical presentation. We could not assess this possibility due to the retrospective nature of this study.

Surprisingly, although we expected that the presence of malignancy would have alerted clinicians to a possible diagnosis of PE, malignancy was significantly more common in the UPE group (39 vs. 23%, $p = 0.0068$). The higher prevalence of malignancy in patients with UPE versus SPE may be explained by the higher likelihood of patients with malignancy undergoing a chest CT than patients with no known malignancy. Pneumonia was more common in patients with UPE than SPE (16.3 vs. 9.07%, respectively, $p = 0.04$). This finding may represent the tendency of physicians to attribute all symptoms and signs to acute pneumonia, neglecting the possibility of coexistent PE.

There was significantly more DVT in the group with UPE than SPE (25 vs. 15.7%, $p = 0.0333$). This finding correlates with the previously reported finding of a high incidence of asymptomatic PE in patients with DVT [15]. Surprisingly, the finding of DVT did not raise suspicion of PE in this patient group, perhaps because of the perception that the diagnosis of PE would not have changed the treatment. However, since patients with PE are in danger of hemodynamic compromise and long-term sequelae, failure to diagnose PE in patients with DVT might put these patients at risk.

None of the findings in ancillary tests, including ECG and chest X-ray, were significantly different between the study groups, which is consistent with their known low sensitivity and specificity in the diagnosis of PE [5, 6, 9, 16–22].

UPE was diagnosed by chest CT with a contrast medium, while SPE was confirmed either by a high probability ventilation/perfusion lung scan or a contrast chest CT angiography. The difference in imaging protocols may create a bias towards diagnosis of larger, more central filling defects in the patients without clinical suspicion of PE, either by ‘missing’ the diagnosis of small, peripheral filling defects or by underreporting it [20, 14]. The fact that small pulmonary emboli may be missed by conventional chest CT was demonstrated in a study by Browne et al. [20], in which oncologic patients undergoing consecutive chest CT scanning also had a chest CT angiogram performed to assess the prevalence of UPE. In that study, small, segmental and subsegmental UPE (39% of 18 UPE cases) were seen only in CT angiogram and not in nonangiography CT scans. In our study we found no significant difference in the distribution of the location of PE between patients with SPE and UPE (table 3). Other studies have also failed to detect such differences [14, 23].

Patients in both groups received anticoagulation treatment, which in most cases was adequate [24]. However, most patients were discharged with VKA and only a minority continued LMWH after discharge. Considering a large subgroup of patients with malignant conditions, this may be in contrast with current guidelines [11]. Due to the large population of patients treated with VKA, we tested the adequacy of anticoagulation in individual patients by looking at PT-INR results over time. We consid-

ered patients to be adequately treated with VKA if their INR was in the therapeutic range of 2–3 for at least 6 consecutive months, or over 80% of the follow-up time (if follow-up was less than 6 months). In this analysis we found that the rate of adequate anticoagulation was similar in the two groups of patients. Consequently, we assume that causes of death in both patient groups may have been coexisting conditions other than the PE itself. We did not find a difference either in the rates of recurrent thromboembolism, bleeding complications or in other outcome measures of chronic illnesses that could explain the differences in mortality. We did find a higher prevalence of malignancy and pneumonia in patients with UPE than in patients with SPE, but the survival difference remained after adjusting for these confounders. We presume that UPE is a surrogate marker of morbidity, as previously proposed [23]. Nevertheless, we could not find coexisting conditions that may explain our observation of excess mortality in UPE.

To the best of our knowledge, this is the first study to assess clinical features of UPE and differentiate them

from SPE. This is also the first study to report prognosis of UPE patients in a mixed inpatient population. This study does have limitations arising from its retrospective methodology, mainly the lack of uniformity in comorbidities and treatment. Our large amount of data from 500 patients, however, enabled us to assess many clinical and prognostic features, perhaps balancing out some limitations.

In summary, we report that patients with UPE have a worse prognosis than patients with SPE. UPE patients also had a higher prevalence of malignancy and acute pneumonia. The survival difference occurred despite anticoagulation therapy. Further prospective studies are needed to assess the reasons for the difference in mortality and to assess whether anticoagulation therapy for UPE is indeed justified.

Financial Disclosure and Conflicts of Interests

None for any of the authors.

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