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Original Article

Long term prognosis of acute pulmonary embolism

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ABSTRACT

Background: Acute pulmonary embolism (PE) can be fatal if left untreated. Long-term prognosis of acute PE in the 21st century has not been fully reported. We aimed to determine the long-term prognosis of patients hospitalized with acute PE and compare survivalof patients with idiopathic and secondary PE.

Materials and methods: We retrospectively analysed a cohort of hospitalized patients with acute PE between 2006 and 2013. Exclusion criteria: < 18 years, venous embolism of non-pulmonary veins, chronic thromboembolic pulmonary hypertension, and presumptive diagnosis without image confirmation. Only patients with a first PE episode were included. End-point: all-cause mortality. Patients were compared according to PE aetiology: idiopathic, secondary to neoplastic conditions and secondary to non-neoplastic conditions. A Cox-regression analysis was used to study the prognostic impact of PE aetiology. RESULTS: We studied 872 hospitalized acute PE patients. Median age 70 years, 56.9% were women. PE was idiopathic in 376 (43.1%), secondary to a neoplastic condition in 284 (32.6%) and secondary to a condition other than neoplasia in 212 (24.3%). Patients were followed for a median 25 months period and 508 (58.3%) died. Patients with PE attributed to a neoplastic condition had the worst survival. Patients with idiopathic PE had a multivariate-adjusted HR of mortality of 1.46 (1.08–1.99) during the over 2-year follow-up period when compared to those with acute PE attributed to a non-neoplastic condition.

Conclusions: Patients with idiopathic acute PE have an almost 50% higher death risk in a median 2-year follow-up period than those with acute PE secondary to a condition other than neoplasia.

1. Introduction

Acute pulmonary embolism (PE) is a major manifestation of venous thromboembolism and is a potentially fatal condition [1,2]. The incidence of PE is increasing, probably due to the introduction of better diagnostic techniques as the routine adoption of computed tomographic pulmonary angiography (CTPA). A study [3] showed that overall age-adjusted incidence of PE did not significantly change in the period before CPTA, but increased by 81% after CTPA was introduced, rising from 62.3 to 112.3 per 100,000 US adults. Similarly, Huanget al [4]. showed that the proportion of PE patients who underwent a CPTA test increased from 25% in 1999 to 85% in 2009 and that during this period the annual event rate of first-time and recurrent PE more than doubled. The hospital mortality associated with acute PE seems to be decreasing although it is estimated that between 5 and 10% of in-hospital deaths are a direct result of PE [5]. Mortality from PE is greatest in the short-term period, but the risk of death persists in the long-term period mainly due to malignancy or cardiopulmonary disease [6,7].

Acute pulmonary embolism can be a systemic manifestation of a neoplastic condition and be part of a paraneoplastic syndrome. Neoplasia frequently courses with hypercoagulability and a prothrombotic status which leads to an increased risk of developing venous thromboembolism (VTE), a major complication of cancer [8–10]. VTE occurs in 4 to 20% of patients being one important cause of mortality in patients with cancer [10].

An acute PE is considered idiopathic when no precipitant/risk factor is found underlying its occurrence. There is no standardized investigation of venous embolisms and, in particular, no defined screening of occult neoplasia has been settled. The percentage of acute PE that are ultimately considered idiopathic is widely variable across studies, with reports from 16.5% to 69% [11–14], mainly depending on the deepness of the physician's investigation. In the medical field,

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idiopathic conditions, tend to be looked at as more benign conditions [15,16].

Long-term prognosis of acute PE according to different aetiologies and precipitating causes in the 21st century has not been fully reported and the prognostic impact of an idiopathic aetiology of an acute PE is not well established. In this study we aimed to determine the long-term prognosis of acute PE and assess if there were survival differences between patients with idiopathic and secondary PE.

2. Materials and methods

We retrospectively analysed all patients hospitalized in Centro Hospitalar São João (CHSJ) with the diagnosis of pulmonary embolism between 2006 and 2013. CHSJ is a tertiary care academic hospital. All patients with the discharge diagnosis code 415.1 according to the International classification of diseases (ICD) 9 were eligible for study entry. Patients were included whether they had been admitted in surgical wards, medical wards, intermediate or intensive care units. PE complicating abortion, ectopic or molar pregnancy; as well as PE complicating pregnancy, childbirth or puerperium were excluded. All registries were reviewed by two experienced internists and patients were excluded if they were under 18 years (paediatrics ward) and if the code assignment was based on the clinician suspicion of PE with no confirmatory imagological examination. Patients with chronic thromboembolic pulmonary hypertension and patients with evidence of organized non-acute pulmonary thrombus on CTPA were not included in the study. Also, only patients with first documented episode of acute PE were included and recurrent PE was an exclusion criterion. Demographic and comorbidity data were collected. Available laboratory data on hemoglobin, creatinine and BNP were also collected. Patients were followed since acute PE diagnosis until October 2017. The occurrence of a neoplasia after acute PE diagnosis, whether still in the hospital or after discharge, was determined by consulting hospital registries. Vital status was ascertained by consulting hospital registries and by telephone contact with the patients or their relatives. When no information was obtained, we consulted the Registo Nacional de Utentes (RNU) platform. Patients were classified as having idiopathic acute PE or PE secondary to a neoplastic disease or a non-neoplastic condition according to the attending physician's information, and, when that information was not available, records were reviewed by two experienced internists for attribution of causality. Idiopathic acute PE was defined as PE in the absence of a known cause; PE secondary to a neoplastic disease was defined if a known or newly diagnosed neoplasia was found; PE secondary to a non-neoplastic condition was defined if secondary to a surgical procedure, coagulation disturbances and thrombophilias, trauma, immobilization or precipitating medication as oral anticonceptives. All patients had acute PE confirmed by computed tomography pulmonary angiography (CTPA) or nuclear ventilation-perfusion (V/Q) imaging.

Comorbidities were defined as follows. Arterial hypertension was defined as the presence of previous diagnosis or record of antihypertensive pharmacological treatment. DM was defined as either a known previous diagnosis or current prescription of either an oral hypoglycemic agent or insulin. Anemia was considered if the hemoglobin level was < 13 g/dL in men and < 12 g/dL in women. Renal dysfunction was considered when plasma creatinine was > 1.5 mg/dL. Lymphopenia was considered when lymphocyte counts were < 1500/μL. Atherosclerotic disease was considered when there was reference to previous diagnosis of cerebrovascular disease, carotid artery disease, coronary heart disease or peripheral artery disease. During patients follow-up the diagnosis of neoplastic disease was also acquainted for.

2.1. Statistical analysis

Categorical variables are presented as counts and proportions and continuous variables are presented as mean (standard deviation). Median (interquartile range) was used to describe variables with a highly skewed distribution. Patients with acute PE secondary to conditions other than a malignant neoplasia, patients with idiopathic acute PE and those with PE attributable to a neoplastic condition were compared. A Chi-square test was used to compare categorical variables; a One-Way ANOVA analysis was used to compare normally distributed continuous variables and a Kruskal-Wallis test to compare continuous variables with skewed distribution. Survival curves of patients with idiopathic acute PE and PE attributable to a neoplastic or non-neoplastic condition was assessed using the Kaplan-Meier method. A Cox-regression analysis was also used to study the prognostic impact of the aetiology in acute PE. Multivariate models were built taking into consideration age and sex, acute PE location and extension as well as comorbidities.

The p value considered for statistical significance was 0.05. Data was stored and analysed using SPSS software (IBM corp, Armonk, NY, version 20.0).

3. Results

Between 2006 and 2013, 872 patients hospitalized in all wards as well as in the intermediate and intensive care units of the CHSJ were diagnosed and treated for an acute PE. Median patients' age was 70 years (range 18–100), 56.9% of the patients were women, in 36.8% the PE was of central arteries and in 56.9% it was bilateral. An echocardiogram was performed in only 54.6% of the patients and in 161 out of 476 (33.8%) of these there was right ventricular dysfunction. Thrombolytic therapy was performed in 8.1% of the patients with the diagnosis of acute PE. In 212 (24.3%) patients a cause other than a neoplastic disease was found to be the factor precipitating acute PE: post-surgery 79, disturbed coagulation and thrombophilias 52, associated with trauma 36, oral anticonceptive 24, immobilization/bedridden status 15 and other causes 6. In 284 patients a known neoplastic condition or a neoplasia identified during hospitalization was found to be the etiological factor behind acute PE and in 376 (43.1%) the PE was considered idiopathic.

Table 1 shows patients characteristics and the comparison between patients according to acute PE aetiology. Patients with idiopathic acute PE were the elder and those with PE secondary to a cause other than neoplasia were the youngest. Men were predominant in the group of PE attributable to a neoplastic condition. Acute PE secondary to neoplasia was more often non-central and unilateral and idiopathic PE more often central and bilateral. Patients with idiopathic PE had higher comorbidity burden and higher BNP level. During follow-up 508 patients died. Patients with PE attributable to a neoplastic condition had the shorter survival and patients with PE attributable to a condition other than a neoplasia survived longer than those with idiopathic PE. Fig. 1 shows the Kaplan-Meier survival curves according to the acute PE aetiology. Patients with PE secondary to a neoplasia had the highest mortality and those with PE secondary to a non-neoplastic condition the best survival. Patients with idiopathic acute PE had a more ominous outcome than those with PE attributable to a non-neoplastic condition. Eleven patients with PE caused by a condition other than neoplasia had, in fact, a known neoplastic condition; and, during follow-up 23 patients with no known neoplasia had a new diagnosis of a malignant condition–five in the group of patients with acute PE considered to be attributable to a cause other than a neoplasia and 18 in the group of patients with acute PE considered to be idiopathic. Even when adjusting for age, sex, location and extension of the PE, comorbidities, laboratory parameters and the presence of a neoplastic condition, whether already known or diagnosed during follow-up, patients with acute idiopathic PE still had worse survival than those with a secondary PE provided that the cause was not a malignant neoplasm. Table 2 shows the association of acute PE aetiology with all-cause mortality in a univariate analysis and in 3 multivariate models. Model 3, the model with adjustment to BNP level, only analyses 582 patients and 320 deaths because in 290 patients no

Table 1
Patients' characteristics and comparison according to acute PE aetiology: idiopathic PE, PE secondary to a neoplastic condition and secondary to a condition other than a neoplasia.

Characteristics	All *N* = 872	PE secondary to a non-neoplastic condition (*N* = 212)	Idiopatic PE (*N* = 376)	PE secondary to a neoplastic condition (*N* = 284)	p value (trend)
Male sex, n (%)	376 (43.1)	78 (36.8	139 (37.0)	159 (56.0)	< 0.001
Age (year), median (IQR)	70 (55–79)	55 (42–73)	75 (62–82)	70 (59–77)	< 0.001
Central PE, n (%)	321 (36.9)	76 (36.0)	155 (41.3)	90 (31.7)	0.04
Bilateral PE, n (%)	496 (56.9)	119 (56.4)	239 (63.6)	138 (48.6)	< 0.001
Atherosclerotic disease, n (%)	237 (27.5)	41 (19.5)	142 (37.9)	54 (19.4)	< 0.001
Arterial hypertension, n (%)	449 (51.8)	92 (43.6)	234 (62.2)	123 (44.1)	< 0.001
Diabetes *mellitus*, n (%)	169 (19.5)	43 (20.4)	76 (20.2)	50 (17.9)	0.72
Neoplasic disease (known or diagnosed after acute PE), n (%)	318 (36.5)	16 (7.5)	18 (4.8)	284 (100)	< 0.001
Hemoglobin (g/dL), mean (SD)	12.2 (2.2)	12.0 (2.4)	12.7 (2.2)	11.6 (2.0)	< 0.001
Leucocytes, median (IQR)	10.26 (7.68–13.46)	10.75 (8.11–13.22)	10.09 (7.81–12.81)	10.37 (6.92–14.66)	0.38
Lymphocytes, median (IQR)	1.49 (0.96–2.12)	1.68 (1.11–2.29)	1.57 (0.96–2.14)	1.29 (0.80–1.77)	< 0.001
Creatinine (mg/dL), median (IQR)	0.91 (0.70–1.30)	0.80 (0.67–1.11)	1.00 (0.80–1.40)	0.90 (0.70–1.20)	< 0.001
C-reactive protein (mg/L), median (IQR)	50.2 (16.8–110.0)	61.4 (18.6 (120.9)	34.8 (14.3–76.4)	68.2 (18.7–147.6)	< 0.001
BNP (pmol/mL), median (IQR)	245.6 (78.2–702.7)	159.2 (39.8–455.8)	361.8 (132.4–871.2)	182.0 (59.9–570.9)	0.001
Death, n (%)	508 (58.3)	62 (29.2)	188 (50.0)	258 (90.8)	< 0.001
Follow-up (months), median (IQR)	25 (1–67)	58 (29–79)	46 (6–72)	2 (0 – 13)	< 0.001

BNP: B-type natriuretic peptide; IQR: interquartile range; PE: pulmonary embolism; SD standard deviation.

BNP measurement was performed. Patients with acute idiopathic PE had a multivariate adjusted (considering age and gender, PE location and extension, comorbidities including neoplasia diagnosis, hemoglobin, creatinine, lymphocytes and C-reactive protein) HR of all cause mortality during a median follow-up of 25 months (1–67) of 1.46 (95% CI: 1.08–1.99). Results were similar when the model included also adjustment for BNP.

4. Discussion

This study shows that acute PE attributable to a neoplasia is associated with the worst prognosis, compared to idiopathic PE and PE secondary to a non-neoplastic condition. Approximately 80% of patients with acute PE attributable to a neoplasia died after 1 year of follow-up (Fig. 1).

An analysis of the RIETE registry [17] has already reported that cancer was a very strong risk factor for pulmonary embolism-related mortality, increasing death risk by approximately 3-fold. Notably, and somehow surprisingly, patients with idiopathic PE had 46% higher risk of death than those with PE secondary to a non-neoplastic condition. Idiopathic conditions are usually looked at as benign in the medical field in general [15,16]. In a much smaller study evaluating 257 patients with acute PE during a median follow-up time of 22 months, Lehmann et al. [18] have also found that idiopathic PE was an independent predictor of long-term mortality (HR: 4.3; 95% CI: 1.7–11). Our study has a comparable rate of idiopathic pulmonary embolism (43.1%) with other reports that described a PE rate ranging from 16.5% in a series of 331 patients [13] to 69% in a series of 237 patients [11]. This variability among studies may reflect the 21st century controversy concerning an extensive search of thrombophilias. While testing for thrombophilias is not indicated in unselected patients presenting with venous thrombosis [19–21] once it does not reduce the recurrence of thromboembolism [22], in selected populations can lead to identification of inherited risk factors and thus influence the management of first-degree relatives. It is widely recognized that the major determinant of recurrent embolic events is previous history of deep vein thrombosis, with accumulative rate of recurrence of about 25% at 5 years and 30% at 10 years in patients with a first episode of VTE [23,24], and that the existence of a prothrombotic condition does not alter, *per se*, the

Fig. 1. Kaplan-meier curves according to pulmonary embolism aetiology.

Table 2
Association of acute PE aetiology with all-cause mortality: univariate analysis and in 3 multivariate models.

Univariate analysis		
	HR (95% CI)	**p value**
PE secondary to a cause other than neoplasia (ref category)	1	
Idiopathic PE	1.98 (1.49–2.64)	< 0.001
PE secondary to neoplasia	6.76 (5.08–8.98)	< 0.001
Multivariate analysis (model 1)		
	HR (95% CI)	**p value**
PE secondary to a cause other than neoplasia (ref category)	1	
Idiopathic PE	1.39 (1.00–1.88)	0.03
PE secondary to neoplasia	3.22 (2.01–5.18)	< 0.001
Age (per year)	1.03 (1.02–1.04)	< 0.001
Male sex	1.19 (0.99–1.44)	0.06
Central PE	0.90 (0.74–1.09)	0.29
Bilateral PE	0.76 (0.64–0.92)	0.004
Atherosclerotic disease	1.20 (0.98–1.48)	0.08
Arterial hypertension	0.73 (0.60–0.89)	0.002
Diabetes *mellitus*	1.23 (0.98–1.53)	0.07
Neoplasia (known or posterior diagnosis)	1.55 (1.00–2.39)	0.05
Multivariate analysis (model 2)		
	HR (95% CI)	**p value**
PE secondary to a cause other than neoplasia (ref category)	1	
Idiopathic PE	1.46 (1.08–1.99)	0.02
PE secondary to neoplasia	3.15 (1.96–5.05)	< 0.001
Age (per year)	1.03 (1.02–1.04)	< 0.001
Male sex	1.14 (0.94–1.38)	0.18
Central PE	0.92 (0.76–1.12)	0.41
Bilateral PE	0.80 (0.66–0.97)	0.02
Atherosclerotic disease	1.21 (0.98–1.50)	0.08
Arterial hypertension	0.73 (0.59–0.89)	0.002
Diabetes *mellitus*	1.22 (0.97–1.53)	0.08
Neoplasia (known or posterior diagnosis)	1.56 (1.01–2.42)	0.04
Anemia	1.08 (0.89–1.31)	0.44
Renal dysfunction	1.23 (0.99–1.58)	0.06
Lymphopenia	1.39 (1.14–1.68)	0.001
C-reactive protein (per 10 mg/L)	1.02 (1.01–1.03)	< 0.001
Thrombolytic therapy	0.77 (0.51–1.16)	0.22
Multivariate analysis (model 3)		
	HR (95% CI)	**p value**
PE secondary to a cause other than neoplasia (ref category)	1	
Idiopathic PE	1.44 (0.99–2.09)	0.05
PE 2° to neoplasia	3.77 (2.12–6.69)	< 0.001
Age (per year)	1.03 (1.02–1.04)	< 0.001
Male sex	1.12 (0.88–1.42)	0.36
Central PE	0.89 (0.70–1.14)	0.36
Bilateral PE	0.72 (0.57–0.91)	0.003
Atherosclerotic disease	1.10 (0.85–1.43)	0.45
Arterial hypertension	0.69 (0.53–0.89)	0.004
Diabetes *mellitus*	1.51 (1.15–1.99)	0.003
Neoplasia (known or posterior diagnosis)	1.46 (0.82–2.26)	0.23
Anemia	1.03 (0.81–1.31)	0.83
Renal dysfunction	1.37 (1.03–1.81)	0.03
Lymphopenia	1.51 (1.19–1.92)	0.001
C-reactive protein (per 10 mg/L)	1.02 (1.00–1.03)	0.04
Thrombolytic therapy	0.73 (0.47–1.15)	0.18
BNP (per 100 pg/mL)	1.34 (1.01–1.78)	0.04

BNP: B-type natriuretic peptide; HR: hazard rarioIQR: interquartile range; PE: pulmonary embolism; SD standard deviation.

therapeutic approach namely the length of anticoagulation [25]. Contrarily, the risk of recurrence in patients with an idiopathic episode of VTE is high [26–29], so it is always licit to extend anticoagulation in patients with low risk of haemorrhagic complications in case of massive PE.

In our study, patients with idiopathic PE were older when compared to patients in the other groups (p value < 0,001), presented more frequently with central and bilateral PE (central PE, p value 0.04; bilateral PE, p value < .001), had more comorbidities as atherosclerotic disease and arterial hypertension and a higher median level of BNP. The higher prevalence of central and bilateral acute PE may result from the lower *à priori* suspicion index; patients with a known neoplastic condition or an evident risk factor such as major surgery or prolonged immobilization were more prone to be diagnosed even with milder signs and symptoms. The higher mortality could have also been attributed to the fact that the diagnosis in acute idiopathic PE was delayed and patients presented with more massive embolisms, results were, however adjusted to these factors and idiopathic PE was independently associated with a more ominous outcome. Both hypertension and atherosclerosis have been found to be associated with an increased risk of venous thromboembolism [30]. This association could be explained by the fact that atherosclerosis is associated with a prothrombotic state contributing to venous thrombosis [30]. The multivariate model also took into consideration the coexistence of comorbidities.

We note that this is a retrospective study and therefore has inherent limitations concerning availability of data. The data collected were

obtained by consulting medical files in the electronic program in use in the hospital, hence the data abstracted were based only in the recorded information in the medical files. The investigation and therapeutic approach was at the discretion of the attending physician. This could have led to an underestimation of the number of patients with PE secondary to neoplasia and non-neoplastic condition because the complete screening for both neoplasia and coagulation disturbances and thrombophilias was not guaranteed due to lack of a uniform protocol and non-consensus concerning which is the best diagnostic/investigation workup in such cases. Furthermore, we do not know for exactly for how long patients were anticoagulated and this would probably have also influenced survival; however, we can expect that patients with PE secondary to conditions other than a neoplasia were anticoagulated for shorter time periods. Times of anticoagulation have been reviewed over time and are as far from consensual. Moreover, it would be interesting to further extend the follow-up period in order to assess if the number of patients with a new diagnosis of neoplasia increases. Therefore, prospective studies with an extended cohort and follow-up period would be important to corroborate our results. However it was not the main goal of our study to determine the incidence of *de novo* diagnosis of neoplasia following an acute PE but to assess if there were survival differences between patients with idiopathic and secondary PE. Despite all the limitations we reinforced the elevated mortality of patients with acute PE secondary to a neoplastic condition and shown that idiopathic acute PE in clearly a non-benign condition with a 46% higher risk of all cause death when compared with acute PE secondary to causes other than neoplasms. Clinicians should eventually look at idiopathic acute PE with more worrisome; and a closer follow-up strategy, eventually looking for hidden predisposing factors that can be addressed or corrected, might be useful. Undoubtedly,

a more clear and uniform approach to acute PE should be settled.

5. Conclusions

Acute idiopathic PE is a worrisome clinical entity with higher mortality than acute PE with identified predisposing risk factor other than a neoplastic condition. Our results suggest that patients with acute idiopathic PE merit closer follow-up and eventually further investigation as they are high risk patients.

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Declarations of Competing Interest

None.

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