

Pulmonary Embolism in Portugal: Epidemiology and In-Hospital Mortality

Embolia Pulmonar em Portugal: Epidemiologia e Mortalidade Intra-Hospitalar



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ABSTRACT

Introduction: In Portugal, the epidemiology of acute pulmonary embolism is poorly understood. In this study, we sought to characterize the pulmonary embolism from the hospital data and evaluate its in-hospital mortality and respective prognostic factors.

Material and Methods: The study used diagnostic related groups data from National Health System hospitals from 2003 to 2013 and National Statistics Institute population data to establish the evolution of admissions with the diagnosis of pulmonary embolism, their in-hospital mortality rates and the population incidence rates. Diagnosis-related group microdata were used in a logit regression modeling in-hospital mortality as a function of individual characteristics and context variables.

Results: Between 2003 and 2013 there were 35,200 episodes of hospitalization in patients with 18 or more years in which one of the diagnoses was pulmonary embolism (primary diagnosis in 67% of cases). The estimated incidence rate in 2013 was 35/100,000 population (≥ 18 years). Between 2003 and 2013, the annual number of episodes kept increasing, but the in-hospital mortality rate decreased (from 31.8% to 17% for all cases and from 25% to 11.2% when pulmonary embolism was the main diagnosis). The probability of death decreases when there is a computerized tomography scan registry or when patients are females and increases with age and the presence of co-morbidities.

Discussion: In the last decade there was an increased incidence of pulmonary embolism likely related to an increased number of dependents and bedridden. However, there was a in-hospital mortality reduction of such size that the actual mortality in the general population was reduced. One possible explanation is that there has been an increase in episodes of pulmonary embolism with incrementally lower levels of severity, due to the greater capacity of diagnosis of less severe cases. Another possible explanation is greater effectiveness of hospital care. According to the logistic regression analysis, improvements in hospital care effectiveness in recent years are primarily responsible for the mortality reduction.

Conclusion: About 79% of the reduction of in-hospital mortality of pulmonary embolism between 2003 and 2013 can be attributed to greater effectiveness of hospital care and the rest to the favorable change in patient characteristics associated with risk of death.

Keywords: Diagnosis-Related Groups; Health Impact Assessment; Incidence; Hospital Mortality; Portugal; Pulmonary Embolism/epidemiology; Pulmonary Embolism/mortality.

RESUMO

Introdução: Em Portugal, a epidemiologia da embolia pulmonar aguda é mal conhecida. Neste estudo, pretendeu-se caracterizar a embolia pulmonar a partir dos dados do internamento hospitalar, assim como avaliar a sua mortalidade intra-hospitalar (definida como mortalidade do internamento hospitalar) e respetivos fatores de prognóstico.

Material e Métodos: Microdados dos Grupos de Diagnóstico Homogéneo dos hospitais do Sistema Nacional de Saúde (2003 a 2013) e dados sobre população do Instituto Nacional de Estatística para estabelecer a evolução dos internamentos, da mortalidade intra-hospitalar e das taxas de incidência na população. Os microdados foram estudados numa regressão *logit* modelizando a mortalidade intra-hospitalar como função de características individuais e de variáveis de contexto.

Resultados: Entre 2003 e 2013 ocorreram 35 200 episódios de internamento (doentes ≥ 18 anos) em que pelo menos um dos diagnósticos foi embolia pulmonar (diagnóstico principal em 67% dos casos). A taxa de incidência estimada em 2013 foi 35/100 000 habitantes (≥ 18 anos). Entre 2003 e 2013, o número anual de episódios foi aumentando, mas a taxa de mortalidade intra-hospitalar foi diminuindo (de 31,8% para 17% em todos os episódios e de 25% para 11,2% nos episódios com embolia pulmonar como diagnóstico principal). Entre 2010 e 2013 a probabilidade de morte reduziu-se com a existência de registo de tomografia computadorizada, em doentes do género feminino e aumentou com a idade e a presença de comorbilidades.

Discussão: Na última década ocorreu um aumento da incidência de embolia pulmonar provavelmente relacionado com um maior número de pessoas dependentes e acamadas. No entanto, verificou-se uma redução da mortalidade intra-hospitalar de tal dimensão que a própria taxa de mortalidade na população em geral se reduziu. Uma explicação possível é que tenha ocorrido um aumento dos episódios de embolia pulmonar com níveis de gravidade incrementalmente menores, pela maior capacidade de diagnóstico de casos menos graves. Outra explicação possível é uma maior efetividade dos cuidados de saúde hospitalares. De acordo com a análise de regressão logística, as melhorias na efetividade dos cuidados hospitalares nos últimos anos são o principal responsável pela redução da mortalidade.

Conclusão: Cerca de 79% da redução da mortalidade intra-hospitalar da embolia pulmonar entre 2003 e 2013 pode-se atribuir à maior efetividade dos cuidados de saúde hospitalares e o restante à alteração favorável nas características dos doentes associadas

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ao risco de morte.

Palavras-chave: Avaliação do Impacto na Saúde; Embolia Pulmonar/epidemiologia; Embolia Pulmonar/mortalidade; Grupos de Diagnósticos Homogêneos; Incidência; Mortalidade Hospitalar; Portugal.

INTRODUCTION

Venous thromboembolism includes deep vein thrombosis and pulmonary embolism (PE) and is the third most frequent cardiovascular disease, with an annual incidence ranging between 100 and 200 per 100,000 population.¹ Pulmonary embolism may be classified as acute or chronic and the patients affected by acute pulmonary embolism develop signs and symptoms of obstructed pulmonary vessels; those affected with chronic pulmonary embolism usually present with progressive dyspnoea related with pulmonary hypertension.³

PE is a common disease, sometimes lethal,⁴ defined as the occlusion of either the main pulmonary artery or one of its branches by thrombi, tumour, air or fat that originated elsewhere in the body. There is an increased risk for PE in chronically bedridden patients, as well as in patients submitted to surgery within the previous three months, with the presence of cancer, heart disease, auto-immune disease and a history of venous thromboembolism. Non-treated PE is associated to a three-month mortality rate of 15%⁵ and of 25 - 30% at five years² and recurrent PE is a frequent cause of death in these patients.

Most patients with PE present with nonspecific clinical manifestations, making the diagnosis challenging.⁶ Prompt diagnosis and treatment may substantially reduce mortality. Approximately 600,000 patients (of all the 42 million decedents) had PE listed on their death certificates (1.5%) and around 200,000 had PE as the underlying cause of death in a study carried out in the USA⁷ regarding a 20-year period (1979-1998). An ever-increasing use of chest computerized tomography (CT) scanning in clinical practice³ almost doubled the estimated incidence of PE (from 62.1 to 112.3 per 100,000 in the USA).⁸

PE's epidemiology in Portugal is not fully known. Our study's primary aim was to characterise PE in the hospital setting over 2003-2013. The secondary aim of the study was to assess in-hospital mortality for PE as well as its prognostic factors.

MATERIAL AND METHODS

The *Administração Central do Sistema de Saúde (ACSS)* database (which records all episodes of inpatient activity in *Serviço Nacional de Saúde (SNS)* Mainland Portugal units) was used for the identification of patients with PE within the Portuguese healthcare system. Other PE episodes having occurred outside SNS units were not included into the study. Diagnosis and procedure codes collected by physicians trained in the use of the International Code of

Diseases (ICD-9-CM) and obtained from medical records were included in ACSS information.

All inpatient episodes regarding patients aged over 18 discharged from hospital between 1 January 2003 and 31 December 2013, assigned with code 415.9 (ICD-9-CM – Other pulmonary embolism or infarction, not elsewhere classified) in whom PE code was the first-listed diagnosis or one of up to 19 other diagnoses were analysed in our study. Estimated data regarding Portuguese population issued by the *Instituto Nacional de Estatística* for the study period were obtained in order to calculate the incidence of inpatient PE episodes.

CCS (Clinical Classification Software) was used for the study of PE underlying comorbidities; this tool merges a set of ICD9-CM diagnosis and procedure codes into a lower number of categories with clinical relevance, i.e. where conditions with a different diagnosis and similar outcomes were merged in order to make statistical analysis easier. Understanding the role of chronic diseases in these patients was considered as relevant and useful, beyond an overall characterisation of comorbidities.

Chronic Condition Indicator (CCI) was used for the identification and quantification of the presence of chronic disorders.⁹ According to this tool, a chronic condition is defined as a condition that lasts of at least 12 months and meets at least one of the following criteria: (i) it places limitations on patient's self-care, independent living and social interactions or (ii) it results in the need for ongoing medical intervention.

In addition, Charlson-Deyo score was used, based on the presence of a set of ICD-9 CM key codes from 19 different clinical categories and showing individual relevance of comorbidities; it may also be used as a marker for clinical complexity, apart from a potential predictor for mortality.

In-hospital mortality for PE was analysed and an explanatory model was developed, in which logistic regressions were used to estimate the probability of death. The results are normally presented as odd ratios. A different presentation of results was used in our study in order to allow for a similar interpretation of the results to coefficients of models of linear regression. A format showing the average effect of changing each variable was selected, allowing for a more intuitive reading of the results. As regards qualitative variables, the described effect regarded a change in the variable from 0 to 1. The linear approximation to the model was used for the other variables, based on sample mean.

In the model, the probability of death for an episode of PE is explained by individual and context variables, including Charlson-Deyo comorbidity score¹⁰⁻¹² adapted to ICD9-CM data. Comorbidity scores are used in clinical research for a quantifiable standardisation of concomitant diseases and their severity, allowing for the comparison between patients or patient groups and between clinical teams/institutions.

STATA 13 package (STATA CORP; College Station, TX, USA) and Microsoft Excel 2010 (Microsoft Corp., Redmond, WA, USA) were used for statistical analysis.

RESULTS

Pulmonary embolism in Portugal based on inpatient data

In total, 35,200 inpatient episodes in SNS units regarding patients aged 18 or over in whom PE code was listed in any position, between 1 January 2003 and 31 December 2013, were found. From these, 23,669 episodes (67%) regarded patients in whom PE was first-listed diagnosis, corresponding to an annual average of 3,200 episodes, from which 2,152 regarded patients with PE as first-listed diagnosis. The average duration of the clinical episodes of PE was of 12.3 days (SD = 10.8) and showed a mild reduction from 2003 (12.3 days) to 2013 (11.5 days). The progression of the overall number of PE episodes as well as the number of episodes regarding patients in whom PE was first-listed diagnosis is shown in Fig. 1. The number of PE episodes has been increasing over time, either with PE

listed as first-listed episode or in any position. A significant increase in the number of PE episodes has been found between 2009 and 2010, as shown in Fig.1, in addition to a significant reduction in the overall number of SNS inpatient episodes.

The number of episodes in which the use of chest CT scanning had been assigned (ICD9-CM code 87.41 – computerized axial tomography of thorax) was obtained in order to improve the characterisation of PE episodes (Fig. 2); it should be mentioned the fact that this codification is not compulsory and therefore this test may have been used more frequently than estimated.

As regards gender distribution over the study period, 61.2% of PE episodes regarded female patients and this percentage remained almost unchanged over time; elderly patients were mostly affected (median age 70, 2003-2013; SD = 15.7) and a slight difference was found between male (68.9 years) and female patients (70.8 years). In addition, median were higher than mean age, which was of 74 years for general population (72 in male and 75 in female). Age and gender distribution of patients admitted with PE is shown in Fig. 3.

The estimated rate of PE episodes per 100,000 people showed a significant increase in PE incidence rate over time in male as in female patients, in whom this was higher (Table 1). As expected, the increase in the number of patients found from 2009 to 2010 led to a significant increase in the incidence rate over the same period.

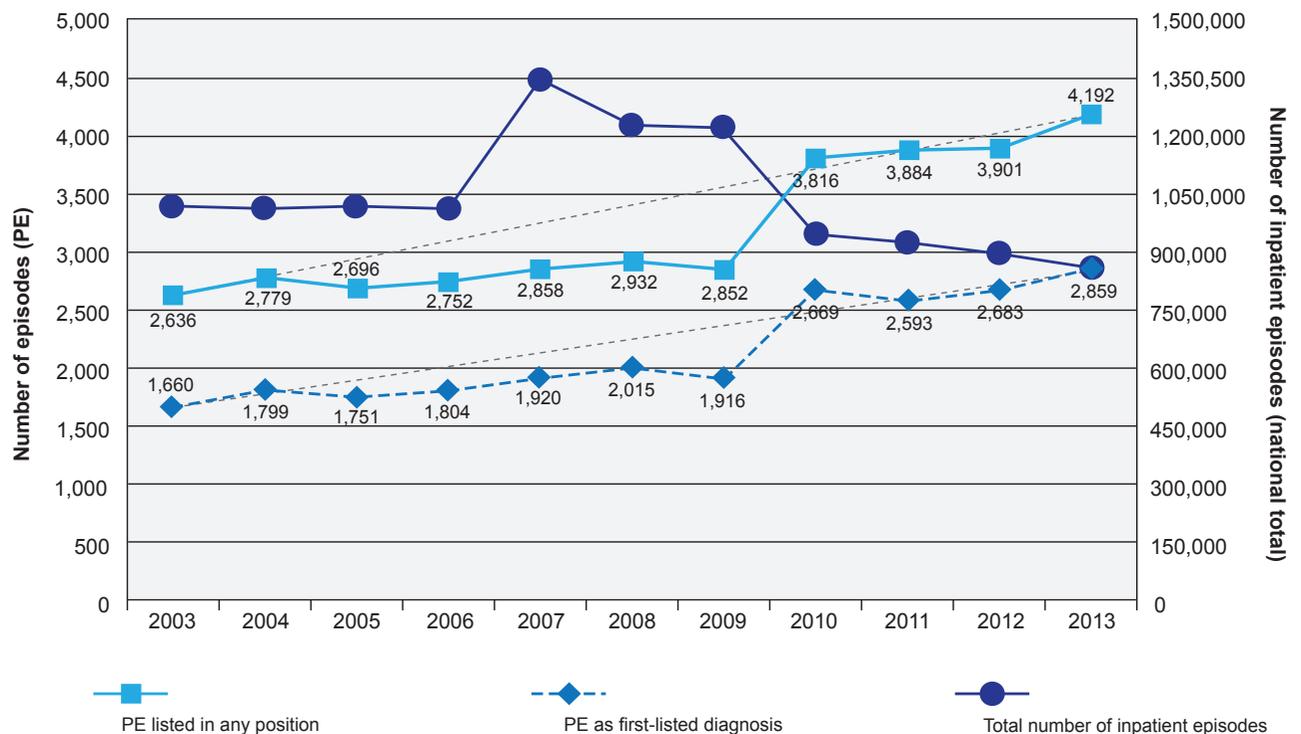


Figure 1 – Inpatient episodes - total number and number of PE episodes (2003-2013)

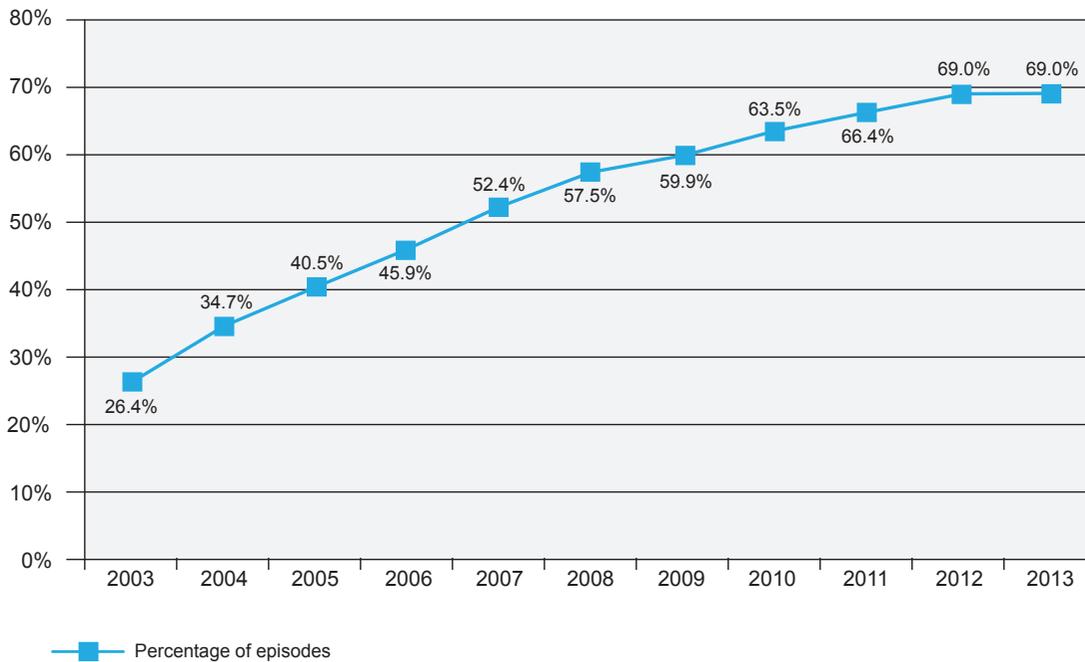


Figure 2 – Percentage of inpatient PE episodes with added code for the use of chest CT scanning (2003-2013)

The number of comorbidities, usually associated to clinical severity, was significantly increased (Fig. 4).

Primary diagnoses of patients with pulmonary heart disease, apart from PE, may be identified using Single-Level CCS score. Those corresponding to at least 1% of overall inpatient episodes are shown in Table 2 and pneumonia, congestive heart failure, stroke, lung cancer, phlebitis, deep venous thrombosis and femoral neck fracture were the most frequently found, having affected 12% of the patients. A comparison between 2003-2009 and 2010-2013 showed changes in Single-Level CCS score distribution, with an increase in the percentage of patients diagnosed with lung cancer from 1.4 to 1.8%, a reduction in those with congestive heart failure from 2.1 to 1.7% and in those with femoral neck fracture from 1.2 to 0.7%.

PE episodes lead to a significant in-hospital mortality rate (16.8%, all years combined) showing gender differences (18.3% in male and 13.2% in female patients). In-hospital mortality rate has significantly changed over time, showing a reduction from 31.8% in 2003 to 17% in 2013 in all patients diagnosed with PE and from 25% to 11.2% in patients in whom PE was first-listed diagnosis (Fig. 5).

Despite the reduction in in-hospital mortality rate, an increased mortality between 2009 and 2010 was found, due to the increased number of episodes. However, a decreasing trend was again found between 2010 and 2013. As expected, in-hospital mortality rate increased with patient's age, with an average of 7.1% in the 18-29 group and 32.8% in patients aged 79 years or over.

In-hospital mortality for PE in Portugal

As previously shown, a significant increase in the number of PE episodes was found in 2009. The analysis of the reasons for in-hospital mortality was confined to the most recent years (2010-2013) and to those episodes regarding patients with PE as first-listed diagnosis. In total, 10,804 episodes and 1,382 decedent patients complying with these criteria were found in the GDH (*Grupos de Diagnóstico Homogéneo*) national database, corresponding to an average in-hospital mortality rate of 12.8%.

A logistic regression model has been used for the analysis of in-hospital mortality for PE, in which the probability of death is explained by individual and context variables. Patient's gender, age, age squared (both patient's age and age squared [over 10] were centred around the mean, in order to reduce problems of multicollinearity) and Charlson-Deyo comorbidity score were the individual variables considered in the study. The presence of pathologies associated to PE (Table 2), such as congestive heart failure, cerebrovascular disease, cancer, pneumonia and femoral neck fracture were also considered. In addition, a qualitative variable regarding the listed use of chest CT scanning was also included. Central results of the logistic multiple regression analysis are shown in Table 3.

Female gender has a protective effect: under similar circumstances regarding the other variables, female patients have a 1.9% lower probability of death when compared to male patients. The effect of patient's age on the

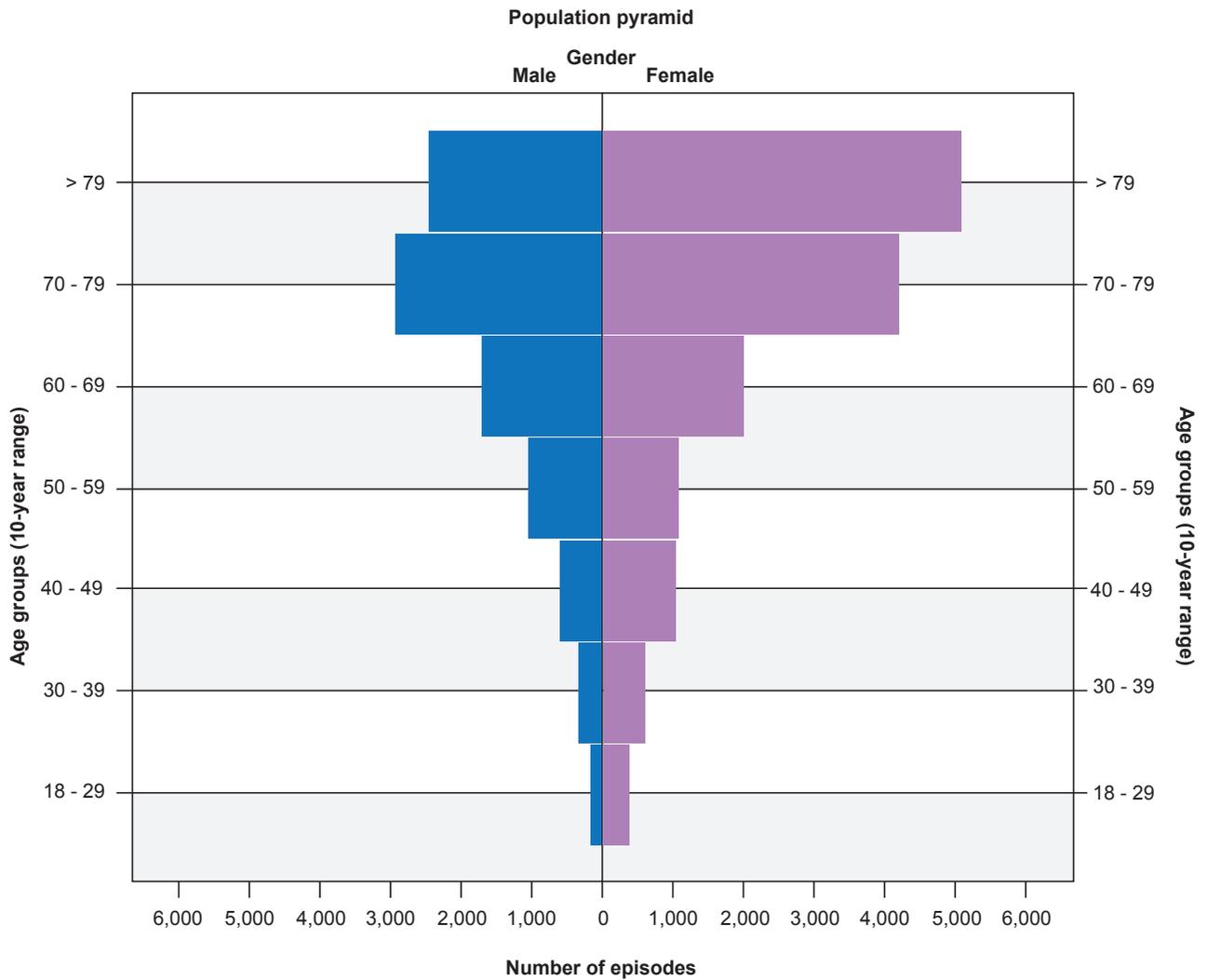


Figure 3 – Age and gender distribution of patients with PE as first-listed diagnosis (2003-2013)

Table 1 - Inpatient PE episodes (2003-2013)

Year	Incidence rate per 100,000 people		
	Male	Female	Overall
2003	16.7	24.1	20.6
2004	19.1	25.1	22.2
2005	18.9	24.0	21.6
2006	19.0	25.0	22.2
2007	18.0	28.4	23.5
2008	20.0	28.7	24.6
2009	19.4	26.8	23.3
2010	26.0	38.1	32.4
2011	25.8	36.5	31.5
2012	26.1	38.5	32.7
2013	29.3	40.0	35.0

Source: Author's calculations based on GDH and INE database

probability of death is also relevant, though not linear, as the quadratic term is also statistically significant. Considering mean age (70 years) in our group of patients as the point of reference and keeping all other variables fixed, the age of 55 corresponds to a 3.5% reduction in the probability of death, while the age of 85 corresponds to a 5.9% increase in this probability.

A second set of coefficients measures the effects of the variables regarding patient's health condition. Charlson-Deyo comorbidity score has a positive and statistically significant coefficient. An increase of one standard deviation in this score lead to a 3% increase in the probability of death. For the whole set of pathologies considered in the study, significantly positive coefficients were found and each one is already an approximate measure of the effect on in-hospital mortality. The most significant effects are those related to the presence of femoral neck fracture and pneumonia, leading to an 11.5 and 7.8 increase in death probability, respectively.

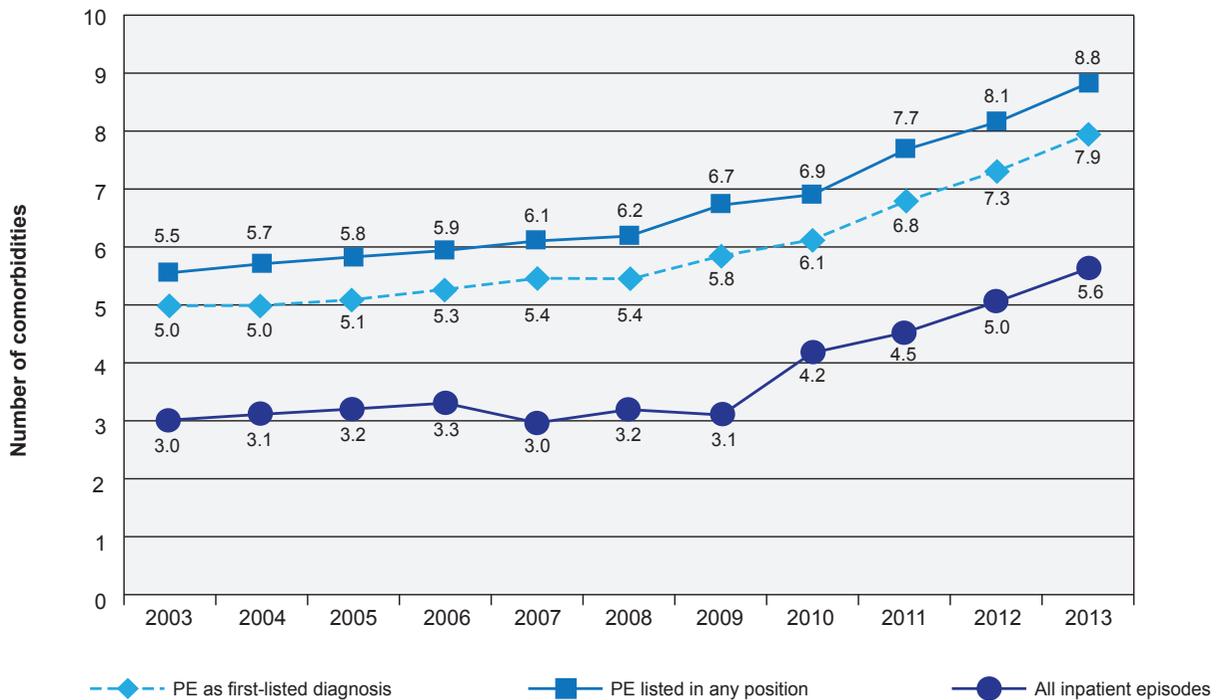


Figure 4 – Average number of comorbidities related to inpatient PE episodes and comparison with comorbidities related to national total inpatient episodes (2003-2013)

Table 2 - Frequency of major Single-Level CSS first-listed diagnoses in inpatient PE episodes

	2003 to 2009		2010 to 2013	
	Number of episodes	% of Overall Episodes	Number of episodes	% of Overall Episodes
Pneumonia	858	4.4%	712	4.5%
Congestive heart failure (non-hypertensive)	411	2.1%	264	1.7%
Acute cerebrovascular disease	371	1.9%	265	1.7%
Lung cancer	267	1.4%	291	1.8%
Phlebitis; thrombophlebitis and thromboembolism	199	1.0%	172	1.1%
Femoral neck fracture	229	1.2%	117	0.7%

Finally, the use of chest CT scanning is a variable with explanatory power and associated to a 12% average reduction in the probability of death.

DISCUSSION

The incidence of PE episodes has been increasing in Portugal over the last ten years and is currently estimated as 35 per 100,000 people and higher in female patients. A gradual increase has been found, even though a more significant increase in the number of PE episodes has been found from 2009 to 2010, i.e. the presence of two different stages in the progression of PE incidence has been found, the first stage up to 2009 and the second between 2010 and 2013.

The analysis of the explanatory factors of in-hospital mortality has been confined to the most recent years, in order to reduce bias and also due to the fact that no obvious reason for such an increase was found by the authors, including a change in coding rules or a proportional increase in the use of chest CT scanning, with a subsequent increase in the number of diagnosed cases.

Comorbidities such as pneumonia, congestive heart failure, cerebrovascular disease, cancer and femoral neck fracture were present in many PE episodes. A high in-hospital mortality rate associated to PE episodes was found, higher in male patients, even though a very positive progression over time has been found, showing a reduction from 31.8% in 2003 to 17% in 2013, all PE episodes combined. For

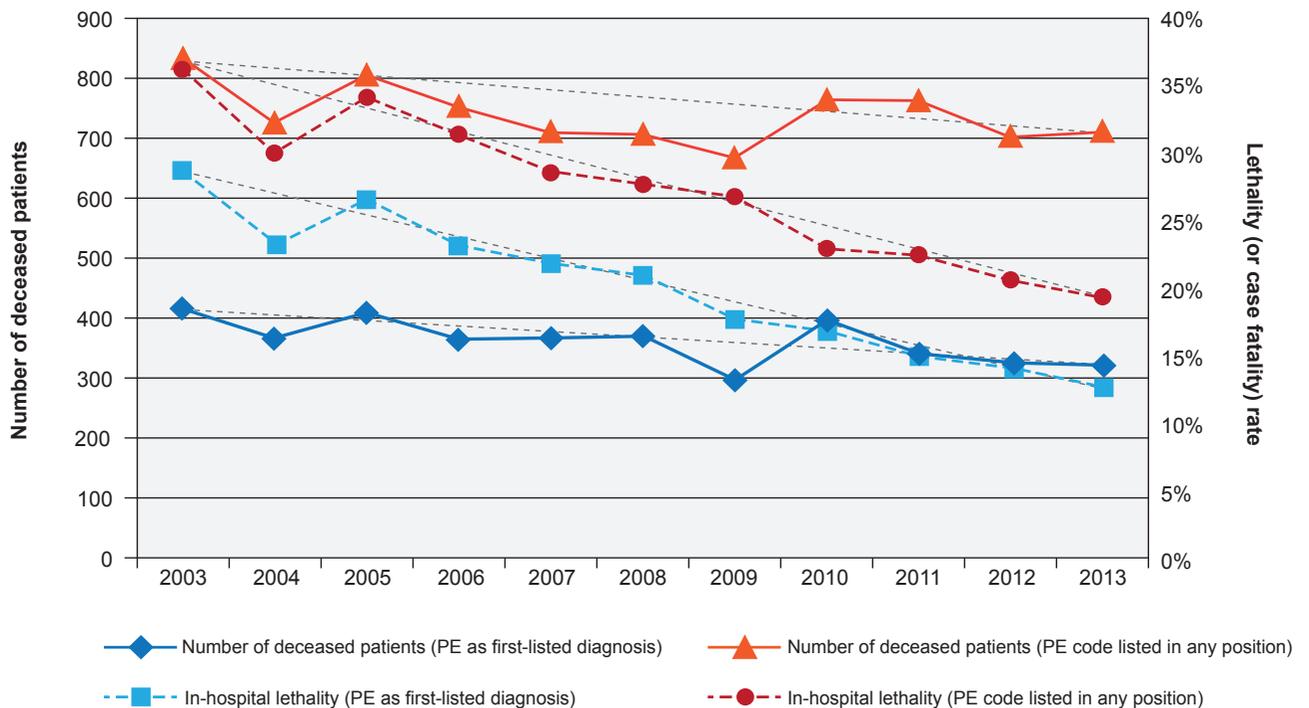


Figure 5 – In-hospital mortality regarding inpatient PE episodes (2003-2013)

reference purposes, information on PE mortality rate in general population aged 18 or over may be added. Mortality rate decreased from 10.4 per 100,000 people in 2003 to 8.7 in 2013, i.e., despite the incidence growth, the reduction in in-hospital mortality was such that even the mortality rate in general population has been reduced. When only considering the patients with PE as first-listed diagnosis, the reduction in mortality rate per 100,000 people was even more pronounced, from 8.2 to 5.7 over the same period of time.

As regards the analysis of mortality rate between 2010 and 2013, the presence of an increase in PE episodes with levels of severity increasingly lower may explain for the reduction in in-hospital mortality for PE, namely due to the ability to reach a diagnosis in less severe clinical situations using chest CT scanning. In fact, chest CT-scanning is independently associated to a significant reduction in the risk of death found in the analysis by logistic regression.

These results may be explained by the fact that the use of chest CT scanning allowed for reaching a diagnosis of PE in less severe clinical situations and subsequently leading to a reduction in the probability of death and by the fact that the use of CT scanning allowed for more accurate and timely diagnoses, improving PE treatment.

Logistic regression estimate allows for a better understanding of the reasons for the reduction in in-hospital mortality rate over time. This may have occurred due to the reduction in the average level of clinical severity of

PE inpatient episodes, i.e. due to favourable changes in clinical conditions of patients over time. As an alternative, the reduction of in-hospital mortality rate may be due to an improved efficiency in PE therapeutic approach. The model

Table 3 - Logistic regression for the analysis of mortality: effects over 2010 – 2013

Variable	Estimates	
	Linear Effect	Standard Error
Female gender	-0.0188**	0.0063
Age	0.0032**	0.0002
Age ²	0.0005**	0.0001
Charlson-Deyo score	0.0154**	0.0016
Cancer	0.0187*	0.0085
Congestive heart failure	0.0163*	0.0075
Cerebrovascular disease	0.0319**	0.0097
Pneumonia	0.0781**	0.0081
Femoral neck fracture	0.1158*	0.0554
Use of chest CT scanning	-0.1205**	0.0060
Observations	10,804	
Pseudo R ²	0.1315	
Log-likelihood	-3,588.07	

CT: Computerized tomography.

The coefficients may be interpreted as in a linear regression. Controls per year and healthcare region were included in the analysis; * $p < 0.05$; ** $p < 0.001$.

allows for a separate identification of both effects.

Some examples of specific comorbidities can help us understand the first explanation. In our group of patients, the percentage of pneumonia episodes decreased from 21.1% in 2010 to 10.1% in 2013. Using the model, this reduction had an estimated effect of around a 0.15% reduction in in-hospital mortality rate, approximately 4% of the 3.7% real reduction. However, changes in other variables have occurred and led to an increased clinical severity of the episodes, as shown by Charlson-Deyo comorbidity score, which has climbed from 1.28 to 1.46. When nothing else was changed, this increase in Charlson-Deyo score would lead to a 0.3% increase in in-hospital mortality. These two examples show the need for an overall analysis.

Whether the effect is due to the change in patient's clinical characteristics or due to improved healthcare may be estimated using the model, assuming that patient's clinical characteristics remained unchanged. The result of this decomposition shows that a 3.7% reduction in in-hospital mortality rate between 2010 and 2013 is responsible for a 0.8% percentage of favourable changes in patient's clinical characteristics and, in 2.9% to an improved treatment. Overall, a 21% reduction in mortality is due to lower clinical severity of PE episodes and 79% is due to improved efficiency in hospital healthcare.

CONCLUSION

The results of our study showed an increased incidence of acute pulmonary embolism over the last ten years which may be explained by increased life expectancy, as well as by a higher number of dependent and bedridden patients.

An increased number of episodes well above the trend were found between 2009 and 2010, for which there is no evident explanation. An incidence rate of 35 per 100,000 people aged 18 or above was found in 2013 in Portugal, based on hospital data. This is below what was found in other countries; an estimated rate of 112 per 100,000 people was found in the USA. This may be explained by differences in the real incidence of acute pulmonary embolism although

it may be partly due to a higher rate of under-diagnosis in Portugal compared to other countries.

In-hospital mortality for pulmonary embolism has been significantly reduced, from 25% in 2003 to 11.2% in 2013, considering pulmonary embolism episodes regarding patients in whom pulmonary embolism was first-listed diagnosis. An analysis based on a logistic regression model for in-hospital mortality between 2010 and 2013 regarding patients with pulmonary embolism as first-listed diagnosis allowed for the decomposition of the progression of in-hospital mortality into two factors. The first one corresponds to clinical severity and the second factor to the efficacy of hospital healthcare regarding diagnosis and treatment of pulmonary embolism. The analysis showed that a 79% reduction in in-hospital mortality is due to improved efficiency in hospital healthcare.

HUMAN AND ANIMAL PROTECTION

The authors declare that the followed procedures were according to regulations established by the Ethics and Clinical Research Committee and according to the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

CONFLICTS OF INTEREST

The authors declare that there were no conflicts of interest in writing this manuscript.

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