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Pulmonary embolism: incidence and outcomes in a twelve-year historical series, in Tuscany - Italy (2010-2021)

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Abstract

Background. *Pulmonary embolism poses a global health concern. Administrative databases serve as valuable sources for broad epidemiological studies on the prevalence and incidence of major diagnoses or diseases***.** *The primary scope is to provide up-to-date insights into Pulmonary Embolism incidence trends, examining shifts in management and outcomes.*
Design. *This retrospective observational study examines a 12-year dataset from hospitals in the Tuscany Region, covering the first two years of the Covid-19 pandemic.*
Methods*. Administrative data from residents aged 18 and older discharged from hospital between 2010 and 2021 were used for the analysis.*
Results. *Hospitalized pulmonary embolism incidence slightly declined from 2010 to 2019 (64.7 to 60.9 x 100,000; p=0.152). Males under 75 showed a higher incidence rate, while females had higher incidence rates in older age groups. In-hospital and 30-day mortality decreased from 2010 to 2019 (p=0.001 and 0.020 respectively). In 2020, 30-day mortality increased (12.4% vs 10.1%, p=0.029), while in-hospital mortality remained stable. One-year mortality was stable from 2010-2019 but increased in 2020 (32.6% vs 29.4%, p=0.037). Considering the multivariable model, one-year mortality is significantly associated with sex, age, and comorbidities.*
Conclusions. *Our study shows that Pulmonary Embolism persists as a relevant burden in Tuscany region, but with improvements in management over the past decade and a decisive change in pharmacological treatment. Gender-related differences emerge, highlighting the need for a gender-specific healthcare approach.*

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Introduction

Pulmonary embolism (PE) is a worldwide health issue representing a common disorder with high mortality and morbidity rates (1). Patients with PE have a case fatality rate of 8% and approximately 10% of symptomatic PE cases are fatal within the first hour after symptoms onset (2). Moreover, PE is the third cause of cardiovascular death after myocardial infarction and stroke, and it is the leading preventable cause of death in hospitalized patients (3,4). Longitudinal data have revealed an increasing trend in annual PE incidence rates over time. Since the incidence of the disease rises with age and due to the aging of Western societies, it can be expected that a larger number of patients will be diagnosed with PE in the future (5). Despite the overmentioned tendency, there is evidence of a decrease in the mortality rate of PE. Such decrease may be attributed to improvements in risk management, but also to a higher number of patients with smaller emboli and low risk of PE-related complications and mortality (6). Nevertheless, in the modern era, since the introduction of computed tomographic pulmonary angiography (CTPA) to establish the diagnosis, an increase of the total number of PE cases and a corresponding decrease in case fatality have been observed (7).

Most of the published information on the prevention, current therapy, and natural history of patients with venous thromboembolism (VTE) came from randomized clinical trials (RCTs), mostly focused to obtain data on efficacy and safety of drugs. Randomized control studies usually involve well-defined study populations excluding complex patients and adopt standardized protocols that are sometimes difficult to implement in routine clinical practice (8). Moreover, RCTs-based recommendations might not be applied to different, broader populations so that the resulting outcomes could not be inferred to different persons with respect to those observed in RCTs. Real world data are crucial for describing the management of PE, because a significant percentage of the affected patients have at least one exclusion criterion preventing their inclusion into randomized clinical trials (8). Administrative structured database data collection can provide complementary data to those from the trials, help understanding the treatment pathway of patients, inform the generation of new hypotheses, and verify the already emerged ones (8). Taking into account databases fueled by real world data, we must consider possible epidemiological differences among populations, due to different prevalence of risk factors, and other distal determinants, such as those regarding the socio-economic status, or the geographical nationality of the recruited persons. So far, for instance, only few studies evaluated the incidence and prognosis of PE in the southern European countries (9).

In the last few years several findings have shown that administrative databases might represent one of the best available sources for wide epidemiological studies regarding prevalence and incidence of major diagnoses or diseases, especially when they are focused on a clearly identified event (10).

This study employs a methodological approach using data from Tuscany Region hospitals' discharge records over a 12-year period, including the initial two years of the Covid-19 pandemic. Our objective is to conduct a trend analysis of pulmonary embolism incidence, offering robust and updated data to enhance understanding of the disease burden. We focus on an unselected population to evaluate changes in management and outcomes over the years, with attention to the pandemic's impact in the last two years of the examined period.

Materials and Methods

We conducted a retrospective observational study, including all individuals resident in Tuscany, aged 18 years or older, discharged from one of the regional hospitals with diagnosis of PE from 2010 to 2021.

The primary outcome measures were trends in incidence rates (crude and adjusted for sex and age), patient's characteristics (sex, age, Charlson Comorbidity Index (11)), length of hospital stay (LOHS), pharmacological treatment at discharge and hard outcomes in terms of in-hospital mortality (IHM), 30-day mortality and one year mortality.

Data were provided by Tuscan Regional Healthcare Agency that is a public entity (Regional Law n. 40/2005) entitled to perform research and analysis. Individual, anonymous data on people residing in Tuscany come from the Regional Healthcare Administrative Data System (RHCADS). The RHCADS comprises several healthcare data sources, including Hospital Discharge Abstracts (HDAs), Registry Offices and data on drug dispensing registry (DDR). Each individual has a unique and anonymous identifier within the RHCADS.

The HDA collects information on demographic characteristics, admission and primary and secondary diagnoses and procedures coded according to the

International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Date of death was reported in Registry Office, while information on medications dispensed in private, public and hospital pharmacies were identified on DDR through the Anatomical Therapeutic Chemical index (ATC).

According to the relevant regulatory provisions and guidelines, the opinion of the Ethics Committee, thus the Institutional Review Board (IRB) approval, was not required for the present activity. This exclusion is determined by the circumstance that in carrying out the activity no relevant ethical issues arise, as the subject matter is regulated by current legislation on planning, management, control, and evaluation of healthcare, as set forth in sheet No. 12 (Attachment A) to the Regional Regulation on data protection (Regulation dated October 26, 2021, No. 37/R, Implementation Regulation of Article 1, paragraph 1, of Regional Law dated April 3rd, 2006, No. 13, concerning the treatment of special categories of personal data and that relating to criminal convictions and crimes by the Tuscany Region, healthcare agencies, entities, companies, and regional agencies, and public entities in respect of which the Region exercises direction and control powers).

The study population includes all Tuscany region residents with a first hospital admission for PE in a calendar year (PE hospital events). More specifically, patients with a primary diagnosis of PE (ICD-9-CM codes 415.11 or 415.19) or with a secondary discharge diagnosis of PE associated with a primary code compatible with PE (ICD-9-CM codes 51881, 51882, 51884, 7991, 4534, 4538, 4536 78551, 4275, 4589) in the hospital discharge form were included. In order to estimate the incidence of PE events requiring hospital care, the first hospitalization in a year was considered for each subject, excluding any hospitalizations in the subsequent 365 days. Other exclusion criteria were admission in a rehabilitation ward and incorrect unique encrypted identifier. According to the clinical characteristics of the index episode, high-risk PE (HRPE) was defined by the presence of at least one of the following criteria: cardiogenic shock (ICD-9-CM code 785.51), cardiac arrest (427.5), transient severe hypotension (458.9), need for mechanical ventilation (96.70, 96.71, 96.72), orotracheal intubation (96.04), cardiopulmonary resuscitation (96.60). Comorbidities were measured using the Charlson Comorbidity Index (CCI).

Pharmacological treatments prescribed within 30 days of hospital discharge considered in the study include: low-molecular-weight heparin (LMWH) therapy (ATC codes B01AB01, B01AB04, B01AB05, B01AB06, B01AB07, B01AB08, B01AB12, B01AX05), indirect anticoagulation therapy (B01AA03, B01AA07), direct oral anticoagulants (DOACs) (B01AF01, B01AE07, B01AF03, B01AF02).

Baseline patient characteristics were expressed using descriptive statistics. Continuous variables were reported as mean with standard deviation (SD) or median with interquartile range (IQR). Categorical variables were reported as counts and percentages. In order to identify changes in trends between 2010 and 2019 (pre-pandemic period), the Mann-Kendall test for trend has been performed. Data between 2020 and 2021 were compared to 2019 to evaluate changes in the burden of disease of PE due to COVID-19 pandemic. A descriptive analysis (chi-square test for categorical data and nonparametric Kruskal-Wallis/ median test for quantitative measurements) were performed. For each analysis, an α level of 0.05 is considered as significant. To study determinants of in-hospital, 30-days and one-year mortality, multivariate logistic regression models were conducted over the 12-year period. The statistical software Stata 15 SE tm was used for the analysis.

Results

During the twelve-year study period (2010-2021), a total of 22,361 PE hospital events in 21,774 subjects were recorded. The proportion of patients with High Risk Pulmonary Embolism (HRPE) decreased from 2010 to 2019 (5.9% vs. 4.2%, $p < 0.001$). Incidence rate of hospitalized pulmonary embolism slightly decreases from 2010 to 2019 from 64.7 x 100,000 to 60.9 x 100,000 (Mann-Kendall test p-value 0.152). The trend is maintained even after standardization by age and sex (Appendix). Notably, this trend remained stable between 2019 and 2021 (Mann-Kendall test p-value 1.000). The reduction in incidence is higher in individuals aged over 85 years (see Figure 1).

The cumulative crude incidence of PE was significantly higher in females (63.1 x 100,000) than in males (55.8 x 100,000, $p<0.001$). Since the median age of the population is 78 years, we subsequently stratified the study population into three age classes (< 75 yo, 75-84 yo, >=85 yo). The incidence rate was more than ten-fold higher in 85 years old or older people than in people younger than 75 years (303.7 per 100,000 inhabitants vs. 27.8 per 100,000 inhabitants).

Sex distribution revealed a higher incidence rate of PE among males under 75, while females exhibited a higher incidence rate in the older age classes (Figure 1). In Table 1 we show in detail the clinical features of patients comparing the first study year (2010), the last pre-pandemic year (2019) and the 2020-2021 pandemic years compared to 2019. Complete data are listed in Appendix. Between 2010 and 2019 we observed significant differences in the proportion of HRPE, Charlson comorbidity index, length of hospital stay (LOHS). Following a substantial reduction between 2010 and 2019, LOHS significantly increased during the pandemic years.

The overall in-hospital mortality (IHM) and the 30-day mortality decreased significantly between 2010 and 2019 (Mann-Kendall test p-value 0.001 and 0.020, respectively, see Figure 2). During 2020, 30-days mortality showed a significant increase compared to 2019 (12.4% vs 10.1% p=0.029) while in-hospital mortality remained stable during the pandemic years (Mann-Kendall test p-value 0.296). No significant differences exist between females and males (8.5% vs. 8.0% respectively, p=0.182 for in-hospital and 13.1% vs 13.4% respectively, p=0.393, for 30-day mortality). Considering the multivariable models, in-hospital and 30-day mortality rates are not associated with sex (OR 0.968, p=0.515) while both increase with age and comorbidities (Table 2). While reduction in IHM was constant during the study periods, 30-days mortality increased between 2010 and 2013, especially in males, and decreased for both sexes beginning 2014 (Figure 2).

Figure 1 - Incidence of PE by sex and age, 2010-2021, Tuscany. (a) Cumulative PE incidence rate; (b) PE incidence rate in individuals younger than 75 years old; (c) PE incidence rate in individuals aged 75 to 84 years; (d) PE incidence rate in individuals older than 85 years.

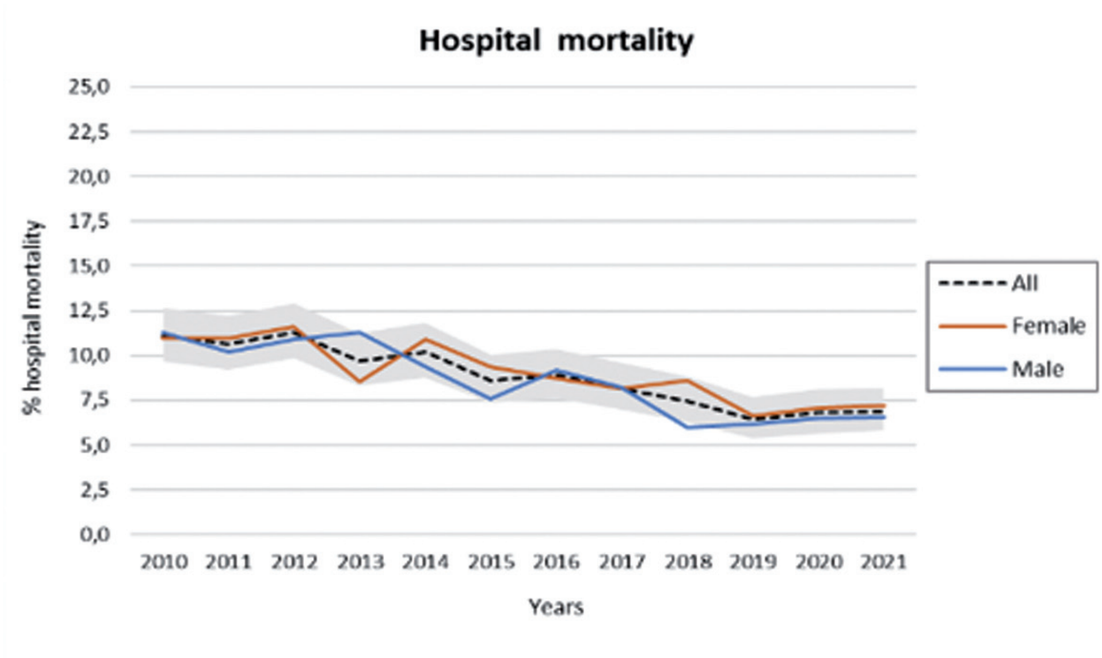
Table 1 - Baselines characteristic of patients across study years: 2010 - pre-pandemic 2019, and pandemic years 2020-2021 vs. 2019.

Characteristics	2010-2021 N (%)	2010 N (%)	2019 N (%)	19 vs 10 p-values	2020 N (%)	20 vs 19 p-values	2021 N (%)	21 vs 19 p-values
Hospital admissions	22,361	1,963	1,924		1,707		1,966 (8.8)	
Massive EP	1,010 (4.5)	115 (5.9)	81 (4.2)	0.019	66 (3.9)	0.600	76 (3.9)	0.585
Sex								
Female	12,646 (56.6)	1,149 (58.5)	1,071 (55.7)	0.071	907 (53.1)	0.126	1,110 (56.5)	0.618
Age								
Mean (SD)	75 (13)	75 (13)	74 (14)		74 (14)		75 (13)	
Median [IQR]	78 [69;85]	78 [69;85]	78 [68;84]	0.773	77 [67;84]	0.150	78 [68;84]	0.858
<75 year	8,745 (39.1)	740 (37.7)	777 (40.4)	0.219	734 (43.0)	0.247	762 (38.8)	0.558
75-84 year	7,997 (35.8)	727 (37.0)	675 (35.1)		583 (34.2)		716 (36.4)	
85+ year	5,616 (25.1)	496 (25.3)	472 (24.5)		390 (22.8)		488 (24.8)	
Charlson index								
CCS 0	7,787 (34.8)	674 (34.3)	740 (38.5)	0.044	647 (37.9)	0.963	734 (37.3)	0.345
CCS 1	4,524 (20.2)	400 (20.4)	389 (20.2)		342 (20.0)		431 (21.9)	
CCS 2-4	6,403 (28.6)	590 (30.1)	528 (27.4)		472 (27.7)		508 (25.8)	
CCS 5-6+	3,647 (16.3)	299 (15.2)	267 (13.9)		246 (14.4)		293 (14.9)	
LOHS								
Mean (SD)	10 (7.5)	11.4 (9)	8.7 (8)		9.3 (7)		9.5 (7)	
Median [IQR]	8 [5;12]	10 [6;14]	7 [5;11]	<0.001	7 [5;12]	0.076	8 [5;12]	0.004
Pharmacological treatments at hospital discharge	%	N (%)	N (%)		N (%)		N (%)	
At least one treatment	87.7	1,455 (83.4)	1,640 (91.1)	<0.001	1,431 (89.9)	0.270	1,640 (89.6)	0.143
low-molecular-weight heparin therapy	40.4	840 (48.1)	576 (32,0)	<0.001	486 (30.5)	0.381	503 (27.5)	0.003
indirect anticoagulation therapy	24.4	830 (47.6)	117 (6.5)	<0.001	68 (4.3)	0.004	65 (3.6)	0.001
DOACs	35.0	21 (1.3)	1,111 (61.7)	<0.001	1,000 (62.9)	0.498	1,212 (66.2)	0.005
Mortality	%	N (%)	N (%)		N (%)		N (%)	
- In-hospital	8.9	218 (11.1)	124 (6.4)	<0.001	116 (6.8)	0.671	136 (6.9)	0.555
- 30-days	13.3	264 (13.4)	195 (10.1)	0.001	212 (12.4)	0.029	223 (11.3)	0.224
- 1-year	33.6	661 (33.7)	566 (29.4)	0.004	557 (32.6)	0.037	616 (31.3)	0.194
Hospital readmissions								
- all causes		236 (13.5)	193 (10.7)	0.011	170 (10.7)	0.972	192 (10.5)	0.822
- for symptoms related to PE		65 (3.7)	63 (3.5)	0.720	42 (2.6)	0.149	58 (3.2)	0.579
- for any major complications of anticoagulation therapy		6 (0.3)	15 (0.8)	0.058	12 (0.8)	0.796	16 (0.9)	0.893

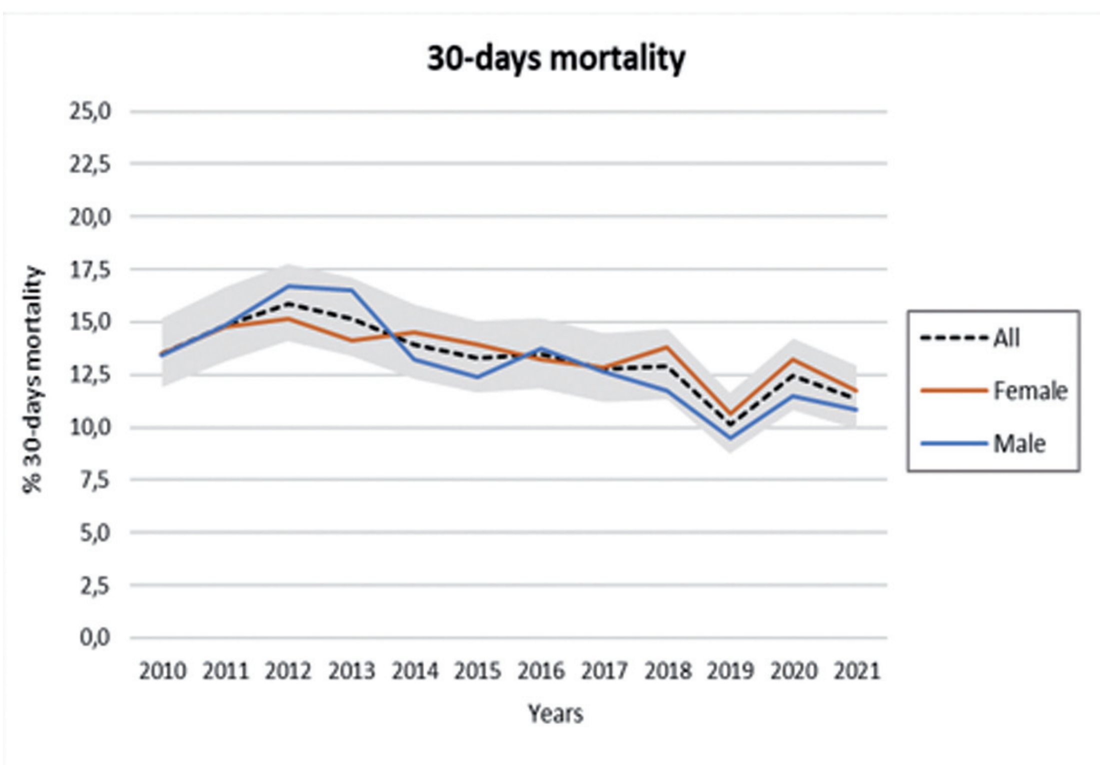
SD, standard deviation; CCI, Charlson comorbidity index; IQR, interquartile range; LOHS, length of Hospital Stay; DOACs, Direct Oral Anticoagulants

Regarding the pharmacological treatments, they were prescribed at the time of discharge from the hospital in 87.7% of patients. During the years, we observed a reduction in the prescription of low molecular weight heparin (LMWH) therapy, from 48% in 2010 to 32% in 2019, and in indirect anticoagulation therapy, from 47.6% in 2010 to 6.5% in 2019 (p<0.001). On the other hand, the prescription of direct oral anticoagulants (DOACs) increased over time, from 1.3% in 2013 to 61.7% in 2019 (p<0.001). Throughout the pandemic years, a similar pattern in pharmaceutical prescriptions as that seen in the years 2010-2019 was observed (see Appendix and Table 1).

The 30-day hospital readmission rate for all causes decreased from 2010 to 2019, but there was



(a)



(b)

Figure 2 - PE Mortality rate by sex, 2010-2021, Tuscany. (a) In hospital mortality rate; (b) 30 days mortality rate

Table 2 - Multiple regression model of variables associated with mortality after a first episode of PE. From the left: the first column shows the variables included in the model. The second, third and fourth columns show the in-hospital mortality, the 30-days mortality and the 1 year mortality. Statistically significant results are highlighted

	In-hospital mortality		30-days mortality		1 year mortality	
	OR	P-value	OR	P-value	OR	P-value
Female	0.968	0.515	0.975	0.554	0.929	0.027
Age (baseline: "Age<75")						
Age 75-84	1.667	<0.001	1.615	<0.001	1.612	<0.001
Age 85+	2.920	<0.001	3.234	<0.001	3.604	<0.001
CCS (baseline: "CCS 0-1")						
CCS 2-4	1.461	<0.001	1.602	<0.001	1.963	<0.001
CCS 5	2.005	<0.001	2.528	<0.001	3.743	<0.001
CCS 6+	2.920	<0.001	2.520	<0.001	17.038	<0.001
Year (baseline year 2010)						
2011	0.949	0.626	1.115	0.256	0.997	0.966
2012	1.000	0.997	1.180	0.079	1.035	0.648
2013	0.843	0.120	1.119	0.243	1.093	0.249
2014	0.906	0.363	1.031	0.749	1.083	0.301
2015	0.730	0.005	0.947	0.578	1.020	0.791
2016	0.769	0.017	0.973	0.779	0.973	0.719
2017	0.697	0.001	0.912	0.353	0.960	0.601
2018	0.634	<0.001	0.941	0.538	0.905	0.195
2019	0.570	<0.001	0.758	0.007	0.865	0.059
2020	0.609	<0.001	0.971	0.779	1.044	0.581
2021	0.602	<0.001	0.841	0.084	0.932	0.355

OR, Odds Ratio; CCI, Charlson comorbidity index

no significant reduction in readmission rates for symptoms related to PE or for any major complication of anticoagulation therapy over the years. The readmission rates remained stable during the pandemic years compared to 2019.

One-year mortality did not change between 2010 and 2019 (Mann-Kendal test: p=0.107). Between 2011 and 2014, males showed a significantly higher one-year mortality. Moreover, one-year mortality shows a significant increase during 2020 compared to 2019 (32.6% vs 29.4%, p=0.037). Considering the multivariable model, one-year mortality is significantly associated with sex, age and comorbidities (Table 2).

Discussion

Based on our findings, the incidence of hospitalized PE in the Tuscany Region, Italy, between 2010 and 2021 was relatively high and exhibited stability throughout the entire observation period, surpassing rates observed in other studies (1, 9). According to other recent analyses, the incidence rate of high-risk pulmonary embolism has decreased over the years. This may be partly attributed to improved diagnostic workup and more effective management right from the initial phases of onset at the emergency department (12). The in-hospital and 30-days mortality was in line with literature findings (13-16), but there was a discernible downward trend until 2019. Furthermore, a notable and statistically significant reduction of the mean duration of hospitalization throughout the study period was found.

Our findings, consistent with existing literature (17), underscore age-stratified differences in PE incidence by gender. Among younger age groups, males exhibited a higher incidence rate compared to females, likely influenced by physiopathological factors associated with venous thromboembolism (18). Conversely, in older age groups, females constituted a larger proportion of patients, possibly reflecting demographic trends in advanced age cohorts (19). Our data confirmed PE as predominantly affecting older individuals, with incidence rates in the over-85 exceeding over tenfold those in people under 75

(17,20,21]. These disparities in PE incidence highlight the complex interplay of age, gender, and underlying health conditions (21).

Unlike the results reported in previous studies showing an increasing trend, our time series analysis indicated a stable incidence rate of PE in patients during the study period. (1,13,22,23). One factor that may explain this trend is that our case definition did not include patients discharged directly from the emergency room (24-27). In recent years, an increasing number of low-risk pulmonary embolism (PE) cases have been managed through rapid discharge and outpatient care, supported by continued anticoagulant treatment at home (28). Another potential factor that could explain the stable trend of incidence rate reported are the preventive strategies to reduce PE in acute ill patients. Preventive strategies, encompassing pharmacological and mechanical approaches, play a critical role in mitigating the risk of PE, especially among elderly patients. Anticoagulant prophylaxis, supported by findings from a comprehensive meta-analysis by the Cochrane Collaboration showing a reduction in PE incidence by up to 60% in medical patients (29). Combining anticoagulants with intermittent pneumatic compression (IPC) further enhances efficacy, reducing PE risk by 70% in high-risk surgical patients (30). Tailored preventive strategies may play a pivotal role in controlling the incidence of new events, contributing to the stable trend of reported incidence rates.

Our study identified a consistent decrease in IHM, consistent with previous research (31-34). This trend may be primarily attributed to an increasing referral to high-volume centers, leading to enhanced interventional and pharmacological treatment. As expected, age and CCI showed a significant association with increase in mortality rate.

It is interesting to note that the COVID-19 pandemic did not significantly influence the incidence of hospital-admitted PE. During the years of the highest pandemic impact (2020-2021) for the hospital admissions burden, the number of hospitalized PE cases showed a slight reduction. Gender differences concerning the incidence rate disappeared. At the same time, in-hospital mortality slightly increased in both sexes, possibly reflecting a higher appropriateness of hospitalization for severe cases of PE, in addition to the direct effect on PE caused by COVID-19 itself, attributable to a higher likelihood of systemic coagulation activation and thrombotic complications in people suffering from COVID-19 (33).

Despite the increasing aging, which affects all the western populations, we observed a decrease in LOHS over time in our study. Age significantly influences hospital stay length in elderly patients due to complex medical conditions, reduced physiological reserves, and increased susceptibility to complications post-surgery or during acute illnesses (34). Despite these challenges, our findings, as reported in recent literature, indicates a global trend towards reducing LOHS (35). Factors contributing to this reduction include streamlined internal diagnostic processes, development of less invasive surgical techniques, simplified discharge procedures, organization of outpatient clinics for follow-up, and shifting preoperative activities to outpatient settings (36).

In our analysis, we observed a 1-year mortality of 33.6%. While several studies indicate a relatively low risk of mortality directly from pulmonary embolism (PE) during anticoagulant therapy (1.5-4%) and even lower post-treatment (less than 0.5% per person-year) (37-39), all-cause mortality rates within the first year after a PE event are notably higher, ranging from 17% to 32% (40,41). It's clear that although the risk of dying specifically from PE while on anticoagulant therapy is relatively low, patients with PE often have underlying medical conditions, contributing to a significantly higher overall mortality rate.

Strengths and limitations

Our study presents both strengths and limitations. Notably, strengths include the substantial number of patients assessed (over 3.5 million), which allowed for further stratification by age and sex, and the extended 12-year period, providing valuable insights into trends in PE hospitalizations and more.

However, a primary limitation of our study stems from the method used to identify patients hospitalized for PE, which relied on ICD-9-CM diagnosis codes. While these codes may have a low accuracy in identifying hospitalized patients with the disease (42), we took precautions by including only patients with a principal diagnosis of PE and those with a secondary diagnosis of PE along with a primary diagnosis of conditions compatible with PE. This approach aimed to prevent the inclusion of cases where pulmonary embolism was associated but not the determining factor for hospitalization. Moreover, we used a washout period of one years, considering only incident cases of PE, potentially leading to underestimation of admission rates.

Another significant limitation pertains to the inability of hospital discharge diagnostic codes to distinguish between PE developed during hospitalization and cases that pre-existed before admission. Consequently, we lack information about the setting of the origin of PE. Furthermore, we acknowledge that detailed clinical data, including laboratory parameters, as well as specific pharmacological and interventional procedures like thrombolysis and catheter-based procedures, are not adequately captured in the current healthcare data flow. As a result, these treatments were not available for analysis.

Additionally, our assessment of mortality was limited to all-cause mortality, both in-hospital and one year after the event. However, prior studies have shown that in-hospital mortality is primarily related to acute PE episodes, while other causes of death, such as comorbidities, impact mortality over the long term (17).

Conclusions

Our investigation shows that PE remains a significant burden, yet it strongly supports the notion that the management of PE has seen remarkable improvement over the years. The results also emphasize the need to redefine care models and healthcare services in both hospital and outpatient settings, given the influence of chronic diseases and age. Considering the ongoing global trend of population aging, we anticipate a continued increase in the overall medical, societal, and economic burden associated with hospital admissions and deaths due to PE in the future. Additionally, in our dataset, we found that female gender was associated with a higher crude incidence of PE. These results agree with findings from previous studies conducted in a similar context (1, 9). The findings highlight significant gender-related differences for PE, emphasizing the importance of addressing gender health disparities (43).

Declarations
Disclosures: The authors have no relevant financial or non-financial interests to disclose.
Data Availability Statement: Data supporting reported results are available upon request to the corresponding author. Data were collected and managed in aggregated form according to European Union Regulation 2106/679 of the European Parliament and the Italian Legislative Decree 2018/101.
Author Contributions: Conceptualization, Gabriele Cerini, Silvia Forni, Carla Lunetta ; methodology, Silvia Forni, Claudia Szasz, Fabrizio Gemmi; formal analysis, Gabriele Cerini, Claudia Szasz, Fabrizio Gemmi.; writing—original draft preparation, Gabriele Cerini, Silvia Forni, Carla Lunetta; writing—review and editing, Leonardo Misuraca, Marisa Carluccio, Guglielmo Bonaccorsi, Chiara Lorini; supervision, Fabrizio Gemmi, Guglielmo Bonaccorsi, Chiara Lorini, Silvia Forni; All authors have read and agreed to the published version of the manuscript.

Riassunto

Embolia polmonare: incidenza ed esiti in una serie storica di dodici anni, in Toscana - Italia (2010-2021)

Contesto. L'embolia polmonare è un problema per la salute a livello globale. I database amministrativi rappresentano fonti per ampi studi epidemiologici sulla prevalenza e incidenza delle principali diagnosi e malattie. L'obiettivo principale è fornire informazioni aggiornate sulle tendenze di incidenza dell'embolia polmonare, esaminando i cambiamenti nella gestione e negli esiti.

Disegno dello studio. Questo studio osservazionale retrospettivo esamina un dataset di 12 anni proveniente dagli ospedali della Regione Toscana, coprendo i primi due anni della pandemia di Covid-19.

Metodi. Per l'analisi sono stati utilizzati i dati amministrativi dei residenti di età pari o superiore a 18 anni dimessi dagli ospedali tra il 2010 e il 2021.

Risultati. L'incidenza di embolia polmonare nei pazienti ospedalizzati è leggermente diminuita dal 2010 al 2019 (da 64,7 a 60,9 x 100.000; p=0.152). Gli uomini al di sotto dei 75 anni hanno mostrato un tasso di incidenza più elevato, mentre le donne hanno registrato tassi di incidenza più alti nei gruppi di età più avanzata. La mortalità in ospedale e a 30 giorni è diminuita dal 2010 al 2019 (p=0.001 e 0.020 rispettivamente). Nel 2020, la mortalità a 30 giorni è aumentata (12.4% vs 10.1%, p=0.029), mentre la mortalità in ospedale è rimasta stabile. La mortalità a un anno è rimasta stabile dal 2010 al 2019, ma è aumentata nel 2020 (32.6% vs 29.4%, p=0.037). L'analisi multivariabile ha mostrato che la mortalità a un anno è significativamente associata a sesso, età e comorbilità.

Conclusioni. Il nostro studio mostra che l'embolia polmonare continua ad avere un peso rilevante in Regione Toscana, ma con miglioramenti nella gestione nell'ultimo decennio e un cambiamento decisivo nel trattamento farmacologico. Emergono differenze legate al genere, sottolineando la necessità di un approccio sanitario orientato alle differenze di genere.

References

1. Dentali F, Ageno W, Pomero F, Fenoglio L, Squizzato A, Bonzini M. Time trends and case fatality rate of in-hospital treated pulmonary embolism during 11 years of observation in Northwestern Italy. Thromb Haemost. 2016 Jan;**115**(2):399-405. doi: 10.1160/TH15-02-0172. Epub 2015 Sep 17. PMID: 26422774.
2. Bělohlávek J, Dytrych V, Linhart A. Pulmonary embolism, part I: Epidemiology, risk factors and risk stratification, pathophysiology, clinical presentation, diagnosis and nonthrombotic pulmonary embolism. Exp Clin Cardiol. 2013 Spring;**18**(2):129-38. PMID: 23940438; PMCID: PMC3718593.
3. Stein PD, Beemath A, Olson RE. Trends in the incidence of pulmonary embolism and deep venous thrombosis in hospi-

talized patients. Am J Cardiol. 2005 Jun 15;**95**(12):1525-6. doi: 10.1016/j.amjcard.2005.02.030. PMID: 15950590.

4. Heit JA. The epidemiology of venous thromboembolism in the community. Arterioscler Thromb Vasc Biol. 2008 Mar;**28**(3):370-2. doi: 10.1161/ATVBAHA.108.162545. PMID: 18296591; PMCID: PMC2873781.
5. ISTH Steering Committee for World Thrombosis Day. Thrombosis: a major contributor to global disease burden. Thromb Res. 2014 Nov;**134**(5):931-8. doi: 10.1016/j.thromres.2014.08.014. Epub 2014 Oct 10. PMID: 25312343.
6. Konstantinides SV, Barco S, Lankeit M, Meyer G. Management of Pulmonary Embolism: An Update. J Am Coll Cardiol. 2016 Mar 1;**67**(8):976-990. doi: 10.1016/j.jacc.2015.11.061. PMID: 26916489.
7. Wiener RS, Schwartz LM, Woloshin S. Time trends in pulmonary embolism in the United States: evidence of overdiagnosis. Arch Intern Med. 2011 May 9;**171**(9):831-7. doi: 10.1001/archinternmed.2011.178. PMID: 21555660; PMCID: PMC3140219.
8. Monreal M, Mahé I, Bura-Riviere A, Prandoni P, Verhamme P, Brenner B, et al. Pulmonary embolism: Epidemiology and registries. Presse Med. 2015 Dec;**44**(12 Pt 2):e377-83. doi: 10.1016/j.lpm.2015.10.006. Epub 2015 Nov 4. PMID: 26547675.
9. de Miguel-Díez J, Jiménez-García R, Jiménez D, Monreal M, Guijarro R, Otero R, et al. Trends in hospital admissions for pulmonary embolism in Spain from 2002 to 2011. Eur Respir J. 2014 Oct;**44**(4):942-50. doi: 10.1183/09031936.00194213. Epub 2014 Jul 3. PMID: 24993910.
10. Mazzali C, Paganoni AM, Ieva F, Masella C, Maistrello M, Agostoni O, et al; HF Data Project. Methodological issues on the use of administrative data in healthcare research: the case of heart failure hospitalizations in Lombardy region, 2000 to 2012. BMC Health Serv Res. 2016 Jul 8;**16**:234. doi: 10.1186/s12913-016-1489-0. PMID: 27391599; PMCID: PMC4939041.
11. Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol. 2011 Mar 15;**173**(6):676-82. doi: 10.1093/aje/kwq433. Epub 2011 Feb 17. PMID: 21330339.
12. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, et al; ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J. 2020 Jan 21;**41**(4):543-603. doi: 10.1093/eurheartj/ehz405. PMID: 31504429.
13. de Miguel-Diez J, Albaladejo-Vicente R, Lopez-de-Andres A, Hernández-Barrera V, Jiménez D, Monreal M, et al. Changing Trends in Hospital Admissions for Pulmonary Embolism in Spain from 2001 to 2018. J Clin Med. 2020 Oct 7;**9**(10):3221. doi: 10.3390/jcm9103221. PMID: 33036474; PMCID: PMC7599502.
14. Minges KE, Bikdeli B, Wang Y, Kim N, Curtis JP, Desai MM, et al. National Trends in Pulmonary Embolism Hospitalization Rates and Outcomes for Adults Aged ≥65 Years in the United States (1999 to 2010). Am J Cardiol. 2015 Nov 1;**116**(9):1436-42. doi: 10.1016/j.amjcard.2015.07.068. Epub 2015 Aug 14. PMID: 26409636; PMCID: PMC4841688.
15. Schissler AJ, Rozenshtein A, Schluger NW, Einstein AJ. National trends in emergency room diagnosis of pulmonary embolism, 2001-2010: a cross-sectional study. Respir Res. 2015 Mar 24;**16**(1):44. doi: 10.1186/s12931-015-0203-9. PMID: 25890024; PMCID: PMC4391335.
16. Bikdeli B, Wang Y, Minges KE, Desai NR. Hospitalizations, Therapies, and Outcomes of Pulmonary Embolism in Medicare Beneficiaries: Trends Are Similar to Europe. J Am Coll Cardiol. 2016 May 31;67(21):2559-60. doi: 10.1016/j.jacc.2016.02.075. PMID: 27230057.
17. Huang W, Goldberg RJ, Anderson FA, Kiefe CI, Spencer FA. Secular trends in occurrence of acute venous thromboembolism: the Worcester VTE study (1985-2009). Am J Med. 2014 Sep;**127**(9):829-39.e5. doi: 10.1016/j.amjmed.2014.03.041. Epub 2014 May 6. PMID: 24813864; PMCID: PMC4161646.
18. Abou-Ismail MY, Citla Sridhar D, Nayak L. Estrogen and thrombosis: A bench to bedside review. Thromb Res. 2020 Aug;**192**:40-51. doi: 10.1016/j.thromres.2020.05.008. Epub 2020 May 11. PMID: 32450447; PMCID: PMC7341440.
19. Eskes T, Haanen C. Why do women live longer than men? Eur J Obstet Gynecol Reprod Biol. 2007 Aug;**133**(2):126-33. doi: 10.1016/j.ejogrb.2007.01.006. Epub 2007 Feb 26. PMID: 17324494.
20. Deitelzweig SB, Johnson BH, Lin J, Schulman KL. Prevalence of clinical venous thromboembolism in the USA: current trends and future projections. Am J Hematol. 2011 Feb;**86**(2):217-20. doi: 10.1002/ajh.21917. PMID: 21264912.
21. Engbers MJ, van Hylckama Vlieg A, Rosendaal FR. Venous thrombosis in the elderly: incidence, risk factors and risk groups. J Thromb Haemost. 2010 Oct;**8**(10):2105-12. doi: 10.1111/j.1538-7836.2010.03986.x. PMID: 20629943.
22. Spencer FA, Emery C, Joffe SW, Pacifico L, Lessard D, Reed G, et al. Incidence rates, clinical profile, and outcomes of patients with venous thromboembolism. The Worcester VTE study. J Thromb Thrombolysis. 2009 Nov;**28**(4):401-9. doi: 10.1007/s11239-009-0378-3. PMID: 19629642; PMCID: PMC3248815.
23. Keller K, Hobohm L, Ebner M, Kresoja KP, Münzel T, Konstantinides SV, et al. Trends in thrombolytic treatment and outcomes of acute pulmonary embolism in Germany. Eur Heart J. 2020 Jan 21;**41**(4):522-529. doi: 10.1093/eurheartj/ehz236. PMID: 31102407.
24. Pauley E, Orgel R, Rossi JS, Strassle PD. Age-Stratified National Trends in Pulmonary Embolism Admissions. Chest. 2019 Oct;**156**(4):733-742. doi: 10.1016/j.chest.2019.05.021. Epub 2019 Jun 21. PMID: 31233745.
25. Barco S, Lankeit M, Binder H, Schellong S, Christ M, Beyer-Westendorf Jet al. Home treatment of patients with

low-risk pulmonary embolism with the oral factor Xa inhibitor rivaroxaban. Rationale and design of the HoT-PE Trial. Thromb Haemost. 2016 Jul 4;**116**(1):191-7. doi: 10.1160/TH16-01-0004. Epub 2016 Mar 24. PMID: 27010343.
26. Vinson DR, Ballard DW, Huang J, Reed ME, Lin JS, Kene MV, et al; MAPLE Investigators of the KP CREST Network. Outpatient Management of Emergency Department Patients With Acute Pulmonary Embolism: Variation, Patient Characteristics, and Outcomes. Ann Emerg Med. 2018 Jul;**72**(1):62-72.e3. doi: 10.1016/j.annemergmed.2017.10.022. Epub 2017 Dec 13. PMID: 29248335.
27. Barco S, Schmidtmann I, Ageno W, Bauersachs RM, Becattini C, Bernardi E, et al; HoT-PE Investigators. Early discharge and home treatment of patients with low-risk pulmonary embolism with the oral factor Xa inhibitor rivaroxaban: an international multicentre single-arm clinical trial. Eur Heart J. 2020 Jan 21;**41**(4):509-518. doi: 10.1093/eurheartj/ehz367. PMID: 31120118.
28. Mastroiacovo D, Dentali F, di Micco P, Maestre A, Jiménez D, Soler S, et al. Rate and duration of hospitalization for acute pulmonary embolism in the real-world clinical practice of different countries: analysis from the RIETE registry. Eur Respir J. 2019 Feb 21;**53**(2):1801677. doi: 10.1183/13993003.01677-2018. PMID: 30578388.
29. Eck RJ, Elling T, Sutton AJ, Wetterslev J, Gluud C, van der Horst ICC, et al. Anticoagulants for thrombosis prophylaxis in acutely ill patients admitted to hospital: systematic review and network meta-analysis. BMJ. 2022 Jul 4;**378**:e070022. doi: 10.1136/bmj-2022-070022. PMID: 35788047; PMCID: PMC9251634.
30. Najjar-Debbiny R, Chazan B, Lobl R, Greene MT, Ratz D, Saint S, et al; Israel IPC Working Group. Healthcare-associated infection prevention and control practices in Israel: results of a national survey. BMC Infect Dis. 2022 Sep 16;**22**(1):739. doi: 10.1186/s12879-022-07721-8. PMID: 36114529; PMCID: PMC9482296.
31. Swan D, Hitchen S, Klok FA, Thachil J. The problem of under-diagnosis and over-diagnosis of pulmonary embolism. Thromb Res. 2019 May;**177**:122-129. doi: 10.1016/j.thromres.2019.03.012. Epub 2019 Mar 14. PMID: 30889517.
32. Barco S, Mahmoudpour SH, Valerio L, Klok FA, Münzel T, Middeldorp S, et al. Trends in mortality related to pulmonary embolism in the European Region, 2000-15: analysis of vital registration data from the WHO Mortality Database. Lancet Respir Med. 2020 Mar;**8**(3):277-287. doi: 10.1016/S2213-2600(19)30354-6. Epub 2019 Oct 12. PMID: 31615719.
33. Middeldorp S, Coppens M, van Haaps TF, Foppen M, Vlaar AP, Müller MCA, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost. 2020 Aug;**18**(8):1995-2002. doi: 10.1111/jth.14888. Epub 2020 Jul 27. PMID: 32369666; PMCID: PMC7497052.
34. Trevisan C, Noale M, Zatti G, Vetrano DL, Maggi S, Sergi G. Hospital length of stay and 30-day readmissions in older people: their association in a 20-year cohort study in Italy. BMC Geriatr. 2023 Mar 21;**23**(1):154. doi: 10.1186/s12877-023-03884-4. PMID: 36941535; PMCID: PMC10029164.
35. Jiménez D, de Miguel-Díez J, Guijarro R, Trujillo-Santos J, Otero R, Barba R, et al; RIETE Investigators. Trends in the Management and Outcomes of Acute Pulmonary Embolism: Analysis From the RIETE Registry. J Am Coll Cardiol. 2016 Jan 19;**67**(2):162-170. doi: 10.1016/j.jacc.2015.10.060. PMID: 26791063.
36. Lauque D, Khalemsky A, Boudi Z, Östlundh L, Xu C, Alsabri M, et al. Length-of-Stay in the Emergency Department and In-Hospital Mortality: A Systematic Review and Meta-Analysis. J Clin Med. 2022 Dec 21;**12**(1):32. doi: 10.3390/jcm12010032. PMID: 36614835; PMCID: PMC9821325.
37. Douketis JD, Gu CS, Schulman S, Ghirarduzzi A, Pengo V, Prandoni P. The risk for fatal pulmonary embolism after discontinuing anticoagulant therapy for venous thromboembolism. Ann Intern Med. 2007 Dec 4;**147**(11):766-74. doi: 10.7326/0003-4819-147-11-200712040-00007. PMID: 18056660.
38. Douketis JD, Kearon C, Bates S, Duku EK, Ginsberg JS. Risk of fatal pulmonary embolism in patients with treated venous thromboembolism. JAMA. 1998 Feb 11;**279**(6):458-62. doi: 10.1001/jama.279.6.458. PMID: 9466640.
39. Kearon C. Natural history of venous thromboembolism. Circulation. 2003 Jun 17;**107**(23 Suppl 1):122-30. doi: 10.1161/01.CIR.0000078464.82671.78. PMID: 12814982.
40. Carson JL, Kelley MA, Duff A, Weg JG, Fulkerson WJ, Palevsky HI, et al. The clinical course of pulmonary embolism. N Engl J Med. 1992 May 7;**326**(19):1240-5. doi: 42.10.1056/NEJM199205073261902. PMID: 1560799.
41. Ng AC, Chow V, Yong AS, Chung T, Kritharides L. Prognostic impact of the Charlson comorbidity index on mortality following acute pulmonary embolism. Respiration. 2013;**85**(5):408-16. doi: 10.1159/000342024. Epub 2012 Nov 10. PMID: 23147354.
42. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet. 1999 Apr 24;**353**(9162):1386-9. doi: 10.1016/s0140-6736-(98)07534-5. PMID: 10227218.
43. Heckbert SR, Kooperberg C, Safford MM, Psaty BM, Hsia J, McTiernan A, et al. Comparison of Self-Report, Hospital Discharge Codes, and Adjudication of Cardiovascular Events in the Women's Health Initiative. Am J Epidemiol. 2004 Dec 15; **160**(12):1152-8. doi: 10.1093/aje/kwh314. PMID: 15583367.

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