Time trends and case fatality rate of in-hospital treated pulmonary embolism during 11 years of observation in Northwestern Italy

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Summary
Pulmonary embolism (PE) is a common disorder with high mortality and morbidity rates. However, population-based information on its incidence and prognosis remains limited. We conducted a large epidemiology study collecting data on hospitalisation for PE (from 2002 to 2012) in a population of about 13 million people in Northwestern Italy. Patients were identified using the ICD-9-CM codes: 415.11, 415.19; gender and age specific incidence rate of PE during the study period was estimated using the resident population for each year of the study. Furthermore, time trends in the in-hospital PE-related mortality and case fatality rate were calculated. Results were adjusted for possible confounders. A total of 60,853 patients (mean age 72.8 years, ± 14.1, 59.6 % females) with PE were included; the overall crude incidence rate for the entire study period was 55.4 and 40.6 events per year per 100,000 inhabitants for women and men, respectively (p < 0.001). However, this difference was completely lost after standardisation for age. The incidence of PE significantly increased in both genders during the study period. In-hospital case fatality rate significantly decreased throughout the study period (p < 0.001) in women (from 15.6 % to 10.2 %) and in men (from 17.6 % to 10.1 %). The observed decrease of the in-hospital case-fatality throughout the study period remained significant also after adjustment for possible confounders. In conclusion, time trends over an 11-year period show an increasing incidence of PE, but a significant reduction in mortality during hospitalisation. Reduction in the case fatality rate remained significant after adjustment for these possible confounders.

Keywords
Venous thromboembolism, pulmonary embolism, mortality, prognosis

Introduction
Pulmonary embolism (PE) is a common disorder with high mortality and morbidity rates (1). Over the last years, there have been marked advances in diagnostic and therapeutic strategies to manage this condition more effectively (2). However, population-based information on the incidence and prognosis of the disease is more limited (3, 4). Most of the epidemiological studies are old and results of these studies were not adjusted for patient characteristics or concomitant diseases. Furthermore, most of available data originate from studies performed either in the United States or in Northern Europe (3–5). Conversely, only few studies evaluated the incidence and prognosis of PE in the southern European countries (6) and possible epidemiological differences among populations, due to different prevalence of predisposing conditions, cannot be excluded.

Recent studies suggest a slight increase in the diagnosis of PE over time (6, 7), while data on trends of PE-related mortality are conflicting (6, 8–10). These discrepancies are likely due to the fact that most of these studies did not distinguish between the first event and recurrence and data were not adjusted for patient characteristics and concomitant diseases. Furthermore, thanks to an improvement of diagnostic techniques, an increased diagnosis of less severe events could not be excluded.

Thus, to provide robust and contemporary data on the epidemiology and prognosis of PE, we aimed to assess the incidence and in-hospital total mortality and case fatality rate of PE in Northwestern Italy over a time period of 11 years (2002–2012), using data recorded in the Lombardy and Piedmont Regions hospital discharge databases, covering a population of more than 13 millions inhabitants. The effect of individual characteristics and the presence of other relevant comorbidities were also investigated. Finally, we provided crude and adjusted data on the time changes in the incidence and inhospital case fatality rate of PE over the study period.

Material and methods
Patient selection and eligibility
The study was conducted in adherence to the Declaration of Helsinki. Information about all hospital admissions for PE between
January 1, 2000 and December 31, 2012 in the Lombardy and Piedmont regions, Italy (total population: 13 million), were obtained from the hospital discharge databases provided by the two Regional Centers for Health Statistics.

PE patients were identified using the following International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes: 415.11, 415.19.

Only patients with a primary or secondary discharge diagnosis (discharge of hospital or death) (on a total of six reported diagnoses and conditions) corresponding to the selected codes were included, and the following variables were collected: gender, date of birth, date and hour of hospital admission and discharge, department of admission and discharge, vital status at discharge, duration of the hospitalisation (in days), primary and up to five secondary discharge diagnoses, and in-hospital diagnostic procedures primary and up to four secondary procedure codes.

Patients names, address, or other potential identifiers were not reported in the database provided by the Regional Centres for Health Statistics to comply with the national law dispositions in terms of privacy. An ad hoc developed identification number was used for each patient, allowing us to identify repetitive hospital admissions.

To distinguish new cases (incident events) from recurrences, we collected only the first hospitalisation with a diagnosis of PE, during the entire study period. Because we did not have information before 2000, we excluded all the events occurred during the first biennium of observation (2000–01). Furthermore, hospitalised patients with a diagnosis of PE and a previous hospital admission for PE in 2000 and in 2001 were not considered as incident cases, and were excluded from the analysis. Thus, only patients with a first episode of PE who were admitted to the hospital between January 1, 2002 and December 31, 2012 were included in this study. Finally, patients admitted to one hospital and then transferred to another hospital were counted as a single event (with the date of hospitalisation referring to the admission hospital and final diagnosis made by the discharging hospital).

Because we performed age-stratified analysis, we excluded patients younger than 20 years old at onset (<0.3% of total cases) to obtain stable and not null age specific rates.

### Incidence, case fatality and mortality rate

We calculated the whole population and gender-specific incidence rate (in terms of 100,000 inhabitants) for the entire population and for five-year age categories dividing incident cases by the corresponding population group according to the National Institute of Statistics.

Concordantly, for each calendar year, specific rates were calculated based on the sum of inhabitants in the Lombardy and Piedmont region, for each year.

Age-standardised incidence rate were calculated based on the total Italian population.

In-hospital case fatality was calculated as the proportion of fatal cases (patients who died during hospitalisation) on the total of incident cases.

### Co-morbidity index

The overall comorbid status of each patient was assessed using the Charlson Comorbidity Index (CCI) (11, 12), which is a summation score based on 17 medical conditions with varying assigned weights (non-age adjusted). A value of 0 indicates no comorbidity, while higher values represent an increasing burden of comorbid illnesses. A score of 1 is given to each of the following conditions: myocardial infarction, cardiac failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, mild liver disease, and diabetes (without organ damage); a score of 2 for hemiplegia, moderate to severe renal disease, any tumour (within the last 5 years), lymphoma, leukaemia, and diabetes with organ damage; a score of 3 for moderate to severe liver disease; and a score of 6 for meta-static solid tumour and acquired immunodeficiency syndrome.

In our analysis, we divided patients in five co-morbidity categories according to their CCI (0 as lowest risk categories, 1, 2, 3, 4 or more)

### Statistical analysis

Baseline patient characteristics were expressed by means of descriptive statistics. Continuous variables were reported as mean with standard deviation (SD) or as median with interquartile range (IQR), categorical variables were reported as counts and percentages. The time trend of the study variables was compared.

Incidence and mortality rates were calculated for both genders and by dividing the population in 11 years of onset (2002–2012) and in 13 5-years age categories (from 20 up to 80 years, last category > 80).

To assess the effect of different age distribution across genders, we estimated the standardised incidence rates using direct standardisation based on the Italian general population.

Mean annual changes with relative 95% confidence interval (CI) over the study period in incidence rates were calculated for both genders using regression models after log transformation of standardised rate, and weighting each annual rate according to the number of incident cases. In-hospital case fatality (proportion of fatal cases on the total hospitalised) was calculated for both genders in each study year. Logistic regression models adjusted for sex and age were designed to analyse variations of case fatality during the study period. Multiple logistic regression models were used also to assess the effect of CCI on case fatality and to control for the effect of CCI and other covariates (age and gender) in observed time trends of case fatality.

Logistic regression models were also designed to investigate possible variability in the period 2002–2012, in the proportion of cases with a specific diagnostic procedure and with a given level of CCI (i.e. ≥ 4).

As a sensitivity analysis, we repeated rate and trend estimates using only patients with a PE diagnosis in the first diagnostic code (excluding patients with PE code reported in the second position).

Statistical significance was set at two-tailed p<0.05. All estimates were made using Stata version 11.2 (StataCorp, College Station, TX, USA)
Results

Patients selection and baseline characteristics

During the eleven years of the study period (2002–2012), we collected a total of 68,627 events (hospital admissions) with a primary or secondary discharge code of PE. Of these, 6,585 patients had two or more hospitalisations for PE during the study period. After the exclusion of patients with a previous hospitalisation for PE during the years 2000 and 2001 and of PE recurrences, a total of 60,853 patients with a first event of PE were included in the analysis.

Baseline characteristics of patients are summarised in Table 1. Briefly, the mean age was 72.8 years, (SD 14.1, median 76), and 36,279 patients (59.6 %) were females. Mean duration of hospitalisation was 14.02 days (SD 11.35 days) during the study period, with only 22.8 % of women and 24.7 % of men hospitalised for less than seven days. Mean CCI was 0.83 (SD 1.28), and it was significantly higher in men (0.95 vs 0.75, p< 0.001); 2,939 patients had a CCI > 4 (4.85 %, 3.89 % in women and 6.25 % in men, p< 0.001). A total of 6,942 patients (11.4 % of the whole population) had a concomitant cancer.

PE incidence and characteristics during the study period

The overall crude incidence rate for the entire study period was 55.4 and 40.6 events per 100,000 inhabitants, for women and men, respectively (p < 0.001). A total of 8,071 patients died during hospitalisation for an in-hospital case fatality rate of 13.3 %. The mean case fatality rate was significantly higher in male patients compared to female patients (13.83 % vs 12.95 %, p 0.002).

Table 1: Baseline characteristics of patients.

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>2002 cases</th>
<th>2012 cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender, n (%)</td>
<td>36,253 (59.6%)</td>
<td>2,805 (60.5%)</td>
<td>3,762 (59.7%)</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>24,560 (40.4%)</td>
<td>1,830 (39.5%)</td>
<td>2,545 (40.4%)</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>72.8 (+ 14.1)</td>
<td>72.0 (+14.0)</td>
<td>72.8 (+14.8)</td>
</tr>
<tr>
<td>Surgical patients, n (%)</td>
<td>2,410 (43,992 (5.5%))</td>
<td>193 (3,355 (5.8%))</td>
<td>262 (4,563 (5.8%))</td>
</tr>
<tr>
<td>Cancer patients, n (%)</td>
<td>6,942 (11.4%)</td>
<td>512 (11.1%)</td>
<td>716 (11.4%)</td>
</tr>
<tr>
<td>CCI&gt;4, n(%)</td>
<td>3,227 (5.3%)</td>
<td>184 (4.0%)</td>
<td>304 (4.8%)</td>
</tr>
<tr>
<td>Median hospitalisation, days (IQR)</td>
<td>12 (8–17)</td>
<td>13 (8–19)</td>
<td>11 (7–16)</td>
</tr>
<tr>
<td>CTPA, n (%)</td>
<td>27,865 (45.7%)</td>
<td>1,016 (22.0%)</td>
<td>3,678 (58.5%)</td>
</tr>
<tr>
<td>Lung Scintigraphy</td>
<td>9,221 (15.1%)</td>
<td>1,500 (32.4%)</td>
<td>314 (5.0%)</td>
</tr>
</tbody>
</table>

SD, standard deviation; CCI, Charlson comorbidity index; IQR, interquartile range; CTPA, computed tomography pulmonary angiography.

Figure 1: Age-specific incidence proportions and distribution according to sex.
From 2002 to 2012, crude PE incidence significantly increased in both genders, from 48.8 to 62.0 per 100,000 inhabitants in women and from 34.9 to 45.8 in men (p < 0.05).

▶ Figure 1 shows age-specific incidence proportions and distribution according to sex. As expected PE incidence increased significantly with age categories.

Women appeared to have a higher crude PE incidence compared to men during all the 11 years of observation of the study (p < 0.001 for all the years of the study). However, this difference completely disappeared when the incidence rates for the two populations were standardised for age (▶ Figure 2).

Both genders showed a significant increase in age-standardised incidence rates over time, but the mean observed annual change was higher in men than in women (+1.2 %, 95 %CI: 0.4 %, 1.9 % vs +0.6 %, 95 %CI 0.1 %, 1.9 %, respectively).

Mean CCI and the proportion of patients with a CCI > 4 was higher in 2012 than in 2002 (in details 4.83 % vs 3.98 %), but a clear increasing trend during the study period was not detected (p for trend n.s.). Similarly, the proportion of PE patients who had cancer was not significantly changed throughout the study period (11.1 % in 2002 to 11.4 % in 2012).

Mean length of hospital stay significantly decreased over the study period, being 15.2 days in 2002 (SD 12.7) and 12.9 (SD 9.2) in 2012 (p< 0.001).

**In-hospital mortality and case fatality rate**

In-hospital mortality rates significantly decreased during the study period (from 7.6 to 6.6 per 100,000 inhabitants in women and from 6.0 to 4.8 per 100,000 inhabitants in men; p < 0.001) (see Suppl. Material, available online at www.thrombosis-online.com). In-hospital PE case fatality rate (the proportion of case who died during hospitalisation) significantly decreased throughout the study period in both genders; from 15.6 % in 2002 to 10.2 % in 2012 (p < 0.001) in women and from 17.6 % in 2002 to 10.1 % in 2012 in men. The temporal trend was more pronounced in men, with a similar case fatality between genders in the last years of observation (▶ Figure 3). The temporal trend for reduction in the case fatality rate appeared similar during the whole study period (▶ Figure 3) and we obtained a similar trend for reduction when we dichotomised our results in until 2008 and from 2009 onwards (p = n.s.).

At the univariate analysis, age, gender, presence of cancer and CCI were all significantly associated with an increased risk of inhospital case fatality. In particular, the case fatality rate increased from 10.0 % in patients with CCI = 0 to 24.3 % in patients with CCI ≥ 4 (p< 0.001). At the multivariate analysis, the following variables remained significantly associated with case fatality: age (odds ratio [OR] 1.038, 95 %CI 1.036–1.041), male sex (OR 1.210, 95 %CI 1.151–1.271), CCI ≥ 4 (OR 3.084 95 %CI 2.810–3.385) (▶ Table 2).

The presence of cancer was not included in the multivariate model since cancer is an item of the CCI.

The observed decrease in the in-hospital case-fatality throughout the study period remained significant also after adjustment for these possible confounders (average OR for one year: 0.952, 95 %CI: 0.943–0.962; p< 0.001).

**CTPA use during the study period**

Finally, when we analysed diagnostic procedures, we observed a significant increase in the use of computed tomography pulmonary angiography (CTPA) (reported in one of the 6 possible procedure codes) (from 22.0 % in 2002 to 58.5 % p< 0.001) and a
decrease in the use of lung scintigraphy throughout the study period (from 32.4% to 5.0% in 2012, respectively, p<0.001). The increased use of CTPA was significantly associated with a lower mortality rate at univariate analysis (OR=0.31, 95%CI 0.29–0.32). Multivariate analysis including all the other potential prognostic risk factors confirmed a significant inverse association between the use of CTPA and in-hospital mortality (adjOR=0.33, 95%CI=0.31–0.35). The time trend in the reduction of case fatality rate of PE remained evident and statistically significant, although reduced, after including the use of CTPA in the multivariate model, (adjOR per year: 0.987, 95%CI: 0.980–0.996; p=0.001).

As a sensitivity analysis, we excluded patients with secondary discharge diagnosis of PE obtaining similar results (data not shown).

**Discussion**

According to the result of our large study, the observed incidence of PE in Northwestern Italy during the period between 2002 and 2012 was considerable and tended to increase over the time. The case fatality rate of this disease is substantial, but tends to decline during the period of observation. Furthermore, mean duration of hospitalisation during the study period was substantial but significantly decreased over the time. These trends from Southern Europe are in agreement with findings of recent studies from US populations (5).

The observed trends in the incidence and case fatality of PE have a number of possible explanations. On the one hand, the increased number of hospitalisations for PE are likely due to continuous improvement in diagnostic strategies, to a greater awareness of PE among clinicians, but, in part, also to a higher rate of incidental diagnoses when diagnostic tests are performed for reasons other than the suspicion of PE (13). Thus, the possibility of an information bias due to an increased use of CTPA could not be excluded. On the other hand, and more importantly, the reduced case fatality rate is possibly due to an increasing diagnosis of PE patients with a less severe clinical presentation, as also suggested by the finding that diagnoses by means of CTPA were found to be associated with reduced in-hospital mortality. However, case fatality resulted significantly reduced during the study period also independently from the higher use of CTPA. Thus, rate a more

**Figure 3**: Temporal trend of case fatality rate in the 11 years of observation of the study.

| Table 2: Independent predictors of in-hospital death at multivariate analysis (including age, gender and Charlson comorbidity index). |
|-------------------------------------------------|-------|-----------------|
| **Age (per increasing year)** | 1.038 | 1.036–1.040 |
| **Male gender** | 1.21 | 1.15–1.27 |
| **CCI = 1** (12,174 patients) | 1.37 | 1.30–1.47 |
| **CCI = 2** (7,144 patients) | 1.85 | 1.73–1.99 |
| **CCI = 3** (3,150 patients) | 2.29 | 2.09–0.52 |
| **CCI ≥ 4** (3,227 patients) | 3.08 | 2.81–3.39 |

*Using CCI=0 (35,252 patients) as the reference. CCI, Charlson comorbidity index; pts, patients.
timely diagnosis of the disease and to continuous improvement in the therapeutic management may have contributed to this result (14).

As expected, age and CCI were significantly associated with an increased mortality rate, whereas female gender was associated with a higher incidence of PE, but with significantly less fatalities. These results were in general in agreement with findings of previous studies in this setting (6, 12, 15). The presence of comorbidities may influence the short and long-term outcome of patients with PE (12), and CCI is a score validated to assess the presence of comorbidities in hospitalised patients using the diagnostic codes of discharge databases. Older patients may have worse baseline clinical conditions independently by the severity of PE and by the presence of other comorbidities registered with the CCI. The role of sex as a prognostic factor is more controversial. Results of several prospective studies have suggested that, in acute PE, male sex is associated with a worse prognosis in comparison to female sex (16, 17). Conversely, recent studies based on diagnostic codes have suggested that female sex was independently associated with higher in-hospital mortality in patients with acute PE (6).

Case fatality rate of PE appeared higher in our population in comparison to the results of recent randomised controlled trials on the treatment of PE (18, 19). Differences in the baseline characteristics (e.g. age) and in the rate of some important comorbidities (e.g. active cancer) may explain these results. Furthermore, although in our study we have no information on PE treated on out-patients basis, these constitute only a small part of the population since, in Italy, the vast majority of patients are still hospitalised for the treatment of acute PE.

Our data may have some implications for clinical practice since a better knowledge on the incidence of PE and on its short-term prognosis may contribute to an improvement in the management of these patients including a better definition of the patients potentially at risk for PE (20–23) and an increased use of antithrombotic prophylaxis in these patients (24, 25).

What is known about this topic?
• Pulmonary embolism (PE) is a common disorder with high mortality and morbidity rates.
• Most of available data originate from studies performed either in the United States or in Northern Europe.

What does this paper add?
• According to the result of our large study, the observed incidence of PE in Northwestern Italy during the period between 2002 and 2012 was considerable and tended to increase over the time.
• The case fatality rate of this disease is substantial, but tends to decline during the period of observation.
• Age and Charlson Comorbidity Index were significantly associated with an increased mortality rate, whereas female gender was associated with a higher incidence of PE, but with significantly less fatalities.

Our study has strengths and limitations. Strengths include the very large sample of the analysed population (> 13 million) and the long period of observation (11 years). Furthermore, differently from previous studies, we tried to only select patients with a first episode of PE to avoid the potential bias of including patients with PE recurrence. The principal limitation of our study is related to the method used to identify patients with PE. ICD-9-CM diagnosis codes may have a low sensitivity and specificity in the identification of patients hospitalised for this disease. However, only patients with the first and second codes of PE were selected to avoid potential false positive diagnoses of this disease. Moreover, previous studies have demonstrated a good accuracy of discharge codes and, in particular, of these codes for the identification of patients with objectively confirmed acute PE (26, 27). Another important limitation concerns the inability of hospital discharge diagnostic codes to distinguish between PE developed during hospitalisation from PE developed prior to hospital admission. Thus, we cannot provide any information on the setting of the origin of PE. Last, we cannot reliably exclude that a proportion of our population was represented by patients with incidentally detected asymptomatic PE, a subgroup of patients that may have a different short-term prognosis in comparison to patients with acute symptomatic PE. However, the majority of these events occur in cancer patients undergoing staging of their disease, and some of these patients are actually treated at home. Furthermore, according to the accepted methodology for ICD codes, asymptomatic findings should never be coded as a first or second diagnosis. Thus, it is unlikely that inclusion of this group of patients may have significantly influenced our results.

In conclusion, the results of our study confirm a not negligible incidence of PE in the Italian population. During the 11 years of observation the incidence of PE appeared to increase, while the in-hospital case fatality rate of PE tends to decrease. Older age, male sex, and CCI were independent predictors of in-hospital mortality. The increased incidence of PE and its decreased case fatality rate throughout the study period may be in part explained by the increased use of CTPA during time.

Conflicts of interest
None declared.

References