Pulmonary embolism and gender: an observational study

Embolia polmonare e genere: uno studio osservazionale

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Summary

Pulmonary Embolism (PE) is a major cause of mortality, morbidity and hospitalization in Europe. Few studies have highlighted sex differences in PE, in particular with regard to hospitalization, outcomes, treatment, complication and mortality.

The aim of this study is to analyze the gender differences in patients hospitalized with a principal diagnosis of PE. This is a retrospective population-based cohort study. Data for all patients discharged with a principal diagnosis of PE (ICD-9 415.1) by Apulian hospitals between 2010 and 2016 were retrieved from the National Hospital Discharge Register Database.

4,795 patients were discharged with a principal diagnosis of PE during the inclusion period. The majority of which were females (2,762; 57.6%). Mean age was significantly higher in women (73.0 *vs* 67.9, $p < 0.001$). Females showed a higher prevalence of hypertensive heart disease (41.1% *vs* 32.9%, $p < 0.001$), arrhythmia (16.3% *vs* 13.9%, $p = 0.023$), diabetes mellitus (14.8% *vs* 11.7%, $p = 0.002$) and obesity (6.6% *vs* 3.5%, $p < 0.001$) and a lower prevalence of chronic obstructive pulmonary disease (10.0% *vs* 18.0, $p < 0.001$), lung failure (11.1% *vs* 13.7%, $p = 0.006$) and cancer (15.3% *vs* 22.9%, $p < 0.001$). The overall incidence rate (F: 17.4 *vs* M: 13.8; AR = +3.6; $p < 0.001$) and the overall mortality rate (F: 1.3 *vs* M: 0.9; AR = +0.3; $p < 0.001$) were higher in women compared to men. The overall case fatality rate was not different between women and men (F: 6.4 *vs* M: 6.4; AR = 0.0; $p = 0.92$).

Findings from our study showed significant sex disparities for age of hospitalization, comorbidities distribution, incidence and mortality, but no differences in the fatality of the disease. Further studies are needed to identify the determinants and consequences of the gender differences in PE.

Key words

Pulmonary embolism • Gender differences • Gender medicine • Venous thromboembolism • Deep vein thrombosis

Riassunto

L'Embolia Polmonare (EP) costituisce un rilevante problema in termini di mortalità, morbilità e ospedalizzazioni in Europa, ma pochi studi hanno analizzato le differenze di genere in questa patologia, in particolare per quanto riguarda ospedalizzazione, esito clinico, terapia, complicanze e mortalità.

Lo scopo dello studio è analizzare le differenze di genere nei pazienti ospedalizzati con una diagnosi principale di EP. Lo studio è di coorte retrospettivo su popolazione. I dati di tutti i pazienti dimessi da ospedali pugliesi con una diagnosi principale di EP (ICD-9 415.1) fra il 2010 e il 2016 sono stati estratti dal registro nazionale delle schede di dimissione ospedaliera.

Nel periodo di inclusione, 4.795 pazienti sono stati dimessi con diagnosi principale di EP, la maggior parte dei quali è costituita da donne (2.762; 57,6%). L'età media è significativamente maggiore nelle donne (73,0 vs 67,9, $p < 0,001$). Le donne mostrano una più alta prevalenza di cardiopatia ipertensiva (41,1% vs 32,9%, $p < 0,001$), aritmia (16,3% vs 13,9%, $p = 0,023$), diabete mellito (14,8% vs 11,7%, $p = 0,002$) e obesità (6,6% vs 3,5%, $p < 0,001$) e una più bassa prevalenza di broncopneumopatia cronica ostruttiva (10,0% vs 18,0, $p < 0,001$), insufficienza respiratoria (11,1% vs 13,7%, $p = 0,006$) e cancro (15,3% vs 22,9%, $p < 0,001$).

Il tasso di incidenza (F: 17,4 vs M: 13,8; AR = +3,6; $p < 0,001$) e il tasso di mortalità complessivi (F: 1,3 vs M: 0,9; AR = +0,3; $p < 0,001$) sono più alti nelle donne rispetto agli uomini. Il tasso di fatalità complessivo non mostra differenze fra uomo e donna (F: 6,4 vs M: 6,4; AR = 0,0; $p = 0,92$).

I risultati del nostro studio mostrano differenze significative in termini di età di ospedalizzazione, comorbilità, incidenza e mortalità, ma nessuna differenza in termini di fatalità della malattia. Ulteriori studi sono necessari per identificare i determinanti e le conseguenze delle differenze di genere nell'EP.

Parole chiave

Embolia polmonare • Differenze di genere • Medicina di genere • Tromboembolismo venoso • Trombosi venosa profonda

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Introduction

Venous Thromboembolism (VTE) encompasses Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE). It is the third most frequent cardiovascular disease with an overall annual incidence of 100/200 per 100,000 habitants [1]. Acute PE is the most serious clinical presentation of VTE. The epidemiology of PE is difficult to determine because it may remain asymptomatic. Its diagnosis may be an incidental finding [2]. Overall, PE is a major cause of mortality, morbidity and hospitalization in Europe. As estimated by an epidemiological model, over 317.000 deaths were related to VTE in six countries of the European Union (with a total population of 454.4 million) in 2004 [2]. Of these cases, 34% presented with sudden fatal PE and 59% were deaths resulting from PE that remained undiagnosed during life. In this epidemiological model, only 7% of the patients who died early were correctly diagnosed with PE before death.

Males older than 40 years are at increased risk of PE and the risk approximately doubles with each subsequent decade, compared with female patients.

Males older than 40 years are at increased risk and the risk approximately doubles with each subsequent decade, compared with female patients [3]. There is an extensive collection of predisposing environmental and genetic factors. In women in reproductive age, oral contraception is the most frequent predisposing factor for VTE [4]. When occurring during pregnancy, VTE is a major cause of maternal mortality [4]. The risk is highest in the third trimester of pregnancy and over the 6 weeks of the postpartum period [5]. Sex differences in PE have been analyzed in few studies. Agarwal et al. [6] assessed differences in outcomes, treatment and complications between female and male patients admitted for PE. The authors found higher complication and adverse event rates in females [6]. Nevertheless, current data on sex disparities in hospitalization rates of VTE and mortality are limited. Two studies observed a higher hospitalization rate among females [7 8], whereas one study did not find a difference between sexes [9].

The aim of the study is to analyze the gender differences in patients hospitalized with a principal diagnosis of PE with regard to patients characteristics, incidence, fatality and mortality.

The aim of this study is to analyze the gender differences in patients hospitalized with a principal diagnosis of PE with regard to patients characteristics, incidence, fatality and mortality.

Materials and methods

This is a retrospective population-based cohort study. Data for all patients discharged with a principal diagnosis of PE (ICD-9 415.1) by Apulian hospitals between January 1, 2010 and December 31, 2016 were retrieved from the National Hospital Discharge Register Database. Comorbidities were recorded through the corresponding ICD-9 codes: thrombophlebitis (451 and 453), Chronic Obstructive Pulmonary Disease (COPD) (491, 492, 494), hypertensive heart disease (401, 402), heart failure (428), respiratory failure (518), arrhythmias (427), diabetes mellitus (250), obesity (278.0), fractures (800-829), cancer (140-239).

In order to acquire data about general Apulian population, we relied on the data of Italian Institute for Statistics (ISTAT: www.demo.istat.it). Statistical analysis was performed using R 3.5.1 (released on 2018-07-02). Categorical variables were reported as absolute and relative frequencies and compared through Pearson χ^2 test. Continuous variables were reported as mean and SD and compared through t test. Incidence Rate (IR) was calculated as number of patients discharged with a principal diagnosis of PE on the Apulian population (per 100,000); we considered only the first hospitalization for PE. Mortality Rate (MR) was calculated as number of patients discharged dead with a principal diagnosis of PE on the Apulian population (per 100,000). Case Fatality Rate (CFR) was calculated as number of dead patients on the total number of patients discharged with PE (per 100). Attributable Rate (AR) was calculated as the difference between females and males specific rates. Statistical significance α was fixed to 0.05.

Results

Table I shows baseline characteristics of patients. 4,795 patients were discharged from Apulian hospital with a principal diagnosis of PE during the inclusion period.

The majority of patients was females, aged > 65 years and at first hospitalization for PE.

The majority of our patients was females (2,762; 57.6%), aged > 65 years (3,417; 71.3%) and at first hospitalization for PE (4,456; 92.9%). The mean age of patients was 70.8 ± 1.3 years. The more frequent comorbidities were hypertensive heart disease (1,804; 37.6%) and thrombophlebitis (1,269; 26.5%).

Table II shows baseline characteristics of patients by gender. Compared to men, mean age was significantly higher in women (73.0 *vs* 67.9, $p < 0.001$), with a higher prevalence of patients aged > 65 years in women (77.8% *vs* 62.4%, $p < 0.001$). As far as comorbidities distribution is concerned, females showed an higher prevalence of hypertensive heart disease

Table I. Baseline characteristics of patients discharged with a principal diagnosis of pulmonary embolism (Puglia 2010-16). Data are n (%) or mean (± SD).

Total (n = 4,795)	
Female gender	2,762 (57.6)
Age	70.8 (±1.3)
Age groups	..
< 41	235 (4.9)
41-65	1,143 (23.8)
65	3,417 (71.3)
Year	..
2010	627 (13.1)
2011	618 (12.9)
2012	572 (11.9)
2013	694 (14.5)
2014	675 (14.1)
2015	802 (16.7)
2016	807 (16.8)
Comorbidities	..
Thrombophlebitis	1,269 (26.5)
COPD	642 (13.4)
Hypertensive heart disease	1,804 (37.6)
Heart failure	254 (5.3)
Lung failure	585 (12.2)
Arrhythmia	731 (15.2)
Diabetes	647 (13.5)
Obesity	255 (5.3)
Fracture	101 (2.1)
Cancer	889 (18.5)
First hospitalization	4,456 (92.9)

(41.1% *vs* 32.9%, p < 0.001), arrhythmia (16.3% *vs* 13.9%, p = 0.023), diabetes mellitus (14.8% *vs* 11.7%, p = 0.002) and obesity (6.6% *vs* 3.5%, p < 0.001) and a lower prevalence of COPD (10.0% *vs* 18.0, p < 0.001), lung failure (11.1% *vs* 13.7%, p = 0.006) and cancer (15.3% *vs* 22.9%, p < 0.001).

The overall incidence of PE was higher in women compared to men and this difference is constant among years.

Table III shows incidence rate (per 100,000) of PE by gender and years of discharge. The overall incidence was higher in women compared to men (17.4 *vs* 13.8; AR = +3.6; p < 0.001) and this difference is constant among years (p < 0.001).

The overall case fatality rate was not different between women and men.

Table IV shows case fatality rate (per 100) of PE by gender and years of discharge. The overall case fatality rate was not different between women and men (6.4 *vs* 6.4; AR = 0.0; p = 0.92). There were no differences in the studied years (p > 0.05), except for 2010, in which the fatality rate was lower in women compared to men (3.8 *vs* 8.5; AR = -4.7; p = 0.013),

Table II. Baseline characteristics of patients discharged with a principal diagnosis of pulmonary embolism by gender (Puglia 2010-16). Data are n (%) or mean (±SD). P values are from $\chi 2$ test and t-test.

	Males (n = 2,033)	**Females (n = 2,762)**	**p**
Age	67.9 (± 1.1)	73.0 (± 1.0)	< 0.001
Age groups	..	..	< 0.001
< 41	119 (5.8)	116 (4.2)	..
41-65	646 (31.8)	497 (18.0)	..
> 65	1,268 (62.4)	2,149 (77.8)	..
Year	..	..	0.549
2010	259 (12.7)	368 (13.3)	..
2011	278 (13.7)	340 (12.3)	..
2012	237 (11.7)	335 (12.1)	..
2013	288 (14.2)	406 (14.7)	..
2014	284 (14.0)	391 (14.2)	..
2015	327 (16.1)	475 (17.2)	..
2016	360 (17.7)	447 (16.2)	..
Comorbidities	..	..	..
Thrombophlebitis	550 (27.1)	719 (26.0)	0.682
COPD	365 (18.0)	277 (10.0)	< 0.001
Hypertensive heart disease	668 (32.9)	1,136 (41.1)	< 0.001
Heart failure	100 (4.9)	154 (5.6)	0.316
Lung failure	279 (13.7)	306 (11.1)	0.006
Arrhythmia	282 (13.9)	449 (16.3)	0.023
Diabetes	238 (11.7)	409 (14.8)	0.002
Obesity	72 (3.5)	183 (6.6)	< 0.001
Fracture	35 (1.7)	66 (2.4)	0.111
Cancer	466 (22.9)	423 (15.3)	< 0.001
First hospitalization	1,898 (93.4)	2,558 (92.6)	0.285

Table III. Incidence Rate (IR) and Attributable Rate (AR) of hospitalization for pulmonary embolism (Puglia 2010-16).

	Males	Females	F - M	$\chi 2$
	IR per 100,000	IR per 100,000	AR	p
2010	11.9	15.8	+3.9	< 0.001
2011	13.2	15.0	+1.8	< 0.001
2012	11.1	15.3	+4.2	< 0.001
2013	13.9	18.1	+4.2	< 0.001
2014	13.3	16.9	+3.6	< 0.001
2015	15.6	20.9	+5.3	< 0.001
2016	17.1	20.0	+2.9	< 0.001
Overall	13.8	17.4	+3.6	< 0.001

Table IV. Case Fatality Rate (CFR) and Attributable Rate (AR) of hospitalization for pulmonary embolism (Puglia 2010-16).

	Males	Females	F - M	$\chi 2$
	CFR per 100	CFR per 100	AR	p
2010	8.5	3.8	-4.7	0.013
2011	10.8	7.1	-3.7	0.106
2012	5.9	8.4	+2.5	0.260
2013	8.7	7.6	-1.1	0.600
2014	3.2	6.6	+3.4	0.044
2015	3.1	5.5	+2.4	0.108
2016	5.8	6.0	+0.2	0.905l
Overall	6.4	6.4	0.0	0.920

and except for 2014, in which the fatality rate was higher in women compared to men (6.6 *vs* 3.2; AR = +3.4; p = 0.044).

The overall mortality was higher in women compared to men and this difference is constant among years.

Table V shows mortality rate (per 100,000) of PE by gender and years of discharge. The overall mortality was higher in women compared to men (1.3 *vs* 0.9; AR = +0.3; p < 0.001) and this difference is constant among years (p < 0.001).

Discussion

In our study, we found lower rates of hospitalization for acute PE in younger female compared with men, probably because younger women may tend to refuse hospitalization as they have other responsibilities as caregivers [9].

The lower admission rate for younger female could be related to the misinterpretations of the signs and symptoms of PE.

Moreover, the lower admission rate for younger female could be related to the misinterpretations of the signs and symptoms of PE, exchanged for those of anxiety because of the similarity of presentation, especially in lower age groups [10 11]. That could lead to a delay in seeking medical advice or in hospital admission. In particular, sex-specific factors can also have an impact on the characteristics of presenting signs and symptoms [12]. In particular, a recent study showed that women have a higher probability of presenting with unprovoked Isolated Distal Deep Vein Thrombosis

Table V. Mortality Rate (MR) and Attributable Rate (AR) of hospitalization for Pulmonary Embolism.

	Males	Females	F - M	$\chi 2$
	MR per 100,000	MR per 100,000	AR	p
2010	1.1	0.7	-0.4	< 0.001
2011	1.5	1.1	-0.4	< 0.001
2012	0.7	1.3	+0.6	< 0.001
2013	1.3	1.5	+0.2	< 0.001
2014	0.5	1.2	+0.7	< 0.001
2015	0.5	1.2	+0.7	< 0.001
2016	1.1	1.3	+0.2	< 0.001
Overall	0.9	1.2	+0.3	< 0.001

(IDDVT) as compared to men [13]. In other study, it has been reported that in patients with provoked DVT, women aged 55-75 had a higher proportion of IDDVT (and a lower proportion of proximal DVT), whereas men had more IDDVT between 18 and 40 years [14]. In women, it has been reported a correlation between the use of tamoxifen in breast cancer and an increased incidence of VTE. In particular, a Danish population study revealed that women treated with tamoxifen were at a higher risk for developing DVT and PE during the first 2 years after the exposure [15].

Findings from this study show a higher prevalence of certain comorbidities in men, while in female a higher prevalence of diabetes and obesity.

However, findings from our study show a higher prevalence of certain comorbidities in men, for example cancer [16], while in female we observed a higher prevalence of diabetes and obesity. In according to other study [17], we did not found differences in intra-hospital fatality rate between men and women. However, previous studies suggest a high prevalence of PE in patients with episodes of exacerbation of symptoms (ECOPD) [18]. In particular, Tillie-Leblond et al. evaluated PE with a frequency of 25% in patients with ECOPD [19]. To this regard, for patients with ECOPD, some PE might be clinically unimportant and the risk of submitting a patient with a clinically insignificant PE to anticoagulant treatment might outweigh the benefit [20]. No study has reported gender differences on PE patients with ECOPD.

Our study was retrospective and therefore limited by potential bias, mainly related to the administrative nature of the data source. Furthermore, we were unable to ascertain how some risk factors for thrombosis may impact thrombosis severity in a different way between men and female, such as smoking, pregnancy [21], oral contraceptives [22] or hormone replacement therapy use [23].

Administrative data does not provide information about medications, prevalence of ECOPD in patients with PE, vital signs and the severity of the condition, which could help interpreting the differences.

In addition, administrative data does not provide information about medications, prevalence of ECOPD in patients with PE, vital signs and the severity of the condition, which could help interpreting the differences. However, we used a validated case-defining criteria using the ICD-9 codes for PE as well as diagnostic procedures codes that has been established in previous studies [24].

Conclusion

Findings from our study showed significant sex disparities for age of hospitalization, comorbidities distribution, incidence and mortality, but no differences in the fatality of the disease.

The study showed significant sex disparities for age of hospitalization, comorbidities distribution, incidence and mortality, but no differences in the fatality of the disease.

Further studies are needed to identify the determinants and the consequences of gender differences in PE.

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Gli Autori dichiarano di non avere alcun conflitto di interesse con l'argomento trattato nell'articolo.