Gender differences in chronic obstructive pulmonary disease: an analysis of hospitalization indicators

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ABSTRACT

Compared to the last two decades, an increase in chronic obstructive pulmonary disease (COPD) prevalence, morbidity, mortality and disability has clearly emerged among women both in Europe and in all other countries. Despite this evidence, in the international guidelines for COPD there are no sex-specific recommendations. The aim of this study is to evaluate gender differences in patients hospitalized for COPD in Puglia (Italy), with regard to number of admissions, mean age, average length of stay in hospital (ALOS), hospital mortality, re-hospitalization and presence of comorbidities. To identify COPD hospitalized patients, we relied on the Puglia Hospital Discharge Register Database. We included all patients discharged with principal diagnosis of COPD with or without exacerbation (respectively ICD-9-CM codes 491.21 and 491.20) between 2005 and 2016. There has been an increase in the proportion of women's hospitalizations for COPD, from 2005 [31.9%, 95% confidence interval (CI) 31.1-32.7] to 2016 (37.9%, 95%CI 36.0-40.0). Women need longer hospitalization and in 2016 the proportion of women's re-hospitalization was greater compared to men. Despite these data, women are less treated with respiratory therapy (ICD-9-CM 93.9x) than men in all the examined years and wards. The prevalence of most common comorbidities is higher among women. The number of COPD hospitalized patients had been reduced in Puglia between 2005 and 2016, with an important increase of female COPD patients, female average age, ALOS and re-hospitalization. Women are treated less and have more comorbidities with a negative impact on clinical progression of COPD, survival and quality of life.

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Key words: Chronic obstructive pulmonary disease; gender differences; hospitalization.

Contributions: IA edited the manuscript and revised it critically for intellectual content. MSG, FP and OVG contributed to the data analysis and interpretation. CP, AF and AMM supervised and revised the study. All authors read and approved the final manuscript.

Conflict of interest: the authors declare no potential conflict of interest.

Note about data and materials: the data supporting the findings of this study are available from Puglia Regional Observatory for Epidemiology but restrictions apply to the availability of these data, which were used under license for the current study, and so they are not publicly available. Data are however available from the authors upon reasonable request and with permission of Puglia Regional Observatory for Epidemiology.

Received for publication: 15 October 2018.
Accepted for publication: 2 January 2019.

Italian Journal of Medicine 2019; 13:38-44
doi:10.4081/itjm.2019.1099

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive condition of the airways characterized by the decay of lung function and episodes of worsening symptoms called exacerbations.[1] Currently, COPD is estimated to be the fourth cause of death worldwide, but many studies provide that it will become the third cause of death globally by 2020.[2] More than 3 million people died of COPD in 2012, accounting for 6% of all deaths globally.[3] With the increasing prevalence of smoking in developing countries, and aging populations in high-income countries, the prevalence of COPD is expected to rise over the next 30 years and by 2030 there could be over 4.5 million of COPD-related deaths per year.[3] Moreover, in 2020 COPD-related disability will rise from ninth to fifth place in terms of disability-adjusted life years (DALYs).[1] So, COPD is a leading cause of morbidity, mortality and disability worldwide and it is associated with premature death and considerable economic burden.[3]

In the past, COPD was always considered to be a disease that mainly affected elderly men, reflecting the

higher prevalence of smoking among men. Now, it is commonly diagnosed in women, as the prevalence of smoking in females has grown progressively in the last years. However, the increased morbidity and mortality from COPD during the last few decades are partly driven by their increase in women.[4]

Already in 2000, in a retrospective analysis of patients with physician diagnosed COPD made from 1990 to 1997 from the General Practice Research Database (GPRD) of the UK, Soriano *et al*.[5] showed that while the prevalence of COPD seemed to have peaked in men at any age, in women there was an increase of 68.7% compared with 25.3% in men. While prevalence in men plateaued in the mid-1990s, there was an important increase in women older than 65 years, and the proportion in women aged 45-65 years approached that in men in later years. COPD prevalence in women is likely to increase markedly because women in all countries adopt the same lifestyle habits as men and are exposed to the same workplace risks.[6] On the other hand, women with COPD may be less likely to be diagnosed and consequently less likely to be treated for their COPD.[6]

More women are also being hospitalized for COPD in the last years:[6] in Canada it was reported an increase in hospitalizations for women, particularly in older age categories[7] and Celli reported an exacerbation rate was 25% higher in women than in men.[8]

Furthermore, an Italian study conducted in Puglia showed that the percentage of hospitalizations among females increased from 27.8% in 2001 to 35.6% in 2011.[9]

Then, mortality for women with COPD in the United States and in Canada is increasing,[6] but in a observational study De Torres[10] showed that in Spain all-cause mortality (40% *versus* 18%) and respiratory mortality (24% *versus* 10%) were higher in males compared to females; indeed, he underlined that considering the BODE index (which includes: body mass index, airflow obstruction, dyspnea, exercise capacity) in females and using the BODE index with Charlson Comorbidity Score in males as the best predictors of mortality, at similar chronic obstructive pulmonary disease severity by BODE index and forced expiratory volume in one second, females show significantly better survival than males.

In conclusion, there has been a rapid increase in the prevalence, morbidity, and mortality of COPD in women over the last two decades;[11] for this reason, it is very important to identify the determinants of COPD in both sexes in order to explain the epidemiological changes of this disease.

Considering these gender differences, current guidelines for the diagnosis and treatment on COPD do not differ from recommendations for female and male patients.

The aim of this study is to evaluate gender differences focusing on the number of hospital admissions, mean age, average length of stay in hospital (ALOS), hospital mortality, re-hospitalization and presence of comorbidities throughout the analysis of hospitalization data in Puglia (Italy) between 2005 and 2016.

Materials and Methods

The Puglia Hospital Discharge Register Database was analyzed for the years 2005-16. The codification of clinical information of diagnoses and procedures performed during the hospital stay was ICD-9-CM, version 2007.

The analysis was performed selecting all hospital discharges with a primary diagnosis of COPD with and without exacerbation (respectively ICD-9-CM codes 491.21 and 491.20).

We calculated the number of admissions by sex, age, ward and hospital, the average length of stay in hospital and the mean age of hospitalized patients. The ALOS was calculated using the ratio between the sum of days spent in hospital, taken from hospital discharge records and the number of admissions.

The analysis of respiratory therapy utilization was carried out using the appropriate codes ICD-9-CM 93.9x and calculating the proportion of hospital discharge records that reported this therapy by sex and ward. The same calculation was carried out to analyze the hospital mortality (patients discharged as *dead*).

We also calculated the frequency of the following comorbidities that can modify the natural history of COPD: diabetes (ICD-9 code 250.x), obesity (ICD-9 code 278.0), anxiety (ICD-9 code 300.x), atrial fibrillation (ICD-9 code 427.31), essential hypertension (ICD-9 code 401), heart failure (ICD-9 code 428) and osteoporosis (ICD-9 code 733.0). For comorbidities, we have examined the first 5 secondary diagnosis fields of the database.

We performed a descriptive analysis with quantitative method. The nominal variables are expressed as proportions, while continuous ones are expressed as means.

Results

Considering the Puglia hospital analysis between 2005 and 2016, the total number of discharges with a primary diagnosis of COPD with or without exacerbation was 93,638. Males were 66.1% (61,888) and females 33.9% (31,750). In particular, in 2005 there were 13,728 admissions for COPD, of which 68.1% were men (9347) and 31.9% women (4381). In 2016 there were 2293 admissions for COPD. Males

were 61.1% (1423) and females 37.9% (870). We observed a modification in gender distribution: M:F ratio decreased from 2.1:1 in 2005 [31.9% of women, 95% confidence interval (CI) 31.1-32.7] to 1.6:1 in 2016 (37.9% of women, 95%CI 36.0-40.0) (Table 1).

More specifically, from 2005 to 2016 admissions for COPD with exacerbation were 74,007, those without exacerbation 19,631; there was a reduction of the number of hospitalizations for both COPD forms (from 10,893 in 2005 to 1783 in 2016 for COPD with exacerbation; from 2835 in 2005 to 510 in 2016 for COPD without exacerbation).

As far as age distribution is concerned, in 2005 52.4% of all patients with COPD with and without exacerbation was 66-80 years old, 26.4% was older than 80 years, 19% was 41-65 years old and 1.6% was 18-40 years old; in 2016 the number of patients over eighty with COPD increased to a percentage of 36.9%, the number of patients between 66 and 80 years old was reduced to 44.8% and the percentage of 41-65 years old patients to 15.3%.

In those years, COPD admissions showed higher prevalence in Internal Medicine Unit, followed by respiratory department, geriatric unit, rehabilitation and long-term wards; in all these wards men were approximately twice as many as women, except for geriatric unit where women were more numerous than in other wards (women 4978, men 7119). In addition, in 2016 there was a reduction of ALOS for all patients with COPD with and without exacerbation compared to previous years, even if women had a greater ALOS compared to men in years between both 2005-08 and 2013-16.

With regard to COPD-exacerbation discharges, the mean age of patients increased from 2005 to 2016, but women were older in all the years of observation; in fact, in 2005 the mean age was 71.4 for men and 74.0 for women, while in 2016 it was 74.8 for men and 76.3 for women. In addition, the ALOS of women with COPD with exacerbation is longer (one day approximately) than men in all the examined wards (Figure 1A) and years (Figure 1B).

In hospitalized patients with a primary diagnosis of COPD with exacerbation, it has not emerged a sex-different hospital mortality, nor a modification of mortality over the considered period (Table 2). The greater number of deaths was in geriatric and long-term wards.

When we focused our analysis on the last three years of observation (2014-16), we observed that the number of re-hospitalized patients with COPD with exacerbation had decreased from 265 (8.7% of admissions in 2014) in 2015 to 178 (5.6% of admissions in 2014) in 2016 and it was greater among males than females, but females proportion increased from 23% in 2015 to 28.7% in 2016. The re-hospitalizations were more prevalent in internal medicine wards (with 133 readmissions in 2015 and 78 in 2016), followed by respiratory units (69 in 2015 and 51 in 2016), geriatric wards (28 in 2015 and 16 in 2016) and rehabilitation wards (27 in 2015 and 17 in 2016).

The respiratory therapy code (ICD-9 93.9x) is more frequently present among male patients for all the wards (Figure 2A) and years (Figure 2B).

In our analysis, diabetes mellitus emerged as the most common secondary diagnosis (18.3%) in all patients with COPD as main diagnosis; it was followed by hypertension (16%), atrial fibrillation

Table 1. Male to female ratio and female proportion (%) of patients hospitalized for chronic obstructive pulmonary disease (ICD-9 491.21 or 491.20), by year.

Year	M:F	%F (95% CI)
2005	2.1:1	31.9 (31.1-32.7)
2006	2.1:1	32.6 (31.8-33.5)
2007	2.1:1	32.7 (31.8-33.5)
2008	2.0:1	33.4 (32.5-34.3)
2009	1.9:1	34.4 (33.4-35.3)
2010	1.9:1	34.0 (33.0-35.0)
2011	1.8:1	35.6 (34.5-36.8)
2012	1.7:1	37.0 (35.7-38.2)
2013	1.8:1	36.2 (34.8-37.6)
2014	1.9:1	34.4 (32.9-35.9)
2015	1.8:1	36.3 (34.5-38.0)
2016	1.6:1	37.9 (36.0-40.0)
Years 2005-16	1.9:1	33.9 (33.6-34.2)

CI, confidence interval. *Data source: Puglia Regional Observatory for Epidemiology, 2005-16.*

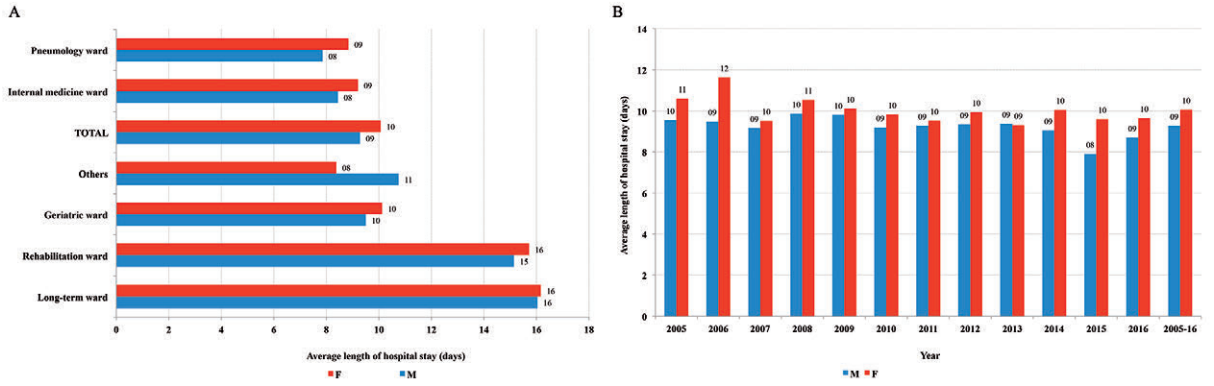

Figure 1. The average length of stay in hospital of patients with main diagnosis of COPD with exacerbation (ICD-9 491.21) by ward and sex (A) and by year and sex (B). ***Data source: Puglia Regional Observatory for Epidemiology, 2005-16.***

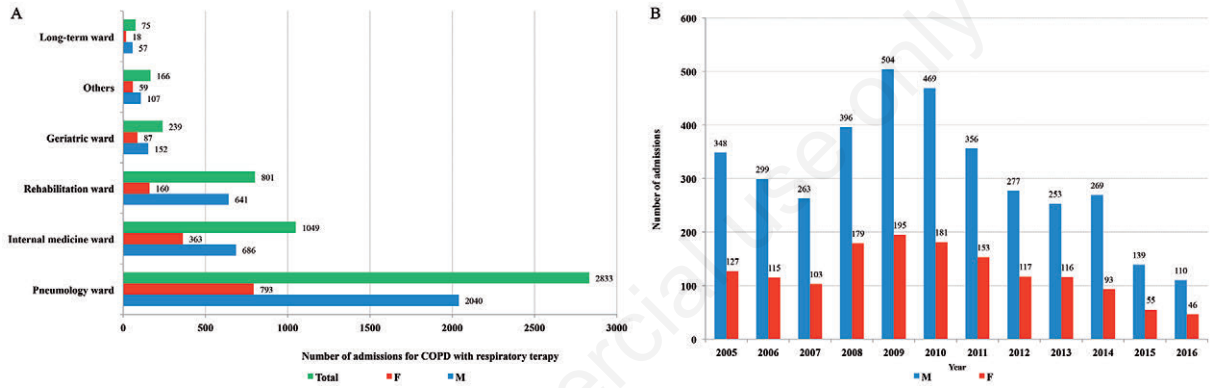

Figure 2. Number of chronic obstructive pulmonary disease hospital discharge records reporting *Respiratory therapy* procedure (ICD-993.9x) by ward and sex (A) and by year and sex (B). ***Data source: Puglia Regional Observatory for Epidemiology, 2005-16.***

Table 2. Hospital mortality of patients hospitalized for chronic obstructive pulmonary disease with exacerbation (ICD-9 421.21), by year (Puglia 2005-16).

Year	Men		Women		All	
	n/N	% (95%CI)	n/N	% (95% CI)	n/N	% (95% CI)
2005	55/7399	0.7 (0.6-1.0)	34/3494	1.0 (0.7-1.4)	89/10893	0.8 (0.7-1.0)
2006	42/6465	0.6 (0.5-0.9)	28/3174	0.9 (0.6-1.3)	70/9639	0.7 (0.6-0.9)
2007	50/6264	0.8 (0.6-1.1)	34/3061	1.1 (0.8-1.5)	84/9325	0.9 (0.7-1.1)
2008	34/5650	0.6 (0.4-0.8)	29/2873	1.0 (0.7-1.4)	63/8523	0.7 (0.6-0.9)
2009	36/5406	0.7 (0.5-0.9)	33/2837	1.2 (0.8-1.6)	69/8243	0.8 (0.7-1.1)
2010	27/4708	0.6 (0.4-0.8)	11/2429	0.5 (0.2-0.8)	38/7137	0.5 (0.4-0.7)
2011	20/3286	0.6 (0.4-0.9)	13/1833	0.7 (0.4-1.2)	33/5119	0.6 (0.4-0.9)
2012	25/2746	0.9 (0.6-1.3)	18/1570	1.1 (0.7-1.8)	43/4316	1.0 (0.7-1.3)
2013	13/2224	0.6 (0.3-1.0)	13/1297	1.0 (0.5-1.7)	26/3521	0.7 (0.5-1.1)
2014	13/2020	0.6 (0.3-1.1)	10/1143	0.9 (0.4-1.6)	23/3163	0.7 (0.5-1.1)
2015	8/1465	0.5 (0.2-1.1)	10/880	1.1 (0.5-2.1)	18/2345	0.8 (0.5-1.2)
2016	18/1061	1.7 (1.0-2.7)	5/722	0.7 (0.2-1.6)	23/1783	1.3 (0.8-1.9)
Years 2005-16	341/48694	0.7 (0.6-0.8)	238/25313	0.9 (0.8-1.1)	579/74007	0.8 (0.7-0.8)

CI, confidence interval. *Data source: Puglia Regional Observatory for Epidemiology, 2005-16.*

(9.6%), obesity (5.6%), heart failure (3.3%), anxiety and depression (2.7%) and osteoporosis (1.2%). The proportion of all comorbidities (anxiety and depression, diabetes, atrial fibrillation, obesity, osteoporosis and heart failure) was higher among female than male patients (Figure 3), except for hypertension in which we have not observed any gender difference.

Discussion

COPD is a leading cause of morbidity, mortality and disability worldwide and it is associated with considerable economic burden[3] as well as with premature deaths.

In our analysis, we underlined a progressive decrease of admissions for COPD with or without exacerbation from 2005 to 2016 because usually patients with COPD are encouraged to home treatment, reducing hospitalization to serious cases. Our research pays attention to the number of hospitalizations which is important to quantify the burden of a disease and to assess the quality of care, but it considers only a portion of patients with COPD because many of them are treated at home and followed-up in outpatient clinics. Nowadays, this often happens.[12] Regarding Puglia, there was a decrease of proportional admissions of

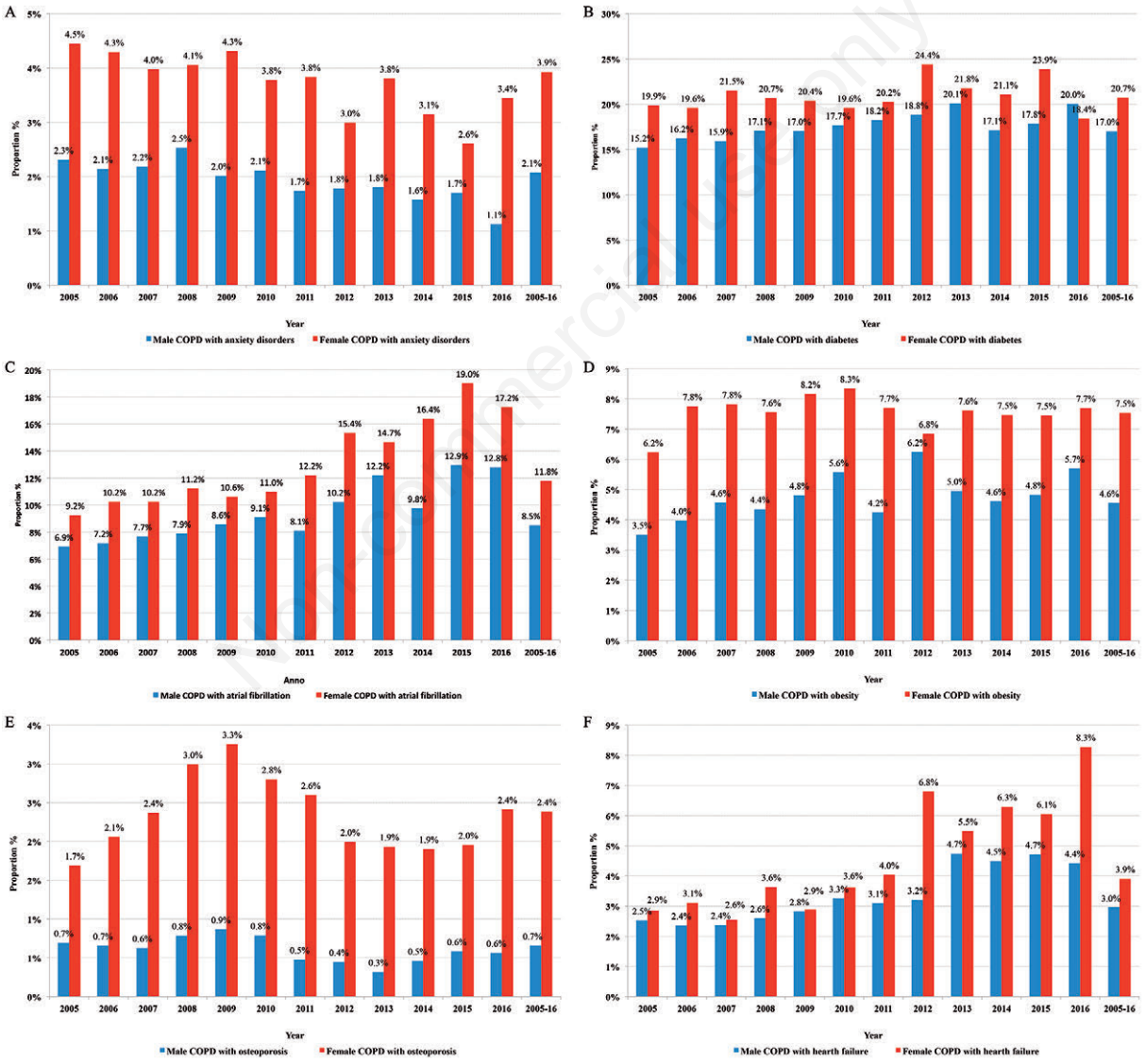

Figure 3. Proportion of hospital admissions with main diagnosis of chronic obstructive pulmonary disease (ICD-9 491.21 or 491.20) and secondary diagnosis of anxiety/depression (A), diabetes mellitus (B), atrial fibrillation (C), obesity (D), osteoporosis (E) and heart failure (F), by year and sex. ***Data source: Puglia Regional Observatory for Epidemiology, 2005-16.***

males, with a consequent increase of female COPD hospitalization from 2005 to 2016; these data can be in accordance with European and American studies[5-8] and confirm the study previously followed in Puglia between 2001 and 2011.[9]

There are many reasons, which can explain the *feminization* of COPD. First of all, women smoke more than in the past and they could be more open to dose-dependent tobacco,[11] so they develop more severe COPD at younger ages than men and with lower levels of smoke;[11] furthermore, women live in the same way as men, and are exposed to the same workplace risks in all countries.[6] Finally, women are exposed to indoor air pollution due to cooking and heating which are women practice.

In these years of observation, the admissions of over eighty years old patients for COPD with and without exacerbation increased (from 26.4% in 2005 to 36.9% in 2016) compared to aging population in every country in the world. In the last analyzed year, there was a higher number of females than males in geriatric departments because women live longer than men, while in the other wards (internal medicine, pneumology, rehabilitation and long-term ward) men admissions were approximately twice as many as women.

In the analysis focused on COPD with exacerbation, the mean age of patients increased also in both genders from 2005 to 2016; furthermore, female patients were older and needed a longer length of hospital stay in all the examined years and wards because COPD tends to be more severe in women, as shown in previous studies.[13] Moreover, the different gender distribution and its modification over the considered period seems not to reflect itself on hospital mortality for COPD with exacerbation, that it turned out to be substantially the same between males and females and over the considered period.

In the last three years of observation, in Puglia there was a reduction of re-hospitalizations from 2015 to 2016, but the proportion of female re-admissions increased in 2016 compared to 2015 in accordance with Canadian data.[7]

During all the observation period, the utilization of respiratory therapy was higher in male patients and in all the examined wards, suggesting that a different therapeutic approach is applied to men.

The COPD's epidemiological and socio-economic impact also increases due to the presence of several comorbidities, which can affect the clinical progression of COPD, combined with the patients' quality of life and survival. In the last decades, many studies[14-20] considered the prevalence of comorbidities in COPD patients with different results. The prevalence of some comorbidities (such as heart failure, osteoporosis, anxiety and depression)[20] was considerably higher in females than in males, showing a clear gender trend which might support the hypothesis of the heavier COPD impact in females than in males worldwide. Arterial hypertension and ischemic heart diseases were the most frequent comorbidities and equally distributed in both sexes, such as obesity and diabetes.[20]

Compared to Dal Negro's study,[20] in our analysis diabetes mellitus was the most common comorbidity. Besides, diabetes, atrial fibrillation, obesity, heart failure, anxiety and depression, and osteoporosis were higher among women compared to men. There were no sex differences for hypertension: it was equally distributed in males and females such as proved in the previous study.[20]

In our study there were important limitations, the main of which is the data source: regardless of the fact that the Hospital Discharge Register Database represents a real and reliable source of information, it provides data only about patients who have been hospitalized. In addition, it does not offer a description of disease severity nor information about smoking habits of patients. We limited our analysis to patients who were hospitalized for two COPD codes (ICD-9-CM 491.20 and 491.21) as main diagnosis, which represents only a minority of COPD-related hospital admissions. In the future, some studies should analyze specific surveys in order to evaluate outpatients' gender determinants.

Conclusions

This study highlighted that there was a reduction in the number of COPD hospitalized patients between 2005 and 2016 in Puglia, but the percentage of female COPD patients admitted to hospital increased significantly during this period, such as female mean age, ALOS and re-hospitalization. In addition, women were treated less than men and had more comorbidities, which could affect the clinical progression of COPD, combined with quality of life and survival.

Further studies are necessary to confirm these data, to evaluate gender differences not only in inpatients but also in outpatients, and to understand what determinants of these gender differences can play an important role in therapy and prognosis.

References

1. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for diagnosis, management, and prevention of COPD; 2014.
2. Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. Lancet 2007;370: 765-73.
3. Global Initiative for Chronic Obstructive Lung Disease.

Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Report 2017. Available from: http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/
4. Barnes PJ. Sex differences in chronic obstructive pulmonary disease mechanisms. Am J Respir Crit Care Med 2016;193:813-24.
5. Soriano JB, Maier WC, Egger P, et al. Recent trends in physician diagnosed COPD in women and men in the UK. Thorax 2000;55:789-94.
6. Han MK, Postma D, Mannino DM, et al. Gender and chronic obstructive pulmonary disease: why it matters. Am J Respir Crit Care Med 2007;176:1179-84.
7. Lacasse Y, Brooks D, Goldstein RS. Trends in the epidemiology of COPD in Canada, 1980 to 1995. COPD and Rehabilitation Committee of the Canadian Thoracic Society. Chest 1999;116:306-13.
8. Celli B, Vestbo J, Jenkins CR, et al; Investigators of the TORCH Study. Sex differences in mortality and clinical expressions of patients with chronic obstructive pulmonary disease. The TORCH Experience. Am J Respir Crit Care Med 2011;183:317-22.
9. Moretti AM, Gallone MS, Parisi D, et al. Gender differences and hospitalization for COPD: an analysis of the data from Puglia (Italy). Ital J Gender-Specific Med 2015;1:66-72.
10. De Torres JP, Cote CG, López MV, et al. Sex differences in mortality in patients with COPD. Eur Respir J 2009;33:528-35.
11. Aryal S, Diaz-Guzman E. Influence of sex on chronic obstructive pulmonary disease risk and treatment outcomes. Int J Chron Obstruct Pulmon Dis 2014;9:1145-54.
12. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1995;152:S77-121.
13. Cote CG, Chapman KR. Diagnosis and treatment considerations for women with COPD. Int J Clin Prat 2009;63:486-93.
14. Halbert RJ, Ntoli JL, Gano A, et al. Global burden of COPD; systematic review and meta-analysis. Eur Respir J 2006;28:523-32.
15. Frank TL, Gazell M-L, Linehan MF, et al. The estimated prevalence of chronic obstructive pulmonary disease in a general practice population. Prim Care Respir J 2007;16:169-73.
16. van der Molen T. Comorbidities of COPD in primary care; frequency, relation to COPD, and treatment consequences. Prim Care Respir J 2010;19:326-34.
17. Garcia-Olmos L, Alberguilla A, Ayala V, et al. Comorbidity in patients with chronic obstructive pulmonary disease in family practice: a cross sectional study. BMC Fam Pract 2013;14:11.
18. Tashkin D, Miravitlles M, Price D, et al. Rate of comorbidities during the 4-year UPLIFT trial in COPD: A post-hoc analysis. Chest 2014;146:67A.
19. Fumagalli G, Fabiani F, Forte S, et al. INDACO project: COPD and link between comorbidities, lung function and inhalation therapy. Multidiscip Respir Med 2015;19:4.
20. Dal Negro RW, Bonadiman L, Turco P. Prevalence of different comorbidities in COPD patients by gender and GOLD stage. Multidiscip Respir Med 2015;10:24.