European Review for Medical and Pharmacological Sciences 2017; 21: 3680-3689

Chronic obstructive pulmonary disease (COPD) exacerbation: impact of comorbidities on length and costs during hospitalization

C. TERZANO[1], V. COLAMESTA[2], B. UNIM[2], S. ROMANI[1], A. MENEGHINI[3], G. VOLPE[3], G. LA TORRE[2]

[1]Respiratory Diseases Unit, Azienda Policlinico Umberto I, Sapienza University of Rome, Rome, Italy
[2]Department Public Health and Infectious Diseases, Sapienza University of Rome, Rome, Italy
[3]Information Systems, RM/A Local Health Unit, Rome, Italy

Abstract. – OBJECTIVE: A retrospective cohort study was performed, using administrative database of the Local Health Unit Roma-A (LHU RM-A). The included subjects were residing in one of the four districts and were hospitalized for COPD exacerbation in healthcare facilities of the LHU during years 2010-2012.

PATIENTS AND METHODS: The aim of the present study is to evaluate the impact of comorbidities, length and costs of hospital stay in patients with COPD exacerbations. Chronic obstructive pulmonary disease (COPD) is often associated with other diseases (cardiovascular diseases, diabetes, metabolic syndrome, chronic renal failure, depression) that can increase risk of mortality and hospitalization.

RESULTS: A total of 1890 COPD patients are included in the study. The mean length of hospitalization is 12.25 days (SD ± 10.91), 11.63 days (SD ± 9.76) and 11.91 days (SD ± 9.69) with a mean cost of hospitalization amounting to euro 3683.48 (SD ± 2037.12), 3356.82 (SD ± 1674.86) and 3706.81 (SD ± 2087.72) in 2010, 2011 and 2012 respectively. The presence and number of comorbidities are positively and significantly associated to the length and cost of hospitalization. In particular, patients with cardiovascular diseases or diabetes mellitus associated with other comorbidities present the highest values of hospital stay and cost. The cost and the length of hospitalization were significantly linked to the number of comorbidities.

CONCLUSIONS: Comorbidities play an important role in the hospital management of COPD exacerbation, increasing health care costs related to this disease.

Key Words:
COPD, Hospitalization, Comorbidities, Cost, Exacerbation.

Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable respiratory disease, characterized by persistent airflow limitation. COPD is a leading cause of mortality and morbidity worldwide[1,2].

COPD represents the fourth cause of mortality and the twelfth cause of disability in the world and it's expected that its impact will increase in coming decades[3]. In 1990 it was the sixth leading cause of death and it's estimated that in 2020 it will become the third leading cause of mortality worldwide, after acute myocardial infarction and cardiovascular diseases[4]. In Italy, in 2002, ISTAT data indicated respiratory diseases as the third leading cause of death. In particular, COPD accounts for about 50% of death for respiratory diseases[5]. In 2008, the Social Impact of Respiratory Integrated Outcomes (SIRIO) study provided the first estimate of the economic burden of respiratory diseases (asthma and COPD) in Italy. The SIRIO study was designed in 2006 as a global outcome study to produce data regarding the socioeconomic impact of the major respiratory diseases (bronchial asthma, COPD, community-acquired pneumonia)[6,7].

GOLD (Global Initiative for Chronic Obstructive Lung Disease) Guidelines consider a combined assessment in patient with COPD including symptom, spirometric classification and risk of exacerbations[1].

Co-morbidities are other chronic diseases associated with COPD and their impact is increasingly recognized[8]. Co-morbidities can develop in all stages of COPD, increasing risk of mortality

Corresponding Author: Giuseppe La Torre, MD; e-mail: giuseppe.latorre@uniroma1.it

and hospitalization in COPD patients[9,10]. Therefore, an exponential increase in cost of treatment is associated with them[11].

COPD often coexists with other diseases that have a significant influence on the prognosis[9,12-14] and shares some features with other diseases.

In particular, cardiovascular diseases are the major comorbidities in COPD, followed by chronic renal failure[10,12].

Metabolic syndrome and diabetes mellitus are common in COPD and diabetes, in particular, negatively affects prognosis[9]. Depression and anxiety are also common in COPD and they are associated with poor prognosis[15].

In 1988 Muñoz et al. showed that co-morbidities in COPD are associated with a more length of hospital stay, higher economic losses in DRG reimbursements, more medical procedures and a higher mortality[16].

A study published in 2010 highlights that number of hospitalizations and length of stay depend mainly on the degree of dyspnea and an index of respiratory functional impairment (REFI index), which consists of: FEV_1 (Forced expiratory volume in the 1st second), RV (Residual volume), PaO_2 (arterial oxygen tension) and $PaCO_2$ (Arterial carbon dioxide partial pressure). This study also shows that the risk of mortality depends on age, smoking status, FEV_1, PaO_2, REFI index, presence of pulmonary heart disease, ischemic heart disease and lung cancer[8].

The aim of the present work is to evaluate the impact of comorbidities, length and costs during hospitalization in patients with COPD exacerbations.

Patients and Methods

Study Design and Sample Selection

A retrospective cohort study was performed according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) Statement[17,18]. The sample was selected from the administrative database of the Local Health Unit Roma-A (LHU RM-A). The included subjects were residing in one of the four districts. Furthermore, they were hospitalized subjects with ICD-9 code (International Classification of Diseases, Ninth Revision, Clinical Modification) 491.21 and chronic obstructive pulmonary disease with (acute) exacerbation as the principal or as one of the five secondary diagnosis in healthcare facilities of the LHU during the time window considered in the analysis (2010-2012). The presence and number of comorbidities of the cohort were analyzed considering different ICD-9 codes for cardiovascular diseases (heart failure-HF, hypertension, atrial fibrillation-AF, acute myocardial infarction-AMI) and diabetes, which are reported in a supplement file (Annex A).

Statistical Analysis

Descriptive statistics was performed for all variables using frequencies and percentages; the differences between groups were calculated with the Chi-Square, *t*-Student, one-way ANOVA tests and Bonferroni correction.

We carried out linear logistic regression analysis (backward method) to assess the association between the dependent variables (a) length of hospital stay and (b) costs of hospitalization and the following covariates: gender, age, number of comorbidities, citizenship, civil status, employment, educational level, districts of the LHU.

The model's goodness of fit was evaluated using the R^2 index and the level of significance was set at $p < 0.05$. For data analysis, the IBM software, Statistical Package for Social Sciences (SPSS), version 19.0 for Windows (SPSS Inc., Chicago, IL, USA) was used.

Results

A total of 1890 COPD patients from the hospitalization databases of the LHU RM-A met the inclusion criteria for the period 2010-2012. The characteristics of the study population are summarized in Table I. In 2010, 639 patients are selected with a mean age of 76.46 years (SD ± 10.58); 347 (54.3%) are males and over 60% of the subjects are married. In 2011, 316 (50.3%) males and 312 (49.7%) females are hospitalized with a mean age of 77.63 years (SD ± 10.18); married subjects are over 60% as in the previous year. In 2012, 623 patients are identified (328 males and 295 females) with a mean age of 77.23 years (SD ± 10.64) and about 40% of the patients are not married.

In the three years, Italians account for almost all the study population (over 90%) and over 40% of the sample reside in the IV district of the LHU RM-A. More than 70% of the sample have a low educational level (i.e.: no qualification, elementary or junior high school) and almost 80% are pensioners. The mean length of hospitaliza-

Annex A. ICD-9 codes selected for the analysis of comorbidities.

Disease	ICD-9 Codes	Disease	ICD-9 Codes
Hypertension	401	**Atrial fibrillation**	42731
	4011		4273
	4010		
	4019	**Heart failure**	428
	40591		4280
	40511		4289
	40501		4281
	405		
	4051	**Diabetes mellitus**	2508
	40519		2503
	40599		25030
	4050		25032
	40509		2501
	4059		25010
			25012
Acute myocardial infarction	410		2507
	4109		2506
	41090		2509
	41091		2505
	41092		2504
	4100		2502
	41000		25020
	41001		25022
	41002		2535
	4102		5881
	41020		250
	41021		6480
	41022		2500
	4103		64800
	41030		25000
	41031		25002
	41032		25080
	4101		25070
	41010		25060
	41011		25090
	41012		25050
	4104		25040
	41040		25082
	41041		25072
	41042		25062
	4105		25092
	41050		25052
	41051		25042
	41052		
	4108		
	41080		
	41081		
	41082		
	412		
	41060		
	41061		
	41062		
	4107		
	41070		
	41071		
	41072		
	4106		

Table I. Characteristics of the study population. A total of 1890 patients are included in the study.

Variables		2010 (N = 639) N (%)	2011 (N = 628) N (%)	2012 (N = 623) N (%)	*p*-value
Gender	Male	347 (54.3)	316 (50.3)	328 (52.6)	0.36*
	Female	292 (45.7)	312 (49.7)	295(47.4)	
Civil status	Married	413 (64.6)	386 (61.5)	367 (58.9)	0.11*
	Not married	226 (35.4)	242 (38.5)	256 (41.1)	
Education level	High^	132 (20.7)	161 (25.6)	165 (26.5)	**0.03***
	Low^^	507 (79.3)	467 (74.4)	458(73.5)	
Citizenship	Italian	627 (98.1)	617 (98.2)	609 (97.8)	0.81*
	Foreign	12 (1.9)	11 (1.8)	14 (2.2)	
Districts of the LHU	RMA-1	163 (25.5)	149 (23.7)	172 (27.6)	0.53*
	RMA-2	127 (19.9)	143 (22.8)	130 (20.9)	
	RMA-3	77 (12.1)	62 (9.9)	65 (10.4)	
	RMA-4	272 (42.6)	274 (43.6)	256 (41.1)	
Actual occupation	Pensioner	509 (79.7)	514 (81.8)	483 (77.5)	0.16*
	Worker/seeking for work	130 (20.3)	114 (18.2)	140 (22.5)	
Presence of comorbidities	None	13 (2.0)	16 (2.5)	26 (4.2)	0.06*
	1-5	626 (98.0)	612 (97.5)	597 (95.8)	
		Mean (SD)	**Mean (SD)**	**Mean (SD)**	
Age	76.46 (10.6)	77.63 (10.2)	77.23 (10.6)	0.13**	
Days of hospitalization	12.25 (10.9)	11.63 (9.8)	11.91 (9.7)	0.55**	
Cost of hospitalization (euro)		3683.48 (2037.1)	3356.82 (1674.9)	3706.81 (2087.7)	**0.002****

*Chi-Square test; **Anova test; ^High: senior high school and academic degree; ^^Low: No qualification/elementary and junior high school; Bold: $p < 0.05$.

tion is 12.25 days (SD ± 10.91), 11.63 days (SD ± 9.76) and 11.91 days (SD ± 9.69) with a mean cost of hospitalization amounting to euro 3683.48 (SD ± 2037.12), 3356.82 (SD ± 1674.86) and 3706.81 (SD ± 2087.72) in 2010, 2011 and 2012 respectively. The majority of the hospitalized patients have at least one comorbidity (98%, 97.5%, 95.8% respectively in 2010, 2011 and 2012).

The variables that can influence the length of hospitalization for COPD exacerbation are depicted in Table II. The number of comorbidities (maximum = 5) is positively and significantly associated to the length of hospitalization (€ = 2.13; β = 1.68; β = 1.80 respectively in 2010, 2011 and 2012). Considering the period 2010-2012, age is also positively associated with the length of hospital stay (β = 0.06; $p = 0.01$). Contrarily, high

Table II. Linear regression analysis to evaluate the possible factors associated with the length of hospital stay.

Covariates	2010 (N = 639) β (*p*)	2011 (N = 628) β (*p*)	2012 (N = 623) β (*p*)	2010-2012 (Total = 1890) β (*p*)
Female gender	-0.18 (0.84)	0.47 (0.54)	0.48 (0.54)	0.21 (0.65)
Age	0.01 (0.81)	0.07 (0.05)	0.07 (0.05)	0.06 (0.01)§
Presence of comorbidities (1-5)	2.13 (< 0.001)§	1.68 (< 0.001)§	1.80 (< 0.001)§	1.87 (< 0.001)§
Italian citizen	2.65 (0.38)	1.80 (0.53)	-1.64 (0.52)	0.29 (0.86)
Married	-1.53 (0.08)	0.03 (0.97)	-0.88 (0.24)	-0.86 (0.06)
Ritired	0.57 (0.58)	0.95 (0.37)	0.39 (0.70)	0.48 (0.44)
High educational level^	0.04 (0.97)	-2.32 (0.01)§	1.37 (0.11)	-0.46 (0.38)
RMA-2 district	-0.01 (0.99)	0.74 (0.42)	0.35 (0.75)	0.55 (0.38)
RMA-3 district	-0.90 (0.50)	0.51 (0.72)	-0.71 (0.58)	-0.36 (0.66)
RMA-4 district	-1.97 (0.02)§	0.43 (0.62)	-0.38 (0.62)	-0.69 (0.14)
R^2 of the model	**0.097**	**0.088**	**0.084**	**0.082**

^High educational level: senior high school and academic degree; §$p < 0.05$.

educational level in 2011 (β = -2.32; $p = 0.01$) and residence in RMA-IV district in 2010 (β = -1.97; $p = 0.02$) are negatively associated, hence they seem to reduce the length of hospitalization.

Possible factors associated with hospitalization costs are presented in Table III. The length of hospitalization (β = 74.41; $p < 0.001$) and the number of comorbidities (β = 98.86; $p = 0.001$) are positively associated with hospital costs in the time window 2010-2012. Also, in 2011 and generally in the three years, being married is related to higher costs for hospitalization (β = 340.05; $p = 0.005$ and β = 256.91; $p = 0.002$ respectively). The R-squared of the models presents the highest value of 0.227 in 2011 (Table III).

The mean days of hospitalization and costs are higher in patients with at least one comorbidity compared to those without, and increase accordingly with the numbers of comorbidities (no comorbidities vs presence of comorbidities in relation to mean days of hospitalization $p < 0.001$; no comorbidities vs presence of comorbidities in relation to cost of hospitalization $p = 0.01$; no comorbidities vs number of comorbidities in relation to mean days of hospitalization $p < 0.001$; no comorbidities vs number of comorbidities in relation to cost of hospitalization $p < 0.001$) (Figure 1).

The mean days of hospitalization and costs in patients with at least one cardiovascular diseases (CVD) and other comorbidities are the highest (mean days = 13.55; mean cost = € 3741.71) ($p < 0.001$ and $p = 0.006$, respectively) (Figure 2).

Considering hypertension, the highest values for length and cost of hospitalization were found in patients without hypertension but with other comorbidities (mean days = 12.24; mean cost = € 3624.28; $p < 0.001$ and $p = 0.02$ respectively). Furthermore, patients with acute myocardial infarction (AMI) or atrial fibrillation (AF) and other comorbidities present the highest values for length and cost of hospitalization (AMI: mean days = 20.25 p 0.04; mean cost = € 5280.95 $p = 0.002$; AF: mean days = 15.53 $p < 0.001$; mean cost = € 4017.2 $p = 0.001$). Patients with heart failure (HF) and other comorbidities also present the highest value for length of hospitalization (mean days = 13.03 $p < 0.001$), whilst the highest costs are attributable to those with comorbidities different from HF (mean cost = € 3625.7 $p = 0.017$). The analyzed CVDs (hypertension, acute myocardial infarction, atrial fibrillation, and heart failure) are presented in Figure 3.

Finally, patients with diabetes mellitus and other comorbidities have the highest length and cost of hospitalization (mean days = 13.17, mean cost = € 3688.59) compared to other groups ($p < 0.001$ and $p = 0.05$ respectively) (Figure 4).

Discussion

The average cost to manage a COPD patient in Italy is still increasing, as compared to what was measured in 2008[19] in a cohort of patients that is comparable in terms of age, sex distribution, and disease severity.

Table III. Linear regression analysis to evaluate the possible factors associated with cost of hospitalization.

Covariates	2010 (N = 639) β (*p*)	2011 (N = 628) β (*p*)	2012 (N = 623) β (*p*)	2010-2012 (Total = 1890) β (*p*)
Female gender	223.54 (0.14)	-126.29 (0.303)	23.80 (0.88)	36.01 (0.67)
Age	1.10 (0.89)	-6.86 (0.25)	-13.94 (0.08)	-4.61 (0.24)
Presence of comorbidities (1-5)	64.36 (0.26)	98.29 (0.02)§	129.73 (0.02)§	98.86 (0.001)§
Italian citizen	-12.03 (0.98)	429.95 (0.35)	48.93 (0.93)	144.19 (0.63)
Married	201.46 (0.22)	340.05 (0.005)§	229.40 (0.14)	256.91 (0.002)§
Pensioner	-63.17 (0.74)	-26.45 (0.88)	345.24 (0.09)	55.46 (0.62)
High educational level^	-57.14 (0.76)	66.98 (0.63)	44.90 (0.80)	21.16 (0.83)
RMA-2 district	132.92 (0.48)	-35.47 (0.84)	-217.57 (0.24)	-60.20 (0.62)
RMA-3 district	-13.67 (0.96)	-254.56 (0.20)	-134.75 (0.59)	-118.02 (0.37)
RMA-4 district	71.55 (0.69)	-172.41 (0.17)	-50.54 (0.79)	-37.34 (0.68)
Days of hospitalization (from 1 onward)	65.68 (< 0.001)§	75.47 (<0.001)§	85.69 (< 0.001)§	74.41 (< 0.001)§
R^2 of the model	**0.124**	**0.227**	**0.189**	**0.171**

^High educational level: senior high school and academic degree; §$p < 0.05$.

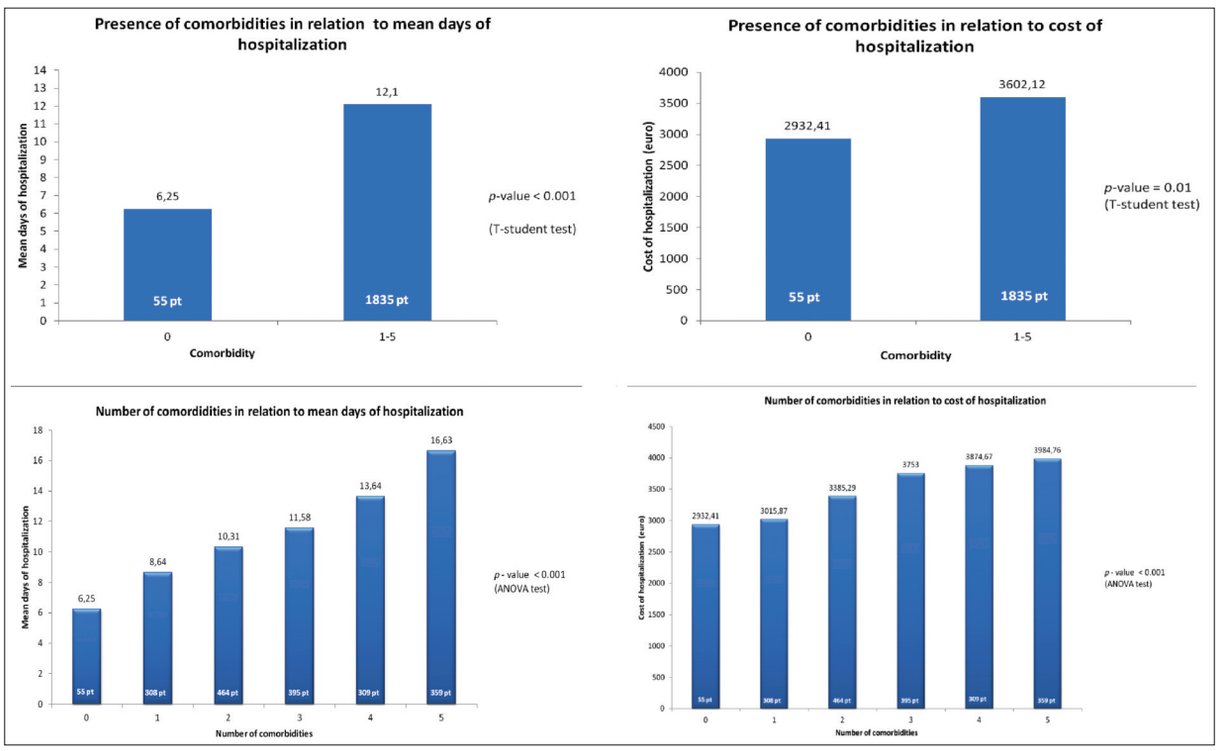

Figure 1. Length and costs of hospital stay in relation to the presence and the number of comorbidities. Pt: patients.

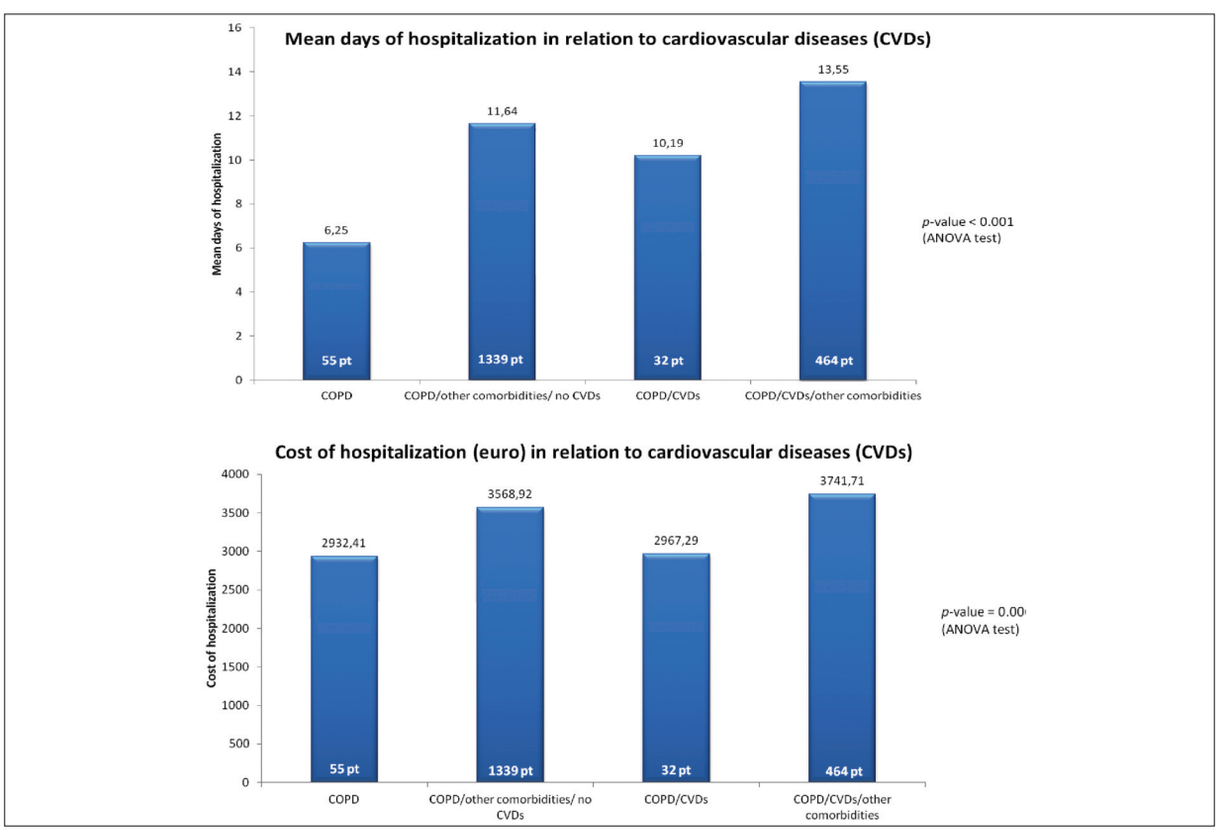

Figure 2. Length and costs of hospital stay in relation to cardiovascular diseases (CVD) (atrial fibrillation, hypertension, heart failure, acute myocardial infarction). Pt: patients.

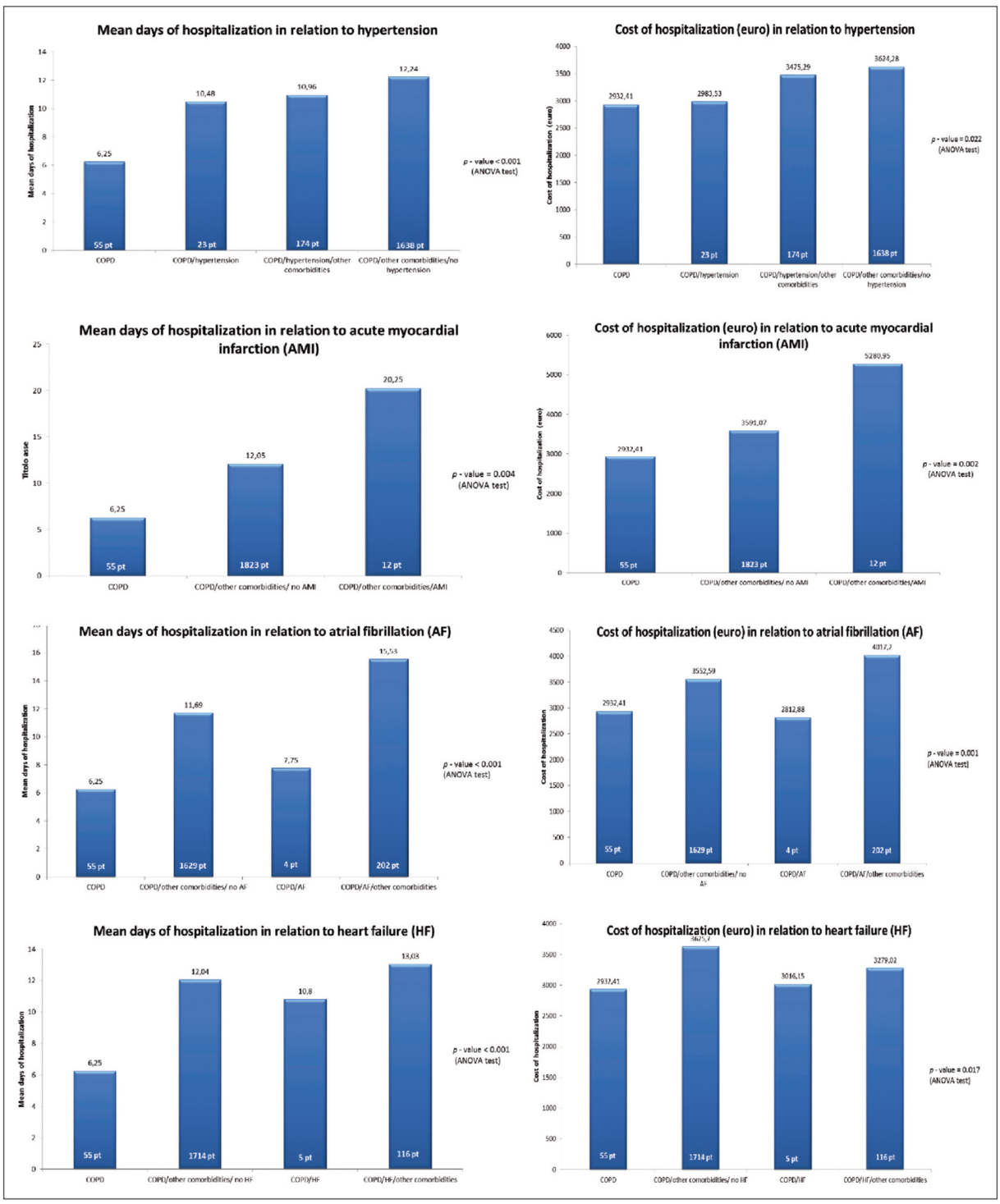

Figure 3. Length and costs of hospital stay in relation to hypertension, acute myocardial infarction, atrial fibrillation, and heart failure. Pt: patients.

Most cost-of-illness analyses show that costs increase substantially with disease severity, and that a significant proportion of the economic burden of COPD can be attributed to exacerbations[20].

A study about the effect of comorbidities on COPD assessment[21], found that patients with 0-1 comorbidity show significant associations between the GOLD score, lung function parameters,

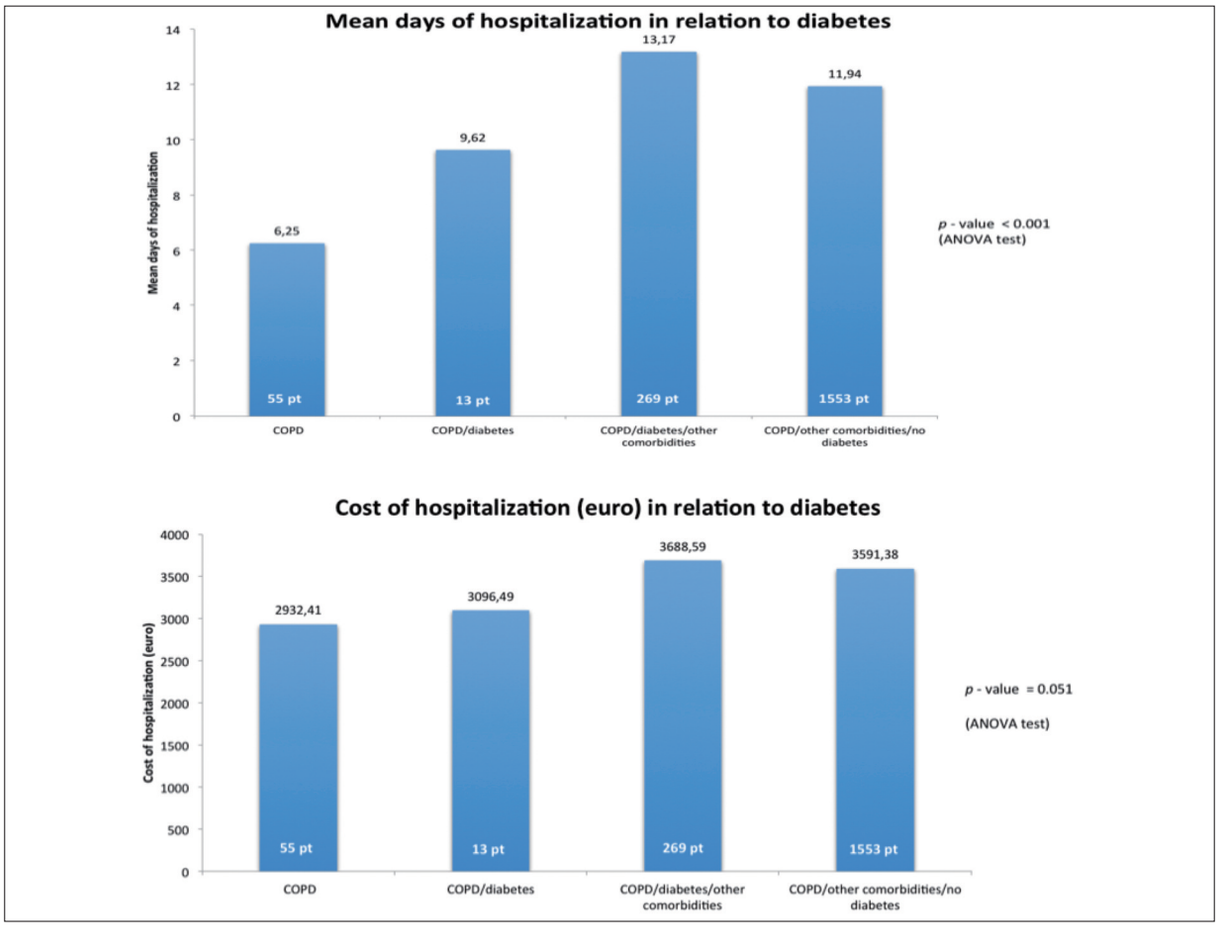

Figure 4. Length and costs of hospital stay and costs in relation to diabetes. Pt: patients.

and emphysema grade. A recent study from general practice found comorbidities to be present in 90% of COPD patients, with 4 ± 2 comorbidities per patient[22], a result that is consistent with our findings. In our work, a number of observations indicate that the cost and the length of hospitalization is potentially influenced by the number of comorbidities as follows, beyond organizational difficulty that could arise, such as the lack of long term care institutions or the disappearance of the parents at the moment of discharge of the patients. Our data show that not only the presence of comorbidities in general would increase the cost and the duration of hospitalization for all patients, but also that this result was significantly linked to the number of comorbidities (from 0 to maximum 5). The evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) trial investigated 2.164 patients with COPD in an outpatient setting and compared these patients with smoking and nonsmoking controls[23]. Comorbidities that were associated with a significantly increased mortality included HFhazard ratio (HR): 1.9, ischemic heart disease (IHD) (HR: 1.5), heart disease in general (HR: 1.5), and diabetes (HR: 1.7). In particular the prevalence of heart failure in COPD cohorts varies between 5.3% and 24.4%[24,25]. Our study analyzed hypertension, AMI, AF, and HF separately. We have highlighted that AMI, AF and HF associated with other comorbidities were significantly associated with higher cost and length of hospitalization. No significant association regarding hypertension and cost/length of hospitalization is shown, though a large number of patients studied was suffering from this disease. These data are important for several reasons, including (1) patients with significant HF are more likely to be hospitalized or seen in specialty outpatient clinics, (2) stable outpatients with COPD are less likely to have active investigation for comorbidities, and (3) accurately diagnosing HF in patients with COPD can be difficult. Considering

that the prevalence of IHD in COPD patients ranges between 16.1% and 53%[26] and that several studies have demonstrated the increased risk of myocardial ischemia in stable COPD during exacerbations and post-exacerbation[27-29], accurate assessment of cardiovascular comorbidities in pre hospitalization can reduce the risks and the subsequent problems related to a long hospitalization. Dalal et al[30] confirm that the addition of CVD to COPD results in a substantial increase in COPD specific costs. In fact, they emphasize that through the 2-year period, the COPD-CVD cohort continued to have higher all-cause total healthcare and medical costs and higher COPD-related total and medical costs relative to the COPD-only cohort. Similarly in our report we found that the presence of comorbidities in general and cardiovascular disease in COPD patients was considered a negative predictor on length of stay and cost of hospitalization. A recent research[31] shown that in patients with COPD exacerbations, changes in blood gases, abnormalities in pulmonary functions and hemodynamic alterations resulting from pulmonary hypertension, may lead to the development of AF. In our study we stressed this aspect considering the role of AF in COPD patients in terms of length of stay and cost of hospitalization. Our data indicate that the AF appears to be an important contributing negative factor in relation to the days and cost of hospitalization in COPD patients with other comorbidities.

In addition to cardiovascular disease, Mannino et al[9] demonstrated increased mortality in COPD patients with diabetes mellitus. In patients with COPD, the prevalence ranges between 10% and 25% for diabetes[26,32]. The exact mechanism of the increased prevalence remains unclear. However, TNF-α and interleukin (IL)-6 are raised in both obesity and COPD, which is correlated with increased insulin resistance[33]. Thus, systemic inflammation is likely to have a role. For these reason in our study we also investigated the role of diabetes in terms of length and costs of hospital stay in COPD patients. Thus we showed that the association of diabetes mellitus with other comorbidities in COPD patients should be considered an important aggravating factor.

Conclusions

Comorbidities play an important role in the hospital management of COPD exacerbation, increasing health care costs related to this disease. In particular, the importance of diagnosing cardiovascular comorbidities and diabetes mellitus in order to avoid the risks of complications, long length of stay and the cost of hospitalization are also stressed.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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