INFLUENCE OF COMORBIDITIES IN STABLE COPD PATIENT MORTALITY

A. Arnedillo Muñoz[1], J.L. López Campos[2], F. Casas maldonado[3], P. Cordero Montero[4], I. Alfageme Michavila[5].

[1]Unidad de Neumología y Alergia. Hospital U. Puerta del Mar (Cádiz). [2]Unidad Médico-Quirúrgica de Enfermedades Respiratorias. Instituto de Biomedicina de Sevilla (IBiS). Hospital U. Virgen del Rocío (Sevilla). CIBER de Enfermedades Respiratorias (CIBERES) [3]Servicio de Neumología. Hospital U. San Cecilio (Granada). [4]Servicio de Neumología. Hospital Infanta Cristina (Badajoz). [5]Servicio de Neumología. Hospital U. Valme (Sevilla).

1st Prize for Best Submission 2016. Project financed by Beca Fundación Neumosur 9/2009

Abstract:

Objective: to assess the relationship between comorbidities and all-cause mortality in stable chronic obstructive pulmonary disease (COPD) patients, in our geographic area.

Methods: Prospective, multicenter, longitudinal study of patients with stable COPD. We recorded demographic characteristics, respiratory functional tests, Charlson comorbidity index and hospital anxiety and depression scale. Patients were followed up for 3 years. In the case of death it was investigated to determine the real cause of death.

Results: 138 patients were studied with a mean age of 66.3 ± 10.3 years and mean FEV_1 of 51.3 ± 16.9%. The mean Charlson index was 4.66 ± 1.57. 17.2% had depression and 12.7% anxiety. Thirteen (9.5%) patients died, 5 of lung cancer, 5 COPD exacerbation, 1 colon cancer, another for acute myocardial infarction (AMI) and another one for congestive heart failure (CHF). In the multivariate analysis the number of comorbidities (HR 1.926; IC 95%: 1.384 - 2.680) and anxiolytic treatment (HR 4.072; IC 95%: 1.106 - 14.987) showed relationship with mortality. Kaplan-Meier suvival plots showed that patients with 2 o more comorbilities, in addition to COPD, have higher mortality than patients with 1 or no comorbidity (35.52 ± 0.2 vs 33 ± 1.3 months, p = 0,039).

Conclusions: The prevalence of comorbidities in patients with stable COPD was high. Mortality in these patients is related to the number of comorbidities and anxiolytic treatment. Mortality was higher in patients with 2 o more comorbidilites.

Key words: COPD, comorbidities, mortality, Charlson index.

INFLUENCIA DE LAS COMORBILIDADES EN LA MORTALIDAD DE PACIENTES CON EPOC ESTABLES

Resumen

Objetivo: Estudiar la relación entre las comorbilidades y la mortalidad por cualquier causa en pacientes con EPOC en fase estable, en nuestro ámbito geográfico.

Material y métodos: Estudio observacional prospectivo longitudinal multicéntrico de una cohorte de pacientes con EPOC en situación estable. Se recogieron datos demográficos, funcionales respiratorios, índice de comorbilidad de Charlson y escala hospitalaria de ansiedad y depresión. Los pacientes fueron seguidos durante 3 años. En el caso de fallecimiento se indagó para determinar la causa de la muerte.

Resultados: Se estudiaron 138 pacientes con una edad media de 66,3 ± 10,3 años y FEV_1 medio de 51,3 ± 16,9%. El índice de Charlson medio fue de 4,66 ± 1,57. Presentaban depresión el 17,2% y ansiedad el 12,7%. Fallecieron 13 (9,5%) pacientes, 5 de cáncer de pulmón, 5 por agudización de la EPOC, 1 por carcinoma de colon, otro por infarto agudo de miocardio (IAM) y otro por insuficiencia cardiaca congestiva (ICC). En el análisis multivariado el número de comorbilidades (HR 1,926; IC 95%: 1,384 - 2,680) y la existencia de tratamiento ansiolítico (HR 4,072; IC 95%: 1,106 - 14,987) se asociaron a mayor mortalidad. El análisis mediante curvas de supervivencia de Kaplan-Meier, mostró que los pacientes con 2 o más comorbilidades, además de la EPOC, presentaban mayor mortalidad que los que tenían una o ninguna (35,52 ± 0,2 vs 33 ± 1,3 meses, p = 0,039).

Conclusiones: La prevalencia de comorbilidades en pacientes con EPOC estable fue elevada. La mortalidad de estos pacientes se relacionó con el número de comorbilidades y el tratamiento ansiolítico. La mortalidad fue superior en aquellos pacientes con 2 o más comorbilidades.

Palabras clave: EPOC, comorbilidades, mortalidad, índice de Charlson.

Received: December 3, 2015. Accepted: February 13, 2017.

Aurelio Arnedillo Muñoz
aure152@separ.es

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is characterized by the chronic limitation of airflow, associated with a chronic inflammatory response in the bronchial tree and lungs, primarily due to the inhalation of tobacco smoke[1]. This inflammatory response does not occur solely at the lung level, as COPD patients also show increased inflammatory markers at the system level and there is a theory that these inflammatory proteins move from the lung to the systemic circulation[2, 3].This systemic inflammation can be seen in other diseases, which are frequently associated with COPD and are known as comorbidities, and it may be implicated in their pathogenesis.

These comorbidities associated with COPD include cardiovascular disease such as coronary heart disease, heart failure, stroke and peripheral vascular disease, neoplasms, diabetes mellitus, anxiety and depression, liver and kidney disease, peptic ulcers, etc. Comorbidities have a significant impact on the prognosis and morbi-mortality for COPD patients and, in fact, they constitute the primary cause of mortality among patients with mild and moderate COPD[4, 5].

Some studies have shown an increase in mortality among COPD patients related to these comorbidities[5-10]. The majority of publications have used the Charlson index to quantify the impact that said comorbidities have on mortality.This index includes many comorbidities/diseases, which are assigned a score. The index is an indicator of mortality in those patients[11].

Data published on the relationship between comorbidities and mortality among COPD patients vary widely and there are factors that can influence this variability such as when patient evaluation is conducted (during admission or a stable period), and the degree of obstruction present; even the geographical region where the study takes place can modify the results[5-10, 12, 13].

Despite the relationship existing between comorbidities and COPD prognosis, until now there has not been data available that connects stable COPD patient mortality and comorbidities in the regions of Andalusia and Extremadura.As a result, our objective has been to study the relationship between comorbidities and mortality by any cause among stable COPD patients, as well as the influence that each of these comorbidities has on said mortality in our geographic region.Our hypothesis is that these comorbidities, particularly some of them, influence mortality among COPD patients.

MATERIAL AND METHODS

A multi-center longitudinal prospective study was designed for a cohort ofstable patients diagnosed with COPD in 5 hospitals in Andalusia and Extremadura.

Patients must have been diagnosed with COPD and met GOLD[1] criteria at least 6 months before their visit, and be smokers or former smokers with exposure intensity of more than 20 packs per year.Those patients presenting with a chronic respiratory disease other than COPD and those who declined to participate in the study or sign the informed consent were excluded. Patients were recruited consecutively through external consults over 3 months and monitoring was carried out for 3 years, from January 2011 to December 2013.

Participatinghospitalswere Hospital Universitario Puerta del Mar (Cádiz), Hospital Universitario Virgen del Rocío (Seville), Hospital Infanta Cristina (Badajoz), Hospital Universitario Virgen de Valme (Seville) and Hospital Universitario San Cecilio (Granada).

All patients completed a standardized questionnaire about demographic data, tobacco use, work status, family situation and level of studies. Average dyspnea was registered using the Modified Medical Research Council (mMRC) scale. Information about current medication and comorbidities was collected using patient medical history and a detailed interview.

Comorbidity was quantified using the Charlson index[11], which was developed to predict mortality in patients with chronic disease.The index assigns each disease/comorbidity a score, which is proportional to the relative risk of dying from the disease.Arterial hypertension (AHT) was collected, which is not included on the Charlson index.Anxiety and depression are also comorbidities that are not included on the Charlson index and have been detected using the Hospital Anxiety and Depression Scale, HAD[14], which has been validated for detecting these diseases. Even so, information about patients' anxiolytic and antidepressant use was collected.A hemogram, basic biochemistry, oxygen saturation measured by pulsioxymetry (SpO2), spirometry with a bronchodilator test and

6-minute walk test were also done.Patients were monitored over 3 years via a visit or phone call every 3 months, collecting information about the need for care facilities and death.

The sample size was calculated analyzing the effect on the Charlson index, accepting a mortality of 10% for stable patients, a standard deviation of 1.1 points on the Charlson index based on previous studies, and accepting an alpha risk of 0.05 and a beta risk of 0.2 in a bilateral contrast.A total of 11 subjects were needed for the first group and 110 for the second to detect a difference greater than or equal to 1 unit on said index.

A descriptive analysis was done for all variables included in the study, using common descriptive statistics.The numerical variables were compared using the independent samples t-test or the Mann-Whitney test when there was abnormal distribution.The chi-square test or Fisher's exact test was used to compare proportions between qualitative variables when they did not meet application conditions.Comparisons between individual predictive variables for mortality were made using Cox regression analysis.To determine mortality indicators, all predictive variables were included in a multivariate Cox proportional hazards model.Kaplan-Meier survival curves were created to see the influence of anxiolytic treatment and comorbidities.The differences between survival curves were evaluated using the log-rank test."P" values less than 0.05 are considered significant.Statistical analysis was done using the SPSS 17.0 software package for Windows.

The study was approved by the Clinical Research Ethics Committee and adheres to the principles of the Declaration of Helsinki for medical research involving human subjects.All participants were informed about the nature of the study and its objectives and agreed to participate by signing an informed consent.Data was collected under strict confidentiality following Spanish Organic Law 15/1999 on the protection of personal data.

Table 1. Details on quantitative population variables

Quantitative variables	Media ± desviación estándar
Age (years)	66.3 ± 10.3
Packs/year	57.9 ± 34.2
Body mass index	28.7 ± 5.5
Post-bronchodilator (postBD) FEV_1 (ml)	1417.7 ± 491.5
Predicted postBD FEV_1 %	51.3 ± 16.9
PreBD FEV_1/FVC%	50.1 ± 16.9
SpO_2	93.9 ± 2.81
Baseline dyspnea (MRC scale)	1.10 ± 1.56
6-minute walk test distance (m)	398.73 ± 131.94
BODE index	3.1 ± 2.1
Charlson index	4.66 ± 1.57
No. of comorbidities excluding COPD	0.94 ± 1.55
Hemoglobin (mg/dl)	14.62 ± 1.71
Total leukocytes ($x10^3$mcL)	9.062 ± 3.615
Lymphocytes (% of total leukocytes)	25.8 ± 10.0
Eosinophils (% of total leukocytes)	2.9 ±5.6

FEV_1: maximum volume exhaled in the first second. FVC: forced vital capacity. BD: bronchodilator. SpO_2: blood oxygen saturation measured by pulsioxymetry. MRC: the Medical Research Council dyspnea scale. COPD: chronic obstructive pulmonary disease.

Table 2. Details on qualitative population variables

Qualitative variables	Number (percentage)
Gender	
- Male	111 (80.4%)
- Female	27 (19.6%)
Tobacco use:	
- Former smoker	98 (71.01%)
- Active smoker	40 (28.9%)

Qualitative variables	Number (percentage)
COPD severity (GOLD)	
1 2 3 4	8 (5.8%) 58 (42.0%) 61 (44.2%) 11 (8.0%)
Treatment with inhaled steroids	105 (76.08%)
Treatment with LABA	105 (76.08%)
Treatment with LAMA	113 (81.8%)
Oxygen therapy	19 (13.7%)
Non-invasive ventilation	13 (9.4%)
Myocardial infraction (history)	17 (12.3%)
Heart failure (history)	11 (8.0%)
Arterial hypertension	47 (34.1%)
Depression (according to HAD)	24 (17.4%)
Anxiety (according to HAD)	18 (13.04%)
Antidepressant treatment	7 (5.1)%
Anxiolytic treatment	16 (11.6)%
Dyspnea severity (MRC)	
0 1 2 3 4	11 (7.97%) 55 (39.85%) 45 (32.60%) 22 (15.94%) 5 (3.60%)
≥ 2 comorbidities (including COPD)	67 (48.6%)
≥ 3 comorbidities (including COPD)	32 (23.2%)
Deaths	
No Yes: Lung cancer: Colorectal cancer: AECOPD: Coronary heart disease: Heart failure:	124 (90.5%) 13 (9.5%) 5 (3.6%) 1 (0.7%) 5 (3.6%) 1 (0.7%) 1 (0.7%)

GOLD: *Global Obstructive Lung Disease*. LABA: beta agonista de acción prolongada. LAMA: anticolinérgico de acción prolongada. AE-POC: Agudización de la EPOC. MRC: Escala de disnea de la *Medical Research Council*. HAD: *Hospital anxiety and depression scale*.

Table 3. Variables with statistically significant differences between deceased and living patients

Variable	Deceased	Living	P
Hemoglobin (mg/dl)	13.43 ± 1.99	14.76 ± 1.63	0.007
Charlson index	6.70 ± 2.01	5.5 ± 1.5	0.038
No. of comorbidities	1.70 ± 0.94	3.46 ± 2.36	<0.001
NIMV	4 (2.9%)	9 (6.5%)	0.006
Antidepressant treatment	3 (2.2%)	4 (2.9%)	0.002
Anxiolytic treatment	5 (3.6%)	11 (8%)	0.002
AMI	5 (3.6%)	12 (8.7%)	0.003
AHT	9 (6.5%)	37 (26.8%)	0.004
CHF	5 (3.6%)	6 (4.3%)	0.001

Values for numerical variables are expressed as average ± standard deviation. For qualitative variables they are expressed as absolute value and percentage.NIMV: non-invasive mechanical ventilation. AMI: history of acute myocardial infarction. AHT: arterial hypertension. CHF: history of congestive heart failure.

Table 4. Predictive variables for mortality. Bivariate analysis using Cox regression

Variable	P	RR	IC 95%	
			Lower	Upper
Hemoglobin (mg/dl)	0.005	0.645	0.474	0.878
Charlson index	0.023	1.498	1.057	2.122
No. of comorbidities	<0.001	1.956	1.457	2.628
NIMV	0.029	4.403	1.167	16.614
Antidepressant treatment	0.035	5.202	1.123	24.103
Anxiolytic treatment	0.008	5.285	1.546	18.067
AMI	0.014	4.687	1.371	16.017
AHT	0.009	5.838	1.548	22.011
CHF	0.004	7.132	1.888	26.947

NIMV: non-invasive mechanical ventilation. AMI: history of acute myocardial infarction. AHT: arterial hypertension. CHF: history of congestive heart failure. P: level of statistical significance. RR: risk ratio CI: confidence interval.

Table 5. Independent mortality risk, adjusted for age and gender and by interaction between risk factors. Multivariate analysis using the Cox proportional hazards model

Variable	P	HR	IC 95%	
			Lower	Upper
Age	0.624	1.019	0.945	1.100
Gender	0.757	1.308	0.239	7.160
No. of comorbidities	<0.001	1.926	1.384	2.680
Anxiolytic treatment	0.035	4.072	1.106	14.987

No.: number.P: level of statistical significance. HR: hazard ratio. CI: confidence interval.

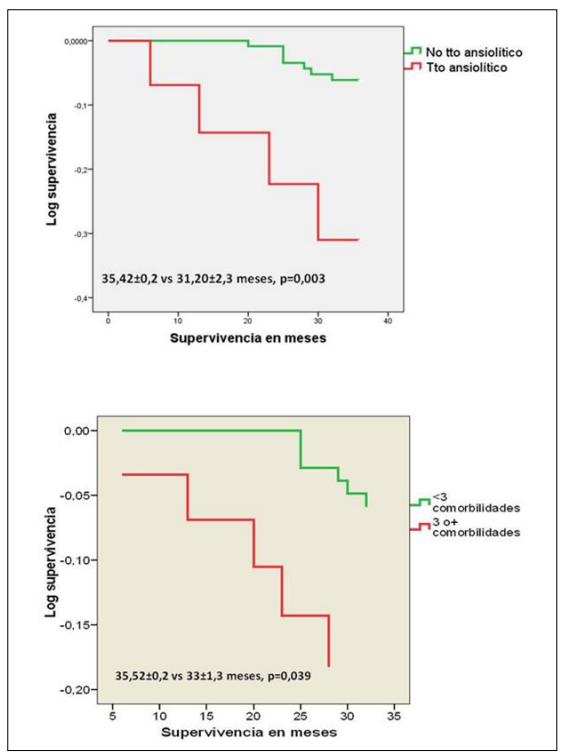

Figure 1. Kaplan-Meier survival curves with log-rank test analysis for patients with and without anxiolytic treatment who have 3 or more comorbidities (including COPD) vs. those with fewer than 3 comorbidities.Tto: treatment. P: level of statistical significance.

RESULTS

The study included 138 patients, whose general data can be found in Tables 1 and 2.The majority of participants were men and a third were current active smokers.The average degree of obstruction was moderate to severe, and more than 80% of the study population belonged to these groups.

The average Charlson index was high, revealing patients presented abundant associated comorbidities, many of which were cardiovascular as can be seen in Table 2.The HAD questionnaire was used to detect depression in 17.4% of patients and anxiety in 13.04%.Nearly 50% of patients presented with 2 or more comorbidities and almost a quarter had 3 or more, including COPD.13 patients (9.5%) passed away during monitoring. The most frequent causes of death were neoplasms and acute exacerbations of COPD (AECOPD).

Table 3 reflects the results of variables which show statistical significance in the bivariate analysis between the group of deceased patients and those who are still living.

Table 4 shows the individual predictive variables for mortality in bivariate analysis using Cox regression.

In the Cox multivariate analysis (Table 5), only the presence of anxiolytic treatment and the number of comorbidities were shown to be independent mortality factors, having been adjusted for age and gender.

Patient survival was compared in function of the number of comorbidities and patients with 2 or more comorbidities in addition to COPD were shown to have a higher mortality than those who presented with 1 or no comorbidities.The Kaplan-Meier survival curves comparing both groups can be seen in Figure 1, as well as the patients with and without anxiolytic treatment.

DISCUSSION

This study describes the relationship between comorbidities and mortality among stable COPD patients from the regions of Andalusia and Extremadura for the first time.According to the results, the global mortality among stable COPD patients is related to the Charlson index; the number of comorbidities, particularly AMI, AHT, and CHF; lower hemoglobin levels and treatment with anxiolytics and antidepressants.However, in the multivariate analysis, only anxiolytic treatment and the number of comorbidities were related to higher mortality.

The first surprising piece of data is the mortality seen within the sample population, which is lower than what was expected at 9.5%.Some authors have described mortality rates one year after hospital discharge at about 28%[12]; but for stable patients undergoing treatment, like those in our study, the mortality rate in the TORCH study[15] at 3 years was 12.6% and the UPLIFT study[16] showed a 14.4% mortality rate at 4 years. These figures are closer to ours, although the studies are older.Some publications have shown a progressive decrease in mortality rates for COPD patients[17, 18], a trend which may justify our lower mortality rate for stable patients at the time of recruitment.

Causes of mortality for our patients are in accordance with information published in the bibliography.Many publications have shown an increased prevalence of mortality from neoplasms, primarily lung cancer and cardiovascular disease[5, 19-21], in addition to deaths caused by acute exacerbations of COPD (AECOPD).The most frequent causes of death among the population of this study were neoplasms and AECOPD, with cardiovascular disease being the third most prevalent.Within cardiovascular diseases, there are authors who have observed higher mortality among patients with AMI and CHF, as seen in our study population[22].

With regard to the relationship between the Charlson index and COPD patient mortality, published results show different findings.Antonelli-Incalzi et al.[6] studied this aspect in a 270-patient cohort, although post-hospitalization. Among this population, the Charlson index did not show predictive capability in the multivariate analysis.Gronewegen et al.[12] also analyzed this prognostic index in patients hospitalized for AECOPD and, although the Charlson index associated it with a significantly higher risk of death, the multivariate analysis was unable to demonstrate an independent association.On the other hand, Almagro et al.[13] studied 135 patients hospitalized for AECOPD. In this case, the Charlson index did significantly associate it with decreased survival.The multivariate analysis revealed that for patients presenting a Charlson index equal to or higher than 3 (the equivalent of 2 chronic diseases or one serious disease in addition to COPD), there was a higher risk of death.In a study on stable COPD patients, Matters et al.[23] also found no association between the Charlson index and mortality after 4.2 years of follow-up.Similar to Gronewegen et al.[12], the present study found a significant association between the Charlson index and a reduced survival rate in patients, but the multivariate analysis did not prove this association.In contrast, in the multivariate analysis the number of comorbidities was indeed independently associated with a higher mortality. Additionally, we have seen that the presence of 2 or more comorbidities is associated with a higher mortality (Figure 1), similar to the results of Almagro et al.[13]. Mortality increased by 1.92 (CI 95%: 1.38-2.68) within the study population among those patients with 3 or more comorbidities (including COPD).

However, we believe that the Charlson index was designed at a time when some of the measured parameters had a significant influence on mortality (such as AIDS, which no longer has the mortality rate it was associated with in the '80s when this index was created).Moreover, the index does not include other important comorbidities such as AHT, anxiety and depression.As a result, we believe that new indexes should be developed which are more realistic than the Charlson index and, above all, aimed toward the specific population of COPD patients.In this sense, the recently described COTE index which uses 12 comorbidities and was developed for COPD patients is promising[7].

With respect to hemoglobin levels, the patients who showed higher mortality had significantly lower hemoglobin levels and, although this was not an independent factor for mortality in the multivariate analysis, some authors have found higher mortality among COPD patients with anemia, in addition to a poorer prognosis during hospitalization for AECOPD[21, 24, 25].

As far as the findings related to anxiety and depression, the prevalence varied considerably depending on the selected population.In a revision of COPD patients, selecting those studies that used the same questionnaire as that used for the present study, Maurer et al.[26] describe anxiety rates of between 13 and 55% and depression rates between 7 and 32%. The prevalence in this study fell within the lower limits of those described.It is important to note the infradiagnosis and infratreatment of these patients, as only 16.6% of those the HAD questionnaire detected as being depressed were undergoing anti-depression treatment and 27.7% were undergoing treatment for anxiety.The present study showed no relationship between anxiety or depression and long-term mortality, but it did link mortality with undergoing anxiolytic treatment.Some authors have described higher mortality among patients with anxiety and depression, as well as longer hospital stays, worse recovery after hospitalization and a higher risk of being readmitted[27-29].

As far as limitations of the present study, one has been the low level of mortality that has been seen.The sample size was calculated for an estimated mortality of 10%, which is low in itself.However, if we calculate a sample for a 9.5% mortality rate, which is what we obtained, a minimum of 11 patients would be needed in the deceased group, the same number for the 10% mor-

tality rate, and 104 for the group of still living patients. As a result, this does not affect the statistic results obtained.

Another limitation is that the diagnoses of anxiety or depression we made in patients were based on the HAD questionnaire without confirming whether the patients actually suffered from these diseases, rather than through a psychiatric study.However, a psychiatric study for our entire population would suppose an extra burden that would be difficult to undertake, which is the reason it was decided to use said questionnaire as it is one of the most frequently used for COPD patients to detect this disease and it has been properly validated.In any case, the questionnaire can give false negatives for patients who have previously been treated with antidepressants or anxiolytics who are taking medication and, in fact, of the patients the questionnaire did not diagnose with depression, three were taking antidepressants. In the case of anxiety, 11 were taking anxiolytics and were not diagnosed with anxiety through the HAD questionnaire.This has likely had an influence on the infradiagnosis of the disease and the fact that anxiolytic treatment was associated with a higher mortality instead of the disease.

In conclusion, there was a high prevalence of comorbidities in our population of stable COPD patients.The most frequent causes of mortality were neoplasms, acute exacerbations of COPD and cardiovascular comorbidity (CHF and AMI).In the multivariate analysis, patient mortality was associated with anxiolytic treatment and the number of comorbidities.Patients with 2 or more comorbidities in addition to COPD showed higher mortality than those who had one or no comorbidities.As a result, we believe that the early detection and treatment of these comorbidities could improve survival among COPD patients.

BIBLIOGRAFIA

1. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for diagnosis, management, and prevention of COPD. Updated 2015. Disponible en: http://www.goldcopd.org/
2. Sinden NJ, Stockley RA. Systemic inflammation and comorbidity in COPD: a result of 'overspill' of inflammatory mediators from the lungs? Review of the evidence. Thorax 2010; 65: 930-6.
3. Fabbri LM, Luppi F, Beghé B et al. Complex chronic comorbidities of COPD. Eur Respir J 2008; 31 (1): 204-12.
4. Mannino DM, Watt G, Hole D et al. The natural history of chronic obstructive pulmonary disease. Eur Respir J 2006; 27: 627-43.
5. Cavaille`s A, Brinchault-Rabin G, Dixmier A et al. Comorbidities of COPD. Eur Respir Rev 2013; 22: 454-475.
6. Antonelli-Incalzi R, Fuso L, De Rosa M et al. Co-morbidity contributes to predict mortality of patients with chronic obstructive pulmonary disease. Eur Respir J 1997; 10: 2794-800.
7. Divo M, Cote C, de Torres JP et al. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. BODE Collaborative Group. Am J Respir Crit Care Med 2012; 186: 155-61.
8. Baty F, Putora PM, Isenring B et al. Comorbidities and burden of COPD: a population based case-control study. PLoS One 2013; 8 (5): e63285.
9. Mannino DM, Thorn D, Swensen A et al. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. Eur Respir J 2008; 32 (4): 962-9.
10. Holguin F, Folch E, Redd SC et al. Comorbidity and mortality in COPD-related hospitalizations in the United States, 1979 to 2001. Chest. 2005: 128 (4): 2005-11.
11. Charlson ME, Pompei P, Ales KL et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40: 373-83.
12. Groenewegen KH, Schols AM, Wouters EF. Mortality and mortality-related factors after hospitalization for acute exacerbation of COPD. Chest 2003; 24 (2): 459-67.
13. Almagro P, Calbo E, Ochoa de Echagüen A et al. Mortality after hospitalization for COPD. Chest 2002; 121 (5): 1441-8.
14. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983; 67: 361–70.
15. Calverley PM, Anderson JA, Celli B et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. TORCH investigators. N Engl J Med 2007; 356 (8): 775-89.
16. Tashkin DP, Celli B, Senn S et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. UPLIFT Study Investigators. N Engl J Med. 2008; 359 (15): 1543-54.
17. Rothnie KJ, Yan R, Smeeth L et al. Risk of myocardial infarction (MI) and death following MI in people with chronic obstructive pulmonary disease (COPD): a systematic review and meta-analysis. BMJ Open 2015; 5 (9): e007824.
18. López-Campos JL, Ruiz-Ramos M, Soriano JB. COPD mortality rates in Andalusia, Spain, 1975-2010: a joinpoint regression analysis. Int J Tuberc Lung Dis 2013; 17 (1): 131-6.
19. Chatila WM, Thomashow BM, Minai OA et al. Comorbidities in chronic obstructive pulmonary disease. Proc Am Thorac Soc 2008; 5 (4): 549-55.
20. Rothnie KJ, Yan R, Smeeth L et al. Risk of myocardial infarction (MI) and death following MI in people with chronic obstructive pulmonary disease (COPD): a systematic review and meta-analysis. BMJ Open 2015; 5 (9): e007824.
21. Cavaillès A, Brinchault-Rabin G, Dixmier A et al. Comorbidities of COPD. Eur Respir Rev 2013; 22 (130): 454-75.
22. Chen W, Thomas J, Sadatsafavi M et al. Risk of cardiovascular comorbidity in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. Lancet Respir Med 2015; 3 (8): 631-9.
23. Maters GA, de Voogd JN, Sanderman R et al. Predictors of all-cause mortality in patients with stable COPD: medical co-morbid conditions or high depressive symptoms. COPD

2014; 11 (4): 468-74.
24. Cote C, Zilberberg MD, Mody SH et al. Haemoglobin level and its clinical impact in a cohort of patients with COPD. Eur Respir J 2007; 29: 923-29.
25. Portillo K, Martinez-Rivera C, Ruiz-Manzano J. Anemia in chronic obstructive pulmonary disease. Does it really matter? Int J Clin Pract 2013; 67 (6): 558-65.
26. Maurer J, Rebbapragada V, Borson S et al. Anxiety and depression in COPD: current understanding, unanswered questions, and research needs. Chest 2008 Oct; 134 (4 Suppl): 43S-56S.
27. de Voogd JN, Wempe JB, Koëter GH et al. Depressive symptoms as predictors of mortality in patients with COPD. Chest 2009; 135 (3): 619-25.
28. Papaioannou AI, Bartziokas K, Tsikrika S et al. The impact of depressive symptoms on recovery and outcome of hospitalised COPD exacerbations. Eur Respir J 2013; 41 (4): 815-23.
29. Papaioannou A, Bartziokas K, Tsikrika S et al. The impact of depressive symptoms on recovery and outcome of hospitalized COPD exacerbations. Eur Respir J 2013; 41: 815-823.