International Journal of Chronic Obstructive Pulmonary Disease Dovepress
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ORIGINAL RESEARCH

Influence of Comorbidities on the Survival of COPD Patients According to Phenotypes

This article was published in the following Dove Press journal:
International Journal of Chronic Obstructive Pulmonary Disease

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Background: Chronic obstructive pulmonary disease (COPD) usually occurs alongside other conditions. Few studies on comorbidities have taken into account the phenotypes of COPD patients. The objective of this study is to evaluate the prevalence of comorbidities included in the Charlson index and their influence on the survival of patients with COPD, taking phenotypes into account.

Methods: An observational study was conducted on a group of 273 patients who had COPD and underwent spirometry in the first half of 2011, with a median prospective follow-up period of 68.15 months. The survival of these patients was analyzed according to the presence of various comorbidities.

Results: Of the 273 patients, 93 (34.1%) died within the follow-up period. An increased presence of chronic ischemic heart disease (CIHD), chronic heart failure (CHF), chronic kidney disease (CKD), and malignancy was found in deceased patients. All of these conditions shorten the survival of COPD patients globally; however, when considering phenotypes, only CHF influences the exacerbator with chronic bronchitis phenotype, CKD influences the non-exacerbator phenotype, and malignancy influences the positive bronchodilator test (BDT) and exacerbator with chronic bronchitis phenotypes. In the multivariate model, advanced age (hazard ratio, HR: 1.05; p=0.001), CHF (HR: 1.74; p=0.030), and the presence of malignancy (HR: 1.78; p=0.010) were observed as independent mortality risk factors.

Conclusion: The survival is shorter in the presence of CIHD in overall COPD patients and also CHF, CKD, and malignancy for certain phenotypes. It is important to pay attention to these comorbidities in the comprehensive care of COPD patients.

Keywords: COPD, phenotypes, comorbidities, risk factors, mortality, survival

Introduction

Chronic obstructive pulmonary disease (COPD) is a widely prevalent condition with high morbidity and mortality rates.[1] It often leads to comorbidities[2–4] because the disease has systemic involvement and shares common risk factors with other pathologies. For this reason, a comorbidome has been described, where the associations of COPD with other diseases are represented.[5]

Numerous studies have analyzed the influence of certain diseases on COPD and vice versa, including ischemic heart disease,[6] heart failure,[7] cerebrovascular disease,[8] diabetes mellitus (DM),[9] and lung cancer.[10]

There are large cohort or population studies that have analyzed the set of comorbid conditions that COPD patients could suffer from. Gershon et al[11] described the prevalence of comorbidities in COPD patients and proposed studies to determine the long-term influence of these conditions on the evolution of COPD.

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http://doi.org/10.2147/COPD.S270770

Although some similar studies exist, most of them have been carried out over a decade ago.[12] For this reason, it is important to obtain updated the data to adapt to changes in the epidemiology of these diseases.

The classification of COPD patients into different phenotypes is a recommendation that has been added to clinical practice guidelines in recent years,[13,14] since not all COPD patients clinically behave in the same way or present the same evolution.[15] Therefore, it is also interesting to investigate the influence of these comorbid conditions on each COPD phenotype.

The objective of the present study was to evaluate the prevalence of comorbidities included in the Charlson index in patients with COPD, both overall and for each phenotype, and to also identify those comorbid conditions associated with higher mortality rates.

Patients and Methods

Design

We conducted an observational non-interventional study of a cohort of patients with established diagnoses of COPD. They were recruited in the stable phase, and a prospective follow-up was made, with the aim of avoiding any possible biases that may exist in a retrospective study.

The patients that participated in the research were over 40 years old and had a history of smoking, with a pack-year index equal to or greater than 10. They had a previous and confirmed diagnosis of COPD, established using a spirometry test, and they underwent scheduled spirometry tests between January 1, 2011 and June 30, 2011.

Those patients who had a forced expiratory volume in one second (FEV1) above 70% of the predicted value were excluded from the study. Further, neither patients with non-obstructive respiratory pathologies nor patients included in clinical trials were admitted.

Parameters

We collected the parameters during recruitment and at the end of the study. The recruitment period ran from January to June 2011, and the follow-up period ended in April 2017.

The demographic data of patients and their comorbidities were collected in the recruitment phase: age, gender, weight, height, body mass index (BMI), date of inclusion, FEV1, smoking history, COPD phenotype, pharmacological treatment of disease, respiratory therapies, and comorbidities included in the Charlson index, which has been widely used to evaluate the prognosis of patients, taking 22 comorbid conditions into account.

Mortality data were collected in the follow-up phase: the last follow-up date of surviving patients and the cause of death and death date of deceased patients.

Definition of Phenotypes

All patients included in the study were classified into one of the following four COPD phenotypes: non-exacerbator (NE), positive response to bronchodilator (PRTB), exacerbator with emphysema (EWE), and exacerbator with chronic bronchitis (EWCB).

The process followed to classify COPD patients into these phenotypes was as follows. First, patients with a positive response to the bronchodilator test, defined by an increment of FEV1 of at least 200 mL in absolute value and at least 12% in comparison to FEV1 without a bronchodilator, were considered to be PRTB phenotype. Third, patients who were not classified into either of these two phenotypes were considered as EWE or as EWCB phenotypes, according to the following criteria: if dyspnea was the patient's main symptom and radiological emphysema or a decrease in the capacity of diffusion of carbon monoxide (DLCO) existed (which supports the diagnosis of emphysema), they were classified as EWE phenotype. If their predominant symptom was cough and expectoration for at least 3 months per year in the last two years, they were considered to be patients with EWCB phenotype.

This classification process did not exactly conform to the definition provided in the Spanish guidelines on COPD (GesEPOC).[13] According to GesEPOC, a patient has asthma-COPD overlap (ACO) phenotype if they demonstrate a very positive response in the bronchodilator test, defined as an FEV1 increment greater than 400 mL in absolute value and 15% in relative value. Similar to other published studies,[15] we think that this definition provides very high specificity but little sensitivity for this phenotype. Instead of the ACO phenotype, we use the PRTB phenotype.

Cause of Death

In the group of deceased patients with a known cause of death, for both in deaths produced inside and outside the hospital, we were able to establish four primary causes of death: respiratory, cardiovascular, infectious, and malignancy. The respiratory causes included COPD exacerbation, respiratory failure, and respiratory acidosis. The cardiovascular causes included acute myocardial infarction, decompensation of heart failure, and pulmonary thromboembolism. The infectious causes included

infections in any location. The malignancy causes included the complications arising from tumor progression without any other underlying causes. If several different causes of death were present, only the predominant one was considered.

Statistical Analysis

A histogram was used to check the normal distribution. The quantitative variables that had a normal distribution were expressed in terms of their mean and standard deviation (SD). The quantitative variables that did not follow a normal distribution were expressed in terms of their median and interquartile range (IQR). Qualitative variables were expressed as frequencies and percentages.

The analysis of variance test was used to compare quantitative variables with normal distribution, while the Kruskal–Wallis test was used to analyze the quantitative variables without normal distributions. Depending on the sample size, the chi-squared test or Fisher's exact test were used to compare qualitative variables and proportions.

The univariate comparison of mortality based on the presence or absence of certain comorbid conditions, was performed using the long-rank test. The analysis of survival was graphically represented in Kaplan–Meier graphs.

A Cox regression was performed during multivariate analysis, with the aim of adjusting mortality to gender, age, phenotypes and pulmonary function with the presence of chronic ischemic heart disease (CIHD), chronic heart failure (CHF), chronic kidney disease (CKD), and malignancy. The proportionality of risks of the included variables was also checked. Further, the level of statistical significance considered for all comparisons was two-tailed $p < 0.05$.

The statistical program used for all analyses was SPSS version 26, except for the graphical representation and the survival analysis, where Stata version 15 was used.

Ethics and Informed Consent

Our study was approved by the Ethics Committee of Gregorio Marañón University General Hospital, with approval code HUIL-1507. Patients signed informed consent prior to taking part in the study.

This study was conducted in accordance with the Declaration of Helsinki.

Results

During the recruitment period, 273 patients met the eligibility criteria. All of them agreed to participate in the study and none withdrew early. Of all the patients included in this study, 243 (89%) of whom were male. The median of the follow-up period was 68.16 months (IQR 40.96–72.12). The mean age was 68 years (SD 10.62). The mean height was 1.63 m (SD 0.08) and the mean weight was 75.03 kg (SD 16.89); therefore, the mean BMI was 28.05 kg/m2 (SD 5.49). Regarding pulmonary function, the mean absolute value of FEV1 was 1211 mL (SD 417) and 48.64% predicted (SD 12.59). At inclusion, 92 patients (34%) were active smokers. In relation to COPD pharmacological treatment, 242 patients (88.6%) had chronic treatment with a long-acting adrenergic β-2-agonist (LABA) at the time of recruitment, 254 patients (93%) were taking a long-acting muscarinic antagonist (LAMA), and 212 (77.7%) were receiving inhaled corticosteroids (ICS). Regarding oxygen and positive pressure therapies, continuous positive airway pressure (CPAP) was used by 31 patients (11.4%), 14 patients (5.1%) were treated with bi-level positive airway pressure (BiPAP) therapy, and long-term oxygen therapy (LTOT) was used in 91 patients (33.3%). Full descriptive data, overall and for each phenotype, are shown in Table 1.

The presence of the comorbidities included in the Charlson index—both overall and for each phenotype—is shown in Table 2. It also shows the scores for this index. A higher proportion of patients with CIHD were observed in the EWCB phenotype (p=0.000), a higher presence of dementia was found in the exacerbator with emphysema phenotype (p=0.017), and the only patient with cerebrovascular disease belonged to the exacerbator with emphysema phenotype (p=0.027).

Table 3 shows the presence of comorbidities included in the Charlson index as a function of survival or death during follow-up. A higher proportion of CIHD, CHF, CKD, and malignancy were found among deceased patients, a finding that was statistically significant (p=0.041, p=0.003, p=0.022 and p=0.004, respectively). In addition, the deceased patient group also had a higher Charlson comorbidity index score (p=0.000).

Figure 1 shows a graphical comparison of the survival rate between COPD patients without comorbidities and those suffering from CIHD, CHF, CKD or malignancy. It is clear that a greater proportion of COPD patients without comorbidities survived in the follow-up period in comparison to patients with comorbidities (Table 3). Figure 2 shows the same comparison, taking COPD phenotypes into account.

Table 4 shows the numerical results for the survival, log-rank, and p-values of COPD patients as a function of COPD phenotypes and comorbid conditions. Comorbid conditions —such as CIHD, CHF, CKD, and malignancy—were shown to reduce the overall survival rates of COPD patients (p=0.012, p=0.000, p=0.050 and p=0.000, respectively).

Table 1 Description and Comparison of General Characteristics of All Patients and According to Phenotypes

Variables	NE Phenotype	EWE Phenotype	EWCB Phenotype	PRTB Phenotype	Overall	*p*-value
Patients, n	135 (49.5)	27 (9.9)	40 (14.7)	71 (26.0)	273 (100.0)	0.464
Male, n (%)	124 (91.8)	22 (81.5)	34 (85.0)	63 (88.7)	243 (89.0)	0.342
Age, years (SD)	69.76 (9.33)	67.44 (11.23)	70.47 (10.10)	63.44 (11.70)	67.99 (10.62)	0.000
Height, m (SD)	1.63 (0.07)	1.61 (0.08)	1.61 (0.08)	1.65 (0.09)	1.63 (0.08)	0.075
Weight, kg (SD)	76.04 (17.75)	71.85 (18.46)	66.78 (10.85)	77.01 (16.94)	75.03 (16.89)	0.130
BMI, kg/m2 (SD)	28.48 (5.83)	27.46 (6.19)	26.82 (3.55)	28.15 (5.44)	28.05 (5.49)	0.365
FEV1, % (SD)	48.57 (12.52)	44.66 (11.82)	42.53 (11.55)	53.71 (11.66)	48.64 (12.59)	0.000
Active smoking, n (%)	36 (26.7)	7 (25.9)	14 (35.0)	35 (49.3)	92 (34%)	0.009
Pharmacological treatment, n (%)						
LABA	111 (82.2)	26 (96.3)	39 (97.5)	66 (93.0)	242 (88.6)	0.009
LAMA	129 (95.6)	25 (92.6)	40 (100.0)	60 (84.5)	254 (93.0)	0.006
ICS	91 (67.4)	23 (85.2)	37 (92.5)	61 (84.5)	212 (77.7)	0.001
Respiratory therapies, n (%)						
CPAP	16 (11.9)	3 (11.1)	2 (5.0)	10 (14.1)	31 (11.4)	0.539
BiPAP	6 (4.4)	2 (7.4)	5 (12.5)	1 (1.4)	14 (5.1)	0.075
LTOT	39 (28.9)	13 (48.1)	25 (62.5)	14 (20.0)	91 (33.3)	0.000
Follow-up, months (IQR)	66.55 (37.83–71.74)	61.32 (35.33–71.94)	41.65 (20.18–71.21)	70.99 (54.13–73.45)	68.15 (40.69–72.12)	0.000
Death, n (%)	49 (36.3)	12 (44.4)	20 (50.0)	12 (16.9)	93 (34.1)	0.001

Abbreviations: NE, non-exacerbator; EWE, exacerbator with emphysema; EWCB, exacerbator with chronic bronchitis; PRTB, positive response to bronchodilator; SD, standard deviation; FEV1, forced expiratory volume in one second; BMI, body mass index; LABA, long-acting beta-2-adrenergic agonist; LAMA, long-acting muscarinic antagonist; ICS, inhaled corticosteroid; CPAP, continuous positive airway pressure; BiPAP, bilevel positive airway pressure; LTOT, long-term home oxygen therapy; IQR, interquartile range.

Table 2 Comorbidities in All Patients and According to Phenotypes

Comorbidity, n (%)	NE Phenotype	EWE Phenotype	EWCB Phenotype	PRTB Phenotype	Overall	*p*-value
CIHD	19 (14.1)	1 (3.7)	14 (35.0)	4 (5.6)	38 (13.9)	0.000
CHF	16 (11.9)	5 (18.5)	9 (22.5)	7 (9.9)	37 (13.6)	0.216
PVD	6 (4.4)	3 (11.1)	1 (2.5)	1 (1.4)	11 (4.0)	0.167
CVD	0 (0.0)	1 (3.7)	0 (0.0)	0 (0.0)	1 (0.4)	0.027
Dementia	0 (0.0)	2 (7.4)	0 (0.0)	3 (4.2)	5 (1.8)	0.017
CLD	135 (100.0)	27 (100.0)	40 (100.0)	71 (100.0)	273 (100.0)	-
CTP	2 (1.5)	0 (0.0)	0 (0.0)	1 (1.4)	3 (1.1)	0.804
Ulcer	8 (5.9)	2 (7.4)	2 (5.0)	2 (2.8)	14 (5.1)	0.742
MLD	4 (3.0)	1 (3.7)	2 (5.0)	2 (2.8)	9 (3.3)	0.924
SLD	1 (0.7)	1 (3.7)	2 (5.0)	3 (4.2)	7 (2.6)	0.299
DM	31 (23.0)	6 (22.2)	14 (35.0)	12 (16.9)	63 (23.1)	0.192
CDM	1 (0.7)	1 (3.7)	0 (0.0)	1 (1.4)	3 (1.1)	0.503
Hemiplegia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
CKD	16 (11.9)	0 (0.0)	4 (10.0)	3 (4.2)	23 (8.4)	0.098
Malignancy	41 (30.4)	5 (18.5)	9 (22.5)	16 (22.5)	71 (26.0)	0.420
Leukemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.4)	0.414
Lymphoma	0 (0.0)	1 (3.7)	0 (0.0)	1 (1.4)	2 (0.7)	0.171
Metastasis	3 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.1)	0.376
HIV	0 (0.0)	0 (0.0)	1 (2.5)	0 (0.0)	1 (0.4)	0.119
Charlson, median (IQR)	2 (1–4)	2 (1–3)	3 (1–4)	2 (1–3)	2 (1–4)	0.082

Abbreviations: NE, non-exacerbator; EWE, exacerbator with emphysema; EWCB, exacerbator with chronic bronchitis; PRTB, positive response to bronchodilator; CIHD, chronic ischemic heart disease; CHF, chronic heart failure; PVD, peripheral vascular disease; CVD, cerebrovascular disease; CLD, chronic lung disease; CTP, connective tissue pathology; MLD, mild liver disease; SLD, severe liver disease; DM, diabetes mellitus; CDM, complicated diabetes mellitus; CKD, chronic kidney disease; HIV, human immunodeficiency virus; IQR, interquartile range.

Table 3 Mortality According to Each Comorbidity and Charlson Index

Comorbidity, n (%)	Death Yes	Death No	*p*-value
CIHD	19 (20.4)	19 (10.6)	0.041
CHF	21 (22.6)	16 (8.9)	0.003
PVD	4 (4.3)	7 (3.9)	1.000
CVD	0 (0.0)	1 (0.6)	1.000
Dementia	3 (3.2)	2 (1.1)	0.341
CLD	93 (100.0)	180 (100.0)	-
CTP	2 (2.2)	1 (0.6)	0.268
Ulcer	7 (7.5)	7 (3.9)	0.248
MLD	4 (4.3)	5 (2.8)	0.495
SLD	3 (3.2)	4 (2.2)	0.693
DM	28 (30.1)	35 (19.4)	0.051
CDM	0 (0.0)	3 (1.7)	0.553
Hemiplegia	0 (0.0)	0 (0.0)	-
CKD	13 (14.0)	10 (5.6)	0.022
Malignancy	34 (36.6)	37 (20.6)	0.004
Leukemia	0 (0.0)	1 (0.6)	1.000
Lymphoma	1 (1.1)	1 (0.6)	1.000
Metastasis	2 (2.2)	1 (0.6)	0.268
HIV	1 (1.1)	0 (0.0)	0.341
Charlson, median (IQR)	3 (2–4)	2 (1–3)	0.000

Abbreviations: CIHD, chronic ischemic heart disease; CHF, chronic heart failure; PVD, peripheral vascular disease; CVD, cerebrovascular disease; CLD, chronic lung disease; CTP, connective tissue pathology; MLD, mild liver disease; SLD, severe liver disease; DM, diabetes mellitus; CDM, complicated diabetes mellitus; CKD, chronic kidney disease; HIV, human immunodeficiency virus; IQR, interquartile range.

However, taking into account the phenotypes, CHF shortened the survival rates in the exacerbator with chronic bronchitis phenotype (p=0.031), CKD reduced survival rates in the non-exacerbator phenotype (p=0.031), and malignancy decreased survival rates in positive bronchodilator response phenotype (p=0.000) and exacerbator with chronic bronchitis phenotype (p=0.003).

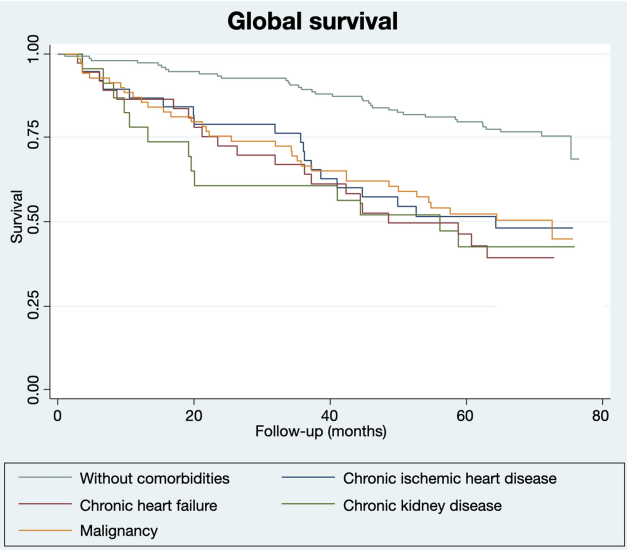

Figure 1 Kaplan–Meier graph of survival according to the presence of chronic ischemic heart disease, chronic heart failure, chronic kidney disease and malignancy in overall COPD patients.

On one hand, Table 5 shows that increased age, CHF, and malignancy are risk factors independently associated with mortality (p=0.001, p=0.030 and p=0.010, respectively). On the other hand, it is shown that a high FEV1 absolute value is a protective factor that is independently associated with mortality (p=0.014).

Table 6 shows the causes of death among patients with comorbid conditions, with a significant increase in mortality. In some cases where death occurred outside of the hospital, information could not be obtained regarding the cause of death. Using the information available regarding the cause of death, we only observed that patients who suffered from malignancies usually died owing to tumor progression (p=0.000).

Discussion

The main conclusion of our study is that there are some comorbid conditions—such as CIHD, CHF, CKD, and malignancy—that reduce the overall survival rates of COPD patients. If we take COPD phenotypes into account, these comorbidities do not affect all COPD patients in the same way: CHF shortens survival rates in the exacerbator with chronic bronchitis phenotype, CKD reduces survival in the non-exacerbator phenotype, and malignancy decreases survival in positive bronchodilator response and exacerbator with chronic bronchitis phenotypes. Two of these comorbidities (CHF and malignancy) and advanced age are risk factors independently associated with mortality. However, improved lung function, defined as a higher absolute value of FEV1, is a protective factor independently associated with mortality. Regarding the cause of death of deceased patients with comorbid conditions, it was only found that patients with malignancy died of this cause.

It is important to note that, in our study, only patients with COPD of at least moderate severity were considered. Therefore, patients with mild COPD have not been taken into account, since survival in these patients could depend more on other diseases than on COPD.

The results obtained in our study are similar to those published by Almagro et al,[16] who also described cardiovascular diseases and CKD as risk factors independently associated with mortality in patients with COPD. The difference between our study and the Almagro study is

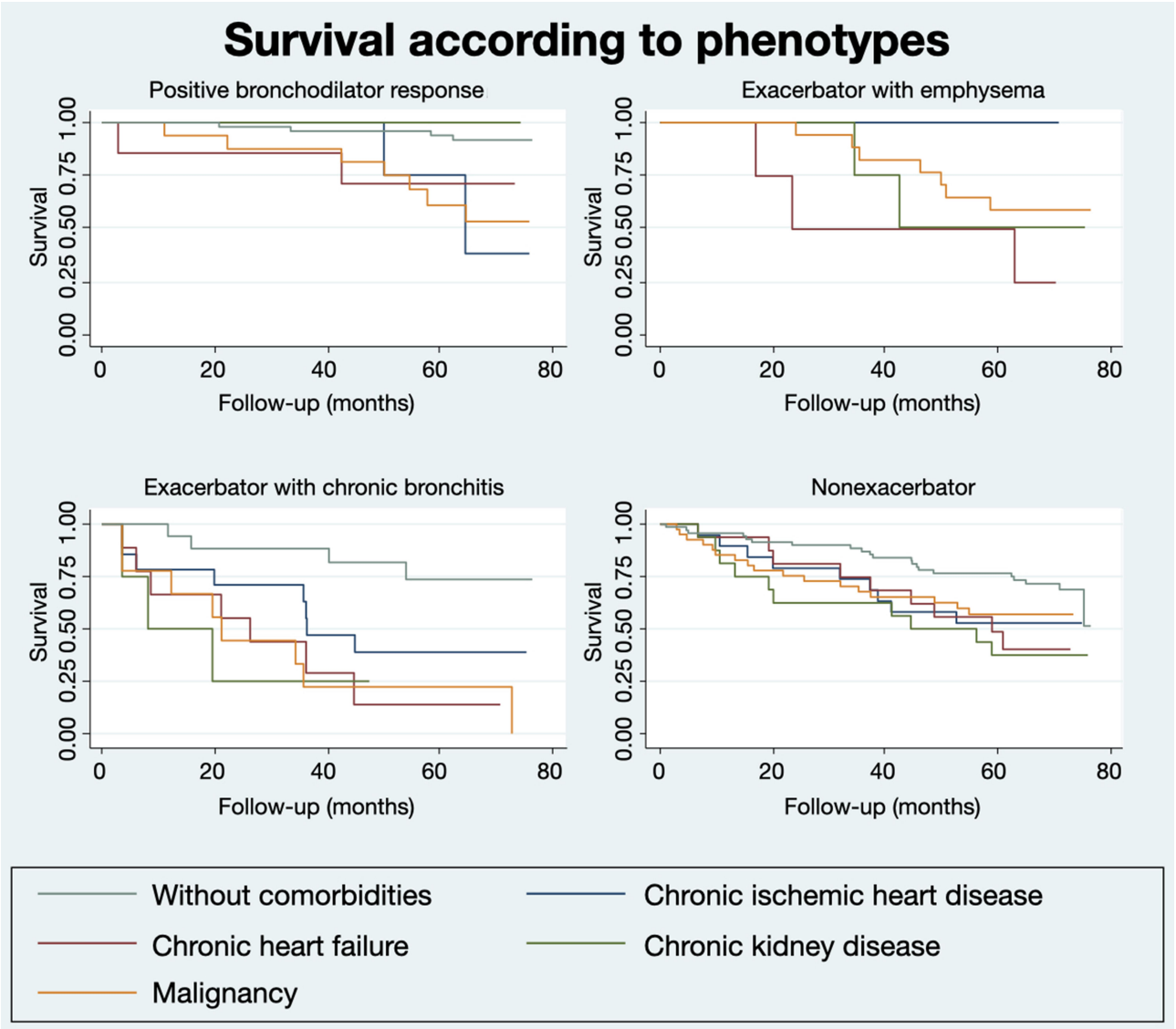

Figure 2 Kaplan–Meier graphs of survival according to the presence of chronic ischemic heart disease, chronic heart failure, chronic kidney disease and malignancy in each phenotype.

that the latter investigates a cohort of COPD patients hospitalized for exacerbation, and our study focuses on a population of stable COPD patients. Therefore, our study takes patients with the non-exacerbator phenotype into account.

From a cardiovascular point of view, numerous studies have shown the negative effect of the coexistence of these diseases with COPD on patient survival.[17–20] These diseases appear together very frequently, possibly due to common pathogenesis through tobacco use and systemic inflammation.[21,22]

Although there are only a few studies on the topic, it has been found that CKD worsens the prognosis of COPD,[7] and vice versa,[23] which aligns with the findings in our study. The pathophysiological mechanism by which this phenomenon occurs is not clear, but it seems that the malnutrition caused by CKD can cause COPD patients to lose exercise capacity faster. As a consequence, they have lower lung function, quality of life, and survival rates.[24]

The relationship between COPD and malignancies, particularly lung cancer, has been widely researched. The significant effect of lung cancer on COPD patients is well known.[25–29] These results are consistent with those of the present study; malignancy is the only comorbid condition that has been found to be a significant cause of death. The mechanism of this association is influenced by not only tobacco use, but also by genetic and molecular mechanisms shared by COPD and malignancies.[30]

Table 4 Survival, Log-Rank and *p*-value in the Univariate Comparison of Survival According to Each Comorbidity and Phenotype

Phenotype		Without Comorbidity	CIHD	CHF	CKD	Malignancy
PRTB phenotype	Survival, months (IQR)	71.0 (68.5–73.7)	57.9 (50.7–70.1)	70.6 (42.4–72.1)	72.9 (71.3–74.0)	61.0 (50.7–72.3)
	Log-rank	-	3.26	0.85	0.71	12.66
	p-value	-	0.071	0.356	0.401	0.000
NE phenotype	Survival, months (IQR)	69.2 (48.4–72.1)	56.6 (31.9–71.3)	57.0 (34.6–70.1)	50.3 (16.3–71.0)	54.8 (21.8–70.0)
	Log-rank	-	1.02	2.37	4.63	1.08
	p-value	-	0.313	0.124	0.031	0.298
EWE phenotype	Survival, months (IQR)	67.4 (49.8–72.7)	71.0 (71.0–71.0)	23.5 (17.0–63.1)	-	42.4 (34.4–42.7)
	Log-rank	-	0.66	2.20	-	0.24
	p-value	-	0.415	0.138	-	0.622
EWCB phenotype	Survival, months (IQR)	63.0 (40.3–71.4)	36.3 (19.9–72.8)	26.4 (8.7–36.3)	13.9 (5.9–33.5)	21.2 (12.3–35.7)
	Log-rank	-	0.23	4.65	2.69	8.71
	p-value	-	0.633	0.031	0.101	0.003
Overall	Survival, months (IQR)	70.0 (58.3–72.6)	50.7 (35.5–71.3)	44.8 (21.2–70.5)	47.4 (13.3–71.5)	52.7 (21.8–70.8)
	Log-rank	-	6.29	14.04	7.97	12.45
	p-value	-	0.012	0.000	0.050	0.000

Abbreviations: NE, non-exacerbator; EWE, exacerbator with emphysema; EWCB, exacerbator with chronic bronchitis; PRTB, positive response to bronchodilator; IQR, interquartile range; CIHD, chronic ischemic heart disease; CHF, chronic heart failure; CKD, chronic kidney disease.

Some studies have found that dementia is a risk factor causing higher mortality;[31,32] however, this was not corroborated by our findings. This could be attributed to the fact that this disease makes it difficult to perform spirometry tests, which is why few patients included in the study present this pathology.

Table 5 Risk Factors Independently Associated with Mortality

Variables	Hazard Ratio	95% CI	*p*-value
Age	1.05	1.02–1.08	0.001
Male	0.55	0.21–1.45	0.216
FEV1	0.92	0.85–0.98	0.014
Phenotypes			
EWE	0.60	0.31–1.14	0.117
EWCB	1.40	0.73–2.71	0.315
NE	1.70	0.99–2.94	0.056
Comorbidities			
Chronic ischemic heart disease	1.14	0.67–1.94	0.628
Chronic heart failure	1.74	1.06–2.86	0.030
Chronic kidney disease	1.49	0.80–2.74	0.214
Malignancy	1.78	1.15–2.76	0.010

Abbreviations: EWE, exacerbator with emphysema; EWCB, exacerbator with chronic bronchitis; NE, non-exacerbator; FEV1, forced expiratory volume in one second; CI, confidence interval.

COPD is a heterogeneous disease, for which different phenotypes have been defined over the years to better classify the disease. Several large-scale studies have shown that the existence of comorbidities differs according to phenotypes.[33,34] The difference could account for the differing influence of each comorbidity on each phenotype found in this study. Future studies should focus on each of these comorbidities to better understand the role they play in the different COPD phenotypes.

On one hand, COPD causes systemic inflammation, which can affect other organs; on the other hand, COPD shares risk factors with other diseases.[2] The comorbidities that have been identified as risk factors independently associated with mortality are possibly caused by a combination of both mechanisms.

The protective effect of elevated lung function found in our study matches evidence found in existing literature.[13,14]

Our study has certain strengths. First, in comparison to studies using retrospective population data—which take into account a wide variety of comorbidities—ours offers a prospective design. To this end, we obtained data on

Table 6 Cause of Death in Patients Presenting Comorbidity

Comorbidity, n (%)	Respiratory	Cardiovascular	Infectious	Malignancy (Tumor Progression)	*p*-value
CIHD	6 (20.7)	0 (0.0)	2 (11.8)	6 (23.1)	0.709
CHF	6 (20.7)	0 (0.0)	4 (23.5)	5 (19.2)	0.887
CKD	4 (13.8)	0 (0.0)	0 (0.0)	4 (15.4)	0.371
Malignancy	6 (20.7)	0 (0.0)	3 (17.6)	24 (92.3)	0.000

Abbreviations: CIHD, chronic ischemic heart disease; CHF, chronic heart failure; CKD, chronic kidney disease.

comorbidities present at the beginning of the study, not at the end of the follow-up period. This allowed us to understand the patient's prognosis from first contact. This prospective design also facilitates the elimination of certain biases present in retrospective studies. Second, in contrast to studies that specifically investigate certain comorbidities, we analyzed all the comorbidities included in the Charlson index. Third, the analysis of comorbid conditions within each COPD phenotype is a novel approach to the topic.

However, our study also has some limitations. First, the comorbid conditions collected are limited to those present at the time of inclusion, without taking into account those that may appear during the follow-up period. Second, the sample size was not sufficient to include patients with low-prevalence comorbid conditions. Third, as this is a single-center study in Spain, the sample only represents the Spanish population. Therefore, it can be difficult to generalize the conclusions for the general population, where the presence of comorbidities may differ. Fourth, our cohort is predominantly male; this may not accurately reflect the presence of comorbidities in women. Finally, because our study is focusses on COPD phenotypes, the patients have not been grouped according to the ABCD GOLD classification. Future studies with specific designs at follow-up and with larger sample sizes are necessary to overcome these limitations.

Conclusions

Chronic ischemic heart disease, chronic heart failure, chronic kidney disease, and malignancy negatively affect the survival rates of patients with COPD. In daily clinical practice, comprehensive care for COPD patients—particularly taking these comorbidities into account—is important owing to their negative effects on COPD patients.

Funding

Menarini supported this study with an unconditional scholarship. This research is a part of the work funded by the Madrid Society of Pneumology and Thoracic Surgery (XVIII Awards Edition, 2018) and the Spanish Society of Pneumology and Thoracic Surgery (project no. 733 of the 2018 edition).

Disclosure

Julio Hernández-Vázquez reports grants from MENARINI, during the conduct of the study. Luis Puente-Maestu reports advisory for MSD, grants from ESTEVE, GSK, NOVARTIS, MENARINI, and personal fees from BOSTON-SCIENTIFIC and CHIESI, outside the submitted work. Javier de Miguel-Díez reports grants from SEPAR and NEUMOMADRID, during the conduct of the study. The authors declare no other potential conflicts of interest for this work.

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