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Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease

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FIGURE LEGENDS

Figure 1. Kaplan-Meier survival curves by frequency of exacerbations in patients with COPD: (A): No AECOPD; (B) patients with one or two AECOPD requiring hospital management; (C): patients with 3 or more AECOPD.

Figure 2. Kaplan-Meier survival curves by severity of exacerbations in patients with COPD: (1): No AECOPD; (2) patients with AECOPD requiring emergency service visits without admission; (3): patients with AECOPD requiring one hospital admission; (4) patients with readmissions.

ABSTRACT

Background: Patients with COPD often present severe acute exacerbations requiring hospital treatment (AECOPD). However, little is known about the prognostic consequences of these exacerbations. The present study investigates whether severe AECOPD exerts a direct effect upon mortality.

Methods: A prospective cohort of COPD patients followed-up on for 5 years is studied. Multivariate techniques are used to analyze the prognostic influence of AECOPD episodes treated in hospital (visits to the emergency service and admissions), patient age, smoking, body mass index, comorbidity, long-term oxygen therapy, forced spirometry and arterial blood gases.

Results: The study comprised 304 male patients with an average age of 71±9 years and a FEV_1 (%) of 46±17%. In the multivariate study, only older age (hazard ratio [HR]: 5.28, 95%CI: 1.75 – 15.93), $PaCO_2$ (HR: 1.07, 95%CI: 1.02 – 1.12) and AECOPD were found to be independent indicators of poor prognosis. The patients with the greatest mortality risk were those with 3 or more AECOPD (HR: 4.13, 95%CI: 1.80 – 9.41).

Conclusions: The present study shows, for the first time, that severe AECOPD have an independent negative impact upon patient prognosis. Mortality is seen to increase with the frequency of severe exacerbations, particularly if these require hospitalization.

Chronic obstructive pulmonary disease (COPD) has become one of the chronic illnesses of greatest social, health care and economical repercussion. COPD is the fourth most frequent cause of death, after neoplastic disease, ischemic heart disease and cerebrovascular diseases (1). However, of all these illnesses, only COPD mortality has increased in recent years and by the year 2020 is expected to become the third leading cause of death in the world (2).

Different authors have investigated the predictive factors associated with increased COPD mortality. Forced expiratory volume in one second (FEV_1) (3,4), patient age (4), hypoxemia (5), hypercapnia (3), comorbidity (3,4,6), pulmonary hypertension (7) and body mass index (BMI) (8) are some of the adverse prognostic variables most commonly cited in the literature. In recent years, other risk factors have also been described, such as dyspnea (9), health-related quality of life (HRQoL)(10) or exercise tolerance (11). Very recently, even a new multifactorial prognostic classification has been proposed: the BODE (body mass index, airflow obstruction, dyspnea, exercise performance) Index. This classification, proposed by Celli et al. (12), stresses the multicomponent nature of COPD and addresses not only its pulmonary consequences but also the systemic manifestations of the disease. None of these studies specifically examine the prognostic influence of acute exacerbations of COPD (AECOPD), despite the fact that the latter play a very relevant role in the natural course of the disease. It has been estimated that COPD patients suffer 1-4 exacerbations per year (13). Such decompensation episodes have an important impact on HRQoL (14), and generate great health care burdens and economical costs. Between 1-2% of all emergency service visits and 10% of all medical admissions are attributable to AECOPD (15). Close to 60% of the global cost of the disease is associated to exacerbation episodes – particularly severe AECOPD requiring hospitalization (16). Despite this strong impact, however, very few series have examined the specific influence of AECOPD upon patient mortality.

Recently, some authors have detected a high mortality rate following hospital admission, ranging between 22-43% after one year and 36-49% after two years, depending on the severity of the COPD study sample involved (17-20). These series have specifically investigated the risk factors associated to mortality after hospitalization. Here again, advanced patient age (17,19,20), $PaCO_2$ (19), PaO_2/FiO_2 (17), BMI (17), serum albumin (17), comorbidity (18,20), cor pulmonale (17,20) and functional status (17,18) have been identified as prognostic variables. These results suggest that the principal determinant of death following hospitalization is the baseline severity of the disease, i.e., the greater the severity of COPD, the greater the likeliness of hospital admission and also of death. However, to date no study has examined the possibility that AECOPD may intrinsically exert a negative effect upon patient prognosis independently of the baseline severity of the disease. The present study investigates whether severe AECOPD, i.e., exacerbation episodes requiring hospital management, exert a direct and independent effect upon COPD patient survival.

METHOD

Subjects

A prospective study was made involving a cohort of 304 male patients with stable COPD. The patients were recruited in the course of 1998, with a subsequent 5-year follow-up period. The general characteristics of the cohort and the selection criteria used are described in detail elsewhere (15). Briefly, the diagnosis of COPD was based on current or past smoking history (>20 pack-year), clinical evaluation, and pulmonary function testing showing airflow obstruction ($FEV_1/FVC<70$) with a change in FEV_1 of less than 200 ml and 12% in the bronchodilator test (21). The severity of the disease was established according to the latest criteria proposed by the GOLD (22). Patients previously diagnosed with bronchial asthma, bronchiectasis, cystic fibrosis, upper airways obstruction or bronchiolitis related to systemic pathology were excluded. All included patients were required to be in a stable phase of the disease, i.e., without AECOPD in the month preceding the study.

Protocol

Age, sex, smoking history, comorbidity, BMI, long-term oxygen therapy (LTOT), forced spirometry and arterial blood gases data were collected in all patients. Comorbidity was quantified according to the index of Charlson et al. (23). This index has been developed to predict mortality among patients with chronic diseases. BMI was calculated by dividing patient body weight (in kg) by the square of height (in m^2). FEV_1 and forced vital capacity (FVC) were determined by forced spirometry *(*Autospiro AS-600, Minato Medical Science S.A, Japan), following the guidelines established by the Spanish Society of Pneumology and Chest Surgery (*Sociedad Española de Neumología and Cirugía Torácica*, SEPAR)(24). The FEV_1 and FVC results are expressed as percentages of the adult reference values (25). Postbronchodilator FEV_1 was used as airflow limitation index, because it is regarded as a better predictor of mortality than prebronchodilator FEV_1 (4).

Exacerbations

Severe AECOPD was defined as any sustained increase in respiratory symptomatology versus the patient baseline situation, requiring modification of habitual medication and hospital treatment (26). A prospective registry was made of all exacerbation episodes requiring hospital management during the year of the study. The patients were divided into three groups according to the number of AECOPD recorded: Group A (patients with no AECOPD); Group B (patients with one or two AECOPD); Group C (patients with 3 or more AECOPD).

Statistical analysis

Descriptive statistics were used to describe the study population at baseline. The comparison of means among the three study groups was based on analysis of variance, with chi-square testing and Bonferroni correction for the comparison of proportions. The survival status of all subjects after 5 years was assessed. All-cause mortality was evaluated. To the effects of survival, January 1, 1998 was taken to be the starting date, while the termination date was defined as December 31, 2002. We first conducted univariate analyses based on the Cox proportional hazards model using each of the potential predictors of respiratory mortality as independent variables and survival status as the dependent variable (27). Survival curves for AECOPD groups were estimated by the Kaplan-Meier product limit method and compared by the log-rank test (28). Independent variables that were associated with respiratory mortality with $p<0.15$ in the univariate analysis were then incorporated into a multivariate analysis also based on the Cox proportional model. An interaction term between the variables and time was introduced in the model to analyze risk proportionality. All statistical analyses were carried out using a statistical software

package (SPSS for Windows, version 11.5; SPSS Inc; Chicago, IL, USA). A p-value of less than 0.05 was considered to be significant.

RESULTS

Subject characteristics

Of the 320 cases of the initial cohort (15), two patients (0.6%) were excluded due to a lack of smoking history, while 11 (3.4%) were excluded due to slight smoking habit (< 20 packs-year). The only women (3 cases, 0.9%) in the study were also excluded, to increase homogeneity. The present study thus comprised a total of 304 male patients diagnosed with COPD (mean age 71±9 years). The baseline characteristics of the patients are shown in Table 1. One hundred and sixty-three cases (53.6%) had suffered no AECOPD (group A); 105 (34.5%) had two or less AECOPD, 60 of them having been hospitalized (group B); and 36 (11.8%) suffered three or more exacerbations, 29 having been admitted at least once during the year of study (group C). In general terms, the patients belonging to this latter group were older and presented more advanced disease, with lower FEV_1, FVC, PaO_2 and higher $PaCO_2$ (Table 1).

Univariate survival analysis

A total of 116 (38.2%) deaths were recorded. Seventy-eight deaths (25.7%) were due to respiratory causes, another 38 patients (12.5%) died of different causes: twelve patients (3.9%) died by cardiovascular disease, 7 (2.3%) by cerebrovascular disease, 11 (3.6%) by neoplasms, 6 (2.0%) by other diseases. In two (0.7%) cases the cause of death was unknown. Thirty-two patients were lost in the course of the 5-year follow-up period (follow-up rate: 89.5%). Table 2 reflects the prognostic influence of the variables included in the univariate analysis.

Figure 1 shows the survival curves according to AECOPD frequency. The patients with frequent exacerbations (Group C) showed the highest mortality (p<0.001), with a risk of death 4.30-fold greater (95%CI: 2.62 – 7.02) than among the patients requiring no hospital management (Group A). Group B also showed significant differences in survival versus Group A (HR: 2.20, 95%CI: 1.45 – 3.33).

Eighty-nine patients (29.3%) were hospitalized at least once during 1998. Mortality in this group was 11.6%, 25.9%, 40.2%, 46.6% and 55.2% after 12, 24, 36, 48 and 60 months, respectively. Patients with only one hospital admission showed poorer survival than those without AECOPD (HR: 2.94; 95%CI: 1.82 – 4.72) or with visits to emergency service without admission. The lowest survival was observed in the group with readmissions (HR: 4.31; 95%CI: 2.70 – 6.88) (Figure 2).

Interaction and confusion among variables

No significant interaction was observed among the different study variables and the prognostic effect of AECOPD. The confounding variables of this association were age, FEV_1%, PaO_2/FiO_2 and LTOT. After adjusting the model for each of them, the presence of AECOPD continued to appear as an independent prognostic variable in all cases (Table 3).

Multivariate analysis of survival

Age, comorbidity index, BMI, FEV_1 (%), FVC (%), PaO_2/FiO_2, $PaCO_2$, long-term oxygen therapy and the number of AECOPD during the year of the study were the variables included in the Cox multiple regression model. In this multivariate model, the frequency of AECOPD, age and Charlson index, were analyzed as categorical variables. The risk proportionality test proved nonsignificant. Hazards ratios were unchanged over time. Table 4 shows the regression model adjusted for all the significant prognostic variables. Severe AECOPD, particularly when multiple, appeared as one of the most relevant inde-

pendent adverse prognostic variables – with an adjusted mortality risk 4-fold greater than for patients without AECOPD. Older age and $PaCO_2$ were also seen to exert a deleterious effect upon survival.

DISCUSSION

To our knowledge, this is the first study reporting that severe exacerbations requiring hospital management are independently associated to all-cause mortality among patients with COPD. Based on our results, the mortality risk increases with the frequency of severe AECOPD. Accordingly, maximum mortality risk corresponded to those individuals presenting three or more exacerbations, particularly if these require hospitalization. We consider that these observations are very important, since the frequency of AECOPD is potentially modifiable.

Different studies have reported a high mortality rate after hospitalization due to AECOPD (17-20). In the most important series published in the literature to date, Connors et al. (17) recorded an in-hospital mortality rate of 11% in patients with acute hypercapnic respiratory failure. During subsequent follow-up, the subjects that survived to the hospitalization presented mortality rates after one and two years of 43% and 49%, respectively. Other series with less severe exacerbations have also reported an important number of deaths after admission – though to a somewhat lesser degree. Almagro et al. (18), in a series of 135 patients, reported respiratory mortality figures of 22% and 35.6% after one and two years, respectively. Gronewegen et al. (19) likewise published a 23% mortality rate after one year in a series of 171 patients. Among COPD patients requiring mechanical ventilation, the deaths are even higher. Seneff et al. (29) reported an in-hospital mortality rate of 24%, with mortality rates after hospital discharge increasing to 59% after one year. Based on these findings, it has been suggested that hospitalization due to AECOPD allows the identification of a subgroup of patients presenting a poorer prognosis (18). In this sense, the most widely accepted hypothesis relates baseline severity of the disease to an increased likeliness of exacerbation – a situation which in turn would explain the poorer survival recorded after hospitalization. This hypothesis is reinforced by identification of the risk factors associated to post-admission mortality, since the variables defining the baseline severity of COPD, such as advanced patient age (17,19,20), hypoxemia (17), hypercapnia (19), BMI (17), comorbidity (18,20), cor pulmonale (17,20) or sustained oral corticoid therapy (19) have been described as mortality predicting factors after admission. We also observed a high mortality among patients requiring hospitalization, with a crude mortality risk 2.94-fold greater than in subjects without AECOPD. However, unlike in the earlier series, our results indicate that AECOPD requiring hospital management *per se* increases the risk of death – independently of other classical prognostic factors such as FEV_1, age, BMI, comorbidity or respiratory failure. Increased mortality is particularly observed in cases requiring hospitalization, and less so in patients requiring emergency visits without admission to hospital – thus suggesting that the severity of exacerbation influences mortality. However, exacerbation recurrence also has an important prognostic character, since the risk was particularly high for patients with three or more AECOPD and for those who had been readmitted. A recent prospective study following patients with severe COPD suggests than those with more frequent exacerbations deteriorate lung function more rapidly (30). This effect, however, also appears to be small, since individuals experiencing exacerbations more often than the median lost lung function at an average of 8 ml per year of FEV_1 more rapidly than those who had exacerbations less often than the median. Although not specifically designed to evaluate exacerbations, the Lung Health Study noted a similar impact of exacerbations on FEV_1 rate of decline in smokers, but no effect upon ex-smokers (31). Both studies suggest that exacerbations accelerate the loss of lung function – this being an indirect indicator of mortality. However, to our knowledge, this is the first study to identify an intrinsic deleterious effect of AECOPD upon patient survival.

The reasons underlying this increase in risk following AECOPD are not clear. The present study was not specifically designed to clarify this aspect. However, the results obtained suggest that as the severity of exacerbation increases (regardless of the baseline severity of the disease), the risk of death also increases. In fact, the hospitalized patients

showed higher mortality figures than the subjects seen in the emergency service but who required no hospital stay (figure 2). Similar results have been reported by other authors. In the series published by Connors et al. (17), the most important predictor of 6-month survival was the overall severity of illness on day 3 of hospital stay, as measured by the acute physiology component of the APACHE score. Blood gas values on hospital admission - another measure of acute abnormality - have also been reported as an independent predictor of survival (17-20). Other aspects intrinsically related to AECOPD may also be implicated in the survival of these patients. Fuso et al. (20), in a retrospective series, showed that the variables reflecting heart dysfunction during exacerbations, such as atrial fibrillation or ventricular arrhythmias, are important determinants of mortality risk. Connors et al. (17) likewise observed that patients presenting congestive heart failure as cause of AECOPD suffered increased mortality. In contrast, an infectious AECOPD etiology does not seem to be a determinant of increased mortality (17,18).

One of the most attractive etiological hypotheses relates inflammation (pulmonary or systemic) triggered during AECOPD to patient survival. Recently, Donaldson et al. (32) have shown that the severity of exacerbations increases over time, as does sputum purulence – this suggesting more inflammation in patients with more severe exacerbations. In our study we only analyzed AECOPD sufficiently serious to require hospital treatment. Therefore, and in accordance with the results of Donaldson el al. (32), it is possible that our patients with AECOPD may have presented greater inflammation. The group of British investigators has also demonstrated a relationship between airway inflammation and the frequency of exacerbations in patients with COPD (33,34). According to these authors, patients with frequent exacerbations present an increased bacterial load in their airways, in stable state. Such lower airway bacterial load is associated to increased airway inflammation and an accelerated decrease in FEV_1 – an indirect but potent mortality indicator. Poorer survival among patients with frequent AECOPD is currently the subject of debate. In a Dutch series (19), the authors recorded no differences in survival rates between those who had been readmitted, and those who had not been readmitted to hospital. In contrast, Connors et al. (17) in a univariate analysis observed an increase in mortality associated to readmission. Mortality after 6 months among the patients readmitted one, two or more times was 27%, 31% and 36%, respectively, while those requiring no readmission presented a mortality of 21% (p=0.004). More recently, a Spanish multivariate study (18) reported a 1.85-fold greater mortality among readmitted subjects after adjusting for other predictive variables. In this same sense, we found that patients with multiple AECOPD admitted to hospital or seen in the emergency service had a markedly greater mortality risk. Accordingly, after adjusting for different prognostic factors, mortality among the above patients was seen to be 4.1-fold greater than among the individuals without AECOPD. These results could support the inflammatory hypothesis, whereby as the frequency of severe AECOPD increases, inflammation and also mortality could likewise increase. However, we did not assess pulmonary or systemic inflammation; further studies in this interesting direction are therefore needed.

To date, the only treatments that have been shown to improve survival in COPD patients have been smoking cessation (35) and oxygen therapy in subjects with respiratory failure (5). If our results are confirmed, then certain therapies capable of reducing the frequency of AECOPD could potentially reduce mortality inherent to exacerbations. Some drugs, such as inhaled steroids (36), inhaled long-acting $beta_2$-agonists (37) or tiotropium bromide (38), have also afforded a significant reduction in the number of exacerbations. This reduction is associated to marked improvement in patient HRQoL (36-38). However, confirmation of our results could suggest that this treatments also could contribute to reduce mortality. In this sense, Soriano et al. (39), in a recent pharmacoepidemiological study, found patients using the combination fluticasone-salmeterol to have better survival than those receiving monotherapy. At present, an important multicenter study is underway

to assess the impact of this combined treatment on patient survival (40). Other management strategies such as measures to combat the high therapeutic failure rate, or early treatment, could also afford benefit in terms of survival if our results are confirmed.

Some limitations of this study should be mentioned. Firstly, only the prognostic influence of AECOPD episodes requiring hospital management was analyzed. It is not clear whether other less severe exacerbation episodes could also exert a prognostic influence. Secondly, although we have attempted to incorporate the prognostic variables most commonly cited in the literature, some parameters that have not been examined – such as for example the degree of dyspnea, HRQoL, exercise tolerance, or pulmonary artery pressure – could possibly also interact with exacerbation and its prognostic repercussions. Nevertheless, in an earlier study (41) in which we considered some of these variables, hospital admission as an expression of severe AECOPD was likewise shown to be an independent predictive variable. Another limitation in our series refers to the cross-sectional data collection. Although most studies adopt this same design, the fact is that longitudinal data (changes in treatment, impairment of lung function, loss of muscle mass, etc.), which could equally condition mortality and interact with future exacerbations, were not available. Lastly, we likewise lack detailed data on the AECOPD episodes (clinical etiology, treatment, etc.) – as a result of which no in-depth evaluation can be made of the causes underlying their future course. In any case, the present study only aims to alert to the prognostic role of AECOPD *per se*, rather than to define the etiopathogenic mechanisms associated to increased the mortality of such exacerbations. In our opinion, further studies are needed, involving specific designs, to address this matter.

In conclusion, our results suggest, for the first time, that severe AECOPD exerts an independent negative prognostic impact – mortality increasing with the frequency of severe exacerbations, particularly if these require hospitalization. Consequently, if these results are confirmed, a reduction in the number and severity of exacerbations could be regarded as priority objectives in the management of COPD.

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TABLE 1
BASELINE CHARACTERISTICS OF THE PATIENTS (n=304).

	All Sample (n=304)	Groups of AECOPD			
		A (n=163, 53.6%)	B (n=105, 34.5%)	C (n=36, 11.8%)	p value
Age (years)	71 ± 9	69 ± 10	72 ± 7	71 ± 9	0.001
BMI (kg/m^2)	28.3 ± 5.1	28.8 ± 5.4	27.7 ± 4.7	27.7 ± 4.1	0.350
Comorbidity index	0.95 ± 1.34	0.90 ± 1.30	0.92 ± 1.21	1.23 ± 1.82	0.422
Comorbidity, n (%)					0.765
- 0	145 (47.7)	80 (48.8)	48 (46.2)	17 (47.2)	
- 1	91 (29.9)	47 (28.6)	35 (33.6)	9 (25.0)	
- ≥2	68 (22.4)	37 (22.6)	21 (20.2)	10 (27.8)	
FEV_1 (l)	1.18 ± 0.64	1.29 ± 0.76	1.11 ± 0.45	0.88 ± 0.33	0.002
FEV_1 % (predicted)	46.4 ± 17.2	49.2 ± 16.6	45.9 ± 17.6	34.5 ± 13.6	<0.001
GOLD classif, n (%)					<0.001
- Stage I	20 (6.6)	15 (9.2)	5 (4.8)	---	
- Stage II	109 (35.9)	66 (40.5)	38 (36.2)	5 (13.9)	
- Stage III	102 (33.6)	57 (35.0)	33 (31.4)	12 (33.3)	
- Stage IV	73 (24.0)	25 (15.3)	29 (27.6)	19 (52.8)	
FVC (l)	2.22 ± 0.67	2.34 ± 0.72	2.12 ± 0.62	1.93 ± 0.62	0.002
FVC % (predicted)	69.4 ± 19.1	72.0 ± 19.3	68.0 ± 18.7	61.1 ± 17.3	0.010
PaO_2 (mmHg)	65.9 ± 11.7	68.3 ± 11.4	64.4 ± 11.2	60.3 ± 12.2	<0.001
$PaCO_2$ (mmHg)	43.7 ± 7.5	42.7 ± 6.3	44.1 ± 7.8	46.5 ± 10.3	0.019

BMI: body mass index. Stage I-IV: GOLD criteria stratification. Values are expressed as the mean ± standard deviation. AECOPD: acute exacerbations of COPD requiring hospital management. Group A: No AECOPD; Group B: patients with one or two AECOPD (emergency visits or hospitalizations); Group C: patients with 3 or more AECOPD.

TABLE 2
PREDICTORS OF MORTALITY: UNIVARIATE ANALYSIS.

	Hazard Ratio (crude)	95% CI	P-value
Age (years)			<0.001
- **< 65**	--	--	
- **65-74**	1.76	0.88 – 3.52	
- **≥ 75**	5.26	2.70 – 10.24	
Current smoking	0.97	0.63 – 1.48	0.873
Cumulative smoking (pack-yr)	1.00	0.99 – 1.01	0.973
Comorbidity index	1.43	1.28 – 1.60	<0.001
Charlson index:			0.002
- **0**	1.00	--	
- **1**	1.32	0.84 – 2.07	
- **≥ 2**	2.20	1.41 – 3.43	
BMI (kg/m^2)	0.94	0.89 – 0.99	0.034
Postbronchodilator FEV_1 % (predicted)	0.96	0.94 – 0.98	<0.001
GOLD stage			<0.001
- I	1.00	--	
- II	3.40	0.81 – 14.21	
- III	5.34	1.29 – 22.07	
- IV	8.34	2.01 – 34.55	
FVC (%) (predicted)	0.98	0.97 – 0.99	0.009
PaO_2 / FiO_2	0.99	0.98 – 0.99	<0.001
$PaCO_2$ (mmHg)	1.05	1.04 – 1.09	<0.001
Long term oxygen therapy	3.42	2.36 – 4.95	<0.001
AECOPD groups			<0.001
- Group A	1.00	--	
- Group B	2.20	1.45 – 3.33	
- Group C	4.30	2.62 – 7.02	

BMI: body mass index. AECOPD: acute exacerbations of COPD requiring hospital management. Group A: No AECOPD Group B: patients with one or two AECOPD (emergency visits or hospitalizations); Group C: patients with 3 or more AECOPD.

TABLE 3

PROGNOSTIC VALUE OF AECOPD FREQUENCY ADJUSTED BY CONFOUNDERS

	Hazard Ratio (adjusted)	95%CI	P-value
AECOPD adjusted by age			
Age (years)			<0.001
- < 65	Ref.categ	---	
- 65-74	1.62	0.80 – 3.25	
- ≥ 75	4.52	2.31 – 8.83	
AECOPD groups			<0.001
- Group A	Ref. categ	---	
- Group B	1.93	1.27 – 2.93	
- Group C	3.64	2.22 – 5.98	
AECOPD adjusted by FEV_1%			
FEV_1% (predicted)	0.99	0.97 – 0.99	0.028
AECOPD groups			<0.001
- Group A	Ref. categ	---	
- Group B	2.08	1.33 – 3.25	
- Group C	3.45	1.99 – 5.99	
AECOPD adjusted by PaO_2/FiO_2			
PaO_2/FiO_2	0.99	0.990 – 0.997	<0.001
AECOPD groups			<0.001
- Group A	Ref. categ	---	
- Group B	2.12	1.37 – 3.29	
- Group C	3.69	2.18 – 6.25	
AECOPD adjusted by LTOT			
LTOT	2.72	1.84 – 4.02	<0.001
AECOPD groups			<0.001
- Group A	Ref. categ	---	
- Group B	1.74	1.14 – 2.67	
- Group C	2.92	1.74 – 4.88	

CI: confidence interval. P-value: level of significance. AECOPD: acute exacerbations of COPD requiring hospital management. Group A: No AECOPD; Group B: patients with one or two AECOPD (emergency visits or hospitalizations); Group C: patients with 3 or more AECOPD. LTOT: Long term oxygen therapy.

TABLE 4
PREDICTORS OF MORTALITY: MULTIVARIATE ANALYSIS.

	Hazard Ratio (adjusted)	95%CI	P-value
Age (years):			0.001
- **< 65**	Ref.categ	---	
- **65 – 74**	1.92	0.64 – 5.25	
- **≥ 75**	5.28	1.75 – 15.93	
Charlson index			0.101
- **0**	Ref.categ	---	
- **1**	1.17	0.59 – 2.29	
- **≥ 2**	2.23	1.06 – 4.69	
BMI (kg/m^2)	0.96	0.89 – 1.03	0.245
FEV_1 % (predicted)	0.97	0.96 – 1.03	0.810
FVC % (predicted)	0.97	0.97 – 1.02	0.695
PaO2 / FiO2	1.00	0.99 – 1.01	0.374
PaCO2	1.07	1.02 – 1.12	0.006
LTOT	1.95	0.93 – 4.12	0.078
AECOPD groups			0.003
- Group A	Ref. categ	---	
- Group B	2.00	1.01 – 3.98	
- Group C	4.13	1.80 – 9.45	

CI: confidence interval. P-value: level of significance. LTOT: Long term oxygen therapy. BMI: body mass index. AECOPD: acute exacerbations of COPD requiring hospital management. Group A: No AECOPD Group B: patients with one or two AECOPD (emergency visits or hospitalizations); Group C: patients with 3 or more AECOPD.