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The impact of depressive symptoms on recovery and outcome of hospitalised COPD exacerbations

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ABSTRACT: The impact of depressive symptoms on outcomes of acute exacerbations of chronic obstructive pulmonary disease (AECOPD) has not been thoroughly evaluated in prospective studies.

We prospectively enrolled 230 consecutive patients hospitalised for AECOPD, without previous diagnosis of depression. Depressive symptoms were evaluated with Beck's depression inventory. Pulmonary function tests, arterial blood gases, COPD assessment test (CAT) and Borg dyspnoea scale were recorded on admission and on days 3, 10 and 40. Patients were evaluated monthly for 1 year.

Patients with depressive symptoms required longer hospitalisation (mean±SD 11.6±3.7 *versus* 5.6±4.1 days, $p<0.001$). Clinical variables improved during the course of AECOPD, but depressive symptoms on admission had a significant impact on dyspnoea ($p<0.001$) and CAT score ($p=0.012$) improvement. Patients with depressive symptoms presented more AECOPD ($p<0.001$) and more hospitalisations for AECOPD ($p<0.001$) in 1 year. In multivariate analysis, depressive symptoms were an independent predictor of mortality (hazard ratio 3.568, 95% CI 1.302–9.780) and risk for AECOPD (incidence rate ratio (IRR) 2.221, 95% CI 1.573–3.135) and AECOPD hospitalisations (IRR 3.589, 95% CI 2.319–5.556) in 1 year.

The presence of depressive symptoms in patients admitted for AECOPD has a significant impact on recovery and is related to worse survival and increased risk for subsequent COPD exacerbations and hospitalisations in 1 year.

KEYWORDS: Beck's depression inventory, chronic obstructive pulmonary disease, depression, exacerbation, survival

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are characterised by a change in patients' baseline dyspnoea, cough and/or sputum beyond normal day-to-day variations with acute onset that may warrant changes in regular medication [1]. AECOPD have significant consequences in the lives of chronic obstructive pulmonary disease (COPD) patients and a negative impact on survival [2].

Depression is a frequent comorbidity in COPD patients [1], with a prevalence of up to 62% in patients with respiratory failure. Recent studies have shown that up to 55% of COPD patients suffer from a clinical diagnosis of anxiety and/or depression [3]. Depression increases physical disability, morbidity and healthcare utilisation [4]. COPD patients often face major physical impairment and embarrassing symptoms [5], while depression by itself is also aggravated by worsening dyspnoea and fatigue, diminishing functional performance and exercise capacity, and is associated with impaired quality of life [6]. Depression is additionally related to AECOPD frequency, with frequent exacerbators presenting higher depression scores compared with infrequent exacerbators [7, 8]. Although it has been reported that depressed COPD patients experience longer hospitalisations for AECOPD [9], the impact of depressive symptoms on the recovery and outcomes from an AECOPD has not been thoroughly studied.

The primary objective of the present prospective study was to evaluate the impact of the presence of depressive symptoms during admission for

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AECOPD on mortality, as well as on the occurrence of subsequent exacerbations and hospitalisations for AECOPD during a 1-year follow-up. Secondary objectives included the impact of depressive symptoms on the outcomes of the exacerbation, including the duration of hospitalisation and the recovery of symptoms and physiological parameters.

MATERIALS AND METHODS

Study subjects

In the present study, we enrolled all consecutive patients admitted to the respiratory medicine departments of two tertiary hospitals (3rd Respiratory Medicine Dept, Sismanogleion General Hospital and Respiratory Medicine Dept, Amalia Fleming General Hospital) in Northern Athens, Greece, with a diagnosis of AECOPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) definition [1] between March 2009 and June 2010. All included patients fulfilled pre-specified severity criteria for hospitalisation (*i.e.* marked increase in dyspnoea, failure of initial outpatient management and/or respiratory failure), according to the GOLD guidelines [1, 10]. All subjects were either current or ex-smokers, with a smoking history of at least 20 pack-years and a previous diagnosis of COPD established by a respiratory physician in their records. COPD diagnosis and severity was established by post-bronchodilator spirometry on stable condition according to GOLD guidelines [11]. Patients with an alternative diagnosis of another acute respiratory condition (*e.g.* pneumonia, pneumothorax, pulmonary embolism, *etc.*) or a history of respiratory disorders other than COPD (*e.g.* asthma, bronchiectasis, pulmonary fibrosis, *etc.*), patients with inability or unwillingness to cooperate with the investigators, as well as patients without availability of spirometry data, were excluded from our study. In order to reduce bias, we also excluded patients with a previous diagnosis of depression under therapy with antidepressants. All patients were invited to participate in the present study on the first day of admission to the respiratory ward by a study investigator, who allowed them enough time to make their decision and assured them that their care would not be affected by their decision to participate in the study. The study protocol was approved by the ethics committees of both hospitals, and all participants provided written informed consent.

Study parameters

The presence of depressive symptoms was assessed with the original Beck's depression inventory (BDI)-I [12]. This is a 21-item self-administered rating inventory measuring attitudes and symptoms of depression, with high internal consistency, and good discriminant and convergent validity [12]. In the present study, we used the optimal cut-off score in the BDI (*i.e.* $\geqslant$19), which distinguishes patients with minimal or mild depressive symptoms from patients with moderate or severe depressive symptoms [13]. This cut-off point was previously used in a recent prospective study that enrolled COPD patients in a similar design to our study [14]. The Greek version of the BDI has been validated in the Greek population and has been evaluated recently in Greek COPD patients [15]. The official translation of BDI was provided by the Hellenic Institute of Psychology and Health (www.ipsy.gr). All patients completed the BDI-I questionnaire on the first day of hospitalisation at their own convenience, after the appropriate medical evaluation and the initiation of treatment for AECOPD.

Spirometric values from the patients' records on stable condition during the 6 months prior to study inclusion were used for the diagnosis and evaluation of COPD severity, according to GOLD guidelines [11]. During the course of the AECOPD, spirometries were performed according to the American Thoracic Society guidelines [16], and post-bronchodilator forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) and FEV_1/FVC were recorded.

The presence of cardiovascular disease in general, as well as the presence of systemic hypertension, coronary artery disease, congestive heart failure, arrhythmias or stroke, was specifically recorded; the presence of diabetes mellitus was also recorded. Additionally, Charlson's comorbidity index score was calculated for each patient, as this index has been shown to predict mortality [17].

The COPD assessment test (CAT) score was used in order to evaluate patients' health status at all time points, using a total score ranging from 0 to 40, corresponding to the best and worst health status in COPD patients, respectively [18]. The CAT score presents significant difference between COPD patients in stable condition and on exacerbation [18]. We used the official Greek translation after written permission by GlaxoSmithKline (Athens, Greece).

The multidimensional ADO and the DOSE indexes were calculated using patients' data on stable condition. The ADO index consists of three parameters (Age, Dyspnoea (according to the Medical Research Council (MRC) scale) and airway Obstruction (as expressed by FEV_1)) [19]. The DOSE index consists of four parameters (Dyspnoea according to the MRC scale, airway Obstruction (as expressed by FEV_1), Smoking status and Exacerbations per year) [20].

Study design

Clinical and physiological parameters (Borg Dyspnoea score, CAT score, FEV_1 % predicted and arterial oxygen tension (P_{aO_2})/inspiratory oxygen fraction (F_{IO_2})) were evaluated on admission (day 1) and on days 3, 10 and 40. Communication by telephone was performed monthly for 1 year and a study investigator recorded the patients' vital status and the numbers of new AECOPD and hospitalisations. In the event that a patient could not be reached on a regular monthly basis, every effort was made to obtain all the necessary information at a following communication. Patients' demographics, including body mass index (BMI), smoking habit, dyspnoea (Borg scale and MRC scale), comorbidities and treatment were recorded. The attending physicians of the two departments, who were responsible for the decisions for AECOPD management and discharge, as well as the investigators involved in patients' follow-up, were blinded to the status of the patients regarding the presence or absence of depressive symptoms. The recording of hospitalisations for AECOPD was based on self-reporting of patients at monthly communications with the study investigators, and was confirmed by hospital records where necessary.

The primary objective of the present prospective study was to evaluate the impact of the presence of depressive symptoms during admission for AECOPD on mortality, as well as on the occurrence of subsequent AECOPD and hospitalisations for AECOPD during a 1-year follow-up. AECOPD were defined as the need for use of antibiotics and/or systemic corticosteroids

on an outpatient basis, whereas the recorded hospitalisations were the ones related to AECOPD. Secondary objectives included the impact of depressive symptoms on the outcomes of the exacerbation, including the duration of hospitalisation and the recovery of symptoms (Borg dyspnoea score and CAT score) and physiological parameters (FEV1 and P_{aO_2}/F_{IO_2}).

Statistical analysis

Categorical variables are presented as n (%), whereas numerical variables are presented as mean±SD or median (interquartile range). Comparisons between groups were performed using Chi-squared tests for categorical data, as well as unpaired t-tests or Mann–Whitney U-tests for normally distributed or skewed numerical data, respectively. Correlations were performed with Spearman's correlation coefficient.

In order to evaluate the target sample size, a power analysis was performed using the PS Power and Sample Calculation Program [21], based on data from a previous study of survival after COPD hospitalisation [10]. Briefly, in order to achieve a Type I error probability of 0.05 with 90% power for a hazard ratio (HR) for mortality between patients with and without clinically significant depression of 3.60, for a median follow-up of 12 months and an estimated median survival of ~30 months after a hospitalisation for AECOPD, a minimum number of 89 and 133 participants would be required in the groups with and without depressive symptoms, respectively.

For the analysis of the primary objective, survival analyses and Cox and Poisson regression analyses were implemented. In detail, the times to death and first AECOPD and hospitalisation for AECOPD according to the presence or not of depressive symptoms were evaluated using Kaplan–Meier survival curves and log-rank tests. Cox regression univariate and multivariate analyses were performed in order to evaluate the influence of depressive symptoms on mortality at the 1-year follow-up. Significant confounders evaluated in Cox regression analyses included age, BMI, sex, current smoking status, Charlson score and GOLD stage. Results are presented as HRs with 95% confidence intervals (CI). Poisson regression univariate and multivariate analyses were additionally performed for the evaluation of the influence of depressive symptoms on AECOPD and hospitalisations for AECOPD in the 1-year follow-up, in order to account for variability in AECOPD and hospitalisation rates between patients [22]. The aforementioned significant confounders were additionally evaluated in the Poisson analysis and the results are presented as incidence rate ratios (IRR) with 95% CI. Skewed data were logarithmically transformed for regression analyses.

For the evaluation of the secondary objectives (*i.e.* changes in the CAT score, FEV1, oxygenation levels as expressed by P_{aO_2}/F_{IO_2} ratio and Borg dyspnoea score in the two study groups), two-way ANOVA with repeated measures (two groups by four time-points) was implemented. In the event of a significant F-ratio for a time and group (patients with or without depressive symptoms) or interactive effect, *post hoc* analyses were used to identify significant differences within group over time, or between groups at each time. AECOPD and hospitalisations are reported both as the proportion of patients with an event, as well as the mean number of events per patient per year.

A p-value <0.05 was considered statistically significant. All tests were two-tailed. Data were analysed using SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

We evaluated 357 consecutive patients admitted to the hospital because of AECOPD; 230 of them were eligible to be included in the present study. The flow chart of the study participants is shown in figure 1. 11 patients were lost to follow-up soon after their discharge due to insufficient contact details in their records. The demographic and functional characteristics of the 230 patients who were included in the study are presented in table 1. Clinically significant depressive symptoms were present in 39% of the COPD patients. Patients with depressive symptoms had more impaired lung function, more comorbidities (as expressed by the Charlson comorbidity index) and more severe disease (as expressed by the GOLD COPD stage, ADO and DOSE indexes) compared with patients without depressive symptoms. Patients were followed up for 11.4±1.9 months.

Effect of depressive symptoms on outcomes of AECOPD

Patients with depressive symptoms required more days of hospitalisation compared with patients without depressive symptoms (11.6±3.7 *versus* 5.6±4.1 days; $p<0.001$). A significant correlation was observed between the BDI-I score and the duration of hospitalisation (in days) during the AECOPD ($p<0.001$, $r=0.695$).

All four parameters related to recovery from AECOPD that were evaluated (Borg dyspnoea scale, FEV1, CAT score and P_{aO_2}/F_{IO_2}) improved in COPD patients both with and without depressive symptoms from day 1 to day 40 ($p<0.001$). In the between-groups analysis, the presence of depressive symptoms

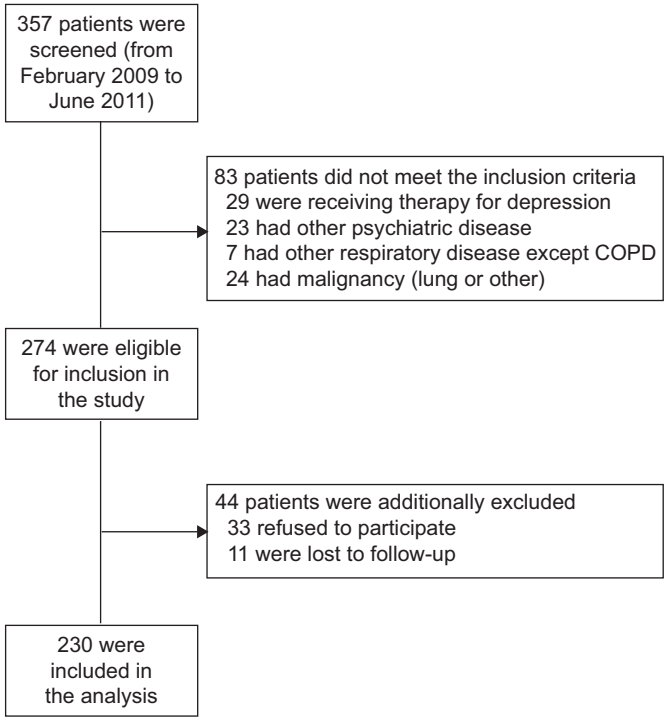

FIGURE 1. Flow chart of study participants. COPD: chronic obstructive pulmonary disease.

TABLE 1 Demographics of the study population

Characteristics	All	No depressive symptoms	Depressive symptoms	p-value
Subjects n	230	139	91	
Male	203 (88.3)	117 (84.2)	86 (94.2)	**0.020**
Age years	71.2±8.8	71.2±8.9	71.3±8.4	0.961
BMI kg·m^{-2}	28.4±7.6	27.5±4.3	29.8±10.7	0.051
Current smokers	75 (32.6)	49 (35.3)	26 (28.6)	0.316
Cigarettes smoked pack-years	75 (60–100)	80 (60–100)	70 (60–90)	0.073
FEV$_1$ % pred	52.8±20.1	60.6±20.7	40.4±10.7	**<0.001**
COPD stage				
I	29 (12.6)	29 (20.9)	0 (0)	**<0.001**
II	80 (34.8)	66 (47.5)	14 (15.4)	
III	91 (39.6)	34 (24.5)	57 (62.6)	
IV	30 (13)	20 (7.2)	20 (22.0)	
Charlson comorbidity index score	2 (1–3)	2 (1–3)	3 (2–4)	**0.002**
ADO index	4.43±1.4	4.1±1.3	4.9±1.4	**<0.001**
DOSE index	2.5±1.5	1.8±1.2	3.6±1.2	**<0.001**
Arterial blood gases				
P_{aO_2}/F_{IO_2} mmHg	315.0±51.2	319.9±51.7	306.4±49.5	0.073
Duration of initial hospitalisation days	7.9±4.9	5.6±4.1	11.6±3.7	**<0.001**
Deaths[#]	28 (12.1)	5 (3.6)	23 (25.3)	**<0.001**
Patients with AECOPD[#]	185 (80.4)	95 (68.3)	90 (98.9)	**<0.001**
AECOPD per patient per year[#]	2.6±2.2	1.56±1.75	4.28±1.78	**<0.001**
Patients with hospitalisation[#]	116 (50.4)	39 (28.1)	77 (84.6)	**<0.001**
Hospitalisations per patient per year[#]	1.02±1.14	0.41±0.86	1.96±1.41	**<0.001**

Data are presented as n (%), mean±SD or median (interquartile range), unless otherwise stated. BMI: body mass index; FEV$_1$: forced expiratory volume in 1 s; % pred: % predicted; COPD: chronic obstructive pulmonary disease; ADO: age, dyspnoea (according to Medical Research Council (MRC) scale) and airway obstruction (as explored by FEV$_1$); DOSE: dyspnoea (according to MRC scale), airway obstruction (as expressed by FEV$_1$), smoking and exacerbations per year; P_{aO_2}: arterial oxygen tension; F_{IO_2}: inspiratory oxygen fraction; AECOPD: acute exacerbations of COPD. [#]: events during the 1-year follow-up. Bold indicates statistically significant differences.

had a significant effect only on the improvement of Borg dyspnoea scale ($p<0.001$) and CAT score ($p=0.012$), but not on the improvement of FEV1 ($p=0.429$) or P_{aO_2}/F_{IO_2} ratio ($p=0.251$) (fig. 2).

Effects of depressive symptoms on 1-year mortality, AECOPD and hospitalisations

The effects of depressive symptoms on 1-year mortality, AECOPD and hospitalisations were the primary outcomes of the present study. There were more deaths in the group with depressive symptoms compared with the group without depressive symptoms during the 1-year follow-up ($p<0.001$). A Kaplan–Meier survival curve evaluating the time to death according to the presence or absence of depressive symptoms is presented in figure 3 ($p<0.001$, log-rank test). In the univariate Cox regression analysis, significant predictors of 1-year mortality were the GOLD COPD stage and the presence of depressive symptoms. In multivariate analysis, the presence of depressive symptoms remained an independent predictor of 1-year mortality (HR 3.568, 95% CI 1.302–9.780; $p=0.013$) (table 2).

Patients with depressive symptoms on admission had more AECOPD and more hospitalisations for AECOPD during the 1-year follow-up compared with COPD patients without depressive symptoms ($p<0.001$ for both comparisons) (table 1). The BDI score was correlated to the number of AECOPD in each patient during follow-up ($p<0.001$, $r=0.651$). Kaplan–Meier survival curves evaluating the time to first AECOPD and hospitalisation for AECOPD according to the presence or absence of depressive symptoms are presented in figure 4 ($p<0.001$ for both comparisons, log-rank tests). In the univariate Poisson regression analysis, significant predictors of AECOPD were age, BMI, MRC dyspnoea score, GOLD stage and the presence of depressive symptoms (table 3). Accordingly, significant predictors of hospitalisations for AECOPD were Charlson comorbidity index, MRC dyspnoea score, GOLD COPD stage and the presence of depressive symptoms (table 3). In multivariate analysis, the presence of depressive symptoms remained an independent predictor of a higher risk for AECOPD (IRR 2.221, 95% CI 1.573–3.135; $p<0.001$) and for hospitalisations for AECOPD (IRR 3.589, 95% CI 2.319–5.556; $p<0.001$) in the 1-year follow-up.

DISCUSSION

In this prospective observational cohort study, we provide evidence that supports our primary objective that the presence of depressive symptoms on admission for an AECOPD, as expressed by an increased BDI score, is an independent predictor of mortality, and risk for AECOPD and hospitalisations for AECOPD in the following year. We have additionally shown that COPD patients with clinically important depressive

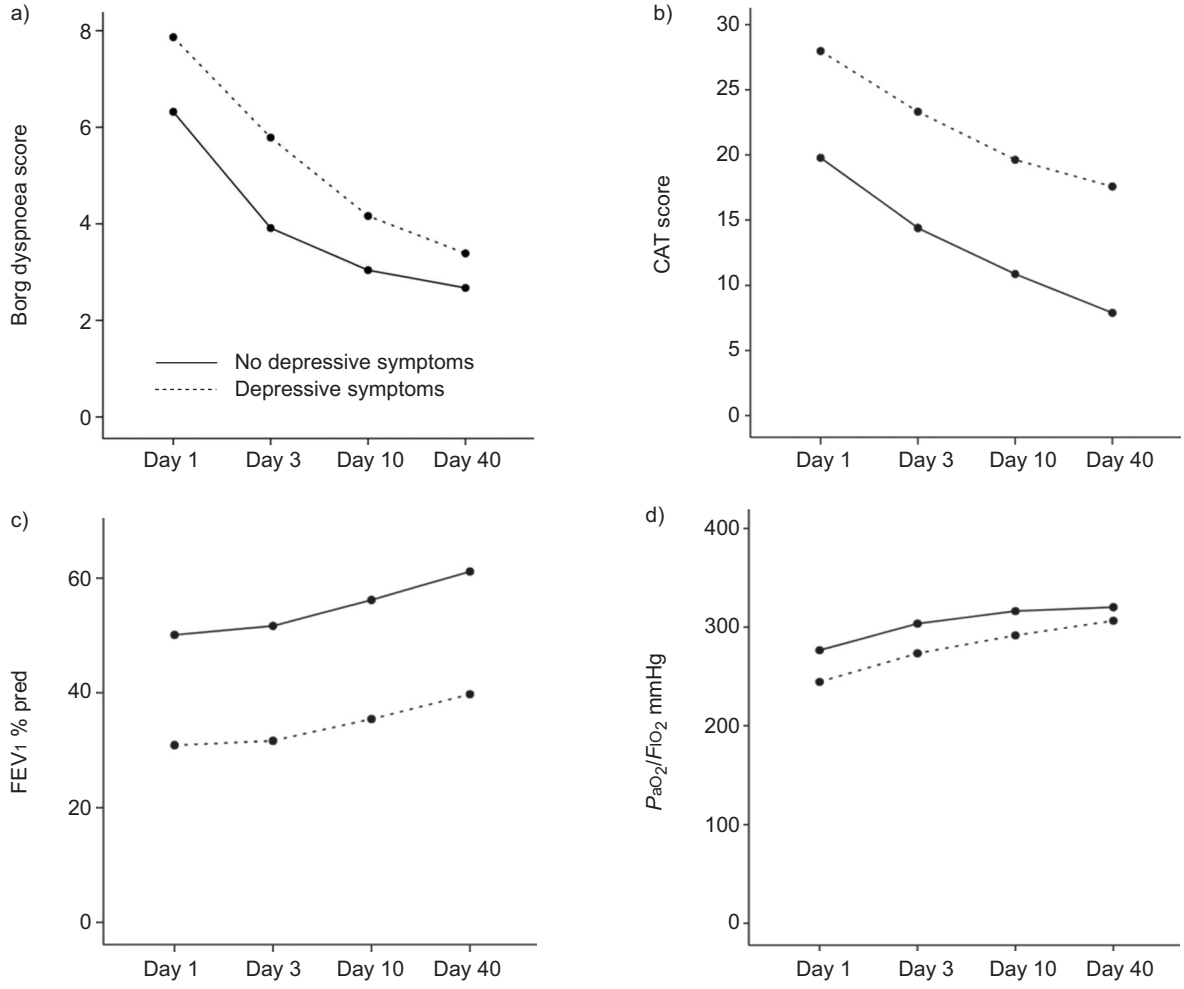

FIGURE 2. Change in patients' status from day 1 to day 40 according to the presence of depressive symptoms for a) Borg dyspnoea score, b) chronic obstructive pulmonary disease assessment test (CAT) score, c) forced expiratory volume in 1 s (FEV_1) and d) arterial oxygen tension (P_{aO_2})/inspiratory oxygen fraction (F_{IO_2}) ratio. % pred: % predicted.

symptoms required longer hospitalisation time and presented slower improvement of dyspnoea and CAT score compared with COPD patients without depressive symptoms. This study has shown that the use of a simple instrument that evaluates the presence of depressive symptoms on admission for an AECOPD may provide valuable information for the short- and long-term outcome of COPD patients.

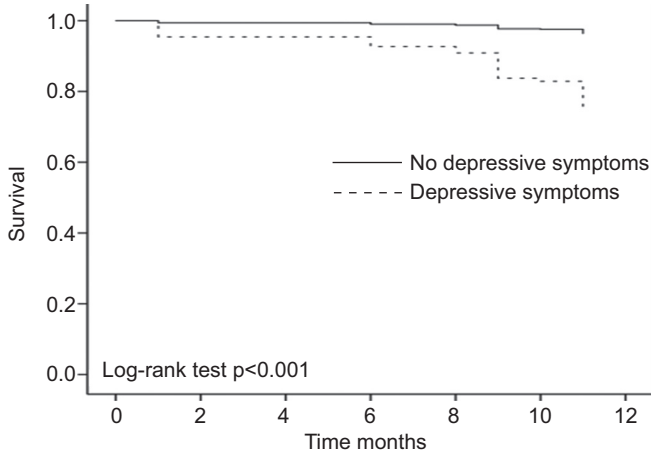

FIGURE 3. Kaplan–Meier curves of 1-year survival of chronic obstructive pulmonary disease patients with and without depressive symptoms.

Although there is one study that has failed to detect any difference in 1-yr mortality in COPD patients with and without depression [23], others have shown that depressive symptoms are independent predictors of mortality in patients with COPD [9, 10, 14]. One possible explanation is that in the first study, FAN *et al*. [23] used a lower cut-off point (BDI $\geqslant$10) that allowed for patients with mild depressive symptoms to be included in the depression group. Moreover, the population of our study is quite different from the National Emphysema Treatment Trial (NETT) study population in the study by FAN *et al.* [23]. The important finding of our study is that the presence of depressive symptoms on the day of hospitalisation for AECOPD is an independent predictor of 1-year mortality, supporting a possible role for the evaluation of this important comorbidity in all hospitalised COPD patients.

In this study, we have observed that the presence of depressive symptoms was associated with a greater risk for AECOPD and

TABLE 2 Univariate and multivariate Cox regression analysis evaluating the effect of depressive symptoms and significant confounders on 1-year mortality

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	0.990 (0.949–1.032)	0.624		
Male sex	1.748 (0.415–7.363)	0.447		
BMI	0.962 (0.906–1.020)	0.193		
Smoking status (current)	0.547 (0.222–1.348)	0.190		
Charlson comorbidity index	1.201 (0.904–1.596)	0.206		
GOLD COPD stage	3.696 (2.191–6.233)	<0.001	2.919 (1.632–5.220)	<0.001
MRC dyspnoea score	1.244 (0.812–1.905)	0.316		
Depressive symptoms	7.605 (2.891–20.006)	<0.001	3.568 (1.302–9.780)	0.013

BMI: body mass index; GOLD: Global Initiative for Chronic Obstructive Lung Disease; COPD: chronic obstructive pulmonary disease; MRC: Medical Research Council.

hospitalisations for AECOPD in the 1-year follow-up. Nine studies examining the prospective associations between clinical levels and symptoms of psychological distress and exacerbation risk for patients with COPD [9, 10, 23–29] were recently evaluated in a review paper [8]. Three of those studies evaluated outpatients [23–25], whereas one included a cohort of elderly medical patients including non-COPD patients [29]. In a study in university hospitals in the Nordic countries, anxiety, but not depression, was a risk factor for rehospitalisation in COPD patients with low health status [28]. In a study with similar design in Singapore, NG *et al*. [9] did not show any difference in the risk for readmission in 1 year. In both those studies, a different tool (the Hospital Anxiety and Depression Scale) was evaluated at discharge [28] or in stable condition at 2–4 weeks after discharge [9], in contrast to the evaluation of the BDI score on admission to our study. However, in a pooled meta-analysis of the data of the above studies, LAURIN *et al*. [24] provided evidence that depression (relative risk (RR) 1.12, 95% CI 1.02–1.24) and comorbid depression and anxiety (RR 1.18, 95% CI 1.01–1.38) were associated with an increased risk for in-hospital-treated exacerbations in patients with severe COPD. Our data provide further evidence that the presence of depressive symptoms evaluated by a simple self-administered questionnaire, such as BDI, may provide important information for the classification of future risk of AECOPD.

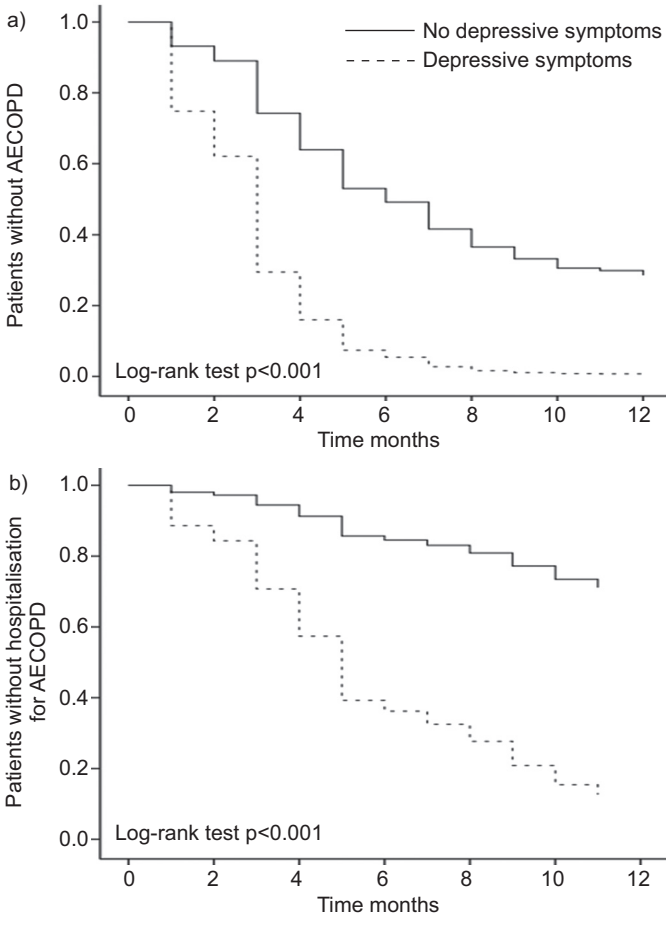

FIGURE 4. Kaplan–Meier curves for a) acute exacerbations of chronic obstructive pulmonary disease (AECOPD) and b) hospitalisation for AECOPD during the 1-year follow-up in patients with and without depressive symptoms.

Depressive symptoms are common in COPD patients. In our study, we identified a higher percentage of patients with depressive symptoms compared with earlier studies [14, 25]. A plausible explanation for this variation is that, in our cohort, COPD patients were older and had more severe disease. Another factor that may have affected our results is the cut-off point of $\geqslant$19 in the BDI score that we selected for the distinction between patients with and without clinically important depressive symptoms. A previous validation study in the Greek general population [30] and a cross-sectional study in COPD patients have used different cut-off points [15]. However, we decided to use the cut-off from the original publication by BECK *et al.* [13] which distinguishes patients with minimal or mild depressive symptoms from patients with moderate or severe depressive symptoms. This cut-off point was also used in a recent prospective study that enrolled COPD patients [14], and used a similar design to that used in our study.

Our study confirms the association between depressive symptoms and COPD severity, expressed not only by differences in

TABLE 3 Univariate and multivariate Poisson regression analysis evaluating the effect of depressive symptoms and significant confounders on acute exacerbations of chronic obstructive pulmonary disease (AECOPD) and hospitalisations for AECOPD

Variable	Univariate analysis		Multivariate analysis	
	IRR (95% CI)	p-value	IRR (95% CI)	p-value
AECOPD in 1-year follow-up				
Age	0.959 (0.959–0.990)	0.002	0.985 (0.968–1.003)	0.108
Male	0.791 (0.515–1.215)	0.286		
BMI	1.025 (1.002–1.049)	0.032	1.001 (0.903–1.021)	0.903
Smoking status (current)	1.007 (0.795–1.458)	0.632		
Charlson comorbidity index	1.048 (0.930–1.180)	0.440		
GOLD COPD stage	2.140 (1.805–2.538)	<0.001	1.633 (1.321–2.018)	<0.001
MRC dyspnoea score	1.352 (1.066–1.716)	0.013	1.060 (0.852–1.318)	0.598
Depressive symptoms	3.666 (2.745–4.895)	<0.001	2.221 (1.573–3.135)	<0.001
Hospitalisations for AECOPD in 1-year follow-up				
Age	1.006 (0.985–1.027)	0.586		
Male	1.547 (0.809–2.959)	0.187		
BMI	1.025 (0.998–1.052)	0.061		
Smoking status (current)	0.826 (0.555–1.228)	0.345		
Charlson comorbidity index	1.272 (1.106–1.463)	0.001	1.160 (1.001–1.345)	0.048
GOLD COPD stage	2.307 (1.849–2.878)	<0.001	1.624 (1.217–2.167)	0.001
MRC dyspnoea score	1.512 (1.191–1.920)	0.001	1.047 (0.807–1.360)	0.726
Depressive symptoms	5.759 (3.918–8.466)	<0.001	3.589 (2.319–5.556)	<0.001

IRR: incidence rate ratios; BMI: body mass index; GOLD: Global Initiative for Chronic Obstructive Lung Disease; COPD: chronic obstructive pulmonary disease; MRC: Medical Research Council.

GOLD stage but also by differences in multidimensional scores, such as the ADO and the DOSE index. A previous study reported an association between depressive symptoms and another multidimensional score, the BODE (Body mass index, airflow Obstruction, Dyspnoea and Exercise capacity) index [31]. Although the BODE index is the most studied multidimensional score assessing COPD severity, we decided to use the ADO and DOSE indexes in our study in order to avoid bias from patients with impaired mobility who would not be eligible to perform a 6-min walking test, which is essential for the evaluation of BODE index [32]. The identification of specific phenotypes of COPD patients with different clinical characteristics, despite the similar spirometric severity, has recently attracted much attention [33]. The possible associations of depressive symptoms with different phenotypes of COPD patients may represent an area of research interest in the future.

A plausible explanation for the finding that COPD patients with depressive symptoms have more severe disease might be the fact that depression seems to affect functioning of the hypothalamic–pituitary–adrenal axis, which might cause deterioration of health status [34]. Additionally, the secondary emotional responses to chronic respiratory disease contribute to the resulting inactivity, deconditioning and morbidity, which finally cause social isolation, fear and depression. Patients with severe COPD very often feel useless, experience reduced sexual activity, depend on others for their personal care and lose interest in life and future projects [35]. Moreover, depressive symptoms can impair self-care, as indicated by continued smoking, lower activity levels and poor medication compliance, which also could lead to an accelerated disease progress [14, 34]. Finally, depression may be related to increased awareness and focus on physical symptoms, which may lead to more frequent utilisation of medical services [36].

Patients with depressive symptoms in our study required longer hospitalisation and presented slower recovery from AECOPD according to the degree of their dyspnoea (assessed by the Borg scale) and their health status (according to the CAT score). A plausible mechanism that might be implicated in the delay of recovery in these patients is that they often present changes in major immune cell classes, such as lowered proliferative response of lymphocytes, lowered natural killer cell activity, and alterations in numbers of several white blood cell populations [37]. As the majority of the triggers of AECOPD are of infectious origin [11], the above immunological abnormalities could contribute in the slower immunological response of the patients, which might result in more prolonged hospitalisation and slower clinical improvement. The fact that no statistically significant difference was observed between patients with and without depressive symptoms in the degree of improvement in FEV_1 and $P_{a}O_2/F_{I}O_2$ further supports the fact that COPD is a multicomponent disease that cannot be characterised only by measurements of lung function and oxygenation [38].

Our study has some potential limitations. First, the assessment of depressive symptoms was conducted on admission for AECOPD, which may reflect an increase of depressive symptomatology [7]. Secondly, the identification of depressive symptoms was based on a standardised questionnaire and not on a structured psychiatric interview. BDI additionally

measures anxiety [13], which indicates that a large part of our patients' symptoms may be related to the presence of anxiety because of increased dyspnoea and stress during hospital admission. Thirdly, in previous studies it has been argued that depressive symptoms obtained with instruments like the BDI are inflated among patients with medical disease because of the confounding role of the symptoms of their underlying disease [14], and this may have further increased the healthcare use of these patients, including hospitalisation. The design of this study (monthly telephone communication) may not have allowed for objective evaluation of the indications for COPD hospitalisation during follow-up. Our study involved patients with a male:female ratio of ~9:1; however, this was also the case in previous studies by our group with a similar design [39, 40], and may reflect the increased prevalence of COPD in males compared with females in Greece [41]. However, the fact that a simple measure of depressive symptoms, such as the BDI, was a significant predictor of clinically important future outcomes in hospitalised COPD patients supports a possible usefulness for this measure in clinical practice. Finally, our study design involving telephone communication may have not allowed us to determine properly the independence of individual exacerbation events and to set criteria to distinguish a new exacerbation event from a relapse of the original exacerbation during follow-up, a limitation that is present in several previous studies evaluating AECOPD [22]. However, the study investigators have meticulously tried to count independent events of AECOPD during follow-up.

In conclusion, our data suggest that the presence of depressive symptoms, as expressed by an increased BDI score, in patients hospitalised for AECOPD has a significant impact on the duration and the recovery from the exacerbation, and represents an independent predictor of mortality and of the risk for future COPD exacerbations and hospitalisations in the following year. The possible effects of the early identification and management of depressive symptoms on the outcomes of patients with COPD should be evaluated in prospective controlled trials.

STATEMENT OF INTEREST

None declared.

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