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# Anxiety-depressive Symptoms in Patients with Chronic Obstructive Pulmonary Disease (COPD) and Impact on Outcome

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## Abstract

**Objectives:** Psychological distress and adversities are more common in Chronic obstructive pulmonary disease (COPD) patients compared with other chronic illnesses. In addition, anxiety and depressive symptoms have evident impacts on COPD patients outcome. The present study designated to investigate whether anxiety and depressive symptoms occur more common in patients with severe and very severe COPD than controls. Also, we assessed the relationship between anxiety-depressive symptoms and quality of life (QOL), functional status and impairment, exacerbations, re-hospitalization, length of stay (LOS) and mortality prediction.

**Methods:** The study sample included 220 patients with severe and very severe COPD, and 220 non-COPD patients as controls. Anxiety-depressive symptoms were assessed in COPD and controls using the Hospital Anxiety and Depression scale (HAD). The COPD group is divided into two groups: the depressed and non-depressed groups. Both groups were followed up for 12 months.

**Results:** The prevalence of anxiety-depressive symptoms was highly significant in severe and very severe COPD patients than non-COPD patients (44.5% compared with 14.5% in controls) When the results were adjusted, the risk was 3.5 times greater for patients. Anxiety-depressive symptoms were significantly associated with more mortality, longer LOS, failure of smoking cessation and worse Saint George Respiratory Questionnaire (SGRQ).

**Conclusion:** Anxiety-depressive symptoms occur more common in patients with severe and very severe COPD than in controls. In addition, anxiety-depressive symptoms are important risk factor for poor QOL, poor functional status and impairment, more exacerbations, more re-hospitalizations, prolonged LOS, failure of smoking quitting and more mortality. Anxiety-depressive symptoms were risk factor independent of physiological measure of disease severity (e.g. FEV1).

**Keywords:** COPD; Anxiety; Depressive; Exacerbation; Functional status; Quality of life; Anxiety and depression scale; Saint George respiratory questionnaire

## Introduction

COPD is a progressive respiratory disorder characterized by airflow obstruction, recurrent symptoms include a cough, sputum production, breathlessness and impaired exercise tolerance [1]. COPD is responsible for substantial human and economic burden throughout the world [2]. Worldwide, COPD was the fifth leading cause of death in 2001 [3] and is projected to be the third leading cause of death by 2020 [4]. Recent findings suggest a 5-year mortality rate following an acute exacerbation of COPD as high as 70% [5].

The association between COPD and psychiatric disorders, in particular generalized anxiety, panic anxiety and depression, has been acknowledged for many years. The prevalence of psychiatric co-morbidity in these patients as well as the effect of treatment and the prognosis remains unsettled [6].

The diagnostic procedure is complicated by an overlap or close association of somatic and psychiatric symptoms in COPD patients suffering from co-morbid anxiety and depression. There is evidence that psychiatric co-morbidity contributes significantly to the functional impairment of COPD patients and that psychiatric treatment may improve not only psychiatric status but also pulmonary function [7].

Psychiatric comorbidity is common in patients with COPD, more so that in other respiratory diseases, such as pulmonary tuberculosis, and also exceeding their prevalence in the general population and in people with many other long-term conditions [8].

Comorbid anxiety in people with COPD is associated with decreased functional status and decreased quality of life. People with COPD and comorbid anxiety may also use health services more, because they have an increased risk of exacerbations and readmissions [9]. Despite the negative impact of anxiety on quality of life and healthcare usage, there has been little research exploring the impact of anxiety among COPD patients [10].

Anxiety and depression are risk factors for re-hospitalization in these patients [11,12]. Irrespective of the presence of somatic diseases, anxiety and depression themselves constitute a substantial risk for increased mortality, although the mechanism for this association is unknown [13,14].

This study aims to investigate whether anxiety-depressive symptoms occurs more common in patients with severe and very severe COPD than in controls. In addition, we assess the relationship between anxiety-depressive symptoms (as a risk factor) and following: quality of life (QOL), functional status and impairment, exacerbations, re-hospitalization, length of stay (LOS) and mortality prediction.

## Patients and Methods

The present study was conducted in Chest Disease Hospital, Kuwait, in the period from January 2011 to December 2012. We collected 220 patients admitted due to acute exacerbations of severe and very severe COPD. A random sample of 220 patients who admitted in medical ward due to medical illnesses other than COPD, over 40 years older acted as controls.

According to the GOLD [15], the diagnostic criteria of COPD patients (inclusion criteria) are: (1) age >40 years, (2) history of smoking index >20 pack/years, (3) FEV1/FVC <70% (4) with FEV1 reversibility <12%. (5) The patient considered to have severe COPD if FEV1 <50% predicted but >30% of predicted, (6) the patient considered to have very severe COPD if FEV1 <30% of predicted or FEV1 <50% predicted plus chronic respiratory failure. The COPD patient considered to have acute exacerbation if there is acute deterioration and increase in the symptoms of chronic dyspnea, sputum production, or sputum purulence [15].

The exclusion criteria were: (1) coexisting active pulmonary tuberculosis, pulmonary fibrosis, pneumothorax, or lung cancer; (2) death during hospital stay; (3) inability to perform spirometry or being too physically ill or mentally incapacitated to participate and (4) receiving corticosteroids or immune-suppressive or any psychiatric medications.

Baseline measurements and assessments were performed when the patients were in stable condition before their discharge at the end of their hospital stay, then 6 months and 1 year later. Baseline measurements-in addition to the above mentioned spirometric data-included socioeconomic data, COPD duration, comorbidities, degree of dyspnea, chronic mucus hypersecretion, arterial blood gases, body mass index, smoking, hospitalizations, number of acute exacerbations and hospitalizations in the preceding year.

Anxiety-depressive symptoms were assessed by the self-report questionnaire "Hospital Anxiety and Depression scale" (HAD). It was developed to detect states of depression, anxiety and emotional distress amongst patients who were being treated for a variety of clinical problems. The scale was not designed to be a clinically diagnostic tool. Scale has 14 items (7 questions relating to anxiety; 7 questions relating to depression), with responses being scored on a scale of 0-3, with 3 indicating higher symptom frequencies. Score for each subscale (anxiety and depression) can range from 0-21 with scores categorized as follows: normal (0-7), mild (8-10), moderate (11-14), severe (15-21). Scores for the entire scale (emotional distress) range from 0-42, with higher scores indicating more distress. Prior to completing the scale patients are asked to “fill it complete in order to reflect how they have been feeling during the past week” [7].

Symptom burden, physical, social functional status and impairment and quality of life were measured using the "Saint George Respiratory Questionnaire" (SGRQ) [8]. The SGRQ is a QOL questionnaire. The questionnaire assesses the patient’s experience of symptoms, the amount of distress caused by symptoms, and the daily activities limitation. Higher scores indicate a worse health status. It has been validated for use in medical patients [9].

Information recorded on vital status, rehospitalizations due to acute exacerbations (including number of exacerbating episodes and LOS), persistent smoking, HAD score, and SGRQ score.

Spirometry was performed using an electronic microspirometer (Micro Medical Ltd, England) when the patient’s condition was stable before the planned discharge and was repeated every month after discharge. Measurements followed American Thoracic Society criteria for spirometric standardization and procedures [10].

### Statistical analysis

Chi square was used to test the significance of differences between two or more categorical values. The multivariate logistic regression analysis was performed using adjusted odds ratio and 95% Confidence intervals. Statistical significance implies P value <0.05 and the statistical analysis was performed using SPSS software (version 17.0).

## Results

Most of the patients were males (n=211, 95.9%), females represent only 5% of severe COPD patients group and 2.5% of very severe COPD patients group. The mean age was (74.4, 66.8 and 63 years) in very severe COPD patients, severe COPD patients and controls respectively. Comorbidities were more common in very severe COPD patients group (77.5%) than severe COPD patients group (62.9%) (Table 1).

| | Severe COPD patients (n=140) | Very severe COPD patients (n=80) | Controls (n=220) |
|---|---|---|---|
| **Male sex** | 133 (95.0%) | 78 (97.5%) | 208 (94.5%) |
| **Low socio-economic** | 120 (85.7%) | 73 (91.3%) | 186 (84.5%) |
| **Comorbidity** | 88 (62.9%) | 62 (77.5%) | 124 (56.4%) |
| **Age, mean (SD)** | 66.8 (9.4) | 74.4 (4.7) | 63 (8.6) |
| **Reversibility mean (SD)** | 5.4% (4.2) | 3.3% (2.6) | |

**Table 1:** General characteristics of the studied patients and controls.

| | n | HAD>8 | Adjusted or (95% CI) |
|---|---|---|---|
| **COPD (whole group)** | 220 | 98 (44.5%) | 1.6 (0.8 to 2.6) |
| **Severe COPD** | 140 | 55 (39.3%) | 2.3 (1.3 to 5.2) |
| **Very severe COPD** | 80 | 43 (53.8%) | 1.2 (0.6 to 2.4) |
| **Controls** | 220 | 32 (14.5%) | 1.0 |

**Table 2:** Prevalence of depression among patients and controls.

In patients with severe and very severe COPD, prevalence of anxiety-depressive symptoms was 44.5% compared with 14.5% in controls. When the results were adjusted for demographic variables and co-morbidity, the risk for anxiety-depressive symptoms were 3.5 times greater for patients with severe and very severe COPD than for controls (Table 2).

Poor reversibility of forced expiratory volume in the first second (FEV1%) predicted, respiratory symptoms, physical, social functional status and impairment of quality of life (assessed by SGRQ) were significantly associated with the scores on the HAD Scale (Table 3).

| | | n = 220 | HAD > 8 (n=98) | Crude or (95% CI) | Adjusted or** (95% CI) |
|---|---|---|---|---|---|
| Age | ≥65 yr | 126 | 65 (51.6%) | 0.8 (0.4-2.1) | 0.6 (0.3-1.4) |
| | <65 yr | 94 | 33 (35.1%) | 1 | 1 |
| Gender | Male | 211 | 96 (45.5%) | 0.9 (0.7-2.5) | 0.5 (0.3-1.3) |
| | Female | 9 | 2 (22.2%) | 1 | 1 |
| Comorbidity | Presence | 152 | 76 (50.0%) | 2.2 (0.3-5.8) | 1.8 (0.6-4.0) |
| | Absence | 68 | 22 (32.4%) | 1 | 1 |
| Reversibility | ≤1.1% | 29 | 19 (65.5%)* | 4.2 (1.5-8.8) | 3.5 (1.2-10.2) |
| | < 1.1-12% | 191 | 79 (41.4%) | 1 | 1 |
| Respiratory Symptoms | Severe | 28 | 15 (53.6%)* | 3.4 (1.5-7.2) | 2.7 (1.7-7.8) |
| | Mild to moderate | 192 | 83 (43.2%) | 1 | 1 |
| Impaired SGRQ score | Severe | 30 | 18 (60.0%)* | 4.8 (1.5-13.7) | 4.6 (1.7-10.2) |
| | Mild to moderate | 190 | 80 (42.1%) | 1 | 1 |
| *p<0.01 (X2 test). **Adjusted for all other variables. | | | | | |

**Table 3:** Demographic, disease-related variables and Anxiety-Depressive symptoms in patients with COPD (n=220).

| **Outcome** | | **Non-depressed Patients (n=122 )** | **Depressed Patients (n=98 )** | **p value** |
|---|---|---|---|---|
| **Mortality (No of deaths after index hospital)** | | 10 (8.2%) | 22 (22.4%) | 0.003 |
| **Hospital readmission** | Patients with >1 readmission, No. (%) | 47 (38.5) | 70 (71.4) | <0.01 |
| | 1-2 Readmissions, No. (%) | 32 (68.1) | 29 (41.4) | |
| | >3 Readmissions, No. (%) | 15 (31.9) | 41 (58.6) | |
| **Hospital length stay/day** | Index hosp.; mean (SD) | 3.8 (2.5) | 5.3 (5.9) | 0.02 |
| | All hosp. including index, mean (SD) | 10.2 (13.0) | 16.7 (16.0) | 0.04 |
| **Change from baseline in FEV1%, mean (SD)** | | −2.8 (35.6) | −1.2 (36.2) | 0.82 |
| **FEV1, % at 1 yr, mean (SD)*** | | 45.8 (20.2) | 48.3 (22.5) | 0.73 |
| **Smoking, No. (%)** | At index hospitalization | 36 (29.5) | 27 (27.6) | 0.72 |
| | At 6 month | 22 (18.0) | 31 (31.6) | <0.001 |
| **SGRQ score, mean (SD)**** | At index hospitalization | 37.9 (14.2) | 52.5 (15.2) | <0.001 |
| | At 6-month follow-up | 37.9 (14.2) | 52.5 (15.2) | <0.001 |
| | At 1-y follow-up | 33.8 (17.4) | 44.7 (16.7) | <0.001 |
| *FEV1, forced expiratory volume in 1st second; **SGRQ, St George Respiratory Questionnaire, measures quality of life; higher scores denote poor compliance or reduced quality of life. | | | | |

**Table 4:** Outcomes of care in patient hospitalized for acute exacerbation of COPD.

There were significantly more deaths after discharge among depressed patients (22.4%) than among non-depressed patients (8.2%) even after controlling of COPD duration and severity (P<0.05). The number of readmitted patients and the total number of readmissions were significantly more in depressed than non-depressed patients (P<0.001).

Depressed patients had a significantly (P<0.05) greater LOS during their index hospitalization (5.9 days) than did non-depressed patients (2.5 days). Also, had a significantly (P<0.05) greater LOS during their all hospitalization (16 days) than did non-depressed patients (13 days). Depression was not associated with FEV1 percentage at baseline or at 1 year. The percentage change in FEV1 at 1 year from baseline was also not significantly greater in depressed patients (P<0.05).

Depressed patients did not differ significantly from non-depressed patients on current smoking during their index hospitalization (P<0.05). However, at 6 months, non-depressed patients had a significantly lowered proportion of current smokers (18%), whereas depressed patients had almost the same proportion of current smokers (31.6%, P<0.05). SGRQ score was significantly worse in depressed than in non-depressed patients, both at the index hospitalization, at 6-month and at 1 year follow-up (P<0.001) (Table 4).

The SGRQ score was significantly worse in depressed than in non-depressed patients, both at the index hospitalization (13.3 points difference P=0.002) and at 1 year (10.1 points difference; P=0.006). We also analyzed the association of ADD (HAD score >8) with COPD outcomes. Given the small numbers and its comorbid association with depression, we found that Anxiety-Depressive symptoms were associated with mortality (Table 5).

| Depression Status | SGRQ subscale score | | | |
|---|---|---|---|---|
| | Symptoms | Activities | Impact | SGRQ |
| | Mean(SD)# | Mean (SD)# | Mean (SD)# | total score Mean (SD)# |
| **Index hospital** | | | | |
| **Depressed patients (n=98)** | 63.3 | 72.5 (1.4) | 36.3 (1.4) | 51.9 (1.2) |
| **Non depressed patients (n=122)** | 51.1 | 60.2 (1.2) | 22.6 (1.3) | 38.6 (1.1) |
| **P value** | 0.003 | 0.002 | <0.001 | 0.002 |
| **At 1 yr follow up** | | | | |
| **Depressed patients** | 63.5 | 64.7 (1.9) | 27.4 (1.8) | 44.7 (1.7) |
| **Non depressed patients** | 51.5 | 54.1 (1.6) | 18.1 (1.5) | 34.6 (1.3) |
| **P value** | 0.006 | 0.02 | 0.01 | 0.006 |

Note: *Higher score denotes reduced quality of life. #Determined by the general linear model test with univariate 1-way analysis of variance. Adjusted for relevant confounders: sociodemographic factors (age, sex); clinical factors (chronic mucus hypersecretion, body mass index, and comorbidity); disease severity markers (duration of chronic obstructive pulmonary disease, number of readmissions, dyspnea, forced expiratory volume in 1 second [percentage of predicted values]); and psychosocial and behavioral factors (e.g. anxiety and smoking).

**Table 5:** St George Respiratory Questionnaire (SGRQ) at index hospitalization and 1-year follow-up in depressed and non-depressed Patients.

## Discussion

This study revealed that the prevalence of anxiety-depressive symptoms in severe and very severe COPD patients was 44.5% and they had a 3.5 times greater risk of anxiety-depressive symptoms than controls who were comparable for demographic variables and the presence of comorbidity. We also found that reversibility in FEV1% predicted, respiratory symptoms, and physical impairment were related to anxiety-depressive symptoms in patients with COPD, whereas age, sex, FEV1, and comorbidity were not.

This study provides preliminary evidence that anxiety-depressive symptoms are an independent prognostic factor for mortality among stable severe and very severe COPD patients, even when adjustments are made for risk factors such as age, sex, and FEV1.

Donohue et al. [11] reported that, in patients with mild to moderate COPD, no increased risk for anxiety-depressive symptoms were seen. We found that anxiety-depressive symptoms were significantly more common in severe and very severe COPD patients than control group. In these patients, anxiety-depressive symptoms were associated with higher mortality, longer index hospitalization and total LOS, failure of smoking cessation at 6 months, and worse physical and social functioning as assessed by the SGRQ at the index hospitalization, 6 months and 1 year later. These statistical data were valid even after controlling for chronicity, severity of COPD, comorbidities, and behavioral, psychosocial, and socioeconomic variables. These data have been reported in previous studies [12-15].

An important finding in this study was that an excess of anxiety-depressive symptoms in hospitalized patients with severe and very severe COPD was associated with increased mortality risk, after controlling for disease severity and other risk factors (Table 4). This is consistent with many literatures documenting that anxiety-depressive symptoms are associated with poor survival of COPD patients [12,13]. Two early studies [14,15] had reported that depression independently

predicted increased mortality after COPD admission (independent of other physiological parameters of disease severity e.g. FEV1).

Studies have consistently found that QOL measures predict subsequent risk of hospital readmission and mortality independent of severity and risk markers [16-20]. Indeed, we have also confirmed in this study that, in addition to depression, the SGRQ symptoms score was also independently associated with readmission risk.

Our observation that anxiety-depressive symptoms were independently associated with mortality and hospital readmission and poor prognostic value. There are many possible mechanisms can be offered [21-23], e.g. depressed patients commonly feeling hopeless and helpless about changing their life circumstances, lacking the drive and motivation to seek help and hospital readmission, with subsequent early death instead. Second, depression can affect the hypothalamic-pituitary-adrenal axis functioning, which could make health status deteriorate. Third, anxiety-depressive symptoms can impair self-care, as indicated by insufficient nutritional intake, continued smoking, lower activity levels, poor medication compliance. These factors also could lead to an accelerated decline in health.

Prevalence of smoking among patients with anxiety-depressive symptoms is generally high [24]. A study found a 2.24-folds increased risk of depression in current smokers as compared with nonsmokers [25]. We found that, in response to routine smoking cessation counseling in the hospitals, a significant proportion of the non-depressed patients had quit smoking at the 6-months follow-up, whereas most of the depressed patients persisted in smoking. This adverse effect of depression on smoking cessation behavior gives support to the role of psychotherapeutic interventions, including Bupropion, Nortriptyline and recently Varenicline (Chantix) therapy, for smoking cessation in patients with COPD [26,27].

Our inability to demonstrate an association of anxiety-depressive symptoms with FEV1 during the index hospitalization and at 1 year is probably not surprising considering the published evidences. Although FEV1 is accepted as a reliable physiological marker of disease severity, it has been shown in many studies to be weakly correlated with QOL measures, suggesting that different dimensions of disease severity and outcomes are measured by physiological (e.g. FEV1) and patient reported outcome measures [28,29].

Poor QOL in patients with COPD has previously been linked to greater use of health resources [30]. The study by Cox et al. [31] suggests that, when QOL improves, even though lung function does not, consultations and hospital admissions decrease. The results of our study are compatible with those of Cox et al in showing that poor QOL is associated with a greater chance of admission, nebulizer provision and long-term oxygen therapy.

Thus QOL outcomes, even when there is no physiological improvement (e.g. FEV1), may be important in assessing the success of interventions in patients with COPD [32,33]. These findings support the role of antidepressant or psychological interventions in depressed patients with COPD to improve outcomes. Several studies have reported that pharmacological treatment in clinically depressed patients with COPD significantly reduces anxiety depressive symptoms [34,35], respiratory symptoms, and day-to-day functioning [36].

## Conclusion and Recommendations

In conclusion, anxiety-depressive symptoms are more common in severe and very severe COPD. In addition, anxiety-depressive symptoms are associated with increased risk of mortality, longer hospitalization LOS, persistent smoking behavior, and failure of smoking cessation, increased symptom burden, poorer physical and social functioning, and reduced QOL.

This association is independent of physiological measure of disease severity (e.g. FEV1) and adds important new information in the treatment of severe and very severe COPD patients. What is needed next are trials of antidepressant and psychological interventions. These interventions should provide conclusive evidence of improved survival, QOL, and self-management behavior and reduced exacerbations, re-hospitalizations.

Psychosocial interventions in the context of a pulmonary rehabilitation program have also been shown to reduce depression and anxiety [36] and to improve QOL [37], but did not modify exercise performance [24].

## Limitations of the study

- Our sample was made up of older subjects with severe and very severe symptoms of COPD, so the results are not generalizable across age, gender; other less grades of COPD severity e.g. mild and moderate COPD patients.
- Self-report of hospitalization episodes and LOS may be less reliable than desired. In addition, we were unable to obtain data on the specific causes of death among some patients, in particular when patients die at home.

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