

Anxiety and depression in COPD patients and correlation with sputum and BAL cytology

Ansietà e depressione nei pazienti con BPCO e correlazione con la citologia dell'espettorato e del BAL

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ABSTRACT

Background and aims: Anxiety and depression are common in patients with chronic obstructive pulmonary disease (COPD). The degree of lung function may not explain anxiety and depression. The aim of our study was to assess the psychological aspects of COPD, to test the BODE index (a composite score of body mass, obstruction, dyspnea and exercise capacity), and to evaluate the association between atypical cytologic findings of sputum, bronchoalveolar lavage (BAL) and the psychological components of the disease.

Methods: COPD was classified according to the GOLD stages based on forced expiratory volume in 1 second (FEV₁) in 60 stable patients. The BODE index was calculated for grading COPD. The Hospital anxiety and depression (HAD) scale was used to appraise the anxiety and depression symptoms. Cytologic examination of sputum and BAL samples were performed in each patient. The cytologic findings were classified as normal, mild, moderate or severe atypia.

Results: The overall prevalence of anxiety and depression symptoms was 41.7% and 46.7% respectively. The prevalence of these symptoms increased with increasing BODE stages and correlated well with the severity of atypical BAL cytology results ($p < 0.001$). Dyspnea and reduced exercise capacity were the predominant mechanisms leading to anxiety and depression symptoms associated with COPD.

Conclusions: We conclude that the BODE index is superior to GOLD stratification for explaining anxiety and depression symptoms in COPD. BAL cytologic findings, which reflect the distal parenchymal lung structure, correlated significantly with the presence of the anxiety and depression symptoms.

Keywords: Anxiety, bronchoalveolar lavage, BODE index,

COPD, depression, GOLD.

RIASSUNTO

Razionale e scopo: Ansietà e depressione sono frequenti nei pazienti con broncopneumopatia cronica ostruttiva (BPCO). Il semplice quadro funzionale può non spiegare adeguatamente ansia e depressione. Scopo del nostro studio era valutare gli aspetti psicologici della BPCO, testare il BODE index (un punteggio composito che tiene conto di massa corporea, ostruzione, dispnea e capacità di esercizio) e valutare l'associazione tra i rilievi patologici nella citologia di espettorato e BAL con la componente psicologica della malattia.

Metodi: La BPCO è stata classificata secondo la stadiazione GOLD basata sul volume espiratorio forzato in un secondo (FEV₁) in 60 pazienti stabili. L'indice BODE è stato calcolato per dare una stima di gravità della BPCO. Per valutare i sintomi di ansia e depressione è stata utilizzata la scala Hospital anxiety and depression (HAD). In ogni paziente è stata effettuata la valutazione della citologia dell'espettorato e del BAL. I risultati della citologia sono stati classificati come normali o con atipia lieve, moderata o grave.

Risultati: La prevalenza complessiva dei sintomi di ansietà e depressione era rispettivamente del 41,7% e 46,7%. La prevalenza di questi sintomi aumentava all'incremento dello stadio BODE e correlava con la gravità delle atipie nel reperto citologico del BAL ($p < 0,001$). I meccanismi prevalenti che inducevano ansietà e depressione in associazione con la BPCO erano la dispnea e la ridotta capacità di esercizio fisico.

Conclusioni: Concludiamo che l'indice BODE è più efficace

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della stratificazione GOLD nello spiegare i sintomi di depressione e ansia nei BPCO. I risultati della citologia sul BAL, che riflettono la struttura del polmone profondo, correlano significativamente con la presenza dei sintomi di ansietà e depressione.

Parole chiave: Ansia, BPCO, depressione, GOLD, indice BODE, lavaggio broncoalveolare.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive disorder with substantial mortality and morbidity. The main goals of treatment in COPD are prevention or slowing of disease progression and improving the quality of life [1]. COPD patients carry a substantial psychological burden related to their disease and frequently suffer from anxiety and depression [2-5]. Anxiety and depression are risk factors for rehospitalisation in these patients [4,6]. 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 [7,8]. The severity of pulmonary function impairment related to anxiety and depression in COPD patients has been the subject of research but in most studies no correlation was found between psychological aspects of the disease and the forced expiratory volume in 1 second (FEV₁) value. On the other hand, the presence of respiratory symptoms leads to significant anxiety or depression and dyspnea has been shown to correlate significantly with anxiety and depression in these patients [9,10].

Lung damage due to the inflammation of small airways appears to be the primary mechanism for dyspnea and physical disability leading to psychiatric comorbidities in COPD patients [2,6,8,9]. Sputum and bronchoalveolar lavage (BAL) cytology may be useful for identifying depression and anxiety in these patients by revealing inflammatory and cellular changes of the lung parenchyma. The aim of our study was to assess the psychological aspects of COPD, evaluate the correlation of the BODE index (a composite score of body mass, obstruction, dyspnea and exercise capacity) with anxiety and depression symptoms, and to evaluate the association between sputum and BAL cytology and the psychological disorders associated with COPD.

PATIENTS AND METHODS

This was a prospective cross-sectional study performed at the Respiratory Diseases Department of Cerrahpasa Medical Faculty between January 2008 and June 2010. The study was approved by the Institutional ethics committee and informed consent was obtained from all patients. Sixty adult patients with stable COPD were included in the study. Inclusion criteria were: COPD diagnosed according to the Global Initiative for Obstructive Lung Disease (GOLD) consensus, stable disease, absence of any other chronic disease, ability to perform a 6-minute

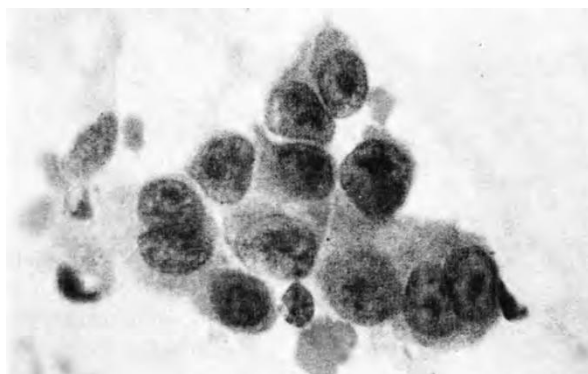
walking test, to complete the questionnaires, and no contraindications for bronchoscopy and BAL. Spirometry was performed according to the ATS/ERS recommendations with a body plethysmograph unit (Zan 500, Messgeraete, Oberthulba, Germany). Blood gases were determined from radial artery samples using the Radiometer ABL800 FLEX blood gas analyzer.

The patients were stratified according to the GOLD classification of severity. Sputum samples were obtained from every patient. If the sputum sample contained 10 or more squamous epithelial cells per low-power (x100) magnification field then the specimen was considered unsatisfactory and was discarded. BAL was performed by instilling five 20 ml aliquots of sterile saline into a subsegment of lingula or middle lobe. After removal of mucus fluid the sample was prepared for cytologic examination by cytocentrifugation. BAL findings were evaluated by a pathologist and a cytologist. Cytologic findings were classified as normal, mild, intermediate or severe atypia. BAL cytology was evaluated according to the staining characteristics, cellular cohesion, nucleus, cytoplasmic features and nucleus cytoplasm ratio epithelial cells, Goblet (brush border) cells, Clara cells, neutrophils, and type I and type II alveolar cells. Mild atypia showed pale, abundant cytoplasm, nucleus with a fine chromatin pattern, round or oval nucleus, and cohesive cell sheets with a mild disruption of the nucleus cytoplasm ratio. Severe atypia revealed acidophilic cytoplasm, discohesive cells, hyperchromatic and irregular nucleus, conspicuous nucleolus and a significant increase in the nucleus cytoplasm ratio. Cytologic findings that did not fit into either mild (Figure 2) or severe (Figure 1) type were designated as intermediate atypia. The cytologic results were classified as follows: normal = 0, mild atypia = 1, intermediate atypia = 2, and severe atypia = 3.

The BODE index was calculated for classification of COPD. The index score comprises body mass index (BMI), FEV₁, dyspnea grade as measured by the Modified Medical Research Council (MMRC) scale, and the 6-minute walking distance (6MWD) [11,12]. The Hospital anxiety and depression (HAD) scale was used for screening psychiatric disorders. It has been used for screening COPD patients previously. The scale consists of seven questions related to anxiety and depression, rated on a 4-point scale. The test provides maximum subscale scores of 21 for anxiety and depression, with a score of ≥ 8 describing the presence of these symptoms [2,3,6,13,14]. In each patient who scored ≥ 8 the existence of anxiety and depression was investigated by a consultant psychiatrist.

Statistical data were expressed as mean \pm standard deviation. Differences between groups were tested with the Student's *t*-test and non-parametric Mann-Whitney test for continuous data. The chi-square test was used for noncontinuous data. To analyze differences of anxiety and depression scores between different stages of COPD one-way ANOVA was used. COPD or BODE stages were compared

FIGURE 1: BRONCHOALVEOLAR LAVAGE (BAL) CYTOLOGY REVEALING SEVERE ATYPIA (PAPANICOLAU, 400x)



by the chi-square test to evaluate how well they explained anxiety and depression symptoms. Linear regression was used for BODE components associated with the HAD scores. Statistical analysis was performed using the SPSS 17.0 statistical package. A p value of less than 0.05 was accepted as statistically significant.

RESULTS

Sixty stable COPD patients (males 35, mean age 66 ± 11 years) participated in the study. The patient characteristics are outlined in Table I. The number of COPD patients in stages II to IV by GOLD classification and the mean BODE index of the patients are shown in Table II. The BODE index ranged from stage II to IV. The mean scores for anxiety and depression were 8.2 ± 4.6 and 7.9 ± 4.3 respectively. Twenty-five patients (41.7%) were found to have symptoms suggestive of anxiety and 28 patients (46.7%) had symptoms suggestive of depression. There was no correlation between the presence of anxiety or depression symptoms and age, gender or

FIGURE 2: BRONCHOALVEOLAR LAVAGE (BAL) CYTOLOGY SHOWING MILD ATYPIA (PAPANICOLAU, 400x)

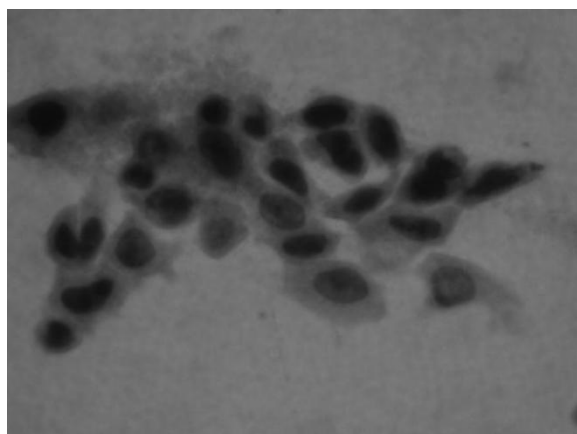


TABLE I: CHARACTERISTICS OF THE PATIENTS

Patient characteristics	N (%)
Male/female (%)	35/25 (58/42)
Age (years)	66 ± 11
Pack-years	58 ± 28
Current smoker (n) (%)	16 (26.7)
Body mass index, kg/m ²	26 ± 4.5
COPD duration (year)	7.45 ± 7.12
LTOT use (n) (%)	10 (16.7)
NIMV use (n) (%)	5 (8.3)
Hospitalization in the previous year (n) (%)	12 (20)
FEV ₁ , liters	1.3 ± 0.5
FEV ₁ (%predicted)	51 ± 15
FVC, liters (%predicted)	2.7 ± 0.7
FVC, %predicted	83 ± 14
FEV ₁ /FVC	51 ± 15
pO ₂ , mmHg	71.3 ± 9.7
pCO ₂ , mmHg	39.8 ± 4.9
MRC dyspnea scale	2.2 ± 1.07
Six-minute walking distance	302 ± 120
BODE index	3.2 ± 2.5

Data are expressed as mean \pm standard deviation (SD).

Definition of abbreviations: BODE, body mass, obstruction, dyspnea and exercise capacity; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in one second; FVC, forced ventilatory capacity; LTOT, long term oxygen therapy; MRC, Medical Research Council; NIMV, non-invasive mechanical ventilation.

smoking level (pack/years) (Table III). Anxiety and depression scores correlated with the BODE index ($K\tau = 0.19$, $p < 0.001$; $K\tau = 0.34$, $p < 0.001$). The prevalence of anxiety increased with increasing BODE index ($\chi^2 = 7.46$, $p < 0.001$) but not with increasing GOLD stages ($\chi^2 = 3.72$, $p < 0.42$). The prevalence of depression increased with both increasing BODE index and GOLD stages ($\chi^2 = 28.54$, $p < 0.001$; $\chi^2 = 38.24$, $p < 0.001$). The mean anxiety score for GOLD stages II, III, and IV was 4.1 ± 2.8 , 7.4 ± 3.8 and 8.9 ± 5.1 , respectively ($p < 0.054$). The mean depression score for GOLD stages II, III, and IV was 2.1 ± 1.6 , 5.8 ± 4.2 and 9.4 ± 5.2 , respectively ($p < 0.001$). The mean anxiety score for BODE stages I, II, III and IV was 5.9 ± 4.1 ,

TABLE II: PATIENT CLASSIFICATION ACCORDING TO GOLD AND BODE INDEXES

Severity of COPD	Patient number (%)	BODE index
Stage II	30 (50%)	1 (1 to 4)
Stage III	20 (33.3%)	4 (3 to 6)
Stage IV	10 (16.7%)	7 (6 to 9)

Definition of abbreviations: BODE, body mass, obstruction, dyspnea and exercise capacity; COPD, chronic obstructive pulmonary disease.

TABLE III: COMPARISON OF VARIOUS PARAMETERS WITH ANXIETY AND DEPRESSION

p	HAD-anxiety	HAD-depression
Age	0.687	0.289
Gender	0,582	0,885
Smoking (pack/years)	0,199	0,083
COPD stage	0,001	0,001
Disease duration (year)	0.078	0.086
Hospital admission	0.326	0.002
Exacerbations per year	0.084	0.17
Borg	0.424	0.118
LTOT	0.349	0.284
NIMV	0.693	0.042

Definition of abbreviations: COPD, chronic obstructive pulmonary disease; HAD, Hospital Anxiety and Depression scale; LTOT, long term oxygen therapy; NIMV, non-invasive mechanical ventilation.

8.2 ± 3.9, 9.7 ± 3.6 and 9.2 ± 5.3, respectively (p < 0.001). The mean depression score for BODE stages I, II, III and IV was 5.2 ± 3.1, 6.8 ± 3.4, 9.4 ± 3.2 and 10.2 ± 4.6, respectively (p < 0.001). Sputum and BAL cytology results with regard to anxiety and depression symptoms are shown in Tables IV and V. Although the correlation of moderate or severe cytologic atypia of sputum was not statistically significant for anxiety or depression symptoms, the specificity and sensitivity was found to be 67.2% and 68.4%, respectively (p < 0.05). The prevalence of both anxiety and depression increased with the increasing severity of cellular atypical findings of BAL cytology ($\chi^2 = 20.36$, p < 0.001; $\chi^2 = 9.46$, p < 0.001). Moderate or severe atypical changes of BAL cytology showed a significant correlation with the anxiety and depression symptoms with an 86% sensitivity and 89% specificity for identifying their presence. The MMRC dyspnea index and 6MWD showed a significant correlation with the increasing degree of atypical changes of BAL cytology ($\beta = 0.284$, p < 0.002; $\beta = 0.426$, p < 0.001). MMRC dyspnea scale was significantly associated both with the anxiety score

($\beta = 0.346$, p < 0.023) and the depression score ($\beta = 0.284$, p < 0.042) while FEV₁ % predicted did not correlate with anxiety or depression score.

DISCUSSION

COPD is considered not only as a disease of the lungs but as a part of the chronic systemic inflammatory syndrome [1]. The complex pathogenesis of COPD along with the associated frequent comorbidities compel further evaluation and staging because the degree of airflow obstruction is not adequate on its own to fully describe this multicomposite disease. Previous studies have revealed symptoms of anxiety and depression in up to 41% and 44% of COPD patients respectively [6,13]. Our results confirm that anxiety and depression symptoms are common in COPD and may correlate with the severity of the disease. Dyspnea due to the reduced exercise capacity is probably the primary factor leading to the psychiatric morbidities encountered in our patients.

The degree of lung function impairment is not adequate on its own to explain the presence of anxiety and depression symptoms in COPD. Our findings are in concordance with previous studies that FEV₁% predicted alone did not predict or correlate with the presence of anxiety and depression symptoms [4,10,13]. Dyspnea and reduced exercise capacity which are indicators of advanced COPD correlated significantly with the presence of the anxiety and depression symptoms. They may be predictive of COPD outcomes. The BODE index was a better predictor of the psychological impact of COPD than the GOLD classification in regard to FEV₁% predicted.

COPD duration, number of yearly exacerbations, and long term oxygen therapy (LTOT) did not correlate with anxiety and depression symptoms. There was a weak correlation of depressive symptoms with the noninvasive mechanical ventilation (NIMV) treatment. Our findings verified that dyspnea correlated with the psychological consequences of COPD.

Another important aspect of our study is the association between atypical changes in BAL cytology with the anxiety and depression symptoms. As the atypical changes of BAL cytology increased in

TABLE IV: DISTRIBUTION OF ANXIETY AND DEPRESSION ACCORDING TO SPUTUM CYTOLOGY CLASSIFICATION

Sputum cytology: n. patients per group	Number of patients with anxiety symptoms (%)	Number of patients with depression symptoms (%)	p
N: 12	3 (25)	2 (16.6)	< 0.36
MA: 16	5 (31.2)	6 (37.5)	< 0.42
IA: 20	11 (55)	12 (60)	< 0.062
SA: 12	7(58.3)	8 (66.6)	< 0.067

Definition of abbreviations: IA, intermediate atypia; MA, mild atypia; N, normal; SA, severe atypia.

TABLE V: DISTRIBUTION OF ANXIETY AND DEPRESSION SYMPTOMS ACCORDING TO BAL CYTOLOGY CLASSIFICATION

BAL cytology: n. patients per group	Number of patients with anxiety symptoms (%)	Number of patients with depression symptoms (%)	p
N: 10	1 (10)	1 (10)	< 0.42
MA: 16	3 (18.7)	4 (25)	< 0.36
IA: 20	12 (60)	14 (70)	< 0.05
SA: 14	10 (71.4)	11 (78.5)	< 0.05

Definition of abbreviations: BAL, bronchoalveolar lavage; IA, intermediate atypia; MA, mild atypia; N, normal; SA, severe atypia.

severity, the prevalence of these symptoms grew higher. This association may be explained by the fact that BAL cytology reflects the structure of the lung parenchyma. As the lung damage gets worse the functional burden of dyspnea increases. Anxiety and depression symptoms were best delineated by dyspnea score and the 6-minute walking distance. Worsening dyspnea affects physical conditioning and produces functional limitation, as demonstrated by the decreased 6MWD, which is probably the predominant mechanism leading to anxiety and depression symptoms in our patients. Patients whose exercise capacity has been limited because of COPD have the greatest risk of psychiatric comorbidities. Atypical changes in sputum cytology were not significantly associated with the presence of anxiety or depression symptoms of COPD, while the sensitivity and specificity of sputum cytology for predicting these symptoms was intermediate. We believe that cytologic examination of sputum samples may be useful for pointing out the psychiatric symptoms in COPD patients. On the other hand, moderate or severe cytologic findings of BAL were able to identify psychiatric comorbidities of the disease. The high correlation of atypical BAL cytology findings with the presence of anxiety or depression symptoms we attributed to the fact that BAL reflects the structure of lung parenchyma. The significant correlation between the severity of the atypical findings of BAL cytology and the MMRC index and the 6MWD shows that the major risk factor for dyspnea and the consequent functional physical limitation is the severity of lung damage which may be identified by BAL cytology.

Our study included a mixture of males and females at different GOLD stages. The small sample size of our study may be considered as a disadvantage in comparison to the other large prospective studies. The HAD questionnaire used in this study may have limitations in diagnosing anxiety and depression but our patients were also evaluated by a consultant psychiatrist. This questionnaire has been used suc-

cessfully in previous studies as a screening tool for psychiatric morbidity [6,15]. We did not compare the current psychiatric status of our patients after psychiatric treatment and pulmonary rehabilitation which may be another limitation of our study. Pulmonary rehabilitation may have had an influence on this because the patients would feel better and gain self-confidence vis-à-vis the functional limitation due to the disease. In addition to the high prevalence of respiratory symptoms, many of the patients had anxiety and depression symptoms. Cognitive and behavioral therapy, psychopharmacology and pulmonary rehabilitation may be useful treatment modalities for psychiatric disorders in COPD patients.

We conclude that anxiety and depression symptoms are common in COPD. The psychological status is important in these patients. Although there is a clear association between dyspnea level and anxiety or depression symptoms, their presence is often underdiagnosed and undertreated especially when they coexist with physical illness [2,16]. The results of our study suggest that the major risk factor for anxiety or depression is dyspnea and the consequent functional physical limitation. Cytologic examination of BAL cytology appears to be a useful modality for identifying patients with psychiatric comorbidities because it reflects the lung damage which is the predominant mechanism underlying dyspnea and the limited physical limitation of COPD patients. BAL cytology can be used along with the HAD index for screening COPD patients to determine the presence of anxiety or depression symptoms. Sputum cytology, in view of its borderline significant association with and intermediate sensitivity and specificity for anxiety and depression scores, may be used as a noninvasive diagnostic tool for identifying psychiatric comorbidities of COPD.

CONFLICT OF INTEREST STATEMENT: None of the authors has any conflict of interest to declare in relation to the subject matter of this manuscript.

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