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Role of Anxiety on Patient Intolerance during Bronchoscopy

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Authors' contributions

This work was carried out in collaboration between all authors. Author CT designed, performed the study, managed the literature searches and wrote the first draft of the manuscript. Author IY wrote the protocol. Author ST was the pathology consultant. Author NY performed cytologic evaluation. Author BYK designed the patient files and HADS forms. Author RY managed the psychiatry consultation. Author RJ performed the statistical analysis. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Aims: There are no current data about the adverse effects of anxiety on patient intolerance during bronchoscopy.The aim of our study was to assess the correlation between anxiety and patient intolerance during bronchoscopy.
Study Design: Retrospective research study
Place and Duration of Study: Department of Pulmonary Diseases, Cerrahpasa Medical Faculty, between January 2010 and 2013 March.
Methodology: Data from 94 patients were analyzed. The mean age of the patients was 59 years. Bronchoscopy was performed for lung cancer in 54, pulmonary nodules in 26 and pulmonary infiltration in 14 patients. Hospital Anxiety Depression scale was used to appraise the anxiety symptoms. Cytologic examination of bronchoalveolar lavage, and sputum samples were performed in each patient when available.

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Results: The anxiety or fear profile of the patients before bronchoscopy were as follows: dyspnea (78%), malignant disease (74%), nasal, laryngeal or tracheal irritation (70%), bronchoscopic findings (68%), and hemorrhage (42%). Bronchoscopic examination was intolerable in 14 cases while there was great difficulty to perform the procedure in 18 patients. Cytologic analysis revealed severe in 18, moderate in 22, and mild dysplasia in 25 patients while it was normal in 29 subjects. Hospital Anxiety Depression scale was over eight in 33 patients. The scale was over eight in 13 out of 14 patients who were intolerant to bronchoscopy. Cytology revealed severe in one and moderate dysplasia in another patient intolerant to bronchoscopy.
Conclusions: Anxiety appears to be the predominant factor for patient intolerance during bronchoscopy. Pulmonary function, atypical or dysplastic cytomorphological changes in sputum or bronchoalveolar lavage cytology did not show correlation with patient performance.

Keywords: Bronchoscopy; bronchoalveolar lavage; sputum; cytology; intolerance; anxiety.

ABBREVIATIONS

BAL: bronchoalveolar lavage
FEV1: forced expiratory volume in one second
FVC: forced vital capacity
HADS: Hospital Anxiety and Depression Scale
COPD: chronic obstructive lung disease

1. INTRODUCTION

Anxiety is common in patients undergoing invasive medical interventions [1]. Increased levels of preoperative stress may be associated with reduced tolerance and adverse effects during the procedure [2]. Flexible bronchoscopy is a frequently used procedure for the diagnosis of pulmonary diseases [3]. Mortality rate and the frequency of major complications are vey low [4]. However, as with any diagnostic intervention, bronchoscopy may pose difficulties, can cause fear and may be stressful for the patient [5,6]. Bronchoscopy is usually performed to obtain pathologic samples in subjects with obstructive lung disease to diagnose lung cancer. It is well known that these patients carry a substantial psychological burden related to their disease and frequently may suffer from anxiety or depression [7-10]. In most patients undergoing invasive medical procedures, anxiety may be related to the symptoms of underlying disease, uncertainity of diagnosis, fear of the unknown or unexpected [11-13]. The psychological stress may further be increased by the probability of lung cancer or investigation of lung lesions suspicious for metastasis for which bronchoscopy is performed. Bronchoscopy, as an invasive procedure by itself may also contribute to patient anxiety due to the concerns about physical discomfort caused by the procedure [14].

Smoking may lead to lung injury that can be identified by the presence of atypical cytomorphological changes of sputum or BAL samples without causing any decline in lung function. Inflammation, metaplasia, hyperplasia in basal cells and increased number of atypic cells are observed in the cytologic specimens of such patients [15-17]. Cellular injury pattern and degree of lung damage due to inflammation of the airways appears to be the fundamental mechanism leading to symptoms and psychiatric comorbidities in the COPD

patients [16-18]. Consequently, remodelling of the lung parenchyma may contribute to poor patient performance during bronchoscopy.

To our knowledge, there are no data about the effect of anxiety on intolerance in patients undergoing bronchoscopy. The present study was designed to evaluate the effect of anxiety on bronchoscopy intolerance and to assess whether abnormalities of lung function, dysplasia detectable through sputum or BAL cytology are associated with patient performance during the procedure.

2. MATERIAL AND METHODS

This is a retrospective study performed at the Pulmonary Diseases Department of Cerrahpasa Medical Faculty between January 2010 and 2013 March. The study has been approved by the IRB/Ethics Committee of Cerrahpasa Medical Faculty. Informed consent was obtained from all patients. Ninety-four adult patients were included in the study. Inclusion criteria were indication for bronchoscopy, absence of any chronic disease other than COPD, to be able to understand and answer the questionnaires, no contraindications for bronchoscopy or bronchoscopic interventions. Other exclusion criteria were confusion due to cerebral disease, dementia, and age over 80 years. All patients gave informed consent. Spirometry was performed according to the ATS/ERS recommendations with a body plethysmograph unit (Zan 500, Messgeraete, Oberthulba, Germany). COPD was classified according to GOLD criteria [19]. Blood gases were determined from radial artery samples using the Radiometer ABL800 FLEX blood gas analyzer.

The patients were given a detailed information about the indication and technique of bronchoscopy. The subjects were asked to state their fears about the procedure. The anxiety and fear profile of the patients before bronchoscopy were as follows: dyspnea (78%), malignant disease (74%), nasal, laryngeal or tracheal irritation (70%), bronchoscopic findings (68%), and hemorrhage (42%). HADS used for screening psychatric disorders [20], was performed just before bronchoscopy and was filled out by the bronchoscopist. The questionnare has also been used for screening COPD patients previously [21-23]. The scale consists of seven questions related to anxiety and depression, rated on a 4-point scale. The test provides a maximum subscale scores of 21 for anxiety and depression with scores of ≥ 8 describing the presence of these symptoms [24-26]. In each patient with this score, existence and symptoms of anxiety was investigated by a consultant psychiatrist.

Bronchoscopy was done for the evaluation of lung cancer in 54, for lung nodules in 26 and for parenchymal infiltrations in 14 patients. Heart rate and blood pressure were monitored during bronchoscopy. Lidocaine (4-9 mg/kg, maximum 400 mg) was used for local anesthesia. Standart dose of midazolam 2 mg was given intravenously for conscious sedation. BAL was performed by instilling five 20 ml alliquots of sterile saline into the involved lung subsegment. After removal of mucus, fluid sample was prepared for cytologic examination by cytocentrifugation. For bronchial lavage, 20 to 50 ml saline was flushed into the lesion site. Transbronchial biopsy was done in 12 patients and needle aspiration biopsy of the subcarenal lymph nodes was performed in 8 subjects. BAL and bronchial biopsies were done in 80 patients.

Difficult bronchoscopy was defined as complete bronchoscopic evaluation with one or more of the following findings: tachycardia over 130/minutes (without hypoxemia), nasopharyngeal closure over two minutes, vocal cord closure lasting more than two minutes, bronchoscopic

inspection time over 15 minutes due to anxiety, excessive gag reflex or cough, and acceptable resistance by the patient. Intolerance to the procedure was delineated as incomplete examination and termination of bronchoscopy despite the use of maximum doses for local anesthesia and conscious sedation.

Sputum and BAL findings were evaluated by a cytologist and a pathologist. The specimens were evaluated according to the cytologic features as loss of cellular cohesion, hyperchromasia, nucleer irregularities and increase of nucleus cytoplasm ratio. Standart criteria was used to assess the cellular cytological changes to classify the sputum or BAL findings as normal, mild, moderate (Fig. 1), or severe (Fig. 2) dysplasia.

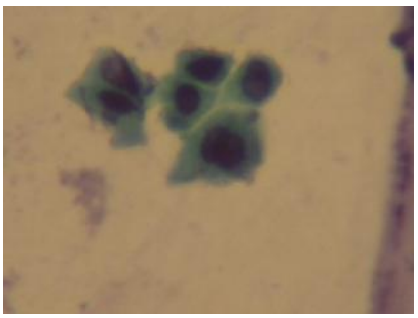

Fig. 1. BAL cytology showing moderate dysplasia with squamous metaplasia, homogenous chromatin distribution and relatively wide cytoplasm (Papanicolau, 400x).

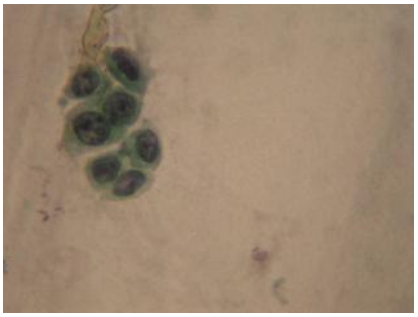

Fig. 2. BAL cytology revealing severe dysplasia with dense heterogenous chromatin distribution, increased nuclear/cytoplasmic ratio and narrow cytoplasm (Papanicolau, 400x).

Statistical data was expressed as means±standart deviations. Differences between groups were compared by Chi square and Kruskal-Wallis test. Statistics were performed by SPSS 17.0. A p value of less than 0.05 was accepted as statistically significant.

3. RESULTS

The mean age of the ninety-four patients was 59 years (range 30-76, SD±14.8), and 64 (68%) were males, and 66 (70%) were outpatients. All patients were current smokers with a mean smoking history of 24.6±8.4 pack years. One patient had severe, 14 patients had moderate and 18 patients had mild COPD according to GOLD consensus criteria. The mean

FEV_1 was 1.96±0.78 ml, the mean FVC was 2.48±0.92 ml and the mean FEV_1/FVC was 68.3±14.6%. Arterial blood gas values were within normal limits in 31 patients while 17 patients had pO_2 levels less than 80 mm Hg, with a mean pO_2 value of 72.4±14.8 mm Hg. None of the patients had elevated pCO_2 levels. The final diagnoses were primary lung cancer [54], pneumonia [12], tuberculosis [8], sarcoidosis [5], lung metastasis [4] and other lung disease [11].

ECG revealed sinus rythm and there were no pathologic ECG findings in any of the patients. The subjects did not have previous or current heart disease. The initial mean heart rate before bronchoscopy was 82±24 per minute. All patients received nasal oxygen and oxygen saturation was over 90 % in each of the subjects during bronchoscopy. Severe anxiety, tachycardia (>140/minute), hand tremor, excessive gag reflex, nasopharyngeal spasm, prolonged or persistent vocal cord disclosure, severe bronchospasm or cough occured in 46 (48.9%) patients. During bronchoscopy sinus tachycardia was observed in 36 (38%) subjects. The mean heart rate was 118±14 per minute. Following bronchoscopy, heart rate returned to normal in each patient. In 12 (86%) patients with bronchoscopy intolerance, the mean rate was 128±26 per minute which returned to normal sinus rythm within 30 minutes following bronchoscopy. The incidence of sinus tachycardia was 61% in patients (n=11) with difficult bronchoscopy. Diastolic blood pressure was over 85 mm Hg in eight (8%) and systolic blood pressure was over 140 mm Hg in six (6%) patients. Ten patients (10%) with high blood pressure occuring during the procedure had bronchoscopy intolerance.

The mean duration of bronchoscopy was 20 minutes. Bronchoscopy was not completed in 14 subjects (15%) because of intolerance. Conscious sedation with 2 mg intravenous midazolam for decreasing anxiety was not useful in these patients. Although difficulty was encountered in 18 patients (19%) during bronchoscopy, the procedure was completed in each subject. The most frequent problems in patients with intolerance were significant tachycardia over 130 per minute (78%), severe anxiety (64%), and prolonged or persistent vocal cord disclosure (59%). No significant complications were reported during or after bronchoscopy, BAL, transbronchial or needle aspiration biopsy. Five patients had prolonged hypoxia due to BAL lasting less than 30 minutes, responsive to nasal oxygen, and four patients had bleeding from the biopsy site, less than 50 ml, which resolved spontaneously.

Twenty patients (21.2%) were found to have symptoms suggestive of anxiety and 8 patients (8.5%) had symptoms suggestive of depression. HADS anxiety score was over 8, mean 12.4±4.2, in all the patients intolerable to bronchoscopy and the high HADS anxiety score showed significant correlation with the patient intolerance during bronchoscopy ($p<0.001$). HADS score was above eight, mean 11.9±3.8, in 16 patients with difficult bronchoscopy. The mean HADS score was 5.2±2.8 in patients with normal bronchoscopy. The mean HADS depression subscale was 5.9±1.8 in our study. Two patients with normal, three patients with difficult bronchoscopy and, five patients with bronchoscopy intolerance had HADS depression subscale over eight, which was not statistically significant.

Cytologic analysis revealed severe dysplasia in 18 (19.1%), moderate dysplasia in 22 (23.4%), mild dysplasia in 25 (26.5%) patients and was normal in 29 (30.8%) subjects. Among 18 patients with difficult bronchoscopy, 1 had severe and 1 had moderate dysplasia. One patient out of 14 who were intolerant to bronchoscopy had severe dysplasia and one had moderate dysplasia (Table 1). Moderate or severe dysplasia did not correlate with poor performance during bronchoscopy ($p<0.26$) Two patients with decreased FEV_1 (2.1%) and one patient (1%) with hypoxia had difficulty during bronchoscopy. There was no correlation

between bronchoscopy performance of the patients and FEV_1, FEV_1/FVC or pO_2 levels ($p<0.18$, $p<0.32$, $p<0.24$). Provision of detailed procedure information did not lead any performance difference between the patients ($p<0.26$).

Table 1. Cytology and bronchoscopy tolerance

	Normal cytology	Mild dysplasia	Moderate dysplasia	Severe dysplasia	p
Normal bronchoscopy	3 (1.7%)	21	20	16	p<0.001
Difficult bronchoscopy	7 (85%)	1	1	1	ns
Bronchoscopy intolerance	19 (79.2%)	3	1	1	ns

Chi square and Kruskal-Wallis test, $p < 0.001$, ns: not signficiant

4. DISCUSSION

Bronchoscopy may occasionally lead to difficulties during the procedure. Drawbacks of bronchoscopy are mainly associated with the performance of the patient or the bronchoscopist. Relatively few studies have investigated the role of anxiety in patients undergoing bronchoscopy (5,6). This is the first study to evaluate the correlation between bronchoscopy related anxiety and patient performance during the procedure. Bronchoscopy is usually performed in patients with COPD which is considered not only as a disease of the lungs but as a part of the chronic systemic inflammatory syndrome [27-29]. Previous studies have revealed symptoms of anxiety and depression up to 41% and 44% of the COPD patients, respectively [23-26]. Intolerance to bronchoscopy may therefore occur in relation to the psychiatric comorbidities of the subjects undergoing the procedure, which are known to be a frequent condition in COPD patients [8-10]. Anxiety in these patients may be aggravated by uncertainity of diagnosis, fear of the unknown or unexpected [5,6]. The stress may further be increased by probability of lung cancer or metastatic lung lesions for which bronchoscopy is carried out. Bronchoscopy, by itself may also contribute to patient anxiety due to the concerns about the physical discomfort caused by the procedure [14].

Of the total fourteen patients intolerable to bronchoscopy, all had anxiety scores over eight. High anxiety scores showed significant correlation with bronchoscopy intolerance. Another interesting conclusion of our study is the presence of sinus tachycardia in all of the subjects intolerable to bronchoscopy. None of these patients had previous or current heart disease and conduction abnormalities. The initial sinus tachycardia in patients with difficulty or intolerance to bronchoscopy may also be regarded as an indirect evidence of anxiety in these patients and return of the normal sinus rythm after discontinuation of bronchoscopy also supports the existence of bronchoscopy associated anxiety. Initial high blood pressures returning to normal after the procedure in ten patients (71%) may be another manifestation of anxiety in this group of patients.

The second factor leading to difficulties or intolerance during bronchoscopy may be the lung inflammation associated with chronic obstructive lung disease since all our patients had a smoking history of at least fifteen packs year. Cytology of bronchoalveolar lavage or sputum specimens may reflect the structure of the lung and is useful for assessing airway inflammation associated with chronic obstructive pulmonary disease [27-29]. Out of eighteen patients with difficult bronchoscopy, one had severe and another had moderate dysplasia. Cytology was normal in 79.2% of the patients with bronchoscopy intolerance, while only one subject had severe, one had moderate and three had mild dysplasia. There was no

correlation between sputum or BAL cytologic dysplasia and patient bronchoscopy performance. These changes, as revealed by cellular dysplasia only in four patients shows that inflammatory changes of the lung due to COPD may only have a negligible effect on patient performance and do not appear to play a significant role on patient tolerance during bronchoscopy.

FEV_1, FEV_1/FVC ratio and low pO_2 levels did not show correlation with bronchoscopy peformance of the patients. Severe lung function impairment and low pO_2 are contraindications for bronchoscopy and therefore, such patients were not included in our study. We did not encounter any bronchoscopy associated problems or difficulties in patients with decreased pulmonary function or low arterial blood gas levels. Decreased pulmonary function parameters in smokers as an indirect marker of lung inflammation seem to have a trivial effect on patient intolerance during bronchoscopy.

Experience of the bronchoscopist is another critical point determining patient tolerance to the procedure [30]. Discomfort at the initial setting or during bronchoscopy may further increase patient anxiety. The bronchoscopists who participated in this study had an experience of at least fifteen years and approximately over two thousand bronchoscopies. Absence of any significant discomfort or intolerance especially during interventions like BAL, transbronchial or needle aspiration biopsy may also be regarded as an adequate bronchoscopy experience of the clinicians in our study. As far as our study is concerned, inexperience of the bronchoscopist is not a crucial factor that leads to patient discomfort, anxiety and consequent intolerance during the procedure. The results of our study suggest that lung inflammation and decreased pulmonary function do not contribute to patient performance during bronchoscopy.

There are several limitations of our study. First, the sample size is small. The results may be considered as patient oriented and subjective reflecting individual characteristics. The postbronchoscopic anxiety states of the subjects were not included. A reproducible and bronchoscopy specific anxiety questionnare may be more useful for the identification of such patients. Bronchoscopists in other centers may use different techniques that may effect patient comfort. We did not include therapeutic bronchoscopic interventions in our study. The ability to adequately and safely perform advanced diagnostic or therapeutic bronchoscopic interventions may arise as a critical factor determining patient comfort during bronchoscopy. Patient discomfort and anxiety may intensify as the number of diagnostic interventions during bronchoscopy increases. Further studies with larger populations are therefore needed for the generalization of findings.

Along with psychiatric comorbidities of COPD, the possibility of a malignant lung disease and an unknown invasive diagnostic intervention would have further increased the negative psychiatric impact on patients undergoing bronchoscopy. We conclude that anxiety is the primary factor for bronchoscopy intolerance. Inflammatory parenchymal changes, reflected as pulmonary function test limitation, moderate or severe dysplastic changes in sputum or BAL cytology, do not play a significant role in patient tolerance. As anxiety appears to be the predominant mechanism for patient intolerance during bronchoscopy, HADS index identifying psychiatric comorbidities may predict serenity during the procedure.

5. CONCLUSIONS

Discomfort, fear or anxiety are expected reactions in patients undergoing bronchoscopy. Anxiety appears to be the key factor for bronchoscopy intolerance. Inflammatory

parenchymal changes of obstructive pulmonary diseases, reflected as moderate or severe dysplastic cellular changes in sputum, or bronchoalveolar lavage cytology do not correlate with bronchoscopy intolerance. Indirect markers of lung inflammation like decreased pulmonary function and low arterial blood gases do not contribute to patient intolerance.

In conclusion, anxiety appears to be the predominant factor for patient performance during the procedure. Existence of COPD, the possibility of a malignant lung disease, the fear of an invasive and an unknown diagnostic intervention may have further increased the negative psychiatric impact on patients leading to anxiety with adverse outcomes during bronchoscopy. Pre-procedural application of Hospital Anxiety Depression Scale may be useful to identify patients who will experience anxiety induced bronchoscopy intolerance.

CONSENT

All authors declare that “written informed consent” was obtained from the participants of this study.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

We declare that our data or presentation of information is not influenced by any personal or finanacial relationship with other people or organizations. We have no financial interests to declare.

REFERENCES

1. Johnson JE, Morrisey JF, Leventhal H. Psychological preparation for an endoscopic examination. Gastrointest Endosc. 1973;19:180-182.
2. Morgan J, Roufeil L, Kaushik S, Bassett M. Influence of coping style and precolonoscopy information on pain and anxiety of colonoscoy. Gastrointest Endosc. 1998;48:119-127.
3. British Thoracic Society guidelines on diagnostic flexible bronchoscopy. Thorax. 2001;56(supp 1):i1-i21.
4. Pue C, Pacht ER. Complications of fiberoptic bronchoscopy at a Univesity hospital. Chest. 1995;107:430-432.
5. Lechtzin N, Rubin HR, White P Jr, Jenckes M, Diette GB. Patient satisfaction with bronchoscopy. Am J Respir Crit Care Med. 2002;166(10):1326-1331.
6. Poi PJH, Chuah SV, Srinivas P, Liam CK. Common fears of patients undergoing bronchoscopy. Eur Respir J. 1998;11:1147-1149.
7. Smoller JW, Pollack MH, Otto MW, et all. Panic anxiety, dyspnea and respiratory disease: theoretical and clinical considerations. Am Rev Respir Crit Care. 1996;154:6-17.
8. Wagena EJ, Arrindell WA, Wouters EF, van Shacyk CP. Are patients with COPD psyhologically distressed ? Eur Resp J. 2005;26:242-248.

9. Gudmundsson G, Gislason T, Janson C, Lindberg E, Suppli Ulrik C, Brøndum E, Nieminen MM, Aine T, Hallin R, Bakke P. Depression, anxiety and health status after hospitalisation for COPD: a multicentre study in the Nordic countries. Respir Med. 2006;100:87-93.
10. Dahlen I, Janson C. Anxiety and depression are related to the outcome of emergency treatment in patients with obstructive pulmonary disease. Chest. 2002;122:1633-1637.
11. Johnson JE, Morrisey JF, Leventhal H. Psychological preparation for an endoscopic examination. Gastrointest Endosc. 1973;19:180-181.
12. Simons RJ,Baily RG, Zelis R, et all. The physiology and psychological effects of the bedside presentation. N Engl J Med. 1989;321:1273-1275.
13. Smoller JW, Pollack MH, Otto MW, et all. Panic anxiety, dyspnea, and respiratory disease: theoretical and clinical considerations. Am Rev Respir Crit Care Med. 1996;154:6-17.
14. Colt HG, Powers A, and Shanks TG. Effect of music on state anxiety scores in patients undergoing fiberoptic bronchoscopy. Chest. 1999;116:819-824.
15. Ronchi MC, Piragino C, Rossi E, et all. Role of sputum differential cell count in detecting airway inflammation in patients with chronic bronchial asthma or COPD. Thorax. 1996;51:1000-1004.
16. Spurzem JR, Thompson AB, Daughton DM, Mueller M, Linder J, Rennard SI. Chronic inflammation is associated with increased proportion of Goblet cells recovered by broncholaveolar lavage. Chest. 1991;100(2):389-393.
17. Linden M, Rasmussen JB, Piitulainen LA, Tunek A, Larson M, Tegner H, Venge P, Laitinen LA, Brattsand R. Airway inflammation in smokers with nonobstructive and obstructive chronic bronchitis. Am Rev Respir Dis. 1993;148(5):1126-1232.
18. Tetikkurt C, Ozdemir I, Tetikkurt S, N Yılmaz M, Ertan T, Bayar N. Anxiety and depression in COPD patients and correlation with sputum and BAL cytology. MRM. 2011;6(4):226-231.
19. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of COPD. 2013.
20. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67:361-370.
21. Ries AL. Impact of chronic obstructive pulmonary disease on quality of life: the role of dyspnea. Am J Med. 2006;119:12-20.
22. Gudmundsson G, Gislason T, Janson C, Lindberg E, Hallin R, Ulrik CS, Brøndum E, Nieminen MM, Aine T, Bakke P. Risk factors for rehospitalisation in COPD: role of health status, anxiety and depression. Eur Respir J. 2005;26:414-419.
23. Wagena EJ, Arrindell WA, Wouters EF, van Shacyk CP. Are patients with COPD psyhologically distressed ? Eur Resp J. 2005;26:242-248.
24. Ng TP, Niti M, Tan WC, Cao Z, Ong KC, Eng P. Depressive symptoms and chronic obstructive pulmonary disease: effect on mortality, hospital readmission, symptom burden, functional status, and quality of life. Arch Intern Med. 2007;167:60-67.
25. Mishima M, Oku Y, Muro S, Hirai T, Chin K, Ohi M, Nakagawa M, Fujita M, Sato K, Shimada K, Yamaoka S, Oda Y, Asai N, Sagawa Y, Kuno K. Relationship between dyspnea in daily life and psycho-physiologic state in patients with chronic obstructive pulmonary disease during long-term domicilary oxygen therapy. Intern Med. 1996;35:453-458.
26. Gudmundsson G, Gislason T, Janson C, Lindberg E, Suppli Ulrik C, Brøndum E, Nieminen MM, Aine T, Hallin R, Bakke P. Depression, anxiety and health status after hospitalisation for COPD: a multicenter study in the Nordic countries. Respir Med. 2006;100:87-93.

27. Celli BR, MacNee W, Agusti A. Standarts for the diagnosis and treatment of of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J. 2004;23:932-946.
28. Jeffery PK. Structural and inflammatory changes in COPD: a comparison with asthma. Thorax. 1998;53:129-136.
29. Pizzichinni E, Pizzichinni M, Efthimidias A, et all. Indices of airway inflammation in induced sputum: reproducibility and validity of cell and fluid-phase measurements. Am J Respir Crit Care Med. 1996;154:308-317.
30. Diette GB, White P, Terry P, Jenkes M, Wise RA, Rubin HR. Quality assessment through patient self-report of symptoms prefiberoptic and post fiberoptic bronchoscopy. Chest. 1998;114:1446-1453.

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