

Research Article**Association between Psychological Status and Dyspnea in Patients with Chronic Obstructive Pulmonary Disease**Sita Sharma¹, Urmila Shakya², Pramod Sharma³, Prakash Limbu⁴^{1,2}Tribhuvan University, Institute of Medicine, Nursing Campus, Nepal³School of Allied Health Sciences, Griffith University, Australia⁴Nepalese Army Institute of Medical Sciences, Nepal

Received 10 April 2017; Accepted 18 May 2017

ABSTRACT

Background: Dyspnea together with anxiety and depression are the most common and important comorbidities in patients with chronic obstructive pulmonary disease. Anxiety and depression can potentiate the intensity of dyspnea in this population. The current study was aimed to investigate the psychological status and perceived level of dyspnea in COPD patients. **Methods:** A cross sectional analytical study was carried out among 221 COPD patients at respiratory outpatient department of Tribhuvan University Teaching Hospital (TUTH), Nepal. Patients' psychological status was assessed using a validated Hospital Anxiety and Depression Scale (HADS) and dyspnea was assessed using the modified Medical Research Council Dyspnea Scale (mMRC). **Results:** Out of 221 patients, 54.5% patients had symptoms suggestive of anxiety (HADS-A Score ≥ 11) and 51.6% patients reported symptoms suggestive of depression (HADS-D Score ≥ 11). Similarly, 92.8% patients reported some degree of dyspnea. Data showed that there was strong positive correlation of dyspnea with anxiety ($r=0.75$, $p<0.001$) and depression ($r=0.79$, $p<0.001$). **Conclusion:** The results from this study concludes that anxiety, depression and dyspnea are common symptom in COPD, and there was a positive correlation of psychological status and perceived level of dyspnea. Psychological status is therefore an important factor to consider when treating patients with dyspnea.

Keywords: COPD, Dyspnea, Anxiety, Depression, HADS.**Introduction**

Chronic Obstructive Pulmonary Disease (COPD) is a lung disease characterized by chronic obstruction of lung airflow that interferes with normal breathing and is not fully reversible[1]. The more familiar terms 'chronic bronchitis' and 'emphysema' are no longer used, but are now included within the COPD diagnosis. COPD is not simply a "smoker's cough" but an under-diagnosed, life-threatening lung disease[2]. Chronic obstructive pulmonary disease (COPD) is defined as "a disease state characterized by the presence of airflow obstruction due to chronic bronchitis or emphysema; the airflow obstruction is generally progressive, may be accompanied by airway hyperactivity, and may be partially reversible" [3].

Anxiety and depression are very common and important comorbidities in patients with COPD[4, 5]. The pathophysiology of these psychological comorbidities in COPD is complex and possibly explained by common risk factors, response to symptomatology and biochemical alterations. The presence of anxiety and/or depression in COPD patients is associated with increased mortality, exacerbation rates, length of hospital stay, and decreased quality of life and functional status[6]. Research over the last two decades have established the higher prevalence of both anxiety and depression in patients with COPD[7-9]. Nonetheless, the impact of anxiety and depression status on other associated comorbidities is difficult to elucidate in patients with COPD. Despite this, it is generally assumed that patients with COPD that experience anxiety and depression would

experience more negative emotions and that these in turn could further exacerbate the comorbidities associated with COPD[10].

Dyspnea or breathlessness is generally related to discomfort associated with breathing, and is very common in COPD that severely affects the quality of life in sufferers[11]. The severity and magnitude of dyspnea increases as the underlying disease progresses, leading to significant disability. For patients with advanced COPD, dyspnea profoundly affects quality of life (QoL) to the extent that patients become isolated, often describing themselves as 'existing' rather than 'living' [11]. Patients with advanced COPD almost universally experience significant dyspnea in the final year of life. Moreover, COPD patients at the end of life experience more dyspnea than lung cancer patients and, despite this they are often prescribed less medication and have less access to comprehensive care than patients dying from lung cancer[12].

Depression and anxiety are psychiatric conditions often associated with poor survival rate and impaired social functioning in chronic illnesses, like chronic obstructive pulmonary disease (COPD) [11]. Common mechanisms for explaining the association of anxiety, depression and COPD include cigarette smoke exposure, physical inactivity, social isolation, multiple episodes of dyspnea and chronic hypoxia. Body-mass index, airflow Obstruction, Dyspnea, and Exercise (BODE) index and the modified Medical Research Council (mMRC) dyspnea score could be associated with anxiety and depression in COPD patients and the screening usually implies administration of simple questionnaires[13]. Although dyspnea in COPD is related to mismatch between ventilatory drive and achieved level of ventilation due to diseased lungs and associated structures, this symptom is also modulated by different psycho-physiological status[10, 14]. Despite this, psychological status is more or less ignored in medical and treatment guides for management of dyspnea in COPD patients[10].

In a study were two hundred and two COPD patients were enrolled to assess their levels of anxiety, depression and their association with dyspnea found that the prevalence of anxiety and depression were high (28.2% and 18.8%) in COPD

even when it was of mild degree[15]. Female patients had higher levels of anxiety and depression and worse symptom-related quality of life. Female patients reported a higher level of dyspnea than males for the same level of ventilatory impairment. Dyspnea was more strongly correlated with depression in women than in men. Female patients appear to be more exposed to psychological impairment, which correlates well with some specific symptomatic aspects of the disease, such as dyspnea[15].

The association between psychological status and dyspnea is not clearly understood. There is therefore a need to explore and establish possible associations between the psychological status and dyspnea level in patient with COPD. The current study was aimed at documenting the psychological status and perceived level of dyspnea and explore association of psychological status with perceived level of dyspnea in COPD patients.

2. METHODS

This descriptive cross-sectional analytical research was carried out on 221 patients diagnosed with chronic obstructive pulmonary disease. The study was undertaken at Tribhuvan University Teaching Hospital (TUTH) Nepal.

2.1 Sampling

The sample was taken from those patients with chronic obstructive pulmonary disease who came for follow up in respiratory outpatient department. Thus non probability, purposive sampling technique was adopted for selecting a total of 221 patients.

Sample size was calculated by using the Cochran's formula[16].

$$n = \frac{z^2pq}{d^2}$$

Where

n= required sample size

z^2 = the value standard normal variate at 95% confidence i.e. 1.96

p= prevalence of dyspnea in Chronic Obstructive Pulmonary Disease i.e. 84.50%= 0.845

q= the proportion in the target population without the characteristic of interest 1-p= 1- 0.845= 0.155

d = the degree precision set at +/- 5% or 0.05

Hence substituting the formula:

$$n = \frac{1.96 \times 1.96 \times 0.845 \times 0.155}{0.05 \times 0.05}$$

$$n = 201$$

Assuming a non-response rate of 10%, then the final sample size was **221**.

2.2 Exclusion criteria

In this study, patient with acute exacerbation, acute chest infection, heart disease and severe case of chronic obstructive pulmonary disease were excluded.

2.3 Research Instrumentation

Data was collected by face-to-face interview method using structured interview schedule containing following parts:

Psychological status was assessed by using a standard and validated 14-item tool, called as Hospital Anxiety and Depression Scale (HADS). Score 0-7 was regarded as normal condition, 8-10 as borderline disorder and 11-21 as abnormal case.

Dyspnea was assessed by using validated standard tools: the modified Medical Research Council Dyspnea Scale (mMRC). The modified Medical Research Council Dyspnea Scale, or mMRC, uses a simple grading system to assess a patient's level of dyspnea, shortness of breath. It is a 5-point scale based on the sensation of breathing difficulty experienced by the patient during daily life activities.

2.4 Data Collection Procedure

Before data collection, research proposal was approved from Research Committee of Maharajgunj Nursing Campus, and ethical clearance was obtained from the Institutional Review Board of Institute of Medicine. The data collection also required researcher to submit a formal request letter from Nursing Campus, Kathmandu to the hospital in order to obtain formal permission for data collection. After obtaining the formal permission from the hospital, purpose of the study was explained to the patient and they were explained about the study. Following this, an informed consent was obtained from each chronic obstructive pulmonary disease

patients prior to data collection who meets the inclusion criteria and also informed about their voluntariness in participation and no any foreseeable risk and harm in the study. Patients were also assured about their confidentiality will be maintained by using code number in all forms, and information obtained will solely be used for research purpose. Patients were given liberty to discontinue participating in the study without any clarification.

At first the OPD record card was reviewed for confirmation of diagnosis. Data was collected by researcher herself through face-to-face interview method. Privacy was maintained by carrying out the data collection procedure from each participant separately and in a separate corner of the Respiratory OPD of TUTH. General information related to demographic, socio-economic, and treatment related information was collected by interviewing with the respondent. After that HADS, and mMRC Dyspnea Scale were obtained. The data collection procedure with each patient was completed in about 20 minutes. All collected information was stored securely in locker and without access to unauthorized data handling.

2.5 Statistical Analysis

The collected data were checked daily and organized for completeness and accuracy. The collected data were then edited, coded, classified and then entered into Excel spreadsheet, which was later transferred to SPSS (Statistical Package for Social Science) version 24. Descriptive statistics such as frequency and percentage were used for categorical variables and mean and standard deviation were used for continuous variables. Inferential statistics such as Spearman Rank Correlation was used to measure the association of psychological status with perceived level of dyspnea. The significance level was set at p value <0.05 and 95% confidence interval.

3. RESULTS

Out of 221 patients recruited for this study, 37.1 % were between the age group 60-69 years. The mean age of patients with COPD was 66.15 ± 10.14 years that ranged between 44 and 90 years. More than half of the patients (53.8%) were female. Similarly, 35.3% COPD patients were literate. Most of the COPD patients (67.4%) were married and

majority of the patients (76%) were living with their children in joint family. Similarly, 61.1% patient's household income was low. Regarding occupation majority of the patients (76.9%) were not working currently. About 62.9% COPD patients

were former smoker. Similarly, more than half (57.5%) patients had no any history of exposure to passive smoking. Likewise, 17.2 % COPD patients had family history of COPD (Table 1)

Table 1: Socioeconomic characteristics of participants

Characteristics	Frequency	Percentage
Age (in Year)		
<60	62	28.1
60-69	82	37.1
≥70	77	34.8
Sex		
Male	102	46.2
Female	119	53.8
Educational Status		
Literate	78	35.3
Illiterate	143	64.7
Marital Status		
Married	149	67.4
Widow/ Widower	72	32.6
Economic Status		
Low	13	5.9
Middle	135	61.1
High	73	33.0
Current Working Status		
Yes	51	23.1
No	170	76.9
Smoking status		
Current smoker	34	15.4
Former smoker	139	62.9
Non smoker	48	21.7
Exposure to Passive Smoking		
Yes	94	42.5
No	127	57.5
History of COPD in Family		
Yes	38	17.2
No	183	82.8

Half of the COPD patient's (50.7%) duration of illness was less than 5 years. Mean value of duration of illness was 6.99 ± 6.34 . More than half of the COPD patient (57%) had previously

hospitalized and 48.4% were hospitalized 1 time in last year. Among COPD patients 20.8% require domiciliary oxygen and 24 % had other health

problem such as hypertension, diabetes, benign prostate hypertrophy and others (Table 2).

Table 2: Health screening of participants

Variables	Frequency	Percentage
Duration of Illness (in Years)		
Less than 5	112	50.7
5-9	60	27.1
10 and more	49	22.2
Mean- 6.99±6.34		
History of Previous Hospitalization		
Yes	126	57.0
No	95	43.0
Status of Hospitalization in Last Year (n=126)		
No hospitalization	35	27.8
1 time	61	48.4
More than 1 time	30	23.8
Domiciliary Oxygen Therapy		
Yes	46	20.8
No	175	79.2
Other Health Problem		
Present	53	24.0
Absent	168	76.0
Type of Health Problem(n=53)		
Hypertension	20	37.7
Diabetes and hypertension	10	18.9
Diabetes mellitus	8	15.1
Benign prostate hypertrophy	5	9.4
Others*	10	18.9

Others* Gastritis, Arthritis, Gout, PIVD, Hypothyroidism, Uterine Prolapsed, Vertigo

Psychological status of COPD patient was measured by Hospital Anxiety and Depression scale (HADS). Among the COPD patients more than half (54.8%) were reported to have symptoms suggestive of anxiety that is Hospital Anxiety and Depression- Anxiety score (HADS-A Score) ≥ 11 and 8.6% were under boarder line disorder that is Hospital Anxiety and Depression- Anxiety score (HADS-A Score) 8-10. Mean of total anxiety score was 11.37 ± 6.89 . Maximum score was 21 and minimum anxiety score was 0. Similarly, among the COPD patients half (51.6%) had symptoms suggestive of depression that is Hospital Anxiety and Depression- Depression score (HADS-D Score)

≥ 11 and 17.2% were under boarder line disorder that is Hospital Anxiety and Depression- Depression score (HADS-D Score) 8 - 10. Mean of total depression score was 11.18 ± 6.01 . Maximum score was 21 and minimum depression score was 0 (Figure 1).

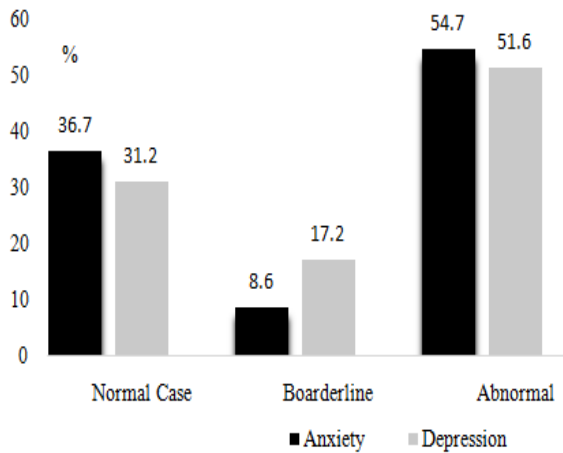


Figure 1: Psychological Status of COPD Patient

Perceived level of dyspnea of COPD patients was measured by the modified Medical Council Research (mMRC) Dyspnea Scale. Almost all (92.8%) patients had some degree of dyspnea. Most of the COPD patients (72%) had modified Medical Research Council (mMRC) dyspnea score ≥ 2 . Among the total patients 32.6% patients had dyspnea grade '3' that is patients had to stop for breath after walking about 100 meters or after a few minutes on the level and 7.2% patients had dyspnea grade '0' that is patients had developed dyspnea only during strenuous exercise (Figure 2).

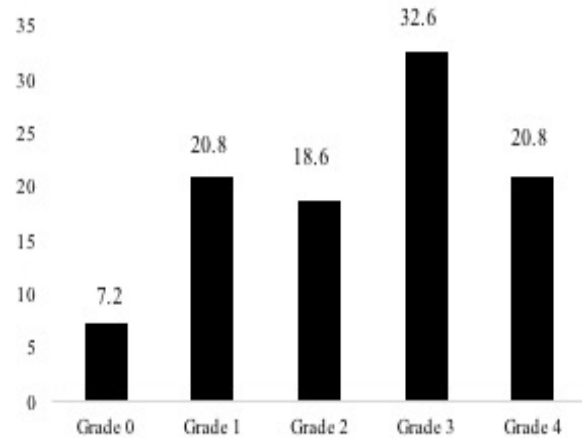


Figure 2: Perceived Level of Dyspnea in COPD Patients

Association of psychological status with perceived level of dyspnea measured by Spearman correlation revealed that there was strong positive correlation between anxiety and perceived level of dyspnea ($r=0.75$, $p<0.001$). Similarly, there was also positive strong correlation between the depression and perceived level of dyspnea ($r=0.79$, $p<0.001$) (Table 3).

Table 3: Association of dyspnea with anxiety and depression

Variables	Mean Value	Standard deviation	Correlation Value	p Value
Anxiety	11.37	6.89	0.75	<0.001
Depression	11.18	6.01	0.79	<0.001

* p significant at ≤ 0.05 , Spearman Rank Correlation

Simple linear regression analysis which was used to predict the level of dyspnea based on anxiety and depression scores. The predicted dyspnea score based on anxiety is equal to 0.863 ± 0.134 (anxiety score). This revealed that dyspnea level in the patients recruited for this study increased by 0.134 unit for every unit increase in anxiety score. Similarly, the predicted dyspnea score based on depression is equal to 0.566 ± 0.163 (Depression score). Patient's level of dyspnea score increased by 0.163 with increase in each score of depression.

4. DISCUSSION

The main finding of current study is that among the COPD patients, anxiety and depression are highly prevalent. More than half of the COPD patients were reported to have symptoms suggestive of anxiety whereas half of the COPD patients' had symptoms suggestive of depression. Likewise, dyspnea is reported to be the primary factor limiting day to day activities for the majority of the patients. Almost all patients felt some degree of dyspnea. Similarly, psychological status that is presence of anxiety and depression are strongly positively correlated with perceived dyspnea level in COPD patients.

The mean age of the patients recruited for this study was 66.15 (10.14) years. The recruited patients' population included even distribution of males and females although number of female patients recruited were marginally higher (male Vs female: 46.2 Vs 53.8). Previous study involving COPD patients have reported higher number of females compared to males[17], however there are other studies which does not align with this. Regarding the educational status, 35.3% of patients were literate. This population cohort was similar to those reported by Bilgic et al. (2010) that shows 39.7 %were literate[18].

Regarding marital status, in this study 67.4% patients were married, 76% patients were from joint family, 61.1% patients had low income and 76.9% were not currently working. These findings are supported by [18], which shows 68% patients were married. However, the same study shows that only 27.9% were not currently working, 74.3% had moderate income level[18].With regard to smoking status, the result showed that 62.9% were former smoker, 15.4% were current smoker and 21.7% were nonsmoker. This result is nearly supported by Balcells at al., (2010) that found 66.6% were former smoker, 32.8% were current smoker and only 0.6% were never smoked[19]. Similarly, 42.5% patients exposed to passive. Study by Roche et al., (2010) finds 48% exposed to passive smoking and Hagstad et al., (2015) find in never-smokers, occupational exposure to gas, dust or fumes was significantly associated with COPD which supports the result of this study[20, 21].

The results from the current study revealed that only 17.2 % patient had history of COPD in their family. This aligns with study conducted by Hersh et al., (2010) that reports parental history of COPD is significant predictor of COPD[22]. Among all the recruited patients, 50.7% of patients were diagnosed with this chronic respiratory condition for less than 5 years. Mean value of duration of illness was 6.99 (± 6.344). More than half of the COPD patients (57%) had previously been hospitalized and 27.6% were hospitalized for the first time in last year. This finding is nearly supported by Tetikkurt et al (2011)[23]. In their study, Tetikkurt et al (2011) had mean value of COPD duration to be 7.45 ± 7.12 and only 20% patients had hospitalized in previous year[23].

Among patients with COPD, 20.8% require domiciliary oxygen and 24 % had other health problems such as hypertension, diabetes, benign prostate hypertrophy etc. This result is contrast with the findings by Balcells et al., (2010)[19], which found 8.2% patient require long-term domiciliary oxygen therapy and 55.8% had other comorbidities.

Hospital Anxiety and Depression Scale (HADS) was used to identify the level of anxiety and depression. The mean HADS anxiety score was 11.37 (6.894) and mean HADS depression score was 11.18 (6.013). More than half of the COPD patients (54.8%) had anxiety score ≥ 11 , that is symptoms suggestive of anxiety and 51.6% patients had depression score ≥ 11 that is symptoms suggestive of depression. This findings is nearly supported by Tetikkurt et al., (2011) which shows the mean scores for anxiety and depression were 8.2 ± 4.6 and 7.9 ± 4.3 respectively in COPD patients[23]. Likewise in their study, 41.7% patients had symptoms suggestive of anxiety and 46.7% had symptoms suggestive of depression. However a study by Puhane et al., (2008) and Janssen et al. (2010) show the mean HADS depression score in COPD patients as 7.63 ± 3.9 and 7.2 ± 0.2 , with 21.6% and 32.1% patients had scores ≥ 11 for anxiety and depression respectively. For the HADS anxiety domain, mean score was 7.03 ± 4.0 and 7.6 ± 0.2 and 22.7%, and 27.4% patients had scores ≥ 11 respectively[24, 25].

The modified Medical Research Council (mMRC) dyspnea scale was used to assess the perceived level of dyspnea in COPD patients. Results showed that almost all patients (92.8%) felt some degree of dyspnea and most of the COPD patients (72%) were mMRC score ≥ 2 . Among the COPD patients, 32.6% patients had mMRC dyspnea grade '3', meaning that "the patient had to stop for breath after walking about 100 meters or after a few minutes on the level" and 7.2% patient had mMRC dyspnea grade '0' that is patient had developed dyspnea "only during strenuous exercise". But the study by Barnes et al., (2013) shows contrast findings as 38% patients were classified as mMRC ≥ 2 . Another contrary study by Mullerova et al., (2014)[26] presents that dyspnea was recorded for the majority of the patients with about 40% reporting moderate or severe dyspnea (MRC ≥ 2)

and Punekar et al. (2016) also identified in their study that nearly half of the patients (47.3%) reported a moderate to severe level of dyspnea (MRC \geq 2). The mean dyspnea score in this study was 2.38 ± 1.22 [27]. Whereas a study by Haruna et al., (2010) shows the mean dyspnea score as 1.1 ± 0.8 [28].

The results from this study a strong positive correlation between level of anxiety and perceived dyspnea ($r=0.75$, $p<0.001$). Similarly, there was also strong positive correlation between the depression level and perceived level of dyspnea ($r=0.79$, $p<0.001$) measured by Spearman Rank correlation. The current findings are supported by previous work of Hanura, et al., (2012), which shows the modified Medical Research Council (mMRC) dyspnea score was significantly correlated with psychological status evaluated by Hospital Anxiety and Depression Scale ($r=0.36$ and $r=0.46$)[28] although these correlations observed in their work were weak. Similarly, Gianjoppe-Santos et al., (2015) have shown that depression and anxiety symptoms had a moderate correlation with dyspnea (HADS: $r=0.46$, $p=0.02$; HADS: $r=0.44$, $p=0.01$)[29]. In contrary Borges-Santos et al., (2015) finds dyspnea was moderately positively correlated with the HADS Depression subscale score ($r=0.40$, $p<0.01$) and dyspnea was not statistically significantly correlated with the HADS Anxiety sub- scale score ($r=0.04$, $p<0.77$)[30].

ACKNOWLEDGEMENT

We would like thank all the participants who showed interest in participating for this study.

CONFLICT OF INTEREST: None

5. REFERENCES

1. Pauwels, R.A., A.S. Buist, P.M. Calverley, C.R. Jenkins, and S.S. Hurd, Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. American journal of Respiratory and Critical care Medicine, 2012.
2. O'Donnell, D.E., R.B. Banzett, V. Carrieri-Kohlman, R. Casaburi, P.W. Davenport, S.C. Gandevia, A.F. Gelb, D.A. Mahler, and K.A. Webb, Pathophysiology of dyspnea in chronic obstructive pulmonary disease: a roundtable. Proceedings of the American Thoracic Society, 2007. 4(2): p. 145-168.
3. Qaseem, A., T.J. Wilt, S.E. Weinberger, N.A. Hanania, G. Criner, T. van der Molen, D.D. Marciniuk, T. Denberg, H. Schünemann, and W. Wedzicha, Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. Annals of internal medicine, 2011. 155(3):179-191.
4. Hynninen, M.J., N. Bjerke, S. Pallesen, P.S. Bakke, and I.H. Nordhus, A randomized controlled trial of cognitive behavioral therapy for anxiety and depression in COPD. Respiratory Medicine, 2010. 104(7): 986-994.
5. Maurer, J., V. Rebbapragada, S. Borson, R. Goldstein, M.E. Kunik, A.M. Yohannes, and N.A. Hanania, Anxiety and depression in COPD: current understanding, unanswered questions, and research needs. Chest, 2008. 134(4_suppl): 43S-56S.
6. Pumar, M.I., C.R. Gray, J.R. Walsh, I.A. Yang, T.A. Rolls, and D.L. Ward, Anxiety and depression-Important psychological comorbidities of COPD. Journal of Thoracic Disease, 2014. 6(11): 1615-1631.
7. Bratas, O., G.A. Espnes, T. Rannestad, and R. Walstad, Pulmonary rehabilitation reduces depression and enhances health-related quality of life in COPD patients--especially in patients with mild or moderate disease. Chronic Respiratory Disease, 2010. 7(4): 229-37.
8. Clary, G.L., Mood disorders in patients with COPD: overview of current research and future needs. Expert Reviews in Neurotherapy, 2003. 3(2): 203-13.
9. Julian, L.J., S.E. Gregorich, G. Earnest, M.D. Eisner, H. Chen, P.D. Blanc, E.H. Yelin, and P.P. Katz, Screening for depression in chronic obstructive pulmonary disease. COPD, 2009. 6(6): 452-8.
10. Sharma, P., N.R. Morris, and L. Adams, Effect of experimental modulation of mood on perception of exertional dyspnea in healthy subjects. Journal of Applied Physiology, 2016. 120(2): 114-120.
11. Parshall, M.B., R.M. Schwartzstein, L. Adams, R.B. Banzett, H.L. Manning, J. Bourbeau, P.M. Calverley, A.G. Gift, A. Harver, and S.C. Lareau,

- An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *American Journal of Respiratory and Critical Care Medicine*, 2012. 185 (4): 432-52.
12. Marciniuk, D.D., D. Goodridge, P. Hernandez, G. Rocker, M. Balter, P. Bailey, G. Ford, J. Bourbeau, D.E. O'Donnell, and F. Maltais, Managing dyspnea in patients with advanced chronic obstructive pulmonary disease: *Canadian respiratory journal*, 2011. 18(2): 69-78.
 13. Postolache, P., M. Costin, E. Dumbravă, and D. Cojocaru, Anxiety and depression in patients with chronic obstructive pulmonary disease: an open agenda for research. *Revista medico-chirurgicala a Societatii de Medici si Naturalisti din Iasi*, 2013. 118(1): 39-44.
 14. Sharma, P., N.R. Morris, and L. Adams, Effect of induced leg muscle fatigue on exertional dyspnea in healthy subjects. *Journal of Applied Physiology*, 2015. 118(1): 48-54.
 15. Di Marco, F., M. Verga, M. Reggente, F.M. Casanova, P. Santus, F. Blasi, L. Allegra, and S. Centanni, Anxiety and depression in COPD patients: The roles of gender and disease severity. *Respiratory Medicine*, 2006. 100(10): 1767-1774.
 16. Barlett, J.E., J.W. Kotrlik, and C.C. Higgins, Organizational research: Determining appropriate sample size in survey research. *Information Technology, Learning, and Performance Journal*, 2001. 19(1): 43-45.
 17. Gudmundsson, G., T. Gislason, C. Janson, E. Lindberg, C.S. Ulrik, E. Brøndum, M.M. Nieminen, T. Aine, R. Hallin, and P. Bakke, Depression, anxiety and health status after hospitalisation for COPD. *Respiratory Medicine*, 2006. 100(1): 87-93.
 18. Tel, H., Z. Bilgiç, and Z. Zorlu, Evaluation of dyspnea and fatigue among the COPD patients. 2012: Intech Open Access Publisher.
 19. Balcells, E., J. Gea, J. Ferrer, I. Serra, M. Orozco-Levi, J. de Batlle, E. Rodriguez, M. Benet, D. Donaire-González, and J.M. Antó, Factors affecting the relationship between psychological status and quality of life in COPD patients. *Health and Quality of Life Outcomes*, 2010. 8(1): 108.
 20. Roche, N., R. Marthan, P. Berger, A. Chambellan, P. Chanez, B. Aguilaniu, P. Brillat, P. Burgel, A. Chaouat, and P. Devillier, Beyond corticosteroids: future prospects in the management of inflammation in COPD. *European Respiratory Review*, 2011. 20(121): 175-182.
 21. Hagstad, S., H. Backman, A. Bjerg, L. Ekerljung, X. Ye, L. Hedman, A. Lindberg, K. Torén, J. Lötvall, and E. Rönmark, Prevalence and risk factors of COPD among never-smokers in two areas of Sweden—Occupational exposure to gas, dust or fumes is an important risk factor. *Respiratory Medicine*, 2015. 109(11): 1439-1445.
 22. Hersh, C.P., J.E. Hokanson, D.A. Lynch, G.R. Washko, B.J. Make, J.D. Crapo, and E.K. Silverman, Family history is a risk factor for COPD. *CHEST Journal*, 2011. 140(2): p. 343-350.
 23. Tetikkurt, C., I. Ozdemir, S. Tetikkurt, N. Yilmaz, T. Ertan, and N. Bayar, Anxiety and depression in COPD patients and correlation with sputum and BAL cytology. *Multidisciplinary Respiratory Medicine*, 2011. 6(4): 226-31.
 24. Puhan, M.A., M. Frey, S. Büchi, and H.J. Schünemann, The minimal important difference of the hospital anxiety and depression scale in patients with chronic obstructive pulmonary disease. *Health and quality of life outcomes*, 2008. 6(1): 46.
 25. Janssen, D.J., M.A. Spruit, C. Leue, C. Gijzen, H. Hameleers, J.M. Schols, and E.F. Wouters, Symptoms of anxiety and depression in COPD patients entering pulmonary rehabilitation. *Chronic Respiratory Disease*, 2010. 7(3): 147-157.
 26. Mullerova, H., C. Lu, H. Li, and M. Tabberer, Prevalence and burden of breathlessness in patients with chronic obstructive pulmonary disease managed in primary care. *PLoS One*, 2014. 9(1): e85540.
 27. Punekar, Y.S., H. Mullerova, M. Small, T. Holbrook, R. Wood, I. Naya, and M. Valle, Prevalence and burden of dyspnoea among patients with chronic obstructive pulmonary disease in five European countries. *Pulmonary Therapy*, 2016. 2(1): 59-72.
 28. Haruna, A., T. Oga, S. Muro, T. Ohara, S. Sato, S. Marumo, D. Kinose, K. Terada, M. Nishioka, and E. Ogawa, Relationship between peripheral airway function and patient-

- reported outcomes in COPD: a cross-sectional study. *pulmonary Medicine*, 2010. 10(1): 10-16.
29. Gianjeppe-Santos, J., A.C. Sentanin, M.S. Barusso, F.P.G. Rizzatti, M. Jamami, and V.A. Pires Di Lorenzo, Impact of exacerbation of COPD on anxiety and depression symptoms and dyspnea in the activities of daily living. *European Respiratory Journal*, 2015. 46(suppl 59).
 30. Borges-Santos, E., J.T. Wada, C.M. da Silva, R.A. Silva, R. Stelmach, C.R. Carvalho, and A.C. Lunardi, Anxiety and depression are related to dyspnea and clinical control but not with thoracoabdominal mechanics in patients with COPD. *Respiratory Physiology and Neurobiology*, 2015. 210: 1-6.