

A Study of Various Predictors of COPD-Related Fatigue (COPD-RF) and its Correlation with other Established Outcome Parameters in COPD

*¹Chaurasia Sheetal, ²Haran Alamelu, ²Chawla Pavny, ²Reddy Anish

¹Manipal Hospital Whitefield, Bangalore, India. ²Vydehi Institute of Medical Sciences and Research Institute, Bangalore, India.

Abstract

Background: Over the years approach to COPD has changed. The focus of evaluation is shifting from physiological outcome parameters to patient centered outcomes. COPD-RF is one such patient related outcome that is of considerable importance to the patients as fatigue is the second common distressing symptom in COPD & is a major concern for the patients. COPD-RF is not only a reflection of airflow limitation severity but also a result of psychological, behavioral and physical factors. Therefore, identification of markers which determine COPD RF is essential to improve patient management. This study aims to identify the predictors of COPD Related fatigue (COPD-RF) and its correlation with other outcome tools like FEV1, 6 minute walk distance (6MWD), MMRC grade, BODE index & inflammatory markers.

Methodology: 50 stable COPD patients were taken in the study. MMRC grade, FEV1, 6MWD, BODE index, CRP level and sputum neutrophil % obtained. COPD-RF was assessed using 13 item (FACIT-fatigue) questionnaire. The correlation analysis was done by spearman rank correlation and ANOVA. Predictors of COPD-RF were identified by multiple linear regression.

Result: Mean age of the population was 56.53 ± 9.29 . All GOLD category of severity was equally represented in the study group. The fatigue score showed significant correlation with inflammatory markers (CRP- $r=-0.675$; neutrophil%- $r=-0.485$) & 6MWD ($r=-.428$). Categorical variables (MMRC, FEV1 GOLD stages & BODE quartiles) also showed significant difference of fatigue among categories. BODE index & serum CRP were identified as the statistically significant predictors of fatigue, suggesting COPD-RF could be a reflection of severity of underlying pathophysiologic process i.e. systemic inflammation.

Conclusion: BODE index and CRP levels are the two important surrogate markers that predicts COPD-RF implying a role of systemic inflammation in the pathogenesis of fatigue. Also COPD-RF could be an indicator of long term prognosis of the disease & should be routinely evaluated during COPD assessment.

Keywords: COPD; Fatigue; COPD related fatigue; FACIT FATIGUE scale; Patient reported outcome.

Introduction

Over the years approach to COPD has changed. The focus of evaluation is shifting from physiological outcome parameter to patient centred outcomes¹. The parameters which are of importance to clinician as marker of disease severity may not be that important to the patient. At the end of the day patient concern is relief of

symptoms and improvement in day to day functioning. There is a correlation between these patient centred and physiological parameters but

Corresponding Author: *Sheetal Chaurasia
Manipal Hospital Whitefield, Whitefield,
Bangalore, India.
sheetal.utkalit@gmail.com

Access this article online

Quick Response Code:



Website:

www.nigerianmedjournal.org

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-Non Commercial-Share Alike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are distributed under the identical terms.

How to cite this article: Chaurasia S, Haran A, Chawla P, Reddy A. A Study of Various Predictors of COPD Related Fatigue (COPD-RF) and its Correlation with other Established Outcome Parameters in COPD. Niger Med J 2022;63;(2):133 - 139

with significant amount of variability observed². This makes separate evaluation of these patient centred outcomes important so that they can be targeted separately in evaluation, treatment and follow up. The newer grouping of COPD patient in GOLD guidelines includes patient reported outcomes like CAT score and Dyspnea grade in categorising the patient³.

Fatigue is an important and highly prevalent symptom in COPD^{4,5}. Fatigue and dyspnea are the two most common distressing symptoms in COPD patient⁶. In particular individuals with COPD have reported that fatigue affects their quality of life through limitation it imposes on motivation, concentration and everyday activities including work, household chores and social and leisure pastimes^{7,8,9}. The restriction it imposes on their everyday lives cause frustration, depression, grief and a sense of loss of control¹⁰. It is one of the major worry for the patient when they visit a doctor but unfortunately it is not paid enough attention due to lack of awareness on impact of fatigue on patients health status as well as lack of clarity on methods to evaluate and manage fatigue.

Despite the importance of evaluation of fatigue in COPD, it has not attained similar amount of attention from the researchers around the world¹¹, the reason being its diverse manifestations, such as physical or mental tiredness¹², lack of energy¹³, loss of attention, concentration or motivation¹⁴ and lack of consensus regarding the definition, interpretation and assessment of fatigue⁹. However from the patients perspective fatigue has important physical, emotional and psychological implications.

COPD is associated with systemic health effects beyond its profound effect on lung functions¹⁵. Dyspnea and fatigue are the two most important symptom experienced by COPD patients⁶. Individual with COPD undergo a high amount of activity restriction and dependency due to fatigue¹⁴. COPD patients have progressive worsening of breathlessness with sequential fall in forced expiratory volume (FEV1)¹⁶.

One of the important reasons for failure of clinician to evaluate fatigue systematically is lack of

consensus regarding the tool for measuring fatigue and the confusion regarding impact of fatigue on the health status of the patient irrespective of patients' severity of COPD¹⁷.

Due to the importance of fatigue and its impact on patients with COPD it is imperative to evaluate fatigue more objectively and routinely. In addition there is lacunae in the understanding of the importance of fatigue, its patho-mechanism, its relation to pathogenesis and severity of COPD among clinicians¹⁸. Knowledge gaps and consensus on the best method to assess it and various interventions required to deal with it also exists. This provides the justification and relevance for more research targeting fatigue in COPD.

This study aimed to evaluate COPD-RF as a patient reported outcome, various predictors of fatigue in COPD and its correlation with other established outcome parameters in COPD.

The specific objectives were to study the correlation of fatigue as measured by FACIT-F scale with various outcome parameters in COPD i.e. FEV1, Dyspnea (MMRC grade), exercise capacity (6 minute walk distance), prognostic indicator (BODE index) and inflammatory markers (serum CRP and sputum neutrophils) and to determine the various predictor of COPD related fatigue among these variables.

Methodology

Study Design: observational study

Study Site: Vydehi Institute of Medical sciences and research centre

Sample Size: Fifty

Inclusion criteria were all stable COPD patients attending the OPD of the pulmonology department of Vydehi Institute of Medical sciences and research centre between a period from July 2015 to June 2016 with a Diagnosis of COPD as per GOLD criteria² i.e. FEV1/FVC < 0.7 (Post bronchodilator).

Exclusion criteria were exacerbation in last 1 month; Presence of other significant respiratory disorder that may add to fatigue experienced by the patient like bronchial asthma, significant bronchiectasis, ILDs, Lung malignancy; Presence of any other systemic disorder unrelated to COPD

like Malignancy, Congestive heart failure, connective tissue disorder, chronic liver and renal disorders.

All suspected COPD patients were screened for inclusion in the study. Detailed history, examination and investigations were done and patients were subjected to spirometry done as per ATS/ERS consensus guidelines¹⁹. Patient who fulfil the inclusion and exclusion criteria were taken in the study. Post bronchodilator FEV1 was noted. BMI was calculated after measuring height and weight. Blood was collected for measuring serum CRP values and induced sputum was examined for sputum cytology and sputum neutrophil count noted. Exercise capacity was measured by 6 minute walk test¹⁹. 6 minute walk distance and end exercise oxygen saturation noted. Grade of dyspnea as per MMRC noted²⁰. BODE index calculated for the patient by summing up scores of BMI, FEV1, MMRC grade and 6MWD²¹. Degree of fatigue experienced by the patient was assessed using functional Assessment Of Chronic Illness Therapy-fatigue scale (FACIT-Fatigue scale)²². FACIT fatigue scale is a simple, self-administered 13 item questionnaire which provides a validated measure of the level of fatigue in chronic diseases^{23,24,25}. Patient has to answer 13 questions using a 7 day recall period. The response to each question is measured on a scale of 0-4 and scored such that the minimum overall score of 0 reflects the highest level of fatigue and maximal score of 52 reflects the lowest possible level of fatigue.

FACIT fatigue scale (FACIT-F scale) was used because it is a simple, inexpensive and reliable measure of fatigue in COPD patients⁸.

Ethical Considerations: Approval for the study was taken from the institutional ethics committee of Vydehi institute of medical sciences and research institute.

Statistical Analysis

Statistical analysis was done by SPSS version 21. All demographic characters were represented using percentages, Mean± SD. The relationship between various prognostic factors was found out using spearman rank order correlation coefficient. Association with the categorical variables like

MMRC, BODE quartiles and 6MWD was done using ANOVA. The possible predictors for fatigue was found out using multivariate logistic regression analysis.

Results

Demographic and study variables

Table 1: Mean of Study Variable

| Demographic characters | mean±SD |
|--------------------------|--------------|
| Age (years) | 56.53±9.27 |
| FEV1 (L) | 1.17±.498 |
| BMI (kg/m ²) | 21.79±4.61 |
| Spo2 (%) | 93±10.87 |
| 6MWD (metres) | 265.48±97.21 |
| Serum CRP (IU) | 2.62±3.15 |
| Sputum neutrophils (%) | 46.49±27.96 |
| BODE index | 5.04±2.21 |

50 patient participated in our study. 88% were male and 12% were females

Table 1 shows demographic characteristics of the study population. Mean age of the population was 56.53 ± 9.29. Study population had a wide variation in the 6MWD with a mean of 265.48±97.21m. Mean oxygen saturation was 93±10.87%. Mean sputum neutrophil was 46.49±27.96% and mean serum CRP of 2.62±3.15 I.U. Mean BODE index was 5.04±2.21.

All COPD patient showed increased amount of fatigue as measured by FACIT fatigue score. All the categorical variables i.e. FEV1,MMRC dyspnea grade, 6MWD, BODE index showed statistically significant difference of fatigue score mong different categories as determined by ANOVA. (Table 2,3,4 respectively).

Table 2: FACIT-F Score by FEV1 Category

| FEV1 | FACIT-FATIGUE | ANOVA |
|----------|---------------|-----------------|
| >80% | 34.5±20.50 | F=5.29; p=0.003 |
| 50%-80% | 39.09±11.91 | |
| 30%-<50% | 27.28±14.5 | |
| <30% | 14.50±9.95 | |

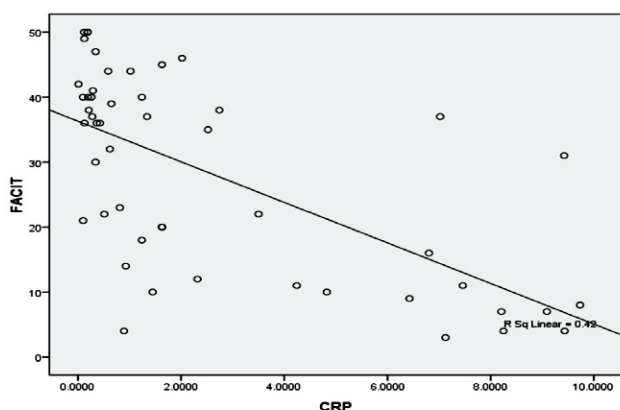
Table 3: Fatigue score by 6 minute walk distance

| 6 Minute Walk distance (m) | FACIT-FATIGUE | ANOVA |
|----------------------------|---------------|------------------|
| ≥350 metres | 34.30±11.08 | F=11.24; P<0.001 |
| 250-349 metres | 35.59±12.67 | |
| 150-249 metres | 18.67±11.63 | |
| <150 metres | 9.33±10.74 | |

Table 4: Fatigue score by BODE quartiles

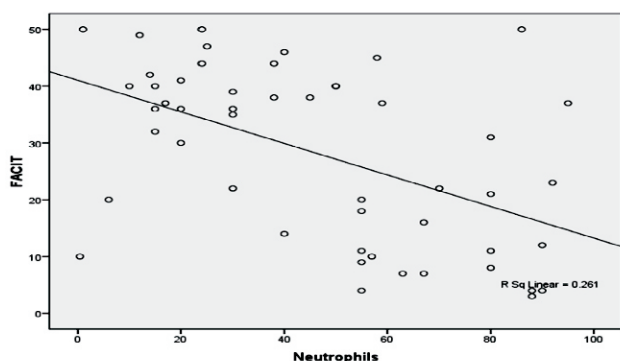
| BODE index | FACIT fatigue | ANOVA |
|------------|---------------|---------------------|
| 0-2 | 40.67±10.91 | F=19.29; p<0.001 |
| 3-4 | 30.33±9.59 | |
| 5-6 | 25.09±12.16 | |
| 7-10 | 13.07±9.94 | |

Both the inflammatory markers i.e. sputum neutrophils percentage and serum CRP also showed statistically significant correlation with Fatigue score. (Figure 1 & 2)



R= -0.675 with a p value <0.001

Figure 1: Correlation of Fatigue Score with Serum Crp



R= -.485, p value <0.001

Figure 2: Correlation of fatigue score with sputum neutrophil

Univariate regression analysis of all above outcome parameters identified only 2 parameter as significant predictor for fatigue, they are BODE index and CRP.(Table:5)

Table 5: Univariate logistic Regression Table

| Model | Regression Coefficients | | P value | 95% Confidence Interval for B | |
|-------------|-------------------------|------------|---------|-------------------------------|-------------|
| | B | Std. Error | | Lower Bound | Upper Bound |
| t Age | -.032 | .170 | .854 | -.375 | .312 |
| FEV1 | -5.959 | 4.044 | .148 | -14.120 | 2.201 |
| Dyspnea | 1.778 | 3.068 | .565 | -4.414 | 7.970 |
| Bodeindex | -5.335 | 1.405 | .000 | -8.170 | -2.500 |
| 6MWD | -.009 | .022 | .687 | -.054 | .036 |
| CRP | -1.280 | .634 | .050 | -2.558 | .000 |
| Neutrophils | -.075 | .058 | .206 | -.193 | .043 |

| Model | Unstandardized Coefficients | | Sig. | 95% Confidence Interval for B | |
|--------------|-----------------------------|------------|------|-------------------------------|-------------|
| | B | Std. Error | | Lower Bound | Upper Bound |
| 1 (Constant) | 51.701 | 3.485 | .000 | 44.689 | 58.712 |
| BODE index | -3.907 | .765 | .000 | -5.445 | -2.369 |
| CRP | -1.484 | .536 | .008 | -2.562 | -.406 |

Multiple regression analysis of BODE index and serum CRP confirmed them to be the predictor of fatigue with F model of: Fatigue=51.701-3.90(*BODE index)-1.48(*CRP) (Table:6)

Table 6: Multivariate logistic regression analysis

| Model | Unstandardized Coefficients | | Sig. | 95% Confidence Interval for B | |
|--------------|-----------------------------|------------|------|-------------------------------|-------------|
| | B | Std. Error | | Lower Bound | Upper Bound |
| 1 (Constant) | 51.701 | 3.485 | .000 | 44.689 | 58.712 |
| BODE index | -3.907 | .765 | .000 | -5.445 | -2.369 |
| CRP | -1.484 | .536 | .008 | -2.562 | -.406 |

A: Dependent variable: fatigue score

Discussion

Fatigue is a very prevalent and distressing symptom for COPD patients. In our study we used FACIT-F scale to assess fatigue because in a previous study FACIT-F had correlated well with a robust COPD specific fatigue scale (the 27 items Manchester COPD Fatigue Scale)²⁶, and it demonstrated strong linear and binary correlation with well-established measures in COPD such as SGRQ, mMRC dyspnoea and 6MWT.

Our study confirmed that fatigue is a commonly encountered symptom in COPD patients, and subjects felt more fatigued with increasing airflow

limitation. We found that experience of fatigue correlated with other commonly evaluated outcome parameters in COPD. There was statistically significant difference in fatigue score among the different categories of MMRC dyspnea grade, BODE index quartiles, FEV1 grades and 6 minute walk distance. This was in concordance with the findings of other investigators who found fatigue to be related to MMRC dyspnea grade,²⁷⁻²⁸ FEV1²⁹⁻³⁰ and BODE index³¹. Regarding 6 minute walk test there was disparity among the researchers with some finding it relating to fatigue^{27,29} while some did not find any statistically significant correlation between the two. We also evaluated the correlation between fatigue and inflammatory markers and found significant correlation between serum CRP and sputum neutrophil levels which is in contrast to the findings of Al shair and group³² and Huong Q.Nguyen et al³³. On univariate regression of all these parameters BODE index and serum CRP levels were found to be the predictor of fatigue in COPD patient which was confirmed by multivariate regression analysis. This finding points toward the fact that genesis of COPD related fatigue is related to systemic inflammation, the main pathogenetic mechanism of COPD. This is important as it links fatigue experienced in COPD to systemic inflammation. Further research in this area can find out the exact mechanism responsible for the experience of fatigue in COPD patients and that may further help in deciding the management strategy for addressing COPD-RF. Further, it also hints that COPD-RF may be a distinct entity different from fatigue experienced in other chronic disease. Also in our study we have correlated both a surrogate of airway inflammation (sputum neutrophil count) as well as systemic inflammation (serum CRP) with fatigue in COPD and interestingly despite both correlating with fatigue, only serum CRP was found to be the predictor of COPD-RF. Additionally identification of BODE index as a predictor of fatigue points toward a relationship between fatigue and mortality in COPD patients, which further highlights the need for fatigue to be assessed and addressed routinely during evaluation of COPD patients. The main hurdle in this is lack of a good number of research in this topic. Given the prevalence of fatigue in COPD and its relationship with pathogenesis and prognosis in COPD patient it becomes all the more imperative to develop specific

tools to assess COPD-RF and special strategies to improve experience of fatigue. Another important area for research would be to see the change in level of fatigue when anti-inflammatory agents like roflumilast and inhaled corticosteroids are used for treating COPD.

There were some weaknesses in our study as well. First the majority of patients were male so we could not look into the role of gender in presence of fatigue in COPD patient. Secondly we have included around 50 patient, study would have been more robust had the number of patients more. thirdly we evaluated fatigue as a unidimensional variable, multidimensional assessment of fatigue would have given more clear understanding of the predictors of fatigue. Also lack of control group is a drawback that we acknowledge.

Despite the above drawbacks our study do identify different correlates of COPD related fatigue. And by identifying systemic inflammation and BODE index as predictor of fatigue, it highlights the complex dynamics between symptomatology (fatigue), pathogenesis (systemic inflammation) and prognosis (BODE index). Additionally marker of airway inflammation (sputum neutrophils) and lung function (FEV1) was not found to be the predictor of COPD RF, this again reiterates the fact that many symptoms of COPD may not be related to lung functions and are instead related to the systemic consequences of COPD. There are very few studies which has explored predictors of fatigue using multivariate analysis. Only 4 studies have used multivariate regression analysis for identifying predictors of fatigue. They have found dyspnea, depression, physical capacity exacerbation rate as predictors of fatigue with two of them using non validated tool for regression analysis. Also the last study identifying the predictors of fatigue was done in 2009.

Conclusion

Fatigue is a highly prevalent symptom in COPD and correlates with all other important outcome parameters in COPD. Serum CRP levels and BODE index have been found to be the predictor of COPD-RF linking genesis of fatigue with pathogenesis (systemic inflammation) and prognosis (BODE index) in COPD. Given the dearth of studies on

COPD-RF which is the second most common symptom experienced by COPD patients and our study suggesting a link between fatigue and COPD pathogenesis and prognosis, we suggest more research to be taken in this field. COPD-RF should be thoroughly evaluated and managed by clinician in every visit by COPD patient irrespective of their COPD stage.

Acknowledgment: Nil

Conflict of interest: No conflict of interest by any of the authors.

References

1. Jones P, Miravittles M, van der Molen T, Kulich K. Beyond FEV₁ in COPD: a review of patient-reported outcomes and their measurement. *Int J Chron Obstruct Pulmon Dis*. 2012; **7**: 697-709. doi:10.2147/COPD.S32675
2. Franssen FM, Alter P, Bar N, Benedikter BJ, Iurato S, Maier D, et al. Personalized medicine for patients with COPD: where are we? *Int J Chron Obstruct Pulmon Dis* 2019; **14**:1465-84.
3. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease updated 2022. <https://goldcopd.org/2022-gold-reports-2/>
4. Kinsman RA, Yaroush RA, fernandeze, Dirks JF, schocket M, Fukuhara J: Symptom and experiences in chronic bronchitis and emphysema. *Chest*. 1983; **83**: 755-61
5. Walke LM, Byers AL, Tinetti ME, Dubin JA, McKorkle R, Fried TR: Range and severity of symptoms over time among older adults with chronic obstructive pulmonary diseases and heart failure. *Archives of Internal medicine*. 2007, **167**: 2503-2508
6. Blinderman CD, Hommel P, billings JA et al. Symptom distress and quality of life in patients with advanced chronic obstructive pulmonary disease. *J Pain symptom Manage* 2009; **38**: 115-123.
7. Kapella MC, Larson JL, Patel MK, Covey MK, Berry JK. Subjective fatigue, influencing variables, and consequences in chronic obstructive pulmonary disease. *Nurs Res* 2006; **55**: 10-7.
8. Baghai-Ravary R, Quint JK, Goldring JJP, Hurst JR, Donaldson GC, Wedzicha JA. Determinants and impact of fatigue in patients with chronic obstructive pulmonary disease. *Respir Med* 2008; **103**: 216-23.
9. Armes J, Krishnasamy M, Higginson IJ. Fatigue in cancer. 1st ed. New York, Oxford University Press 2004.
10. Ream E, Richardson A. fatigue in patients with cancer and COPD: A phenomenological enquiry. *Int J Nurs Stud*. 1997; **34**: 44-53
11. Lewko, A., Bidgood, P.L. & Garrod, R. Evaluation of psychological and physiological predictors of fatigue in patients with COPD. *BMC Pulm Med* **9**, 47 (2009). <https://doi.org/10.1186/1471-2466-9-47>
12. Vandevoorde J, Verbanck S, Gijssels L, et al. Early detection of COPD: a case finding study in general practice. *Respir Med* 2007; **101**: 525-30.
13. Gift AG, Shepard CE. Fatigue and other symptoms in patients with chronic obstructive pulmonary disease: do women and men differ? *J Obstet Gynecol Neonatal Nurs* 1999; **28**: 201-8.
14. Lewko A, Bidgood P, Jewel A, Garrod R. A Comprehensive Literature Review of COPD-Related Fatigue. *Curr Resp Med Rev* 2012; **5**: 370-382.
15. Agusti AG, Noguera A, Sauleda J, Sala E, Pons J, Busquet X. Systemic effects of chronic obstructive pulmonary disease. *Eur Respir J* 2003; **21**: 347-60.
16. Donaldson GC, Wilkinson TMA, Hurst JR, Perera WR, Wedzicha JA. Exacerbations and time spent outdoors in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005; **171**: 446e52.
17. Goërtz YMJ, Spruit MA, Van 't Hul AJ, Peters JB, Van Herck M, Nakken N, et al. Fatigue is highly prevalent in patients with COPD and correlates poorly with the degree of airflow limitation. *Ther Adv Respir Dis* 2019; **13**: 1753466619878128.
18. Kentson M, Tödt K, Skargren E, Jakobsson P, Ernerudh J, Unosson M, et al. Factors associated with experience of fatigue, and functional limitations due to fatigue in patients with stable COPD. *Ther Adv Respir Dis* 2016;

- 1 0 : 4 1 0 - 2 4 .
<https://pubmed.ncbi.nlm.nih.gov/27591046/>
19. ATS/ERS task force: standardisation of lung function testing. V. Brusasco, R. Crapo and G. Viegi. *Eur Respir J* 2005; **26**:153–161.
 20. American Thoracic Society. ATS Statement: Guidelines for the Six-Minute Walk Test. *Am J Respir Crit Care Med*. 2002; **166**:111–117.
 21. Bestall JC, Paul EA, Garnham R, Jones PW, Wedzicha JA. Usefulness of the medical research council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 1999; **54**:581e6.
 22. BODE index: a new tool to stage and monitor progression of chronic obstructive pulmonary disease -Claudia G. Cote, Bartolome R. Celli, Pneumonol Alergol. *Pol*. 2009; **77**: 305–313
 23. Cella D. Manual of the functional assessment of chronic illness therapy (FACIT) measurement system. Evanston, IL: Center on Outcomes, Research, and Education (CORE), Evanston Northwestern Healthcare and Northwestern University; 1997.
 24. Yellen SB, Cella DF, Webster K, Blendowski C, Kaplan E. Measuring fatigue and other anemia-related symptoms with the functional assessment of cancer therapy (FACT) measurement system. *J Pain Symptom Manage* 1997; **13**:63e74.
 25. Cella JS, Lai- J-S, Chang CH, Peterman A, Slavin M. Fatigue in cancer patients compared with fatigue in the general United States population. *Cancer* 2002; **19**:528e38.
 26. Al-shair K, Kolsum U, Berry P, Smith J, Caress A, Singh D, Vestbo J. Development, dimensions, reliability and validity of the novel Manchester COPD fatigue scale. *Thorax*. 2009; **64**:950–955.
 27. Woo K. A pilot study to examine the relationships of dyspnoea, physical activity and fatigue in patients with chronic obstructive pulmonary disease. *J Clin Nurs* 2000; **9**: 526-33.
 28. Kinsman RA, Yaroush RA, Fernandez E, Dirks JF, Schocket M, Fukuhara J. Symptoms and experiences in chronic bronchitis and emphysema. *Chest* 1983; **83**:755-6
 29. Breslin E, Van der SC, Breukink S, et al. Perception of fatigue and quality of life in patients with COPD. *Chest* 1998; **114**: 958-64.
 30. Oh EG, Kim CJ, Lee WH, Kim SS. Correlate's of fatigue in Koreans with chronic lung disease. *Heart Lung* 2004; **33**:13-20.
 31. Inal-Ince D, Savci S, Saglam M, et.al. Fatigue and multidimensional disease severity in chronic obstructive pulmonary disease. *Multidiscip Respir Med* 2010; **5**:162-7
 32. Al-shair K, Kolsum U, Dockry R, Morris J, Singh D, Vestbo J. Biomarkers of systemic inflammation and depression and fatigue in moderate clinically stable COPD. *Respir Res* 2011; **12**: 3
 33. Huong Q Nguyen, Jerald R herting, Vincwnt S. Fan et al. Symptom profile and inflammatory markers in moderate to severe COPD. *BMC Pulm. Med*. 2016; **16**:17