Original Article

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

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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 COPR-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 outcomes[1]. 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

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with significant amount of variability observed[2]. 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 patient[3].

Fatigue is an important and highly prevalent symptom in COPD[4,5]. Fatigue and dyspnea are the two most common distressing symptoms in COPD patient[6]. 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 control[10].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 world[11], the reason being its diverse manifestations, such as physical or mental tiredness[12], lack of energy[13], loss of attention, concentration or motivation[14]and lack of consensus regarding the definition, interpretation and assessment of fatigue[9]. However from the patients perspective fatigue has important physical, emotional and psychological implications.

COPD is associated with systemic health effects beyond its profund effect on lung functions[15]. Dyspnea and fatigue are the two most important symptom experienced by COPD patients[6]. Individual with COPD undergo a high amount of activity restriction and dependency due to fatigue [14]. copd patients have progressive worsening of breathlessness with sequential fall in forced expiratort 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 COPD[17].

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 clinicians[18]. 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 evaluated 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 aamong 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 criteria[2] 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 guidelines[19]. 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 test[19]. 6 minute walk distance and end exercise oxygen saturation noted. Grade of dyspnea as per MMRC noted[20]. BODE index calculated for the patient by summing up scores of BMI, FEV1, MMRC grade and 6MWD[21].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 patients[8].

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 of2.62±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	

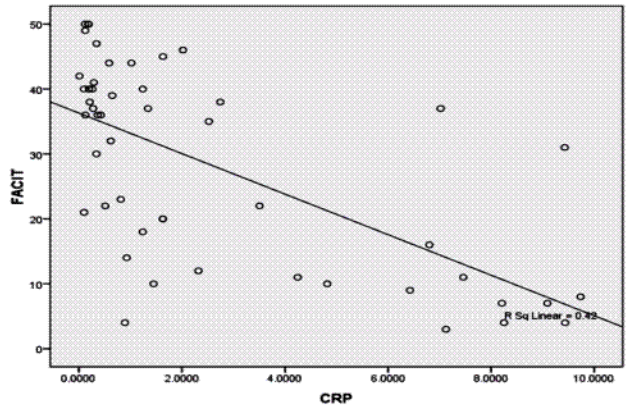
Table 3: Fatigue score by 6 minute walk distance

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

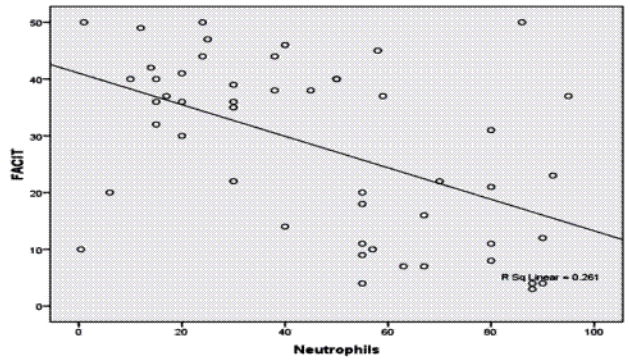
BODE index	FACIT_fatigue	ANOVA
0-2	40.67±10.91	F=19.29; p<0.001
3-4	30.33±9.59	
5-6	25.09±12.16	
7-10	13.07±9.94	

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			95% Confidence Interval for B	
		B	Std. Error	Sig.	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 prevalant 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] FEV1[29-30] and BODE index[31]. 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 group[32] and Huong Q.Nguyen et al[33]. 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 assesss 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 dyanamics between symptomatology (fatigue), pathogenesis (systemic inflammation) and prognosis(BODE index). Additionaly 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.

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