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Identification of Frequent Exacerbator Phenotype in Local COPD Patients: Development of Predictive Models for Frequent Exacerbations

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ABSTRACT

Acute exacerbations are important events in the natural history of chronic obstructive pulmonary disease (COPD). Their frequency is directly related to the prognosis of the disease. The objective of this study was to identify the 'frequent exacerbator' phenotype and determine the risk factors for increased frequency of acute exacerbations in local chronic obstructive pulmonary disease (COPD) patients in a cross sectional analytical study design. For this purpose 137 patients were included in the study after obtaining necessary permissions from the ethical board of the hospital. COPD was diagnosed on the basis of clinical symptoms and a post bronchodilator values of FEV1/FVC<0.70 on spirometry. Frequent exacerbator's were defined as patients experiencing 2 or more exacerbation episodes per year, which merited visited to the hospital. Average number of hospital visits for exacerbations per year, smoking history, family history of smoking related chronic lung disease in first degree relatives and presence of comorbidities were recorded from patient history and medical records. Body mass index was calculated and complete pulmonary function tests were recorded using electronic spirometer. Three multiple linear regression models were created with mid maximal expiratory flow, FEV1, and FVC as surrogate markers for lung function in different models. We found that 28 (20.4%) of our COPD patients were frequent exacerbators. All three multiple linear regression models for identifying risk factors for frequent exacerbations were significant ($p< 0.001$). The model in which mid maximal expiratory flow was used as a surrogate marker for lung function, accounted for the change in the dependent variable to the greatest degree (Adjusted $R^2= 0.38$, $p< 0.001$). Overall the three models consistently showed that positive family history, high body mass index, heavy smoking, poor lung function (mid maximal expiratory flow/FEF2575, FEV1 and FVC), older age and requirement of steroid therapy predicted increased frequency of exacerbations. To conclude lung function (FEF2575%, FEV1 % predicted and FVC% predicted), longer smoking history, higher body mass index, succumbing to COPD at a younger age, and a positive family history of chronic lung disease in first degree relatives are important risk factors for frequent exacerbations of COPD.

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Authors' Contribution
TAS designed the study and wrote the manuscript. MSS developed the idea and supervised the project. TAS, AH, SM and AG analysed the data. AH, SM, AG processed patients. MSS, AH, SM and AG critically analysed the manuscript.

Key words
AECOPD, COPD, Exacerbation, Frequent exacerbator phenotype, Risk factors, Lung function.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common, preventable, treatable but incurable disease marked by persistent respiratory symptoms and airflow limitation associated with airway and/or alveolar abnormalities. It is usually caused by significant exposure to noxious particles or gases especially cigarette smoke and its major COPD symptoms include dyspnea, chronic cough and sputum production (Vogelmeier *et al*., 2017). OPD may be punctuated by acute worsening of respiratory symptoms, called exacerbations.

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According to World Health Organization (2017) 65 million people suffer from moderate to severe chronic COPD worldwide. In 2005, 5% of all deaths globally were attributed to COPD, almost 90% of COPD deaths occur in low- and middle-income countries like Pakistan. It is estimated that by in 2020, COPD will become the third leading cause of death in the world (López-Campos *et al*., 2016).

One of the most significant factors contributing to morbidity and the risk of mortality in COPD patients is frequency of exacerbations (Schmidt *et al*., 2014). Exacerbations are defined as episodes of acute worsening symptoms in the natural history of COPD. Acute Exacerbations of COPD or 'AECOPD's are caused by complex interactions between the patient's immune system, respiratory viruses, and airway bacteria, which

aggravate the inflammatory status of the airway. This leads to worsening of the symptoms. Viral, bacterial infections as well as environmental pollution are considered important triggers of exacerbation. It is estimated that 50% of exacerbations are not reported by patients at all (Seemungal *et al*., 2000). This figure is likely to be much higher in Pakistan owing to the lack of awareness as well as limited availability and utilization basic health facilities (Shaikh and Hatcher, 2004).

Not only are AECOPDs important risk factors for mortality, but they also significantly reduce the quality of life and impose a substantial financial burden on the patient and the healthcare systems (Blasi *et al*., 2014). It is therefore imperative to characterize the phenotype of frequent exacerbators in our set-up and identify risk factors for early detection of this phenotype. We thus designed a cross sectional analytical study to determine the factors affecting the frequency of acute exacerbations of chronic obstructive pulmonary disease (AECOPDs) in local COPD patients.

MATERIALS AND METHODS

A hundred and thirty seven (137) patients were included in the study after obtaining necessary permissions from the Ethical Board of Mayo Hospital, King Edward Medical University, Lahore. All patients who were diagnosed with COPD and were stable enough to perform the spirometry maneuver were included in the study. Patients with symptoms suggestive of asthma and the severely ill those who were admitted in the wards were excluded from the study.

COPD was diagnosed according to the criteria laid out by the Global Initiative of Chronic Obstructive Lung Disease (GOLD) which is based on clinical symptoms and a post bronchodilator values of FEV1/FVC<0.70 on spirometry. Patient data was collected including the average number of moderate to severe exacerbations, smoking history, family history of smoking related chronic lung disease in first degree relatives and presence of comorbidities. Moderate to severe exacerbations were defined as worsening of COPD symptoms which required the patient to go to the hospital for treatment. Co-morbidities were identified from medical records and smoking history was recorded in pack years. Pack years were calculated by dividing the average number of cigarettes smoked per day by twenty and multiplying them by the number of years of smoking. Height was measured in meters, weight was noted in kilograms (kg) and body mass index was calculated in kg/m^2. Complete pulmonary function tests were recorded using electronic spirometer. The patient was given two puffs of bronchodilator (Salbutamol, 200 mcg) and after 15-20 min patients were asked to inhale and exhale into the mouth piece of the spirometer with full effort. Best of three readings was considered.

Statistical analysis

Results were recorded in mean±SD. For purposes of comparison, three categories of 'exacerbators' were created; those experiencing two or less (≤2), two to six and more than six (>6) episodes of exacerbations per year. Mean lung functions (including forced expiratory volume in the first seconf (FEV1), FEV1 percentage predicted, forced vital capacity (FVC), FVC percentage predicted, FEV1/FVC, FEV1/FVC percentage predicted, peak expiratory flow (PEF), PEF percentage predicted and forced expiratory flow at 25-75% of forced vital capacity (FEF2575%) and FEF2575% percentage predicted) were compared between the three exacerbator categories by analysis of variance (ANOVA). Variables which were not normally distributed were transformed to their natural log. Multiple linear regression analysis was conducted with 'number of exacerbations' as dependent variable and age, smoking history, family history of smoking related chronic lung disease in first degree relatives, presence of comorbidities, body mass index and lung functions as independent variables. Three predictive models were created, each time with either FEF2575%, FEV1 percentage predicted or forced vital capacity percentage predicted FVC % predicted as a marker for lung function in the model. Significance was set at p≤0.05.

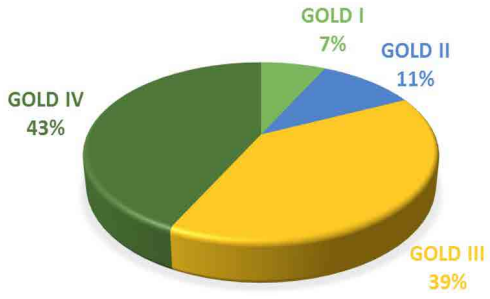

Fig. 1. Distribution of the frequent exacerbator phenotype in different GOLD stages.

RESULTS

Patient characteristics are shown in Table I. 20.4% of our COPD patients were 'frequent exacerbators' experiencing 2 or more exacerbations per year with most of this phenotype occurring in GOLD stages III and IV (Fig. 1). Analysis of variance showed that mean FEV1 (p=0.02), FEV1 percentage predicted (p=0.01), FVC (p=0.02), FVC percentage predicted (p=0.02) and FEF2775% (p=0.04)

and FEF2575% percentage predicted (p=0.02) differed significantly in the three groups of exacerbators (Fig. 2, Table II). Based on these results FEF2575%, FEV1% predicted and FVC% predicted were used as lung function variables in multiple regression models.

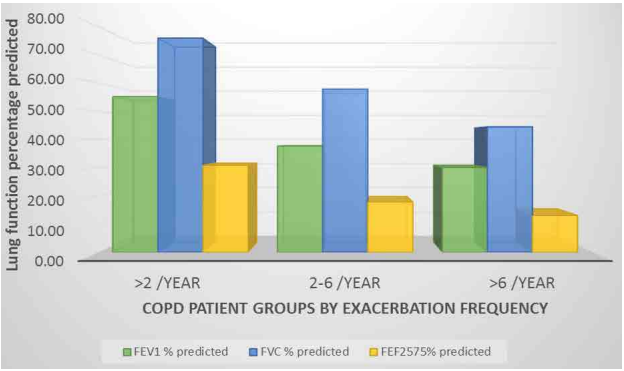

Fig. 2. Mean lung function in different groups of exacerbators.

Table I.- Patient characteristics (n=137).

Charateristics	(Mean±SD) / n (%)
Age in years	61.77±12.00
Pack years of smoking	36.37±28.48
Body Mass Index in kg/m^2	21.17±4.25
Gender	All male
FEV1 % predicted	44.84±21.26
FVC % predicted	69.39±30.07
FEV1/FVC%	51.07±10.82
Peak expiratory flow (L/min)	2.33±1.17
FEF2575%	0.75±0.58
GOLD STAGE (n=124)	Stage I=8 (6.5%); Stage II=35 (28.2%); Stage III=46 (37.1%); Stage IV=35 (28.2%)

Smoking status (n=134)	never smokers= 6 (4.5%);
	ex-smokers= 69 (51.5%);
	current smokers=59 (44%)

Comorbidities (n=102)	None recorded in medical records=63 (61.8%); recorded=39 (38.2%)
Positive family history for chronic respiratory illness (n=89)	No history=69 (77.5%); History present=20 (22.5%)
Oral or inhaled steroid treatment	No=100 (75.2%); Yes=33 (24.8%)
Exacerbator phenotypes	
Frequent	≥2 exacerbations/year = 28 (20.4%)*
Infrequent	<2 exacerbations/year = 109 (79.6%)

Table II.- Mean lung function variables in infrequent and frequent exacerbations of COPD.

	Exacerbations/year	
	< 2.0	2+
	Mean±SD	Mean±SD
FEV1*	1.45±0.83	0.97±0.49
FEV1 % predicted*	55.98±28.59	36.69±16.32
FVC*	2.49±1.08	1.83±0.79
FVC % predicted*	76.63±32.62	56.19±21.54
FEV1/FVC	57.25±14.83	51.96±7.23
FEV1/FVC% predicted	73.67±19.46	67.56±9.52
PEF	2.93±1.66	2.30±1.05
PEF % predicted	37.85±20.67	29.56±12.33
FEF2575*	1.08±0.96	0.60±0.28
FEF2575 % predicted*	31.34±23.54	17.19±8.06

*The differences are statistically significant at p<0.05.

Table III.- Multiple regression model showing factors affecting frequency of hospitalizations in COPD with Mid-maximal expiratory flow (FEF2575%) as a marker of lung function.

Risk factors	B[a]	Beta[b]
Positive family history[c]	1.55**	0.33**
Body Mass Index kg/m^2 (natural log)	2.21*	0.23*
Smoking history in pack years (natural log)	0.54*	0.24*
Mid-maximal expiratory flow in% (natural log)	-1.32***	-0.50***
Steroid use	0.77	0.18
Age in years (natural log)	-2.37*	-0.28*
Presence of comorbidities	0.04	0.01

Adjusted R^2=0.38, ANOVA p<0.001; [a]B, unstandardized coefficient; [b]Beta, standardized coefficient; [c]first degree relatives who suffered from smoking related respiratory disorders. * p<0.05; **p<0.01; ***p<0.001.

The results of all three models were significant and comparable with slight variations as given below. It is to be noted that poor lung function (FEF2575%, FEV1% predicted and FVC% predicted) in all three models, had the greatest impact on exacerbation frequency.

In the first multiple linear regression model (Adjusted R^2= 0.38, ANOVA: p< 0.001) it was seen that heavy smoking (beta =+0.24; p=0.03), positive family history (Beta =+0.33; p<0.01), high body mass index (Beta =+0.23; p=0.04), younger age of presentation (Beta = -0.28; p=0.02) and poor mid maximal expiratory flow/FEF2575 (Beta =-0.9; p<0.001) were associated with increased rate of COPD exacerbations as shown in Table III. In the second model (Adjusted R^2= 0.37, ANOVA: p< 0.001) it was seen that heavy smoking (beta =+0.22; p=0.04), positive family history (Beta =+0.35; p<0.01), high body

mass index (Beta = +0.26; p=0.03), steroid treatment (Beta =+0.23; p=0.03) and poor FEV1% predicted (Beta = -0.45; p<0.001) were associated with increased rate of COPD exacerbations as shown in Tables IV and V. The third model (Adjusted R^2= 0.36, ANOVA: p< 0.001) revealed that heavy smoking (Beta =+0.26; p=0.02), positive family history (Beta =+0.34; p<0.01), high body mass index (Beta = +0.22; p=0.055), steroid treatment (Beta =+0.26; p=0.02) and poor FVC% predicted (Beta = -0.41; p<0.001) were associated with increased rate of COPD exacerbations as shown in Tables IV and V.

Table IV.- Model Summaries of three predictive multiple linear regression models with different lung function variables.

Model summary	Model-FEF2575*	Model-FEV1	Model-FVC
R^2	0.45	0.44	0.43
Adjusted R^2	0.38	0.37	0.36
ANOVA	<0.001	<0.001	<0.001

DISCUSSION

In the current study we developed regression models to identify risk factors which predicted increased frequency of exacerbations in a cohort of Pakistani COPD patients. To the best of our knowledge, identification of the frequent exacerbator phenotype and the associated risk factors are being reported for the first time from the subcontinent.

The evaluation of COPD longitudinally to identify predictive surrogate endpoints (ECLIPSE) study first identified frequent exacerbators as the subgroup of COPD patients undergoing 2 or more exacerbation episodes per year (Reinhold *et al*., 2017). Frequent exacerbator is now being reported in literature as distinct phenotype of COPD patients which can be found in all disease stages (Alexopoulos *et al*., 2015; Blasi *et al*., 2017; Capozzolo *et al*., 2017; McGarvey *et al*., 2015; Miravitlles *et al*., 2013; Mirza and Benzo, 2017; Nachef and Mador, 2017; Wedzicha *et al*., 2013). The frequent exacerbators (FEs) have greater local and systemic inflammation (Del Río *et al*., 2016), poorer adaptive immunity (Geerdink *et al*., 2016), worse quality of life, increased mortality, and a greater decline in lung function (Blasi *et al*., 2017). Furthermore, this phenotype is also associated with high risk for comorbidities including atherosclerosis (Lange *et al*., 2016).

There is compelling evidence to suggest that risk and disease course of COPD varies in different ethnicities (Gilkes *et al*., 2016, 2017; Martin *et al*., 2012). It is therefore imperative that the exacerbation phenotype is characterized in our population. In our cohort of 137 COPD patients, we found 28 (20.4%) frequent exacerbators. The ECLIPSE cohort which identified this phenotype for the first time reported 29% frequent exacerbators in the first year of their longitudinal study (Hurst *et al*., 2010). These figures are congruent with our results. However as far as the distribution of the frequent exacerbators in the different GOLD stages is concerned there is slight discrepancy from our findings. Hurst *et al*. (2010) reported 22%, 33%, and 47% frequent exacerbator phenotypes in GOLD stages II, III and IV, respectively. Whereas in our cohort only 11% frequent exacerbators belonged to GOLD stage II, 39% were from GOLD stage III and 43% suffered from GOLD stage IV COPD. Frequency of frequent exacerbators, reported by Hurst *et al*. (2010) in GOLD stages III and IV, corroborate our results however we noticed much lower representation of frequent exacerbators in stage II than Hurst *et al*. (2010) (11% versus 22%). This difference could be attribute to ethnic differences in the two cohorts. Similarly, McGarvey *et al*. (2016) reported 28% frequency of the frequent exacerbator phenotype in a large population based study from the UK. These figures are also

Table V.- Comparison of three predictive multiple linear regression models with different lung function variables.

Risk factors	B[a]			Beta[b]		
	Model-FEF2575	Model-FEV1	Model-FVC	Model-FEF2575	Model-FEV1	Model-FVC
Positive family history	1.55**	1.65**	1.60**	0.33**	0.35**	0.34**
Body Mass Index kg/m^2 (natural log)	2.21*	2.48*	2.05	0.23*	0.26*	0.22
Smoking history in pack years (natural log)	0.54*	0.51*	0.59*	0.24*	0.22*	0.26*
Lung function variable (natural log)	-1.32***	-1.71***	-2.05***	-0.49***	-0.45***	-0.41***
Steroid use	0.77	1.01*	1.13*	0.18	0.23*	0.26*
Age in years (natural log)	-2.37*	-1.40	-1.04	-0.28*	-0.17	-0.12
Presence of comorbidities	0.04	-0.07	-0.09	0.01	-0.02	-0.02

[a]B, unstandardized coefficient; [b]Beta, standardized coefficient;* p≤0.05; **p<0.01; ***p<0.001.

close to our results. However contrary to our findings, Han *et al*. (2017) and Le Rouzic *et al*. (2017) have recently reported much lower frequencies of 2% and 11%, respectively for this phenotype. Although these figures are very small as compared to our findings, they may reflect greater representation of patients belonging to GOLD stages I and II. This is consistent with our study in that we found that only 7% and 11% of frequent exacerbators belonged to GOLD stages I and II, respectively.

Internationally, researchers have identified multiple factors for identification of patients at risk of frequent exacerbations of COPD. Amongst the demographic factors, female gender and older age tend to be associated with frequent exacerbations (McGarvey *et al*., 2015). Our subjects were all men so we cannot comment on the effect of gender, however contrary to previous research, in our cohort we found an inverse relationship of age with frequency of exacerbations. The patients who tended to acquire COPD at a younger age seemed to suffer from a worse disease course with more frequent exacerbations of COPD as compared to their older counterparts. It may be that these younger patients with early onset COPD may be genetically predisposed to succumb to COPD, and may suffer from a more severe course. This hypothesis is partially supported by recent unexpected findings of Sanchez-Salcedo *et al*. (2014) who found that the clinical symptoms and lung functions of younger COPD patients did not differ significantly from older patients even though one would anticipate the older patients to have a worse disease course. Future studies can shed more light on the disease process of early onset COPD patients.

Increased body mass index was also associated with frequent exacerbations in our cohort. Our findings are consistent with several recent studies. Bhadeka *et al*. (2010) observed that obesity was associated with poor outcomes in COPD. Similarly Liu *et al*. (2015) found that obese COPD patients were more likely to have frequent productive cough and shortness of breath as compared to normal weight patients. Most recently, Lambert *et al*. (2017) have shown that obesity in patients with COPD may contribute to poor prognosis and greater odds of severe acute exacerbations, independent of comorbidities. There are however some researchers who have found the opposite association of obesity with COPD outcomes. In a Taiwanese population Wei *et al*. (2017) found low BMI to be associated with poorer outcomes. Similarly a study from Slovenia found low BMI associated with poor outcomes in COPD (Lainscak *et al*., 2011). Along the same lines, a meta-analysis in 2012 showed that lower BMI was associated with increased mortality in COPD patients (Cao *et al*., 2012). These differences in the effect of BMI on COPD disease course may be attributed to differences in ethnicity. This argument is supported by studies which show that effects of obesity and adiposity on the disease courses of various chronic illnesses are different in diverse ethnicities (Haldar *et al*., 2015; Katz *et al*., 2000).

We also found that patients with longer smoking histories were more likely to suffer from increased frequency of acute exacerbations. This is in agreement with literature. It has long been known that smoking is the major avoidable risk factor for development of COPD (Alberg *et al*., 2014; Laniado-Laborín, 2009). However while 85% of COPD patients are likely to be smokers (Brashier and Kodgule, 2012), it is estimated that only 50% cigarette smokers develop COPD (Lundbäck *et al*., 2003). This may be due to genetic predisposition of patients and may explain why some studies have failed to show significant association of smoking history with COPD outcomes including frequency of exacerbations (Geerdink *et al*., 2016; Han *et al*., 2017; Kessler *et al*., 1999; Le Rouzic *et al*., 2017).

Investigators have also identified some clinical features as risk factors for frequent exacerbations. These include higher baseline symptom burden, weakened lung function variables (FEV1 percent predicted, inspiratory capacity percentage predicted/FIVC%, FEF25-75%, residual volume/total lung capacity percentage), co-morbid diseases, previous exacerbations and radiological evidence of small airway abnormality (Blasi *et al*., 2017; Capozzolo *et al*., 2017; Del Río *et al*., 2016; Ekström *et al*., 2016; Han *et al*., 2017; Le Rouzic *et al*., 2017; McGarvey *et al*., 2015; Wan *et al*., 2011). In agreement with literature we found an inverse association of exacerbation frequency with lung function variables including FEV1, FVC and FEF25-75%. The previously reported CT evidence of small airway abnormality is also in agreement with our finding of low FEF25-75% as this lung function variable is indicative of small airway disease (Contoli *et al*., 2010; Simon *et al*., 2010; Verbanck *et al*., 2004). However, we did not find any statistically significant association of presence of comorbidities with frequency of exacerbation in our cohort. This is probably due to the fact that we considered history and medical records alone for assessing the presence of comorbidities rather than extensive laboratory and radiological investigations.

Our results also show that patients who tended to take steroid treatment (oral or inhaled) tended to have more frequent exacerbations. This is in agreement with findings of Klopf *et al*. (2016) who also found more frequent exacerbators in the group assigned inhaled corticosteroids (ICS) along with bronchodilators as compared to the groups not taking inhaled steroids. Steroid treatment may make patients susceptible to repeated infections and hence increase the frequency of exacerbations. Other researchers

have reported lack of any association (McGarvey *et al*., 2015; Price *et al*., 2013). These differences may also be linked to different ethnicities and the fact that the cohorts included in these studies comprise of diverse COPD phenotypes each of which is distinct with respect to disease course and response to treatment.

We also found family history of chronic lung disease in first degree relatives as a risk factor for frequent exacerbations. This information gathered from patient history serves as a surrogate to assess genetic predisposition of the patients to chronic respiratory illness. A recent exhaustive review by Pouladi *et al*. (2016) summarizes the complex genetic background of chronic respiratory illnesses including COPD, asthma, interstitial lung disease and sarcoidosis. There is also evidence of common susceptibility genes for chronic respiratory illnesses (Meyers *et al*., 2004; Postma *et al*., 2011). Thus our results are in agreement with these concepts.

There are several limitations to our study. First, this is a pilot study from only one tertiary hospital which caters to the patients from lower socioeconomic status from Lahore and its suburbs. However, this study provides the first data of its kind from any segment of COPD population from Pakistan and is thus a significant contribution to understanding the frequent exacerbator phenotype from this region. Secondly, while noting the risk factors we limited ourselves to the routinely recorded history and clinical examination features without any biochemical, genetic or radiological test results. This may seem to limit the robustness of the prediction model on the surface. We however aimed to design a prediction model based on routinely recorded clinical parameters to enhance the applicability of using this model to identify patients at high risk for frequent exacerbations. Our proposed model fulfills this criteria.

CONCLUSIONS

Poor lung function (FEF2575, FEV1% predicted, FVC% predicted) longer smoking history, higher body mass index, succumbing to COPD at a younger age, steroid treatment and a positive family history of chronic lung disease in first degree relatives are important risk factors for frequent exacerbations of COPD.

Statement of conflict of interest

Authors have declared no conflict of interest.

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