Original Article

Clinical and pulmonary functions profiling of patients with chronic obstructive pulmonary disease experiencing frequent acute exacerbations

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ABSTRACT

Purpose: The present study aimed at clinical and pulmonary functions profiling of patients with chronic obstructive pulmonary disease (COPD) to anticipate future exacerbations. **Methods:** The study included 80 COPD patients; 40 patients had ≥2 acute exacerbations during preceding 1 year (frequent exacerbation [FECOPD] group) and 40 patients had <2 acute exacerbations during preceding 1 year (infrequent exacerbation [I-FECOPD] group). Clinical profile, sputum microbiology, blood gas analysis, spirometric indices, and diffusion capacity (transfer test) variables were assessed. Groups' comparison was performed using an independent *t*-test for numeric scale parameters and Chi-square test for nominal parameters. Pearson's and Spearman's correlation coefficients were derived for numeric scale parameters and numeric nominal parameters, respectively. Multinomial logistic regression analysis was done using SPSS software. **Results:** FECOPD group contained younger patients than in I-FECOPD group although the difference was not statistically significant. There was no significant difference between two groups regarding smoking pack-years and duration of illness. FECOPD group had significantly more expectoration score and Modified Medical Research Council dyspnea scores. Cough score and wheeze score did not differ significantly between two groups. More patients in FECOPD group (12/40 vs. 4/40) had lower airway bacterial colonization. Arterial blood gas parameters were more deranged in FECOPD group. Spirometric indices (forced expiratory volume during 1st s) as well as transfer test (both diffusing capacity for carbon monoxide and transfer coefficient of the lung values) were significantly reduced in FECOPD group. **Conclusions:** The patients in FECOPD group had clinical, spirometric, and transfer test profiling suggestive of a severe COPD phenotype, the recognition will help in predicting future exacerbations and a better management.

KEY WORDS: Acute exacerbations, chronic obstructive pulmonary disease, clinical profile, spirometric indices, transfer test

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases.[1] As per the World Health Organization (WHO) database,[2] about 3 million deaths were caused by the disease in 2015 that amounts to 5% of all deaths globally in that particular year; COPD is the fourth leading cause of death in the world at present and

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is projected to be third by 2030. In a qualitative review of studies by Halbert *et al*.,[3] the overall prevalence in adults varied between 4% and 10% in countries where it had been rigorously measured. In another review and meta-analysis[4] of 37 studies, pooled prevalence was observed to be 7.6% for overall COPD, 6.4% for chronic bronchitis alone, and 1.8% for emphysema alone. The prevalence estimates ranged widely from 0.2% to 37% in one review,[5] while it was 2.1%–26.1% in another.[6]

The natural course of COPD often involves exacerbations defined as an acute event characterized by the worsening of patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication.[1] Alternative definition suggested being "a worsening of respiratory symptoms, which required treatment with oral corticosteroids or antibiotics, or both."[7] The average frequency of exacerbations in COPD patients has varied from 0.68 per patient-year[4] to as high as 7.5 per patient-year[5] in different studies. Exacerbations are often responsible for rapid deterioration in pulmonary function, deterioration of short- and long-term quality of life, increased socioeconomic burden, very high healthcare resources utilization, and increased mortality of COPD patients. Despite drawing attention of medical workers for acute exacerbations in COPD, there is a paucity of work assessing the impact of decreased diffusing capacity for carbon monoxide (DLCO) in COPD patients over acute exacerbations and after extensive medical literature search over PubMed and PMC; we could find only one study recently published from Korea which has observed that low DLCO was associated with the risk of acute exacerbation.[8]

The present study intends to identify variables associated with the frequent exacerbations in COPD including the clinical characteristics, spirometric indices, DLCO, and microbiological parameters. Our objective was (i) to assess DLCO not assessed extensively previously and (ii) to assess all mentioned parameters in single study to identify comprehensive outcome in the same study population. This will help anticipate future exacerbations to have a better management strategy.

METHODS

Study subjects

The present study was undertaken at the Department of Respiratory Medicine at our Institute. The study comprised of 80 COPD patients; the diagnosis of COPD was based on the GOLD guidelines. The COPD patients with postbronchodilator forced expiratory volume during first second (FEV1)/forced vital capacity (FVC) <0.70 in the absence of any other alternative diagnosis, and who gave their explicit written consent, were included. These patients were categorized to one of two groups in accordance with the findings of Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints study[9] that suggest that a history of two or more annual exacerbations represents a frequent exacerbation phenotype. Accordingly, in the present study, Group 1, the frequent exacerbator group (FECOPD), included COPD patients with two or more episodes of exacerbations during preceding 1 year and Group 2, the infrequent exacerbator group (I-FECOPD), comprised of COPD patients with <2 episodes of exacerbations during preceding 1 year.

Smoking pack-years

The COPD patients included were either smokers or ex-smokers. Smoking pack-years were calculated taking into consideration of mode of smoking (bidi, cigarette, or hookah), daily consumption, and total years smoked. One pack-year was 20 cigarettes smoked every day for 1 year.[10] For bidi, cigarette equivalents were calculated by applying a weight of 0.5 to bidis,[11] and for hookah, 12.5 g of loose tobacco was equivalent to one packet of 20 cigarettes.[12]

Assessment of exacerbations

The occurrence of exacerbations was determined by asking the patient, "Have you had a flare-up of your chest trouble in the last 12 months?" If the answer was yes, the patient was prompted with the question, "How was the flare-up treated?" It was considered an exacerbation if the answer suggested an admission to hospital or any additional antibiotic and/or steroid intake at home. The accuracy of patient-reported exacerbation frequency in COPD has been proved by Quint *et al*.[13] in their study.

Clinical parameters

The patients were assessed for the duration of illness due to COPD. The symptoms were elicited in detail and appropriate scoring/grading was done as shown in Box 1.

Investigations

The patients were analyzed for arterial blood gas analysis, sputum microbiological examination, i.e., pyogenic culture and sensitivity, digital radiograph chest, and pulmonary function tests including spirometry and transfer study.

Procedure of spirometry

The spirometry was carried out over PK Morgan Transfer Test Model C, Kent, UK, a dry rolling seal system. Short-acting bronchodilator was withheld for 6 h, long-acting bronchodilator for 12 h, and sustained release theophylline for 24 h, before carrying out pulmonary function tests. The values of the spirometric indices parameters were measured before and 20 min after bronchodilator (200 μg inhaled salbutamol). Spirometric indices were calculated using best out of three technically satisfactory performances as per the recommendations of American Thoracic Society.[14] The parameters used for analysis purpose included FVC, FEV1, the ratio of FEV1 to FVC expressed as a fraction (FEV1/FVC), peak expiratory flow rate (PEFR), forced mid-expiratory flow rate ($FEF_{25\%–75\%}$), and postbronchodilator reversibility.

Procedure of transfer study

Transfer study was conducted using standard single-breath DLCO test technique, which is also recommended by the American Thoracic Society guidelines.[15] PK Morgan Transfer Test Model C System, Kent, UK, was used for this purpose. The following transfer study parameters were considered for statistical analysis:

1. DLCO (mL/mmHg/min)
2. Transfer coefficient of the lung (DLCO/alveolar volume) (KCO[mL/mmHg/min/L]).

Statistical analysis

The data were evaluated for completeness and consistency and were coded. Statistical analyses were performed using unpaired (independent) *t*-test for all the numeric scale parameters and Chi-square test for all nominal parameters. Pearson's and Spearman's correlation coefficients were derived for all numeric scale parameters and numeric nominal parameters, respectively. Multinomial logistic regression was applied for two models using SPSS Statistics for Windows, Version 20.0. (Armonk, NY: IBM Corp), the dependent variable being the FECOPD group and the I-FECOPD group being the reference category. The first model included Modified Medical Research Council (MMRC) grade, body mass index (BMI), PaO2, FEV1, and KCO. The second model included expectoration score.

RESULTS

In the present study, 80 COPD patients were included, 40 each in FECOPD group and in I-FECOPD group. The details of patients' characteristics are shown in Table 1. FECOPD group comprised of younger patients than in I-FECOPD group although the difference was not statistically significant ($P = 0.33$). Statistically significant differences between these two groups were observed regarding expectoration scores, wheeze scores, dyspnea scores, and bacterial lower airways colonization.

Spirometry parameters in FECOPD group and I-FECOPD group are shown in Table 2. The decline in both FEV1 and FVC was more in FECOPD group and the differences were statistically significant. PEFR and $FEF_{25\%–75\%}$ were also reduced in FECOPD group, but the differences were not statistically significant. The details of arterial blood gas parameters in both FECOPD group and I-FECOPD group were as shown in Table 2; the mean values of PaO_2 and SaO_2 were significantly lower in FECOPD group. Table 2 also illustrates transfer test parameters in FECOPD group and I-FECOPD group; both DLCO and KCO were statistically reduced in FECOPD group.

Table 3 shows the correlation coefficient of study parameters to the frequency of exacerbations. Pearson's correlation was derived for continuous numeric values, and Spearman's correlation was derived for nominal values. A negative value of the coefficient of correlation indicates inverse correlation; the exacerbations frequency increased as the value of a particular parameter including age, BMI, PaO_2, SaO_2, FEV1, PEFR, $FEF_{25\%–75\%}$, DLCO, and KCO decreased. A positive value of the coefficient of correlation indicates direct correlation; the exacerbations frequency increased as the value of a parameter among cough score, expectoration score, wheeze score, MMRC grade, duration of illness, pack-years, $PaCO_2$, and HCO_3 increased.

Table 4 displays multivariate logistic regression analysis outcomes. Patients who had a higher value of BMI or

Box 1: Grading of clinical symptoms

Cough
- Score 0: No cough
- Score 1: Occasional cough present on <7 days in the last 1 month
- Score 2: Frequent cough present on 7-21 days in the last 1 month
- Score 3: Persistent cough present on >21 days in the last 1 month
- Score 4: Persistent cough present daily, disturbing the daily routine

Expectoration
- Score 0: No expectoration
- Score 1: Expectoration present, but scanty in amount
- Score 2: Average expectoration of about 20 mL/day over last 1 month
- Score 3: Average expectoration of about>20-50 mL/day over last 1 month
- Score 4: Average expectoration of>50 mL/day over last 1 month

Dyspnea: MMRC dyspnea scale was used to assess dyspnea severity in these patients
- Score 0: I only get breathless with strenuous exercise
- Score 1: I get short of breath when hurrying on level ground or walking up a slight hill
- Score 2: On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own pace
- Score 3: I stop for breath after walking about 100 yards or after a few minutes on level ground
- Score 4: I am too breathless to leave the house or I am breathless when dressing

Wheeze
- Score 0: Audible wheeze not reported by patient
- Score 1: Audible wheeze reported by patient

MMRC: Modified Medical Research Council

Table 1: Comparison between frequent exacerbation and infrequent exacerbation groups with respect to patient's characteristics, clinical features, and microbiological outcome

Parameters	FECOPD group	I-FECOPD group	Statistical significance of difference (*P*)
Number of patients (*n*)	40	40	-
Male/female	32/8	37/3	0.11
Age, mean±SD (year)	60.2±11.2	62.3±7.8	0.33
Duration of illness, mean±SD (year)	11.4±5.3	9.4±5.9	0.10
Smoking pack-years, mean±SD (year)	30.8±15.7	28.5±12.8	0.47
Cough scores, mean±SD	2.4±1.1	1.9±1.3	0.13
Expectoration scores, mean±SD	2.2±1.1	1.1±1.1	<0.01
Wheeze scores, mean±SD	0.4±0.5	0.2±0.4	0.09
Dyspnea scores	2.3±0.9	1.7±1.1	0.03
Lower airway colonization	12/40	4/40	0.02
Pseudomonas aeruginosa	12.5%	7.5%	-
Streptococcus pneumoniae	10%	2.5%	-
Haemophilus influenzae	7.5%	5%	-

SD: Standard deviation, FECOPD: Frequent exacerbation, I-FECOPD: Infrequent exacerbation

Table 2: Comparison between frequent exacerbation and infrequent exacerbation groups with respect to spirometric, arterial blood gases, and transfer test parameters

Criteria	Parameters	Mean±SD		Statistical significance of difference (*P*)
		FECOPD group (*n*=40)	I-FECOPD group (*n*=40)	
Spirometry	FVC (L)	2.62±0.65	2.89±0.53	0.05
	FEV1 (L)	1.27±0.42	1.66±0.43	<0.01
	FEV1/FVC ratio	0.51±0.09	0.56±0.10	0.06
	PEFR (L/m)	197.8±77.8	224.0±85.8	0.25
	$FEF_{25\%-75\%}$ (L/m)	52.2±19.7	56.1±27.9	0.21
Arterial blood gas	PaO_2	68.7±10.6	76.6±10.7	<0.01
	$PaCO_2$	45.3±6.5	43.1±4.8	0.10
	pH	7.39±0.044	7.41±0.03	0.31
	HCO_3	27.8±5.4	25.7±4.7	0.08
	SaO_2	92.8±2.6	94.4±2.4	<0.01
Transfer test	DLCO (mL/mmHg/min)	16.15±5.88	18.86±5.03	0.03
	KCO (mL/mmHg/min/L)	3.35±1.18	3.85±1.02	0.04

FVC: Forced vital capacity, FEV1: Forced expiratory volume during 1st s, PEFR: Peak expiratory flow rate, $FEF_{25\%-75\%}$: Forced mid-expiratory flow rate, DLCO: Diffusing capacity for carbon monoxide, KCO: Transfer coefficient, FECOPD: Frequent exacerbation, I-FECOPD: Infrequent exacerbation, SD: Standard deviation

Table 3: Correlations of study parameters to number of exacerbations

Parameter	Coefficient of correlation	Two-tailed significance
Age*	−0.32**	<0.01
Cough score#	0.21	0.06
Expectoration score#	0.41**	<0.01
Wheeze score#	0.07	0.54
MMRC grade#	0.21	0.06
Duration of illness*	0.09	0.41
Pack-year*	0.08	0.48
BMI*	−0.16	0.15
PaO_2*	−0.32**	<0.01
$PaCO_2$*	0.08	0.46
HCO_3*	0.07	0.56
SaO_2*	−0.31**	<0.01
FEV1*	−0.38**	<0.01
PEFR*	−0.20	<0.07
FEF*	−0.09	<0.44
DLCO*	−0.16	0.15
KCO*	−0.15	0.19

*Pearson correlation was derived for all continuous numeric values, #Spearman's correlation was derived for all nominal (graded) values, **Correlation is significant (two-tailed). FEV1: Forced expiratory volume during 1st s, PEFR: Peak expiratory flow rate, FEF: Forced expiratory flow, DLCO: Diffusing capacity for carbon monoxide, KCO: Transfer coefficient, BMI: Body mass index, MMRC: Modified Medical Research Council

Table 4: Multivariate logistic regression

	aOR	95% CI	*P*
MMRC grade	1.954	1.002-3.810	0.04
BMI	0.817	0.682-0.980	0.03
PaO_2	0.942	0.854-1.040	0.24
FEV1	0.092	0.018-0.480	<0.01
KCO	0.875	0.387-1.978	0.75

FECOPD group being the dependent and I-FECOPD group being the reference category. KCO: Transfer coefficient, BMI: Body mass index, MMRC: Modified Medical Research Council, FEV1: Forced expiratory volume during 1st s, CI: Confidence interval, aOR: Adjusted odds ratio, FECOPD: Frequent exacerbation, I-FECOPD: Infrequent exacerbation

FEV1 were less likely to be in FECOPD group rather than I-FECOPD group. However, with higher MMRC scores, the odds of being in FECOPD group increased.

DISCUSSION

Exacerbations are frequent events during the natural course of COPD; the disease is often aggravated as a consequence of these episodes. They are the major cause of the morbidity and mortality in COPD patients. Some COPD patients are more prone to the exacerbations than others with similar disease severity suggesting a separate phenotype of COPD. The present study evaluates clinical, microbiological, spirometric, and lung transfer (diffusion) test parameters for anticipating future exacerbation.

Although advancing age leads to decline in lung function in normal individuals as well as in COPD patients, the impact of progressive age over exacerbations has not been unambiguous. EFRAM study[16] and Lee *et al*.[17] found no impact of age on exacerbations. Some workers[18,19] have observed that the frequent exacerbators were younger than the infrequent exacerbators. However, other studies[20-24] have found that older COPD patients experience more exacerbations. Our study observed that the FECOPD group contained younger patients than the I-FECOPD group although the difference was not statistically significant. The coefficient of correlation was indicative of an inverse relationship between age and exacerbation frequency in our study. Probably, COPD patients who are more prone to have repeated exacerbations represent a different phenotype, in which the COPD onset is earlier and have more severe course with frequent acute exacerbations and may merely not present an advance course during COPD disease.

Our study and majority of other studies[9,19,24-26] have found more females in the FECOPD group than the I-FECOPD group; however, a definite conclusion cannot be reached due to a lower fraction of female patients in these individual studies. This may also suggest poor access to COPD care by female COPD patients due to financial constraints or social taboos or simply due to self-negligence to COPD symptoms.

One prior study[23] and our study have observed that longer duration of illness has been linked with frequent exacerbations. Although statistically it was not significant, a study including more COPD study individuals may provide a clear scenario. As COPD has a known progressive downhill course, more duration of illness may be expected to lead to more severe or advanced disease with frequent exacerbations.

Smoking is known as a risk factor associated with a more rapid decline in FEV1. Prior studies observed that smoking cessation leads to a reduction in the frequency of acute exacerbation in COPD patients[19] and that risk reduction was correlated with the period of smoking cessation.[9] However, a large number of previous studies[17,22-24,27] and our study also have observed that the quantum of smoking (smoking pack-years) was not significantly related to the frequency of exacerbations. Probably, COPD patients with frequent exacerbations represent a separate phenotype and have more disease severity even with less quantum of smoking.

Previous studies[18,20,23,28,29] found out that chronic cough and chronic sputum production were significantly higher in frequent exacerbators. Miravitlles *et al*.[20] showed that chronic mucus hypersecretion was significantly associated with frequent exacerbations. Our study has observed expectoration scores to be significantly higher in frequent exacerbators and statistically significant in the regression model. The evidence is in favor of chronic productive cough signifying airway inflammation being a risk factor for exacerbations or associated with exacerbations.

In the present study, MMRC dyspnea scores were significantly higher in the frequent exacerbators, and multivariate regression model also suggested MMRC dyspnea grade having a significant independent association with the frequency of exacerbations. Prior studies have also observed that chronic dyspnea and higher dyspnea scores were linked with frequent exacerbations in COPD patients.[9,17,18,22,24,27,28] Seemungal *et al*.[30] showed that daily wheeze was significantly associated with frequent exacerbations. We also found the majority of COPD patients with wheeze in the FECOPD group.

Our study observed that mean FEV1 was significantly lower in the frequent exacerbators compared to the infrequent exacerbators; there was a significant inverse relationship between the frequency of exacerbations and FEV1. The multivariate regression analysis revealed a significant independent association of FEV1 with the frequency of exacerbations. The previous studies which have evaluated the impact of FEV1 on the frequency of exacerbations observed that a low FEV1 is associated with frequent exacerbations.[9,17,19,21,22,24,27,31] Faganello *et al*. have shown that the frequent exacerbators had a significantly lower FVC than the infrequent exacerbators.[21] Lee *et al*. recorded a significantly lower FEV1/FVC ratio in FECOPD group.[17] In our study, this ratio was lower in the FECOPD group but was not statistically significant. It appears that exacerbations lead to poor lung functions and lower lung functions further lead to exacerbations making it a vicious cycle.

After extensive medical literature search, we could find only one study by Lee *et al*. published recently from Korea, who have observed that low DLCO was associated with the risk of acute exacerbation,[8] and to the best of our knowledge, our study is the next one to have assessed the relationship of DLCO and KCO with the exacerbation frequency. In our study, the mean value of DLCO was significantly lower in the frequent exacerbators than the infrequent exacerbators. The mean value of KCO was also significantly lower in the frequent exacerbators compared to infrequent exacerbators. We have also analyzed the distribution of COPD patients in FECOPD and I-FECOPD group as shown in Figure 1 for DLCO parameter and in Figure 2 for KCO parameter. The graphical presentations clearly reflect a skew to left (signifying poor transfer values) in frequent exacerbators both for DLCO and KCO. Transfer test parameters need to be studied in more future studies to establish a clear and unequivocal association.

CONCLUSIONS

We have found that a productive cough, dyspnea, and lower BMI clinically; lower airway bacterial colonization; lower PaO_2 and SaO_2 on blood gas analysis; lower FEV1, FVC, DLCO, and KCO on lung function testing were predictors of frequent COPD exacerbations. It appears that observed clinical characteristics, arterial blood gas analysis, bacterial colonization pattern, spirometric indices, and transfer test parameters were suggestive of a distinct COPD phenotype more prone to have COPD frequent acute exacerbation. The identification of clinical and lung function parameters that is linked to COPD acute exacerbation shall help in

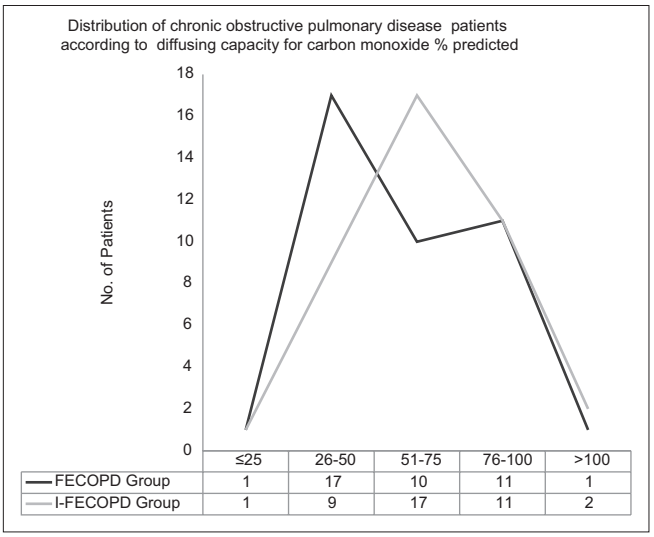

Figure 1: Graphical representation of distribution of patients according to transfer coefficient of the lung values represented as % predicted values

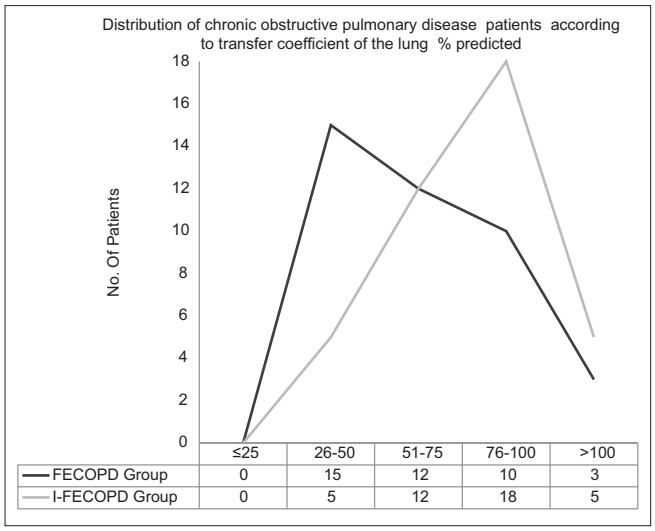

Figure 2: Graphical representation of distribution of patients according to diffusing capacity for carbon monoxide values represented as % predicted values

predicting future exacerbations more confidently and this will also help in prevention and better management of acute exacerbations in these patients.

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Conflicts of interest

There are no conflicts of interest.

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