Original Article

A search for covert precipitating clinical parameters in frequent exacerbators of chronic obstructive pulmonary disease

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ABSTRACT

Introduction: Acute exacerbations are a significant source of morbidity and mortality associated with chronic obstructive pulmonary disease (COPD). Some patients suffer an inordinate number of exacerbations while others remain relatively protected. The aim of this study was to evaluate the potentially modifiable precipitating parameters of frequent severe exacerbations requiring hospital admission in COPD. **Materials and Methods:** Consecutive patients admitted with acute exacerbation of COPD for a period of one year in a tertiary care hospital were evaluated prospectively. Data regarding the number of exacerbations in the previous year, current comorbidities, medications, and clinical and functional status of COPD patients were evaluated. **Results:** We included 98 COPD patients (81.63% men) admitted consecutively with exacerbations in our department. The mean number of severe exacerbations was (2.42 per patient/per year), and 65% of the patients had frequent severe exacerbations. Multivariate analysis indicated that serum uric acid, serum total IgE, depression and anxiety, gastroesophageal reflux disease symptoms, air pollution, poor adherence to inhaled therapy, and irregular outpatient followup visits were independent predictors of frequent severe exacerbations. **Conclusion:** COPD patients with frequent exacerbations should be carefully assessed for modifiable confounding risk factors regardless of poor lung function to decrease exacerbation frequency and related poor prognosis. Raised serum total IgE levels may point towards atopy as an additional comorbidity in COPD while uric acid can have a clinically useful role in risk stratification in a primary care setting.

KEY WORDS: Chronic obstructive pulmonary disease, exacerbation, serum IgE, uric acid

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a dynamic chronic disease which is characterized by an unrelenting decline in the lung function and exercise capacity.[1] The underlying condition is interrupted by aggravation of symptoms which vary in severity and frequency.

Exacerbations are important events in the course of the disease because negative impact on the patients quality of life, accelerated decline in the lung function, additional burden of hospitalization, high economic consequences, and mortality.[2]

The annual rate of COPD exacerbations has been estimated between 0.5 and 3.5 exacerbations per year.[3] Exacerbations were once considered to be of minimal importance which was primarily based on the pivotal 10-year study by Fletcher *et al.*, which found no relation between decline in the lung function and respiratory infections.[4]

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Many triggering factors for acute exacerbation of COPD (AE-COPD) have been identified;[5] Most exacerbations appear to be associated with infective causes, either bacterial or viral, although "noninfective" causes such as air pollution may also contribute.

It is of immense importance to fully explore etiology and pathogenesis of AE-COPD. The identification of risk factors for AEs may permit the implementation of measures aimed at avoiding these complications. In a further step, identification of COPD patients with risk factors that are correlated with high possibility of exacerbations may alert treating physicians and may induce a closer look and subsequently may lead to acceptance of preventive measures.

Aim of the study

The aim of the study is to evaluate the potentially modifiable precipitating factors, particularly unexplored parameters in frequent severe exacerbations requiring hospital admission in COPD.

MATERIALS AND METHODS

Setting

Patients admitted with AE-COPD in a tertiary care center in Lucknow, India, during 1-year period were studied. COPD was defined according to the GOLD guidelines.

Patients with reversible airflow obstruction and with any other chronic respiratory disease including asthma, bronchiectasis, malignancy, any known gastroesophageal disease such as cancer, achalasia, active peptic ulcer disease, Zollinger–Ellison syndrome, mastocytosis, scleroderma, and those who were not willing to participate in the study were excluded from the study.

Although exacerbation frequency generally increases with declining lung function, recent work suggests that the "frequent exacerbator" phenotype remains a distinct subgroup in all GOLD stages.[6]

COPD exacerbations that required oral steroids and/or antibiotics that resulted in emergency room admission or hospitalization were defined as severe exacerbations. Emergency room admission or hospitalization was required when patients needed oxygen therapy, noninvasive/invasive mechanical ventilation, and/or had severe baseline disease or severe comorbidities.

Consecutive patients admitted with AE-COPD with informed consent were evaluated prospectively. Each patient's demographic details, previous medical history, smoking history/pack years, exacerbation and vaccination history, presenting symptoms were evaluated. Previous history of exacerbations and other prospective data were collected either through available health records/prescriptions or by direct interaction with the patient. Patient's home environment data including passive smoking, air pollution, and any family member suffering from respiratory infections were studied.

On admission, a routine workup including complete blood count and biochemistry was collected from each patient upon arrival to the emergency room. A self-administered gastroesophageal reflux disease (GERD) questionnaire was used to evaluate GERD symptoms. Hospital anxiety and depressive score was used for evaluation of anxiety and depression. The hospital anxiety and depression scale is a self-assessment screening questionnaire. The scoring provides information on the potential presence as well as the severity of anxiety and/or depression disorders. While it is used in hospitals, it is also used in private practices. This scale along with a clinical examination is used for diagnosis. Each item on the questionnaire is scored from 0 to 3 and this means that a person can score between 0 and 21 for either anxiety or depression. A cutoff point of 8/21 was used for diagnosis of anxiety/depression.

Analysis

The subjects were divided into two groups based on the frequency of exacerbations. Frequent exacerbator is defined as patient who has 2 or more exacerbations per year while infrequent exacerbator will be defined as those with <2 exacerbations per year [Table 1]. Patients' characteristics were compared in the two sets of groups and analyzed. Chi-square and *t*-tests and multivariate analysis were used to compare variables.

RESULTS

A total of 98 patients including 81.63% males with a mean age of 62.93 ± 9.62 years were enrolled. A smoking history in 79.59% of our patients was observed which is probably due to the high percentage of men in our study.

The various patient characteristics are depicted in Table 2.

The data were analyzed based on the frequency of exacerbations. We undertook this study to determine the clinical factors associated with "frequent exacerbator" status within a population of subjects with severe COPD.

The proportion of exposure to pollution was found to be higher in infrequent exacerbation patients (82.35%) as compared to frequent exacerbation patients (71.88%), but this difference was not found to be statistically significant ($P = 0.417$) [Table 3].

Smoking history was similar in both the groups, suggesting a high prevalence of smokers in COPD patients

Table 1: Subjects divided into two groups

Group	Particulars	No. of patients	Percentage
Group A	Infrequent exacerbators	34	34.6
Group B	Frequent exacerbators	64	65.4

Table 2: Patient characteristics

Category	Total percentage (*n*)
Sociodemographics	
Total patients	98
Age (mean), years	62.93 (9.62)
Male%	81.63% (80)
Body mass index	25.93
smokers	81.63% (80)
vaccination	4.08% (4)
Comorbidities	
Diabetes	20.4% (20)
Hypertension	18.3% (18)
IHD	2% (2)
OSA	2% (2)
Pulmonary hypertension	6.1 (6)
Depression and anxiety	38.7% (38)
GERD	81.6% (80)

Table 3: Group comparison of risk factors in patients having different exacerbation frequencies

Variables	Infrequent exacerbation (*n*=34)		Frequent exacerbation (*n*=64)		Statistical significance	
	n	Percentage	*n*	Percentage	χ^2	*P*
Exposure to pollution	28	82.35	53	71.88	0.659	0.417
Smoker	28	82.35	52	81.25	0.009	0.924
Vaccination	0	0.00	4	6.25	1.108	0.293
Family history of URTI	0	0.00	4	6.25	1.108	0.293
BMI (kg/m^2)	25.53	2.07	26.16	2.86	−0.797	0.429

URTI: Upper respiratory tract infection, BMI: Body mass index

Table 4: Group comparison of comorbidities in chronic obstructive pulmonary disease patients having different exacerbation frequencies

Variables	Infrequent exacerbation (*n*=34)		Frequent exacerbation (*n*=64)		Statistical significance	
	No.	%	No.	%	χ^2	'*p*'
Diabetes	8	23.5	12	18.75	0.860	0.354
Hypertension	10	29.41	8	12.50	2.118	0.146
IHD	2	5.88	0	0.00	1.922	0.166
OSA	0	0.00	2	3.13	0.542	0.461
PAH	2	5.88	6	9.38	0.181	0.671
Depression/anxiety	10	29.41	28	43.75	0.961	0.327

IHD: Ischemic heart disease, OSA: Obstructive sleep apnea PAH: Pulmonary hypertension

in general [Table 2]. There was also no statistically significant difference in the comorbidities in between the two cohorts, and the prevalence of depression in frequent exacerbators (43%) was more than that in infrequent exacerbators (23.5%) [Table 4].

None of the patients having infrequent exacerbation was vaccinated while 4 (6.25%) patients of frequent exacerbation were vaccinated.

We found that COPD patients with GER symptoms were more likely to experience exacerbations than those lacking these symptoms. Objectively

Table 5: Group comparison of hematological and biochemical variables in chronic obstructive pulmonary disease patients having different exacerbation frequencies

Variables	Infrequent exacerbation (*n*=34)		Frequent exacerbation (*n*=64)		Statistical significance	
	Mean	SD	Mean	SD	'*t*'	'*p*'
Haemoglobin	10.26	3.10	10.01	2.67	0.877	0.449
WBC	9.78	3.04	9.16	2.46	0.766	0.447
S.Protein	7.09	0.88	6.77	0.83	1.277	0.208
S.Albumin	3.39	0.42	3.48	0.56	−0.558	0.580
S.Urea	46.47	16.71	41.04	19.62	0.969	0.337
S.Creatinine	1.23	0.32	1.13	0.61	0.595	0.555
S.Hematocrit	39.71	10.08	39.25	8.47	0.168	0.867
S.UricAcid	4.43	1.16	5.34	1.48	−2.208	0.032
IgE	171.76	117.55	480.47	410.56	−3.022	0.004

SD: Standard deviation, WBC: White blood cell

Table 6: Multivariate analysis of possible risk factor variables

Risk factor	*R*	*P*
GERD		
Serum uric acid	0.41937	<0.003
Serum IgE	0.57151	0.003
Follow-up frequency	0.3337.	<0.05
Duration of hospital stay	0.4764	<0.05

GERD: Gastroesophageal reflux disease

evaluating the presence of GER in such patients might determine future strategies to reduce or control GER and subsequently, decrease the number of COPD exacerbations.

Spearman correlation analysis results indicated that frequent severe exacerbations were positively correlated with the serum uric acid (UA) level (R = 0.41937: P =0.00271) [Tables 5 and 6 and Figure 1].

Spearman correlation analysis results indicated that frequent severe exacerbations were positively correlated with the serum IgE levels (R = 0.57151: P =0.003) [Figure 2].

DISCUSSION

We found a high percentage of patients with significant comorbidities such as diabetes (20.4%) and hypertension (18.3%) which are consistent with many other comorbidities that may have a significant impact on prognosis. A very high percentage of patients with depression/anxiety (38.77%) and GERD (81.6%) were found in the study group.

Rascon-Aguilar *et al*. demonstrated a correlation between reflux symptoms and high frequency of exacerbations, which suggests GERD as a modifiable risk factor for COPD exacerbations. Analysis of COPD patients receiving antireflux therapy showed that the patients who had controlled or nonsymptomatic GER tended to have a low frequency of exacerbations.[7] A study cohort (ECLIPSE) consisting of 2118 subjects with COPD, 335 smokers without COPD

(smokers), and 243 nonsmokers without COPD (nonsmokers) found that 26%, 12%, and 7% of COPD, smokers, and nonsmokers, respectively, had some forms of depression.

Smoking and air pollution continue to be a significant factor contributing to the high rate of exacerbations in COPD patients. Among all the respiratory conditions, COPD has the most correlation with air pollution and has been linked to rapid expansion of cities and industrialization.[8,9]

A very low patient population (4/88) was found to be vaccinated by either influenza or pneumococcal vaccine. In view of the usefulness of vaccination in preventing serious exacerbations, the low percentage cannot be overlooked. The duration of hospital stay was significantly more in the frequent exacerbation group than in the infrequent exacerbation group [Table 7].

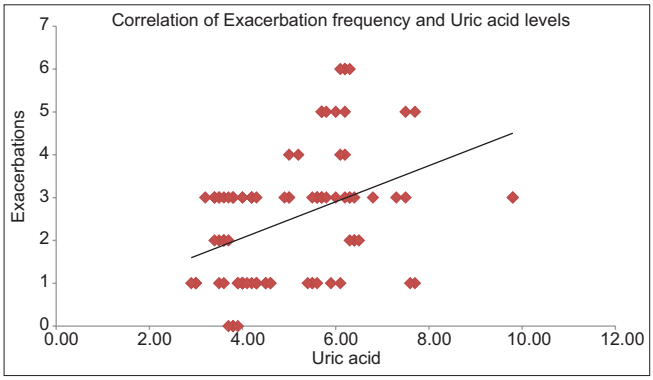

Figure 1: Correlation of exacerbaion frequency and uric acid levels

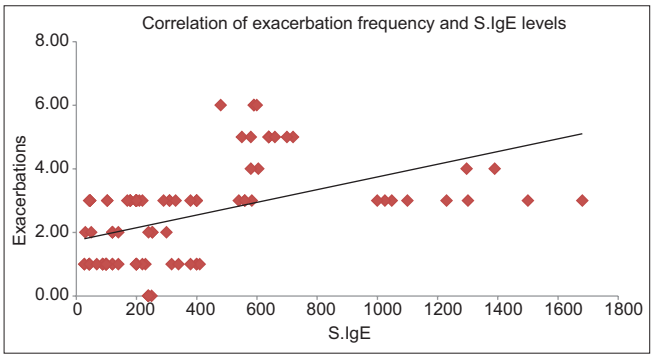

Figure 2: correlation of exacerbation frequency and serum IgE levels

Table 7: Group comparison of hospital stay and clinical data in chronic obstructive pulmonary disease patients having different exacerbation frequencies

Variables	Mean±SD				Statistical significance (*P*)
	Infrequent exacerbation (*n*=34)		Frequent exacerbation (*n*=64)		
Follow-up frequency	6.13	3.43	2.82	3.86	<0.001
Hospital stay (days)	5.00	0.61	6.97	1.80	<0.001
Duration of illness	3	0.72	4	0.61	0.343

SD: Standard deviation

Cao *et al*. conducted a study of 186 patients with moderate to severe COPD having one or more admissions for AEs concluded that male gender, >5 years of disease duration, forced expiratory volume in 1 s (FEV_1) <50% predicted, use of psychotropic drugs, vaccination, and pulmonary rehabilitation were significantly associated with frequent readmissions in COPD.[10]

Elevation of serum UA levels has been observed in hypoxic subjects including patients with COPD. UA is a biomarker of xanthine oxidase activity and is an important source of reactive oxygen species.

Positive correlations were seen between UA levels and inflammatory markers such as C-reactive protein and interleukin-6.[11]

A similar study was done in Japan to find the association between spirometric values and serum UA levels. Forced vital capacity percentage predicted and FEV_1% predicted were significantly associated with UA levels.[12]

A possible explanation given was that hypoxia in subjects with impaired pulmonary function can induce the production of UA, and impaired pulmonary function induces pulmonary hypertension, oxidative stress, and inflammation. Elevated levels of UA cause also cause systemic inflammation which can result in impairment of pulmonary function.

In another recent study, low levels of serum UA were seen to be associated with higher frequency of COPD and lung cancer in smokers.[13]

UA can have a clinically useful role in risk stratification in the first contact setting also requires more evaluation and studies. COPD patients with raised total serum IgE levels had a longer duration of disease, had an earlier onset of breathlessness on the background of chronic sputum production, higher smoking index, frequent exacerbations, and had substandard lung function.[14]

Raised serum total IgE levels may point toward atopy as an additional comorbidity in COPD. Serum IgE levels can be postulated to have an effect on the natural history of progression of COPD or in some cases, may be a useful marker to reflect the severity of disease.

CONCLUSIONS

COPD patients with a high number of previous exacerbations should be carefully evaluated for modifiable risk factors so as bring about a change in the frequency of exacerbations and related morbidity and mortality. Smoking, air pollution, GERD, and depression/anxiety continue to be a significant factor contributing to the high rate of exacerbations in COPD patients. The usefulness of

vaccination in preventing serious exacerbations cannot be overlooked. Raised levels of serum UA and IgE can be found in frequent exacerbators. Raised serum total IgE levels may point toward atopy as an additional comorbidity in COPD while UA can have a clinically useful role in decision-making, however, requires further investigation.

This study however suffers from a recall bias as the previous records and history are directly through interaction with the patient and this could have had an impact on the results.

Frequent exacerbators can be recognized early and adequate measures and treatment advised for betterment of quality of life and prevention of morbidity and mortality.

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Conflicts of interest
There are no conflicts of interest.

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