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Original Research Article

A study of clinical/biological markers of exacerbation/progression in a cohort of patients admitted with acute excerbation of COPD

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ABSTRACT

Background: Exacerbations of chronic obstructive pulmonary disease increases the morbidity, hospital admissions, mortality, and strongly influence health-related quality of life. The aims of this study to know the Clinical profile of COPD and acute exacerbation, Role of clinical markers in diagnosis and follow up of exacerbation.
Methods: A prospective study of a cohort of 60 patients hospitalized for AECOPD was undertaken to identify markers for frequent exacerbation and progression of disease. Advised to fill the SGRQ questionnaire, At the time of discharge 6MWT done and analyzed. C Reactive protein levels at the time of admission done and analyzed. Sputum grams stain culture, total counts and differential counts done and analyzed. At the time of discharge spirometry done both pre and post bronchodilators by using asthalin inhaler with or without spacer, results were analyzed.
Results: There was statistically significant drop in the SPO2 levels in frequent exacerbators over 6 months follow up time. There was statistically significant elevation of sputum Neutrophil counts in frequent exacerbators and Eosinophil counts in infrequent exacerbators, there was a drop in the CRP levels of from the time of initial exacerbation to 6 months follow up time. There was statistically significant drop in FEV1 in frequent exacerbators over 6 months follow up study. The drop of 6MWT was more in patients, who had frequent exacerbations.
Conclusions: Patients with more frequent exacerbation have more symptoms, drop in the saturation level and have more sputum neutrophil counts. Patients with more frequent exacerbations will have more deterioration of lung functions (FEV1.6MWT).

Keywords: Biomarkers, COPD, Exacerbation, Pulmonary function test, Smoking

INTRODUCTION

COPD is defined as a common preventable and treatable disease is characterized by persistent airflow limitation that is usually progressive and associated with enhanced chronic inflammatory response in the airways and lung to noxious particles or gases.[1] COPD is a major cause of health care burden worldwide and the only leading cause of death that is increasing in prevalence. COPD prevalence was 8% according to the BTS guidelines and 14% according to GOLD criteria in 2003.[2] On reviewing the different population studies from India, it was reported that the COPD prevalence rates in male subjects had varied from 2.12-9.4% in studies from North and 1.4-4.08% from South India.

Exacerbations of chronic obstructive pulmonary disease increases the morbidity, hospital admissions, mortality, and strongly influence health-related quality of life, some patients are prone to frequent exacerbations, which are associated with considerable physiologic deterioration and increased airway inflammation. Patients are at

increased risk of readmission and 34% of patients were readmitted with a recurrent exacerbation within the 3months following their discharge.[3] Exacerbations are associated with the acute production of increased levels of a variety of endogenous inflammatory mediators and cytokines and are heterogeneous at a cellular level, have clinical implications, some of the well-known biomarkers of inflammation are CRP, BNP, Serum Fibrinogen, TNF-A, IL-6, IL-8, Procalcitonin, neutrophils, there was a significant rise of inflammatory markers serum IL-6, serum CRP and sputum IL-6 at exacerbation.[3]

The most common cause for exacerbation is infection. These infective episodes may be due to bacterial, viral and rarely fungal infections, these exacerbation episodes accelerate lung function decline and considerably increases the morbidity, mortality and healthcare costs, some patients are prone to frequent exacerbations and these patients have worse health status, greater limitation of their daily activities, and faster disease progression.[4] Studies have shown that after the index exacerbation, patients are at increased risk of readmission and Donaldson and Wedzicha JA et al. showed that 34% of patients were readmitted with a recurrent exacerbation within the 3months following their discharge for exacerbation.[3] Hence it is necessary to identify factors that are associated with exacerbation and progression of disease following exacerbation.

In this study we plan to follow a cohort of patients with AECOPD with serial clinical and laboratory markers and look for parameters that are associated with exacerbation and progression of disease. This will help to identify: Clinical profile of COPD and acute exacerbation; Role of clinical markers in diagnosis and follow up of exacerbation; Study which serial lab value helps to project the disease progression; Understanding might help to improve treatment of COPD.

METHODS

A prospective study of a cohort of 60 patients hospitalized for AECOPD was undertaken to identify markers for frequent exacerbation and progression of disease. Institution ethical committee approved our and consent was taken from patient's attenders for enrolling in our study. The Study criteria includes: Patients diagnosed as COPD (GOLD guidelines) with FEV1/FVC <70% and no significant reversibility after inhaled bronchodilators who attended the St. John's hospital OPD and Emergency from January 2012 to October 2012; Age 40-85years; Pts in acute exacerbation and excludes: Patients suffering from other Obstructive lung disease like Bronchial asthma and airway diseases like Bronchiectasis and interstitial lung diseases; Patients suffering from other chronic inflammatory diseases like Tuberculosis, leprosy, sarcoidosis, Collagen vascular/Connective tissue diseases e.g. Rheumatoid arthritis; Patients suffering from acute coronary event in the last 3weeks.

After proper history, initial assessment and evaluation done, the first venous sample was taken in the ward and appropriate treatment started according to standard hospital protocols. Routine blood investigations were done, and the results analyzed. Chest X rays were ordered and interpreted. The findings ranged from a normal Chest X ray to hyper inflated lung fields to infiltrates. Arterial blood gases done to look for the respiratory failure and to rule out other metabolic causes, SPO2 monitored for the titration of O2. GRBS level done and analyzed. C Reactive protein levels at the time of admission done and analyzed. Sputum grams stain culture, total counts and differential counts done and analyzed. At the time of discharge spirometry done both pre-and post-bronchodilators by using asthalin inhaler with or without spacer, results were analyzed. Advised to fill the SGRQ questionnaire, at the time of discharge 6MWT done and analyzed. During the follow up study i.e. at the end of 2nd month and 6th month repeated SGRQ questionnaire, CRP levels, GRBS levels, blood TC/DC sputum TC/DC, SPO2, 6MWT and Spirometry done and analyzed.

Descriptive and inferential statistics has been used. Continuous variables are presented as Mean $\pm$SD (range) and categorical variables are presented as proportion (%). Statistical significance was assessed at a P value <0.05. Student t test (two tailed, independent) was used to find the significance of continuous variables between two groups. The Statistical software's SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel were used to generate graphs, tables etc.

RESULTS

We found there was statistically significant improvement of the SGRQ questionnaire, symptoms domain and total (global) domain in control groups. There was statistically significant drop in the SPO2 levels in frequent exacerbators over 6 months follow up time, there was statistically significant elevation of sputum neutrophil counts in frequent exacerbators and Eosinophil counts in infrequent exacerbators. There was a drop in the CRP levels of from the time of initial exacerbation to 6 months follow up time. There was statistically significant drop in FEV1 in frequent exacerbators over 6months follow up study. The drop of 6MWT was more in patients, who had frequent exacerbations.

DISCUSSION

Exacerbations of chronic obstructive pulmonary disease increases the morbidity, hospital admissions, mortality, and strongly influence health-related quality of life, some patients are prone to frequent exacerbations, which are associated with considerable physiologic deterioration and increased airway inflammation. Half of COPD exacerbations are caused or triggered primarily by

bacterial and viral infections (rhinovirus), but air pollution can contribute to an exacerbation.[3]

Table 1: The baseline laboratory parameters of the patients (cases and controls) with COPD.

Characteristic	Controls (n=20)	Cases (n=40)	P value
Hemoglobin	13.25±1.3	12.94±1.44	0.046*
Total counts	11456.34 ± 1678.56	12348.32±1898.59	<0.001**
GRBS	158.9±22.08	170.58±25.6	<0.001**
Spo2	86.45±3.65	86.18±3.71	<0.001**
CRP	10.70±0.98	16.40±1.22	0.341
Sputum Neutrophils	67.65±6.05	72.05±6.57	0.015*
Lymphocytes	26.35±4.69	23.67±5.10	0.055+
Eosinophils	4.70±1.56	3.68±1.66	0.028*

Table 2: The comparison of SGRQ over 6months in patients (cases and controls) with COPD.

Characteristic	Mean ± standard deviation			P value
	Admission	2nd month	6th month	
Symptoms domain cases/controls	78.46	76.46	79.76	0.042
	56.46	54.64	52.26	<0.001*
Activity domain cases/controls	64.56	63.56	64.64	0.056
	46.24	45.64	42.84	0.034*
Impact domain cases/control	82.46	83.36	82.42	0.074
	72.42	71.26	68.46	0.0327*
Total cases/controls	74.34	74.24	74.42	0.046*
	62.34	62.42	58.46	<0.001*

Table 3: The comparison of Laboratory parameters between Cases and Controls over 6months.

Characteristic	mean ± standard deviation			f value	P value
	Admission	2nd month	6th month		
Haemoglobin					
Cases Controls	12.94±1.44	12.92±1.25	12.81±1.25	F=2.487	P=0.090+
	13.25±1.3	13.16±1.47	13.08±1.44	F=1.154	P=0.326
Total counts					
Cases Controls	12348.32±1898.59	11340.24±674.52	9678.46±742.42	F=129.733	P<0.001**
	11456.34 ± 1678.56	10468.26±548.42	8964.56±642.42	F=246.643	P<0.001**
Sputum neutrophils					
Cases	72.05±6.57	70.04±4.57	68.56±4.34		0.015*
Controls	67.65±6.05	60.34±5.85	54.56±6.23		0.025*
Spo2					
Cases	86.18±3.71	88.18±2.23	85.68±3.15	F=11.128	P<0.001*
Controls	86.45±3.65	87.95±2.93	88.65±2.62	F=4.021	P=0.026*
GRBS					
Cases	170.58±25.6	139.88±22.4	122.35±19.	F=177.810	P<0.001*
Controls	158.9±22.08	129.75±19.4	111.45±17.	F=79.338	P<0.001**
CRP					
Cases	16.40±1.22	10.16±0.42	4.73±0.21	F=12.124	0.341
Controls	10.70±0.98	7.21±0.39	1.73±0.2	F=14.242	0.704

More severe exacerbations are associated with increased airway and systemic inflammation; patients with increased airway inflammation show faster FEV1 decline; this explains disease progression due to severity of exacerbation.[5] Studies by. Wedzicha JA et al shown that after the index exacerbation, patients are at increased

risk of readmission and 34% of patients were readmitted with a recurrent exacerbation within the 3months following their discharge.[3] In a study by Donaldson GC et al, patients were divided into frequent (>2 exacerbations/year) and infrequent (<2 exacerbations/year) exacerbators, the patients with history of frequent exacerbation had faster FEV1 decline than patients who had infrequent exacerbations.[6] Jadwiga A. Wedzicha and Gavin C. Donaldson in their study, measured the effect of exacerbation frequency on quality of life with the St George's Respiratory Questionnaire (SGRQ), which showed clearly that those who had >2 exacerbations were significantly effected as compared to those who had <2 exacerbations in a year.[5] CRP is an acute phase reactant protein which is part of the pentraxin group.

It is a pattern recognition molecule, binding to specific molecular configurations that are typically exposed during cell death or found on the surfaces of pathogens. Its rapid increase in synthesis within hours after tissue injury or infection suggests that it contributes to host defense. CRP was considered for the study because of relatively faster processing, it is easier availability and reproducibility. It has been well evaluated in the setting of acute coronary syndromes as well as acute inflammatory states for prognostication and for the management. Few studies showed significant association between the elevation of CRP and AE-COPD.

Age distribution in our study group: Our study subjects were 60 in number, whose age ranged from 50-84 years with a mean age of 64.25years and SD of ±8.67. Asthana et al have reported in a group of 1501 COPD patient that the mean age was 44.7years with an SD of ±11.1 years.[7] Mean age of 69.3years with SD of ±7.8 was reported in a group of 73 subjects, by Perera et al.[8] A study by Lange et al showed that the age distribution of COPD was more than 40 years, and the subjects who smoked more than 25years have 30-40% of increased risk of developing COPD.[9]

BMI: In our study group the average BMI was 19.77 with a standard deviation of ±3.23. 46.7% of the patients had normal BMI and 45% had a BMI of less then18.5 Jorgen Vestbo postulated that though BMI is an indicator of poor prognosis in COPD patients, fat free mass index was crucial to prognosticate mortality in patients. A Study of 1898 patient in Copenhagen found that even in patients whose BMI was normal, morbidity and mortality is more affected in patients with reduced FFMI (FFMI; fat-free mass/weight^2).[10] In a study done by Perera et al found that the mean BMI was 26.2 with SD of ±6.43.[11]

This is in contrast to the study done by Raida et al shown that patients with BMI of 21 and less had a higher risk of exacerbation.[12] In comparison to the above studies our study group average BMI was 19.77, possibility of difference may be due to Nutritional deficiency and Ethnicity.

Duration of symptoms: COPD typically presents after a minimum 20years of smoking. So, symptoms start in the 4th or the 5th decade. In our study, we found that the duration of COPD >10years was 35 (58.3%) whereas duration <10years was 25 (41.7%).

Smoking: In our study, smokers were 45 (75.0%) which was significantly high. appears to be an important risk factor for the development of COPD and remaining 15 (25%) people were non-smokers developed COPD, had history of exposure of biomass.

Current smokers were 29 (48.33%), has statistically significant association with frequency of exacerbations, and the mean pack years was 20-30 pack years, Carolyn E. Behrendt, showed approximately one fourth of the COPD cohort is non-smokers and the etiology can be ascribed to biomass exposure, and genetic predisposition.[13] In comparison to the above studies our study group showed the mean pack years was 20 to 30, possibility of the difference may be due to the type of the cigarettes, age of start of smoking.

Correlation of SGRQ in cases and controls: Of the 60 subjects, 40 cases who were considered to be had frequent exacerbations in the last 6months, 20 patients were controls, who had less frequent exacerbations in the last 6months, comparison between these two groups, found there was statistically significant improvement of the symptoms domain and total (global) domain in control groups. Jadwiga A Wedzicha et al states that patients who suffered infrequent exacerbations <2 in the previous year had less symptoms compared patients who suffered frequent exacerbations (3to 8 in the previous year).[14]

Correlation of Sputum Neutrophil counts in cases and controls: In our study we found the sputum Neutrophil counts were elevated in cases, whereas Eosinophil counts were elevated in controls at the time of admission, which was statistically significant, and over a period of 6months' time the drop of neutrophils were more in controls, the levels of neutrophil counts were more in people having frequent exacerbation possibly because the people with high neutrophil counts had decreased response to inhaled corticosteroids, along with other factors like smoking and this will explains possibility of poor controlled COPD.

Whereas the more Eosinophil counts in the sputum in controls explains the good response with inhaled steroids with good control of disease. J.A. Wedzicha, et al explains, the predominance of neutrophils in the sputum is associated with a poorer prognosis.[15]

Correlation of CRP at admission and follow up: In our study group, CRP levels checked at the of admission and during the follow up study, we found, the CRP levels at the time of admission in cases was 16.40, where as in controls 10.70 and dropped to 4 .73 and 1.73 in cases and

controls. Paul Man et al showed that CRP levels dropped significantly with treatment with corticosteroids in patients with acute exacerbation of COPD.[16]

Correlation of spirometry in cases and controls: A comparison study between cases and controls over 6months observed that in cases FVC was dropped from 2.83-2.57, whereas in controls 2.77-2.66 with percentage of change was 9.18% and 3.97%.

Similarly, the FEV1 value in cases was dropped from 1.50-1.35, whereas in controls from 1.50-1.47 with percentage of change was 10% and 2% with significant P value. Drop of FEV1/FVC ratio in cases from 53.59 to 46.48%, whereas in controls from 54.85 to 50.78 with percentage of change is 13.26 and 7.42%, the patients who had frequent exacerbations (>4exacerbation/year) had more drop of lung volumes (both FVC and FEV1) compared to the people who had less frequent exacerbations (<4exacerbation/year). Jadwiga A Wedzicha and Gavin C Donaldson states that patients who suffered infrequent exacerbations <2 in the previous year had less drop in the FEV1 compared to the patients who suffered frequent exacerbations (3to 8 in the previous year).[17]

Correlation of 6MWT in cases and controls: A comparison study of 6MWT between cases and controls over 6months showed that it has dropped from 391.45 to 366.63 in cases, whereas in controls from 377.15 to 366.75.

The people who had frequent exacerbation (>4exacerbation/year) had more drop of 6MWT compared to the peoples who had less frequent exacerbation (<4 exacerbations). Celli, et al found that the 6MWD declined by 72m. year following the exacerbation and more in frequent exacerbators in 2year follow up study.[15]

The limitation of the study was the study group was 60. Valuable data is obtained in studies with large Study groups. Longer the duration (>1year) of the study, would have better Results (COPD is a chronic disease).

CONCLUSION

Current smoking has significant association with frequency of exacerbations. Patients with more frequent exacerbation have more symptoms, drop in the saturation level and have more sputum neutrophil counts. Patients with more frequent exacerbations will have more deterioration of lung functions (FEV1.6MWT).

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