



ROLE OF BLOOD EOSINOPHIL COUNT AS A PREDICTOR OF EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ARTICLE INFO

Article History:

Received 10th October, 2019

Received in revised form 2nd

November, 2019

Accepted 26th December, 2019

Published online 28th January, 2020

Key words:

Chronic obstructive pulmonary disease,

Exacerbation, Eosinophilia

ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is currently the fourth leading cause of death world wise. The clinical course of the disease is marked by exacerbations. In 10-40% of COPD cases eosinophilic airway inflammation have been reported during both stable disease and exacerbations. The clinical characteristics of individuals with COPD and high levels of blood eosinophils are likewise largely unknown. The aims of the study was to assess correlation of blood eosinophils as a predictor of exacerbations of COPD patients.

Methods: This was a hospital based prospective observational study. A total number of 153 COPD patients were included in the study. The diagnosis of COPD was based on symptoms and was confirmed by spirometry.

Results: Out of the total (153) COPD patients included in our study, (92)60.13% were males and (61)39.87% were females. Among these patients, (98)64.05% patients had exacerbation, out of which, (68)69.38% patients were male and (30)30.61% patient were female. In this study it was shown that mean blood eosinophil count and absolute eosinophil count in 68 male COPD exacerbation was 3.22 ± 1.16 and 0.32 ± 0.13 respectively and in 30 female patients with COPD exacerbation, it was 3.47 ± 1.01 and 0.33 ± 0.11 respectively. Blood eosinophil $> 2\%$ was in 43.80% male patients and 17.0% female patients respectively with exacerbation and 3.92% male patients and 5.88% female patients respectively without exacerbation. The p value was 0.0191, which was significant.

Conclusion: In this study it was found that exacerbation rates increased progressively with increasing eosinophil counts in percentage of leukocytes starting at 2%.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is currently the fourth leading cause of death world wise [1]. It is projected to rank third among all causes of death by 2020[2]. WHO estimates suggest that 90% of COPD-related deaths occur in low and middle income countries [3]. India and China constitute 33% of the total human population and account for 66% of the global COPD mortality [3].

The natural history of COPD are cough, phlegm and exertional dyspnea which vary over time in each individual patient and are often underreported. Severity of symptoms often correlates poorly with loss of lung function and hence most cases have severe obstruction by the time they seek medical help [4].

The clinical course of the disease is marked by exacerbations. These are events where there is increase in severity of symptoms which warrant an increase in intensity of treatment [1]. COPD exacerbations of the disease are associated with poor quality of life as well as increased morbidity and mortality[5, 6].

During exacerbations, inflammation in the airway increases and while this inflammation in COPD patient is primarily neutrophilic, in some patients it is associated with an increased sputum eosinophil count of more than 3% [7,8]. In 10-40% of COPD cases eosinophilic airway inflammation have been reported during both stable disease and exacerbations [9, 10]. Evidence suggests that this eosinophilic inflammatory endotype can be identified in stable disease states and that sputum eosinophilia in stable conditions predicts the eosinophilic endotype of a future exacerbation[8]. Furthermore, sputum eosinophilia during stable disease is associated with a favourable response to corticosteroid therapy [9,11].

In clinical studies of COPD patients, there is a fair correlation between blood and sputum eosinophil counts with a differential count of 2% or higher in blood and a positive predictive value of 90% for an increased sputum eosinophil count, suggesting that blood eosinophils might be a more easy accessible biomarker of eosinophilic airway inflammation[8]. It has been suggested that blood eosinophil in COPD patients can be used to direct systemic corticosteroid therapy during exacerbations [12] and a recent post-hoc analysis found that

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COPD patients with high levels of blood eosinophils have greater reduction in exacerbation rates when treated with an inhaled corticosteroid [13,14]. In general population settings, it is largely unknown whether higher levels of blood eosinophils are associated with increased exacerbations among individuals with COPD. The clinical characteristics of individuals with COPD and high levels of blood eosinophils are likewise largely unknown in this setting. Keeping all these points in mind an attempt was made to undertake this study with the aims to assess correlation of blood eosinophils as a predictor of exacerbations of COPD patients.

MATERIALS AND METHODS

This was a hospital based prospective observational study carried out in the Department of Pulmonary Medicine, Different units of Internal Medicine and allied specialties, Gauhati Medical College & Hospital, Guwahati, from 1st July 2017 to 30th June 2018. A total number of 153 COPD patients were included in the study. Ethical clearance was obtained from the Ethical Committee of the Institution prior to the onset of study. Patients with bronchial asthma, interstitial lung diseases, malignancy, bronchiectasis, patients not giving consent and patients of COPD on inhaled corticosteroids were excluded from the study.

The diagnosis of COPD was based on symptoms and was confirmed by spirometry. Any subject having history of dyspnea or chronic cough or sputum production for at least three months in two consecutive years, with history of exposure to risk factors (tobacco smoke, environmental tobacco smoke [ETS], biomass fuel smoke, occupational dusts along with a post-bronchodilator forced expiratory volume in 1st second/forced vital capacity ratio (FEV1/FVC) <70% was confirmed as COPD.

An exacerbation is defined as an event in the natural course of the disease characterized by a change in the patient’s baseline dyspnea, cough, and / or sputum that is beyond the normal day-to-day variations, is acute in onset and may warrant a change in regular medication in a patient with underlying COPD. On the basis of the post bronchodilator FEV1 % predicted, stable COPD patients were classified into- Stage I – Mild COPD : FEV 1 /FVC < 0.70, FEV 1 ≥ 80% ,Stage II – Moderate COPD : FEV 1 /FVC < 0.70, 50 % ≥ FEV 1 < 80% ,Stage III – Severe COPD : FEV 1 /FVC < 0.70, 30% ≥ FEV 1 < 50% and Stage IV– Very severe COPD : FEV 1 /FVC < 0.70, FEV 1 < 30%. Blood eosinophil count is measured in % & in number of cells per liter (109 Cells/L) for every patient in the study at baseline.

The descriptive statistical analysis of data has been done. The age and sex distribution of all patients, severity of COPD, exposure history, blood eosinophil counts and its relation to COPD have been represented graphically. Statistical analysis of data was done using SPSS 20. Appropriate statistical methods were applied as and when necessary. P values less than 0.05 were considered as statistically significant.

RESULTS AND OBSERVATION

A total number of 153 COPD patients, 92 (60.13%) were males and 61(39.87%) were females were included in the study. The male to female ratio was 1.51:1.0. The highest number of cases 35.95 % were seen in the age group of 60 – 69 years followed by 32.68% in the age group of 70 -79 years.

The mean age of the patients with standard deviation was 68.08 ±10.71.[Table:1]

Table 1 Age wise distribution of cases

Age group in years	Number of patients	Percentage
40 – 49	10	6.54
50 – 59	18	11.76
60 – 69	55	35.95
70 – 79	50	32.68
80 – 89	20	13.07
TOTAL	153	100

In this study it was seen that the highest number of cases (87.58%) presented with cough followed by shortness of breath in 81.04% of patients. Fever was the presenting complaint in 39.22%, drowsiness in 22.88% patients, and chest pain in 14.37 % of cases.[Table:2]

Table 2 Clinical features of the total cases in the study group

Presenting complaints	Number	Percentage
cough	134	87.58%
Shortness of breath	124	81.04 %
Fever	60	39.22 %
Drowsiness	35	22.88 %
Chest pain	22	14.37 %

In this study of 153 patients, stage 1, stage 2, stage 3, and stage 4 COPD cases were 12(7.84%), 54(35.29%), 54(35.29%) and 33(21.58%) respectively. Least number of cases were in stage 1 followed by stage 4 COPD.[Table:3]

Table 3 Distribution of cases in various stages of COPD

Stages	Total Cases	Percentage
1	12	7.84
2	54	35.29
3	54	35.29
4	33	21.58

In this study, it was found that among male patients, 35(38.04%) patients were in stage 2, 30(32.60%) patients in COPD stage 3, 19(20.65%) patients in COPD stage 4 and 8(8.69%) patients in stage 1 of COPD. The highest numbers of cases were seen in the stage 2 and lowest numbers of cases were in stage 1 of COPD. In female, highest number of cases 24(39.34%) were seen in the stage 3 followed by 19(31.1%) cases in the stage 2, 14(23.0%) cases in the stage 4 of COPD and 4(6.6%) cases were in the stage 1 of COPD.[Table:4]

Table 4 Gender wise distribution of cases in various stages of COPD

Stages	Male	Percentage	Female	Percentage
1	8	8.69	4	6.6
2	35	38.04	19	31.1
3	30	32.60	24	39.34
4	19	20.65	14	23.0

In this study out of 153 patients 98(64.05%) patients had exacerbation. Patient came with exacerbation in different stage of COPD were 8, 30, 35, and 25 in stage 1, 2, 3 and 4 respectively. Highest cases of exacerbation (35.71%) was in the stage 3 and lowest (8.17%) in the stage 1 of COPD.[Table:5]

Table 5 Number of patients in exacerbation in various stages of COPD.

Stages	Total(exacerbation)	Percentage
1	08	8.17
2	30	30.61
3	35	35.71
4	25	25.51
total	98	100

Out of 98 COPD patients with exacerbation 68(69.38%) patients were male and 30(30.61%) patient were female. Maximum number of male patients (68.57%) was in COPD stage-3 followed by COPD stage-2 and maximum number of female patients in COPD stage-2 followed by COPD stage-3.[Table:6]

Table 6 Gender wise distributions of patients in exacerbation in various stages of COPD.

Stages	Male	Percentage	Female	Percentage
1	06	75	02	25
2	20	66.67	10	33.33
3	24	68.57	11	31.43
4	18	72	07	28

Eosinophil percentage was calculated and it was observed that, in male and female patients eosinophil percentage and mean was 2.82, 2.53 and 2.70 +/- 1.23 respectively. The Eosinophil count (109 cells/L) in males was 0.29 and in females was 0.27±0.23 and mean Eosinophil count(109 cells/L) was 0.28 +/- 0.17.[Table:7]

Table 7 Gender wise distribution of mean eosinophil count

Gender	Eosinophil count (%)	SD	Eosinophil count (109 cells/L)	SD
Male	2.82	1.23	0.29	0.13
Female	2.53	1.21	0.27	0.23
Both	2.70	1.23	0.28	0.17

In this study it was shown that mean blood eosinophil count and absolute eosinophil count in 68 male COPD exacerbation was 3.22±1.16 and 0.32±0.13 and in 30 female patients with COPD exacerbation it was 3.47±1.01 and 0.33±0.11.[Table:8]

Table 8 Distribution of mean blood eosinophil count with gender wise exacerbation.

Gender	BE (%)	SD	ABE	SD	Exacerbation	Exacerbation (%)
Male	3.22	1.16	0.32	0.13	68	44.44
Female	3.47	1.01	0.33	0.11	30	19.61
Both	3.30	1.12	0.32	0.12	98	64.05

Mean blood eosinophil count in percentage (BE (%)) was calculated and it was shown that mean blood eosinophil percentage was 2.1,2.71, 3.59, 4.01 in stages 1, 2, 3, 4 of COPD respectively. Highest mean blood eosinophil percentage was found in COPD stage-4 followed by COPD stage-3 and COPD stahe-2.[Table:9]

Table 9 Distribution of mean eosinophil count with number of cases with exacerbations in different stages of COPD

Stages	BE (%)	SD	Number of cases in exacerbation
1	2.10	0.43	08
2	2.71	0.69	30
3	3.59	0.98	35
4	4.01	1.25	25

In this study it was shown that blood eosinophil > 2% was in 67(43.80%) of male and 26(17.0%) of female patients with exacerbation and 6(3.92%) of male patients and 9(5.88%) of female patients without exacerbation. The p value was 0.0191, which was significant.[Table:10]

Table 10 Gender wise distribution of cases with blood eosinophil count (≥ 2%) and exacerbation

Gender	No. of cases of exacerbation, (BE% ≥ 2)	Percentage of total cases	No. of cases without exacerbation, (BE% < 2)	Percentage Of total cases	P value
Male	67	43.80	06	3.92	0.0191
Female	26	17.00	09	5.88	
Both	93	60.78	15	9.80	

It was also shown that patients with COPD exacerbation with blood eosinophil count <2% in male and female patients was 1(0.65%) and 4(2.61%) respectively, and blood eosinophil count <2% in patients without COPD exacerbation was 18(11.76%) and 22(14.38%) in male and female patients respectively, which was statistically not significant. [Table:11]

Table 11 Gender wise distribution of cases with blood eosinophil count (< 2%) and exacerbation

Gender	No.of cases of exacerbation, (BE% < 2)	Percentae of total cases	No.of cases without exacerbation, (BE% < 2)	Percentage of total cases	P value
Male	01	0.65	18	11.76	0.3783
Female	04	2.61	22	14.38	
Both	05	3.27	40	26.14	

DISCUSSION

In this study total 153 patients was included, out of which 92 (60.13%) were males and 61 (39.87%) were females and male to female ratio was 1.51 : 1.0. The mean age of the patients with standard deviation was 68.08 ± 10.71. The finding in our study is comparable to the previous multi-centric study done by S K Jindal *et al*, conducted in both the urban and the rural populations at Bangalore, Chandigarh, Delhi and Kanpur including 1450 cases of COPD with male to female ratio of 1.56 : 1.36 [15].

The mean age of the patients with standard deviation was 68.08 ± 10.71. The cases were between the ages of 40 – 89 years. The highest number of cases, (35.95 %) were seen in the age group of 60 – 69 years followed by 32.68 % in the age group of 70 –79 years. The lowest number of cases, 6.54% was seen in the age group of 40-49 years. In the study done by D Gothi *et al*, the cases of COPD were above 40 years of age with mean age 54 years (age range 40 to 75 years)[16].

In this study it was seen that the highest number of cases (87.58%) presented with cough followed by shortness of breath. (81.04%). Fever was seen in 39.22% patients and drowsiness in 22.88% patients. In a study conducted by Teeku Sinha *et al*, in 75 cases to study the clinical profile of patients with COPD, it was found that incidence of shortness of breath was 100%, cough in 48%, expectoration was 26%, Edema was 17.33 % and chest pain was 2.67% [23]. On a similar study by Kormmann *et al* it was seen that in 210 patients of COPD, cough was present in 84% cases whereas dyspnea was the presenting complaint in 70% cases [17].

In this study, out of 153 diagnosed cases of COPD, 7.84% cases were classified as mild (stage I), 35.29% as moderate (stage II), 35.29% as severe (stage III) and 21.58% as very severe COPD. Highest number of cases (35.29%) belonged to stage III or severe COPD which was equal to stage II. In the study by Kornmann *et al*, based on GOLD criteria, 37% had 0, 5% had I, 46% had II and 12% had III COPD [19]. In the OLIN(ObstructiveLung disease in Northern Sweden) study by Lindberg *et al*, 8.2% had mild COPD, 5.3% had moderate COPD, 0.7% had severe and 0.1% had very severe COPD [18].

In our study of 153 diagnosed cases of COPD, mean blood eosinophil (%) was 2.70. Among male patients mean blood eosinophil (%) was 2.82% and among females patients it was 2.53%. In our study, 98 cases (64.05%) had exacerbation; the mean blood eosinophil (%) of those patients was 3.30. Out of 98 cases, 68(69.39%) males had exacerbation whose mean

blood eosinophil(%) was 3.22 and 30(30.61%) female patients had exacerbation whose mean blood eosinophil(%) was 3.47. Maximum cases (22.88%) with exacerbations with mean blood eosinophil(%) of 3.59 was in the stage III of COPD followed by 19.61% in stage II with mean blood eosinophil(%) of 2.71 and 16.34% was in stage IV of COPD with mean blood eosinophil of 4.01 %. Least cases(5.23%) with exacerbation were reported in stage I of COPD with mean blood eosinophil (%) of 2.10.

In our study of 153 diagnosed cases of COPD, 108(70.59%) patients had blood eosinophil (%) $\geq 2\%$. Out of 108 patients, only 93(60.78%) patients came with exacerbation during follow up period. In males 67(43.80 %) patients and in females 26(17%) patients had exacerbation when blood eosinophil(%) $\geq 2\%$. P value was calculated and it was found 0.0191, which was statistically significant. Out of 98 cases of exacerbation, only 5(3.27%) patients had exacerbation with blood eosinophil (%) < 2 .

In a study conducted by Signe Vedel-Krogh et.al in Copenhagen general population with regard to exacerbations and characteristics of individuals with COPD with blood eosinophils above versus below 2%, 63% of all participants in the Copenhagen General Population Study had an eosinophil count equal to or above 2% [19]. Findings in our study is comparable with the Copenhagen general population study.

In our study, it was also observed that out of 153 patients of COPD, 45 (29.41%) patients had blood eosinophil (%) less than 2 and 5(3.27%) patients came with exacerbation during follow up period of 1 year. Study conducted by Singh D et.al, in the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) study cohort, only 37% of the patients with COPD had persistently increased blood eosinophils at or above 2%, but in the same study only 14% had no eosinophil count greater than or equal to 2% in the 3-year observation period [20].

In our study 70.59% of patients had blood eosinophil (%) $\geq 2\%$. The study done by Pavord ID et.al showed depending on what cut-off is used, a large number of patients with COPD may have “elevated” blood eosinophil counts; a review of three large trials found that 57–75% of patients with COPD had blood eosinophil levels $\geq 2\%$ [21]. In a study of Pascoe S et.al. it was found that exacerbation rates increased progressively with increasing eosinophil counts in percentage of leukocytes starting at 2%, indicating that blood eosinophils could be used as a prognostic marker of future COPD exacerbations [22].

CONCLUSION

In this study it was found that exacerbation rates increased progressively with increasing eosinophil counts in percentage of leukocytes starting at 2%. It indicates that blood eosinophils could be used as a prognostic marker of future COPD exacerbations.

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How to cite this article:

Ritesh Kumar, Basanta Hazarika and Jogesh Sarma (2020) 'Role of Blood Eosinophil Count as A Predictor of Exacerbation of Chronic Obstructive Pulmonary Disease', *International Journal of Current Advanced Research*, 09(01), pp. 21066-21070. DOI: <http://dx.doi.org/10.24327/ijcar.2020.21070.4131>
