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ASSOCIATION BETWEEN EOSINOPHIL LEVEL AND PREDICTION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE EXACERBATION

[1]Ahmed Rabeih Mohammed, [2]Mostafa I. Ragab,[3] Ali Nagat Mohammed,[4] Maha E. Alsadik

Chest Diseases Department, Faculty of Medicine, Zagazig University, Egypt.

Corresponding author: Ahmed Rabeih Mohammed, Email:a7medbi3a@gmail.com

ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is a common treatable and preventable diseasecharacterized by progressive airflow limitation with an enhanced chronic inflammatory response in the airways.Acute exacerbation of COPD is associated with substantial morbidity and mortality.This study aimed to predict the outcome and future risk of COPD exacerbations and to improve the health quality of COPD patients.**Patients and methods:** A Cohort prospective study was designed to investigate thirty four hospitalized COPD patients with COPD exacerbation whether in the ward or in the ICU and follow up them for 12 months.**Results:**Outcome of the exacerbation at admission among the studied patients; 32.4% of had sputum eosinophilia and most of them (76.5%) received LABA as treatment before admission. There was no statistically significant association between eosinophils level at admission and the outcome among the studied group where one patient (9.1%) died among patients with eosinophilia≥2% and also one patient (4.3%) died among patients with eosinophils<2%.Only (31.25%) of the survived patients had sputum eosinophilia(>1.25%), half of them (50.0%) had future single exacerbation, about one third (34.4%) had two exacerbations and (15.6%) had no further exacerbations. all of them (100.0%)received LABA, LAMA and ICS as a triple therapy. There was statistically significant higher TLC, neutrophil count and longer hospital stay among patients with eosinophils<2% than patients with eosinophils ≥2%. But regarding degree of exacerbation, management and outcome, there was no statistically significant difference between patients with low and high eosinophilia**. Conclusion:**High neutrophil level in peripheral blood duringfollow up period of COPD patients, besides low eosinophil level in both blood and sputum are considered predictor factors for future COPD exacerbations.

Keywords: COPD;Eosinophils; Neutrophil;CAT Score; Exacerbations

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major health problem due to its high prevalence, increasing incidence, and associated familial, social, and economic burdens **(1)**.Acute exacerbations of chronic obstructive pulmonary disease (COPD) substantially contribute to high morbidity and mortality rates worldwide which leads to an economic and social burden **(2)**.The prevalence of COPD is directly related to the prevalence of tobacco smoking, although in many countries, outdoor, occupational and indoor air pollution resulting from the burning of wood and other biomass fuels are major COPD risk factors **(3)**.

Lung injury in emphysema occurs as a result of inflammatory and destructive processes in response to cigarette smoking. In patients with COPD, pro-inflammatory and pro-destructive pathways are activated, other anti-inflammatory, anti-oxidant, or repair pathways are down-regulated resulting in lung destruction. Under smoke exposure conditions, epithelial cells and recruited inflammatory cells produce proteinases and oxidants causing lung damage by apoptosis and destruction of the extracellular matrix (ECM) **(4)**. The wide variety of inflammatory mediators that have been increased in COPD

patients attract inflammatory cells from the circulation (chemotactic factors), increasing the inflammatory process (pro-inflammatory cytokines), and induce structural changes (growth factors) **(5)**.

Eosinophils are key immune-effector and inflammatory cells. They have diverse functions, with roles in homeostasis and disease in various tissues, including the lungs **(6)**.Interventional studies additionally suggest that high blood eosinophilia level at stable state might predict a better treatment response to inhaled corticosteroid use and could therefore be used to guide therapy **(7)**.

The aim of the present study to predict the outcome and future risk of COPD exacerbations and to improve the health quality of COPD patients.

Patients and Methods:

An observational analytical prospective cohort study included 34 patients with Chronic obstructive pulmonary disease (COPD) who admitted COPD exacerbationat Chest Department, Zagazig university hospitals and outpatient clinics.

Inclusion criteria:

Patients with COPD exacerbation of both genders. An exacerbation of COPD is a sustained worsening of the patient's condition and symptoms (as increase dyspnea, increase cough, and change of the colour of cough) from the stable state and beyond normal day-to-day variations that is acute in onset and may warrant additional treatment in a patient with underlying COPD **(8)**.

Exclusion criteria:

Bronchial asthma patients, COPD patients admitted due to other medical conditions as lung cancer and patients with parasitic infestations were excluded.

Operational Design:

All patients in the study were subjected tofull medical history taking including smoking history. The grade of cigarette smoking can be determined from mild to severe according to the number of pack- year (Number of cigarettes per day * number of years /20)**(9)**.

Clinical examination was performed for all studied patients. Dyspnea grading using the modified British Medical Research Council (mMRC) questionnaire as follows Grade 0: (I only get breathlessness with heavy exercise), Grade 1 (I get shortness of breath when hurrying on level ground or walking up a slight hell), Grade 2 (on level ground, I walk slower than people of the same age because of breathlessnee, or have to stop for breath when walking at my own pace), Grade 3 (I stop for breath after walking about 100 yards or after a few minutes on level ground), Grade 4 (I am breathless to leave the house or I am breathless when dressing) **(8)**.COPD Assessment Test (CAT score) was recorded from Mild (0-10), Moderate (11 – 20), Severe from (21 – 30) to Very severe (31 – 40)**(10)**.

Routine laboratory investigations were performed including: CBC with differential leucocytic count. Liver function tests including hepatic serum enzymes (ALT and AST). Kidney function tests including both serum Urea and Creatininelevels.Random serum glucose level. Urine analysis and Stool analysis to exclude parasitic infestations.

Eosinophils estimation:

Measuring circulating and sputum eosinophils and total leucocytic count in exacerbated COPD patients was done at admission to determine the possibility of eosinophilic or neutrophilic airway inflammation. An eosinophilic exacerbation was defined as serum eosinophilic count >2%. A neutrophilic exacerbation was defined as a leucocytic count >11000 leucocytes/ ml or a neutrophilic proportion >65%. Cases that met both eosinophilia and neutrophiliawas categorized as eosinophilic exacerbation **(11)**.

Presence or absence of sputum eosinophils as a pointer to eosinophilic airway inflammation which is commonly associated with eosinophilic exacerbation. Natural sputum or induced sputum after hypertonic saline nebulization, then using cell spread technique is satisfactory used eosinophil cut-offs >1.25% for sputum as the threshold to categorise high and low eosinophil counts **(12)**.

SpirometricVentilatory Function testing using Minispir Flow- Volume Curve (MIR – Medical research, Inc., New Berlin, Wisconsin, USA) after stabilization of chest condition (at least 3 months after exacerbation). COPD severity according to spirometric ventilator functional assessment as follows (after stabilization of chest condition): Mild COPD group: FEV1 ≥80% predicted, Moderate COPD group: FEV1 50: 80% predicted, Severe COPD group: FEV1 30:50% predicted and Very severe group: FEV1 <30% predicted.

Follow up:

All patients were followed up every 3 months (or when their symptomps increased) for 1 year duration (by re-assessing mMrc and CAT score). All COPD patients were adherent to triple therapy (LABA, LAMA, ICS) after the first exacerbation. Assessment of number, severity, type (eosinophilic or neutrophilic), as well as outcome of exacerbations (either survival or death) was done.

Statistical analysis:

The data analyzed using Statistical Package for Social Science (SPSS) version 16. Qualitative and quantitative data were represented.Chi square (X^2) tests were used to detect relation between different qualitative variables. Fishers' exact test used if cell expected value is less than 5.Independent T test and Mann Whitney test were used.Binary logistic regression analysis was used to find significant predictors among the studied group**(13)**.The significance Level for all above mentioned statistical tests done, the threshold of significance is fixed at 5% level (P-value).*P value of >0.05 indicates non-significant results (NS).*P value of <0.05* indicates significant results (S).

RESULTS:

The current study showed mean age of the studied patients (65.5 years), 70.6% were males and most of them were smokers (55.8%)**(Table 1)**.Regarding outcome of the exacerbation at admission among the studied patients; 32.4% of had sputum eosinophilia and most of them (76.5%) received LABA as treatment before admission**(Figure 1)**. There was no statistically significant association between eosinophils level at admission and the outcome among the studied group where one patient (9.1%) died among patients with eosinophilia≥2% and also one patient (4.3%) died among patients with eosinophils<2%**(Figure 2)**.Regardingsputum and blood eosinophils after 3 months;only (31.25%) of the survived patients had sputum eosinophilia(>1.25%), half of them (50.0%) had future single exacerbation, about one third (34.4%) had two exacerbations and (15.6%) had no further exacerbations. all of them (100.0%)received LABA, LAMA and ICS as a triple therapy**(Figure 3)**.There was statistically significant higher TLC, neutrophil count and longer hospital stay among patients with eosinophils<2% than patients with eosinophils ≥2%. But regarding degree of exacerbation, management and outcome, there was no statistically significant difference between patients with low and high eosinophilia**(Table 2)**.Regardingbinary logistic regression analysis,the exacerbation occurrence with lower blood eosinophils levels, lower sputum eosinophils or high neutrophils were statistically significant had worse prognosis and more future exacerbations among the studied group**(Table 3)**.The predictive ability of eosinophils level showed high eosinophilia level had the ability to detect (31.3%) of the actual patients' outcome with (32.4%) accuracy in differentiation between discharge and death. Also, high eosinophilia level had the ability to detect (29.6%) of the future exacerbation with (34.4%) accuracy**(Table 4)**.

Table (1): Socio-demographic data of the studied patients:

Demographic data	**The studied group (n=34)**

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		Mean ± SD **Median (Range)**
Age (years)		**65.3±6.9** **65.5 (47-81)**
Gender N (%)	**Males**	**24 (70.6%)**
	Females	**10(29.4%)**
Smoking index	**Non**	**7 (20.6%)**
	Ex-smoker	**8 (23.5%)**
	Smoker	**19(55.8%)**
History	**Cigarette smoker Only**	**7 (20.6%)**
	Goza consumer Only	**8 (23.5%)**
	Combined	**4 (11.8%)**

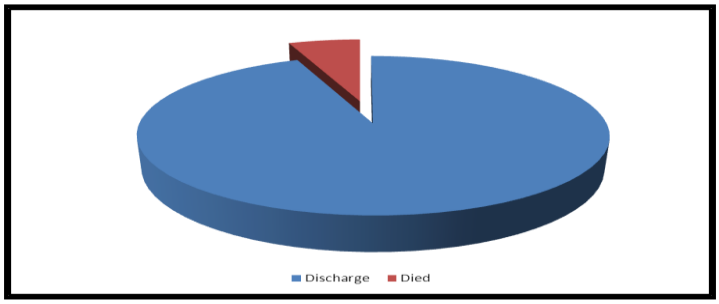

Figure (1): Pie chart for the outcome among the studied patients

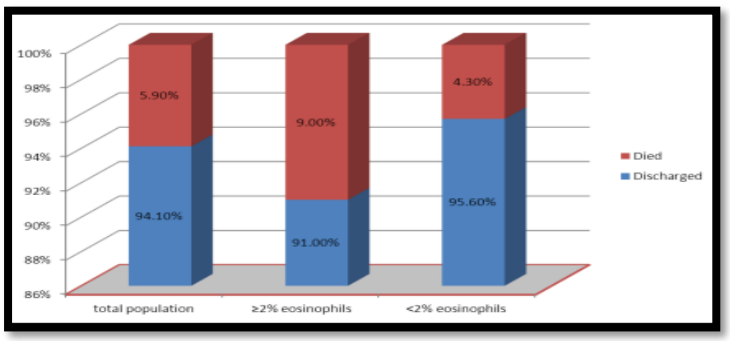

Figure (2): Bar chart for relation between eosinophils level at admission and the outcome among the studied patients.

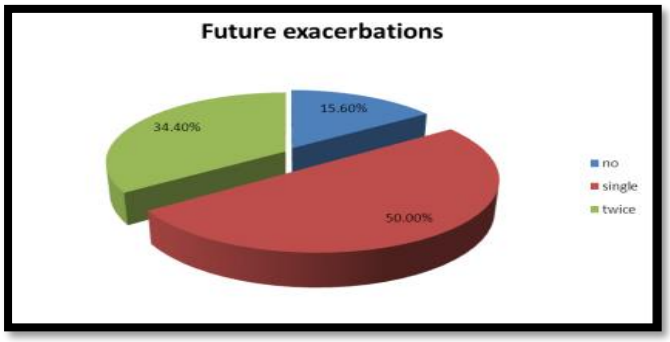

Figure (3): Pie chart for the future exacerbations among the studied patients.

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Table (2): Relation between eosinophils levels at the 1st future exacerbation and the exacerbation characteristics among the studied patients:

Variable	Eosinophilsat the 1st exacerbation <2% (19) **Mean ± SD (Median)**	Eosinophils at the 1st exacerbation ≥2% (8) **Mean ± SD (Median)**	Test	p-value
TLC at the 1st exacerbation **(*1000)**	**31.9±48.6 20.5**	**14.6±2.8 14.5**	**3.6**	0.001**
Neutrophils at the 1st exacerbation (%)	**78.7±4.3 77.9**	**62.8±2.7 62.3**	**9.5**	0.001**
Hospital stay **(days)**	**3.7±0.3 5**	**2.1±0.2 4**	**2.5**	0.01*
Variable	Eosinophilsat the 1st exacerbation <2% (19) NO. (%)	Eosinophils at the 1st exacerbation ≥2% (8) NO. (%)	χ^2	p-value
Severity of exacerbation **Moderate Severe**	**10(52.6%) 9(47.4%)**	**5(62.5%) 3(37.5%)**	**0.2**	**0.6**
Management **Conservative (18) Non-invasive (5) Invasive (4)**	**12(63.2%) 4(21.0%) 3(15.8%)**	**6 (75.0%) 1 (12.5%) 1 (12.5%)**	**0.3**	**0.8**
Site of care **Home (12) Ward (6) ICU (9)**	**8(42.1%) 4(21.0%) 7(36.9%)**	**4 (50.0%) 2(25.0%) 2(25.0%)**	**0.4**	**0.84**
The outcome **Survive (25) Died(2)**	**18(94.7%) 1(5.3%)**	**7 (87.5%) 1(12.5%)**	**FET**	**0.8**

FET =Fischer Exact test*Statistically significant difference (P ≤ 0.05)Statistically highly significant difference (P ≤ 0.001)**

Table (3): Binary logistic regression analysis for predictor factors for future COPD exacerbations:

Variables	Regression coefficient	Sig	Odds ratio (CI)
Age	**0.2**	**0.5**	**0.7 (0.2-1.9)**
Smoking	**0.1**	**0.7**	**0.4 (0.2-1.04)**
Sex	**0.5**	**0.20**	**0.97 (0.94-1.06)**
Eosinophils	**2.8**	0.03*	**17.2 (1.4-20.6)**
Neutrophils	**1.7**	0.01*	**5.2 (1.4-18.9)**
CAT score	**0.1**	**0.07**	4.7(0.1-12.0)
mMRC grade	**0.4**	**0.7**	**1.5 (0.1-17.1)**
Sputum eosinophils	1.8	0.03*	**8.6(1.4-13.1)**

*****Statistically significant difference (P ≤ 0.05)

Table (4): The predictive ability of eosinophils level at admission for prediction of patients' outcome and future exacerbations among the studied group:

Variable	Sensitivity	Specificity	PVP	PVN	Accuracy

Patients' outcome	**31.3%**	**50.0%**	**90.9%**	**4.3%**	**32.4%**
The future exacerbation	**29.6%**	**60.0%**	**80.0%**	**13.6%**	**34.4%**

DISCUSSION:

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is defined as acute worsening of respiratory symptomps that is beyond normal day to day variation and lead to additional therapy **(8)**. AECOPDs are transient periods of increased symptoms of dyspnea, sputum purulence, and sputum volume, but they may also encompass minor symptoms of nasal blockage/discharge, wheeze, sore throat, cough, fever, chest tightness or discomfort, fatigue/reduced energy, sleep disturbance, or limited physical activity **(14)**.

Traditionally, airway eosinophilia and T-helper cell type 2 (Th2) inflammation has been considered associated with allergic airway disorders such as asthma, and airway neutrophilia with COPD. However, other studies have reported that 20% to 40% of patients with COPD show sputum eosinophilia in the stable state **(15)**.

A Cohort prospective study was designed to investigate thirty four hospitalized COPD patients with COPD exacerbation whether in the ward or in the ICU and follow up them for 12 months forpredicting the outcome and future risk of COPD exacerbations and to improve the health quality of COPD patients.

In our study, the mean age of the studied patients (65.5 years), 70.6% were males and most of them were smokers (55.8%). In the contrary, some studies have even suggested that women are more susceptible to the effects of tobacco smoke than men, leading to more severe disease for equivalent quantity of consumed tobacco. This observation has been validated in human pathology specimens, which have demonstrated a greater burden of small airway disease in females compared to males with COPD despite a similar history of tobacco smoke exposure **(16)**.

Acigarette smoking is the most common risk factor for COPD. Cigarette smoking can induce a higher prevalence of respiratory symptoms and lung function abnormalities, a greater annual rate of decline in FEV1 and a greater COPD mortality rate than in non- smokers. Even passive exposure to cigarette smoke, also known as environmental tobacco- may also lead to rise in respiratory symptoms and eventually COPD by increasing the lung's total burden of inhaled particles and gases **(17)**.

In the current study, the relation between eosinophil levels and future exacerbation occurrence among COPD patients, there was no statistical significant association between eosinophil levels after 3 months and the occurrence of future exacerbations (80% in eosinophilic group and 86.4% in neutrophilic group). These findings were approximated with those reported by **Jabarkhil et al., (18)** stated that the clinical features and treatment outcome of eosinophilic and neutrophilic exacerbations were mostly similar to subsequent exacerbations at follow up period. The short term outcome of elevated eosinophils during an exacerbation was good in their study population.

In the current study, during the follow up period (12 months), acute exacerbations occurred once in 16 patients and twice in 11 patients only. Eosinophilic group had shorter hospital stay, higher home care and less need for ICU admission. The above results in this study are similar with that of **Holland et al.,(19)** reported that among 811 COPD patients in their study, (13.2%) had an eosinophilic exacerbation, the eosinophilic group had less need for non-invasive ventilation, shorter inpatient stay compared to the neutrophilic group. The peripheral blood eosinophil count may be a useful marker for predicting clinical progress in COPD patients exhibiting acute exacerbations during hospitalization.

In this study, the binary logistic regression analysis for predictor factors for future COPD exacerbations howed that the predictor factors for occurrence of acute exacerbations were low blood eosinophils, low sputum eosinophils and high neutrophils in blood.The present study findings were approximated with that mentioned by **Hye et al., (11)**revealed that acute exacerbation of COPD is associated with substantial morbidity and mortality. It is known that such exacerbation is typically associated with an increase in neutrophilic airway inflammation (and to a lesser extent, eosinophilic).As expected, the bacterial cluster was the largest, but the eosinophilia predominant cluster constituted for 28% of all exacerbations. Inhaled or systemic steroids are used to minimize the symptoms of eosinophilic airway inflammation in patients with severe COPD exacerbations.

However, treatment failure is more common in (neutrophilic group compared to eosinophilic) COPD patients receiving steroids. Ultimately, eosinopenia is associated with acute infection and inflammation. These conditions - combined with leukocytosis- are predictive for further bacterial infection. Eosinopenia is known to be an independent predictor of in-hospital mortality in patients with AECOPD. Treatment outcomes differ by the cause of exacerbation, thus phenotyping of COPD exacerbation is clinically important. The rate of respiratory Icu admission and mechanical ventilation were higher in neutrophilic group. Both total and early mortality were also higher in neutrophilic group. So, phenotyping of airway inflammation is important both for management and prognosis of COPD patients.

CONCLUSION

High neutrophil level in peripheral blood duringfollow up period of COPD patients, besides low eosinophil level in both blood and sputum are considered predictor factors for future COPD exacerbations.As regard the binary logistic regression analysis for predictor factors of future exacerbation among the studied patients, neutrophilic exacerbation had worse prognosis and more frequent exacerbations.

No conflict of interest.

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