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ORIGINAL ARTICLE

Eosinophil Level as a Predictor of Outcome in Exacerbated Chronic Obstructive Pulmonary Disease

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ABSTRACT

Background: The responsibility of eosinophilic inflammation in chronic obstructive pulmonary disease (COPD) exacerbations is hardly observed compared to asthma. We, therefore, aimed to study the possible function of eosinophilic airway inflammation (EAI) on acute exacerbations' result in COPD-patients.

Methods: A total of 34 of exacerbated COPD patients were included in an observational prospective cohort study. Total leucocytic count, eosinophils, neutrophils count, and sputum eosinophils were then measured on admission, which were repeated after 3 months of stabilizing the exacerbated chest condition. Evaluation of patient's outcome of exacerbation, Spirometric ventilatory function testing after stabilization, follow up of all patients every 3 months for one year, and reassessing mMrc scale and CAT score were also performed.

Results: The mean age of the included 34-exacerbated COPD patients in our study was about 65.3±6.9 years, where most of them were males (70.6%). Additionally, 55.8, 55.9, and 44.1% of the patients were smokers, admitted at ward, and admitted at ICU, separately. Blood eosinophil (≥2%) and sputum eosinophilia (>1.25%) were presented in 32.4% of the current patients. Most importantly, no statistically significant correlation among eosinophil levels on admission and the exacerbation outcome was noted. Analogously, no statistically significant variation among patients with low and high eosinophils levels for their mMRC-grade and CAT-score at charge after 3, 6, and 9 months of follow up.

Conclusion: EAI constitutes a lesser part besides neutrophilic inflammation in COPD exacerbations. There was an irrelevant correlation among eosinophils ratios at admission and the outcome.

Keywords: COPD; Exacerbation; Eosinophils; Inflammation.

INTRODUCTION

COPD is a heterogeneous disorder with patients, showing various clinical and pathophysiological characteristics. The recognition of COPD-phenotypes with particular features may permit pointed medication approaches towards precise biological pathways [1]. The eosinophilic inflammation was previously believed to be a distinctive characteristic of asthma instead of the COPD. However, findings were reported that several COPD-patients with EAI occurs. Such was found even after insularity of patients with any asthma's characteristics, namely B-agonist reversibility, bronchial hyperactivity, and atopy

or a childhood record of asthma [2]. Although, responsibility of eosinophilic inflammation in COPD-exacerbations is hardly observed compared to the asthma, but it has newly spotlighted. Many findings have connected between high-blood eosinophils and COPD-exacerbations with successive events. The findings of these reports are slightly unclear. Probably because some results linked between it and the higher rate of exacerbations [3], and vice versa were reported in other reports [2]. We, thus, aimed to study the possible function of EAI on acute exacerbations' outcome in COPD-patients.

PATIENTS AND METHODS

This analytical prospective cohort study was performed at the Chest Department, Zagazig University hospitals and outpatient clinic in the period from May 2019 to May 2020. Meanwhile, written notified consent was acquired from all contributors. The study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. Also, the study was completed according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies including humans.

A total of 34 of COPD-patients were admitted, due to COPD exacerbation, according to the GOLD guidelines 2019 [4]. While the following conditions were precluded: 1) bronchial asthma patients, 2) COPD-patients admitted due to other medical conditions as lung cancer, and 3) patients with parasitic infestations. All patients in this study were exposed to the following : Documenting the full medical history i.e., smoking, and clinical examination with dyspnea grading using adjusted British Medical Research Council (mMRC) questionnaire and COPD-assessment test (CAT score) [5]. Chest X-ray (both Postero anterior and Lateral views), arterial blood gases (ABGs), routine laboratory investigations (CBC containing, total and differential leucocytic count, liver and kidney function tests), and analysis of urine and stool for exclusion of parasitic infestations were also evaluated.

Total leucocytic count, eosinophils, neutrophils count, and sputum eosinophils were then measured on admission, which were repeated after 3 months of stabilizing the exacerbated chest conditions. An eosinophilic exacerbation was identified as serum eosinophilic count >2%. A neutrophilic exacerbation was identified as a leucocytic count >11000 leucocytes/mL or a neutrophilic proportion >65%. Cases that matched with both eosinophilia and neutrophilia were–categorized as eosinophilic exacerbation [6]. Natural sputum or induced sputum after hypertonic saline nebulization was used to detect sputum eosinophilia, where the eosinophil cut-offs >1.25% for sputum was used as the outset to categorize up and down eosinophil counts in the sputum [7]. And according to the results of blood and sputum eosinophil level our patients were classified into two groups (group with eosinophilic exacerbation and the other group with neutrophilic exacerbation). Evaluation of patient's outcome of exacerbation (either survival or death) was also performed.

Spirometric ventilatory function testing was also measured using Minispir Flow- Volume Curve (MIR – Medical research, Inc., New Berlin, Wisconsin, USA) after stabilization of chest conditions (at least 3 months after exacerbation). All COPD-patients were adherent to triple therapy (LABA, LAMA, and ICS) after hospital discharge. Follow up of all the patients every 3 months or when their symptoms increased for a total of one year by re-assessing mMrc and CAT score was considered.

Statistical analysis

SPSS ver. 16 was used to code, enter, portray, and analyze the assembled data. The quantifiable data were introduced as mean±SD which were examined by one way analysis for variance (F test). Additionally, Chi square or Fisher exact tests was used to present and analyze the qualitative data (number and percentage). P-value <0.05 is measured significant.

RESULTS

A total of 34 exacerbated COPD-patients were included in this study, where their mean age was 65.3±6.9 years, and most of them were males with a ratio of 70.6%. Regarding smoking

history, 55.8% of the patients were smokers and 23.5% were a Goza consumer. As tabulated in **Table 1**, most of the patients had high mMRC-grade (3.5±0.5), high CAT-score (24.6±7.4), and HTN was the commonest comorbidity (50%) followed by DM (41.2%).

A total of 55.9 and 44.1% of patients were admitted at ward and in ICU, respectively. Regarding the patient's outcome, 94.1% of them were discharged, while 5.9% died. Concerning blood eosinophil ≥2% and sputum eosinophilia >1.25%, both were presented in 32.4% of the patients (the same patients with blood eosinophilia were found to have sputum eosinophilia) while ratios of 67.6% were in neutrophilic exacerbation (**Table. 2**). No statistically significant relations among eosinophil levels on admission and the outcome were found. This may be because one patient (9.1%) died among patients with eosinophilia ≥2%, and one patient (4.3%) died among patients with eosinophil <2% (neutrophilic exacerbation) (**Table. 3**).

After 3 months of stabilization of COPD-exacerbation, we noticed that insignificant lower values of FEV1/FVC% and FEV1(% predicted) in patients with eosinophilic exacerbation than those of neutrophilic exacerbation were happened (**Table. 4**). Regarding blood and sputum eosinophilia after 3 months of exacerbated COPD-conditions stabilization, only 31.25% of the survived patients had eosinophilia (**Table. 5**). There was no statistically significant difference in term of the difference in CAT-score at admission after 3, 6, and 9 months follow up among patients with up and down eosinophils levels. Conversely, a high significant decrease on CAT-score after 3, 6, and 9 months follow up on both patients with high and low eosinophils levels was observed (**Table. 6**). There was no statistically significant variation in term of the difference in mMRC-grade at admission, after 3, 6, and 9 months among patients with low and high eosinophils levels. Inversely, a high significant decrease on mMRC after 3, 6, and 9 months on both patients with high and low eosinophils levels was found (**Table. 7**).

Table (1) Socio-demographic and clinical data of the studied patients.

Demographic data		**The studied group (n=34)**
Age (years) **mean ± SD (Range*)***		65.3±6.9 (47-81)
Gender N (%)	**Males**	24 (70.6%)
	Females	10(29.4%)
Smoking N (%)	**Non**	7 (20.6%)
	Ex-smoker	8 (23.5%)
	Smoker	19(55.8%)
	Cigarette smoker Only	7 (20.6%)
	Goza consumer Only	8 (23.5%)
	Combined	4 (11.8%)
Clinical data		
m-MRC grade **mean ± SD (Range*)***		3.5±0.5 (3-4)
CAT score **mean ± SD (Range*)***		24.6±7.4 (12-37)

Co-morbid N (%)	***No***	6 (17.6%)
	D.M	14 (41.2%)
	HTN	17 (50.0%)
	GERD	1 (2.9%)
	IHD	5 (14.7%)
	Hypo-thyrodism	1 (2.9%)
	CLD	1 (2.9%)
	Old stroke	2 (5.9%)

Table (2) Site of admission , outcome, eosinophil level and neutrophil level.

Variables		**The studied group (n=34)**
		N (%)
Site of admission	***Ward***	19 (55.9%)
	ICU	15 (44.1%)
Outcome	***Discharge***	32 (94.1%)
	Died	2 (5.9%)
***Blood eosinophil* ≥2% *and Sputum eosinophila* >1.25%**		11(32.4%)
Neutrophils >11000* leucocytes/ml *or neutrophilic proportion >65%		23 (67.6%)

Table (3) Relation between eosinophils level on admission and the outcome among the studied patients.

Sputum eosinophils% N=34	**Blood eosinophilis% N=34**	**The outcome**		**χ^2**	**p-value**	**Odds ratio (95% CI)**
		Discharged NO. (%)	***Died NO. (%)***			
<1.25(23)	**<2(23)**	22 (95.6%)	1(4.3%)			
≥1.25(11)	**≥2 (11)**	10 (90.9%)	1 (9.1%)		0.6	0.45 (0.03-8.02)
Total		32 (94.1%)	2 (5.9%)	FET		

Table (4) Relation between eosinophils levels at admission and spirometric ventilatory function after 3 months follow up among the studied patients.

Variables	**Eosinophils at admission < 2%(neutrophilic exacerbation)** *mean ± SD (median)*	**Eosinophils at admission ≥2%** *mean ± SD (median)*	**t- test**	**p-value**
FEV1/FVC%	54.1±14.1 57	50.2±17.4 56.5	0.7	0.5
FEV1% predicted	51.1±12.2 54	47.1±15.4 50.5	0.8	0.4

Table (5) Sputum and blood eosinophils after 3 months among the studied patients.

Variables		The studied group (n=32) NO (%)
Blood eosinophil after the 3 months (no=32)	*<2%*	22 (68.75%)
	≥2%	10 (31.25%)
Sputum eosinophil after the 3 months*(no=32)*	*<1.25%*	22 (68.75%)
	≥1.25%	10(31.25%)

Table (6) Comparing CAT between patients with eosinophils<2% and ≥2% at admission, after 3, 6 and 9 months follow up.

Variables	**Eosinophils at admission < 2% (NO.=23)** *Mean ± SD (Median)*	**Eosinophils at admission ≥ 2% (NO.=11)** *Mean ± SD (Median)*	**t- test**	**p-value**
CAT at admission (No of patients)	24±6.9 22 (23)	25.8±8.3 26.5 (11)	0.2	0.7
CAT after 3 months (No of patients)	13.7±5.3 14 (22)	14.7±6.1 16.5 (10)	M.W 0.4	0.6
CAT after 6 months No of patients	18.04±6.4 16 (21)	19.3±8.6 18 (9)	M.W 0.4	0.6
CAT after 9 months No of patients	14.7±6.3 11 (21)	18.9±7.9 19 (9)	M.W 1.6	0.1
P-value for repeated measures	**0.001****	**0.001****		

**Statistically highly significant difference (P ≤ 0.001)

Table (7) Comparing mMRC grade between patients with eosinophils<2% and ≥2% at admission, after 3, 6 and 9 months follow up.

Variables	**Eosinophils at admission <2% (NO.=23)** *Mean ± SD (Median)*	**Eosinophils at admission ≥2%(NO.=11)** *Mean ± SD (Median)*	**t- test**	**p-value**
mMRC at admission (No of patients)	3.4±0.5 3 (23)	3.7±0.49 4 (11)	0.2	0.7
mMRC after 3 months (No of patients)	2.3±0.7 2 (22)	2.5±0.9 3 (10)	0.6	0.5

mMRC after 6 months (No of patients)	2.9±0.7 3 (21)	3.0±0.9 3 (9)	0.3	0.7
mMRC after 9 months (No of patients)	2.57±0.7 2 (21)	3.0±0.8 3 (9)	1.5	0.1
P-value for repeated measures	**0.001****	**0.001****		

**Statistically highly significant difference ($P \leq 0.001$)

DISCUSSION

COPD now is one of the top three causes of death globally and 90% of these deaths occur in low- and middle– income countries [8]. Exacerbations are correlated with airway inflammation increases and lung function's declines. Although a neutrophilic predominant inflammation was regarded as a tradition response, EAI may also be vital, predominantly in more acute COPD-exacerbations [2].

The responsibility of eosinophilic inflammation in COPD-exacerbations is hardly noted compared to the asthma, but it has newly spotlighted. Many reports have connected between high blood eosinophils and COPD exacerbations with successive events. The findings of these reports are slightly unclear. Probably because some results linked between it and the higher rate of exacerbations [3], and vice versa were reported in other reports [2]. Blood eosinophils were also accompanying with lengthier hospital lodging and higher risk of death [9]. However, other reports found that no variance in the mortality was mentioned [10].

Herein, a Cohort prospective study was intended to explore 34 hospitalized COPD-patients in exacerbation with follow up after 3 months from stabilization of exacerbated COPD condition. This was to distinguish the conceivable role of EAI in the result of acute exacerbations in COPD-patients.

In our study, regarding the socio-demographic data of the studied patients (**Table. 1**), the mean age was 65.3±6.9, where 70.6 and 55.8% were males and smokers, respectively. It was intensely found that age is often itemized as a risk issue for COPD. It is uncertain whether healthful aging leads to COPD or reveals the sum of accumulative lifelong exposure. Aging of the airway and parenchyma mimic sum of the operational fluctuations allied with COPD [11].

Previously, COPD occurrence and mortality are reportedly superior among men than women, matching with our study. But it was recently reported that the COPD occurrence is almost equivalent in men and women, doubtless revealing the altering patterns of tobacco smoking [12].

Other kinds of tobacco ingestion such as pipes, cigars, marijuana, and goza may also cause COPD-pathogenesis. In this context, Salem et al., [13] reported that goza consumption is more hazardous than cigarette smoking in inducing COPD, due to more duration of the puff, more suction pressure, and more incidence of cross infection among goza consumers. This explanation agreed with our results, where goza consumers and cigarette smokers were 23.5 and 20.6% of the studied patients (**Table. 1**).

Neutrophilic exacerbation was marked in 23 patients (67.6%) and eosinophilic exacerbation was presented in 11 patients (32.4%), agreed with the results of Adir et al., [14] who reported that EAI occurs in 20-40% of COPD-patients. He also found that eosinophil levels (both when clinically stable and during exacerbation) were unconnected with amplified risk of prospect severe exacerbation of COPD. Moreover, treatment with inhaled corticosteroid (ICS) showed insignificant relationship with risk lessening of severe AECOPD in patients with low or high eosinophils level.

In the contrary, Bafadhel et al. [1] reported that a subsection of COPD-patients with EAI occurs, even after a cautious exclusion of

patients with any characteristics of asthma, such as post bronchodilator reversibility test, bronchial hyperresponsiveness, and atopy or a childhood history of asthma.

Remarkably, the patients display the utmost response to corticosteroid treatment. Likewise, sputum eosinophil numbers are boosted in a subsection of COPD-exacerbations and titrating corticosteroid treatment based on the sputum eosinophil counts decreases the exacerbation proportions. Additionally, there are parallel rises the in sputum and blood eosinophil numbers during COPD-exacerbations.

Thus, using blood eosinophils as a replacement marker for airway eosinophils to direct oral corticosteroid remedy for the cure of COPD-exacerbations improved the clinical recovery. Taken together, these clarifications recommended that EAI in COPD is a prophetic biomarker of corticosteroid responsiveness during clinical steadiness and exacerbations. These findings are matched with that of Brightling et al., [2] who informed that 37% of COPD-patients have blood eosinophil counts persistently >2% and suggested that increased eosinophil levels in COPD are related to amplified response. Decreased eosinophil count <2% associates other immune cell kinds in disease pathophysiology, i.e., neutrophils, which are identified to produce emphysema.

Regarding the site of admission and outcome (**Table 2**), most patients were admitted in the ward (55.9%) and 2 cases died, where one with neutrophilic exacerbation (4.3%). And the other suffered from eosinophilic exacerbation (9%), with no statistically significant relation among eosinophil levels on admission and the outcome (**Table 3**).

Our findings were matched with that of Kang et al., [6] who likened between the clinical features and treatment endings of COPD-patients with neutrophilic and eosinophilic exacerbations based on whole blood count. The author found that about 29.3% of hospitalized COPD-patients with acute exacerbations had peripheral eosinophilic count >2%. Patients with eosinophilic COPD-exacerbation also had good clinical outcome and lesser initial deathrate than those with the neutrophilic exacerbations. One thinkable elucidation for the relation between poor prognosis and neutrophilic exacerbation is that neutrophilia is recognized to be an indicator of bacterial infection. COPD-exacerbations instigated by bacterial infection are correlated with lengthier hospital resides and more exacerbations.

Conversely, there is an epidemiological proof of the relation between the peripheral blood eosinophil count and death from COPD-exacerbations [15]. Corticosteroid therapy seems to have a choosy inhibitory influence on EAI in COPD. A further validation for the role of EAI in the beginning of COPD-exacerbations is specified by consistent sign that corticosteroid treatment rises the recovery rate from severe exacerbations and inhibits its incidence.

These findings were in line with those reported by Jabarkhil et al., [16] who stated that the clinical characteristics and treatment ending of eosinophilic and neutrophilic exacerbations were mainly like successive exacerbations at follow up period. The short-term consequence of increased eosinophils during an exacerbation were not bad in their study populace, but the raised blood eosinophils was not found as a foreteller of upcoming exacerbations as mentioned by others.

Sivapalan et al., [17] suggested that eosinophilic exacerbation of COPD-patients is more regular and has a bad outcome compared to the neutrophilic phenotype, disagreed with our findings. After 3 months, blood and sputum eosinophil levels were re-evaluated to the remaining patients under the stable conditions of the disease, with blood and sputum eosinophilia were found in 10 patients (**Table 5**).

Regarding the comparison among COPD-patients with high and low eosinophilic count in the clinical manifestations in both mMRC-scale and CAT-score during the follow up period; high statistically significant improvement over time of 12-months follows up was found (**Tables 6&7**). These findings may be attributed to the regular adhesion to treatment of triple therapy (LABA, LAMA, and ICS). Beside the close contact follow up when respiratory symptoms increased. These results are also similar with that of Jabarkhil et al., [16] who reported a better

clinical outcome, higher FEV1%, fewer symptoms, and lower mMRC-score during follow up period after regular triple therapy.

The results of the current study cannot be regarded apart from its limitations. First, the relatively small-sized sample would limit the generalizability of our findings. Second, bronchoalveolar lavage which is more sensitive in detection of eosinophilic airway inflammation is hindered by the instability of COPD-patient.

CONCLUSION

EAI constitutes a lesser part besides neutrophilic inflammation in COPD-exacerbations. FEV1/FVC% and FEV1 (% predicted) were lower in COPD-patients with eosinophilic exacerbation than neutrophilic one. There was an irrelevant association among eosinophils levels at admission and the outcome.

Conflict of interest

The authors declared that they have no conflicts of interest with respect to the authorship and publication of this article.

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