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Original Article

Blood eosinophils and its relation to sputum inflammation and sputum bacterial load in patients with acute exacerbation of chronic obstructive pulmonary disease

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ABSTRACT

Background: little is recognized on the role eosinophils in the pathophysiology of acute exacerbation of chronic obstructive pulmonary disease (AECOPD).

Objective: To assess the relationship between eiosinophilic AECOPD and sputum inflammation and bacterial load.

Methodology: A cross-sectional study was done on 80 out of 189 patients presented by clinical picture of AECOPD. Spirometry, total and differential leucocytic count (TLC), sputum bacterial load and culture were done for all participants. They were divided into two subgroups based on blood eosinophils %; eosinophil ^{high} AECOPD (≥2%) and eosinophil ^{low} AECOPD (< 2%).

Results: Among the studied patients; 51.25% have eosinophil^{high} and 48.75% have eosinophil ^{low} AECOPD. Patients with eosinophils ^{high} AECOPD had higher age, BMI, smoking status, smoking index, wheezes and FVC%, with more severe COPD and more severe AECOPD (p0.018) than those with eosinophil ^{low} AECOPD. In patients with eosinophil ^{high} AECOPD the blood TLC/cm^3 and neutrophil % were significantly lower, while lymphocyte % and eosinophil /cmm^3 were higher significantly than eosinophil ^{low} AECOPD (p 0.001 each). Regarding sputum inflammatory cells they had significant increase of sputum lymphocyte % and eosinophil/cm^3 and % with significant decrease of sputum neutrophils % (p<0.05). In eosinophil ^{high} AECOPD subgroup the blood eosinophil /cmm^3 was positively correlated with age, BMI and smoking index, blood lymphocytes % eosinophils %, sputum lymphocytes % and sputum eosinophils and it was negatively correlated with blood TLC, blood and sputum neutrophils, FEV_1/FVC ratio, FEV_1 % FEF25-75 % and FVC%. The sputum bacterial load was non-significantly lower in eosinophil ^{high} than eosinophil ^{low} AECOPD (61.0% vs. 74.4%, p=0.20).The type of the isolated bacteria didn't differ between both AECOPD subgroups (p=0.17).

Conclusion: Eosinophilic AECOPD is common and it was related to airway inflammation and it didn't' affect sputum bacterial load or type of isolated bacterial species.

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Keywords: Airway inflammation, eosinophilic AECOPD, sputum eosinophilia, sputum bacterial load

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INTRODUCTION

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are accompanying with notable morbidity and mortality [1]. Most AECOPD are linked to neutrophilic airways inflammation, however, a significant percentage of AECOPD demonstrate eosinophilic airway inflammation [2].Eosinophils are innate immune cells that beneath some conditions can be enrolled into the lungs, where they have partially

understood role in health and disease. It has been found in the bronchi, parenchyma, and circulation of COPD patients, in both stable and exacerbated periods [3].

Continuing bacterial infection in COPD patients leads to greater neutrophilic inflammation in the lungs. The relation between bacterial infection and eosinophilic inflammation in AECOPD is not well-known. There may be an opposite relationship between these items, as peripheral eosinophil numbers are recognized to be decreased during severe bacterial infection. The presence of such an opposite relationship would propose that the interaction between bacterial infection and eosinophils determine steroid responsiveness in patients with COPD [4].Additionally, bacterial infections are identified to induce eosinopenia and patients with eosinophils ≤2% may have higher bacterial colonization [5].Several researches have studied the association of eosinophilia with clinical outcome of COPD patients nevertheless the evidence is contradictory. Moreover, studies examining the usefulness of peripheral eosinophils in identifying sputum eosinophilia in COPD are lacking [6]. Accordingly, this study was carried out to assess the relationship between eiosinophilic AECOPD and sputum inflammation and sputum bacterial load.

SUBJECTS AND METHODS

Type, place and duration of the study: This observational cross-sectional study was done at chest diseases department Al-Zahraa University hospital, from November 2017 till October 2019

Study participants: it was conducted on 80 out of 189 known COPD patients presented with symptoms and signs of AECOPD. The diagnosis and severity of COPD was done according to the modified criteria defined in **GOLD (2017)** [1] (had irreversible/partially reversible airflow obstruction (post-bronchodilator $FEV_1/FVC\%$ <0.7, FEV_1<80% and FEV_1increased< 200 mL, or < 12% of baseline value 20 minutes after 400 µg Salbutamol inhalation given via a metered-dose inhaler device. Additionally, the diagnosis and severity of AECOPD was assessed according to **Anthonisen, et al.** [7] criteria. Patients with other chest diseases were excluded from the study.

Ethical considerations: An informed written consent was gotten from each patient before participation into the study. Every patient had the right to reject participation or take out from the study without affecting their rights of medical care. Moreover, data were nameless and coded to guarantee privacy of the participants. This study was approved by the institutional review board of committee of faculty of medicine for girls, Al-Azhar University (IRB 202002164).

Detailed history of age, sex, body mass index measurements (weight in kg/ height in m^2), smoking status (ex-smokers, smokers, and non-smokers) and smoking index in pack/year (number of packs smoked per day multiplied by smoking years) were recorded.

Blood and sputum total and differential leucocytic count using hematological analyiser (Sysmex XE-21N, Kobe, Japan) including total leucocytic (TLC)/cmm^3, lymphocytes %, neutrophil%, eosinophils count/cmm^3 and percentage were measured. Blood eosinophil counts were described as an absolute count (cells/µL) or as a percentage of total leucocytes; researches demonstrated that these two methods are matched [8-9]. Eosinophilia is commonly defined as ≥2% eosinophils in the blood or ≥3%in the sputum [6,10]. According to this cutoff value the studied patients were classified into two subgroups %; 1) eosinophils ^{high} AECOPD subgroups (eosinophils ≥ 2%) and 2) eosinophils ^{low} AECOPD subgroups (eosinophils< 2%).

Spirometry was performed using (MEDISOFT-HYPERAIR compact + flow meter pulmonary function Testing-Belgium). The following indices were recorded; forced expiratory volume in first second (FEV_1%), forced vital capacity (FVC %), FEV_1/FVC ratio, and forced expiratory flow rate 25%-75% ($FEF_{25-75\%}$) Spirometric-indices were considered using the best out of three technically adequate performances in agreement with **Miller et al.** recommendations [11].

Sputum cultures and colony forming unit count. Sputum samples were collected before starting antibiotics therapy. Morning sputum samples were placid in a sterile container and delivered rapidly to the microbiology laboratory where they immediately processed. Before culturing sputum sample, a Gram stain was done to assess the quality of the sample. Sputum samples harboring ≥10 leucocytes with<25 squamous epithelial cells per low-power field (<10/LPF), were accepted and cultured [12]. If the sample was considered of good quality (lower respiratory tract specimen), examination of the slide under oil immersion (1000X) magnification for bacteria and fungi were done and proceed with culturing the specimen. Microbiological cultures were done on ordinary media used for the isolation and identification of respiratory pathogens including blood agar, chocolate agar, and MacConkey agar. After 24 hours of aerobic incubation, the grown colonies were identified using gram stain and biochemical reactions [13].Quantitative cultures were done using the calibrated loop method. 0.1 ml of specimen was plated onto solid media and colonies forming unit (CFU) were counted after 24 hours incubation. Specimens with colony CFU count ≥ 10^4 /ml were considered infections and further processed for identification of bacteria using gram stain

and biochemical reactions, while specimens with CFU count < 10^4 /ml were considered colonization [14].

Statistical analysis of data

The data were coded and fed to computer on excel sheet. The data was tabulated and analyzed by using (SPSS) program on windows 7 version 17.0 (SPSS Inc.; Chicago, USA).Descriptive variables were expressed as mean ± SD and median interquartile range (IQR) for numerical variables, and as % for categorical and nominal variables. When a data set has outliers or extreme values, we summarize a typical value using the median as opposed to the mean. When a data set has outliers, variability is often summarized by IQR, which is the difference between the first and third quartiles (IQR = Q3-Q1).Comparisons to evaluate the difference between the groups was done using the Chi-square (X^2) test for categorical and nominal variables and Student's t-test for numerical variables. A linear correlation coefficient was used for determination of strength and direction of relationship between two numerical variables in the same group. Statistical significance was considered at a p-value <0.05 (CI at 95%).

RESULTS

The age, male sex, BMI, smoking status, smoking index and FVC% were significantly increased in eosinophil ^{high} than eosinophil ^{low} AECOPD (p= <0.5).. Although eosinophil ^{high} AECOPD patients have non-significant decrease of FEV_1%, they had higher frequencies of severe and very severe COPD than those with eosinophil low AECOPD (0.018) ***(Table 1)***. Among Anthonisen criteria only wheeze was significantly higher in patients with eosinophil ^{high} compared to those with eosinophil ^{low} AECOPD (p= 0.041). Moreover, patients with eosinophil ^{high} AECOPD had more severe acute exacerbation (p= 0.001) ***(table 2)***.

The blood TLC/cm^3 and neutrophil % were significantly lower (p= 0.001 each), while blood lymphocyte % and eosinophil / cmm^3 were significantly higher (p= 0.001 each) in eosinophil ^{high} AECOPD than eosinophil ^{low} AECOPD. There were significant increases of sputum lymphocyte % and eosinophil/cm^3, and % with significant decrease of sputum neutrophils % in eosinophil ^{high} AECOPD than eosinophil ^{low} AECOPD (p<0.05) ***(table 3)***. In eosinophil ^{high} AECOPD subgroup the blood eosinophil /cmm^3 was positively correlated with age, BMI, smoking index,(p<0.05). It was negatively correlated with FEV_1/FVC ratio, FEV_1 % FEF25-75% and FVC%, blood neutrophils % and positively correlated with blood lymphocytes % and eosinophils % (p<0.05). Moreover, it was positively correlated with sputum lymphocytes % and eosinophils and negatively correlated with sputum neutrophils ***(table 4)***.

The sputum bacterial infection (bacterial load) was non-significantly lower in eosinophil ^{high} than eosinophil ^{low} AECOPD (61.0% vs.74.4%, (p=0.20). Additionally, the type of the isolated bacteria did not differ between both AECOPD subgroups (p=0.17). However, candida was non-significantly common in eosinophils ^{low} AECOPD subgroup (p=0.17) ***(table 5)***.

Table (1): Comparison of demographic data, spirometric-indices and COPD severity between eosinophil ^{high} and eosinophil ^{low} AECOPD subgroups

Item		Eosinophil ^{high} AECOPD (No. = 41)	Eosinophil ^{low} AECOPD (No. = 39)	Test	P
Age/ year	Mean ± SD	57.56 ± 5.74	54.03 ± 4.13	3.14•	0.002
Sex	Male	36 (87.8%)	21 (53.8%)	11.25*	0.001
	Female	5 (12.2%)	18 (46.2%)		
BMI (k/m^2)	Mean ± SD	26.16 ± 3.71	24.34 ± 1.78	2.78•	0.007
Smoking status	Smokers	33 (80.5%)	18 (46.2%)	12.08*	0.002
	Ex-smokers	7 (17.1%)	12 (30.8%)		
	Non-smokers	1 (2.4%)	9 (23.1%)		
Smoking index (pack/year)	Mean ± SD	27.85 ± 10.81	19.25 ± 9.96	3.33•	0.001
FEV_1/FVC ratio	Mean ± SD	60.90 ± 5.81	63.19 ± 5.09	1.87•	0.06
FEV_1 %	Mean ± SD	55.92 ± 18.90	62.12 ± 9.85	1.82•	0.07
FVC	Mean ± SD	74.56 ± 5.62	70.71 ± 8.90	2.32•	0.023
FEF25-75%	Mean ±S D	49.32 ± 7.89	51.31 ± 7.47	1.15•	0.25
COPD severity	Mild	3 (7.3%)	0 (0.0%)	10.07*	0.018
	Moderate	22 (53.7%)	33 (84.6%)		
	Severe	11 (26.8%)	5 (12.8%)		
	Very Severe	5 (12.2%)	1 (2.6%)		

P-value >0.05: Non-significant; P-value <0.05: Significant; P- *: Chi-square test; •: Independent t-test, FEV_1/FVC: forced expiratory volume in first second, FEV_1: forced expiratory volume in first second, FEVE25-75%: forced expiratory flow at 25-75% of vital capacity, BMI: body mass index

Table (2): Comparison of anthesonin criteria and acute exacerbation severity between eosinophil ^{high} and eosinophil ^{low} AECOPD subgroups

Item		Eosinophil ^{high} AECOPD (No. = 41)	Eosinophil ^{low} AECOPD (No. =39)	Test *	p
		No. (%)	No. (%)		
Increased Dyspnea		37 (90.2%)	29 (74.4%)	3.49	0.06
Increased Sputum volume		35 (85.4%)	29 (74.4%	1.51	0.21
Increased sputum purulence		25 (61.0%)	17 (43.6%)	2.42	0.12
Cough		41 (100.0%)	39 (100.0%)	-	-
Wheezes		40 (97.6%)	33 (84.6%)	4.19	0.041
Fever		13 (31.7%)	17 (43.6%)	1.20	0.27
URTI		11 (26.8%)	11 (28.2%)	0.02	0.89
Increase RR> 20%		12 (29.3%)	15 (38.5%)	0.75	0.38
Increase HR > 20%		9 (22.0%)	13 (33.3%)	1.29	0.25
Cyanosis		11 (26.8%)	8 (20.5%)	0.440	0.50
Hemoptysis		8 (19.5 %)	4 (10.3%)	1.34	0.24
Exacerbation severity	**Mild**	1 (2.4%)	13 (33.3%)	17.12	0.001
	Moderate	13 (31.7%)	15 (38.5%)		
	Severe	27 (65.9%)	11 (28.2%)		

P-value >0.05: Non-significant; P-value <0.05: Significant; *: Chi-square test, RR: respiratory rate, HR: heart rate, URTI: upper respiratory tract infections

Table (3): Comparison of blood and sputum total and differential leucocytic count between eosinophil ^{high} and eosinophil ^{low} AECOPD subgroups

Item		Eosinophil ^{high} AECOPD (No. = 41)	Eosinophil ^{low} AECOPD (No. = 39)	Test	P
Blood TLC/ cmm^3	Mean ± SD	10.87 ± 1.81	12.59 ± 2.24	3.78•	0.001
Blood Neutrophil %	Mean ± SD	61.76 ± 6.10	70.67 ± 5.87	6.65•	0.001
Blood Lymphocyte %	Mean ± SD	34.56 ± 3.93	25.90 ± 5.25	8.38•	0.001
Blood Eosinophil / cmm^3	Mean ± SD	0.34 ± 0.06	0.20 ± 0.04	12.9•	0.001
	Range	0.25 – 0.46	0.1 – 0.24		
Sputum TLC/ cmm^3	Mean ± SD	1.40 ± 0.36	1.35 ± 0.29	0.10•	0.91
Sputum neutrophils %	Mean ± SD	75.27 ± 5.37	79.61 ± 4.00	4.08•	0.001
Sputum lymphocytes %	Mean ± SD	5.43 ± 1.02	4.95 ± 0.60	2.52•	0.013
Sputum eosinophil / cmm^3	Mean ± SD	0.39 ± 0.06	0.26 ± 0.04	10.80•	0.001
	Range	0.3 – 0.52	0.17 – 0.33		
Sputum eosinophil %	Mean ± SD	4.20 ± 1.20	2.62 ± 0.42	7.78•	0.001
	Range	2.95 – 7.1	1.77 – 3.21		

P-value >0.05: Non-significant; P-value <0.05: Significant; *: Chi-square test; •: Independent t-test, TLC: total leucocytic count

Table (4): Correlation of blood eosinophil/ cmm^3 with studied variables in eosinophil ^{high} AECOPD subgroup

Item	Eosinophil ^{high} AECOPD (No. =41)	
	R	p
Age /year	0.73**	0.001
BMI (kg/m^2)	0.94**	0.001
Smoking index (pack/year)	0.93**	0.001
FEV_1/FVC ratio	-0.94**	0.001
FVC %	-0.94**	0.001
FEF25-75%	-0.94**	0.001
FEV_1 %	-0.94**	0.001
Blood TLC/ cmm^3	0.18	0.24
Blood neutrophil %	-0.92**	0.001
Blood lymphocyte %	0.92**	0.001
Blood Eosinophil %	0.93**	0.001
Sputum TLC/ cmm^3	-0.92**	0.000
Sputum neutrophils %	-0.89**	0.000
Sputum lymphocytes %	0.87**	0.001
Sputum Eosinophil / cmm^3	0.99**	0.001
Sputum Eosinophil %	0.92**	0.001

FEV1/FVC: forced expiratory volume in first second, FEV1: forced expiratory volume in first second, FEVE25-75%: forced expiratory flow at 25-75% of vital capacity, BMI: body mass index, TLC: total leucocytic count

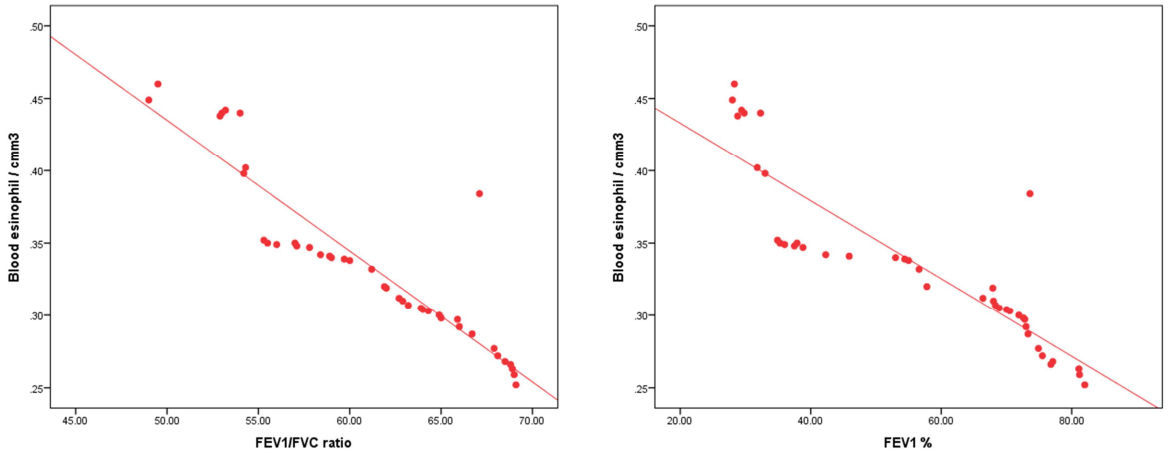

Figure (1): Correlation of blood eosinophil/ cmm^3 with FEV_1/FVC ratio, FEV_1% and FVC% in eosinophil high AECOPD subgroup

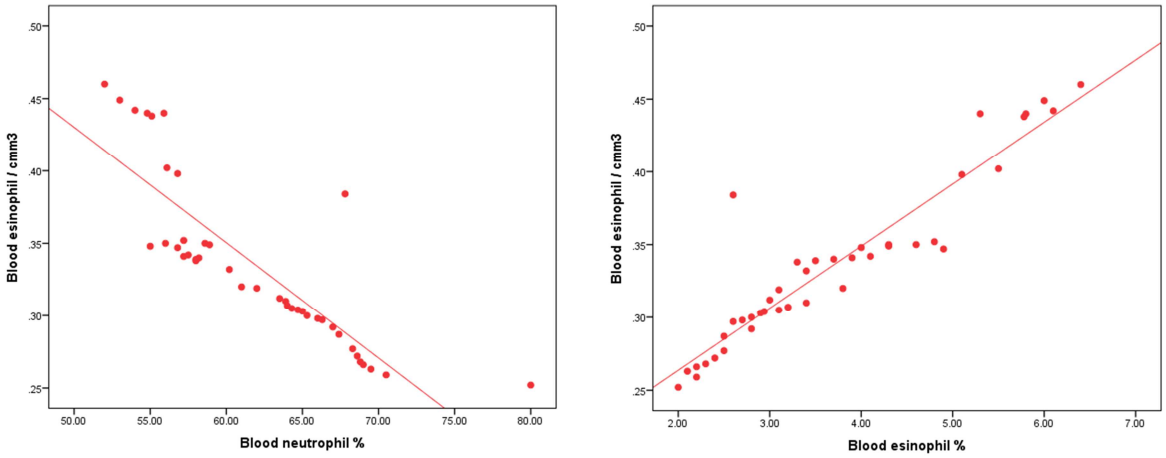

Figure (2): Correlation of blood eosinophil/ cmm^3 with blood neutrophils % and eosinophils % in eosinophil ^{high} AECOPD subgroup

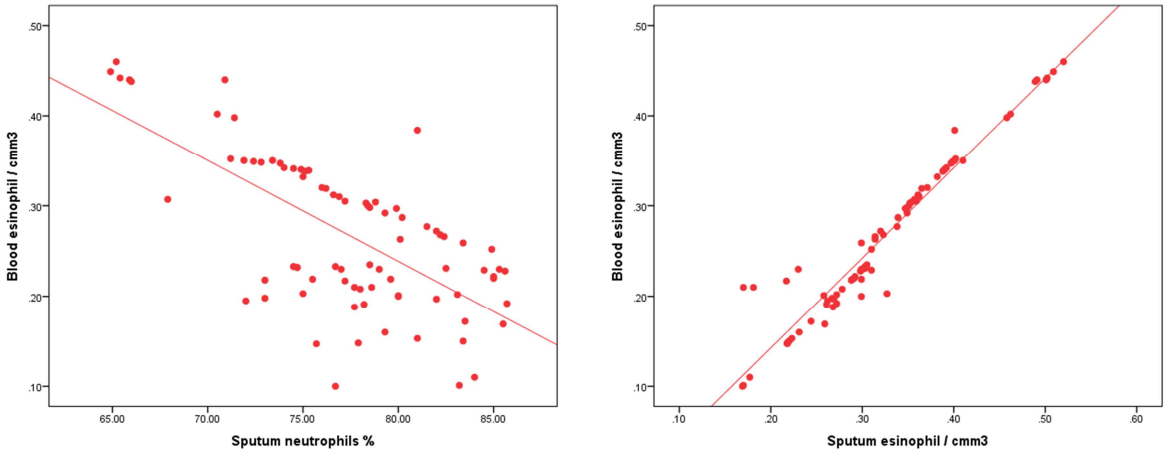

Figure (3): Correlation of blood eosinophil/ cmm^3 with blood neutrophils % and eosinophils % in eosinophil ^{high} AECOPD subgroup

Table (5): Comparison of sputum bacterial culture and load between eosinophil ^{high} and eosinophil ^{low} AECOPD subgroups

Sputum culture and bacterial load		Eosinophil ^{high} AECOPD No. (%)		Eosinophil ^{low} AECOPD No. (%)		Test *	p
Bacterial load	Colonization (< 10 ^{4}/ml CFU)	16	(39.0%	10	25.6%	1.63	0.20
	Infection (≥ 10 ^{4} /ml CFU)	**25**	**61.0%**	**29**	**74.4%**		
Organisms	No growth	16	39.0%	8	20.5%	7.75	0.17
	Streptococcal pneumoniae	5	12.2%	7	17.9%		
	Hemophalus influenzae	9	22.0%	8	20.5%		
	Staphylococcus aureus	6	14.6%	5	12.8%		
	Pseudomonas aeruginosa	3	7.3%	2	5.1%		
	Candida	2	4.9%	9	23.1%		

P-value >0.05: Non-significant; P-value <0.05: Significant;*:Chi-square test, CFU: colony forming unit

DISCUSSION

The underlying inflammatory pattern in COPD patients can differ; it is most commonly dominated by neutrophils, CD8$^+$T cells, and macrophages. Eosinophils may show an important role in bronchial inflammation in some COPD patients [15]. Yet, researchers studying the use of peripheral eosinophils in identifying sputum eosinophilia in COPD are lacking[6]. Therefore, this study was carried out to assess

the relationship between eiosinophilic AECOPD and sputum inflammation and sputum bacterial load.

The main finding of the current study is that 51.25% of the studied patients had eosinophil ^{high} AECOPD and 48.75% of them had eosinophil ^{low} AECOPD. This finding is combatable with earlier studies identifying increased eosinophilic airway inflammation at the time of COPD exacerbation [2], [10], [16-19].Similar results were reported by **Kim et al.**[20] as the prevalence of eosinophilic inflammation during acute exacerbation in blood and sputum was 49.7% and 23.9% respectively. Additionally, other studies have described association between higher eosinophils counts and increased risk of exacerbation [10], [18-19]. **Fujimoto et al.** [21] reported that eosinophil concentrations were significantly increased during stable-and unstable-COPD than healthy non-smokers. Moreover, higher levels of eosinophil chemotactic factors were detected in sputum of AECOPD patients compared to stable phase. However, slightly lower prevalence of eosinophils count had been reported by **Choi et al.** [22] as 28.2% of AECOPD patients have eosinophil counts of ≥2% and 74.2% have eosinophil counts of <2%.

Our study revealed that the age, BMI, smoking status, and smoking index (pack/year) and male gender were significantly higher in eosinophil ^{high} than eosinophil ^{low} AECOPD patients. Moreover, the blood eosinophil /cmm^{3}were positively correlated with age, BMI and smoking index in eosinophil ^{high} AECOPD. The predominance of males in our eosinophil ^{high} AECOPD patients may be ascribed to the degranulatory consequence of estradiol on peripheral eosinophils, it is suggested that estrogen acts directly on the eosinophils, possibly through specific hormone receptors [23]. Additionally, smoking affects degree of airway inflammation and increase migration of eosinophils from the blood to airways [2], [24]. In accordance with our results previous studies reported that COPD patients with blood eosinophilia were older in age, with higher male proportion, and had a smaller percentage of current smokers [6], [8]. **Mathur et al.** [25] study revealed important influence of increasing age on blood eosinophil stability, which suggest the use of eosinophils as a biomarker in routine COPD management. On the other hand, **Choi et al.** [22] documented that no significant difference in age, gender, smoking status or smoking index was found between COPD patients with eosinophils count ≥ 2% and those with eosinophils count <2%.

In the current study chest wheeze was significantly common in patients with eosinophil ^{high} than those with eosinophil ^{low} AECOPD. Additionally, patients with eosinophil ^{high} AECOPD had more severe acute exacerbation compared to those with eosinophil ^{low} AECOPD. This finding pointed out that in some COPD patients; eosinophils leads to inflammation that promotes bronchial narrowing, exhibited more severe airway inflammation and more severe acute exacerbation attacks [2], [24].Additionally, it has been suggested that incidence and severity of AECOPD was a consequence of reduced macrophage efferocytosis of eosinophils [26].

Other studies documented a relationship between high eosinophil concentration and AECOPD; they also noted higher eosinophils levels during exacerbation phase compared to stable phase, with increased risk of exacerbation [2], [10], [17-19]. In the Copenhagen General Population Study a high peripheral eosinophil concentrations at baseline predicted an increased frequency of severe exacerbations over a 3-year follow up [10]. In other studies, high eosinophil levels were linked to an increased risk of future exacerbations [10], [18], [27-29] .**Siva et al.** [30] found that there is an association between eosinophilic airway inflammation and severe AECOPD. Similarly, **Vedel-Krogh et al.**[10] reported that the elevated peripheral eosinophil concentrations subgroup have greater chance of suffering from wheezing during a cold attacks. Conversely, a retrospective study suggested that higher eosinophils counts protected against disease exacerbation. While, other researches failed to detect any relationship [6], [10], [31]. This disparity may be ascribed to different COPD severities included in several studies and timing of blood sampling. Other possible confounding variables may include type of specimens, characteristics of the study patients, and presence other pre-existing diseases.

Reports of relationships between eosinophils, FEV_1 and exacerbation fluctuate, but evolving evidence suggests determination of eosinophils has clinical relevance [8], [10], [32].The present study found that patients with eosinophil ^{high} AECOPD had more severe COPD with significantly higher FVC% and non-significant decrease of FEV_1% than eosinophil ^{low}. In eosinophils ^{high} AECOPD group the blood eosinophils /cmm^3 were negatively correlated with FEV_1/FVC ratio, FEV_1 % and FEF25-75 %. These findings support the earlier one stated that eosinophils roam to the lungs under effects of cytokines. When in the lungs it releases pro-inflammatory mediator's e.g. basic protein, cytokines and growth factors which promote persistent severe airway inflammation and airflow limitation [33], [34-36]. The precise nature of the relation between eosinophilic inflammation rates of decline in pulmonary functions in COPD patients remains unclear [17]. In a small number of patients with moderate–severe COPD, lower FEV_1 values were related to higher sputum concentrations of eosinophils and eosinophil cationic protein, potentially suggesting a

link between airway eosinophilia and airflow obstruction [37]. Our finding is consistent with earlier work shown an association between eosinophilic airway inflammation and severe COPD [2], [16], decrease in FEV_1 [24], and decline in lung function [8]. **Choi et al.** [22] reported that the absolute FEV_1 was significantly lower in in COPD patients with high eosinophils count, however, the FEV_1 % and FEV/FVC ratio were non-significantly differed between COPD patients with high and low eosinophils count. Additionally most of COPD patients with eosinophils ≥ 2 have moderate or severe COPD. In the COPD cohort of the Copenhagen General Population Study, individuals with greater peripheral eosinophil concentrations (≥340 cells/μL) had somewhat lower FEV_1% compared to individuals with lower eosinophil counts [10]. Results from another cross-sectional study support a negative relationship between the sputum eosinophilia and FEV_1 [38]. Moreover, **Bafadhel et al.** [2] reported that there was an relationship between the peripheral eosinophil count and death from AECOPD. In contrast, in the ECLIPSE study, a subgroup of patients with blood eosinophil counts ≥2% had a higher mean FEV_1% than patients with blood eosinophil counts <2% [8]. **Górska et al.** [39] reported that neutrophilic phenotype of COPD was related to more severe airway obstruction and air trapping.

The current study demonstrated that the blood TLC/cm^3 and blood neutrophils % were significantly lower, while blood lymphocyte % was significantly higher in eosinophil ^{high} than eosinophil ^{low} AECOPD. Moreover, in eosinophil ^{high} AECOPD subgroup, the blood eosinophil /cmm^3 was negatively correlated with blood neutrophils % and positively correlated with blood lymphocytes % and eosinophils %. This matched with **Bafadhel et al.** [2] as they found that neutrophil-lymphocyte ratio was significantly higher in the non-eosinophilic group. Also, **MacDonald et al.** [40] documented that eosinophil counts were negatively correlated with TLC and neutrophil count. Our result was not matched with that reported by **Siddiqui et al.** [18] as they found higher TLC count in eosinophilic high COPD group.

The recognition and quantification of airways eosinophilia mostly necessitate the assessment of sputum [6]. However, the capability of blood eosinophils to predict sputum eosinophilia has been described, with promising results [41-44]. Our study revealed that the sputum lymphocytes %, eosinophils/cmm^3, and eosinophils % were significantly increased, while the sputum neutrophils % was significant decreased in eosinophil ^{high} compared to eosinophil ^{low} AECOPD. Moreover, in eosinophil ^{high} AECOPD subgroup, the blood eosinophils/ cmm^3 was negatively correlated with sputum neutrophils % and positively correlated with sputum lymphocytes %, and eosinophils /cmm^3, and percentage. Similarly, **Belda et al.** [45] shown increases in lymphocyte% in high eosinophilic AECOPD group. Blood eosinophils⩾2% recognized sputum eosinophilic inflammation (>3%) at exacerbation, with 90% sensitivity and 60% specificity [2]. Additionally, eosinophilic COPD, defined as sputum eosinophils levels ≥3%, is reported in up to 28% of patients during exacerbations [2], and in 34% [40] and 38% [46] of COPD patients during periods of stability. There is reasonably good association between blood and airway eosinophil concentrations [20]. **Kolsum et al.** [4] reported that at exacerbation there was a stronger correlation of blood eosinophil % and absolute counts with sputum eosinophil %. Other studies reported that the blood eosinophils was correlated with both the percentage and number of sputum eosinophils [2], [6], [8],.[47]. Absolute blood eosinophil count was predictive of sputum eosinophilia. However, **Negewo et al.** [6] documented that the blood lymphocytes and TLC were non-significantly differ between two subgroups.

Bacteria play a significant role in AECOPD [48]. In this regards, our study revealed that sputum bacterial infection was non-significantly higher in eosinophil ^{low} than eosinophil ^{high} AECOPD (74.4% vs. 61.0%). Also, the type of the isolated bacteria did not differ between both AECOPD subgroups. These findings have a probable implication for upcoming therapeutic clinical trials and eosinophil targeted treatment with a view to stratifying patient care as postulated by **Kim et al.** [20]. The relationship between bacterial infection and eosinophil concentrations is not established in COPD [49,50]. This relationship could be bidirectional; a decrease in circulating eosinophils in eosinophils low AECOPD could be consequence of adrenal glucocorticoid stimulation in response to the stress of bacterial infection or the rapid collection of eosinophils at the inflammatory site [4]. On the other hand, the mechanism responsible for decreasing eosinophil levels during bacterial infection is uncertain. Eosinophils can activate innate immune responses to microbes through the release of extracellular DNA traps and the expression of specific pattern recognition receptors including Toll like receptor-4 [51-52]. Moreover, **Kolsum et al.** [4] documented that patients with eosinophil levels ≥2% may have better capability of clearing the lungs of infections before developing pneumonia compared to patients with <2% eosinophil levels, due to the antimicrobial defense of eosinophils. Bacterial infections stimulate bronchial smooth muscle cells to release C-X-C motif chemokine (CXCL)-8 that increase neutrophil recruitment, furthermore, eosinophilic proteins have bactericidal activity [53]. Our results were matched with **Bafadhel et al.** [54] and **Soler et al.** [55] as they showed negative relationship between sputum eosinophils and sputum bacterial load

throughout the stable phase with reduced blood eosinophil during AECOPD associated with bacterial infection. **Kim et al.** [20] reported that eosinophilic AECOPD are less commonly associated with airway bacterial infection, with the prevalence of airway bacterial infection at exacerbations greater among low eosinophils group over time. Bacterial AECOPD had been formerly documented to be less commonly accompanied with sputum eosinophilia. **Cheng and Lin** [56] found that COPD patients with eosinophil counts (≥3%) had no difference in pneumonia incidence than those with low eosinophils counts. Results from a much larger retrospective study revealed that COPD patients had fewer attacks of pneumonia if they had a blood eosinophil ≥2% [28].In agreement with this result, a negative relationship between bacterial infection and blood eosinophil has been detected in patients with AECOPD [57]. There may be an inverse relationship between blood eosinophils and bacterial infection, as blood eosinophil counts area known to be reduced during severe bacterial infection [49-50].

The prevalence of bacterial infection and colonization in our study (61.0% and 74.4%) was comparable to that reported in previous studies as; **Kolsum et al.** [4] reported a prevalence of52%, **Bafadhel et al.** [54] reported 51% a prevalence and **Barker et al.** [58] reported 77% prevalence. **Choi et al.** [22] reported that only bacterial pathogen was significantly identified in in COPD patients with eosinophils count < 2% than COPD patients with eosinophils count ≥2% (29.7% vs. 20.0%). Additionally, the bacterial- viral pathogen was identified in COPD patients with eosinophils count < 2% compared to COPD patients with eosinophils count ≥2% (17.0% vs. 7.4%).

The main strength of the current study is that we defined bacterial load based on the quantitative culture in addition to a species specific. The present study has some limitations that deserve to be mentioned; first we categorize blood eosinophilia based on eosinophil % which is affected by calculations of percentage relative to neutrophils. Our result may be underpowered due to small sample size.

CONCLUSION

Eosinophilic AECOPD is common; it was related to airway inflammation. The non-significant inverse relationships between eosinophil count and bacterial loads may be a significant factor in determining therapeutic plane to the patients. The clinical significance of this study lies in the fact that a very simple test may permit the physician to definitely stratify underlying inflammatory types of AECOPD.

Conflict of interest

The authors declared that there is no direct or indirect conflict of interest

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الملخص العربي

الحمضات فى الدم وعلاقتها بالتهابات البصاق والحمل البكتيرى فى البصاق في مرضى التفاقم الحاد لمرض ضيق الشعب الهوائية المزمن

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ملخص البحث :

الخلفية: لا يُعرف سوى القليل عن دور الحمضات في الفيزيولوجيا المرضية للتفاقم الحاد لمرض ضيق الشعب الهوائيه المزمن.

الهدف: تقييم علاقة الحمضات في مرضي التفاقم الحاد لمرض ضيق الشعب الهوائيه المزمن مع الإلتهابات بالبصاق والحمل البكتيري فى البصاق.

الطرق: أجريت دراسة مستعرضة على 80 من أصل 189 مريضا من مرضي التفاقم الحاد لمرض ضيق الشعب الهوائية المزمن وقد خضع جميع المشاركين لقياس وظائف التنفس، عدد كريات الدم البيضاء الكلي والنوعى، مزرعه وحمل بكتيري للبصاق. تم تقسيمهم إلى مجموعتين فرعيتين على أساس نسبة حمضات الدم؛ مجموعة مرضي التفاقم الحاد لمرض ضيق الشعب الهوائيه المزمن ذوي الحمضات المرتفعه (≤2%) ومجموعة مرضي التفاقم الحاد لمرض ضيق الشعب الهوائيه المزمن ذوي الحمضات المنخفضة <2%

النتائج :بين المرضي الذين شملتهم الدراسة 51.25 ٪ مريضا لديهم حمضات مرتفعة و 48.75 ٪ لديهم حمضات منخفضة. المرضى ذوى الحمضات المرتفعة كانوا أكبر سنا، مع زيادة مؤشر كتلة الجسم، حالة التدخين، معدل التدخين، الأزيزا والسعة الحيوية للرئة، كما كان مرض ضيق الشعب الهوائية المزمن و تفاقمه أكثر حدة لديهم مقارنة مع المرضى ذوى الحمضات المنخفضة. في مرضى التفاقم الحاد ذوى الحمضات المرتفعة كانت كرات الدم البيضاء و خلايا العدلات أقل بينماكانت الخلايا اللمفاوية و خلايا الحمضات و نسبتها أعلى أحصائيا عنهم فى مرضى التفاقم الحاد ذوى المحمضات المنخفضة. فيما يتعلق بالخلايا الألتهابية البصاق كانت الخلايا الليمفاوية وخلايا الحمضات و نسبتها أعلى بينما خلايا العدلات كانت أقل احصائيا في مرضى التفاقم الحاد ذوى الحمضات المرتفعة مقارنة مع المرضى ذوى الحمضات المنخفضة. فى مجموعة التفاقم الحاد ذوى الحمضات المرتفعة كانت خلايا الحمضات بالدم تتناسب طرديا مع السن، مؤشر كتلة الجسم، معدل التدخين، الخلايا الليمفاوية و نسبة خلايا الحمضات بالدم, الخلايا الليمفاوية و نسبة خلايا الحمضات بالبصاق، بينما تتناسب عكسيا مع كرات الدم البيضاء، خلايا العدلات بالدم و البصاق، النسبة ما بين أقصى معدل للزفير فى الثانية الأولى / السعة الحيوية للرئة، أقصى معدل للزفير فى الثانية الأولى، تدفق الزفير القسري 25-75%، السعة الحيوية للرئة. كان الحمل البكتيري فى البصاق أقل بشكل غير واضح أحصائيا في المرضى ذوى الحمضات المرتفعة عنه فى المرضى ذوى الحمضات المنخفضة. كما أن نوع البكتيريا المعزولة لم يختلف بين مجموعتين التفاقم الحاد لمرض ضيق الشعب الهوائية المزمن.

الأستنتاجات: زيادةالحمضات في التفاقم الحاد لمرض ضيق الشعب الهوائية المزمن شائع ومرتبطًا بالتهابات الشعب الهوائية ولا يؤثر على الحمل البكتيري للبصاق أو أنواع البكتيريا المعزولة.

كلمات مفتاحية: التهابات الشعب الهوائية، التفاقم الحاد لمرض ضيق الشعب الهوائية بالحمضات، حمضات البصاق، الحمل البكتيرى فى البصاق

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