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Can blood eosinophil count be used as a predictive marker for the severity of COPD and concomitant cardiovascular disease? The relationship with the 2023 Version of the Global Initiative for Chronic Obstructive Lung Disease Staging

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Abstract. – OBJECTIVE: This study was designed to investigate the relationship between eosinophil count and cardiovascular disease (CVD) in subjects with chronic obstructive pulmonary disease (COPD) and the correlation between eosinophil count and the risk of exacerbations in COPD.

PATIENTS AND METHODS: The study included 405 patients who met the study inclusion criteria. Of the participants, 100 (25%) were classified as Global Initiative for Chronic Obstructive Lung Disease (GOLD) A, 105 (26%) as GOLD B, and 200 (49%) as GOLD E. Routine blood tests (including leukocyte count and differential leukocyte count, hemoglobin, and platelet count) were carried out using an automated hematology analyzer.

RESULTS: The eosinophil count and eosinophil percentage were significantly higher in 158 patients with COPD and concurrent CVD than in the COPD patients without concurrent CVD [2.95 (2.4), *p*=2.309e-11, 1.9 (2), *p*=5.02e-08, respectively). The prevalence of CVD was higher in the GOLD E group that experienced prominent exacerbations, and while the eosinophil count was also higher (*p*=.03) in this group, the eosinophil percentage did not differ significantly in this group of patients.

CONCLUSIONS: The results of our study indicate a strong relationship between eosinophils and cardiovascular events in COPD subjects, particularly in subjects at high risk of exacerbations and cardiovascular complications.

Key Words:
Chronic obstructive pulmonary disease, Eosinophils, Cardiovascular disease.

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the three leading causes of morbidity and mortality worldwide[1]. Comorbidities, especially cardiovascular diseases, are known to have a significant impact on prognosis. Mortality related to COPD has been found to be associated mostly with cardiovascular comorbidities[2], and based on this strong relationship, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) considers cardiovascular disease (CVD) to be the most important potential co-existing condition in cases of COPD. The GOLD thus recommends[3] the routine investigation of patients with COPD for the presence of CVD but offers no recommendations on how to perform such investigations.

The heterogenicity of inflammatory patterns in patients with COPD has recently attracted significant attention[4]. Until recently, COPD was considered to be a neutrophil-mediated inflammatory disease, unlike asthma in which a Th2-mediated eosinophilic response is involved, although cases of eosinophil-associated airway inflammation have been reported[5,6] to a certain extent in COPD patients with stable disease and during exacerbations. The required facilities for sputum analysis, however, are not widely available, and such processes require particular technical expertise. Based on evidence[7,8] indicating the participation of eosinophils in the peripheral blood in the

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pathophysiological mechanisms of the disease and their easy accessibility, it has been suggested that peripheral blood eosinophils may serve as a marker of eosinophilic airway inflammation. Furthermore, studies[9] analyzing the relationship between eosinophil count and coronary artery disease (CAD) have reported that, despite the low number of eosinophils in atherosclerotic plaque, eosinophils could promote plaque progression in the coronary arteries and lead to cardiovascular events through the release of mediators.

The increasing interest in the recognition of inflammatory patterns in COPD is aimed at identifying disease characteristics that may be targeted by particular therapeutic interventions[10]. Although targets of different conditions may be similar, the identification of these targets may aid in the identification of patients who would benefit most from specific therapies. Aside from studies[11,12] suggesting the use of blood eosinophil count as a biomarker to determine the risk of exacerbations and to predict response to corticosteroid therapy, the finding that it can also be used to determine the risk of cardiovascular events may promote the development of a customized therapy targeting the above-mentioned specific phenotype. In this regard, eosinophils may be considered a promising biomarker for the identification of patients with COPD who may have poor cardiovascular outcomes. In light of these data, the present study evaluates the relationship between the peripheral blood eosinophil count of patients with COPD and the risk of exacerbations and cardiovascular events through the application of the latest version of the GOLD criteria and examines the potential use of blood eosinophils as a biomarker for the prediction of response to therapeutic interventions.

Patients and Methods

Study Population and Study Design

The inclusion criteria of the study were patients presenting to the Chest Disease Clinic of the Sütçü İmam University Faculty of Medicine who were diagnosed with COPD based on the GOLD criteria. The GOLD 2023 Report[1] is the fifth extensive revision of the GOLD, containing an update of all the data examined by the Science Committee from 2021 to 2022 and an evaluation and revision of all the recommendations related to the diagnosis, assessment, and treatment of COPD. The main steps in the multidimensional approach to the assessment suggested in the 2011 GOLD report[13] were the incorporation of patient-reported outcomes and emphasis on the importance of exacerbations in the management of COPD. This version[13] relied on both the severity of airflow obstruction (GOLD grades 1-4) and the frequency of previous exacerbations. The GOLD 2023 Report[1] recommends further improvements to the combined A-B-C-D assessment approach, recognizing the clinical significance of exacerbations independent of the severity of the patient's symptoms. While groups A and B have remained unchanged, groups C and D have been merged to create one group named "E" to emphasize the clinical significance of exacerbations. The GOLD criteria for COPD stages are defined as follows:

1-GOLD A: 0 or 1 moderate exacerbations/not leading to hospitalization, Medical Research Council (mMRC): 0-1 or COPD assessment test (CAT)<10

2-GOLD B: 0 or 1 moderate exacerbations/not leading to hospitalization, mMRC≥2 or CAT≥10

3-GOLD E: ≥2 moderate exacerbations or ≥1 leading to hospitalization[1].

The GOLD grades of the participants in the present study were determined accordingly.

The patients' demographic characteristics and medical history, as well as such clinical data as any history of metabolic or CVD, history of exacerbations or hospital admissions within the last year, and smoking status, were retrieved from the standard medical patient records. Smoking status was expressed in pack years and calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked.

Patients with autoimmune disorders, permanently taking systemic glucocorticoids due to COPD, histories of allergic disease, parasitic infections, concurrent infections, malignancies, severe impairment in liver and kidney function, asthma, heart failure or shock, rheumatic heart disease and valvular heart disease were excluded from the study to limit the potential confounding factors.

The presence of CVD was defined as a history of CAD, heart failure or arrhythmia. The CAD was defined as a positive clinical history of CAD, abnormal stress test results including ischemia, or the presence of >50% stenosis detected by coronary angiogram. Heart failure was defined as the

presence of functionally or structurally impaired ventricular filling or blood ejection. Arrhythmia was defined as the presence of an irregular heart rhythm, including both very fast and very slow heart rates.

Routine blood tests (including leukocyte count and differential leukocyte count, hemoglobin, and platelet count) were carried out using a Sysmex XN-1000 automated hematology analyzer (Sysmex XN-1000 Corporation, HQ: Kobe, Japan). The study was approved by the Aydın Adnan Menderes University Ethics Committee and conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

Descriptive statistics included means, standard deviations, medians, minimums and maximums, frequencies and ratios. The statistical analysis of the study data was performed using R version 4.1.2 (2021-11-01) [R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria]. A Shapiro-Wilk Normality test was used to test the distribution of the variables; Bartlett's test was used to evaluate the homogeneity of variances; an analysis of variance (ANOVA) (Tukey test) or independent samples *t*-test was used, depending on the number of groups and parametric assumptions to analyze the independent quantitative variables. A Kruskal-Wallis test or Mann-Whitney U test was used if the parametric assumptions were not met. A Fisher's exact test or a Chi-square test was used in the analysis of independent qualitative variables. Pearson's correlation coefficient or Spearman's rank correlation coefficient was used for the correlation analysis. A p-value lower than 0.05 (p-value<0.05) was considered statistically significant.

Results

The study included 405 patients who met the study inclusion criteria. Of the participants, 100 (25%) were classified as GOLD A, 105 (26%) as GOLD B and 200 (49%) as GOLD E. The characteristics of the patients are presented in Table I. The mean age was 61.84 years, 85% of the patients were males, and the severity of the airflow limitation ranged from mild to severe, as estimated by forced expiratory volume in 1 s (FEV_1).

There were significant differences between the GOLD categories in terms of absolute eosinophil count and eosinophil percentage (Table I) (Figure 1), and a significant difference in the eosinophil counts and eosinophil percentages of the subjects in categories A and E (p<.0001), and those in categories B and E (p<.0001). Eosinophil percentages showed a similar distribution between females and males (p=.55), although the eosinophil percentage increased with increasing age (p=.03, r=0.10). The COPD subject subgroups were also compared in terms of eosinophil count and eosinophil percentages based on FEV_1 GOLD stages, the CAT (<10 *vs.* >10), the patient's exacerbation history (0-1 *vs.* ≥2) and the mMRC dyspnea scale (0-1 *vs.* ≥2). The eosinophil count and eosinophil percentage differed significantly according to the category of each COPD parameter (Table II).

Significant differences were also revealed when the subjects were grouped according to the presence of concurrent CVD and hypertension.

Table I. Characteristics of the study population.

Subjects	
Gender, M/F	85%/15%
Age, years	61.84 [IQR=15]
Traditional risk factors for CVD	
Smoking, packs/year	35 [IQR=12.5]
BMI (kg/m^2)	25.30 [IQR=4.8]
Diabetes mellitus (n, %)	No: 360 (89%)
Yes: 45 (11%)	
Hypertension (n, %)	No: 295 (73%)
Yes: 110 (27%)	
CVD (n, %)	No: 247 (61%)
Yes: 158 (39%)	
GOLD subgroups	
A	100 (25%)
B	105 (26%)
E	200 (49%)
Predicted FEV_1	
≥80%	54 (13%)
50-80%	173 (43%)
50-30%	138 (34%)
<30%	40 (10%)
CAT, mean	10 [IQR=6]
<10	198 (49%)
≥10	207 (51%)
Exacerbations (Total)	
0-1	204 (50%)
≥2	201 (50%)
mMRC	
0-1	178 (44%)
≥2	227 (56%)
Eosinophil count	2.1 [IQR=2.2]
Eosinophil percentage	2 [IQR=2.1]

CVD: Cardiovascular Disease, BMI: Body Mass Index, GOLD: Global Initiative for Chronic Obstructive Lung Disease, CAT: COPD Assessment Test, mMRC: modified Medical Research Council dyspnea scale, IQR: interquartile range, FEV_1, forced expiratory volume in 1 s.

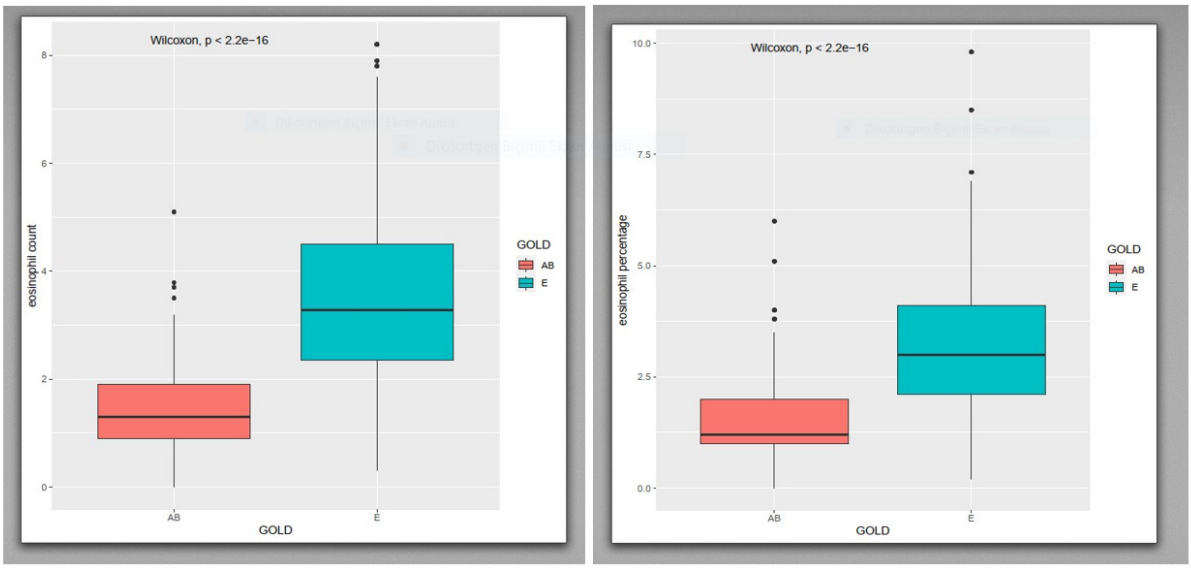

Figure 1. Eosinophil count and eosinophil percentage of subjects grouped according to Global Initiative for Chronic Obstructive Lung Disease categories.

Table II. Peripheral blood eosinophil count and percentage of blood eosinophils of subjects in COPD subgroups.

Variable		Eosinophil count			Eosinophil percentage		
		n	Median [IQR]	p	n	Median [IQR]	p
Gender	Female	61	2.1 [2.2]	0.74	61	2 [2.1]	**0.55**
	Male	343	2.1 [2]		343	2.1 [1.9]	
FEV_1 (GOLD stages)	1 (≥80%)	54	1.23 [1.4]	**1.514e-13**	54	1.6 [1.6]	**2.13e-08**
	2 (50-80%)	173	1.60 [0.4]		173	1.55 [2]	
	3 (50-30%)	138	3.10 [3.1]		138	3 [1.7]	
	4 (<30%)	40	2.5 [2.2]		40	3 [2]	
FEV_1 (median split)							
GOLD stages	A	100	1.1 [0.8]	**<2.2e-16**	100	1.03 [0.9]	**<2.2e-16**
	B	105	1.6 [1]		105	1.30 [1]	
	E	200	3.3 [2.2]		200	3 [2]	
CAT	<10	198	1.6 [1.7]	**5.939e-07**	198	2 [2.1]	**0.01674**
	≥10	207	2.5 [2.4]		207	2 [2]	
Exacerbations	0-1	204	1.3 [1]	**<2.2e-16**	204	1.2 [1]	**<2.2e-16**
	≥2	201	3.2 [2.2]		201	3 [2]	
mMRC	0-1	178	1.6 [2.1]	**0.0002485**	178	2 [2.1]	**0.0184**
	≥2	227	2.3 [2.1]		227	2 [2]	
BMI	≥30	63	2.1 [2]	0.2063	63	3 [2.1]	**0.02796**
	<30	342	2.1 [2.2]		342	2 [2.1]	
CVD	No	247	1.60 [1.5]	**2.309e-11**	247	3.0 [1.9]	**5.02e-08**
	Yes	158	2.95 [2.4]		158	1.9 [2]	
DM	No	360	2.1 [2]	0.08	360	2 [2.1]	**0.002142**
	Yes	45	2.5 [2.5]		45	3 [2.2]	
HT	No	295	1.9 [2]	**2.105e-05**	295	2 [2]	**7.259e-05**
	Yes	110	2.6 [2.6]		110	2.8 [2]	
CVD in GOLD E stage	No	87	3.2 [1.5]	0.038	87	3 [1.75]	0.33
	Yes	113	3.5 [2.9]		113	3.1 [1.9]	

COPD: Chronic obstructive pulmonary diseases, GOLD: Global Initiative for Chronic Obstructive Lung Disease, CAT: COPD Assessment Test, BMI: Body Mass Index, mMRC: modified Medical Research Council dyspnea scale, CVD: Cardiovascular Disease, DM: Diabetes Mellitus, HT: Hypertension, IQR: interquartile range, FEV_1, forced expiratory volume in 1 s.

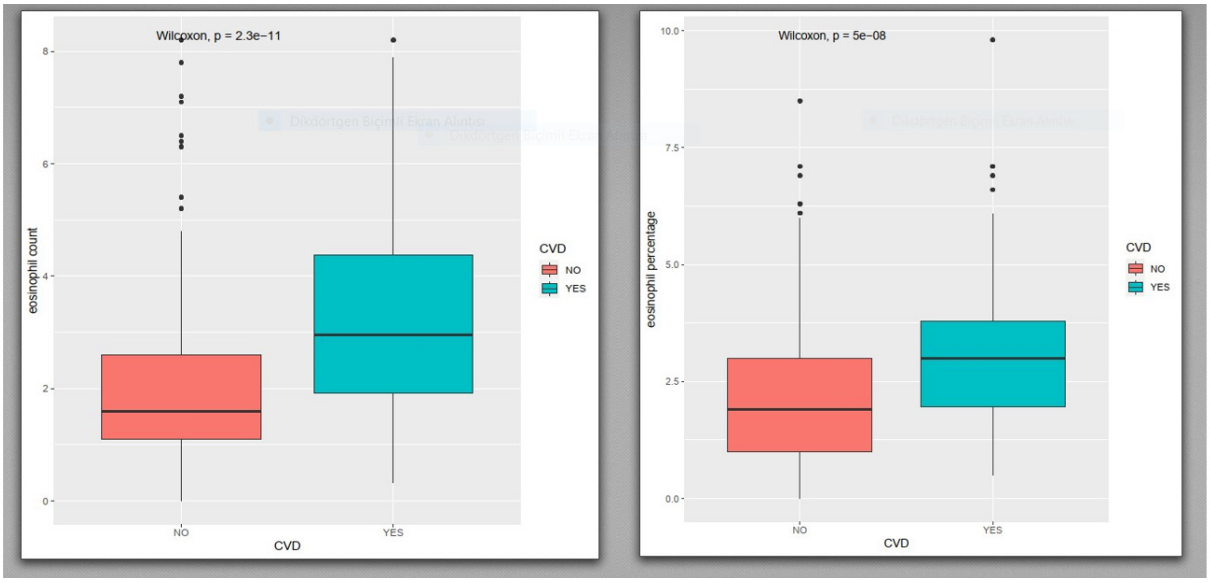

Figure 2. Eosinophil count and eosinophil percentage in subjects with and without cardiovascular disease in COPD subjects.

The eosinophil count and eosinophil percentage were significantly higher in 158 patients with COPD and concurrent CVD than in the COPD patients without concurrent CVD [2.95 (2.4), *p*=2.309e-11, 1.9 (2), *p*=5.02e-08, respectively] (Table II) (Figure 2). The prevalence of CVD was higher in the GOLD E group, and while the eosinophil count was also higher (*p*=.03) in this group, the eosinophil percentage did not differ significantly in this group of patients (Table II) (Figure 3).

A Pearson's correlation analysis revealed the eosinophil count and eosinophil percentage to be significantly inversely correlated with the percentage of predicted FEV_1 (r=-0.32, *p*=4.307e-11, r=-0.24, *p*=9.303e-07, respectively). Furthermore, a positive correlation was found between eosinophil count and eosinophil percentage and the results of CAT, mMRC dyspnea scale and exacerbation history (r=0.31, *p*: 3.026e-10, r=0.20, *p*=7.77e-05, r=0.26 *p*=8.724e-08, r=0.20 *p*=4.676e-05, r=0.6 *p*=2.2e-16, r=0.6 *p*=2.2e-16, respectively) (Table III) (Figure 4).

The potential factors defining CVD were further examined with univariate analysis, and all parameters that were found to be related to CVD at a significance level lower than 0.1 were further evaluated with a multiple regression analysis. Sex, hypertension, diabetes mellitus (DM), number of exacerbations, age, FEV_1, body mass index (BMI), and smoking history were included in the final regression model, and five factors other than age, DM, and smoking history were subsequently identified as independent predictors of CVD (Table IV).

In the present study, we concluded two major findings. First, the blood eosinophil counts are significantly higher in the GOLD-E category, underlining the clinical importance of exacerbations independent of the severity of the patient's symptoms. Second, in this same group of pa-

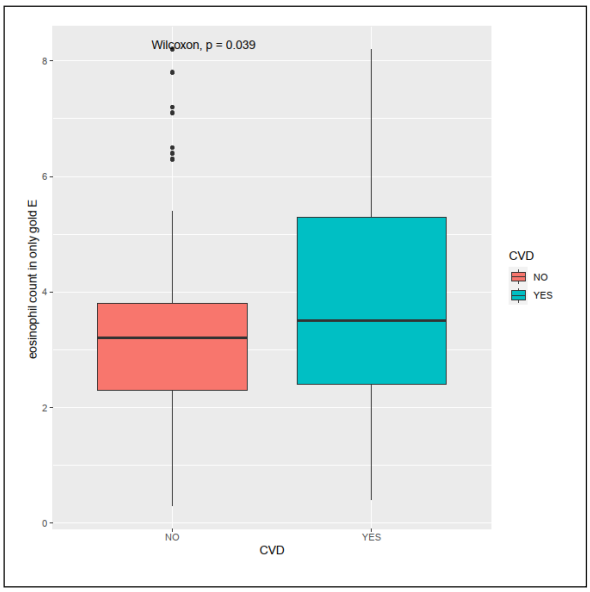

Figure 3. Eosinophil count in subjects with and without cardiovascular disease in COPD with Global Initiative for Chronic Obstructive Lung Disease E stage.

Table III. Results of Spearman's correlation analysis on all subjects included in the study.

Variable	Eosinophil count		Eosinophil percentage	
	r	p	r	p
BMI	0.0016	0.974	0.071	0.15
Age (year)	0.05	0.2802	0.10	0.03
CAT	0.31	**3.026e-10**	0.20	**7.77e-05**
mMRC	0.26	**8.724e-08**	0.20	**4.676e-05**
Exacerbations	0.6	**2.2e-16**	0.6	**2.2e-16**
FEV_1	-0.32	**4.307e-11**	-0.24	**9.303e-07**

BMI: Body Mass Index, CAT: COPD Assessment Test, mMRC: modified Medical Research Council dyspnea scale, FEV_1, forced expiratory volume in 1 s.

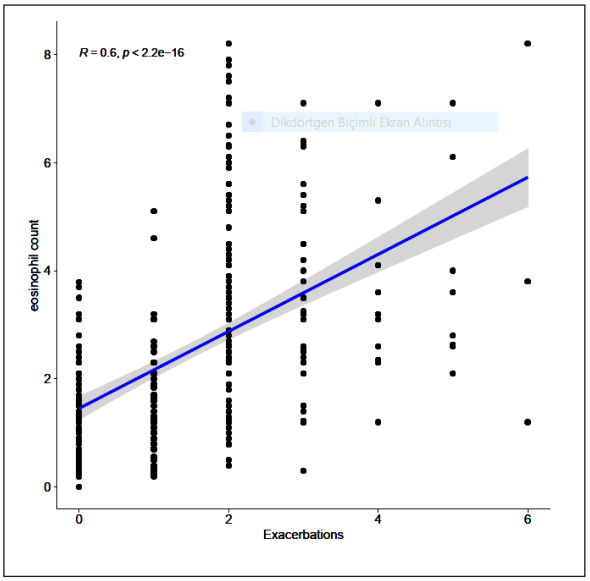

Figure 4. Correlation of level eosinophil count and number of exacerbations in COPD subjects.

tients, the prevalence of CVD was higher and blood eosinophil counts were significantly higher in patients with COPD and concurrent CVD than those without CVD.

Discussion

The present study evaluates the relationship between blood eosinophil count in COPD patients and the latest version of the GOLD staging guideline and concurrent CVD. The results of the study revealed that blood eosinophil counts were significantly higher in the GOLD-E category, underlining the clinical importance of exacerbations independent of the severity of the patient's symptoms. Furthermore, in this same group of patients, the prevalence of CVD was higher and blood eosinophil counts were significantly higher in patients with COPD and concurrent CVD than those without CVD.

Eosinophilic airway inflammation is typical of asthma and has also been noted in some patients with COPD. Such inflammatory patterns can exist either as a result of concurrent asthma in patients with COPD (asthma-COPD overlap) or yet-to-be-understood mechanisms that cause airway eosinophilia in COPD patients. Eosinophilic airway inflammation can be determined by measuring eosinophil levels in the sputum or in the blood, and there have been a few studies[14] to date reporting a relationship between sputum eo-

Table IV. Risk factors for cardiovascular diseases in subjects with COPD (multivariate analysis).

	Odds ratio	Confidence Interval 95%	p
Age (year)	0.98	0.96-1.00	0.10
Gender (Male)	0.46	0.24-0.88	**0.019**
DM	1.56	0.77-3.19	0.21
HT	3.47	2.08-5.86	**2.40e-06**
BMI (kg/m^2)	0.90	0.84-0.96	**0.00183**
FEV_1	0.98	0.97-0.99	**0.05**
Exacerbations	3.37	2.02-5.71	**4.16e-06**
Smoking history	1.0	0.98-1.02	0.94

COPD: Chronic obstructive pulmonary disease, BMI: Body Mass Index, DM: Diabetes Mellitus, HT: Hypertension, FEV_1, forced expiratory volume in 1 s.

sinophil levels and blood eosinophil counts. Due to the fact that the collection of induced sputum and bronchoalveolar lavage fluid and bronchial biopsy require particular expertise and are contraindicated in those with severe or unstable forms of the disease, peripheral blood sampling and the measurement of blood eosinophil count are a more accessible mean of evaluating eosinophil-associated airway inflammation. A cut-off value of 2% for blood eosinophils (equivalent to approximately 150 cells/μL absolute count) is within the published normal ranges that are used as the threshold in most studies[15] conducted to date and is a cut-off value that is sensitive in the prediction of eosinophil-associated airway inflammation and eosinophil-associated exacerbations[16].

Distinguishing between patients with COPD and those with eosinophil-associated airway inflammations based on patient characteristics and clinical features can be difficult. In a prospective cohort study[17] of approximately 3,200 participants (never smokers, participants without COPD, patients with mild-to-moderate COPD and those with severe COPD), 1,091 participants were grouped according to the blood eosinophil count (<1%, 1-3%, >3%), and those with higher eosinophil counts were found to be more likely to be older and males. Similarly, the Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) study[18] also found that patients with persistently high blood eosinophil counts ≥2% tended to be older and were more likely to be males. In the present study, eosinophil counts showed a similar distribution between males and females but increased with age.

In the ECLIPSE study[18], fewer smokers and patients with higher FEV_1 (but not clinically significant), higher lean body mass indices, lower mMRC dyspnea scale scores and lower BODE (body mass index, airflow obstruction, dyspnea, and exercise capacity) indices were identified in the groups with an eosinophil count of ≥2%. In the present study, blood eosinophil counts were significantly higher in the patients with high mMRC dyspnea scale and CAT scores and in those with a BMI ≥30, although eosinophil counts increased as FEV_1 decreased. In another study[19] evaluating 7,225 patients with COPD, similar to the ECLIPSE study, the blood eosinophil count was ≥2% in fewer smokers and male subjects, while no difference was reported in the FEV_1 and mMRC scores. Another study[16] reported a relationship between high eosinophil counts and the male gender, obesity, history of COPD exacerbations and history of asthma.

Studies[11,12,20-23] investigating the relationship between blood eosinophil count and the prognosis of COPD have reported considerably varied results. While some[20-22] have identified no relationship between eosinophil count and the incidence of exacerbations, others[11,12,23] have reported higher incidences of exacerbations in those with higher eosinophil counts Another study[24] reported 30 times higher eosinophil content in biopsy specimens collected during COPD exacerbations than in those collected during stable periods of COPD. There have also been studies[19] reporting an elevated blood eosinophil count to be associated with an increased risk of COPD exacerbation. These findings have led to the hypothesis that blood eosinophil levels could have the potential to be used as a prognostic marker for the prediction of exacerbation risk. Data derived from prospective, randomized and controlled studies[25] suggest that patients with moderate-to-severe COPD and with blood eosinophil levels ≥2% or ≥150 cell/μL who were not treated with inhaled corticosteroids (ICS) were more likely to experience exacerbations than those with low blood eosinophil levels. There have been a vast number of studies[26,27] reporting the ability of blood eosinophil count to predict the magnitude of the effect of ICS therapy (added to the regular bronchodilator therapy) in preventing future exacerbations. Thus, the GOLD guideline recommends the incorporation of blood eosinophil count into clinical assessments as an evaluation of the risk of exacerbations. Similarly, in the present study, a positive correlation was identified between eosinophil count and eosinophil percentage and the incidence of exacerbations. Blood eosinophil counts were found to be significantly elevated in Group E, in which the clinical significance of exacerbations has been emphasized.

There are observational cohort studies[17,18] in the literature in which no strong relationship was reported between blood eosinophil count and risk of exacerbations. This may be attributed to the fact that the majority of patients in these cohorts have not experienced exacerbations or that those with high baseline blood eosinophil counts may be on ICS-containing therapies that suppress exacerbations.

Another point of controversy is that a single blood eosinophil count estimation may not reflect the cell model in a particular patient, and this assumption directs attention to the stability of these

values over time. In the ECLIPSE study[18], which was a 3-year follow-up study, the values remained stable above or below a pre-specified cut-off level in only 51% of the patients, while other cohort studies[28,29] have reported better stability based on the finding that 69.3% of patients had similar eosinophil counts throughout a single year. The lack of long-term follow-up in the present study prevented the evaluation of the stability of blood eosinophil counts.

Prospective studies[30] have identified a relationship between blood eosinophil count and the risk of CVD, with the assumption that eosinophils are associated with myocardial damage and thrombosis in acute coronary syndrome. Acute coronary syndrome develops as a result of thrombus formation on torn or eroded coronary plaque, and while there are many mechanisms underlying coronary plaque instability, the most common pathways are plaque ruptures leading to the activation of a systemic inflammatory response and local inflammatory cell infiltration[31] Eosinophils, basophils, and mast cells, as mediators of allergic inflammatory responses, may also be involved in this pathogenetic mechanism. The components of eosinophilic granules may intervene in inflammatory cell activation. It has been shown[32] that eosinophilic granule proteins result in platelet activation and thrombus formation through thrombomodulin inhibition, and it has, therefore, been suggested that eosinophils could become a new biomarker in CVD risk stratification as a result of the low cost of testing and easy accessibility.

Clinical studies[33,34] evaluating the correlation between eosinophil count and CVD risk have found a significant correlation and have found a high eosinophil count to be associated with increased mortality rates. In a postmortem study[35] of patients who died of acute myocardial infarction, eosinophil counts in inflammatory response were found to be higher in patients with cardiac ruptures than in those who did not sustain a cardiac rupture. In the present study, blood eosinophil counts were significantly higher in the patients with COPD and accompanying CVD.

In contrast, a further study[30] reported that a low eosinophil percentage pointed to severe myocardial damage in patients with acute coronary syndrome and could be linked to heart failure and an increased incidence of death due to coronary disease in the short term[35]. There are also studies[36-38] reporting no independent relationship between elevated eosinophil counts and the prevalence and severity of CAD.

It has been suggested[2] that the relationship between COPD and CVD depends on various parameters, such as shared risk factors (smoking, aging), overlapping symptoms (dyspnea, exercise limitation), and pathophysiological processes (systemic inflammation, increased oxidative stress). In addition to this relationship, recent evidence[39] suggests an association between COPD exacerbations and acute cardiovascular events and that the presence of CVD increases the risk of frequent exacerbations. In the presence of systemic inflammation, patients with COPD are particularly susceptible to vascular events following an exacerbation[40]. This is supported by the findings in the present study, in which the incidence of CVD was higher in the GOLD E group, in which exacerbations were the prominent feature. The eosinophil count in peripheral blood provides additional predictive power to models using conventional risk factors for the prediction of CAD or acute coronary artery thrombotic events in COPD patients that fall into this category.

The present study has several limitations; the first is the relatively small sample size, which may have caused an underrepresentation of patients with COPD. Furthermore, all patients were in the stable period, and thus, a comparison of blood eosinophil levels could not be made between the stable periods and exacerbation periods. In addition, no control group was included in the study, as the main objective was to investigate the associations of eosinophil count in subgroups of patients with COPD. Secondly, the contribution of eosinophilic inflammation to exacerbations is vague. An important point that needs to be taken into consideration when interpreting the value of peripheral blood eosinophils as a prognostic factor in COPD is the correlation with eosinophilic activity in the respiratory tract. The present study evaluated peripheral blood samples due to ease of accessibility. Finally, the present study cannot speculate on the long-term effects of eosinophils on prognosis due to the single-center and retrospective study design and the lack of long-term follow-up. There is a need for further studies involving a larger number of patients to confirm the findings of the present study. As a final note, the cross-sectional nature of the study data prevented the establishment of a causal relationship.

Current Knowledge

The presence of cardiovascular comorbidities in patients with COPD has long been known, and the co-existence of these conditions is known to

result in poorer outcomes than other conditions alone. Although the exact mechanism underlying the association of these two conditions is not yet fully understood, the GOLD guideline recommends the management of cardiovascular comorbidities. In recent years, eosinophils have attracted substantial interest as an important factor in the pathogenesis of COPD and as a potential biomarker.

Contributions of the Paper

There is growing interest in the identification of potential biomarkers that can be measured accurately and repeatedly for the prediction of clinical outcomes. The results of the present study suggest that elevated blood eosinophil levels can be used to identify patients with COPD who are at risk of frequent exacerbations and cardiovascular events. It would be beneficial in future studies to determine to what extent peripheral blood eosinophils make an additional contribution from the perspective of clinicians before suggesting their widespread use in this regard.

Conclusions

The results of the present study suggest that eosinophils could be useful in determining the severity of COPD. The elevated eosinophil counts identified in a subgroup of patients with COPD can be considered a possible mechanism underlying both an increased risk of exacerbation and increased cardiovascular morbidity in patients with COPD. For this reason, blood eosinophil levels may be regarded as a prognostic biomarker. Therefore, blood eosinophils may be used to identify patients at high risk of exacerbations and cardiovascular complications. Further studies are needed to determine the precise cut-off levels and their implications on clinical care.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Contributions

Conceptualization; FB and AS, Methodology; FN and AS, Formal analysis; FB and AS, Data curation; FB and OY, Writing-original draft; FB, Writing-review and editing; OY, Visualization; FB and AS, Supervision; FB. All authors have read and agreed to the published version of the manuscript.

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Ethics Approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the Clinical Studies Ethics Committee of the Faculty of Medicine at Aydın Adnan Menderes University (Protocol number 2023/39 – Date: 09.03.2023).

Informed Consent

Informed consent was obtained from all subjects involved in the study.

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Data Availability

Data to support the findings of this study are available upon reasonable request.

References

1) Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD), (2023) Available at: http://goldcopd.org.
2) Trinkmann F, Saur J, Borggrefe M, Akin I. Cardiovascular Comorbidities in Chronic Obstructive Pulmonary Disease (COPD)- Current Considerations for Clinical Practice. J Clin Med 2019; 8: 69.
3) Vestbo J, Hurd SS, Agustı´ AG, Jones PW, Vogelmeier C, Anzueto A, Barnes PJ, Fabbri LM, Martinez FJ, Nishimura M, Stockley RA, Sin DD, Roisinet RR. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease: GOLD Executive Summary. Am J Respir Crit Care Med 2013; 187: 347-365.
4) Barnes PJ. Inflammatory endotypes in COPD. Allergy 2019; 74: 1249-1256.
5) Papi A, Romagnoli M, Baraldo S, Braccioni F, Guzzinati I, Saetta M, Ciaccia A, Fabbri LM. Partial reversibility of airflow limitation and increased exhaled NO and sputum eosinophilia in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2000; 162: 1773-1777.
6) Gao P, Zhang J, He X, Hao Y, Wang K, Gibson PG. Sputum inflammatory cellbased classification of patients with acute exacerbation of chronic obstructive pulmonary disease, PLoS One 2013; 8: e57678.

7) Singh D, Bafadhel M, Brightling CE, Sciurba FC, Curtis JL, Martine FJ, Pasquale CB, Merrill DD, Metzdorf N, Petruzzelli S, Tal-Singer R, Compton C, Rennard S, Martin UJ. Blood eosinophil counts in clinical trials for chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2020; 202: 660-671.

8) Mycroft K, Krenke R, Gorska K. Eosinophils in COPD. Current concepts and clinical implications. J Allergy Clin Immunol Pract 2020; 8: 2565-2574.

9) Verdoia M, Schaffer A, Cassetti E, Di GG, Marino P, Suryapranata H, Luca GD. Absolute eosinophils count and the extent of coronary artery disease: a single centre cohort study. J Thromb Thrombolysis 2015; 39: 459-466.

10) McDonald VM, Fingleton J, Agusti A, Hiles SA, Clark VL, Holland AE, Marks GB, Bardin PB, Beasley R, Pavord ID, Wark PAB, Gibson PG. Treatable traits: a new paradigm for 21st century management of chronic airway diseases: Treatable Traits Down Under International Workshop report. Eur Respir J 2019; 53: 1802058.

11) Gonzalez-Barcala FJ, San-Jose ME, Nieto-Fontarigo JJ, Calvo-Alvarez U, Carreira JM, Garcia-Sanz MT, Muñoz X, Perez-Lopez-Corona MP, Gómez-Conde MJ, Casas-Fernández A, Valdes-Cuadrado L, Mateo-Mosquera L, Salgado FJ. Blood eosinophils could be useful as a biomarker in chronic obstructive pulmonary disease exacerbations. Int J Clin Pract 2019; 73: e13423.

12) Chapman KR, Hurst JR, Frent SM, Robert Fogel ML, Donald Banerji TG, Patalano F, Goyal P, Pfister P, Kostikas K, Wedzicha JA. Long-term triple therapy de-escalation to indacaterol/glycopyrronium in patients with chronic obstructive pulmonary disease (SUNSET): a randomized, double-blind, triple-dummy clinical trial. Am J Respir Crit Care Med 2018; 198: 329-339.

13) Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2011. Available at: http://www. goldcopd.org/.

14) Hastie AT, Alexis NE, Doerschuk C, Hansel NN, Christenson S, Putcha N, Ortega VE, Peters SP, Barr RG, Couper DJ, Hoffman EA, Kanner R, Kleerup E, Martinez FJ, Woodruff PG, Han MK, Meyers DA, Curtis JL, Bleecker ER. Blood eosinophils poorly correlate with sputum eosinophils, and have few associations with spirometry, clinical and quantitated computed tomography measures compared to sputum eosinophils in the SPIROMICS cohort. Am J Respir Crit Care Med 2016; 193: A6168.

15) Bafadhel M, McKenna S, Terry S, Mistry V, Reid C, Haldar P, McCormick M, Haldar K, Kebadze T, Duvoix A, Lindblad K, Patel H, Rugman P, Dodson P, Jenkins M, Saunders M, Newbold P, Green RH, Venge P, Lomas DA, Barer MR, Johnston SL, Pavord ID, Brightling CE. Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. Am J Respir Crit Care Med 2011; 184: 662-671.

16) Landis S, Suruki R, Bonar K, Hilton E, Compton C. Blood eosinophil levels in COPD patients in the UK Clinical Practice Research Datalink (CPRD). Am J Respir Crit Care Med 2016; 193: A6329.

17) Weir M, Zhao H, Han MK, Kanner R, Pirozzi CS, Scholand MB, Hoffman EA, Martinez FJ, Criner GJ. Eosinophils in chronic obstructive pulmonary disease, the SPIROMICS cohort. Am J Respir Crit Care Med 2014; 189: A5902.

18) Singh D, Kolsum U, Brightling CE, Locantore N, Agusti A, Tal-Singer R. ECLIPSE investigators. Eosinophilic inflammation in COPD: prevalence and clinical characteristics, Eur Respir J 2014; 44: 1697-1700.

19) Vedel-Krogh S, Nielsen SF, Lange P, Vestbo J, Nordestgaard BG. Blood eosinophils and exacerbations in COPD: the Copenhagen General Population Study. Am J Respir Crit Care Med 2016; 193: 965-974.

20) Landis S, Suruki R, Maskel J, Bonar K, Hilton E, Compton C. Demographic and clinical characteristics of COPD patients at different blood eosinophil levels in the UK Clinical Practice Research Datalink. COPD 2018; 15: 177-184.

21) Greulich T, Tuffers J, Mager S, Eder A, Maxheim M, Alter P, Schmeck B, Vogelmeier CF. High eosinophil blood counts are associated with a shorter length of hospital stay in exacerbated COPD patients - a retro- spective analysis. Respir Res 2020; 21: 106.

22) Nunez A, Marras V, Harlander M, Mekov E, Esquinas C, Turel M, Lestan D, Petkov R, Yanev N, Pirina P, Negri S, Miravitlles M, Barrecheguren M. Association between routine blood biomarkers and clinical phenotypes and exacerbations in chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2020; 15: 681-690.

23) Soler-Cataluna JJ, Novella L, Soler C, Nieto ML, Esteban V, Sánchez-Toril F, Miravitlles M. Clinical characteristics and risk of exacerbations associated with different diagnostic criteria of asthma-COPD Overlap. Arch Bronconeumol 2020; 56: 282-290.

24) Saetta M, Di Stefano A, Maestrelli P, Turato G, Ruggieri MP, Roggeri A, Calcagni P, Mapp CE, Ciaccia A, Fabbri LM. Airway eosinophilia in chronic bronchitis during exacerbations. Am J Respir Crit Care Med 1994; 150: 1646-1652.

25) Pascoe S, Locantore N, Dransfield MT, Barnes NC, Pavord ID. Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials, Lancet Respir Med 2015; 3: 435-442.

26) Bafadhel M, Peterson S, De Blas MA, Calverley PM, Rennard SI, Richter K, Fagerås M. Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive

pulmonary disease: a post-hoc analysis of three randomised trials. Lancet Respir Med 2018; 6: 117-126.

27) Lipson DA, Barnhart F, Brealey N, Brooks J, Criner GJ, Day NC Dransfield MT, Halpin DMG, Han MK, Jones CE, Kilbride S, Lange P, Lomas DA, Martinez FJ, Singh D, Tabberer M, Wise RA, Pascoe SJ, IMPACT Investigators. Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD. N Engl J Med 2018; 378: 1671-1680.

28) Long GH, Southworth T, Kolsum U, Donaldson GC, Wedzicha JA, Brightling CE, Singh D. The stability of blood eosinophils in chronic obstructive pulmonary disease. Respir Res 2020; 21: 15.

29) Casanova C, Celli BR, de-Torres JP, Martínez-Gonzalez C, Cosio BG, Pinto-Plata V, Ramos PL, Divo M, Fuster A, Barba GP, Rubio MC, Solanes I, Aguero R, Feu-Collado N, Alfageme I, Diego AD, Romero A, Balcells E, Llunell A, Galdiz JB, Marin M, Moreno A, Cabrera C, Golpe R, Lacarcel C, Soriano JB, López-Campos JL, Soler-Cataluña JJ, Marin JM. Prevalence of persistent blood eosinophilia: relation to outcomes in patients with COPD. Eur Respir J 2017; 50: 1701162.

30) Jiang P, Wang DZ, Ren YL, Cai J, Chen B. Significance of eosinophil accumulation in the thrombus and decrease in peripheral blood in patients with acute coronary syndrome. Coron Artery Dis 2015; 26: 101-106.

31) Crea F, Libby P. Acute coronary syndromes: the way forward from mechanisms to precision treatment. Circulation 2017; 136: 1155-1166.

32) Mukai HY, Ninomiya H, Ohtani K, Nagasawa T, Abe T. Major basic protein binding to thrombomodulin potentially contributes to the thrombosis in patients with eosinophilia. Br J Haematol 1995; 90: 892-899.

33) Toor IS, Jaumdally R, Lip GY, Millane T, Varma C. Eosinophil count predicts mortality following percutaneous coronary intervention. Thromb Res 2012; 130: 607-611.

34) Klisic A, Radoman Vujačić I, Vučković LJ, Ninic A. Total leukocyte count, leukocyte subsets and their indexes in relation to cardiovascular risk in adolescent population. Eur Rev Med Pharmacol Sci 2021; 25: 3038-3044

35) Atkinson JB, Robinowitz M, McAllister HA, Virmani R. Association of eosinophils with cardiac rupture. Hum. Pathol 1985; 16: 562-568.

36) Shah AD, Denaxas S, Nicholas O, Hingorani AD, Hemingway H. Low eosinophil and low lymphocyte counts and the incidence of 12 cardiovascular diseases: a CALIBER cohort study. Open Heart 2016; 3: e000477.

37) Verdoia M, Schaffer A, Cassetti E, Di GG, Marino P, Suryapranata H, Luca GD. Absolute eosinophils count and the extent of coronary artery disease: a single centre cohort study. J Thromb Thrombolysis 2015; 39: 459-466.

38) Verdoia M, Schaffer A, Barbieri L, Sinigaglia F, Marino P, Suryapranata H, Luca GD, Novara Atherosclerosis Study Group (NAS). Eosinophils count and periprocedural myocardial infarction in patients undergoing percutaneous coronary interventions. Atherosclerosis 2014; 236: 169-174.

39) Westerik JAM, Metting EI, van Boven JFM, Tiersma W, Kocks JWH, Schermer TR. Associations between chronic comorbidity and exacerbation risk in primary care patients with COPD. Respir Res 2017; 18: 31.

40) Hurst JR, Hagan G, Wedzicha JA. Mechanism of statin associated mortality reduction in COPD. Chest 2007; 132: 1409-1410.