Original Article

Prevalence and Clinical Outcomes of Eosinophilic COPD in a Saudi Population: A Retrospective Study

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Abstract

Objective: This study assessed the prevalence of eosinophilic chronic obstructive pulmonary disease (COPD) among a selected Saudi population and examined its correlation with baseline characteristics, clinical outcomes, exacerbation risk, and current management.

Materials and Methods: This retrospective single-center study was conducted over a 2-year period. The patients were divided into two groups based on the blood eosinophil count at the time of diagnosis: eosinophilic COPD (≥300 cells/μl) and non-eosinophilic COPD (<300 cells/μl) groups.

Results: Overall, 156 patients were included, of which 76 (48.7%) and 80 (51.3%) patients belonged to the eosinophilic and non-eosinophilic COPD groups, respectively. There were no significant differences between both groups regarding age, gender, smoking status, coexisting morbidities, FEV1, FEV1/FVC, and COPD severity (for all, $P > 0.05$). Besides, there were no significant differences between both groups regarding the frequency and numbers of exacerbations, emergency room visits, in-patient hospitalizations, and intensive care unit admissions (for all, $P > 0.05$). Among patients with eosinophilic COPD, 64 patients (84.2%) were correctly receiving the triple therapy of long-acting β2 agonists + long-acting muscarinic antagonist + inhaled corticosteroids, whereas 4 patients (5.26%) were incorrectly receiving the dual therapy of long-acting β2 agonists + inhaled corticosteroids. Univariate regression analyses revealed that heart failure, GOLD 3 severity, use of triple therapy, and use of non-invasive ventilation were significantly correlated with a higher risk of COPD exacerbation. Conversely, higher FEV1 was significantly correlated with lower risk of COPD exacerbation. The eosinophilic COPD phenotype was not found to be a significant independent variable of COPD exacerbation.

Conclusion: This study found that among Saudi patients with COPD, there was no clinically important relationship between baseline blood eosinophil count and the rate of exacerbation.

Keywords: Chronic obstructive pulmonary disease, eosinophil, exacerbation, inhaled corticosteroids, Saudi Arabia

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Submitted: 29-Apr-2024 **Revised:** 05-Oct-2024 **Accepted:** 06-Nov-2024 **Published:** 11-Jan-2025

Access this article online	
Quick Response Code:	Website: https://journals.lww.com/sjmm
	DOI: 10.4103/sjmms.sjmms_248_24

How to cite this article: Alshehri F, Alghamdi M, Aloqabi FA, Ibrahim A, Tayeb N, Hassosah M, *et al*. Prevalence and clinical outcomes of eosinophilic COPD in a Saudi population: A retrospective study. Saudi J Med Med Sci 2025;13:53-60.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a substantial source of morbidity and mortality universally. A recent systematic review and modelling analysis study documented that nearly 392 million individuals aged 30–79 years had COPD by the end of 2019.[1] Besides, a recent Global Burden of Disease study reported that COPD was the third leading cause of mortality globally, with roughly 3.2 million deaths in 2019.[2] A recent modeling study predicts that global COPD cases among individuals aged ≥25 will rise by 23% from 2020 to 2050, nearing 600 million patients. The burden is expected to increase most significantly among women, with female cases projected to rise by 47.1%, compared to a 9.4% increase for males. In addition, cases in low-and middle-income regions are anticipated to more than double those in high-income regions by 2050.[3] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2024 report defines COPD as a diverse pulmonary ailment marked by persistent respiratory manifestations (for example, shortness of breath, cough, spitting, and/or exacerbations) stemming from irregularities in the airways (for example, bronchitis and bronchiolitis) and/or alveoli (for example, emphysema), resulting in enduring, frequently advancing, and airflow blockage (i.e., post-bronchodilation forced expiratory volume during the first second/forced vital capacity [FEV1/FVC] <0.7).[4]

The primary risk factor for COPD is smoking, which significantly contributes to the development and progression of the disease. However, COPD can also occur in non-smokers due to other risk factors, including long-term exposure to air pollution, occupational dust and chemicals, and genetic predispositions such as alpha-1 antitrypsin deficiency.[4,5]

GOLD 2024 report has integrated the blood eosinophil count as a biomarker to gauge the effectiveness of inhaled corticosteroids (ICS) in preventing exacerbations.[4] Specifically, the GOLD guidelines recommend that patients with blood eosinophils >300 cells/μl should be managed by triple therapy comprising ICS, long-acting β2 agonists (LABA), and long-acting muscarinic antagonist (LAMA).[6] Indeed, COPD encompasses different phenotypes, including the eosinophilic COPD phenotype,[7] which affects about 19% to 67% of COPD patients,[8] and can exist in stable or acute exacerbation forms.[9] Notably, the level of eosinophilic airway inflammation has been depicted to correlate well with the peripheral blood eosinophilic count among COPD patients.[10,11]

Several studies have investigated the role of peripheral blood eosinophil count on exacerbation risk among COPD patients treated with ICS. However, the results have been largely conflicting and limited by small sample sizes, varying cutoffs of blood eosinophilic counts, and diverse patient populations. Some studies revealed a beneficial effect of ICS in decreasing exacerbations among COPD patients with elevated eosinophilic counts.[12-15] Conversely, a *post hoc* analysis of combined data from 11 clinical trials indicated that peripheral blood eosinophil count was not significantly associated with reduced exacerbation among COPD patients taking ICS at baseline.[16] Indeed, the reliability of blood eosinophil count in predicting COPD exacerbations continues to be a matter of debate.

To the best of our knowledge, only one study from Saudi Arabia investigated the clinical characteristics and outcomes related to eosinophilic COPD.[17] Studying eosinophilic COPD in Saudi Arabia is crucial because geographic factors can introduce unique characteristics. Personalized medicine relies on population-based data to inform management strategies, emphasizing the importance of investigating this aspect within the Saudi population. This study aims to enrich the existing literature by assessing the prevalence of the eosinophilic phenotype of COPD among a selected Saudi population and examine its correlation with baseline characteristics, clinical outcomes, and exacerbation rates. In addition, this study aims to review the treatments administered to the patients with COPD.

MATERIALS AND METHODS

Ethical approval

The study was carried out in accordance with the guidelines of the Declaration of Helsinki, 2013, and the research protocol was approved by the Research Ethics Committee at King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia.

Study design, setting, and sample size

The retrospective, single-center study was conducted at King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia, and included all Saudi patients with COPD who met the inclusion criteria between January 1, 2022, and December 31, 2023. The patients were divided into two groups based on the peripheral eosinophil count at the time of diagnosis: eosinophilic COPD group (≥300 cells/μl) and non-eosinophilic COPD group (<300 cells/μl). There was no formal sample size calculation; rather, non-probability consecutive sampling technique was applied. We reviewed all patients with a diagnosis of COPD over 24 months and empirically aimed for a minimum inclusion of at least 100 subjects in our study sample.

Eligibility criteria

The inclusion criteria comprised patients (i) aged ≥40 years with a confirmed diagnosis of COPD, according to the GOLD 2024 guidelines,[4] (ii) a follow-up of at least 12 months, and (iii) with complete data. All patients received spirometry testing and COPD diagnosis was based on the presence of clinical symptoms indicative of COPD diagnosis (for example, dyspnea, productive cough, and exertional dyspnea), post-bronchodilation FEV1/FVC <0.7, and potential history suggestive of exposure to toxic substances/environment, most notably smoking.

The exclusion criteria comprised patients aged <40 years who had (i) coexisting asthma and COPD overlap, (ii) hypersensitivity or allergy, (iii) autoimmune diseases, (iv) parasitic infections, (v) history of receiving systemic steroids, (vi) no spirometry test, (vii) follow-up of <12 months, and (viii) incomplete data.

Outcomes

A predefined data collection sheet was designed to gather information pertaining to demographic characteristics, COPD-related clinical findings, exacerbation history, and current treatment. Demographic characteristics comprised age, gender, smoking status (never, current, ex-smoker, and unknown), and coexisting morbidities (i.e., hypertension, diabetes mellitus, dyslipidemia, ischemic heart disease, arrhythmia, heart failure, stroke, obstructive sleep apnea, and anxiety). COPD-related clinical findings comprised FEV1, FEV1/FVC, and COPD severity according to GOLD criteria based on FEV1 (GOLD 1: ≥80%, GOLD 2: 50%–79%, GOLD 3: 30%–49%, and GOLD 4: <30%).[4] The exacerbation history comprised numbers of exacerbations, emergency room visits, in-patient hospitalizations, and intensive care unit admissions, in addition to the frequency of exacerbations over the past 12 months. COPD exacerbation was defined in line with the consensus Rome proposal adopted by the GOLD 2024 report, in which exacerbation of COPD is described as an event marked by worsening dyspnea and/or cough with sputum over a period of up to 14 days, potentially accompanied by increased respiratory rate and/or heart rate. This exacerbation is often linked with heightened local and systemic inflammation triggered by airway infection, pollution, or other insults to the airways.[18] The current treatment data comprised the intake of LAMA, LABA, ICS, ICS+LABA, triple therapy (LAMA+LABA+ICS), theophylline, long-term oxygen therapy, and non-invasive ventilation.

Statistical analysis

The data were entered into Microsoft Excel sheet and checked for validity and completeness by two independent reviewers prior to statistical analysis. The descriptive data were reported as numbers and percentages, whereas the numerical data were reported as means ± standard deviations (SDs) or medians and interquartile ranges (first quartile to third quartile), as appropriate depending on the normality of data. The Shapiro–Wilk test of normality was used to determine if the numerical outcome was normally distributed. Student's *t*-test (parametric) or Mann–Whitney *U* test (nonparametric) were used for univariate analysis of numerical data. The chi-square test was used for univariate analysis of categorical data. Univariate logistic regression analyses were performed to identify the factors that could emerge as independent variables of COPD exacerbation (at least one episode), and data were reported as odds ratio (OR) with 95% confidence interval (CI). All analyses were two-tailed and $P < 0.05$ was considered statistically significant. All data were analyzed using the STATA software (StataCorp LLC, College Station, TX), version 18.0, for Windows.

RESULTS

Overall, 156 patients were included in the study, of which the majority (80.1%) were female. In addition, 76 (48.7%) and 80 (51.3%) patients belonged to the eosinophilic and non-eosinophilic COPD groups, respectively. There were no significant differences between both groups regarding age, gender, smoking status, coexisting morbidities, FEV1, FEV1/FVC, and COPD severity [Table 1]. Besides, there were no significant differences between both groups regarding the frequency of exacerbations, numbers of exacerbations, emergency room visits, in-patient hospitalizations, and intensive care unit admissions [Table 2]. Notably, although the frequency of exacerbations was higher in the eosinophilic group compared with the non-eosinophilic group (46.1% vs. 40%), this difference was not statistically significant ($P = 0.853$).

Table 3 shows the results of univariate regression analyses for risk factors of COPD exacerbation. The results revealed that heart failure (OR =2.06, 95% CI: 1.04–4.06]; $P = 0.037$), GOLD 3 severity (OR =3.99, 95% CI: 1.32–12.02; $P = 0.014$), use of triple therapy (OR =2.93, 95% CI: 1.02–8.39; $P = 0.046$), and use of non-invasive ventilation (OR =3.02, 95% CI: 1.33–6.85; $P = 0.008$) were significantly correlated with a higher risk of COPD exacerbation. Conversely, every unit increase in FEV1 was significantly correlated with a 4% decrease in the risk of COPD exacerbation (OR =0.96, 95% CI: 0.94–0.98; $P < 0.0001$). Despite the eosinophilic COPD phenotype being associated with a higher risk of COPD exacerbation, the correlation was not statistically significant (OR =1.28, 95% CI: 0.68–2.42; $P = 0.446$). The current treatments for all COPD patients are

Table 1: Demographic characteristics and COPD-related clinical findings of the included patients

Variables	All patients (*N*=156), *n* (%)	Eosinophilic COPD (*n*=76), *n* (%)	Non-eosinophilic COPD (*n*=80), *n* (%)	*P*
Age (years), mean±SD	74±9 (50–99)	78.4±9.1 (50–99)	72.7±8.7 (54–90)	0.0596
Age group (years)				
40–59	7 (4.5)	2 (2.6)	5 (6.3)	0.147
60–79	100 (64.1)	45 (59.2)	55 (68.8)	
≥80	49 (31.4)	29 (38.2)	20 (25)	
Gender				
Male	31 (19.9)	19 (25)	12 (15)	0.118
Female	125 (80.1)	57 (75)	68 (85)	
Smoking status				
Never	18 (11.5)	12 (15.8)	6 (7.5)	0.446
Current	41 (26.3)	17 (22.4)	24 (30)	
Ex-smoker	67 (43)	33 (43.4)	34 (42.50)	
Not known	30 (19.2)	14 (18.4)	16 (20)	
Coexisting comorbidities				
Ischemic heart disease	37 (23.7)	23 (30.3)	14 (17.5)	0.061
Heart failure	51 (32.7)	28 (36.8)	23 (28.8)	0.282
Diabetes mellitus	68 (43.6)	33 (43.4)	35 (43.8)	0.967
Stroke	20 (12.8)	7 (9.2)	13 (16.3)	0.189
Arrhythmia	12 (7.7)	5 (6.9)	7 (8.8)	0.611
Dyslipidemia	37 (23.7)	22 (29)	15 (18.8)	0.134
Obstructive sleep apnea	14 (9)	9 (9.2)	7 (8.8)	0.920
Anxiety	12 (7.7)	6 (7.9)	6 (7.5)	0.926
Hypertension	104 (66.7)	53 (69.7)	51 (63.8)	0.428
FEV_1 (%), mean±SD	60.9±17.8 (22–99)	59.2±16.5 (22–90)	62.7±18.9 (26–99)	0.2517
FEV/FVC (%), median (IQR)	65 (56–68)	65.5 (56.5–68)	64.5 (55–68.5)	0.7570
COPD severity				
GOLD 1	24 (15.9)	8 (10.53)	16 (20)	0.409
GOLD 2	86 (55.1)	45 (59.21)	41 (51.25)	
GOLD 3	37 (23.7)	18 (23.68)	19 (23.75)	
GOLD 4	9 (5.8)	5 (6.58)	4 (5)	

FEV_1 – Forced expiatory volume in the 1st s; FVC – Forced vital capacity; GOLD – Global initiative of obstructive lung disease; IQR – Interquartile range; SD – Standard deviation; COPD – Chronic obstructive pulmonary disease

Table 2: COPD exacerbation history over the past 12 months

Variables	All patients (*N*=156) median (IQR)	Eosinophilic COPD (*n*=76) median (IQR)	Non-eosinophilic COPD (*n*=80) median (IQR)	*P*
Exacerbation episodes	0 (0–1.5)	0 (0–1.5)	0 (0–1)	0.4503
Emergency room visits	0 (0–1)	0 (0–2)	0 (0–1)	0.4374
Inpatient hospitalizations	0 (0–0.5)	0 (0–1)	0 (0–0)	0.6598
ICU admissions	0 (0–0)	0 (0–0)	0 (0–0)	0.3713
Exacerbation frequency				0.583
None	89 (57.05)	41 (53.95)	48 (60)	
≥1	67 (42.95)	36 (46.05)	32 (40)	

Descriptive data were reported as *n* (%). The nonnormally distributed numerical data were reported as medians and interquartile ranges (first quartile–third quartile). COPD – Chronic obstructive pulmonary disease; ICU – Intensive care unit; IQR – interquartile range

summarized in Table 4. Of the 76 patients with eosinophilic COPD, only 64 patients (84.2%) received the triple therapy of LABA+LAMA+ICS, whereas 4 patients (5.3%) received the dual therapy of LABA+ICS.

DISCUSSION

This retrospective study revealed that the frequency of eosinophilic COPD phenotype was nearly 49% among Saudi patients. Our study found no significant differences between eosinophilic and non-eosinophilic COPD groups regarding demographical characteristics, COPD-related clinical findings, exacerbation history, and current treatment. Univariate regression analyses revealed that heart failure, GOLD 3 severity, use of triple therapy, and use of non-invasive ventilation were significantly correlated with a higher risk of COPD exacerbation. Conversely, higher FEV1 values were significantly correlated with lower risk of COPD exacerbation. The eosinophilic COPD phenotype did not emerge as a significant independent variable of COPD exacerbation.

Interestingly, females made up approximately 80% of the COPD population in our study. While COPD has traditionally been more prevalent in males, particularly in regions with higher smoking rates among men, this trend is changing in some areas. Increasing numbers of females are being diagnosed, especially in low- and middle-income countries where smoking rates among women are on the

rise. This observation is further supported by a recent modeling study projecting these trends through 2050.[3]

In our study, almost half of the patients with COPD had the eosinophilic phenotype. Wu and colleagues conducted a recent systematic review and meta-analysis of 19 trials (comprising 40,112 COPD patients) and demonstrated that the occurrence of eosinophilic COPD averaged at 55% across all examined studies, and ranged from as low as 19% to as high as 67%.[8] Moreover, the investigation found that eosinophilic COPD was significantly linked to male gender, higher body mass index, ex-smoking status, and prior history of ischemic heart disease. Nonetheless, no significant correlations were identified between eosinophilic COPD and age, current smoking status, FEV1, GOLD severity, diabetes mellites, and hypertension. In our study, none of the demographic features and clinical profiles of COPD were significantly linked to the eosinophilic phenotype of COPD compared with the non-eosinophilic phenotype of COPD.

Table 3: Univariate analysis of the exacerbation risk factors among patients with COPD

Variable	Odds ratio	95% CI	*P*
Age (continuous)	1.02	0.98–1.05	0.392
Age group (years)			
40–59	Reference	-	-
60–79	1.00	0.51–2.00	0.991
Gender			
Female	Reference	-	-
Male	0.47	0.21–1.03	0.061
Smoking status			
Never	Reference	-	-
Current	0.80	0.269–2.46	0.697
Ex-smoker	1.14	0.40–3.25	0.802
Not known	0.72	0.22–2.38	0.594
Coexisting comorbidities			
Ischemic heart disease	0.56	0.26–1.21	0.142
Heart failure	2.06	1.04–4.06	0.037
Diabetes mellitus	1.67	0.88–3.17	0.119
Stroke	0.87	0.33–2.26	0.776
Arrhythmia	1.96	0.59–6.47	0.27
Dyslipidemia	1.02	0.482–2.14	0.967
Obstructive sleep apnea	1.00	0.33–3.02	0.994
Anxiety	0.94	0.29–3.12	0.926
Hypertension	1.68	0.84–3.35	0.139
FEV_1 (continuous)	0.96	0.94–0.98	<0.0001
FEV/FVC (continuous)	1.00	0.99–1.01	0.595
COPD severity			
GOLD 1	Reference	-	-
GOLD 2	1.37	0.51–3.66	0.532
GOLD 3	3.99	1.32–12.02	0.014
GOLD 4	4.86	0.94–25.08	0.059
Eosinophilic COPD phenotype	1.28	0.68–2.42	0.446
LABA	0.32	0.04–2.95	0.316
LAMA	0.18	0.02–1.48	0.11
LABA + ICS	0.65	0.16–2.69	0.551
LABA + LAMA + ICS	2.93	1.02–8.39	0.046
Theophylline	1.82	0.82–4.02	0.138
LTOT	5.65	2.34–13.64	0
NIV	3.02	1.33–6.85	0.008

COPD – Chronic obstructive pulmonary disease; FEV_1 – Forced expiatory volume in the 1st s; FVC – Forced vital capacity; GOLD – Global initiative of obstructive lung disease; ICS – Inhaled corticosteroids; NIV – Noninvasive ventilation; LABA – Long-acting beta 2 agonists; LAMA – Long-acting muscarinic antagonists; LTOT – Long-term oxygen therapy, CI – Confidence interval

Exacerbations of COPD have been negatively linked to adverse effects on health, disease progression, and prognosis.[18] Numerous risk factors for COPD exacerbation have been documented in literature, encompassing gastroesophageal reflux, deteriorating lung function, worse quality of life, and concurrent increase of several inflammatory markers (e.g., C-reactive protein, fibrinogen, and white blood cell count).[19,20] In addition, peripheral eosinophil blood count has gained popularity as a potential biomarker that can forecast exacerbation of COPD.[21] Notably, blood eosinophil levels have been observed to correlate well with sputum eosinophils in COPD patients.[10,11] In a meta-analysis of 15 high-quality studies exploring the impact of blood eosinophil count on the clinical outcomes of patients with COPD with acute exacerbations, elevated eosinophil levels during acute exacerbation of COPD were linked to favorable outcomes, such as reduced mortality risk and shorter hospitalization. Nonetheless, patients experiencing eosinophilic acute exacerbations of COPD exhibited elevated readmission rates, underscoring the significance of post-discharge surveillance.[22] The study concluded that the peripheral blood eosinophil count holds promise as a valuable biomarker for forecasting prognosis and customizing individualized treatment in patients with acute

Table 4: Treatment for the chronic obstructive pulmonary disease patients

Variables	All patients (*N*=156), *n* (%)	Eosinophilic COPD (*n*=76), *n* (%)	Non-eosinophilic COPD (*n*=80), *n* (%)	*P*
LABA	5 (3.2)	3 (4)	2 (2.5)	0.608
LAMA	8 (5.1)	4 (5.3)	4 (5)	0.941
ICS	1 (0.6)	1 (1.3)	0	0.303
LABA + ICS	9 (5.8)	4 (5.26)	5 (6.3)	0.792
LABA + LAMA + ICS	134 (85.9)	64 (84.2)	70 (87.5)	0.555
Theophylline	31 (19.9)	18 (23.7)	13 (16.3)	0.245
LTOT	32 (20.5)	15 (19.7)	17 (21.3)	0.815
NIV	31 (19.9)	16 (21.1)	15 (18.8)	0.719

ICS – Inhaled corticosteroids; LABA – Long-acting beta 2 agonists; LAMA – Long-acting muscarinic antagonists; LTOT – Long-term oxygen therapy; NIV – Noninvasive ventilation; COPD – Chronic obstructive pulmonary disease

exacerbations of COPD.[22] In our study, we found no clinically important relationship between baseline blood eosinophil count and exacerbation rate. Our finding was in line with post-hoc analysis that pooled data from 11 Phase III and IV randomized clinical trials and observed no clinically significant correlation between the baseline blood eosinophil count and exacerbation rate among patients with COPD.[16] Similarly, Halpin *et al.* evaluated 73,189 COPD patients and found that blood eosinophil count did not significantly enhance the prediction of future exacerbation risk.[23] Conversely, Wu *et al.* studied 897 Chinese COPD patients, finding that 205 (23%) had elevated blood eosinophil counts. Their analysis revealed a significant correlation between high eosinophil levels and an increased risk of exacerbations.[24] It is assumed that eosinophilic exacerbations occur more frequently in primary care settings than in hospital care. Unfortunately, our study cannot confirm that all COPD exacerbations treated in the community were accurately captured, which limits the interpretation of our results. Overall, this observation underscores the importance of monitoring and managing eosinophilic activity in outpatient populations and highlights the need for primary care providers to be particularly vigilant during COPD exacerbations.

In our study, unexpectedly, the use of triple therapy (an ICS-containing regimen) had been associated with a higher risk of COPD exacerbation. Ding *et al.* conducted a meta-analysis of 54 randomized controlled trials comprising 57,333 patients with COPD.[25] The authors demonstrated that ICS-containing combination therapy significantly correlated with lower rate of moderate/severe exacerbations, lower rate of yearly exacerbations necessitating hospitalization, and improved quality of life scores compared to non-ICS-containing therapy.[25] However, the impact on trough FEV1 was similar between treatments containing ICS and those without.[25]

Blood eosinophil levels have emerged as a valuable biomarker predicting response to ICS among patients with COPD.[21] In fact, based on the GOLD 2023 guidelines, the primary considerations for initiating ICS treatment include the patient's history of previous exacerbations, history of coexisting asthma, and their blood eosinophil count.[6] The latter consideration has been derived based on high-quality investigations.[12,13,15,26-28] The addition of ICS demonstrates minimal to no effect when the blood eosinophil count is <100 cells/μl and could be potentially harmful in patients with repeated pneumonia incidents or history of mycobacterial infection. Indeed, a systematic review and meta-analysis of 18 randomized controlled trials confirmed the elevated risk of pneumonia among patients with COPD who use ICS.[29] Moreover, Dalin *et al.* conducted a systematic review of 11 clinical trials with close to 30,000 patients with COPD, and revealed that ICS did not appear to provide benefit for COPD patients with an eosinophil count <150 cells/μl, and COPD exacerbation risk significantly increased in patients with high eosinophil count when discontinuing ICS.[30] Georgiou *et al.* conducted a review of 10 clinical trials and 6 observational studies involving 166,671 COPD patients.[31] Their findings indicated that discontinuing ICS therapy was both safe and feasible, with no impact on exacerbation rates or lung function compared to those patients who continued ICS. However, the authors recommended that patients should continue long-term bronchodilation therapy upon withdrawal of ICS to achieve the best clinical results.[31] However, patients with blood eosinophil counts ≥300 cells/μl are likely to benefit significantly from ICS treatment.[32,33] It must be noted that blood eosinophil levels fluctuate over the course of COPD, making phenotyping challenging based on a single measurement.[34] Therefore, decisions regarding ICS treatment can be guided by past eosinophil counts, as the repeatability of blood eosinophil counts in a sizable primary care population seems plausible.[35]

The most recent GOLD 2024 guidelines recommend the use of triple therapy comprising LABA+LAMA+ICS in patients with blood eosinophil count of >300 cells/μl.[4] Moreover, the current recommendation no longer supports the use of LABA+ICS in COPD.[6] Instead, if there is a need for an ICS intervention, then the triple therapy of LABA+LAMA+ICS has demonstrated superiority over the dual therapy of LABA+ICS, and thus is preferred.[13,26] In cases where COPD patients also have asthma, they should be managed as asthma patients.[36] In our study, of the 76 patients with eosinophilic COPD, only 84.2% of patients were correctly treated with the triple therapy of LABA+LAMA+ICS. Moreover, 5.7% of patients (n = 4) were incorrectly treated with the dual therapy of LABA+ICS. These findings suggest inappropriate administration and lack of adherence to the current treatment guidelines by the treating physicians, which could have adverse patient-related outcomes and poor prognosis, if not rectified promptly.

Elevated circulating eosinophil levels in patients with COPD indicate an elevated risk of COPD exacerbations and suggest a greater likelihood of responding to the preventive effects of ICS.[32] Our study has several important clinical implications that ought to be addressed. As per the new GOLD 2023 guidelines for COPD, patients with eosinophilic COPD and hospitalized exacerbation

were administered the triple therapy to improve their outcomes. Besides, any patients identified during our study who required triple therapy were commenced on appropriate therapy. Those patients identified as receiving ICS unnecessarily were at increased risk of pneumonia, and thus had their treatment adjusted. Undertaking the study also favorably served to educate the treating physicians on the importance of phenotyping patients with COPD and is expected to improve adherence to the new COPD management guidelines to improve the clinical outcomes of patients with COPD.

Strengths and limitations

A key strength of this study is being the second-ever study from Saudi Arabia, thereby enriching the limited existing literature on eosinophilic COPD locally and internationally. Researching eosinophilic COPD in Saudi Arabia is essential due to the influence of geographic factors, which can introduce distinct characteristics. Tailoring medical interventions based on population-specific data is pivotal for personalized medicine, underscoring the necessity of exploring this facet within the Saudi population. Tashkin *et al*.[37] recently conducted a review of COPD pharmacotherapy in the Gulf countries, concentrating on inhaled treatments, and noted that pressurized metered-dose inhalers, dry powder inhalers, soft mist inhalers, and nebulizers were commonly used for delivering medications to COPD patients in the region. The study concluded that the management strategies for COPD in the Gulf countries were largely similar to those used elsewhere in the world.[37]

Our study has several shortcomings that need to be addressed. First, the small sample size could have negatively affected the power of conclusions. Second, the study was conducted in a single hospital, which could have adversely restrained the number of patients and introduced selection bias. Third, the peripheral blood eosinophil stability cannot be confirmed, which could have culminated in an incorrect classification of the eosinophilic COPD phenotype. It is well known that blood eosinophils are responsive to individual patient conditions and can fluctuate around the cutoff value, shifting above and below, depending on the set threshold of 300 cells/μl. Fourth, we did not holistically evaluate the severity of COPD exacerbation during every incident. Fifth, the data on current treatment should be carefully interpreted as the selection of therapy was determined by attending physicians, introducing potential additional confounding factors, which is a typical characteristic of real-world data.

In view of the limitations of the current study, future research should aim to include multi-center studies with large sample sizes. Moreover, equally important clinical outcomes should be evaluated, such as length of hospital stay, rate of 30-day readmission, and mortality. Additional studies may include the differential impact of ICS on patients with eosinophilic COPD during stable and acute exacerbation states.

CONCLUSIONS

This study found that the frequency of eosinophilic COPD phenotype was nearly 50%, and there was no significant difference between eosinophilic and non-eosinophilic COPD groups in terms of demographic characteristics, COPD-related clinical findings, exacerbation risk, and current treatment. The eosinophilic COPD phenotype was not a significant independent variable of COPD exacerbation. Additional research is necessary to assess this phenotyping biomarker more thoroughly for predicting prognosis in COPD patients.

Ethical considerations

The research protocol was approved by the Research Ethics Committee at King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia (Approval no.: REC 852). Requirement for patient consent was waived owing to the study design. The study adhered to the principles of the Declaration of Helsinki, 2013.

Peer review

This article was peer-reviewed by three independent and anonymous reviewers.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions

Conceptualization: F.A., A.A., H.F., Y.V.; Methodology: F.A., A.A., Y.V.; Data analysis: A.A.; Writing–original draft preparation: F.A., M.A., F.A.A, A.A.; Writing – review and editing: A.I., N.T., M.H., H.F., Y.V.; Supervision: A.A., H.F., Y.V.

All authors have read and agreed to the published version of the manuscript.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

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