DOI: https://doi.org/10.53350/pjmhs20231710464

ORIGINAL ARTICLE

Assessment of the Relationship Between Small Airways Dysfunction and Neutrophilic Inflammation in Exacerbated Chronic Obstructive Pulmonary Disease Patients

AJMAL KHAN[1], MUHAMMAD ABBAS[2]
[1]*Senior Medical Officer, Family Physician, Mardan Medical Complex, Mardan*
[2]*Associate Professor Medicine, Medical B Unit, BKMC/MMC Mardan*
Correspondence to: Muhammad Abbas, Email address: docabbas1@hotmail.com

ABSTRACT

Background: Small-airway dysfunction (SAD) is an under-recognized but significant aspect of chronic obstructive pulmonary disease (COPD). Neutrophilic inflammation also plays a significant part in exacerbations of COPD, although the connections between neutrophilic inflammation and small-airway impairment during such exacerbations are poorly understood. The aim of this study was to evaluate the relation between neutrophilic inflammation and SAD in AECOPD patients.

Material and Methods: This was an analytical cross-sectional study of 88 patients suffering from AECOPD. Demographic and clinical data were collected, followed by pulmonary function testing and laboratory studies in Mardan Medical Complex, from February 2023 to July 2023. The main indicator of small-airway function was forced expiratory flow at 25-75% of forced vital capacity (FEF_{25-75}%). The absolute neutrophil count, the neutrophil percentage, the neutrophil-to-lymphocyte ratio (NLR), and the C-reactive protein (CRP) were evaluated. Correlation and multivariable logistic regression analyses were carried out.

Conclusion: SAD was found in 65 (73.9%) patients. FEF_{25-75}% was inversely correlated with absolute neutrophil count ($p<0.001$), neutrophil percentage ($p<0.001$), NLR ($p=0.001$), and CRP ($p=0.008$). Pulmonary function and neutrophilic inflammatory markers were significantly higher in patients with SAD. Absolute neutrophil count ($p=0.018$) and NLR ($p=0.036$) were still independently associated with SAD on multivariable analysis.

Conclusion: Small-airway dysfunction was common in AECOPD and was significantly associated with increased neutrophilic inflammation. The results indicate that the peripheral airway impairment may interact with neutrophilic inflammatory activity during COPD exacerbations.

Keywords: COPD; acute exacerbation; small-airway dysfunction; neutrophils

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common and progressive respiratory condition that is defined by chronic respiratory symptoms and airflow limitation caused by abnormalities in the airways and/or alveoli[1] It continues to be a leading cause of morbidity, disability, health service utilization, and premature death globally[2] Important risk factors for COPD were identified as smoking, biomass exposure, occupational exposure to dust or smoke, male sex, and low body mass index, highlighting the particularly high burden in resource-limited settings[3]

Acute exacerbations of COPD (AECOPD) are important events in the course of the disease and are linked to worsening respiratory symptoms, reduced quality of life, rapid decline in lung function, hospitalisation and mortality[4] They typically occur as a result of a respiratory infection, exposure to environmental pollutants, or any other "insult" to the airways that exacerbates both airway and systemic inflammation[5] The physiological effects of exacerbations are not limited to the larger conducting airways, however, as increased mucus production, airway wall edema, recruitment of inflammatory cells, and bronchoconstriction all serve to further constrict airways and worsen expiratory limitation of airflow[6] Abnormalities of the peripheral or small airways are now known to play an important role in the pathogenesis of COPD and could also make significant contributions to airflow limitation, air trapping, and ventilation heterogeneity[7]

Small-airway dysfunction (SAD) refers to abnormalities of the small airways in general, below 2 mm in diameter, and may include narrowing, wall thickening, mucus plugging, inflammatory infiltration, and obliteration or loss of terminal bronchioles[8] Small airways make up only a small part of total airway resistance in normal conditions and therefore may show little abnormality in conventional spirometric parameters until the small airways are significantly involved[9] Traditional laboratory tests like forced expiratory volume in one second (FEV_1) therefore may only partially represent peripheral airway disease[10] The SAD in COPD and its relationship with air trapping and disease severity have been confirmed by a number of physiological and imaging methods, including forced oscillation techniques, lung-volume measurements, multiple-breath washout, and inspiratory-expiratory computed tomography[11, 12] During acute exacerbations, inflammatory edema and increased mucus burden could further compromise these already narrowed peripheral airways, making SAD particularly relevant to exacerbation severity[13]

Although small airways involvement is now recognized as a key component of COPD, the relationship between objective small-airway dysfunction and neutrophilic inflammatory activity during acute exacerbations is still not well understood, especially in routine clinical populations and in resource-limited settings. Traditional approaches to the assessment of AECOPD remain largely symptom- and spirometry-based, and focus on peripheral airway oxygenation and general inflammatory markers, while failing to account for clinically relevant peripheral airway abnormalities. The relationship between easily measurable neutrophilic inflammatory indices and small-airway dysfunction would help to clarify the mechanisms underlying exacerbation and help to identify those with a more inflammatory-small-airway phenotype. The present study was therefore undertaken to determine the relationship between small-airway dysfunction and neutrophilic inflammatory activity in patients with exacerbation of COPD.

MATERIAL AND METHODS

A hospital-based analytical cross-sectional study was conducted in the Department of Mardan Medical complex, over a period of six months, from in Mardan Medical Complex, from February 2023 to July 2023.

The sample size was determined using the software OpenEpi version 3.01, based on the reported association between small-airway dysfunction and neutrophilic inflammation in a prior study by Day et al (2021) published in Chest. In their study of 39 patients with COPD, several measures of small-airway dysfunction showed significant correlations with bronchoalveolar lavage neutrophil proportions, including a strong correlation between R5-R19 and neutrophil proportion ($r = 0.795$, $p = 0.001$)[11] Using an anticipated correlation effect of approximately $r = 0.30$, a 95%

Received on 15-08-2023
Accepted on 27-10-2023

confidence level, and 80% statistical power, the required sample size was calculated and, after allowing for potential incomplete data/non-response, a final sample size of 88 patients was selected for the present study.

A non-probability consecutive sampling technique was used. Patients were included if they were 40 years of age or older, had a previous diagnosis of COPD or a new diagnosis based on accepted clinical and spirometric criteria, and were seen with an acute exacerbation of COPD, which was defined as an acute worsening of the symptoms of COPD that necessitated additional treatment. Patients were included if they were clinically stable enough to perform pulmonary function testing and they gave written informed consent. Male and female patients were eligible to participate. Patients who had been diagnosed with asthma, bronchiectasis, interstitial lung disease, active pulmonary tuberculosis, lung malignancy, or other major respiratory diseases that were known to potentially impact small-airway function or inflammatory markers were excluded. Other exclusion criteria included acute pneumonia as the main diagnosis, active malignancy, active systemic inflammatory/autoimmune disease, or known immunodeficiency. Where possible, patients who were taking systemic steroids or antibiotics before evaluation were excluded, as this could significantly affect the inflammatory response measured. Hemodynamically unstable patients and those who declined to consent were excluded, as were patients who could not perform reliable pulmonary function testing.

After obtaining approval from the institutional ethical review committee, eligible patients were approached after their initial clinical assessment. The purpose and procedures of the study were explained, and informed written consent was obtained. Data collection was done using a structured data collection proforma, which contained sociodemographic and clinical details. Data on age, sex, smoking history, smoking exposure (in pack-years), COPD duration, previous exacerbations, comorbidities, current medications, and clinical characteristics of the current exacerbation were collected.

A clinical examination was carried out; respiratory rate, pulse rate, blood pressure, oxygen saturation, and respiratory symptoms were evaluated. The severity of the COPD was graded on the basis of spirometric results and the GOLD system.[14] After the patient was clinically stabilized to cooperate with the chest X-ray, pulmonary function testing was performed. Small airway parameters were noted as the main physiological measure of small airway dysfunction. Smaller values of FEF_{25-75}% were taken as an indicator of more severe small-airway disease following appropriate interpretation with respect to predicted values and spirometric results.

Venous blood samples were drawn at presentation prior to, or as early as, treatment was initiated. A complete blood count was conducted, which included total leukocyte count, absolute neutrophil count, neutrophil percentage, and lymphocyte count. The neutrophil to lymphocyte ratio (NLR) was determined as the ratio of the absolute neutrophil count (ANC) to the absolute lymphocyte count (ALC). In addition, another marker of systemic inflammatory activity, serum C-reactive protein (CRP), was measured. The main analysis compared the association of small-airway dysfunction with neutrophilic inflammatory parameters: neutrophil percentage, absolute neutrophil count, and NLR.

Data collected were entered and analyzed using IBM SPSS Statistics version 26.0. Normality tests were used for the evaluation of the distribution of continuous variables. Normally distributed quantitative variables were presented as mean ± standard deviation, whereas non-normally distributed variables were presented as median with interquartile range (IQR). For categorical variables, frequencies and percentages were used to describe them. The main analysis aimed at estimating the correlation of measures of small airway dysfunction, especially FEF_{25-75}%, with neutrophilic inflammation markers such as absolute neutrophil count, neutrophil percentage, and NLR. Pearson's correlation was used for normally distributed continuous variables; otherwise, Spearman's rank correlation was used.

Patients were classified in terms of the presence or absence of small-airway dysfunction, and the chi-square test was used to compare categorical variables. Independent-samples t-test and Mann-Whitney U test were used to compare continuous variables between groups according to data distribution. Binary logistic regression was used, as appropriate, to determine factors independently associated with small-airway dysfunction. All variables that showed a clinically relevant association or a p-value <0.20 were included in the multivariable model. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were reported. In the adjusted analysis, potential confounding factors like age, sex, smoking exposure, severity of COPD, and relevant comorbidities were taken into account. All statistical parameters were set at a two-sided p-value < 0.05.

RESULTS

A total of 88 patients with AECOPD were included. The mean age was 61.8 ± 9.7 years, and 72.7% were male. The median smoking exposure was 35 pack-years (24-48); more than half were current smokers. The median time since the diagnosis of COPD was 6 years (range 3-10 years), and 59.1% had suffered an exacerbation within the year before the study. The most common comorbidities were hypertension and diabetes mellitus. The mean respiratory rate was 25.4 ± 4.8 breaths/min, and the mean oxygen saturation was 89.7 ± 4.6%. (Table 1)

Table 1: Baseline Demographic and Clinical Characteristics of Study Participants (n=88)

Variable	n(%)/mean ± SD
Age (years)	61.8 ± 9.7
Age ≥65 years	34 (38.6)
Male	64 (72.7)
Female	24 (27.3)
Current smokers,	48 (54.5)
Former smokers	31 (35.2)
Never smokers	9 (10.2)
Smoking exposure (pack-years), median (IQR)	35 (24-48)
COPD duration (years), median (IQR)	6 (3-10)
Previous exacerbation in the past year	52 (59.1)
Hypertension	31 (35.2)
Diabetes mellitus	24 (27.3)
Ischemic heart disease	16 (18.2)
Respiratory rate (breaths/min)	25.4 ± 4.8
Oxygen saturation (%)	89.7 ± 4.6
Heart rate (beats/min)	101.6 ± 15.2

Table 2: Pulmonary Function and Inflammatory Characteristics of Participants (n=88)

Variable	n(%)/mean ± SD/median (IQR)
FEV_1 (% predicted)	45.8 ± 15.1
FVC (% predicted)	67.4 ± 14.8
FEV_1/FVC ratio	0.49 ± 0.09
FEF_{25-75}% (% predicted)	29.6 ± 12.7
Small-airway dysfunction	65 (73.9)
No small-airway dysfunction	23 (26.1)
Absolute neutrophil count (×10⁹/L)	8.2 (6.4-10.5)
Neutrophil percentage (%)	78.6 ± 8.2
Lymphocyte count (×10⁹/L)	1.4 (1.0-1.8)
NLR	5.9 (4.0-8.2)
CRP (mg/L)	42 (24-78)

Table 3: Correlation between Small-Airway Dysfunction and Neutrophilic Inflammatory Markers

Variable correlated with FEF_{25-75}%	Correlation coefficient	p-value
Absolute neutrophil count	−0.43	<0.001
Neutrophil percentage	−0.39	<0.001
NLR	−0.35	0.001
CRP	−0.28	0.008
FEV_1 (% predicted)	0.62	<0.001
Smoking exposure (pack-years)	−0.31	0.003
COPD duration	−0.24	0.024

Table 4: Comparison of Participants With and Without Small-Airway Dysfunction

Variable	Small-airway dysfunction (n=65) n(%)/mean ± SD/median (IQR)	No small-airway dysfunction (n=23) n(%)/mean ± SD/median (IQR)	p-value
Age (years)	62.5 ± 9.3	59.9 ± 10.5	0.279
Male sex	49 (75.4)	15 (65.2)	0.348
Smoking exposure (pack-years)	38 (27-52)	28 (18-42)	0.028
COPD duration (years)	7 (4-11)	5 (2-8)	0.041
Previous exacerbation	43 (66.2)	9 (39.1)	0.025
FEV_1 (% predicted)	41.5 ± 12.8	57.9 ± 14.7	<0.001
FEV_1/FVC	0.46 ± 0.08	0.57 ± 0.08	<0.001
Neutrophil count (×10^9/L)	8.8 (6.9-11.2)	6.7 (5.3-8.2)	0.003
Neutrophil percentage (%)	80.3 ± 6.9	73.9 ± 9.1	0.002
NLR	6.5 (4.5-8.9)	4.6 (3.1-6.4)	0.008
CRP (mg/L)	48 (29-84)	31 (18-56)	0.015

Table 5: Association of Clinical and Inflammatory Variables with Small-Airway Dysfunction: Univariate Logistic Regression

Predictor	OR	95% CI	p-value
Age (per year)	1.02	0.98-1.06	0.291
Male sex	1.64	0.62-4.34	0.321
Smoking exposure (per 10 pack-years)	1.28	1.02-1.61	0.034
COPD duration (per year)	1.09	1.01-1.18	0.026
Previous exacerbation	3.05	1.11-8.39	0.031
FEV_1 (% predicted)	0.94	0.91-0.97	<0.001
Absolute neutrophil count	1.32	1.10-1.58	0.003
Neutrophil percentage	1.10	1.03-1.18	0.005
NLR	1.16	1.04-1.30	0.008
CRP	1.01	1.00-1.02	0.019

Table 6: Multivariable Logistic Regression for Factors Independently Associated With Small-Airway Dysfunction

Predictor	Adjusted OR	95% CI	p-value
Smoking exposure (per 10 pack-years)	1.21	0.96-1.53	0.104
Previous exacerbation	2.31	0.79-6.75	0.127
COPD duration (per year)	1.05	0.96-1.15	0.276
FEV_1 (% predicted)	0.95	0.91-0.98	0.003
Absolute neutrophil count	1.25	1.04-1.51	0.018
NLR	1.14	1.01-1.29	0.036
CRP	1.01	0.99-1.02	0.084

PFT revealed moderate-to-severe airflow limitation (mean FEV_1 45.8 ± 15.1% predicted and FEV_1/FVC ratio 0.49 ± 0.09). The mean FEF_{25-75}% was 29.6 ± 12.7% predicted, with small-airway dysfunction found in 65 (73.9%) patients. Median absolute neutrophil count was 8.2 (6.4-10.5) ×10^9/L, while mean neutrophil percentage was 78.6 ± 8.2%. The median NLR and CRP were 5.9 (4.0-8.2) and 42 (24-78) mg/L, respectively. (Table 2)

FEF_{25-75}% demonstrated significant inverse correlations with absolute neutrophil count (p<0.001), neutrophil percentage (p<0.001), NLR (p=0.001), and CRP (p=0.008). There was a strong positive correlation between FEF_{25-75}% and FEV_1 (p<0.001), and the inverse correlation of smoking exposure and COPD duration with small-airway function was less strong. (Table 3)

Patients with small-airway dysfunction were much more likely to have a longer duration of COPD, higher smoking exposure and a history of exacerbations. Additionally, they showed markedly reduced FEV_1, FEV_1/FVC, and absolute neutrophil count, neutrophil percentage, NLR, and CRP levels, and elevated absolute eosinophil count, eosinophil percentage, and EOS. There was no significant difference in the ages and sex ratio of the two groups. (Table 4)

Smoking exposure, COPD duration, prior exacerbation, lower FEV_1, higher absolute neutrophil count, neutrophil percentage, NLR, and CRP were independently associated with small-airway dysfunction in univariable logistic regression analysis. The strongest association was observed for FEV_1, with lower FEV_1 being associated with increased odds of small-airway dysfunction (p<0.001). (Table 5)

Multivariable adjustment showed that lower FEV_1, higher absolute neutrophil count, and higher NLR were still significant independent risk factors for small-airway dysfunction. Absolute neutrophil count was found to be associated with 1.25-fold higher odds of small-airway dysfunction (p=0.018), and for every unit increase in NLR, the odds increased by about 14% (p=0.036). Smoking exposure, duration of COPD, number of exacerbations, and CRP were no longer independent factors. (Table 6).

DISCUSSION

In the present study, small-airway dysfunction (SAD) was found to be very common among patients presenting with acute exacerbation of COPD, with 73.9% of the participants having reduced FEF_{25-75}%. Importantly, greater dysfunction of small airways was significantly correlated with increased neutrophilic inflammatory activity. FEF_{25-75}% had significant negative correlations with ANC, neutrophil%, NLR, and CRP, indicating that the peripheral airway impairment and neutrophilic inflammation may be closely related aspects of the pathophysiology of AECOPD. This was especially relevant to Day et al., 2021, who specifically examined the interrelationship between SAD, neutrophilic inflammation, and exacerbation frequency and found significant associations between a number of measures of SAD and neutrophilia in the peripheral airways.[1] This is because the investigators used several independent measures of peripheral airway disease in their study, which further strengthens the biological plausibility of the association observed in the present study[11]

This was also consistent with a high prevalence of SAD seen in our cohort, as well as in the wider literature, which shows peripheral airway pathology is a frequent finding in COPD. Our patients had reduced FEF_{25-75}%, which may reflect small-airway involvement, which is consistent with the concept that small airways are an important contributor to airflow obstruction, not just a secondary process in advanced COPD, as reported by Chukowry et al. (2021), who reviewed the evidence of small-airway involvement in COPD and its close link with these structural abnormalities[15] These abnormalities were demonstrated by Polosukhin et al. (2021) in small airway pathological changes in COPD[16]

The strong positive correlation between FEF_{25-75}% and FEV_1 we observed also confirmed the relationship between peripheral and global airflow limitation. However, significant SAD was found in our population, suggesting that peripheral airway involvement cannot be fully characterised by conventional spirometry. Other studies indicated that the physiological methods detected small-airway abnormalities in symptomatic patients with preserved pulmonary function, with impulse oscillometry showing high sensitivity for detection of SAD, implying that small-airway abnormalities could be missed if the use of FEV_1 was limited[17, 18]

In particular, the inverse relationship of FEF_{25-75}% and absolute neutrophil count in our study was significant. The neutrophil counts and percentage of neutrophils were higher in patients with SAD than in patients without SAD, indicating greater

neutrophilic activity in the whole body in relation to more peripheral airway impairment. This was consistent with Day et al (2021), who showed direct evidence that small-airway abnormalities are associated with neutrophilic airway inflammation, which could be responsible for narrowing peripheral airways by causing epithelial damage, mucus hypersecretion, and inflammatory remodelling. The findings were thus consistent with the idea that the observed association was not solely the result of overall severity of airflow obstruction but was the result of an inflammatory aspect of the small airways disease[11]

Study of NLR as a marker of COPD inflammatory activity also corroborated the relationship with SAD in the present study. Ellingsen et al. (2021) evaluated 466 patients with COPD and found that elevated NLR was more frequent among patients with previous exacerbations; furthermore, continuous NLR remained associated with subsequent AECOPD after adjustment for confounders[19] Karauda et al. (2021) likewise reported that NLR was associated with prognosis in patients experiencing COPD exacerbations, supporting its usefulness as an accessible marker of systemic inflammatory burden.[7] Our finding that NLR remained independently associated with SAD after multivariable adjustment therefore suggested that NLR might provide clinically useful information about the inflammatory phenotype accompanying peripheral airway impairment[20]

The relationship between NLR and the outcomes of AECOPD was also strengthened by the systematic review and meta-analysis of Paliogiannis et al. in 2022 that included 15 studies with over 10,000 patients with AECOPD. A higher NLR was significantly associated with worse clinical outcomes, with the certainty of evidence dependent on the type of clinical outcome and type of analysis, supporting the interpretation of our results, as a higher NLR would suggest higher levels of inflammatory activity during AECOPD, even if it was not specifically analyzed as the variable of interest in the present study. Therefore, the relationship between high NLR and SAD in our group might be a significant inflammatory pattern of clinical importance and not just a laboratory finding[21]

The finding that patients with COPD were also more likely to have elevated CRP was consistent with the known link between severity of COPD exacerbation and systemic inflammation. In the multivariable model, however, CRP lost its independent significance, while absolute neutrophil count and NLR remained significant. The discovery led to the idea that perhaps there was a greater relationship between the neutrophil-based measures and small-airway impairment than between the nonspecific systemic inflammatory markers. The difference was important because the inflammation of COPD was heterogeneous, and neutrophilic inflammation is one of the important patterns of inflammation that correlates with more severe disease and exacerbations. The results of Ellingsen et al. 2021 also suggested that NLR could give information that went beyond traditional clinical parameters regarding exacerbation risk[19]

The present study also found the relationship between smoking exposure and SAD to be similar to that observed in previous studies. There was a higher cumulative smoking exposure among participants with SAD, but this was not independently significant after adjustment. Peng et al. (2021), in a large community-based study of IOS-defined SAD, identified smoking history among the important risk factors for small-airway dysfunction and reported that individuals with SAD had poorer lung function, increased airway resistance, and greater emphysema and gas trapping[22] This supported our finding that cumulative tobacco exposure was associated with impaired peripheral airway function while also indicating that the relationship between smoking and SAD was potentially mediated or modified by established COPD severity and inflammatory activity. (ScienceDirect)

The clinically relevant finding of a significant association between previous exacerbations and SAD was also found. Patients with SAD were more likely to have a history of previous exacerbations, indicating that peripheral airway impairment may be a marker of patients with a more unstable COPD phenotype. The study by Day et al. (2021) showed an interrelationship between SAD, neutrophilic inflammation, and exacerbation frequency, supporting this observation in particular[11] Similarly, the findings of Ellingsen et al. (2021) indicated that increased NLR was associated with a history of exacerbations and subsequent exacerbation risk, suggesting that there might be a cycle where inflammation leads to small-airway dysfunction, impaired peripheral airway clearance, and increased susceptibility to exacerbation[19]

Our observations are consistent with that raised by Polosukhin et al. (2021), who showed that small-airway abnormalities, mucus accumulation, and loss of alveolar attachments are associated with COPD-related small-airway airflow limitation, and with those of Liu et al. (2022), who demonstrated that small-airway disease and emphysema are associated with persistent small-airway airflow limitation in COPD[16, 23]

The overall conclusion of the present study was to provide clinically relevant evidence showing the presence of small airway dysfunction in AECOPD and its strong association with systemic neutrophilic inflammation. The consistency of our findings with those of Day et al. and the supporting data from the study of efficacy of SAD, NLR, smoking exposure, and COPD exacerbations indicated that there may be a cross-phenotype of physiological dysfunction and neutrophilic inflammation that could define an exacerbated COPD phenotype. The current analysis included both SAD and inflammatory biomarkers in one analysis, which may offer a novel tool for determining patients with significant peripheral airway involvement, as opposed to examinations of either SAD or inflammatory biomarkers alone. Impulse oscillometry, multiple-breath washout, quantitative CT and direct airway inflammatory sampling may be used in future prospective studies to further determine the temporal and mechanistic links between neutrophilic inflammation and small-airway dysfunction.

Limitations: There were limitations to the study. Determination of a temporal or causal relationship between neutrophilic inflammation and small-airway dysfunction was not possible because of its cross-sectional design. The small number of participants and one-center study design may have impacted the generalizability of the results to other populations. The main measurement used to determine small-airway dysfunction was FEF_{25-75}%, a clinically feasible value that is related to lung volume, but is not a definitive endpoint parameter for peripheral airway disease alone. There were no more specific techniques, such as impulse oscillometry, multiple-breath washout, and quantitative inspiratory-expiratory CT. In addition, inflammatory markers were used in the systems, not airway, and inflammatory markers may have been affected by the acute exacerbations. Lastly, there was no long-term follow-up to assess whether the inflammatory and physiological changes noted predicted future exacerbations or disease progression.

CONCLUSION

Small-airway dysfunction was very common and was inversely correlated with markers of neutrophilic inflammation in acute exacerbation of COPD. After controlling for all the relevant clinical factors, higher ANC and NLR remained independently associated with small airway dysfunction. These results agree with the idea of the linkage between neutrophilic inflammation and peripheral airway impairment in AECOPD. Small airway function assessment, combined with assessment of inflammatory markers, might then help to give further information about a patient's physiological and inflammatory phenotype during exacerbations. Additional prospective multicenter investigations involving more sensitive tools of small-airway disease and direct assessment of small-airway inflammation are warranted to determine the underlying mechanisms and implications of this relationship.

REFERENCES

1. Stolz, D., et al., Towards the elimination of chronic obstructive pulmonary disease: a Lancet Commission. The Lancet, 2022. 400(10356): p. 921-972.
2. Viegi, G., et al., Global burden of chronic respiratory diseases. Journal of aerosol medicine and pulmonary drug delivery, 2020. 33(4): p. 171-177.
3. Safiri, S., et al., Burden of chronic obstructive pulmonary disease and its attributable risk factors in 204 countries and territories, 1990-2019: results from the Global Burden of Disease Study 2019. BMJ, 2022. 378.
4. Ritchie, A.I. and J.A. Wedzicha, Definition, causes, pathogenesis, and consequences of chronic obstructive pulmonary disease exacerbations. Clinics in Chest Medicine, 2020. 41(3): p. 421.
5. Sapey, E. et al., Building toolkits for COPD exacerbations: lessons from the past and present. Thorax, 2019. 74(9): p. 898-905.
6. Alobaidi, N.Y., et al., An overview of exacerbations of chronic obstructive pulmonary disease: Can tests of small airways' function guide diagnosis and management? Annals of thoracic medicine, 2020. 15(2): p. 54.
7. Santus, P., et al., The relevance of targeting treatment to small airways in asthma and COPD. Respiratory care, 2020. 65(9): p. 1392-1412.
8. Bao, M.W., et al. Is small airway dysfunction an abnormal phenomenon for patients with normal forced expiratory volume in 1 second and the ratio of forced expiratory volume in 1 second to forced vital capacity? Annals of Allergy, Asthma & Immunology, 2022. 128(1): p. 68-77. e1.
9. Almeshari, M.A., J. Stockley, and E. Sapey, The diagnosis of asthma. Can physiological tests of small airways function help? Chronic Respiratory Disease, 2021. 18: p. 14799731211053332.
10. Kakavas, S., et al., Pulmonary function testing in COPD: looking beyond the curtain of FEV1. NPJ Primary Care Respiratory Medicine, 2021. 31(1): p. 23.
11. Day, K., et al., Interrelationships among small airways dysfunction, neutrophilic inflammation, and exacerbation frequency in COPD. Chest, 2021. 159(4): p. 1391-1399.
12. Singh, D., et al., Small airway disease in chronic obstructive pulmonary disease: insights and implications for the clinician. Current opinion in pulmonary medicine, 2020. 26(2): p. 162-168.
13. MacLeod, M., et al., Chronic obstructive pulmonary disease exacerbation fundamentals: diagnosis, treatment, prevention and disease impact. Respirology, 2021. 26(6): p. 532-551.
14. Arinc, S., M. Agca, and F. Yaman, Evaluation of nutritional status in COPD according to the GOLD-2015 staging system: a prospective observational study. European Journal of Clinical Nutrition, 2020. 74(9): p. 1354-1361.
15. Chukowry, P.S., D.A. Spittle, and A.M. Turner, Small Airways Disease, Biomarkers and COPD: Where are We? Int J Chron Obstruct Pulmon Dis, 2021. 16: p. 351-365.
16. Polosukhin, V.V., et al., Small airway determinants of airflow limitation in chronic obstructive pulmonary disease. Thorax, 2021. 76(11): p. 1079-1088.
17. Li, L.Y., et al., Impulse oscillometry for detection of small airway dysfunction in subjects with chronic respiratory symptoms and preserved pulmonary function. Respir Res, 2021. 22(1): p. 68.
18. Chiu, H.Y., et al., Small Airway Dysfunction by Impulse Oscillometry in Symptomatic Patients with Preserved Pulmonary Function. J Allergy Clin Immunol Pract, 2020. 8(1): p. 229-235.e3.
19. Ellingsen, J., et al., Neutrophil-to-lymphocyte ratio, blood eosinophils and COPD exacerbations: a cohort study. ERJ Open Research, 2021. 7(4): p. 00471-2021.
20. Karauda, T., et al., Eosinopenia and neutrophil-to-lymphocyte count ratio as prognostic factors in exacerbation of COPD. Scientific Reports, 2021. 11(1): p. 4804.
21. Zinellu, A., et al., A Comprehensive Systematic Review and Meta-Analysis of the Association between the Neutrophil-to-Lymphocyte Ratio and Adverse Outcomes in Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease. J Clin Med, 2022. 11(12).
22. Peng, J., et al., Clinical characteristics of and risk factors for small airway dysfunction detected by impulse oscillometry. Respiratory Medicine, 2021. 190: p. 106681.
23. Lu, L., et al., Discordant Spirometry and Impulse Oscillometry Assessments in the Diagnosis of Small Airway Dysfunction. Frontiers in Physiology, 2022. Volume 13 - 2022.

This article may be cited as: Khan A., Abbas M., Assessment of the Relationship Between Small Airways Dysfunction and Neutrophilic Inflammation in Exacerbated Chronic Obstructive Pulmonary Disease Patients. Pak J Med Health Sci, 2023; 17(10): 464-468.