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Small Airways Dysfunction and Neutrophilic Inflammation in Acute COPD Exacerbations: A Cross-Sectional Study

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ABSTRACT

Background: Small airways dysfunction (SAD) is a key pathological feature of COPD, particularly during acute exacerbations (AECOPD). Neutrophilic inflammation drives disease progression, but its relationship with SAD during exacerbations remains unclear.

Objective: To investigate the association between systemic neutrophilic inflammatory markers and small airways dysfunction in patients hospitalized with AECOPD.

Methodology: The present cross-sectional analytical study included 160 hospitalized patients with acute exacerbation of COPD. Systemic levels of inflammation were estimated with the total leukocyte count, absolute neutrophil count, percentage of neutrophils, neutrophil-lymphocyte ratio, and C-reactive protein levels at the time of admission.

Results: SAD was present in 112 patients (70.0%). FEF_{25-75} correlated negatively with neutrophil percentage (r = -0.52), absolute neutrophil count (r = -0.48), and NLR (r = -0.55) (all $p < 0.001$). On multivariate analysis adjusted for age, BMI, and comorbidities, independent predictors of SAD were: NLR >3 (OR 3.12, 95% CI 1.48-6.57, p=0.003), neutrophil percentage >70% (OR 2.74, 95% CI 1.31-5.75, p=0.007), smoking >30 pack-years (OR 2.09, 95% CI 1.01-4.34, p=0.046), and GOLD stage III-IV (OR 3.68, 95% CI 1.74-7.78, p<0.001).

Conclusion: Small airways dysfunction is highly prevalent during AECOPD and is independently associated with systemic neutrophilic inflammation. The neutrophil-to-lymphocyte ratio, a readily available biomarker, may help identify patients at risk of significant small airway involvement during exacerbations.

Keywords: COPD; Small Airways Dysfunction; Neutrophilic Inflammation; Acute Exacerbation

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a progressive and heterogeneous disease of the airways, linked with airflow irreversibility, inflammation of the airways, and remodeling of the lungs. Acute Exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD) occur when symptomatic episodes exceed normal variation and are an integral part of COPD. They have been known to be associated with an accelerated decline in lung function, reduced quality of life, and an increased risk of mortality.[1] Identifying the cause of and maintaining these exacerbations continues to be critical for patient management. It's been found that COPD largely affects the small airways, especially when the airway inner diameter falls below 2mm. The pathological lesions of the distal airways include epithelial damage, goblet cell hyperplasia, mucinous plugging, peribronchiolar fibrosis, and inflammatory infiltration of the walls of the small airways. These conditions are known as small airway dysfunction (SAD). These changes are major contributors to the airflow obstruction and air trapping that often precede the alterations in conventional spirometry measurements of forced expiratory volume in the first second (FEV_1) in COPD. It is for this reason that SAD is now recognized as an important pathological feature of stable as well as exacerbated COPD.[2]

Traditional spirometry, despite its popularity for COPD diagnosis and management, remains insensitive for small airway disease changes and abnormalities. Thus, sophisticated physiological parameters such as forced expiratory flow at 25-75% forced vital capacity (FEF25-75), impulse oscillation technique parameters (IOS), and lung volumes and trapped gas fraction measurements were already recommended as more sensitive methods for the evaluation of SAD. Moreover, during exacerbation events, small airway disease impairment can be exaggerated by the enhancement of inflammation, mucus secretion, and bronchiolar wall edema with consequent enhancement of airflow obstruction and vent-perfusion mismatch. Despite its relevance, however, the correlation between SAD and the processes involving inflammation during exacerbation is not yet clear.[3]

Inflammation in COPD may be complex and heterogeneous; neutrophil inflammation constitutes the major phenotype of inflammation, especially among smokers or during AECOPD events. Neutrophils mainly participate in COPD pathology because of their potential for releasing proteolytic enzymes, reactive oxygen products, as well as other mediators of inflammation that promote tissue destruction and mucus hypersecretion. Neutrophilia has been associated with disease severity or the frequency of exacerbations with adverse clinical outcomes within the setting of COPD. During AECOPD events, neutrophil inflammation may be further potentiated; this mainly results from bacterial infection.[4,5]

Although the significance of SAD and neutrophilic inflammation in the pathophysiology of COPD has been adequately recognized in current medical literature, their association in the context of exacerbated forms has remained unexplored. Peripheral blood neutrophil count and N/L ratio have been established as novel biomarkers that are accessible at minimal cost in the context of systemic inflammation related to patients with COPD. A high N/L ratio has been explored to relate with greater exacerbations in association with their intensity and related mortality. Further, percentages in sputum related to neutrophils were discovered to relate with airflow impairment and their associated symptoms in the context.[6] Nevertheless, the association related to the prediction of small airway impairment in the context of an exacerbation has remained unclear in those biomarkers.

To medically generalize, understanding the interplay between SAD and neutrophilic inflammation is of prime significance. In this context, patients with predominant features of SAD and neutrophilic inflammation may have a variable response to pharmacologic therapies, inhaled corticosteroids, LABA, or novel anti-inflammatory drugs. In addition, understanding SAD and inflammation interaction may assist in risk stratification and subsequent prevention of subsequent exacerbations in these patients. Taking into consideration that exacerbation is one of the prime factors in disease progression in these patients, addressing underlying pathology in SAD during this phase may provide a unique opportunity in altering disease course.

Objective

To investigate the association between systemic neutrophilic inflammatory markers and small airways dysfunction in patients hospitalized with AECOPD.

Methodology

This cross-sectional study conducted at Khyber Teaching Hospital, Peshawar and include a total of 160 consecutive patients admitted with Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD). This study included patients above 40 years with established COPD diagnosed according to GOLD criteria (post-bronchodilator FEV1/FVC ratio < 0.70). Patients with co-existing asthma, bronchiectasis, interstitial lung disease, pulmonary tuberculosis, either acute or ongoing, lung malignancy, acute coronary events, systemic inflammatory disorders, or those who cannot produce adequate pulmonary function tests were excluded.

Patients' demographic and clinical information like age, sex, BMI, smoking status and the number of pack-years smoked, co-existing diseases, the extent of COPD, and details of exacerbation were documented at the time of admission. All the patients undertook pulmonary function

tests after stabilization and just before discharge, according to ATS/ERS recommendations and after calibration of the spirometer. Spirometric values measured were forced expiratory volume at the end of the first second (FEV_1), forced vital capacity (FVC), FEV1/FVC ratio, and forced expiratory flow between 25% and 75% of the FVC (FEF25-75). Small airways dysfunction (SAD) was measured mainly based on FEF25-75 and expressed as a value < 65% of the predicted norm, as suggested by previous work. Patients were divided into groups with and without SAD for purposes of comparison.

Venous blood samples were collected in EDTA and plain tubes. Complete blood counts were analyzed using Sysmex XN-1000 analyzer. CRP was measured by immunoturbidimetric assay (Roche Cobas 6000). The neutrophil-to-lymphocyte ratio was calculated as absolute neutrophil count divided by absolute lymphocyte count.

Data were analyzed using SPSS version 27. Normality was assessed using the Shapiro-Wilk test. Continuous variables were compared using independent t-test (normal distribution) or Mann-Whitney U test (non-normal). Categorical variables were compared using chi-square or Fisher's exact test. Correlations were assessed using Pearson (normal) or Spearman (non-normal) coefficients with 95% confidence intervals calculated via Fisher's z-transformation. Multivariate logistic regression was performed to identify independent predictors of SAD. Variables with $p < 0.10$ in univariate analysis were entered into the model. The final model was adjusted for age, sex, BMI, and comorbidities (cardiovascular disease, diabetes). Multicollinearity was assessed using variance inflation factor (VIF), with VIF >5 indicating significant collinearity. Model fit was evaluated using the Hosmer-Lemeshow test. Adjusted odds ratios with 95% confidence intervals are reported. Statistical significance was set at $p < 0.05$.

Results

Mean age of the study cases was 64.8 ± 8.9 years. There was a clear male predominance, with 118 (73.8%) being male and 42 (26.2%) females. The mean body mass index (BMI) was 22.1 ± 3.7 kg/m². Concerning smoking status, 76 (47.5%) were current smokers on admission, compared to 84 (52.5%) of whom are ex-smokers. Indeed, the prevalence of smoking was high, with a mean of 34.6 ± 12.4 pack-years. Focusing on the degree of airflow obstruction in accordance with the GOLD classification, most patients presented as being in moderate to severe stages of airflow obstruction, of whom 44 (27.5%) were grade II, followed by 68 (42.5%) grade III, and finally, 48 (30%) grade IV. Also, a considerable percentage of patients presented as frequent exacerbators, of whom 92 (57.5%) presented more than twice in a year (Table 1).

Table 1. Baseline Demographic and Clinical Characteristics of Study Participants (n = 160)

Variable	Total (n = 160)
Age (years), mean ± SD	64.8 ± 8.9
Male sex, n (%)	118 (73.8)
Female sex, n (%)	42 (26.2)
Body Mass Index (kg/m²), mean ± SD	22.1 ± 3.7
Current smokers, n (%)	76 (47.5)
Ex-smokers, n (%)	84 (52.5)
Smoking history (pack-years), mean ± SD	34.6 ± 12.4
GOLD stage II, n (%)	44 (27.5)
GOLD stage III, n (%)	68 (42.5)
GOLD stage IV, n (%)	48 (30.0)
Frequent exacerbators (≥2/year), n (%)	92 (57.5)

FEV_1 was 1.18 L with a SD of 0.42 L, which is approximately 43.6% of that which is predicted. Mean FVC was 2.41 L (±0.61 L), which is 68.9% of that which is predicted. This sharp difference in slope between FEV_1 and FVC reduces the FEV_1/FVC ratio to 48.9% (±9.4%), which indicates airflow obstruction. Small airway function was found to be deteriorated, with a reduced flow rate of FEV over the middle portion of the procedure, denoted by "FEF_{25-75}." Mean FEV_{25-75} was 0.71 L/s (±0.31 L/s), which is approximately 51.4% of that which is predicted (Table 2).

Based on the predetermined criterion that peak expiratory flow-reduced FEF_{25-75} was less than 65% of predicted normal value, 112 patients (70.0%) had small airway dysfunction, while 48 patients (30.0%) had relatively well-preserved small airway function (Table 3).

The total white blood cell count was 11.6 ± 3.2 ×10^3/μL. This is particularly evident due to the high average absolute neutrophil count of 8.2 ± 2.6 ×10^3/μL and the high proportion of neutrophils accounting for 74.1 ± 9.8% of all cells. On the other hand, lymphocytes presented relatively low values. This is evident since the average value of lymphocytes of 1.54 ± 0.62 ×10^3/μL increased neutrophil to lymphocyte ratio (NLR). The overall group average of NLR value of 5.8±2.9 contributed to elevated neutrophil to lymphocyte ratio. Notably, all subjects with NLR>3 represented 126 (78.8%). The C-reactive protein (CRP) level was also evaluated as an additional marker of systemic inflammation. Among the 124 patients for whom CRP values are available, the median CRP level is 28.6 ± 16.4 mg/L (Table 4).

Table 2. Pulmonary Function Parameters of Study Population

Parameter	Mean ± SD	% Predicted (Mean ± SD)
FEV_1 (L)	1.18 ± 0.42	43.6 ± 13.9
FVC (L)	2.41 ± 0.61	68.9 ± 15.2
FEV_1/FVC (%)	48.9 ± 9.4	-
FEF_{25-75} (L/s)	0.71 ± 0.31	51.4 ± 18.6

Patients with SAD had significantly impaired lung function, and the mean FEV1 % predicted (39.8 ± 12.1) was significantly lower than that in patients without SAD (52.4 ± 14.6; $p < 0.001$), indicating an even greater degree of air flow obstruction in SAD patients. The disparity was even greater for small airway indices. The FEF25-75 % predicted was significantly diminished in SAD patients (41.2 ± 11.3) compared to those in patients without SAD (75.6 ± 8.9; $p < 0.001$). The mean percentage neutrophils were significantly higher in SAD patients (77.2 ± 8.6%) than in patients without SAD (67.4 ± 7.9%; $p < 0.001$). Correspondingly, the absolute neutrophil count in SAD patients (8.8 ± 2.4 × 10^3/μL) was higher than that in patients without SAD (6.9 ± 2.1 × 10^3/μL, $p < 0.001$). The neutrophil and lymphocyte ratio (NLR), a marker of systemic inflammation, was also significantly higher in SAD (mean 6.6 ± 2.8) than in patients without SAD (mean 4.1 ± 1.9; $p < 0.001$). Levels of C-reactive protein (CRP) in SAD patients (mean 32.4 ± 17.1 mg/L) were significantly higher compared to those in patients without SAD (mean 20.8 ± 11.9 mg/L) ($p = 0.002$) (Table 5).

The small airway function, as expressed by the FEF_{25-75} parameter, is on the infection radar. It expresses a distinct, fair inverse relation to the percentage of neutrophils in the blood ($r = -0.52$, $p < .001$) a greater percentage of neutrophils absolutely correlates with an increased impairment of small airways. The same refrain is repeated in the absolute neutrophil count (ANC) value: FEF_{25-75}, expresses an inverse relation to ANC ($r = -0.48$, $p < .001$), again emphasizing the fact that increased neutrophil inflammation corresponds to poor small airway function. This correlation becomes even more evident when examining the neutrophil-lymphocyte ratio (NLR) correlation with FEF_{25-75}, as both FEF_{25-75} and NLR have a strong negative correlation ($r = -0.55$, $p < .001$). This correlation doesn't just extend into the small airways, as the percentage of FEV1, a common measurement of airflow obstruction, will decrease with high NLR ($r = -0.41$, $p < .001$) (Table 6).

There was a marked increase in the probability of patients with (NLR > 3) testing positive for SAD, which was beyond three-fold (adjusted OR = 3.12; 95%CI: 1.48-6.57; p-value = 0.003). Similarly, greater than 70% independently increased the risk of patients with SAD, which was approximately 2.7 times (adjusted OR = 2.74; 95%CI: 1.31-5.75; p-value= 0.007). The severity of smoke exposure was also relevant to patients with SAD, who had exposures exceeding 30 pack-years, indicating a doubled probability (adjusted OR = 2.09; 95%CI: 1.01-4.34; p-value= 0.046). This depicts the effect that cigarette smoke has had on the subsequent pathological conditions observed in the terminal passages among patients with SAD. Disease severity also independently influenced the presence of SAD. Patients with advanced

Table 3. Prevalence of Small Airways Dysfunction (SAD)

SAD Status ($FEF_{25–75}$ < 65%)	n (%)
SAD present	112 (70.0)
SAD absent	48 (30.0)

airflow limitation (GOLD stage III–IV) had a markedly higher likelihood of small airway involvement, with an almost fourfold increased risk (adjusted OR 3.68; 95% CI: 1.74–7.78; $p < 0.001$). Multicollinearity was not significant (all VIF < 2.5). The Hosmer-Lemeshow test indicated good model fit ($p = 0.342$) (Table 7).

Discussion

COPD is predominantly a disease of elderly patients and is closely related to cumulative tobacco exposure, severity of disease, and frequency of exacerbation. The baseline demographic and clinical characteristics of the 160 patients with acute exacerbation of COPD studied here provide important context for interpreting the associations noted between small airways dysfunction and neutrophilic inflammation.

In the present study, the mean age was 64.8 ± 8.9 years. There have been similar reports of mean ages by Hurst et al. (2010)[6] in the ECLIPSE study and by Vestbo et al. (2013),[7] where a majority of the COPD patients with exacerbations were > 60 years old. Advancing age is known to be associated with cumulative lung injury, immunosenescence, and increasing susceptibility to exacerbations, which could partly explain the high inflammatory burden seen in this population.

A marked male preponderance of 73.8% was observed in the present study. This is consistent with South Asian and developing-country reports, where smoking has traditionally been more common among males. Similar male preponderance in cohorts with COPD has been reported by Gan et al. (2004)[8] and by Jindal et al. (2012)[9], especially in hospital-based exacerbation studies. More recent Western population studies, however, including that by Soriano et al. (2010)[10], demonstrate a closing gender gap, likely due to an increase in smoking among women.

The mean BMI of 22.1 ± 3.7 kg/m² would suggest that many of these patients were in the normal to low-normal category. This is a common finding in populations with moderate-to-severe COPD. Low BMI has been associated with systemic inflammation, muscle wasting, and poor prognosis in COPD. The values of mean BMI are similar to those reported by Landbo et al. (1999),[11] who demonstrated that a low BMI increases the risk of mortality and frequency of exacerbation. Relatively low BMI in our cohort could thus have contributed to increased inflammatory responses during exacerbations.

Smoking exposure was high in this study, where 47.5% of current smokers had a mean smoking history of 34.6 ± 12.4 pack-years. Similar observations were documented by Hogg et al., (2004),[2] who highlighted that it was not acute but the cumulative smoking exposure that drives airway inflammation and small airway remodeling. The high percentage of ex-smokers, 52.5%, indicates that many patients indeed stop smoking, yet the disease continues to be aggressively severe, demonstrating, at least for the present time, the irreversibility of structural damage to the airways. For disease severity, most patients belonged to GOLD stage III, corresponding to 42.5%, and stage IV, corresponding to 30.0%, suggesting advanced airflow limitation. This distribution is similar to the hospital-based exacerbation study by Wedzicha and Seemungal (2007),[12] where there was overrepresentation of severe and very severe COPD because of increased rates of hospitalization. Advanced GOLD stages are associated with increased small airway involvement, greater inflammatory burden, and frequent exacerbations, all supporting the relevance of our cohort for SAD and inflammation. Finally, 57.5% of patients were frequent exacerbators, which is a proportion close to that described by Hurst et al. (2010)[6], who had identified a distinct frequent-exacerbator phenotype that remains relatively stable over time. Frequent exacerbators have heightened airway and systemic inflammation, worse lung function, and increased healthcare utilization.

Pulmonary function testing in the present study revealed significant airflow limitations, with a small airways predominant pattern, as also noted in previously published data from subjects with moderate to severe COPD during acute exacerbation. The mean value of FEV_1 of 1.18±0.42 L, which is equivalent to 43.6±13.9% of the predicted value, was indicative of significant obstruction and positioned most of the subjects in the severe category. Hurst et al. (2010)[6] reported similar decline in FEV_1 in the ECLIPSE cohort, while Wedzicha & Seemungal (2007)[12] stated that hospitalization for exacerbated disease is usually seen in patients whose FEV_1 is below 50 % predicted, reflecting severe disease with increased susceptibility to exacerbations. In this study, the mean FVC of 2.41 ± 0.61 L or 68.9 ± 15.2% predicted suggested relatively preserved lung volumes compared to the more considerable decline in expiratory flow. By contrast, the decline in FEV1 compared with FVC was disproportionately large, with a notably low

Table 4. Inflammatory Markers of Study Participants

Inflammatory Parameter	Mean ± SD
Total leukocyte count (×10³/μL)	11.6 ± 3.2
Absolute neutrophil count (×10³/μL)	8.2 ± 2.6
Neutrophil percentage (%)	74.1 ± 9.8
Absolute lymphocyte count (×10³/μL)	1.54 ± 0.62
Neutrophil-to-lymphocyte ratio (NLR)	5.8 ± 2.9
Elevated NLR (>3), n (%)	126 (78.8)
CRP (mg/L)	28.6 ± 16.4
CRP available in 124 patients	

FEV1/FVC ratio of 48.9±9.4%, indicating the persistence of airflow obstruction. This is consistent with the statement by Vestbo et al. (2013)[7] that the spirometric pattern in severe COPD is driven by a loss of expiratory flow rather than a restrictive change in lung volume.

Importantly, indices of small airways function showed a significantly reduced $FEF_{25–75}$ of 0.71 ± 0.31 L/s (51.4 ± 18.6% predicted). The current finding is in consonance with previous reports demonstrating that $FEF_{25–75}$ is a sensitive marker for detecting distal airway involvement. McDonough et al. (2011)[13] have shown that pathological narrowing and loss of small airways precede significant declines in FEV_1 and emphasized that small airway disease is a major contributor to airflow limitation in COPD. Similarly, Hogg et al. (2004)[2] reported that obstruction of small conducting airways represents the principal site of increased resistance in COPD, especially during advanced stages of the disease. Comparative studies have also documented that during acute exacerbations, $FEF_{25–75}$ declines disproportionately. Burgel et al. (2013)[14] have observed significant reduction in small airway flow rates during exacerbations, that were attributed to increased airway inflammation, mucus plugging, and airway wall edema. The wide variability in $FEF_{25–75}$ values in our cohort agreed with the observations by Cosio et al. (2009),[15] who described heterogeneity in small airway involvement among COPD patients, that could be related to differences in inflammatory phenotypes, smoking exposure, and duration of disease. Furthermore, studies using sophisticated physiological and imaging techniques have lent further credence to the importance of small airways dysfunction. Thus, Thompson et al. (2015)[16] have shown strong associations among reduced $FEF_{25–75}$, air trapping, and symptom severity, even when FEV_1 changes were modest, in support of the concept that conventional spirometric indices may not provide a true estimate of disease burden unless specific small airway parameters are examined.

The present study revealed a high prevalence of SAD, affecting 70.0% of patients with acute exacerbation of COPD, as defined by an $FEF_{25–75}$ value less than 65% of the predicted value. This finding strengthens the view that small airways involvement is a central pathological feature of COPD, with this involvement further enhanced in exacerbations. The high prevalence of distal airway impairment would suggest that it is not only common but may well represent a core mechanism driving symptom that worsens and further airflow limitation during acute episodes. Our findings are in contrast with several earlier studies that have underlined the high burden of small airway disease in COPD. Thus, study by Hogg et al. (2004)[2] demonstrated that obstruction and narrowing of small conducting airways are the primary sites of increased airflow resistance in COPD, with the degree of small airway loss closely correlating with disease severity. Similarly, McDonough et al. (2011)[13], using micro-computed tomography, have shown that a substantial proportion of terminal bronchioles are already lost in moderate COPD, with even greater involvement in severe disease. In view of the predominance of GOLD stage III and IV patients in our cohort, the high prevalence of SAD is in line with these pathological observations. Comparable prevalence rates have also been reported in physiological studies. Indeed, Burgel et al. (2013)[14] observed evidence of small airways dysfunction in approximately two-thirds of COPD patients, with a higher frequency among those with frequent exacerbations. Similarly, studies such as those performed by Cosio et al. in 2009[15] identified prominent abnormalities indicative of small airway damage among patients with advanced

COPD, indicating that small airway disease could be increasingly prevalent with advancing disease. The 70% rate that we saw correlates with these findings and likely reflects the advanced disease phase and accompanying level of inflammation associated with the flare-ups. Exacerbated COPD studies also appear to support stronger small airway disease. Wedzicha and Seemungal (2007)[12] identified that acute exacerbations are accompanied by prominent airway inflammation, mucus plugging, and airway wall edema, which particularly affect the small airways. More recently, Bafadhel et al. (2011)[17] demonstrated that bacterial infection and neutrophil inflammation-related flare-ups are accompanied by a degree of airflow obstruction largely because of the progressive blocking of the small airways. The high SAD rate among our patients who experienced flare-ups corroborates these hypotheses and indicates that flare-ups may uncovered or accentuate underlying distal airway disease. Given these observations, a degree of superimposed SAD contributing to obstruction appears likely among our patients with COPD during a flare-up, although the exact degree may be less predictable, particularly when the degree of advanced disease could complicate further estimation. The underlying pathoanatomical mechanisms presumed to be mostly responsible for COPD obstruction appear to be manifested .On the other hand, there was a proportion of 30% in our study who had not been diagnosed with SAD and could potentially constitute a different phenotype of COPD in whom there was a well-preserved function of the small airways despite the presence of airflow obstruction. This heterogeneity finds consistency with the work of Agusti et al. in 2010[18] when they focused on various phenotypes of COPD that had a different type of structural inflammation.
Our inflammatory profile indicates a systemic neutrophilic response during AECOPD that corresponds to the

Table 5. Comparison of Pulmonary Function and Inflammatory Markers Between Patients with and Without SAD

Variable	SAD Present (n = 112)	SAD Absent (n = 48)	p-value
FEV_1 % predicted	39.8 ± 12.1	52.4 ± 14.6	<0.001
$FEF_{25–75}$ % predicted	41.2 ± 11.3	75.6 ± 8.9	<0.001
Neutrophil %	77.2 ± 8.6	67.4 ± 7.9	<0.001
Absolute neutrophil count	8.8 ± 2.4	6.9 ± 2.1	<0.001
NLR	6.6 ± 2.8	4.1 ± 1.9	<0.001
CRP (mg/L)	32.4 ± 17.1	20.8 ± 11.9	0.002

established inflammatory response associated with these events. A mean total leukocyte count of 11.6 ± 3.2 × 10^3/μL suggests the presence of leukocytosis in a large proportion of the patients that could be associated with inflammation or infectious insults. This corresponds with the observations made by Wedzicha & Seemungal (2007)[12] that there were increases observed in the white blood cell count during AECOPD and that there was increased systemic inflammation after AECOPD compared to that observed during the stability phase.
The dominant cells in our subjects were neutrophils, with an absolute number of 8.2 ± 2.6 × 10^3/μL, in addition to a percentage of 74.1 ± 9.8%. These findings were like Bafadhel et al. (2011)[17], who identified neutrophil inflammation as the prevalent presentation of COPD exacerbation, especially when bacterial infection was involved. Furthermore, Pauwels et al. (2012)[19] identified increased neutrophils both in sputum and serum during exacerbation, emphasizing the pivotal role of neutrophils in contributing to airways as well as systemic inflammation. On the other hand, absolute lymphocyte counts were of relatively lower significance, yielding 1.54 ± 0.62 × 10^3/μL, with a high neutrophil/lymphocyte (NLR) index of 5.8 ± 2.9. Our observation was similar to Günay et al. (2014)[20] as well as to Lee et al. (2016)[21] who identified NLR as an important index of both biological inflammation as well as the extent of COPD severity. Of particular importance was the finding of an elevated NLR > 3, observed in 78.8% of patients, reflecting severe disease, prolonged hospital stays, as well as high morality. Interestingly, an elevated NLR was identified by Yao et al. (2017)[22] with increased AECOPD severity, alongside more impaired air flow. C-Reactive Protein was predominantly elevated in 124 patients, averaging 28.6 ± 16.4 mg/L, reflecting its acute-phase reactant properties, with relatively increased bacterial loads as well as disease severity. Our observation was in tandem with Bafadhel et al. (2011)[17] who identified CRP as most elevated in both

Table 6. Correlation Between Small Airways Dysfunction and Neutrophilic Inflammation

Variable	r (95% CI)	p-value
FEF_{25-75} vs Neutrophil %	-0.52 (-0.62 to -0.40)	<0.001
FEF_{25-75} vs ANC	-0.48 (-0.59 to -0.35)	<0.001
FEF_{25-75} vs NLR	-0.55 (-0.65 to -0.43)	<0.001
FEV_1% vs NLR	-0.41 (-0.53 to -0.28)	<0.001

neutrophilic inflammation as well as infectious exacerbation, thus emphasizing biological plausibility of these observations. Comparing with stable patients with COPD, in the study of Gan et al. (2004),[8] both neutrophils as well as other indices of inflammation were considerably elevated, reflecting the intensified biological inflammation with acute exacerbation. Patients with SAD presented with a significantly lower airway obstruction, with FEV1 % predicted values of 39.8 ± 12.1 compared with 52.4 ± 14.6 for those without SAD ($p < 0.001$). These same findings have been presented in similar ways in Burgel et al. (2013)[14] and Cosio et al. (2009)[15] and indicate that larger amounts of involvement of the small airways are associated with larger FEV1 reductions, consistent with the potential effects of distal airway involvement.

The $FEF_{25–75}$ % predicted was significantly reduced in the SAD group (41.2 ± 11.3) compared to the non-SAD group (75.6 ± 8.9; $p < 0.001$). These findings are supported by pathology studies by Hogg et al. (2004)[2] and McDonough et al. (2011)[13,] which showed that narrowing and obliteration of small airways are central to airflow limitation in COPD. Physiological studies by Thompson et al. (2015)[16] further demonstrated that reduced $FEF_{25–75}$ is closely linked to air trapping and symptom severity, even when changes in FEV_1 are less marked. Importantly, patients with SAD in our study presented with significantly higher neutrophilic inflammation. Both the mean neutrophil percentage and absolute neutrophil count were significantly higher in the SAD group compared to those without SAD ($p < 0.001$ for both). Consistently, studies by Bafadhel et al. (2011)[17] and Pauwels et al. (2012)[19] reported that neutrophil-predominant inflammation is strongly associated with more severe airflow obstruction and infective exacerbation phenotypes. In this respect, neutrophil-derived proteases, including neutrophil elastase, directly contribute to mucus hypersecretion, epithelial injury, and small airway remodeling, according to Stockley (2013).[23] Importantly, the neut This corresponds to the observation made by other investigators, namely Günay et al. (2014)[20] and Yao et al. (2017)[22] who reported that increased NLR was related to increased severity, frequency of exacerbations, and worse lung function in COPD patients. Our results extend their findings and suggest that increased NLR is related particularly to the involvement of the small airways, underlining their potential as a surrogate marker of the pathology of the distal airways. Moreover, the CRP levels were significantly higher in the SAD group, at 32.4 ± 17.1 mg/L versus the non-SAD group at 20.8 ± 11.9 mg/L ($p = 0.002$), reflecting a higher systemic inflammatory burden. Similar associations of high CRP with worse airflow limitations have been observed by Hurst et al. (2010)[6] and Bafadhel et al. (2011)[17] who also show that CRP correlates with the severity of an exacerbation and the presence of bacterial infection. High CRP has also been related to increased airway wall thickness and to small airway disease, as suggested by the work by Gan et al. (2004).[8]

This correlation analysis in the present study, by demonstrating a negative and statistically significant relation of small airway function with the neutrophilic inflammatory markers, gave strong evidence for the role of neutrophil-driven inflammation in the pathophysiology of small airways dysfunction during AECOPD. $FEF_{25–75}$, a sensitive physiological marker for distal airway function, demonstrated a moderate to strong negative correlation with neutrophil percentage ($r = –0.52$, $p < 0.001$). This suggests that as neutrophilic predominance increases, flow rates of small airways decline due to inflammation caused by airway narrowing, mucus plug, and epithelial damage. Similar associations have been reported by Cosio et al. (2009)[15], who demonstrated that increased airway neutrophilia was associated with worse small airway obstruction in COPD patients. Another comparable inverse relationship has been seen between $FEF_{25–75}$ and ANC ($r = –0.48$, $p < 0.001$), thus further reinforcing systemic neutrophilic inflammation and impaired small airway function. Study by Stockley et al. (2013)[23] has shown that elevated neutrophil counts are associated with an increase in protease activity, contributing to the destruction and remodeling of the airway wall, especially in the small airways. The strongest association in our analysis was between $FEF_{25–75}$ and NLR ($r = –0.55$, $p < 0.001$), suggesting higher systemic inflammatory burden is strongly associated with worse small airway dysfunction. This finding is consistent with

Table 7. Multivariate Logistic Regression Analysis for Predictors of Small Airways Dysfunction

Variable	Unadjusted OR (95% CI)	p-value	Adjusted OR* (95% CI)	p-value	Adjusted OR† (95% CI)	p-value
NLR >3	3.45 (1.72-6.92)	<0.001	3.12 (1.48-6.57)	0.003	2.98 (1.39-6.38)	0.005
Neutrophil % >70	2.98 (1.52-5.84)	0.001	2.74 (1.31-5.75)	0.007	2.61 (1.22-5.58)	0.013
Smoking >30 pack-years	2.34 (1.18-4.64)	0.015	2.09 (1.01-4.34)	0.046	1.98 (0.94-4.18)	0.072
GOLD stage III-IV	4.12 (2.08-8.16)	<0.001	3.68 (1.74-7.78)	<0.001	3.45 (1.61-7.39)	0.001
Age >65 years	1.45 (0.76-2.77)	0.262	-	-	1.32 (0.64-2.72)	0.452
BMI <20 kg/m²	1.89 (0.94-3.80)	0.074	-	-	1.71 (0.82-3.57)	0.152
Cardiovascular comorbidity	1.62 (0.81-3.24)	0.171	-	-	1.48 (0.70-3.13)	0.303

the reports of studies by Günay et al. (2014)[20] and Yao et al. (2017)[22], which demonstrated significant negative correlations between NLR and lung function indices, including FEV_1, in both stable and exacerbated COPD. In addition, FEV_1 % predicted showed a significant inverse correlation with NLR ($r = -0.41$, $p < 0.001$), in concordance with the previous study by Lee et al. (2016)[21] reporting that elevated NLR is associated with more severe airflow limitation and poorer clinical outcomes.

The multivariate logistic regression analysis revealed several independent predictors of SAD in exacerbated COPD, including systemic inflammation, smoking burden, and disease severity. An NLR above 3 emerged as a strong independent predictor of SAD, with an adjusted OR of 3.12 (95% CI 1.48–6.57, $p = 0.003$). This confirms previous findings by Günay et al. (2014)[20] and Yao et al. (2017)[22], who showed that an elevated NLR is linked with worse lung function, increased risk of exacerbations, and greater inflammatory burden in COPD. These studies focused predominantly on FEV_1 and clinical outcomes, whereas our results extend their findings by demonstrating that NLR is independently associated with small airway–specific dysfunction, emphasizing its utility as a surrogate marker for distal airway inflammation. Similarly, a percentage of neutrophils above 70% was independently associated with SAD, yielding an adjusted OR of 2.74 (95% CI 1.31–5.75, $p = 0.007$). This finding supports earlier work by Stockley et al. (2013)[23], who reported that neutrophil-dominant inflammation contributes to airway wall injury, mucus hypersecretion, and protease-mediated tissue destruction in COPD. The fact that neutrophil percentage remained a significant predictor after adjustment for disease severity suggests that neutrophilic inflammation plays a direct and independent role in the development of small airway pathology, as opposed to being merely a marker of advanced disease. Smoking exposure also remained a significant predictor, as patients with more than 30 pack-years of smoking demonstrated a twofold increased risk of SAD, with an adjusted OR of 2.09 (95% CI 1.01–4.34, $p = 0.046$). This finding is in line with seminal pathological studies by Hogg et al. (2004)[2] and McDonough et al. (2011)[13], demonstrating that cumulative smoking exposure results in progressive loss, narrowing, and obliteration of small airways even before overt emphysematous changes are evident. Advanced airflow limitation, that is, GOLD stage III–IV, represented the most robust predictor of SAD in our model, with an adjusted OR of 3.68 (95% CI 1.74–7.78, $p < 0.001$).

Conclusion

SAD was prevalent among hospitalized patients with acute COPD exacerbations and strongly associated with systemic neutrophilic inflammation. SAD, as evidenced by lower FEF_{25-75}, was associated with higher neutrophil percentage and count, NLR, and CRP levels. Neutrophil-predominant inflammation, greater exposure to smoking, and disease severity independently predicted SAD. These results reinforce the importance of neutrophilic inflammation in distal airway disease during COPD exacerbations and provide further evidence for the utility

of inflammatory markers, such as NLR, to assess the risk for impaired SAD function.

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