# RESEARCH

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# Relationship between airway inflammation, small airway dysfunction, and frequency of acute exacerbations in patients with chronic obstructive pulmonary disease

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# Abstract

**Context** Recurrent exacerbations in COPD patients are associated with accelerated reduction in lung function. Airway inflammation and small airway dysfunction were recognized for a long time as an essential feature of COPD.

**Aim** To study the relationship between neutrophilic airway inflammation, small airway dysfunction, and frequency of acute exacerbations in COPD patients.

Settings and design This was a cross-sectional study.

Patients and methods Thirty COPD patients were enrolled and classified into two groups: infrequent exacerbators (IFE) "who developed ≤ 1 exacerbation per year" and frequent exacerbators (FE) "who developed ≥ 2 exacerbations per year" in the last year prior to this study. All patients included in the study underwent clinical evaluation, and assessment of small airway dysfunction by pulmonary function testing (MEF 25–75, RV/TLC, and DLCO) and paired inspiratory and expiratory HRCT-chest to measure the mean lung density (MLD) as well as assessment of neutrophilic airway inflammation by taking BAL via bronchoscopy and examined for differential cell count.

**Results** The small airway dysfunction is more severe in the case of the FE COPD group as there were statistically significant differences between FE and IFE COPD groups in %MEF 25–75 and RV/TLC (p=0.038 and p=0.030, respectively). The mean value of the BAL neutrophil % was higher in FE than in IFE COPD patients but without a significant statistical difference (p=0.513). There were statistically significant negative correlations between %FEV1 (p=0.026), %FVC (p=0.020), and %MEF25–75 (p=0.005) and MLD(E/I) in all studied COPD patients.

**Conclusion** COPD patients associated with small airway dysfunction and increased BAL neutrophil cell count are more prone to frequent exacerbations.

**Trial registration** ClinicalTrials.gov NCT06040931. Registered 18 Sept 2023—Retrospectively registered. **Keywords** COPD, Airway inflammation, Small airway dysfunction, BAL

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# Background

Chronic obstructive pulmonary disease is associated with chronic inflammation and this ongoing inflammation may result in airway remodeling and excessive mucus plugging within the small airways [1].

There is evidence that diseases of small airways (airways of less than 2 mm diameter) might be the earliest histopathological changes in COPD. Several studies stated that there was a significant loss of small airways outstrips the development of airflow obstruction or emphysema in COPD patients [2].

Small airway dysfunction (SAD) has been known for a long time as a central feature of COPD. It was reported that the inflammatory cell infiltration in the submucosa combined with the destruction and narrowing of small airways in COPD increases the disease severity. The presence of SAD in the early stages of COPD is well established and becomes more widespread over time as COPD progresses to more severe stages [3]. There is increased neutrophilic inflammation in the airways of COPD patients during both stable periods and exacerbations [4].

Airway inflammation rich in neutrophils is a common feature of many airway diseases and is linked to disease progression, usually irrespective of the initiating cause or underlying diagnosis [5].

Many studies found that the frequent COPD exacerbations are associated with the presence of small airway dysfunction and related to increased cellular inflammation, especially neutrophils [6, 7].

So; the aim of this work is to study the relationship between neutrophilic airway inflammation, small airway dysfunction, and frequency of acute exacerbations in COPD patients.

# **Patients and methods**

This a cross-sectional study was conducted at the Chest Medicine Department, Mansoura University Hospitals, during the period from October 2021 to October 2022 after the Institutional Research Board (IRB) approval (MS.21.08.1628), and written informed consent was obtained from every patient before the procedure after a detailed explanation of the procedure and possible complications.

Thirty COPD patients were recruited from the outpatient chest clinic with all inclusion criteria and devoid of any of the exclusion criteria.

# Inclusion criteria

Male patients (diagnosed with COPD according to GOLD 2021) aged 40 years or more and either non-smokers or

ex-smokers (who stopped smoking for at least 6 months before the study).

# **Exclusion criteria**

Any patients with the following conditions were excluded from the study: current smokers, concurrent pulmonary diseases (e.g., bronchiectasis and interstitial lung disease), patients unfit or have any contraindications for bronchoscopy such as bleeding tendency or on anticoagulant therapy, refractory respiratory failure ( $PaO_2$  remains less than 60 mm Hg despite maximal oxygen supplementation), severe cardiac disease (unstable angina, myocardial infarction within last 6 weeks, or decompensated heart failure), patients with immunosuppressive states (e.g., patients with malignancy or patients under chemotherapy), and patients with history of exacerbations less than 1 month before enrollment.

The enrolled COPD patients were divided into 2 groups: [7, 8]. *Infrequent exacerbators (IFE) group: (14 patients)* patients with infrequent exacerbation (IFE) " $\leq$ 1 exacerbation during the last year". *Frequent exacerbators (FE) group: (16 patients)* patients with frequent exacerbation (FE) " $\geq$ 2 exacerbations per year in the preceding 12 months before enrolment".

# Methods

### **Clinical evaluation**

All participants underwent thorough history taking and physical examination, stress on smoking history, symptoms and signs of exacerbation of COPD, and associated comorbidities.

# Laboratory workup

Complete blood count (CBC), INR, arterial blood gases (ABG), liver, and kidney function.

# Radiologic workup

High-resolution computed tomography (HRCT) of the chest was performed using a chest multidetector CT scan (Philips Ingenuity Core 128 scanner, Philips Medical Systems®, Eindhoven, The Netherlands) and measuring the mean lung density (MLD) as a parameter of SAD. The helical CT scan was done from the root of the neck to the upper pole of the kidney level for all patients during the end of inspiration and end of expiration using a 1-mm slice thickness. Reconstruction of images in axial, coronal, and sagittal reformats was done with standard pulmonary filtering. All digital imaging and communications in medicine (DICOM) data of thin CT chest cuts were analyzed using Synapse 3D Fujifilm Medical Systems version 3.5 on specific workstations for automated analysis and segmentation of lung densities. At first, the lungs were segmented into right and left lungs; after that,

the total lung volume, area of low attenuation percentage (LAA%), and MLD of both lungs were automatically calculated. Low attenuation area of inspiration values less than -950 HU on the inspiratory scan while low attenuation area of expiration values less than -856 HU on the expiratory scan, a CT marker of gas trapping was calculated, MLD E/I% (the ratio of the mean lung density during paired inspiratory and expiratory scans) [9–11].

# **Pulmonary function tests**

Spirometry to measure %FEV1, %FVC, FEVI/FVC, and % FEF 25–75, diffusion lung capacity for carbon monoxide (%DLCO) using single breath out test and body plethysmography to measure %RV, %TLC, and RV/TLC was done using Smart pft body (Medical Equipment Europe), Germany.

# Bronchoscopy

Bronchoscopy was done using high-definition (HD) bronchoscope (Pentax EB- 1970TK, 3.2) to take BAL for the differential cell count and assessment of airway inflammation. BAL was done in the most affected segment(s) by pathology as proved by radiographic changes or from the middle lobe and lingua in wide-spread affection. The bronchoscope is advanced as far as a sub-segmental bronchus until it is wedged. Installing 20 ml aliquots of sterile warm saline solution in each affected segment. The total volume of instilled lavage fluid will be 1–3 ml per kg body weight or at least 100 ml of normal saline [12]. Maintaining wedge position, apply gentle suction. Collecting the lavage specimen in the collection trap. The patient was observed until fully awake to rule out any complications.

### BAL preparation and examination

The first portion of the retrieved BAL was not used as it may contain cells motored from a large airway. BAL fluid was put in formalin for a short period and then put in tubes and then put in the centrifuge for centrifugation and cell block formation centrifugation was done for 10 min and at room temperature to isolate cell pellet. The supernatant was taken and put on a cassette and then in the processor machine for paraffin block formation. Then, hematoxylin & eosin stained slides were made from the paraffin blocks. The stained smear slides and the available cell blocks were examined under the microscope. Differential cell counts were performed and percentages of each type of cell (neutrophils, lymphocytes, macrophages, eosinophils) and which of them predominates [13].

# Statistical analysis

The collected data were coded, processed, and analyzed using the SPSS (Statistical Package for Social Sciences) version 15 for Windows<sup>®</sup> (SPSS Inc., Chicago, IL, USA). Qualitative data was presented as number and percent. Comparison between groups was done by chi-square test. Quantitative data was tested for normality by the Kolmogrov-Smirnov test. Normally distributed data was presented as mean  $\pm$  SD. Student's *t* test was used to compare between two groups. *F* test (one-way ANOVA) was used to compare between more than two groups. Pearson's correlation coefficient was used to test the correlation between variables. *P*<0.05 was considered to be statistically significant.

# Ethics approval and consent to participate

The study protocol has been approved by the Institutional Research Board, Faculty of Medicine, Mansoura University, with the research proposal code: **MS.21.08.1628**. Precautions were used to protect participants' privacy as patients were given the option to participate or not, also the study findings were exclusively used for scientific purposes. Personal data were hidden from any public use.

# Results

This study included thirty COPD patients, and they were divided into two groups: group I; infrequent exacerbators (IFE) which represent about 46.7% of them and group II; frequent exacerbators (FE) which represent 53.3%.

Table 1 demonstrates that both study groups {frequent exacerbators (FE) and infrequent exacerbators (IFE) COPD patients} are matched regarding age, BMI, BW, height, and smoking status. Also, the frequent exacerbators COPD patients group exhibits more symptoms and higher grades of severity indices and assessment scores as there were statistically significant differences between both groups (FE & IFE COPD patients) regarding mMRC scale (p = < 0.001), CAT score (p = < 0.001), revised ABCD ( $p = \langle 0.001 \rangle$ , GOLD grades (p = 0.035), and number of exacerbations over the last year before the study (p < 0.001). In GOLD 2023, the revised ABCD classification was changed to ABE; however, the proposal for this study was submitted to our IRB in 2021, and the practical part and statistics were finished by the end of 2022 before publishing GOLD 2023. So, our study plan was completed according to the revised ABCD. All patients in the FE group can be categorized as group E and most patients in the IFE group fall into A&B groups according to GOLD 2023.

Table 2 illuminates that the mean value of the BAL neutrophil % is higher in case of the FE group than the IFE group but without a significant statistical difference

	Infrequent exacerbators (IFE) (n = 14) Mean ± SD	Frequent exacerbators (FE) ( $n = 16$ ) Mean $\pm$ SD	t	Р
Age (years)	63.93±9.55	63.81±12.06	0.029	0.977
Body weight (kg)	80.64±9.93	77.81±9.01	0.819	0.420
Height (cm)	171.79±8.27	170.56±3.24	0.547	0.589
BMI (kg/m²)	27.52±4.19	26.73±2.82	0.615	0.543
Smoking index (pack/year)	34.39±36.02	40.2±35.55	0.444	0.661
mMRC scale	1.14±0.86	2.31±0.7	4.084	< 0.001*
CAT score	$8.5 \pm 4.74$	18.56±4.7	5.827	< 0.001*
Revised ABCD	$1.43 \pm 0.94$	$3.75 \pm 0.58$	8.281	< 0.001*
GOLD grades	$2.07 \pm 0.92$	2.81±0.91	2.217	0.035*
Number of exacerbations over the last year	$0.43 \pm 0.65$	2.44±1.03	6.284	< 0.001*

Table 1 Demographic data and clinical characteristics of the studied COPD patient's groups

\* P value is less than 0.05

**Table 2** BAL cellular pattern and blood gases of the studied COPD patient's groups

BAL	Infrequent exacerbator (IFE) (n = 14) Mean ± SD	Frequent exacerbators (FE) (n = 16) Mean ± SD	t	Р
Neutrophil%	56.79±28.80	63.44±26.25	0.662	0.513
Lymphocytes%	10±17.1	$10.63 \pm 13.4$	0.112	0.912
Eosinophil %	14.64±24.22	11.88±22.87	0.322	0.750
Macrophage%	11.07±17.12	7.81±9.12	0.638	0.531
РН	$7.4 \pm 0.03$	$7.39 \pm 0.03$	0.994	0.329
PCO2	$40.5 \pm 2.98$	$41.43 \pm 3.79$	0.735	0.468
HCO3	21.71±1.33	$23.91 \pm 2.63$	2.867	0.009*
SPO2	96.71±1.07	95.38±2.19	2.081	0.047*

\* P value is less than 0.05

**Table 3** Markers of small airway dysfunction in the studiedCOPD patient's groups

	Infrequent exacerbators (IFE) (n = 14) Mean ± SD	Frequent exacerbators (FE) (n = 16) Mean ± SD	Τ	Р
%MEF 25-75	30.36±16.37	19±12.06	2.181	0.038*
RV/ TLC	$49.5 \pm 9.53$	$56.88 \pm 8.15$	2.286	0.030*
%DLCO	$69.93 \pm 19.67$	$68.13 \pm 28.5$	0.199	0.844
MLD (E/I ratio)	$0.96 \pm 0.03$	$0.97 \pm 0.03$	0.766	0.450

\* P value is less than 0.05

(P=0.513), and also, no significant statistical difference between both groups as regards other cells: lymphocytes% (P=0.912, eosinophil % (P=0.750) and macrophage% (P=0.531). Also, there were great statistically significant differences between FE and IFE groups considering blood gases data;  $HCO_3$  (P=0.009) and  $SPO_2$  (P=0.047)).

Table 3 clarifies small airway dysfunction parameters in both IFE and FE COPD patients. There were great statistically significant differences between the IFE and FE groups regarding %MEF 25–75 (p=0.038) and RV/TLC (p=0.030) as there was more deterioration in case of the FE group. However, no significant difference between them as regards %DLCO and MLD (E/I) ratio.

Regarding the correlation between lung function parameters, HRCT measurements, and BAL neutrophil %, we found negative correlations between %FEV1, %FVC, FEV1/FVC, %MEF 25–75, and %DLCO) and BAL neutrophil % while there were positive correlations between %RV, RV/TLC, and BAL neutrophil % but without statistical significance. There were negative correlations between LAA% inspiration, MLD inspiration and expiration, and BAL neutrophil %, while there were positive correlations between LAA% expiration, MLD (E/I) ratio, and BAL neutrophil % but without statistical significance.

Also we found statistically significant negative correlations between MLD (E/I) ratio and %FEV<sub>1</sub> (p=0.026), %FVC (p=0.020), and %MEF 25–75 (p=0.005) as shown in Fig. 1.

# Discussion

The airway inflammation in COPD is characterized by an influx of neutrophils and macrophages in the airway as well as elevated macrophage and lymphocyte numbers in the airway wall [6].

There are different methods for the detection of small airway dysfunction (SAD) including chest multidetector CT scan and measuring the mean lung density (MLD),



Fig. 1 This figure demonstrates a statistically significant negative correlation between MLD (E/I) ratio and MEF-25–75 (p = 0.005) and a negative correlation between BAL Neutrophil % and MEF 25–75 but without statistical significance

pulmonary function tests using spirometry, and body plethysmography for assessment of lung volume and capacities (%FEV<sub>1</sub>, %FVC, FEV<sub>1</sub>/FVC, %MEF 25-27, %RV, TLC and RV/TLC) [6, 7], all of these were done in our study as well as bronchoscopy was carried out also and BAL was taken and examined for differential cell count to assess airway inflammation.

In our study, there was no difference between both study groups (IFE and FE) considering demographic data: age, BMI, BW, height, and smoking status (Table 1), and this is consistent with Day and colleagues [7] who found that no significant difference in any of the reported demographic features between the IFE and FE groups. Also, we found that there were statistically significant differences between both studied groups (IFE and FE COPD patients) as regards GOLD grades, mMRC scale, revised ABCD, and CAT score  $\{(p=0.035), (p<0.001), \}$ (p = < 0.001) (p = < 0.001) and (p = 0.047), respectively}, and this may explain significant increasing in the number of exacerbations in case of FE COPD patients (Table 1) and this in concordance with Aaron and colleagues [14] who reported with transitional regression models that patients experience a significant acceleration in the rate of exacerbations over just 1 year. However, this is not consistent with Donaldson and colleagues [15] who showed that annual exacerbation frequency for patients remained constant during the study which may be due to the duration of the study, which was 6 years and a large number of the studied patients.

In this study, there were strong statistically significant differences as regards spirometry parameters (%FEV<sub>1</sub>, %FVC, and %MEF25–27) {(p=0.008), (p=0.008), & (p=0.038), respectively} between the studied groups (IFE and FE COPD patients) and this not consistent with

a study done by Day and colleagues [7] who found that no significant difference in any of the reported spirometry parameters between the IFE and FE groups. This is because we include all GOLD grades in our study; however, Day and colleagues include only GOLD grades I & II. In a study done by Fujimoto and colleagues [16], they compared stable COPD and unstable COPD (frequent exacerbation over 2-3 years) patients, and it was found that the %FEV<sub>1</sub> was significantly lower (p < 0.01) and (RV/ TLC) was significantly higher (p < 0.05) in patients who developed exacerbation compared with patients who did not develop exacerbation. Tumkaya and colleagues [17] found that all the spirometry data (%FEV<sub>1</sub>, %FVC, FEV<sub>1</sub>/ FVC, & %MEF 25-75) had statistically significant differences, and this may be due to a large sample of patients that includes the healthy control group (healthy smokers and non-smokers and COPD patients). Regarding blood gas parameters in this study, there were statistically significant differences between the studied groups (IFE and FE COPD patients) with respect to HCO<sub>3</sub> and SPO<sub>2</sub>  $\{p=0.009 \text{ and } p=0.047, \text{ respectively}\}$  (Table 2). Our results were not in line with Lapperre and colleagues [6] and Day and colleagues [7], as they found no significant difference in any of the reported blood gas parameters between the IFE and FE groups.

Day and colleagues [7] studied the relation between different COPD exacerbation phenotypes and neutrophilic inflammation, and they found that there is significantly more BAL neutrophils% was present in FE COPD patients compared with IFE COPD patients (P=0.036) and also in a study done by Lapperre and colleagues [6] (P=0.039). Also, Fujimoto and colleagues [16] found that during exacerbation in the unstable COPD group, the total cell counts and absolute numbers of lymphocytes,

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neutrophils, and eosinophils, as well as relative eosinophil counts, in sputum showed an additional significant increase over those in the stable phase. In our study, there was increased BAL neutrophil% in FE COPD patients compared with IFE COPD patients but without a significant statistical difference (p = 0.513) (Table 2). In the current study, as regards markers of SAD, there were statistically significant differences between both IFE and FE COPD patients regarding %MEF25–75 (p = 0.038) and RV/TLC (p=0.030); however, there were no significant differences between both IFE and FE COPD patients in case of %DLCO and (MLD E/I) (Table 3). According to Day and colleagues [7], when all COPD patients were analyzed, only resistance at 5 Hz minus 19 Hz (R5-R19) and residual volume to total lung capacity ratio (RV/ TLC) was associated significantly with increased BAL neutrophil proportions. There were no significant associations found between any markers of SAD and BAL neutrophil proportions in the infrequent exacerbators group when assessed separately; however, in case of FE patients, significant moderate to very strong associations were found between resistance at 5 Hz minus 19 Hz (R5-R19), area of reactance (AX) and ratio of the (MLD E/I), residual volume to total lung capacity ratio (RV/TLC), and BAL neutrophil proportions.

In our study, lung functions were correlated negatively with HRCT parameters. The strongest significant correlations were seen between the MLD (E/I ratio) and (%FEV1, %FVC, & %MEF25–75) {(p=0.026), (p=0.020), and (p=0.005), respectively}. On the other hand, there was no significant correlation being seen between other parameters and this is in agreement with O'Donnell and colleagues [11] who found Lung function correlated moderately strongly with HRCT parameters. The strongest correlations seen in smokers were between the MLD (E/I) ratio and airway obstruction (%FEV1, %MEF50, and RV/TLC) on the other, with no correlation being seen with TLCO or KCO. However, our results were not consistent with Day and colleagues [7] and this may be due to only GOLD I&II was included in their study.

No reported significant post-bronchoscopy complications apart from 4 patients developed post-bronchoscopy respiratory distress due to bronchospasm that was relieved by nebulized bronchodilators and steroids.

# Conclusion

The presence of small airway dysfunction and airway inflammation in patients with COPD may be considered as an indicator of liability for increased frequency of exacerbations. Dynamic inspiratory and expiratory HRCT-chest is a promising tool for assessing gas trapping and a good indicator of lung function deterioration in COPD patients.

# Limitations

There were some limitations in this study like a small sample size, enrollment of all GOLD grades of COPD patients, and it was better to be confined only to specific GOLD grades and no studying of neutrophil-related inflammatory mediators that strengthen our results for clarifying the relationship between neutrophilic airway inflammation and frequency of COPD exacerbation as well as no studying other valuable technique for measurement of small airway dysfunction that is not available in our institute like forced oscillation technique (FOT).

### Abbreviations

BAL	Bronchoalveolar lavage
COPD	Chronic obstructive pulmonary disease
DLCO	Diffusing capacity of the lungs for carbon monoxide
FE	Frequent exacerbators
FEF25-75	Forced expiratory flow between 25 and 75% of the forced
	vital capacity (FVC)
FEV1	Forced expiratory volume in 1st second
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HRCT	High-resolution computed tomography
IFE	Infrequent exacerbators
LAA% expiration	Low attenuation area percentage in expiration
LAA% inspiration	Low attenuation area percentage in inspiration
MLD E	Mean lung density in expiration
MLD I	Mean lung density in inspiration
MLD(E/I)	Mean lung density expiration/inspiration ratio
mMRC	Modified British Medical Research Council
RV	Residual volume
SAD	Small-airway dysfunction
TLC	Total lung capacity

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None/not applicable.

# Authors' contributions

Design and conception by Ahmed Mansour, Taha Taha Abdelgawad, and Ahmed Fouda, data gathering by Azza Eliwa, interpretation of radiologic investigation by Doaa Khedr, interpretation of BAL results by Ramy A. Abdelsalam, statistical analysis by Ahmed Mansour, Taha Taha Abdelgawad and Ahmed Fouda, and medical writing by Taha Taha Abdelgawad and Ahmed Mansour. The manuscript was revised by all authors. The writers reviewed the final manuscript and gave their approval.

### Funding

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### Availability of data and materials

The author may be contacted for reasonable requests on the datasets utilized and/or analyzed in the present study.

# Declarations

### Ethics approval and consent to participate

The study protocol has been approved by the Institutional Research Board, Faculty of Medicine, Mansoura University, with the research proposal code: MS.21.07.1578. Precautions were used to protect participants' privacy as patients were given the option to participate or not, also the study findings were exclusively used for scientific purposes. Personal data were hidden from any public use.

### **Consent for publication**

Not applicable.

### **Competing interests**

The authors declare that they have no competing interests.

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