Monaldi Archives for Chest Disease

eISSN 2532-5264 https://www.monaldi-archives.org/

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Monaldi Arch Chest Dis 2024 [Online ahead of print]

To cite this Article:
Hegde M, Raj S, Pattanshetti AS, et al. **Gaining insights into chronic obstructive pulmonary disease exacerbation through emerging biomarkers and the chronic obstructive pulmonary disease assessment test score.** *Monaldi Arch Chest Dis* doi: 10.4081/monaldi.2024.2955

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Gaining insights into chronic obstructive pulmonary disease exacerbation through emerging biomarkers and the chronic obstructive pulmonary disease assessment test score

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Contributions: all authors contributed equally to conceptualising the study and conducting the literature review, and they collaborated in writing and revising the manuscript. All the authors have read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest: the authors declare no conflict of interest.

Ethics approval and consent to participate: the study was approved by the Ethical Committee of KLE College of Pharmacy. (IEC Reference Number: KLECOPH/IEC/2023-24/09).

Informed consent: the patients and their families were explained about the study written informed consent was obtained from all the participants.

Funding: none.

Availability of data and materials: data and materials are available from the corresponding author upon request.

Acknowledgments: the authors would like to express their sincere gratitude to KLE-Suchirayu Hospital (A unit of HCG), for their invaluable support and provision of research opportunities, their collaboration and facilitation of this research endeavour. Most importantly, we extend

our deepest appreciation to all the patients and their families who graciously permitted and supported our research efforts. Their willingness and cooperation were instrumental in the successful execution of this study.

Abstract

Chronic obstructive pulmonary disease (COPD), a leading cause of mortality and morbidity, presents significant challenges, particularly with exacerbations, which drastically impact patients' health and healthcare costs. The Global Initiative for Chronic Obstructive Lung Disease guidelines recommend comprehensive assessments beyond spirometry, with the COPD assessment test (CAT) emerging as a pivotal tool. Despite its utility, the relationship between CAT scores and specific biomarkers during exacerbations remains unclear. Hence, this study aims to assess the correlation between the CAT score and specific circulating biomarkers. A cross-sectional study from August 2023 to January 2024 included 59 COPD patients with exacerbations who underwent pulmonary function tests and completed the CAT score assessment. The CAT score cut-off point was set at 20, where a CAT score <20 indicated a low impact on health status and a CAT score 20 indicated a high impact on health status. On the same day, measurements of neutrophils, leukocytes, eosinophils, C-reactive protein, and procalcitonin were conducted. Patients with CAT scores 20 had significantly higher levels of neutrophils (p=0.001), leukocytes (p=0.006), procalcitonin (p=0.010), and forced expiratory volume in the first second/forced vital capacity (p=0.002), but lower eosinophil levels (p=0.025). A positive correlation existed between total CAT score and neutrophils (p=0.001), leukocytes (p=0.000), and procalcitonin (p=0.010), while eosinophil levels showed a negative correlation (p=0.025). The spirometry parameters showed no correlation with the total CAT score. This study highlights the link between CAT and key inflammatory biomarkers, supporting the use of blood biomarkers to identify COPD patients at risk of exacerbations.

Key words: COPD, exacerbation, biomarkers, COPD assessment test, CAT, correlation, ECOPD.

Introduction

Chronic obstructive pulmonary disease (COPD) stands as a notable contributor to mortality and morbidity worldwide [1]. The 2019 GBD report shows COPD as India's second leading cause of death and disability-adjusted life years (DALYs), with a prevalence of 37.8 million [2,3]. COPD can manifest as exacerbations of COPD (ECOPDs) characterized by a sudden worsening of respiratory symptoms necessitating additional therapy, significantly adding to the overall burden of the disease. They are linked with a rapid decline in lung function, diminished quality of life, elevated mortality rates, and escalated healthcare expenses.

Hence, the prevention and management of ECOPDs represent a primary objective in COPD patient care [4]. COPD is marked by chronic inflammation, both locally and systemically, leading to lung function decline, respiratory failure, pulmonary hypertension, and mortality. Exacerbations pose challenges due to their high morbidity and mortality rates, impacting patients' quality of life. Pinpointing exacerbation causes via respiratory samples is uncertain due to colonization in certain patients [5].

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline recommends various symptomatic assessments beyond just measuring dyspnoea with lung function [4]. Among various questionnaires evaluating health-related quality of life (HRQoL), the COPD Assessment Test (CAT) is commonly employed in routine clinical practice. This eight-item questionnaire provides a straightforward and convenient measurement, designed to quantify the impact COPD symptoms have on patient health status and quality of life (QoL), with scores ranging from 0 to 40 [6].

Given the challenges posed by COPD exacerbations and the need for personalized patient management, novel strategies are essential. While spirometry has long served as the primary measure for tracking COPD progression, its ability to capture the systemic manifestations and diverse trajectories of COPD is limited [7-9]. Consequently, measuring circulating biomarkers in peripheral blood has emerged as a promising avenue for enhancing COPD management. Some of these biomarkers have been investigated to shed light on their potential associations with COPD outcomes:

- Eosinophils: Elevated levels of eosinophils correlate with critical outcomes like increased readmissions and longer hospital stays, indicating disease severity [10-12].
- Procalcitonin: Although debated, procalcitonin serves as a marker for bacterial infection and shows potential in distinguishing between viral and bacterial exacerbations. However, its reliability varies, and further research is needed to assess its utility in predicting antibiotic needs during exacerbations [13-15].

- Neutrophils: Extensive studies have identified blood neutrophil counts (BNCs) as strong predictors of future exacerbations and mortality in stable COPD. However, their specific role during exacerbations remains unclear, limiting our understanding [16,17].
- Leucocytes: Elevated white blood cell (WBC) counts are associated with current smoking and COPD severity, suggesting potential as a prognostic biomarker. However, studies on leukocyte levels have primarily focused on stable COPD, lacking data on their behaviour during exacerbations. Additionally, the absence of data on other inflammatory markers and lung function parameters should be considered when interpreting their prognostic value [18].
- C-reactive protein (CRP): CRP is a commonly employed systemic biomarker reflecting the total systemic burden of inflammation in individuals. Elevated serum CRP levels are observed in stable COPD and correlate with disease severity and adverse health outcomes, particularly in patients with mild-to-moderate severity of COPD. Additionally, increased CRP levels are linked with an increased risk of COPD exacerbations [19-21].

Currently, CAT is increasingly utilized for assessing and monitoring COPD. Meanwhile, various serum biomarkers associated with inflammation, hospitalization, and mortality have been identified in COPD patients [22].

However, their relationship with CAT scores during exacerbations remains unclear. Therefore, this study investigates the association between CAT scores and specific biomarkers (neutrophils, eosinophils, leucocytes, procalcitonin, CRP, and spirometric parameters) in patients experiencing ECOPD.

Materials and Methods

Study design

The study design employed was cross-sectional, spanning from August 2023 to January 2024. The sample size was established through a pilot study. Following this, 59 COPD-diagnosed patients admitted to KLE-Suchirayu Hospital (A unit of HCG), Hubli, India, were included in the study (Figure 1).

Ethical considerations

The patients and their families were explained about the study written informed consent was obtained from all the participants. The study was approved by the Ethical Committee of KLE College of Pharmacy. (IEC Reference Number: KLECOPH/IEC/2023-24/09.)

Study population

Inclusion criteria: Patients of both genders were included if they were 40 years of age, and had post-bronchodilator $FEV_1/FVC<0.7$ and $50\% < FEV_1 < 80\%$ predicted.

Exclusion criteria: Patients were excluded if they had; (1) stable COPD ($FEV_1/FVC < 0.7$, $FEV_1>80\%$ predicted); (2) a respiratory disorder other than COPD; (3) chronic inflammatory disease like inflammatory bowel disease, vasculitis, rheumatoid arthritis etc; (4) Malignancy of any kind; (5) Pregnant and lactating women.

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) for Windows version 26.0. A CAT score cut-off point of 20 was utilized, where:

- A CAT score < 20 indicated a low impact on health status.
- A CAT score 20 indicated a high impact on health status.

Patient demographic information was documented, dividing smoking status into two groups: smokers (currently smoking) and non-smokers (former smokers and patients who did not smoke). Additionally, the smoking index (SI) was computed for individuals in the smoking group. Based on the smoking index (SI) as a criterion, patients were sorted into the following categories: Light smokers (SI=1-100); Moderate smokers (SI=101-300); and Heavy smokers (SI 301).

Patients were further stratified based on the presence or absence of co-morbidities. The results were expressed as mean ± standard deviation (SD) or percentage, as applicable. The correlation between the CAT score and COPD biomarkers and the comparison between the two CAT score groups was analysed using Pearson correlation and Student's t-test respectively.

Results

The clinical characteristics of the study subjects are summarised in Table 1. The study population included 41 (31%) males and 18 (69%) females. Patient's ages ranged from 46 to 87 years and the mean age of the population was 69.27 years (S.D=10.6). 27 (45.8%) out of 59 patients did not have any co-morbidities. 25 (42.4%) patients were smokers and the mean smoking index was 254.84 (SD=137.564) The mean FVC (% pred) was 69.1% (SD=10.5) while the mean FEV_1/FVC was 0.56 (SD=0.08). The mean CAT score stood at 25.07 (SD=8.1). All patients were admitted to the intensive care unit (ICU) for appropriate management.

Relationship between chronic obstructive pulmonary disease assessment test score and biomarker levels

The results of the statistical comparisons, examining differences in biomarker levels between patients with CAT scores < 20 and those with CAT scores 20, are summarized in Table 2. Statistically significant differences were observed in the biomarker levels between patients in the CAT < 20 and CAT 20 categories.

Patients in the CAT 20 groups exhibited significantly higher levels of neutrophils, leucocytes, and procalcitonin ($p < 0.05$), while levels of eosinophils and FEV_1/FVC were lower ($p < 0.05$). No significant differences were found in the levels of CRP, FVC, FEV_1, FVC % pred, and FEV_1 % pred. CAT scores exhibited significant differences concerning age, while gender and smoking index did not demonstrate any significant differences.

Correlation between chronic obstructive pulmonary disease assessment test score and biomarkers

Table 3 displays the correlations between multiple biomarkers and the total CAT score. Neutrophils (r=0.407, p=0.001), leucocytes (r=0.495, p=0.000), and procalcitonin (r=0.331, p=0.010) levels exhibited a significant positive correlation with the overall CAT score.

Conversely, eosinophil levels (r=-0.292, p=0.025) demonstrated a significant negative correlation with the total CAT score. Importantly, none of the spirometry parameters correlated with the overall CAT score.

Discussion

In our study, we initially screened 86 patients, with 59 eventually included. We observed a significant age difference between groups with different CAT scores, with patients having CAT Score 20 displaying a higher mean age (Mean (SD) = 72.24 (9.10), p=0.001). However, no statistically significant differences were noted in terms of gender and smoking index between the two CAT score categories.

Our study aimed to explore the correlation between inflammatory biomarkers in COPD and CAT scores. CRP is frequently used in clinical settings as an inflammatory marker, with higher values typically seen in severe COPD compared to mild-to-moderate cases. However, in our analysis, no significant difference in CRP levels was found among patients with different CAT score results. Furthermore, we observed no correlation between CRP levels and CAT scores, consistent with findings from a study by Abd-Elaziz et al [23].

Serum leukocyte count serves as another indicator of inflammation. Specific cytokines like IL-8, released by macrophages in response to infection, stimulate haematopoiesis, leading to elevated serum leukocyte counts [24,25]. A direct link between the severity of infection and

leukocyte count indicates that heightened serum leukocyte count is directly correlated with both increased frequency and severity of exacerbations in COPD patients [21,26]. Moreover, elevated leukocyte and neutrophil counts have been significantly associated with mortality [27]. In line with this, our study found elevated leukocyte and neutrophil counts in hospitalized patients experiencing ECOPD (CAT Score 20). This increase correlated with the total CAT score, indicating a significant impact on health status, consistent with Lonergan et al.'s study [17].

Our research also revealed a significantly negative correlation between eosinophilic levels and the total CAT score. Patients with CAT Score 20 had lower eosinophil levels compared to those with a CAT Score < 20. These findings align with studies conducted by Cui Yanan et al. [28], Wu et al. [29], and Jabarkhil et al. [30]. A growing number of researchers view eosinophils as a biomarker, suggesting that eosinophilic inflammation represents a prevalent phenotype in COPD [31,32]. However, the influence of smoking on eosinophilic inflammation, as noted by Chis et al. [33], must be considered.

Procalcitonin, the precursor to calcitonin, secreted in response to bacterial infections or nonspecific inflammation, holds promise in distinguishing between bacterial-triggered COPD exacerbations and others [34]. Our study found significantly higher procalcitonin levels in patients with CAT 20, consistent with observations by Borsi H et al. [35], and Pazarli et al. [36]. Furthermore, elevated procalcitonin levels correlated significantly with the total CAT score.

Regarding spirometry parameters, we observed a significantly lower FEV_1/FVC ratio in patients with CAT Score 20. However, we found no statistically significant correlation between spirometry variables and the total CAT score. While spirometric findings are directly related to respiratory functions and the severity of symptoms, an improvement in spirometric results doesn't always translate to an enhancement in patients' quality of life [37]. Using spirometric findings to measure quality of life can be beneficial for treating patients with COPD. However, in some cases where symptoms improve without significant changes in spirometric results, relying solely on spirometry may be misleading [38,39].

The current study has limitations, including its cross-sectional design, restriction to a single centre, and small sample size. Furthermore, the potential influence of patients' medications on systemic inflammatory response and health status, which could impact the study results, was not accounted for.

In summary, our study underscores the correlation between CAT and inflammatory biomarkers such as neutrophils, leukocytes, eosinophils, CRP, and procalcitonin. These findings advocate for the utilization of circulating blood biomarkers in identifying COPD patients at higher risk of exacerbations. Nonetheless, longitudinal multicentre studies are essential to further explore

the relationship between CAT and biomarkers, ultimately enhancing exacerbation risk prediction in COPD patients.

Conclusions

Our study highlights the intricate relationship between COPD patients' CAT scores and various inflammatory biomarkers, shedding light on potential indicators for exacerbation risk. While age differences were significant among CAT score groups, gender and smoking index showed no notable differences. Notably, CRP levels did not vary significantly across CAT score categories, suggesting its limited utility in predicting exacerbations.

Conversely, elevated leukocyte and neutrophil counts correlated with the total CAT scores, indicating their potential as markers of exacerbation severity. Furthermore, the negative correlation between eosinophil levels and CAT scores underscores the importance of considering eosinophilic inflammation in COPD management. Higher procalcitonin levels in patients with elevated CAT scores hinted at its potential in discerning exacerbation types.

However, spirometry parameters did not align significantly with CAT scores, emphasizing the need to routinely employ multiple biomarkers in health assessments in COPD care. Despite insightful findings, the study's limitations warrant further longitudinal multicentre investigations to refine exacerbation risk prediction and tailor treatment strategies for COPD patients.

References

1. Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. Lancet 2007;370:765-73.
2. Salvi S. Letter from India. Respirology 2018;23:1074-5.
3. Salvi S, Kumar GA, Dhaliwal RS, et al. The burden of chronic respiratory diseases and their heterogeneity across the states of India: the Global Burden of Disease Study 1990-2016. Lancet Glob Health 2018;6:e1363-74.
4. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. 2023. Available from: goldcopd.org/wp-content/uploads/2023/03/GOLD-2023-ver-1.3-17Feb2023_WMV.pdf.
5. Jones PW, Angusti AGN. Outcomes and markers in the assessment of chronic obstructive pulmonary disease. Eur Respir J 2006;27:822-32.

6. Jones PW. COPD assessment test - rationale, development, validation and performance. COPD 2013;10:269-71.
7. Agusti A, Sobradillo P, Celli B. Addressing the complexity of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2011;183:1129-37.
8. Lange P, Celli B, Agustí A, et al. Lung-function trajectories leading to chronic obstructive pulmonary disease. N Eng J Med 2015;373:111-22.
9. Hoenderdos K, Condliffe A. The neutrophil in chronic obstructive pulmonary disease. Am J Respir Cell Mol Biol 2013;48:531-9.
10. Singh D, Kolsum U, Brightling CE, et al. Eosinophilic inflammation in COPD: prevalence and clinical characteristics. Eur Respir J 2014;44:1697-700.
11. Tashkin DP, Wechsler ME. Role of eosinophils in airway inflammation of chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2018;13:335-49.
12. Vedel-Krogh S, Nielsen SF, Lange P, et al. Blood eosinophils and exacerbations in chronic obstructive pulmonary disease. The Copenhagen general population study. Am J Respir Crit Care Med 2016;193:965-74.
13. Chirouze C, Schuhmacher H, Rabaud C, et al. Low serum procalcitonin level accurately predicts the absence of bacteremia in adult patients with acute fever. Clin Infect Dis 2002;35:156-61.
14. Christ-Crain M, Jaccard-Stolz D, Bingisser R, et al. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. Lancet 2004;363:600-7.
15. Corti C, Fally M, Fabricius-Bjerre A, et al. Point-of-care procalcitonin test to reduce antibiotic exposure in patients hospitalized with acute exacerbation of COPD. Int J Chron Obstruct Pulmon Dis 2016;11:1381-9.
16. Ghorani V, Boskabady MH, Khazdair MR, Kianmeher M. Experimental animal models for COPD: a methodological review. Tob Induc Dis 2017;15:25.
17. Lonergan M, Dicker AJ, Crichton ML, et al. Blood neutrophil counts are associated with exacerbation frequency and mortality in COPD. Respir Res 2020;21:166.
18. Koo HK, Kang HK, Song P, et al. Systemic white blood cell count as a biomarker associated with severity of chronic obstructive lung disease. Tuberc Respir Dis (Seoul) 2017;80:304-10.
19. Black S, Kushner I, Samols D. C-reactive Protein. J Biol Chem 2004;279:48487-90.
20. Man SFP. C-reactive protein and mortality in mild to moderate chronic obstructive pulmonary disease. Thorax 2006;61:849-53.
21. Thomsen M, Ingebrigtsen TS, Marott JL, et al. Inflammatory biomarkers and exacerbations in chronic obstructive pulmonary disease. JAMA 2013;309:2353-61.

22. Pinto-Plata V, Casanova C, Müllerova H, et al. Inflammatory and repair serum biomarker pattern. Association to clinical outcomes in COPD. Respir Res 2012;13:71.
23. Abd-Elaziz AA, Alwahsh RA, Abd-Elaal GA, Tameem AAM. Correlation between CAT score, inflammatory markers and pulmonary function tests in patient with acute exacerbation of COPD. Egypt J Chest Dis Tuberc 2017;66:243-6.
24. Chung KF. Cytokines in chronic obstructive pulmonary disease. Eur Respir J Suppl 2001;34:50s-9s.
25. Bienvenu J. Exploration of cytokines in inflammation in biological fluids. C R Seances Soc Biol Fil 1995;189:545-55. [Article in French].
26. Hurst JR, Vestbo J, Anzueto A, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med 2010;363:1128-38.
27. Celli BR, Locantore N, Yates J, et al. Inflammatory biomarkers improve clinical prediction of mortality in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2012;185:1065-72.
28. Cui Y, Zhan Z, Zeng Z, et al. Blood eosinophils and clinical outcomes in patients with acute exacerbation of chronic obstructive pulmonary disease: a propensity score matching analysis of real-world data in China. Front Med (Lausanne) 2021;8:653777.
29. Wu HX, Zhuo KQ, Cheng DY. Peripheral blood eosinophil as a biomarker in outcomes of acute exacerbation of chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2019;14:3003-15.
30. Jabarkhil A, Moberg M, Janner J, et al. Elevated blood eosinophils in acute COPD exacerbations: better short- and long-term prognosis. Eur Clin Respir J 2020;7:1757274.
31. Kim VL, Coombs NA, Staples KJ, et al. Impact and associations of eosinophilic inflammation in COPD: analysis of the AERIS cohort. Eur Respir J 2017;50:1700853.
32. Ko FWS, Chan KP, Ngai J, et al. Blood eosinophil count as a predictor of hospital length of stay in COPD exacerbations. Respirology 2020;25:259-66.
33. Chis AF, Pop CM. Correlations between neutrophil to lymphocyte ratio, blood eosinophils and clinical characteristics in chronic obstructive pulmonary disease. Med Pharm Rep 2020;93:169-74.
34. Biju PG, Garg S, Wang W, et al. Procalcitonin as a predictive biomarker for total body irradiation-induced bacterial load and lethality in mice. Shock 2012;38:170-6.
35. Borsi H, Nia E, Mal-Amir M, Raji H. Relationship between serum procalcitonin level and chronic obstructive pulmonary disease. J Family Med Prim Care 2019;8:738-40.
36. Pazarli AC, Koseoglu HI, Doruk S, et al. Procalcitonin: is it a predictor of noninvasive positive pressure ventilation necessity in acute chronic obstructive pulmonary disease exacerbation?. J Res Med Sci 2012;17:1047-51.

37. Bagheri MH, Hosseini SK, Mostafavi SH, Alavi SA. High-resolution CT in chronic pulmonary changes after mustard gas exposure. Acta radiol 2003;44:241-5.
38. Jones PW, Baveystock CM, Littlejohns P. Relationships between general health measured with the sickness impact profile and respiratory symptoms, physiological measures, and mood in patients with chronic airflow limitation. Am Rev Respir Dis 1989;140:1538-43.
39. Jones P, Harding G, Wiklund I, Berry P, et al. Improving the process and outcome of care in COPD: development of a standardised assessment tool. Prim Care Respir J 2009;18:208-15.

Table 1. Clinical characteristics of patients (n=59).

Variables	Mean ± SD or N (%)
Age	69.27 ± 10.6
Gender	
Male	41 (31%)
Female	18 (69%)
Comorbidities	
None	27 (45.8%)
Diabetes Mellitus	15 (25.4%)
Hypertension	10 (16.9%)
Cardiovascular Diseases	5 (8.5%)
Other	2 (3.4%)
Smoking	
Smokers	25 (42.4%)
Non-smokers	34 (57.6%)
Smoking Index	
Light smokers	3 (12%)
Moderate smokers	12 (48%)
Heavy smokers	10 (40%)
Spirometry Parameters	
FVC, L	3.08 ± 0.4
FVC, % pred	69.19 ± 10.5
FEV_1, L	2.27 ± 0.3
FEV_1, % pred	54.09 ± 12.8
FEV_1/FVC	0.56 ± 0.08
CAT Score	25.07 ± 8.1
Biomarkers	
Neutrophils (%)	80.70 ± 9.9
Eosinophils (%)	1.29 ± 1.4
Leucocytes (10^9/L)	13.66 ± 3.8
CRP (mg/dl)	60.74 ± 28.1
Procalcitonin (ng/dl)	1.32 ± 1.1

Table 2. Differences in biomarker levels across CAT score categories.

Variables	Mean ± SD		t-test	
	CAT<20	CAT 20	t	p-value
Biomarkers				
Neutrophils (%)	73.5 ± 15.4	82.9 ± 94	-3.366	0.001
Eosinophils (%)	2.05 ± 1.71	1.06 ± 1.29	2.305	0.025
Leucocytes (10^9/L)	11.2 ± 2.17	14.4 ± 3.96	-2.831	0.006
CRP (mg/dl)	67.2 ± 35.1	58.7 ± 25.6	0.985	0.329
Procalcitonin (ng/dl)	0.66 ± 1.5	1.53 ± 1.1	-2.650	0.010
FVC, L	3.98 ± 0.4	3.82 ± 0.4	1.108	0.281
FEV_1, L	2.40 ± 0.3	2.23 ± 0.3	1.347	0.183
FEV_1/FVC	0.60 ± 0.1	0.54 ± 0.1	-3.372	0.002
FVC % pred	67.83 ± 10.8	69.62 ± 10.5	-0.548	0.586
FEV_1 % pred	55.27 ± 11.6	53.7 ± 13.3	0.419	0.679
Demographic data				
Age	59.71 ± 10.1	72.24 ± 9.10	-4.142	0.001
Gender • Male • Female	 11 (18.6%) 3 (5.08%)	 30 (50.8%) 15 (25.4%)	-0.889	0.380
Smoking index	213.29 ± 84.5	271 ± 152.3	-1.201	0.244

Table 3. Correlation of biomarkers with the total CAT score.

Biomarkers	CAT Score	
	r	p-value
Neutrophils (%)	0.407	0.001**
Eosinophils (%)	-0.292	0.025*
Leucocytes (10^9/L)	0.495	0.000*
CRP (mg/dl)	-0.129	0.329
Procalcitonin (ng/dl)	0.331	0.010*
FVC, L	-0.155	0.240
FEV_1, L	-0.176	0.183
FEV_1/FVC	-0.074	0.577
FVC % pred	-0.052	0.697
FEV_1 % pred	0.072	0.586
**Correlation is significant at the 0.01 level (2-tailed). *Correlation is significant at the 0.05 level (2-tailed).		

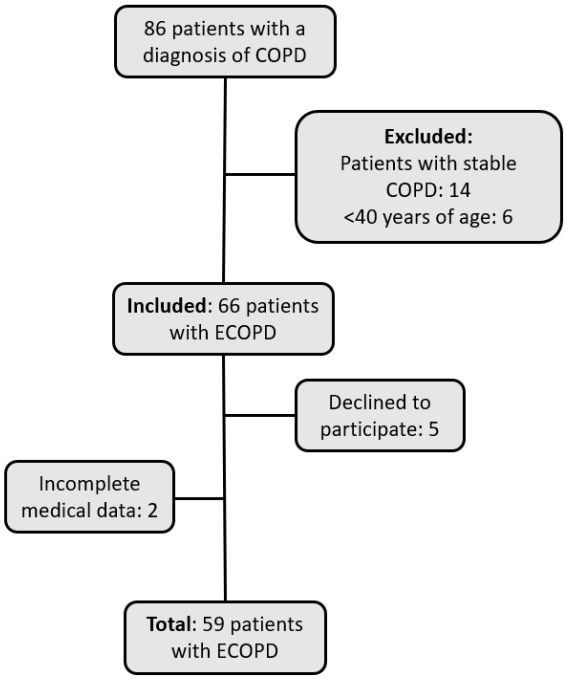

Figure 1. Study subject enrolment process. COPD, chronic obstructive pulmonary disease; ECOPD, exacerbations of chronic obstructive pulmonary disease.