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

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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. 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.

Introduction

Chronic obstructive pulmonary disease (COPD) stands as a notable contributor to mortality and morbidity worldwide [1]. The 2019 Global Burden of Disease report shows COPD as India's second leading cause of death and disability-adjusted life years, 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 (QoL), 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' QoL. Pinpointing exacerba-

tion causes *via* respiratory samples is uncertain due to colonization in certain patients [5].

The Global Initiative for Chronic Obstructive Lung Disease guideline recommends various symptomatic assessments beyond just measuring dyspnoea with lung function [4]. Among various questionnaires evaluating health-related QoL, the COPD Assessment Test (CAT) is commonly employed in routine clinical practice. This 8-item questionnaire provides a straightforward and convenient measurement, designed to quantify the impact COPD symptoms have on patient health status and QoL, with scores ranging from 0 to 40 [6].

Given the challenges posed by ECOPD 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 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 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 behavior 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 ECOPD [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 forced expiratory volume in the first second (FEV_1)/forced vital capacity (FVC)<0.7 and 50%<FEV_1<80% predicted.

Exclusion criteria: patients were excluded if they had i) stable COPD (FEV_1/FVC<0.7, FEV_1>80% predicted); ii) a respiratory disorder other than COPD; iii) chronic inflammatory disease like inflammatory bowel disease, vasculitis, rheumatoid arthritis, *etc.*; iv) malignancy of any kind; v) pregnant and lactating women.

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) for Windows version 26.0 (IBM, Chicago, IL, USA). A CAT score cut-off point of 20 was utilized, where: CAT<20 indicated a low impact on health status and CAT≥20 indicated a high impact on health status.

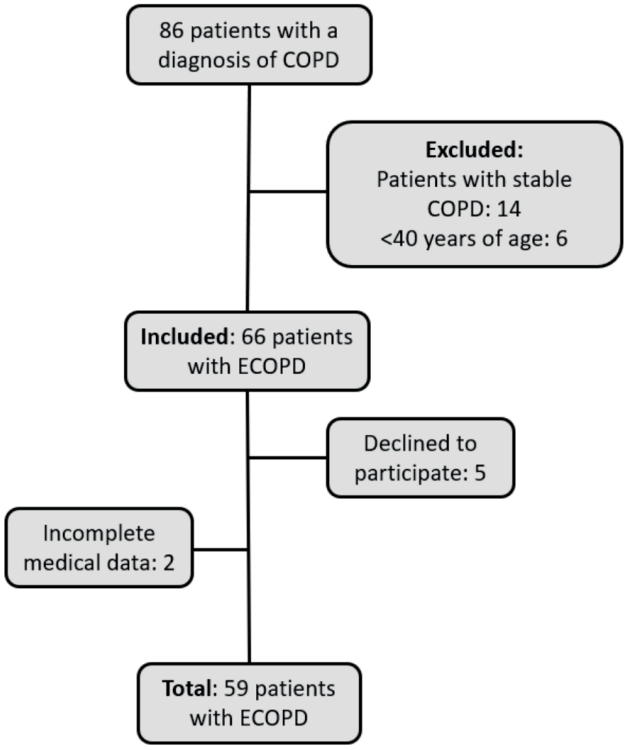

Figure 1. Study subject enrolment process. COPD, chronic obstructive pulmonary disease; ECOPD, exacerbations of chronic obstructive pulmonary disease.

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 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 comorbidities. 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 analyzed using Pearson correlation and Student's *t*-test, respectively.

Results

The clinical characteristics of the study subjects are summarized 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 (SD=10.6). 27 (45.8%) out of 59 patients did not have any comorbidities. 25 (42.4%) patients were smokers, and the mean SI was 254.84 (SD=137.564) The mean FVC (%predicted) 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 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<20 and those with CAT≥20, are summarized in Table 2. Statistically significant differ-

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

SD, standard deviation; FVC, forced vital capacity, FEV_1, forced expiratory volume in the first second; pred, predicted; CAT, chronic obstructive pulmonary disease assessment test; CRP, C-reactive protein.

Table 2. Differences in biomarker levels across chronic obstructive pulmonary disease assessment test score categories.

Variables	Mean±SD		t-test	
	CAT<20	CAT≥20	t	p
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		-0.889	0.380	
Male	11 (18.6%)	30 (50.8%)		
Female	3 (5.08%)	15 (25.4%)		
Smoking index	213.29±84.5	271±152.3	-1.201	0.244

SD, standard deviation; FVC, forced vital capacity, FEV_1, forced expiratory volume in the first second; pred, predicted; CAT, chronic obstructive pulmonary disease assessment test; CRP, C-reactive protein.

ences 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 %predicted, and FEV_1 %predicted. CAT scores exhibited significant differences concerning age, while gender and SI did not demonstrate any significant differences.

Correlation between the 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≥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 SI 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 interleukin 8, released by macrophages in response to infection, stimulate hematopoiesis, 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 ECOPD 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≥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≥20 had lower eosinophil levels compared to those with CAT<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 ECOPD and others [34]. Our study found significantly higher procalcitonin levels in patients with CAT≥20, consistent with observations by Borsi *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≥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 does not always translate to an enhancement in patients' QoL [37]. Using spirometric findings to measure QoL can be beneficial for treating COPD patients. 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 center, 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 multicenter studies are essential to further explore the relationship between CAT and biomarkers, ultimately enhancing exacerbation risk prediction in COPD patients.

Table 3. Correlation of biomarkers with the total chronic obstructive pulmonary disease assessment test score.

Biomarkers	CAT Score	
	r	p
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

FVC, forced vital capacity, FEV_1, forced expiratory volume in the first second; pred, predicted; CAT, chronic obstructive pulmonary disease assessment test; CRP, C-reactive protein. **Correlation is significant at the 0.01 level (2-tailed). *Correlation is significant at the 0.05 level (2-tailed).

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

SI 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 multicenter investigations to refine exacerbation risk prediction and tailor treatment strategies for COPD patients.

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