Original Article

Comparison of Inflammation Biomarkers among Chronic Obstructive Pulmonary Disease Groups: A Cross Sectional Study

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Abstract

Background: The Global Initiative classification (GOLD) for chronic obstructive pulmonary disease (COPD), which relies on the practical issues of treatment of this complex and heterogeneous disease, may not be reliable in predicting disease severity and prognosis as the term of inflammation is excluded from the definition. **Aim:** The aim of this study was to determine systemic inflammatory markers in GOLD ABCD groups and to compare these parameters according to clinical and functional features. **Methods:** The study included 60 COPD patients and 59 healthy subjects. Comparisons were made with the pulmonary function test, transthoracic echocardiography and the six-minute walk test (6MWT). The COPD assessment test (CAT), modified Medical Research Council (mMRC), and index scores of body mass index, airflow obstruction, dyspnea, and exercise capacity (BODE) were recorded. The systemic inflammatory state was assessed using C-reactive protein, fibrinogen, tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, IL-8 and IL-18. **Results:** The levels of all serum inflammatory markers were higher in the COPD group than in the control group. TNF-α and IL-6 were significantly higher in the symptomatic groups (B and D) than in the less symptomatic groups (A and C) ($P < 0.05$). Spirometric parameters were more severe in Group D, followed by groups C, B and A, respectively. The 6MWT and the BODE scores were worst in Group D, followed by groups B, C and A. **Conclusion:** The results suggest that bronchodilator treatment alone might be insufficient in Group B patients, as the systemic inflammatory markers in addition to exercise capacity and mortality predictors were at the worst level in Groups D and B.

Keywords: *Chronic obstructive pulmonary disease, inflammation, interleukin-6, tumor necrosis factor-alpha*

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Introduction

The current guidelines define chronic obstructive pulmonary disease (COPD) as a common, preventable and treatable lung disease that is characterized by respiratory symptoms and permanent limitation of airflow, related to airway and/or alveolar abnormalities caused by serious exposure to harmful particles or gasses.[1] The 2017 'Global Initiative for Chronic Obstructive Lung Disease (GOLD)' report excluded the term inflammation from the definition, although the text emphasized the significance of inflammation.[2] The term COPD covers several distinct disease phenotypes[2] and this heterogeneity is considered to be the underlying reason for differences in treatment responses among patients.

The GOLD classification, designed primarily as a strategy for patient management, aims to increase awareness of COPD and prevent under and over

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diagnosis that can lead to under- and over-treatment, respectively. Until 2011, the GOLD recommendations were based only on forced expiratory volume in one second (FEV1). However, due to weak correlation between this parameter, quality of life and clinical symptoms, the GOLD report was revised in 2011,[3] and according to symptoms and risk factors for exacerbation, and a classification system which divided patients into 4 groups (A, B, C, and D) was accepted. However, the reliability of this classification is unclear as it is thought that this classification is not sufficient for predicting the severity and prognosis of COPD.

Patients in different GOLD groups might differ according to disease exacerbation and symptoms. However, the severity of the systemic inflammation might aid in assessing the severity of the disease, prognosis and follow-up among these patient groups. Therefore, we intended to compare the clinical data, functional features and the severity of inflammation in patients classified according to the GOLD 2017 recommendations.

Methods

Study design

This study was designed as a prospective cross-sectional clinical study. Clinical Research Ethics Committee for non-invasive studies of Adnan Menderes University, Turkey approved the study (Protocol number: 2015/728). All participants were briefed about the concept of the study and written consent was obtained from the participants. Sociodemographic data including age, sex, and physical characteristics such as height and weight of the patient and control groups were recorded. The number of packs smoked per year (packs/yrs) was also recorded. The formula for body mass index (BMI) calculation: weight/(height) ^{2} (kg/m^2).

The clinical characteristics of the patients with COPD were identified by the COPD assessment (CAT) and modified Medical Research Council (mMRC) tests. mMRC can determine the level of respiratory disability that is caused by dyspnea. It uses a grading system between 0 and 4.[4] CAT is a patient completed test that measures the effects of COPD on patients. This questionnaire is related to the symptoms, sleep, symptoms, exercise limitation and confidence. Each item has a point between 0 and 5 and the total score can be between 0 and 40.[5] The mMRC and CAT scores of the patients were used for classification. Patients with a CAT score lower than 10 and mMRC grade 0-1 were classified as patients with fewer symptoms, while those with a CAT score equal to or higher than 10 and mMRC ≥ grade 2 were classified as patients with more symptoms.[3] The previous year's history of exacerbations guided us to calculate the risk of exacerbations. Patients who were not hospitalized due to exacerbations or those with fewer than two exacerbations were included in the low-risk patient group.

All subjects performed a 6-minute walk test (6MWT) and spirometry. The subject was seated and Jaeger Master Scope spirometer was used for spirometry in the pulmonary function test laboratory of our hospital, following the American Thoracic Society (ATS)/ European Respiratory Society (ERS) criteria.[6] All tests were conducted by a single technician who was qualified in pulmonary function testing. The bronchodilation test which measured FEV1 (%, L), FVC (forced vital capacity) (%, L), and FEV1/FVC (%) was performed 15 minutes after salbutamol inhalation (400 μg, 4 puffs). ATS/ERS criteria were used to evaluate the best acceptable and reproducible pulmonary function test results. The patient's functional capacity was determined using the 6MWT. The patient was instructed to walk on a flat surface for six minutes at maximum speed. Pulse oximetry was used to measure the oxygen saturation before and after the walk test, and status of fatigue and dyspnea were recorded. 6MWT was performed in all patients, and the data were recorded for calculating the BODE index score.[7] The COPD-related mortality risk was calculated using the BODE index score and higher scores meant increased risk of mortality. The scores obtained from 6MWT for exercise capacity, mMRC for dyspnea, FEV1 for airway obstruction, and BMI were added to determine the BODE index score.[8] All subjects underwent echocardiography, which was performed by a cardiologist, and systolic pulmonary arterial pressure (sPAP) was recorded.

The systemic inflammatory state was determined by measuring the levels of following indicators: interleukin (IL) -6, -8, -18, tumor necrosis factor-alpha (TNF-α), serum C-reactive protein (CRP) and fibrinogen. Blood samples were drawn from the patients following standardized procedures and stored at freezer -80°C. Serum levels of interleukin-6, -8, -18, TNF-α, CRP and fibrinogen were determined by a commercial human enzyme-linked immunosorbent assay kit (Elabscience Biotechnology, Wu Han, China) at 450 nm and a standard curve with a Bioelisa Reader Elx800 (BioTek Instruments).

Patient selection

The study group comprised 60 stable COPD patients. The inclusion criteria were: a history of biomass exposure or smoking for ≥10 years, aged ≥40 years, no history of exacerbation in the four weeks prior to the study, and a post-bronchodilator FEV1/FVC ratio of <0.70.[3] Patients with comorbidities such as

cardiovascular disease, chronic inflammatory disease, diabetes mellitus, malignancy, those with an active infection during enrolment for the study, and those who were unable to perform on the effort test for any reason other than COPD were not included in the study. The control group comprised 59 healthy individuals who met the following criteria: aged ≥40 years, no evidence of obstructive/restrictive pulmonary disorder based on the pulmonary function test, no active infection during enrolment for the study and no condition that hindered walking.

Statistical analysis

The results of the study were evaluated by SPSS for Windows version 20 (IBM, Armonk, NY, USA). Kolmogorov-Smirnov test was run to see whether quantitative variables were normally distributed. The normally distributed variables were given as mean ± standard deviation and as median (25^{th}-75^{th} percentiles) for the variables which were not distributed normally. Categorical variables were given as percentages and frequencies. Two groups were compared using the Student's *t* test, and in cases where the preconditions were not met, the Mann–Whitney U test was used. One-way Analysis of Variance (ANOVA) with Tukey's test was run to compare 3 or more groups if the conditions were met, and the Kruskal–Wallis and the Bonferroni-Dunn tests were used in cases where the preconditions were not met. Fisher's exact and Chi-square tests were utilized to analyze the categorical variables. The Monte Carlo simulation method was used to include frequencies that were expected to be <20% in the analysis. For correlation analysis, Pearson correlation coefficient was utilized when the preconditions of the parametric test were met, while the Spearman correlation coefficient was used when the preconditions were not met. $P < 0.05$ showed statistical significance.

Results

The demographic data and levels of inflammation markers of the patient and control groups are shown in Table 1. The mean ages of the 60 COPD patients and the 59 healthy controls were not significantly different (64.88 ± 10.21 and 62.54 ± 7.96 years, respectively, $P = 0.166$). The number of male and female subjects were similar in COPD and control groups (58/2 vs. 57/2, $P = 0.684$). The patients had significantly lower mean BMI than the subjects in the control group ($P < 0.001$). The smoking index of the study group was more prominent compared to the control group (42.52 ± 25.08 vs. 28.29 ± 16.34 cigarette pack-years, $P = 0.002$).

The spirometry measurements revealed that FVC (% predicted), FEV1 (L and % predicted) and FEV1/FVC values were significantly lower in the COPD group compared to the control group ($P < 0.001$). In the COPD group, statistically significantly lower values were recorded for the spO_2, 6MWT and BODE index score results than the control group ($P < 0.001$). The mMRC scores and sPAP values were higher in the COPD group than in the control group ($P < 0.001$).

Serum inflammation markers comparison showed significantly high levels of CRP ($P < 0.05$), and fibrinogen, IL-6, -8, -18 and TNF-α ($P < 0.001$, for all). When we categorized the COPD patients according to the GOLD 2017 classification, majority of the patients were categorized as GOLD groups A and B (36.7%, 33.3%), followed by GOLD groups D and C (16.7%, 13.3%). The features that could have potentially contributed to the

Table 1: Demographic characteristics, functional parameters and inflammatory markers of the patients with COPD and the control group

Parameter	COPD (*n*:60)	Control (*n*:59)	*p*
Age [years]	64.88±10.21	62.54±7.96	0.166
Sex n (%) (M/F)	58/2	57/2	0.684
BMI [kg/m^2]	24.71 (21.81-26.95)	27.66 (25.95-31.34)	<0.001
Smoking index	44 (30-52.75)	27 (15-40)	0.002
FVC [L]	3.21±0.97	3.53±0.87	0.09
FVC (% pred.)	81.48±19.93	102.24±1257	<0.001
FEV1 [L]	1.88±0.74	3.07±0.51	<0.001
FEV1 (% pred.)	65.68±20.53	103.16±12.77	<0.001
FEV1/FVC	57.33±10.24	79.73±4.82	<0.001
Oxygen saturation	96.5 (95-97)	98 (97-98)	<0.001
6MWT [m]	408 (317-454)	454 (408-499)	<0.001
CAT	7.5 (4-15.75)	-	-
mMRC	1 (1-2)	0 (0-0)	<0.001
BODE	1 (0-3)	0 (0-0)	<0.001
sPAP [mmHg]	30 (28-32)	26 (22-28)	<0.001
CRP [mg/L]	2.32±1.25	1.73±1.17	0.025
Fibrinogen [mg/dl]	328.85 (294-358.95)	274.5 (239.3-340.1)	<0.001
TNF-α [pg/ml]	26.1 (20.1-50.1)	10.36 (7.96-13.64)	<0.001
IL-6 [pg/ml]	30 (16.27-41.52)	10.93 (8.32-19.8)	<0.001
IL-8 [pg/ml]	87.94 (32.75-158.2)	22.03 (18.97-23.64)	<0.001
IL-18 [pg/ml]	37.5 (32.81-50.93)	15.64 (12.64-26.25)	<0.001

Data presented as mean±standard deviation or median (25th - 75th percentiles). COPD=chronic obstructive pulmonary disease; BMI=body mass index; FVC=forced vital capacity; %pred.=percent predicted; FEV1=forced expiratory volume in one second; spO_2=pulse oxygen saturation; 6MWT=6-minute walk test; CAT=COPD assessment test; mMRC=modified Medical British Research Council dyspnea questionnaire; BODE=BMI (B), airflow obstruction (O), dyspnea (D) and exercise capacity (E); sPAP=systolic pulmonary arterial pressure; CRP=C-reactive protein; TNF-α = tumor necrosis factor alpha; IL-6=interleukin-6; IL-8=interleukin-8; IL-18=interleukin-18

Table 2: Demographic characteristics, functional parameters, and inflammation markers of the COPD groups

Variables	Group A (*n*:22)	Group B (*n*:20)	Group C (*n*:8)	Group D (*n*:10)	*P*
Age [years]	63.95±11.9	65.1±9.73	69.5±6.7	62.8±9.58	0.660
Sex [n (%)] F/M	0 (0)/22 (100)	1 (5)/19 (95)	0 (0)/8 (100)	1 (10)/9 (90)	0.550
BMI [kg/m^2]	25±4.07	24.46±4.25	24.76±3.46	23.6±4.79	0.827
Smoking index	40 (17-52.5)	45 (30-52)	53 (27-80)	37 (35-48.5)	0.562
FVC [L]	3.72±0.96[bc]	3.32±0.84[bc]	2.86±0.55	2.16±0.55	<0.001
FVC (% pred.)	88.82±18,71[bc]	86.1±17,09[bc]	78.2±20.1[c]	58,5±9,04	<0,001
FEV1 [L]	2.3±0.68[bc]	2.05±0.59[bc]	1.52±0.41[c]	0.92±0,21	<0.001
FEV1 (% pred.)	76.13±12.36[bc]	72.7±16.43[bc]	58.9±18.6[c]	33.9±5.15	<0.001
FEV1/FVC	61.68±8.4[bc]	61.5±6.88[bc]	52.5±6.94[c]	43.2±7.68	<0.001
Oxygen saturation	97 (95.75-98)	96 (95-97)	96.5 (95.25-97)	96 (94.75-97)	0.356
6MWT [m]	454 (379.5-504.75)[abc]	385 (283.55-467.5)[bc]	419.5 (363-454)[c]	317.4 (153-345.75)	0.003
CAT	3.5 (2-4.25)[abc]	13.5 (10-17.75)[bc]	5 (4-5.75)[c]	19 (16.5-22.5)	<0.001
mMRC	1 (1-1)[ac]	2 (1-2)[bc]	1 (1-1)[c]	3 (2-3)	<0.001
BODE	0 (0-1)[abc]	1 (1-2.75)[bc]	1 (1-2)[c]	6 (5-7.25)	<0.001
CRP [mg/L]	2.43±1.26	2.07±1.42	3.12±0.89	1.94±0.92	0.162
Fibrinogen [mg/dl]	306.95 (266.37-348.25)	339.75 (300.5-375.2)	331.6 (303.7-357.45)	351.9 (284.72-382.37)	0.207
TNF-α [pg/ml]	23.61 (18.48-28.17)[abc]	44.57 (22.97-71.53)[bc]	27.31 (19.75-47.68)[c]	50.44 (19.74-107.11)	0.045
IL-6 [pg/ml]	20.78 (15.39-30.09)[ac]	38.23 (23.03-64.8)[bc]	25.09 (11.27-36.47)[c]	61.96 (34.26-133.31)	0.002
IL-8 [pg/ml]	62.69 (30.73-135.32)	105 (35.96-170.5)	101.66 (88.64-192.62)	50.64 (27.53-89.93)	0.246
IL-18 [pg/ml]	35 (32.5-42.5)	40 (36.56-60)	41.87 (33.75-50)	40.62 (30.93-69.37)	0.266
sPAP [mmHg]	28 (24-32)	30 (28-31)	31 (25-33.5)	32 (26.5-35)	0.318

Data presented as mean±standard deviation or median (25th - 75th percentiles). [a]Different from group B; [b]Different from group C; [c]Different from group D; COPD=chronic obstructive pulmonary disease; BMI=body mass index; FVC=forced vital capacity; % pred.=percent predicted; FEV1=forced expiratory volume in one second; spO2=pulse oxygen saturation; 6MWT=6-minute walk test; CAT=COPD assessment test; mMRC=modified Medical British Research Council dyspnea questionnaire; BODE=BMI (B), airflow obstruction (O), dyspnea (D) and exercise capacity (E); CRP=C-reactive protein; TNF-α = tumor necrosis factor alpha; IL-6=interleukin-6; IL-8=interleukin-8; IL 18=interleukin-18; sPAP=systolic pulmonary arterial pressure

Table 3: The correlations of inflammatory parameters with functional parameters in COPD patients

Variables		CRP	TNF-α	IL-18	IL-6	IL-8	Fibrinogen
FVC [L]	r	0.068	−0.167	−0.020	−0.271*	0.048	−0.131
	p	0.605	0.201	0.878	0.036	0.715	0.317
	n	60	60	60	60	60	60
FEV1 [L]	r	0.126	−0.226	−0.052	−0.278*	0.028	−0.094
	p	0.336	0.083	0.692	0.031	0.834	0.477
	n	60	60	60	60	60	60
FEV1 (% pred.)	r	0.176	−0.271*	−0.095	−0.296*	0.116	0.021
	p	0.180	0.036	0.470	0.021	0.379	0.874
	n	60	60	60	60	60	60
FEV1/FVC	r	0.239	−0.268*	−0.115	−0.200	−0.019	0.012
	p	0.066	0.038	0.381	0.125	0.888	0.926
	n	60	60	60	60	60	60
6MWT [m]	r	0.003	0.033	−0.317*	−0.423**	−0.143	−0.107
	p	0.983	0.804	0.014	0.001	0.276	0.416
	n	60	60	60	60	60	60
CAT	r	−0.207	0.279	0.178	0.360**	0.048	0.170
	p	0.113	0.031*	0.174	0.005	0.714	0.193
	n	60	60	60	60	60	60
mMRC	r	−0.425**	0.475**	0.198	0.494**	−0.130	0.080
	p	0.001	0.0001	0.130	0.001	0.321	0.546
	n	60	60	60	60	60	60

Contd...

Table 3: Contd...

Variables		CRP	TNF-α	IL-18	IL-6	IL-8	Fibrinogen
BODE	r	−0.319*	0.367**	0.294*	0.541**	0.029	0.161
	p	0.014	0.004	0.024	0.001	0.830	0.224
	n	59	59	59	59	59	59

* $P<0.05$, ** $p<0.01$, COPD=chronic obstructive pulmonary disease; BMI=body mass index; FVC=forced vital capacity; FEV1=forced expiratory volume in one second; % pred.=percent predicted; 6MWT=6-minute walk test; CAT=COPD assessment test; mMRC=modified Medical British Research Council dyspnea questionnaire; BODE=BMI (B), airflow obstruction (O), dyspnea (D) and exercise capacity (E); sPAP=systolic pulmonary arterial pressure; CRP=C-reactive protein; TNF-α = tumor necrosis factor alpha; IL-6=interleukin-6; IL-8=interleukin-8; IL 18=interleukin-18

disease severity (i.e. BMI, spO2 and sPAP) and COPD risk factors (i.e. age, sex, and smoking index) were comparable between the COPD groups ($P > 0.05$). The lowest values for spirometric parameters were recorded in Group D, and the values were gradually increased in Groups C, B, and A, respectively. The lowest 6MWT and BODE index score results were recorded in Group D, while scores in Groups B, C, and A were higher. Higher mMRC and CAT scores were recorded in Groups B and D, in agreement with the GOLD classification, as patients in both of these groups are classified as symptomatic.

In the evaluation of the inflammation markers, the levels of CRP, fibrinogen, IL-8, and IL-18 were not statistically significantly different between the groups according to the GOLD classification ($P > 0.05$). Group D had the highest levels of IL-6 and TNF-α, and the levels gradually decreased in Groups B, C, and A, respectively ($P < 0.05$). The inflammation markers, functional parameters and the demographic characteristics of the patients in accordance with GOLD classification are presented in Table 2.

The correlation analysis between the inflammatory and functional parameters indicated that the FVC (L) and FEV1 (L) had a negative correlation with the IL-6 level and the FEV1/FVC had a negative correlation with the TNF-α level. A negative correlation was shown between FEV1 (%) and both the TNF-α and IL-6. A negative correlation was present between the 6MWT performance and IL-6 and IL-18 levels. The CAT score and the mMRC showed a positive correlation with the TNF-α and IL-6 levels, and there was a positive correlation between BODE index score and TNF-α, IL-6, and IL-18 levels. The correlations of the inflammatory markers with the functional parameters in patients with COPD are presented in Table 3.

Discussion

In our study, the relationship between inflammatory markers and COPD was assessed in the light of the GOLD classification 2017 report, which excluded the term of inflammation from the definition. The GOLD classification is based on the practicalities of treatment of this complex and heterogeneous disease, and may not be reliable in predicting disease severity and prognosis. The outcomes of the current study indicated a significant correlation between the inflammation markers and BODE index score, and therefore it is certain that there is a need for further studies investigating the phenotypical characteristics of systemic inflammation in patients classified as GOLD group B.

The effects of genetic, biological, clinical, and environmental factors are important in disease management and determining the severity of chronic diseases. Therefore, interactions between these determinants should be taken into consideration. In COPD patients, body mass poses a risk factor for morbidity and mortality, and recent studies have revealed that the number of patients with low BMI in advanced stages of disease has increased, as determined by spirometry.[9,10] In addition to cachexia, the incidence of myofibrillary protein destruction is also high among COPD patients.[11] This leads to structural deformities in skeletal muscle, resulting in limited mobility.[12] In patients with COPD, exercise capacity is a powerful determinant of quality of life and mortality.[13] In the present study, the BMI values were lower in COPD patients compared to the control subjects, which was consistent with previous findings in literature, although the COPD sub-groups did not have significant differences.

Although stable endotypic characteristics for COPD have not yet been defined clearly, several studies have indicated a cross-sectional relationship of various biological markers with mortality and morbidity in COPD. For example, in the 'Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE)' study, 16% of patients exhibited elevations in 2 or more systemic inflammatory indicators, which were not increased at all in 30% of the patients, providing further evidence of the heterogeneous nature of COPD endotypes.[14] In the current study, we showed elevated levels of several inflammatory factors including CRP, TNF-α, fibrinogen, IL-6, -8 and -18 were in COPD group, in agreement with previous

studies reporting that IL-6, IL-8, TNF-α, CRP and fibrinogen levels were higher in COPD patients than in control groups.[14-17] Agusti *et al*. reported that patients in COPD group had elevated levels of fibrinogen, CRP and IL-6 levels compared to both smoker and non-smoker control subjects. The same study also found that the levels of TNF-α and IL-8 were elevated in the smoker non-COPD group and this effect was attributed to smoking.[14] Although studies with different results have been published, in the current study, we showed higher levels of IL-8 and TNF-α in patients with COPD, and our results are consistent with most of the studies in literature. The higher smoking rate in the COPD group can be considered to have contributed to these findings.

Currently, COPD is considered a hypernym, with patients presenting with distinct clinical, pathophysiological and radiological phenotypes.[18] These COPD phenotypes can differ in symptoms, exacerbations, response to treatment, prognosis and/or mortality. The efficacy of the staging systems established for disease management in predicting the prognosis of COPD is debatable. Until recently, the staging only utilized the FEV1 values, but the FEV1 value alone is inadequate for the prediction of prognosis and mortality. Celli *et al*. have monitored COPD patients for three years revealed that the most important factors in predicting mortality were age, BODE index score and a history of hospitalization.[19]

The ABCD GOLD classification, which takes into account the presence of symptoms and exacerbation risk, is superior to the staging system using FEV1 for the prediction of exacerbations,[20,21] although not superior in respect of predicting mortality.[20,22-24] The efficacy of the GOLD classification is controversial with regard to predicting mortality and prognosis in patients with COPD. A recent study using this classification has shown that group C patients are considered a high-risk group, while the mortality rates were higher in group B patients than group C patients.[25] Lange *et al*. have reported that patients in GOLD groups B and D had higher mortality rates than those in GOLD groups A and C.[21] In addition, in GOLD groups B and D, comorbidity rates were also higher, which the authors argued might have influenced the mortality rates. Johannessen *et al*. found that the respiratory-related and overall mortality rates were higher in group B than group C patients, which they attributed to the superiority of dyspnea in predicting mortality.[23] Soriano *et al*. and Agusti *et al*., have shown comparable mortality rates in patient groups B and C.[24,26] In the current study, the BODE index score, which is used to predict mortality, was elevated in GOLD groups B and D compared to those in groups C and A. Although it was thought that the increased mortality rate in GOLD group B was associated with the higher rate of comorbidities,[21] the COPD patients in the current study had no comorbidities, suggesting that inflammation might play an independent role in mortality in patients with GOLD group B.

Agusti *et al*. reported that the highest rate of persistent systemic inflammation was in GOLD group B, followed by GOLD group D.[26] In the current study, IL-6 and TNF-α levels were higher in patients in GOLD groups B or D compared to those in GOLD groups A or C ($P = 0.045$ and $P = 0.02$, respectively). Another study revealed that the inclusion of inflammatory biomarkers in evaluation via clinical predictor variables was superior in predicting mortality and that IL-6 was the most prominent of these markers.[19] Yet another study has suggested that IL-6 might have an effect on increased mortality risk in respiratory disorders.[27]

In the current study, the BODE index score, which is utilized in predicting mortality, had a positive correlation with IL-18, IL-6 and TNF-α, similar to a report by Khan *et al*., who also reported a positive correlation between BODE index and IL-6, TNF-α and CRP.[28] They also found that IL-6 had a negative correlation with FEV1 (%) and a positive correlation with 6MWT and mMRC. In our study, IL-6 was determined to be positively correlated with the CAT score and mMRC and negatively correlated with the FVC (L), FEV1 (L), FEV1 (%) and the 6MWT result.

Last but not the least, some other factors such extracellular vesicles (EV) and dysfunctional endothelium of lung may be effecting the pathophysiology of COPD, resulting in increased levels of inflammation and increased frequency of exacerbations. It has been reported that a dysfunctional epithelium can increase inflammation in lungs by upregulating the expression of cell adhesion molecules such as intracellular adhesion molecule-1 (ICAM-1) or platelet endothelial cell adhesion molecule-1 (PECAM-1) via transendothelial migration. In addition, endothelial apoptosis and cell senescence may contribute to the pathogenesis of COPD.[29]

In recent years, a body of evidence has shown the importance of EV in COPD development. EV are nano-sized particles which are composed of lipid and proteins and are classified as apoptotic bodies, exosomes, microvesicles and exosomes, depending on their sedimentation rates in centrifugation. Microvesicles (MV) can be released from almost any cell and they are mainly originated from endothelium, platelets and leukocytes. Microvesicles can play roles in proinflammatory reactions such as releasing the

proinflammatory cytokines, activating the endothelial and immune cells, increasing leukocyte mobility and generating monomeric CRPs. Further, they have roles in anti-inflammatory activities such as releasing the anti-inflammatory cytokines and reducing sepsis (for leukocyte derived MVs) that suppress the endothelial cell activation (for endothelium derived MVs) and the leukocyte activation (for platelet derived MVs).[30,31] It is known that smoking, oxidative stress, bacterial and viral infections and other hazardous substances irritate the bronchial epithelial cells which is the lining of the airways, resulting in increased MV release and increased inflammation and exacerbations in patients with COPD.[32] Even though it is possible to isolate MVs from the bodily fluids (similar to liquid biopsy) by centrifugation which makes them ideal for diagnostic purposes, technical difficulties such as lack of a standardized protocol, inconsistent results of different studies, differences in methods and need for specialized equipment are the major downsides of MVs to be used for diagnostic purposes.[30] However, in the future, it may be possible to these particles.

There were some limitations to the current study. The participants were relatively low in number and thus the human data was limited, although it can be considered that there was sufficient evidence and details of the role of inflammation in COPD provided by the subjects selected through independent random sampling. Further studies with greater numbers of patients would provide stronger data.

Conclusion

The systemic inflammatory markers were higher in the patients with COPD than the subjects in the control group and in patients classified as GOLD groups B and D than those in GOLD groups A and C. While GOLD group D defines symptomatic COPD patients with an increased exacerbation risk, GOLD group B covers symptomatic patients with no risk of exacerbation. The current study finding of higher levels of inflammatory markers in GOLD groups B and D patients raises the question of whether bronchodilator treatment might be convenient for patients in GOLD group B and suggests that some patients might benefit from anti-inflammatory treatment. A significant correlation between the inflammation markers and the BODE index score found in the current study supports this suggestion.

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Conflicts of interest

There are no conflicts of interest.

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