

EVALUATION OF SYSTEMIC INFLAMMATORY MARKERS IN COPD PATIENTS DURING STABLE AND EXACERBATION PHASES

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ABSTRACT

Background: Chronic Obstructive Pulmonary Disease (COPD) is a progressive inflammatory disorder characterized by irreversible airflow limitation and recurrent exacerbations that accelerate morbidity and mortality. Systemic inflammation plays a crucial role in disease progression, yet variations in inflammatory marker levels during stable and exacerbation phases remain under-evaluated in regional populations.

Objective: To assess and compare systemic inflammatory markers—C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- α)—in COPD patients during stable and exacerbation phases and determine their clinical significance.

Methods: This cross-sectional study was conducted across tertiary care centers in Punjab, Pakistan, from January 2024 to December 2024. A total of 100 spirometry-confirmed COPD patients were enrolled, equally divided into stable and exacerbation groups. Venous blood samples were collected for quantitative estimation of CRP, IL-6, and TNF- α using high-sensitivity immunoturbidimetric and ELISA assays. Data were analyzed using SPSS v26, and $p < 0.05$ was considered statistically significant.

Results: Mean serum CRP, IL-6, and TNF- α levels were significantly higher during exacerbation (27.9 ± 7.8 mg/L, 12.2 ± 3.5 pg/mL, and 18.7 ± 4.9 pg/mL, respectively) compared with the stable phase (8.6 ± 3.4 mg/L, 4.1 ± 1.6 pg/mL, and 9.4 ± 3.1 pg/mL; $p < 0.001$). A strong positive correlation was observed between IL-6 and TNF- α ($r = 0.79$) during exacerbations, indicating synergistic cytokine activation.

Conclusion: Systemic inflammation markedly intensifies during COPD exacerbations, with CRP, IL-6, and TNF- α serving as reliable biomarkers for disease monitoring. Regular assessment of these markers may enhance early detection, therapeutic optimization, and prevention of recurrent exacerbations.

Keywords: Chronic obstructive pulmonary disease, systemic inflammation, CRP, IL-6, TNF- α , exacerbation phase, cytokines

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INTRODUCTION

The Chronic Obstructive Pulmonary Disease (COPD) is another widely spread, preventable and treatable lung disease that is distinguished by the constant constriction of the airflow that is generally progressive and characterized by an increased inflammatory reaction in the airways and lungs to the harmful particles or gases¹. The disease causes significant burden to the public health of the entire world and ranks as the third cause of death worldwide, killing almost 3.2 million people every year based on the World Health Organization (WHO). In developing nations such as Pakistan, COPD prevalence keeps on increasing because

of the high prevalence of tobacco smoking, exposure of biomass fuels and late diagnosis².

Pathophysiologically, COPD entails chronic inflammation of the airway epithelium, neutrophil, macrophages, and T-lymphocyte infiltration and alveolar architecture destruction leading to emphysematous alterations and airflow obstruction. But increasing evidence indicates that COPD is not a localized pulmonary disease only, it is a systemic inflammatory disease which plays a role in various extrapulmonary manifestations in the body which include, skeletal muscle wasting, cardiovascular diseases, osteoporosis and metabolic

disorders. The pro-inflammatory cytokines and acute-phase reactants in blood mediate these systemic changes³.

The major biomarkers of systemic inflammation among these include C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- α). CRP is a protein produced by the hepatocytes on being stimulated by IL-6 and is commonly utilized as an indicator of inflammation and tissue damage⁴. IL-6 is a versatile cytokine which modulates the immune responses, hematopoiesis and acute-phase responses, whereas TNF- α is essential in the occurrence and maintenance of inflammatory cascades and oxidative stress. High concentrations of these markers in COPD patients have been reported consistently with cases being reported especially during acute exacerbations⁵.

COPD exacerbations refer to the acute increase or decrease of respiratory symptoms beyond day-to-day fluctuations, and usually necessitate a change of medicine or even hospitalization. These attacks are the cause of worsened decline of lung function, higher healthcare use, and risk of death. Exacerbations are known to be also associated with the increases in systemic inflammation, which contribute further to the airways injury and the systemic complications. However, the scale and trend of inflammatory markers increase during steady and acute stages are dynamic across populations because of genetic, environmental, and lifestyle variations⁶.

Therefore, the assessment of systemic inflammatory biomarkers of COPD patients is a helpful instrument to comprehend the disease activity, exacerbation anticipation, and treatment efficacy. Within the context of Pakistani, this kind of data is not abundant regardless of the great COPD burden and risks of environmental exposure⁷.

Thus, the research problem of the given study was to determine the quantitative values of serum CRP, IL-6, and TNF- α in patients with COPD at the stable and exacerbation stages and to investigate their relationships with each other and their clinical significance in monitoring and management of the disease⁸.

MATERIALS AND METHODS

Study Design and Setting: The study is a cross-sectional observational study that was conducted at several tertiary care hospitals in Punjab, Pakistan, during a period of one year between January 2024 and December 2024. The research was done in partnership with pulmonology and internal medicine departments of the chosen teaching hospitals in an attempt to determine the systemic inflammatory profile of patients diagnosed with Chronic Obstructive Pulmonary Disease (COPD) either at their stable or exacerbation stage. Ethical approval of the study was given by institutional ethical committees of all the centers before the study started. The informed consent of all the participants was taken up in written versions before they were enrolled and all the procedures were done in

accordance with the standard ethical principles of the Declaration of Helsinki.

Population and Grouping of the Study: This study has purposively sampled 100 patients who have confirmed COPD using a non-probability sampling method. The diagnosis of COPD was made following the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2024 guidelines, which was a post-bronchodilator FEV₁/FVC ratio below 0.70 on spirometries. The respondents were separated into two equal groups based on the clinical condition at the time of enrollment. Group I consisted of 50 patients in the stable phase of COPD who did not have any recent exacerbations or infections within a period of six weeks, whereas Group II consisted of 50 patients presenting with acute exacerbation of COPD, which is the sudden worsening of respiratory symptoms e.g. dyspnea, cough, or sputum production requiring medical attention or hospitalization.

Inclusion and Exclusion Criteria: Both genders aged 40-75 years were eligible to take part as patients. All the individuals were included with a confirmed diagnosis of COPD and agreed to complete an informed consent in writing. Patients were also excluded in case of the following conditions that have been known to influence systemic inflammation such as bronchial asthma, pulmonary tuberculosis, interstitial lung disease or lung malignancy. Cases of autoimmune disease, recent pulmonary infection (four weeks), and those who either had had systemic corticosteroid or immunosuppression agents in the past four weeks or those who had been administered antioxidants within a month before the survey were also not eligible. Moreover, those with chronic kidney disease, hepatic dysfunction and cardiovascular failure were not eligible to participate.

Clinical and Demographic Assessment: The demographic information of the patients such as age, gender, smoking history, occupational exposure, as well as the duration of the disease were recorded using a structured questionnaire. Every participant had a detailed clinical examination with particular consideration towards the examination of the respiratory system. Spirometric assessment was conducted in order to establish the level of airflow limitation and categorize the disease in GOLD staging. Past exacerbations in the last year were also recorded so that they could be compared. This clinical assessment provided proper grouping of the participants and elimination of confounding variables.

Laboratory Procedures and Blood Sampling: Five milliliters of venous blood were taken under aseptic precautions of each participant. Ten minutes centrifugation of blood samples at 3000 rotations per minute (rpm) followed and serum was separated and stored at a minimum of -80°C until further biochemical evaluation. Immunoturbidimetric assay was conducted on an automated chemistry analyzer to measure the C-reactive protein (CRP) level. The levels of serum interleukin-6 (IL-

6) and tumor necrosis factor-alpha (TNF-6) were measured via the enzyme-linked immunosorbent assay (ELISA) assays (Bioassay Technology Laboratory, Shanghai, China) according to the standard procedures offered by manufacturers. All assays were done in duplicate to limit inter-assay variability and stringent quality control measures were observed during the entire laboratory operations.

Data Analysis and Statistical Methods: All the data gathered were inputted and processed in Statistical Package of the Social Sciences (SPSS) version 26.0 (IBM Corp., Armonk, NY, USA). The quantitative variables like age, duration of disease, serum levels of inflammatory markers were used to portray mean plus standard deviation (SD) whereas the categorical variables such as gender and smoking status were used to describe the frequency and percentage. Independent samples t-test was used in comparing the continuous variables between the groups, which were stable and exacerbation groups, and the Chi-square test was used in the comparison of the categorical variables. The interrelationships within the systemic inflammatory markers (CRP, IL-6, and TNF- α) were measured using the Pearson correlation coefficient (r). All analyses were regarded as significant at p-value below 0.05.

Ethical Considerations: This study complied rigidly with the global standards of conducting research on human subjects. All the participating tertiary care hospitals obtained ethical approval of the Institutional Review Boards (IRBs) before collecting any data. The consent form was signed by the participants who were well informed on the purpose of the study, the risks or dangers involved, and the advantages of the study. Participants were ensured confidentiality and anonymity at all levels and all the biological samples were treated and disposed in accordance with biosafety guidelines. The patients still had the right to exit the study any time without compromising their standard of care.

RESULTS

Demographic and Baseline Characteristics: This study enrolled 100 patients who received Chronic Obstructive Pulmonary Disease (COPD) diagnosis, including 50 patients in the stable stage and 50 patients in the exacerbation stage. The mean of the ages of the respondents was 59.2 ± 7.1 years ranging between 42 and 75 years. Gender distribution indicated that there were 74 male and 26 female patients with COPD, and this illustrates the male composition of COPD that was recorded amongst the local people owing to the high rates of smoking exposures among men. The sample size in the stable group was 36 males (72%), and 14 females (28%), and the exacerbation group had 38 males (76%), and 12 females (24%), which did not show any statistically significant gender difference between the two groups ($p = 0.63$). The stable phase disease duration and exacerbation disease duration were 6.7 ± 2.3 and 7.1 ± 2.5 years respectively ($p = 0.41$), which showed no difference in disease chronicity between the two groups. Most of the patients, 82% were present or former smokers, which acclaims cigarette smoking as the leading etiological agent collaborating with the development and advancement of COPD in this sample.

All the participants had the following baseline demographic characteristics (see Table 1).

Table 1 demonstrates that both groups were statistically comparable in age, gender, body mass index, and smoking history, ensuring homogeneity and eliminating demographic confounding effects on inflammatory marker outcomes.

Comparison of Systemic Inflammatory Markers Between Stable and Exacerbation Phases: C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha) serum levels were checked and compared between COPD patients in their stable and exacerbation phases. The comparison shows a significant and statistically significant rise of all three systemic inflammatory markers in the state of exacerbation in comparison to the stable disease condition ($p < 0.001$ in all respects).

Table 1: Demographic and Baseline Characteristics of the Study Population

Variable	Stable Phase (n=50)	Exacerbation Phase (n=50)	p-value
Mean Age (years)	58.7 ± 7.3	59.8 ± 6.9	0.45
Male : Female	36 : 14	38 : 12	0.63
Mean Disease Duration (years)	6.7 ± 2.3	7.1 ± 2.5	0.41
Current/Formers Smokers (%)	80	84	0.56
Mean BMI (kg/m ²)	22.6 ± 3.1	21.9 ± 3.5	0.28

Table 2: Comparison of Systemic Inflammatory Marker Levels Between Stable and Exacerbation Phases

Inflammatory Marker	Stable Phase (Mean $\pm$ SD)	Exacerbation Phase (Mean $\pm$ SD)	p-value
CRP (mg/L)	8.6 ± 3.4	27.9 ± 7.8	<0.001
IL-6 (pg/mL)	4.1 ± 1.6	12.2 ± 3.5	<0.001
TNF- α (pg/mL)	9.4 ± 3.1	18.7 ± 4.9	<0.001

The statistical significance of the differences in biomarkers levels observed was as demonstrated in Table 2, which validated the strong reaction in the inflammatory response to the exacerbation episodes. The relationship is dynamic as the proportional rise of these cytokines suggests that inflammatory processes are coupled between airway inflammation and systemic immune activation and the wider extent of the inflammatory burden in COPD. The steady increase in the CRP even during the exacerbation is also an indication of its usefulness as an effective clinical indicator to recognize and track acute deterioration in COPD patients.

Correlation Analysis of Inflammatory Markers.

The results were further analyzed to determine how the serum inflammatory biomarkers relate to each other in each group. There was a close positive relationship between IL-6 and TNF- α in exacerbation ($r = 0.79$, $p < 0.001$), indicating a simultaneous induction of pro-inflammatory pathways by the two cytokines. There was also moderate correlation between CRP and IL-6 ($r = 0.67$, $p < 0.01$) given that under systemic inflammatory conditions, IL-6 stimulates hepatic production of CRP. Conversely, the correlations between the markers were less strong in the stable phase whereby the IL-6 and TNF- α had an r -value of 0.41 ($p = 0.04$) meaning that the presence of low-grade inflammation is evident even when there is no acute exacerbation.

Table 3 presents the findings of correlation analysis.

Table 3: Correlation Coefficients Between Inflammatory Markers in COPD Patients

Parameter Pair	Stable Phase (r)	Exacerbation Phase (r)	p-value
IL-6 vs TNF- α	0.41	0.79	<0.001
CRP vs IL-6	0.35	0.67	<0.01
CRP vs TNF- α	0.29	0.61	<0.01

As shown clearly in Table 3, systemic inflammatory markers are better correlated in exacerbations and that these mediators are synergistic in acute disease activity. The significant increase in IL-6 and TNF- α levels is indicative of an exaggeration of an inflammatory cascade that plays a role in systemic effects of COPD such as oxidative stress, endothelial dysfunction and tissue damage.

Inflammatory Response Gender-Based Analysis: Sub group analysis was done to examine the possibility of gender differences in the expression of systemic inflammatory markers. Mean CRP levels among male subjects were 9.2 ± 3.5 mg/L at the stable period and 28.4 ± 7.2 mg/L at exacerbation, but among the female patients, these were 7.9 ± 3.0 mg/L and 26.7 ± 8.1 mg/L, respectively. The same case was observed with IL-6 and TNF- α which were significantly more elevated in males but showed no significant difference between

genders after the smoking status was adjusted ($p = 0.12$). These data indicate that though absolute levels of inflammatory markers are usually marginally higher in males, percentage change during an exacerbation proceeds in a trended fashion in both sexes, which confirms the overall systemic nature of COPD inflammation regardless of sex.

Concisely, the findings of the current research indicate that systemic inflammatory biomarkers, i. e. CRP, IL-6, and TNF- α , are markedly higher in COPD patients during acute attacks than in the non-flare period. The noted associations between these biomarkers (Table 3) support that the action of cytokine-driven inflammatory processes enhances during exacerbations, which increases pulmonary and systemic effects. Additionally, the validity of the findings is enhanced by demographic similarity between groups (as summarised in Table 1) because it reduces confounding factors including age, gender and smoking status. Taken together, these results support the idea that COPD cannot be viewed only as a localized airways disease but a general inflammatory condition, and that the measurement of serum biomarkers can be a useful addition to the clinical treatment and prognostic evaluation of the patient.

DISCUSSION

The current research gives considerable understanding of the systemic inflammatory dynamics of the Chronic Obstructive Pulmonary Disease (COPD) through comparison of the level of inflammatory markers in stable and exacerbation phases in patients in tertiary care centres in Punjab, Pakistan⁹. These results indicate that during exacerbation serum levels of CRP, IL-6 and TNF- α were significantly higher than when the disease is at rest, which highlights the essentiality of systemic inflammation in the pathophysiology of COPD. This cytokine intensification pattern in cases of acute exacerbation is in line with the idea that COPD is a chronic inflammatory disease with periodical systemic amplification by means of infections, pollutants, or other external factors¹⁰.

The observed rise in CRP in exacerbation is consistent with the hepatic reaction to stimulating IL-6, which is an acute-phase reactant that is indicative of the systemic system of inflammation. As a cost-effective and easy-to-detect biomarker, CRP has the potential to find clinical use in tracking disease progression and risking exacerbations. Findings of this research are similar to the findings of Agusti et al. (2018) and De Torres et al. (2016), who stated that serum CRP levels increase significantly during exacerbations and correlate with a greater risk of hospitalization and adverse outcomes¹¹. High CRP has also been associated with a reduction in lung function (FEV₁) and cardiovascular comorbidities typical of COPD and so has been postulated to indicate not only pulmonary but also the systemic burden of the disease¹².

Likewise, the significant increase of interleukin-6 (IL-6) a pro-inflammatory cytokine central to the acute-phase response was also observed during the exacerbation phase than in the stable period. The IL-6 has a dual action as it mediates local airway inflammation as well as enhancing hepatic production of acute-phase proteins, such as CRP. High IL-6 has been linked with high levels of oxidative stress, muscle wasting and metabolic dysregulation which all lead to systemic expression of COPD^{1,3}. The current outcome confirms previous data obtained by Pinto-Plata et al. (2017) and Singh et al. (2019) which mentioned IL-6 as a strong indicator of disease severity and exacerbation rate. Interestingly, IL-6 levels were also highly correlated with TNF-alpha ($r = 0.79$, $p < 0.001$) in our experiment, which was an indication of synergistic activation of the inflammatory signaling pathways in acute disease flares¹⁴.

Another of the major inflammatory cytokines, tumor necrosis factor-alpha (TNF-alpha), increased significantly in cases of exacerbation compared to the condition of stable COPD. TNF-alpha is also known to cause neutrophilic inflammation, alveolar epithelial cell apoptosis and airways remodelling, which perpetuate the chronic inflammation^{9,10}. It is increased by continuous immune activation, which does not remain in the pulmonary compartment, but spreads to systemic tissues. Similar statements were made by Wouters et al. (2017) and Barnes (2016), who also referred to TNF-a role in perpetuating the chronic inflammatory environment of COPD, attributing its increase to the dysfunction of the endothelium and cardiovascular morbidity¹⁵. TNF-alpha also showed a close relationship with IL-6 and CRP in the study being analyzed, which once again supports the interaction between the two cytokines in enhancing systemic inflammation^{13,14}.

The gender distribution of this study showed that there was a male dominance which is in line with the epidemiological data in the South Asia where the rate of smoking and occupational exposures are very high in the case of men. Nevertheless, the tendency towards the increase of cytokines during exacerbation was similar in both sexes, which may indicate that the occurrence of inflammatory response mainly depends on the disease, but not gender. This finding is corroborated by previous findings that show that although the symptom profile can vary in women, there is similarity in inflammatory biomarker responses in males and females when they have the same severity of disease¹⁶.

The findings are also important in the understanding of clinical importance of systemic inflammation in the management of COPD. The high levels of CRP, IL-6, and TNF-alpha during the exacerbations make them the prospective biochemical markers of disease instability. Periodic monitoring of these indicators may assist clinicians to recognize the patients at risk of exacerbation, target anti-inflammatory interventions, and evaluate the

response of treatment. Furthermore, the fact that the low-grade inflammation persists even in the stable phase suggests that anti-inflammatory interventions can be useful in the course of the disease and not only in the case of acute exacerbation¹⁷.

When compared to other world data, the extent of cytokines rise in the Pakistani cohort seems to correlate with the findings around the world, but there were a little higher CRP levels detected. This can be an indication of variance in exposure to the environment, level of air pollution, genetic predisposition or access to health care^{16,18}. Rahman and Adcock (2018) also made similar observations and noted that regional differences in oxidative stress and inflammatory markers were observed because of different air quality indices and smoking rates. Thus, the clinical usefulness of monitoring inflammation in COPD in developing countries can be improved when local population-based biomarker reference ranges are used¹⁸.

In general, the findings support the idea that COPD is a systemic inflammatory illness but not a pulmonary one. The fact that the levels of cytokines increase during exacerbation and their interrelationships is another biological fact that proves the relevance of biomarker surveillance to the process of COPD management¹⁹. Additionally, the research results can lead to new anti-cytokine treatment approaches that would regulate the activity of IL-6 or TNF-a and potentially decrease the rate and intensity of exacerbations²⁰.

CONCLUSION

The current research indicates that systemic inflammatory markers such as C-reactive protein, interleukin-6, and tumor necrosis factor-alpha are highly increased during an acute exacerbation of COPD compared to the stable period, which is an indication of increased systemic inflammatory load that goes along with clinical worsening. The correlations between these markers that were observed show that the cytokine cascade that is involved in the development of pulmonary and extrapulmonary complications is interlinked. These observations reaffirm the fact that COPD must be treated as a chronic systemic inflammatory disease and not a disease that is limited to airways. Regular monitoring of these biomarkers could be helpful in early case of exacerbations, stratifying risk, and therapeutic choices, especially in resource constrained environments with clinical signs often being difficult to make the distinction between stable and exacerbation states. The addition of monitoring inflammatory markers into routine COPD treatment processes may help in individual-based care, enhance prognostic efficiency, and decrease morbidity and hospitalization. These findings should be confirmed by future multicentric cohort studies and longitudinal follow-up studies to investigate the prognostic relevance of cytokine modulation therapies in COPD.

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