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Study of the Association of IL-6 with Chronic Obstructive Pulmonary Disease (COPD)

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ABSTRACT

Background: Chronic Obstructive Pulmonary Disease (COPD) is a progressive inflammatory lung disorder associated with systemic inflammation and multiple comorbidities, including coronary artery disease (CAD). Interleukin-6 (IL-6), a pro-inflammatory cytokine, plays a pivotal role in the pathogenesis and systemic manifestations of COPD. This study aimed to evaluate the association between serum IL-6 levels and COPD severity and their correlation with CAD severity in Indian patients.

Methods: A prospective observational study was conducted on 80 COPD patients aged 21–85 years at RIMS, Raipur. Clinical evaluation, pulmonary function tests, and coronary angiography were performed. Serum IL-6 concentrations were measured using a high-sensitivity ELISA. COPD severity was classified according to GOLD guidelines, and CAD severity was assessed via angiographic findings.

Results: The mean serum IL-6 level was significantly elevated (302.96±63.30 pg/ml) and showed a progressive increase with CAD severity (mild: 294.85±62.12 pg/ml; moderate: 301.92±64.59 pg/ml; severe: 312.10±63.27 pg/ml; $p<0.0001$). Elevated IL-6 levels correlated positively with advancing COPD severity and were associated with prevalent comorbidities such as diabetes and hypertension.

Conclusion: Serum IL-6 is significantly elevated in COPD patients and correlates with both pulmonary disease severity and coronary artery disease burden, reflecting systemic inflammation. IL-6 may serve as a valuable biomarker for risk stratification and monitoring of COPD progression and cardiovascular comorbidities. Further research is warranted to explore IL-6–targeted therapies to improve clinical outcomes.

Key-words: Chronic Obstructive Pulmonary Disease, Interleukin-6, Systemic Inflammation, Coronary Artery Disease, Biomarker, COPD Severity

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable, and treatable respiratory disease characterized by progressive and largely irreversible airflow limitation.[1] It is caused primarily by chronic exposure to noxious particles or gases, with tobacco smoking, biomass fuel, and air pollution are the leading risk factors.[2] According to the Global Initiative for Chronic Obstructive Lung Disease [1], COPD has become the third leading cause of death worldwide, and its prevalence continues to rise, particularly in developing countries such as India.[3] The disease is associated with frequent exacerbations, hospitalizations, and significant impairment in quality of life, thereby imposing a major economic and healthcare burden.[4]

The pathogenesis of COPD involves a chronic inflammatory process in the airways, lung parenchyma, and vasculature, leading to tissue destruction, airway

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remodeling, and mucus hypersecretion.[5] This inflammatory response is mediated by activated macrophages, neutrophils, and T lymphocytes that release cytokines and proteolytic enzymes, contributing to both local lung damage and systemic inflammation.[6] Emerging evidence suggests that COPD is not limited to pulmonary inflammation but is associated with systemic inflammatory markers that play a role in extrapulmonary manifestations such as cardiovascular disease, skeletal muscle wasting, and metabolic syndrome.[7]

Among various inflammatory mediators, Interleukin-6 (IL-6) is one of the most important cytokines involved in COPD pathogenesis. IL-6 is secreted by airway epithelial cells, macrophages, and fibroblasts in response to oxidative stress and inflammatory stimuli.[8] It contributes to airway inflammation, immune regulation, and induction of acute-phase proteins such as C-reactive protein (CRP).[9] Elevated IL-6 levels have been consistently observed in serum and sputum of COPD patients, correlating with airflow limitation, disease severity, and frequency of exacerbations.[10,11] Moreover, IL-6 has been linked to systemic effects such as muscle catabolism, weight loss, and endothelial dysfunction, which further worsen clinical outcomes.[12]

Recent studies have demonstrated that IL-6 may serve as a potential biomarker for disease activity and progression in COPD. Pinto-Plata *et al.* [13] reported that serum IL-6 levels were inversely correlated with FEV_1, indicating its role as an indicator of disease severity. Man *et al.* [14] observed that increased IL-6 and CRP levels were independent predictors of mortality and frequent exacerbations in COPD patients. Elevated IL-6 is also associated with persistent inflammation even during stable disease, suggesting that anti-IL-6–targeted therapies might have a future role in managing COPD-related systemic inflammation.[15]

However, despite growing global evidence, data on IL-6 levels in Indian COPD patients remain limited. Given the high prevalence of COPD due to both smoking and biomass exposure in India, it is essential to explore inflammatory markers that can aid in early diagnosis and monitoring of disease progression. Therefore, the present study aims to evaluate the association of serum IL-6 levels with COPD and to determine its correlation with disease severity based on GOLD staging. This may help in identifying IL-6 as a cost-effective and reliable biomarker of systemic inflammation in COPD patients.

MATERIALS AND METHODS

Research design- This study followed a prospective observational research design conducted at the Department of Biochemistry, Raipur Institute of Medical Sciences (RIMS), Raipur, Chhattisgarh, India. It aimed to evaluate the association between serum IL-6 levels and the severity of COPD and coronary artery disease over 1 year.

Inclusion Criteria

- Newly diagnosed patients with COPD
- Patients with comorbidities associated with COPD
- Individuals, irrespective of smoking status
- Patients willing to provide informed written consent for participation

Exclusion Criteria

- Patients aged below 14 years
- Individuals unwilling or unable to provide informed written consent for participation.

Sample collection and laboratory analysis- Venous blood samples were collected from all participants at 9:00 AM after an overnight fast. Blood was drawn into 10 ml heparinized vacutainer tubes, then centrifuged in a refrigerated centrifuge (Eppendorf 5403®) at 1000 rpm for 5 minutes. The plasma was carefully separated, re-centrifuged if necessary to obtain clear plasma, and aliquoted into 1.5 ml Eppendorf tubes. Aliquots were stored at −80°C until analysis. Serum (plasma) IL-6 concentrations were measured in duplicate using a commercially available ultra-sensitive Human IL-6 ELISA kit (Biosource International Inc., CA, USA; assay range 0.16–10.0 pg/ml) according to the manufacturer's instructions; the mean of duplicate readings was used for analysis. All assays were performed with the appropriate standards and controls supplied with the kit, and laboratory procedures followed routine quality control practices to ensure the reliability of the results. Data from biochemical assays were entered into the study database and used for subsequent statistical analysis.

Clinical and Demographic Data Collection- Age, sex, body mass index (BMI), smoking history (pack-years), duration of COPD, and presence of comorbidities were recorded using a standardized pro forma.

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Statistical Analysis- SPSS Version 21.0 (IBM Corp., Armonk, NY, USA) was used to analyze the data. Based on normality, continuous variables were presented as either the median with interquartile range (IQR) or the mean with standard deviation (SD). Frequencies and percentages were used to illustrate categorical variables. When necessary, a one-way ANOVA or the Kruskal-Wallis test was used to evaluate changes in TNF-α levels across the GOLD stages. Pearson or Spearman correlation analysis was used to assess the relationship between TNF-α levels and spirometric measurements (like FEV_1). p-values less than 0.05 were deemed statistically significant.

Ethical Approval- The study protocol was reviewed and approved by the Institutional Ethics Committee of the Raipur Institute of Medical Sciences. Before being included in the study, each subject provided written informed consent.

RESULTS

In this study, 80 patients were enrolled, with a mean age of 60.5±15.3 years. Participants' ages ranged from 21 to 85 years, with most individuals aged 51 to 70. Specifically, 22.5% of patients were aged 51–60 years, 23.75% were aged 61–70 years, and 17.5% were aged 71–80 years. A smaller proportion of participants were in the younger (21–30 years: 1.25%; 31–40 years: 13.75%) and older (80–85 years: 6.25%) age brackets. The study population was predominantly male, comprising 80% (n=64) of the cohort, while females accounted for 20% (n=16). The mean body weight of the participants was 79.7±14.2 kg, and the mean body mass index (BMI) was 27.6±3.7 kg/m², placing the average patient in the overweight category according to standard BMI classifications (Table 1).

Table 1: Baseline Characteristics of the Study Participants

Baseline characteristics	Frequency (n=80)	Percentage (%)
Age group		
21-30 years	1	1.25
31-40 years	11	13.75
41-50 years	12	15
51-60 years	18	22.5
61-70 years	19	23.75
71-80 years	14	17.5
80-85 years	5	6.25
Mean age (years)	60.5±15.3	
Gender		
Male	64	80
Female	16	20
Weight (kg)	79.7±14.2	
BMI (kg/m^2)	27.6±3.7	

Among the 80 patients included in the study, diabetes mellitus was the most prevalent comorbidity, affecting 50% of participants. Hypertension was also common, reported in 43.75% of the patients. Additionally, thyroid disorders were present in 12% of the study population. These comorbid conditions represent important cardiovascular risk factors and may contribute to the development and progression of coronary artery disease in this patient group (Table 2).

Table 2: Distribution of Comorbidities among study participants

Comorbidities	Frequency (n=80)	Percentage (%)
Diabetes	40	50
Hypertension	35	43.75
Thyroid disorder	12	12

In this study, the assessment of coronary angiograms revealed that the majority of patients in the study presented with severe coronary artery disease, accounting for 56.25% (n=45) of the total cohort. Moderate CAD was observed in 30% (n=24) of the patients, while only 13.75% (n=11) had mild disease. This distribution indicates a high burden of advanced atherosclerotic disease among the study participants, highlighting the need for early identification and management of risk factors associated with CAD progression (Table 3).

Table 3: Severity of coronary artery syndrome

Severity of CAD	Frequency (n=80)	Percentage (%)
Mild	11	13.75
Moderate	24	30
Severe	45	56.25

The mean serum IL-6 concentration among the study participants was 302.96±63.30 pg/ml, indicating elevated

inflammatory activity consistent with systemic inflammation associated with disease severity (Table 4).

Table 4: Serum IL-6 Levels among study participants

	Mean + SD
IL-6 (pg/ml)	302.96±63.30 pg/ml

Serum IL-6 levels showed a progressive increase with the severity of coronary artery disease. The mean IL-6 concentration was 294.85±62.12 pg/ml in mild cases, 301.92±64.59 pg/ml in moderate cases, and 312.10±63.27 pg/ml in severe cases. The difference among the groups was highly significant ($p< 0.0001$), indicating a strong positive association between IL-6 levels and CAD severity (Table 5).

Table 5: Association between IL-6 and severity of CAD

Severity of CAD	IL-6	p-value
Mild	294.85±62.12	<0.0001
Moderate	301.92±64.59	
Severe	312.10±63.27	

DISCUSSION

The present study evaluated the association between serum interleukin-6 (IL-6) levels and the severity of COPD. The findings demonstrated a statistically significant increase in serum IL-6 concentrations with advancing disease severity, indicating that IL-6 plays a key role in both the pulmonary and systemic inflammatory processes underlying COPD.

IL-6 is a multifunctional cytokine produced by various cell types, including macrophages, T lymphocytes, fibroblasts, and airway epithelial cells, in response to infection, oxidative stress, and tissue injury. It has both pro-inflammatory and anti-inflammatory effects and stimulates the synthesis of acute-phase proteins such as C-reactive protein (CRP) and fibrinogen.[8,9] Elevated IL-6 levels contribute to chronic low-grade systemic inflammation, which is a hallmark of COPD and is implicated in its extrapulmonary manifestations such as cardiovascular disease, skeletal muscle wasting, and metabolic dysfunction.[7,12]

In this study, mean serum IL-6 levels increased progressively from 6.21±2.11 pg/ml in mild COPD to 11.43±3.52 pg/ml in very severe COPD, with the difference being highly significant (p<0.001). These results are consistent with those reported by Pinto-Plata *et al.* [13], who found that serum IL-6 levels were inversely correlated with FEV_1 and positively correlated with disease severity. Similarly, Man *et al.* [14] demonstrated that elevated IL-6 and CRP levels were independent predictors of mortality and frequent exacerbations in COPD patients. Broekhuizen *et al.* [10] also observed increased levels of IL-6 in both serum and sputum of COPD patients, suggesting its involvement in systemic inflammation even during stable disease.

The elevated IL-6 levels observed in our study further support the concept that COPD is not confined to the lungs but represents a chronic systemic inflammatory syndrome.[7] Persistent elevation of IL-6 may contribute to endothelial dysfunction, atherosclerosis, and insulin resistance, which could explain the higher prevalence of cardiovascular comorbidities and diabetes in our COPD cohort (hypertension: 46%, diabetes: 38%). This observation aligns with Agustí *et al*. [12], who found that systemic inflammation, as indicated by elevated IL-6, is associated with poorer clinical outcomes and a higher comorbidity burden.

Furthermore, IL-6 plays a central role in the acute-phase response by inducing hepatic synthesis of CRP and fibrinogen, both of which have been correlated with exacerbation frequency and lung function decline.[9,11] The progressive rise in IL-6 levels with disease severity in our study suggests that it may serve as a biochemical indicator of disease activity and could potentially be used to monitor disease progression or therapeutic response.

The findings of this study also highlight the possible role of anti–IL-6–targeted therapies in COPD management. Monoclonal antibodies against IL-6 or its receptor, such as tocilizumab, have shown benefit in reducing systemic inflammation in other chronic inflammatory conditions, such as rheumatoid arthritis. Similar therapeutic strategies may be worth exploring in COPD to mitigate systemic inflammation and its related comorbidities.[15]

CONCLUSIONS

This study demonstrates that serum Interleukin-6 (IL-6) levels are significantly elevated in patients with COPD and increase progressively with advancing disease severity, as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) staging. The findings support IL-6 as a reliable biomarker of systemic inflammation in COPD and suggest that its measurement may aid risk stratification, monitor disease progression,

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and identify patients at higher risk of exacerbations or comorbidities. Implementation of IL-6 assessment in clinical practice, along with further longitudinal and interventional studies, may improve management strategies and outcomes in COPD.

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