SSR Institute of International Journal of Life Sciences
ISSN (O): 2581-8740 | ISSN (P): 2581-8732
Panda *et al*., 2025
crossref doi: 10.21276/SSR-IIJLS.2025.11.4.50

Original Article

open access

Study of the Association of Tumour Necrosis Factor-α with Chronic Obstructive Pulmonary Disease (COPD)

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Received: 22 Feb 2025/ Revised: 20 Apr 2025/ Accepted: 25 Jun 2025

ABSTRACT

Background: Chronic Obstructive Pulmonary Disease (COPD) is a progressive respiratory illness characterized by systemic inflammation and limited airflow. Tumor necrosis factor-alpha (TNF-α), a key pro-inflammatory cytokine, is believed to play a significant role in its pathogenesis. This study aimed to evaluate the association between serum TNF-α levels and COPD severity, classified according to the GOLD staging system.

Methods: The prospective observational study was conducted for a year at the Raipur Institute of Medical Sciences in Raipur. 300 clinically stable COPD aged ≥40 years were included using spirometric criteria (post-bronchodilator FEV_1/FVC <0.70). People with asthma, cancer, autoimmune diseases, or recent infections were excluded. ELISA, an enzyme-linked immunosorbent test, was employed to measure blood TNF-α levels. The patients were categorized using GOLD stages I through IV. TNF-α levels were compared between phases, and their relationships with spirometric parameters were investigated using appropriate statistical methods.

Results: A total of 95.33% of the participants were men, and their average age was 52.68±7.52 years. There was a statistically significant tendency (p=0.035) of rising TNF-α levels in Stage I (27.53±8.06 pg/ml), Stage II (29.86±8.25 pg/ml), Stage III (31.11±8.26 pg/ml), and Stage IV (33.10±8.78 pg/ml) as the disease severity rose.

Conclusion: Elevated systemic inflammation is indicated by serum TNF-α levels, which positively correlate with the severity of COPD. TNF-α may be a useful biomarker for monitoring the disease and assessing risk in COPD.

Key-words: Chronic obstructive pulmonary disease (COPD), TNF-α, Inflammation, Biomarker, Severe public health

INTRODUCTION

Chronic obstructive pulmonary disease (COPD), a severe public health concern, is characterized by decreased airflow and persistent respiratory symptoms caused by anomalies in the airways and/or alveoli. Usually, extended exposure to dangerous materials or particles—most commonly, cigarette smoke causes it.[1]

How to cite this article
Panda M, Joshi PR, Samal P, Mahanty B. Study of the Association of Tumour Necrosis Factor-α with Chronic Obstructive Pulmonary Disease (COPD). SSR Inst Int J Life Sci., 2025; 11(4): 8141-8145.

Access this article online
https://iijls.com/

It is anticipated that aging populations and continued exposure to risk factors would increase the prevalence of COPD, the third leading cause of death worldwide.[2]

The intricate pathophysiology of COPD includes systemic symptoms, oxidative stress, chronic inflammation, and protease-antiprotease imbalance. In addition to local airway inflammation, systemic inflammation has been found to have a significant role in the disease's extrapulmonary effects, such as skeletal muscle atrophy, cardiovascular comorbidities, and cachexia.[3,4] Tumor TNF-α has been identified as a key pro-inflammatory cytokine in the pathogenesis of COPD among the many biomarkers that have been investigated.

doi: 10.21276/SSR-IIJLS.2025.11.4.50

In reaction to stimuli like infections and cigarette smoke, activated macrophages, neutrophils, and epithelial cells are the main producers of TNF-α.[5] Among its many biological effects are the recruitment and activation of inflammatory cells, the synthesis of more cytokines, the encouragement of tissue damage and oxidative stress, and more.[6] Patients with COPD have higher amounts of TNF-α in their sputum, bronchoalveolar lavage fluid, and systemic circulation, and there is evidence that TNF-α expression is correlated with the severity of the condition.[7,8]

Additionally, TNF-α has been linked to several systemic symptoms of COPD, including the cachectic phenotype seen in the later stages of the disease, anorexia, increased resting energy use, and muscle catabolism.[9] Moreover, TNF-α has been connected to several systemic effects of COPD, such as increased resting energy consumption, anorexia, and muscular catabolism, as well as the cachectic phenotype observed in the disease's latter stages.

MATERIALS AND METHODS

Place of Study and Research Design– This prospective observational study was conducted over one year in the Department of Biochemistry at the Raipur Institute of Medical Sciences (RIMS), Raipur, Chhattisgarh, India.

Inclusion criteria

- Patients aged ≥40 years
- Clinically stable individuals diagnosed with COPD, as per GOLD 2024 guidelines
- Post-bronchodilator FEV_1/FVC ratio <0.70 on spirometry
- No acute exacerbation or respiratory infection in the preceding four weeks

Exclusion Criteria

- History of bronchial asthma or interstitial lung disease
- Active pulmonary tuberculosis
- Autoimmune disorders or systemic inflammatory diseases
- Malignancies
- Use of systemic corticosteroids or immune-suppressive drugs
- Recent infections (within 4 weeks before enrollment)

Sample Collection and Laboratory Analysis- Five milliliters of venous blood were extracted in an aseptic environment following an overnight fast. Before being analyzed, the serum was kept at -80°C after being separated by centrifugation for ten minutes at 3000 rpm. As directed by the manufacturer, serum TNF-α levels were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit. Each sample was examined twice, and the results were reported in picograms per milliliter (pg/ml).

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

Statistical Analysis- Data were analyzed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean±SD or median (IQR), and categorical variables as frequencies and percentages. Group differences in TNF-α across GOLD stages were assessed using one-way ANOVA or Kruskal–Wallis test. Correlations with spirometric parameters (e.g., FEV_1) were evaluated using Pearson or Spearman tests. A $p<0.05$ was considered 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

The majority of the study population (76.67%) was between the ages of 41 and 60, with 4.33% being under 40 and 19% being over 60. 52.68±7.52 years was the average age. At 95.33%, men made up the vast bulk of the sample, whereas women made up 4.67%. In terms of smoking history, 51% and 72.33% of participants, respectively, had never smoked or were not now smokers, whereas 49% of participants had previously smoked and 27.67% were current smokers. 38.67% of the participants had a body mass index (BMI) between 18.5 and 22.9 kg/m², 22% were between 23 and 24.9 kg/m², and 39.33% were over 24.9 kg/m², according to the BMI distribution. According to Table 1, the average BMI was 24.28±3.17 kg/m².

doi: 10.21276/SSR-IIJLS.2025.11.4.50

Table 1: Baseline demographic, clinical, and anthropometric characteristics

Baseline characteristics	Frequency (n=300)	Percentage (%)
Age group		
≤40 years	13	4.33
41-60 years	230	76.67
>60 years	57	19
Mean age	52.68±7.52 years	
Gender		
Male	286	95.33
Female	14	4.67
Previous smoker		
Yes	147	49
No	153	51
Current smoker		
Yes	83	27.67
No	217	72.33
BMI		
18.5-22.9 kg/m^2	116	38.67
23-24.9 kg/m^2	66	22
>24.9 kg.m^2	118	39.33
Mean BMI	24.28±3.17 kg/m^2	

Of the individuals in our study, 49% had diabetes mellitus, whereas 51% did not. A significantly higher percentage of patients (52.67%) had hypertension, while 47.33% had no history of the condition (Table 2).

Table 2: Distribution of comorbidities among study patients

Comorbidities	Frequency (n=300)	Percentage (%)
Diabetes		
Yes	147	49
No	153	51
Hypertension		
Yes	158	52.67
No	142	47.33

The 300 patients in our study had a very equal distribution of COPD severity throughout the four GOLD stages. According to Table 3, 26.33% of patients had Stage I (mild) COPD, 24.33% had Stage II (moderate), 25% had Stage III (severe), and 24.33% had Stage IV (extremely severe) (Table 3).

Table 3: Distribution of COPD patients by GOLD stage

GOLD Stage	Frequency (n=300)	Percentage (%)
Stage I	79	26.33
Stage II	73	24.33
Stage III	75	25
Stage IV	73	24.33

According to GOLD staging, the mean serum levels of tumor necrosis factor-alpha (TNF-α) grew steadily as the severity of COPD worsened. The average TNF-α levels in Stage I patients were 27.53±8.06 pg/ml, followed by Stage II patients at 29.86±8.25 pg/ml, Stage III patients at 31.11±8.26 pg/ml, and Stage IV patients at 33.10±8.78 pg/ml. Systemic inflammation and the severity of COPD were positively correlated, as evidenced by the statistically significant variations in TNF-α levels between the phases (p=0.03) (Table 4).

Table 4: Association between GOLD stage and TNF-α

GOLD Stage	TNF-α (Mean±SD)	p value
Stage I	27.53±8.06	0.03
Stage II	29.86±8.25	
Stage III	31.11±8.26	
Stage IV	33.10±8.78	

DISCUSSION

Biomarkers are any imaging measurements, laboratory-based test markers, or clinical traits that characterize disease activity. These markers are useful for assessing the progression of diseases and the effectiveness of treatments.[10]

By identifying those with COPD who are more prone to progress, more customized treatment could be provided, thereby slowing the disease's course. Current strategies for treating chronic illnesses, including COPD, medicine, pulmonary rehabilitation, and quitting smoking, may be enhanced by the use of biomarkers. Identifying those who are quick decliners in the early stages of the disease, forecasting disease progression in all severity groups of

COPD, and monitoring therapy responsiveness are just a few advantages of measuring biomarkers for COPD progression (and not only susceptibility to COPD).[11]

Other than FEV1, trustworthy biomarkers for COPD are still being sought after. It is still difficult to provide trustworthy data to validate biomarkers prior to clinical use. Important issues that require attention include the practical usefulness of biomarkers about alternative biomarkers, the reliability and accuracy of biomarkers for the clinical state of interest, and the evaluation of clinical utility and cost-effectiveness. The validation of biomarkers (biomarker qualification) for COPD may have clinical benefits for patient risk stratification and outcome indicators of efficacy and safety in drug development and other clinical studies.[12]

According to our research, serum TNF-α levels significantly and gradually rise from mild (Stage I) to extremely severe (Stage IV) COPD, indicating that systemic inflammation gets worse as the illness worsens. This is in line with the pathophysiological picture of COPD as a condition where extrapulmonary effects and airway remodeling are caused by both systemic and local inflammatory components.[13]

These results are in line with a meta-analysis by Gan et al. that found that patients with advanced COPD have higher levels of systemic inflammation, as seen by higher levels of circulating TNF-α and other markers, compared to those in mild or moderate stages.[14] Similarly, Selvarajah et al. discovered that blood TNF-α concentrations were greater in COPD patients with more frequent exacerbations and airway limitation, indicating that TNF-α might be a biomarker for the severity and progression of the illness.[15]

Nevertheless, some research has shown inconsistent findings. Keatings et al., for example, found that TNF-α was high in sputum but not always in serum samples, indicating that the inflammatory profile may vary between systemic circulation and local lung compartments.[16] These disparities could result from variations in patient demographics, sample kinds, or test sensitivity.

The majority of the participants in our study were middle-aged men with a substantial smoking history, which is in line with the risk profiles and demographics documented in the global epidemiology of COPD. As observed in other cohorts, the systemic burden of COPD is also reflected in the increased prevalence of comorbidities, including diabetes and hypertension.[17] These coexisting disorders could lead to elevated systemic inflammation, which could complicate the clear correlation between TNF-α and the severity of COPD.

The observational design and sample size restrict the ability to infer causality, even if our results support the importance of TNF-α as a marker of illness severity. To determine whether TNF-α levels can forecast the course of a disease or a patient's reaction to treatment, more long-term research is required. Furthermore, certain preclinical models indicate that investigating targeted anti-TNF therapies may open up new therapeutic options.

CONCLUSIONS

This prospective observational study found a substantial correlation between greater blood tumor necrosis factor-alpha (TNF-α) levels and the severity of chronic obstructive pulmonary disease (COPD). The consistent increase in TNF-α with rising GOLD stages demonstrates the significance of systemic inflammation in the pathogenesis and development of COPD. Measuring TNF-α could be a helpful biomarker for assessing the disease's severity and guiding targeted therapy strategies. More thorough research is required to examine TNF-α's potential as a therapeutic target and prognostic marker in the treatment of COPD.

ACKNOWLEDGMENTS

The authors express sincere gratitude to the Department of Biochemistry and the administration of DRIEMS Institute of Health Sciences and Hospital for their support in statistical analysis. We also thank the Raipur Institute of Medical Sciences for providing laboratory facilities and patient data, and all participating patients for their valuable cooperation.

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doi: 10.21276/SSR-IIJLS.2025.11.4.50

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