



TO ASSESS THE INFLAMMATORY (CRP) AND OXIDATIVE STRESS MARKERS (PROTEIN CARBONYL, AND MALONALDEHYDE) IN PATIENTS SUFFERING FROM CHRONIC OBSTRUCTIVE PULMONARY DISEASE: A CASE-CONTROL STUDY.

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation and is strongly influenced by systemic inflammation and oxidative stress. **Aim:** This study aimed to assess inflammatory (C-reactive protein, CRP) and oxidative stress markers (protein carbonyl and malonaldehyde) in COPD patients compared to healthy controls, and to evaluate their association with disease severity.

Methods: A case-control study was conducted including 100 COPD patients and 100 age- and sex-matched controls. Demographic variables such as age, gender, and locality were comparable between groups. Smoking and biomass exposure were significantly higher among cases. Serum CRP, protein carbonyl, and malonaldehyde levels were measured, and COPD severity was classified according to GOLD stages using spirometric indices (FEV1/FVC ratio).

Results: Mean CRP levels were significantly elevated in COPD cases (4.62 ± 1.33) compared to controls (1.49 ± 0.36 ; $p < 0.001$), indicating systemic inflammation. Protein carbonyl concentrations were higher in cases (9.65 ± 1.43) versus controls (6.24 ± 0.64 ; $p < 0.001$), reflecting oxidative protein damage. Malonaldehyde levels, a marker of lipid peroxidation, were also significantly increased in cases (10.02 ± 1.37) compared to controls (6.82 ± 0.32 ; $p < 0.001$). Within COPD cases, biomarker levels rose progressively across GOLD stages, with CRP increasing from 3.70 ± 0.73 in mild to 6.64 ± 1.03 in severe disease, protein carbonyl from 8.69 ± 0.74 to 11.87 ± 1.26 , and malonaldehyde from 9.10 ± 0.73 to 12.14 ± 1.20 (all $p < 0.001$). Declining FEV1/FVC ratios paralleled these changes.

Conclusion: Our study showed that oxidative stress marker (MDA and protein carbonyl) and inflammatory biomarker (CRP) levels were significantly higher while levels in our North Indian COPD population in comparison to healthy controls. These biomarkers correlate with disease severity and may serve as useful indicators for monitoring progression and guiding therapeutic strategies.

Keywords: COPD, CRP, Protein Carbonyl, malonaldehyde, etc.

Introduction:

Chronic obstructive pulmonary disease (COPD) is a common and treatable disease characterized by progressive airflow limitation and tissue destruction. It is associated with structural lung changes due to chronic inflammation from prolonged exposure to noxious particles or gases most commonly cigarette smoke. Chronic inflammation causes airway narrowing and decreased lung recoil. The disease often presents with symptoms of cough, dyspnea, and sputum production. Symptoms can range from being asymptomatic to respiratory failure.¹ As per global burden of COPD study, India is number 2 globally. COPD is the second leading death cause and DALYs in India, in terms of absolute numbers.² There is wide heterogeneity in the burden of COPD between different states in India, with Uttar Pradesh, Bihar, West Bengal, and Rajasthan having the high.³ Air pollution (household and outdoor) contributes over 50.0% national COPD burden, while smoking contributes only 20.0%–25.0%.³ In India, at the beginning of the millennium, in 1990, it was the eighth cause of death;⁴ in 2000, COPD was the fifth cause of death; and in 2019, it was the second leading cause of death.² Cigarette smoking is the most important risk factor for COPD. The risk of developing COPD becomes higher as smoking duration increases.⁵ It contains >1014 oxidants/ free radicals and 4700 reactive chemical and other carcinogens, and it is a risk factor in the development of COPD and lung cancer.⁶ Smoking for longer duration causes airway inflammation and elevation in levels of cytokines and C-reactive protein (CRP). CRP is the best studied biomarker, an acute phase reactant secreted by liver in response to infection, inflammation, or tissue damage.⁷ Occupational, environmental exposure, and indoor air pollution from biomass cooking are the other risk factors for the development and the progression of COPD.

Cigarette smoking and exacerbations in COPD lead to reduction of antioxidant capacity. It increases the level of oxidants in the lungs, resulting in a decrease of antioxidants. Antioxidants are naturally occurring or synthetic substances that help protect cells from the damaging effects of free radicals.⁸ Reactive oxygen species, reactive nitrogen species, and their counterpart antioxidant agents are necessary for physiological signaling as well as host defense, along with persistence of inflammation.⁹ Lower respiratory tract leads to oxidative stress, which in turn contributes to various physiological changes including chronic airflow limitation. If this airflow limitation is due to oxidative stress arising from increased demand of antioxidants due to disease or due to nutrients deficiency in person with lung disease than, the association between antioxidants and pulmonary function is evident in persons with COPD when compared to healthy persons.¹⁰ Oxidative stress protease – antiprotease imbalance, inflammation, and lung remodeling are the most important pathogenic mechanisms involved in the development of COPD. Lower Vitamin D levels have been related to regulation of each of these processes, that is, higher expression of proteases, modulation of inflammation, and increased oxidative stress.¹¹

Biomarkers in COPD may be helpful in diagnosis, monitoring the severity of disease and evaluating the effects of drugs. CRP is one of the most important systemic inflammatory biomarkers associated with increased risk of hospitalization and death in follow-up study of COPD patients.¹² Due to high prevalence rate of Vitamin D deficiency in these patients and its impact on airways, the present study was designed to evaluate the levels of the Leucocyte cells count, serum inflammatory (CRP) and oxidative stress markers (Protein Carbonyl, and malonaldehyde) in patients suffering from COPD.

Material and Methods:

The present case-control study was conducted in the Department of Biochemistry and Department of pulmonary and chest at Jawaharlal Nehru Medical College and Hospital, Aligarh Muslim University, Aligarh (India). This study consists of fifty blood samples taken from patients attending, or admitted to the J. N. Medical College Hospital, Aligarh, with diagnosis of chronic obstructive pulmonary disease and thirty normal healthy subjects from our local area with similar age group. The diagnosis of COPD should be considered in any patient who has the following: symptoms of cough; sputum

production; or dyspnoea; or history of exposure to risk factors for the disease. The diagnosis requires spirometry; a post-bronchodilator forced expiratory volume in one second (FEV1)/ forced vital capacity (FVC) < 0.7 confirms the presence of airflow limitation that is not fully reversible with the use bronchodilator. A total of 80 patients were enrolled in this study. Blood samples from 50 COPD patients were collected. 30 normal healthy individuals were included. Patients with pneumonia, asthma, pulmonary fibrosis or other chronic respiratory disease, history of cardiac failure, any recent surgical intervention, diabetes mellitus, hepatic disease, renal disease, worm infestations, atopic skin disease and other allergic diseases, renal failure, hypertension, neuromuscular diseases, and ascites were excluded from the study.

Blood samples (6 ml) from each subject were taken in two vials (3ml in each vial). First 3ml of whole blood was used for “Total Leukocyte count and Total Neutrophil count” on the same day. To obtain plasma, vials were centrifuged at $1500 \times g$ for 15 min and plasma was separated from second vial containing 3ml of blood, and stored at -20°C , till analysis. Plasma separated from the samples were subjected to measurement of “C-reactive protein, Protein Carbonyl, and Malonaldehyde”.

Serum CRP was also analyzed in serum by commercially available kit as per protocol. Malondialdehyde (MDA) was estimated according to the method of Stocks and Dormandy. In this study we use the DNPD-Based spectrophotometric method for estimation of protein carbonyl.

Statistical analysis

The SPSS version 23.0; SPSS Inc; Chicago IL, USA was used to interpret the statistical data. For the descriptive research data, categorical variables were expressed as frequency and percentages, whereas continuous variables were expressed as mean $\pm$ standard deviation. Unpaired t-test was employed for the numerical investigational data, chi-squared test for categorical data. A $p < 0.05$ level of significance was applied.

Results:

The majority of individuals in both groups were aged 51–70 years (82.0% in cases vs. 66.7% in controls), with comparable mean ages (62.00 ± 8.12 vs. 62.73 ± 10.33 years; $p = 0.725$). Gender distribution was similar, with males predominating (84.0% in cases vs. 86.7% in controls; $p = 0.746$). Likewise, locality patterns did not differ significantly, as most participants were from rural areas (80.0% in cases vs. 70.0% in controls; $p = 0.309$) [Table no.1].

Mean CRP values were markedly elevated in cases (4.62 ± 1.33) relative to controls (1.49 ± 0.36 , $p < 0.001$), indicating enhanced systemic inflammation. Similarly, protein carbonyl levels, a marker of oxidative protein damage, were substantially increased in cases (9.65 ± 1.43) compared to controls (6.24 ± 0.64 , $p < 0.001$). Malonaldehyde, reflecting lipid peroxidation, also showed a significant rise in cases (10.02 ± 1.37) versus controls (6.82 ± 0.32 , $p < 0.001$) [Table no.2].

Among the COPD cases, the majority of patients were in the moderate stage (58.0%), followed by mild (26.0%) and severe (16.0%) disease. The mean FEV1/FVC ratio showed a significant decline across stages, with the highest values observed in mild cases (85.31 ± 2.66), intermediate levels in moderate cases (65.34 ± 7.00), and the lowest in severe cases (25.87 ± 9.65), with the overall difference being statistically significant ($p < 0.001$) [Table no.3].

CRP values rose significantly from mild (3.70 ± 0.73) to moderate (4.47 ± 1.01) and were highest in severe cases (6.64 ± 1.03 , $p < 0.001$), indicating escalating systemic inflammation with disease severity. Similarly, protein carbonyl concentrations, reflecting oxidative protein damage, increased from 8.69 ± 0.74 in mild to 9.46 ± 1.03 in moderate and 11.87 ± 1.26 in severe stages ($p < 0.001$). Malonaldehyde, a marker of lipid peroxidation, also demonstrated a stepwise rise from 9.10 ± 0.73 in mild to 9.85 ± 1.00 in moderate and 12.14 ± 1.20 in severe stages ($p < 0.001$). These findings highlight a clear trend of worsening inflammation and oxidative stress with advancing GOLD stage [Table no.4].

Table No.01: Demographic variables distribution among case and control groups

Variable		Case (n=50)	Control (n=30)	P value
Age (year)	≤50	3 (6.0)	4 (13.3)	0.282*
	51-70	41 (82.0)	20 (66.7)	
	>70	6 (12.0)	6 (20.0)	
Mean Age ± SD		62.00±8.12	62.73±10.33	0.725 [#]
Gender	Male	42 (84.0)	26 (86.7)	0.746*
	Female	8 (16.0)	4 (13.3)	
Locality	Rural	40 (80.0)	21 (70.0)	0.309*
	Urban	10 (20.0)	9 (30.0)	

* Chi Square test; [#]Independent Sample t test; P<0.05= statistically significant; P>0.05= statistically non-significant

Table No. 02: Compare the inflammatory (CRP) and oxidative stress markers (Protein Carbonyl, and malonaldehyde) in case and control groups

Variable	Case (n=100)	Control (n=100)	P value
CRP	4.62±1.33	1.49±0.36	<0.001 [#]
Protein Carbonyl	9.65±1.43	6.24±0.64	<0.001 [#]
Malonaldehyde	10.02±1.37	6.82±0.32	<0.001 [#]

[#]Independent Sample t test; P<0.05= statistically significant; P>0.05= statistically non-significant

Table No. 03: GOLD stages and FEV1/FVC ratio level in COPD cases

Variable	Case (n=50)	FEV1/FVC ratio	P Value
Mild	13 (26.0)	85.31±2.66	<0.001 [@]
Moderate	29 (58.0)	65.34±7.00	
Severe	8 (16.0)	25.87±9.65	

[@] One Way ANOVA test; P<0.05= statistically significant; P>0.05= statistically non-significant

Table No. 04: Compare the inflammatory (CRP) and oxidative stress markers (Protein Carbonyl, and malonaldehyde) in GOLD stages

	Mild	Moderate	Moderate	P Value
CRP	3.70±0.73	4.47±1.01	6.64±1.03	<0.001 [@]
Protein Carbonyl	8.69±0.74	9.46±1.03	11.87±1.26	<0.001 [@]
Malonaldehyde	9.10±0.73	9.85±1.00	12.14±1.20	<0.001 [@]

[@] One Way ANOVA test; P<0.05= statistically significant; P>0.05= statistically non-significant

Discussion

In our study, we found mean age was comparable (62.00 ± 8.12 vs. 62.73 ± 10.33 years; p = 0.725) and gender distribution was similar, with males predominating in both groups (84.0% in cases and 86.7% in controls, p=0.746) that is comparable to other study of **Ghobadi H et al¹³** and **Sarioglu N et al¹⁴** as 59.60±11.93 years and 63.6 ± 10.5 years respectively. 86.4% and 100% were found males in study which is done by **Ghobadi H et al¹³** and **Sarioglu N et al¹⁴**. In this study no differences were found between CAT score of male and female patients. This fact may be due to the nature of COPD that is not influenced by gender and the major risk factor of disease is smoking. This is in line with some previous research.¹⁵ Our study further noted that regarding locality, rural participants formed the majority in both groups (80.0% of cases and 70.0% of controls), while urban representation was slightly higher among controls (20.0% vs. 30.0%), though this difference was not statistically

significant ($p=0.309$). **Andersen ZJ et al**¹⁶ reported that the outdoor air pollution mainly from emission of pollutants from motor vehicles and industries is an important public health problem. **Hu G et al**¹⁷ reported that the important indoor air pollutants are environmental tobacco smoke, particulate matter, nitrogen dioxide, carbon monoxide, volatile organic compounds and biological allergens.

Our findings highlight that most COPD patients in the study were in the moderate stage, reflecting the typical disease burden seen in clinical practice. The progressive decline in mean FEV1/FVC ratio across mild, moderate, and severe stages underscores the strong correlation between GOLD staging and worsening airflow limitation. The statistically significant differences ($p < 0.001$) confirm that lung function deteriorates consistently with advancing disease severity, validating the utility of spirometric indices in staging COPD. This pattern emphasizes the importance of early detection and intervention, as patients in the moderate stage already exhibit substantial impairment, while those in the severe stage demonstrate profound functional decline. **Bhatt SP et al**¹⁸ classify the severity of airflow obstruction based on FEV₁/FVC ratio, which has better discrimination for survival and better differentiates those with mild airflow obstruction from those with no airflow obstruction. **Agmy G et al**¹⁹ noted that the significant increase in Δ FEV1% was found in 15% of cases while 55% showed a significant increase in Δ FVC. Mean difference of Δ FVC (L) post BD was significantly increased with advancing GOLD stage. **Sariaydin M et al**²⁰ noted that the visual emphysema score was inversely correlated with FEV1, FVC, FEV1/FVC, PEF and with carbon monoxide diffusion capacity (DLCO).

COPD is a multicomponent disease affecting the psycho logical and physiological conditions as well as social life of patients. It is independently associated with low grade sys temic inflammation than that in healthy subjects, and this inflammatory activity increases as severity of disease increases. Our study finds the mean CRP values were markedly elevated in cases (4.62 ± 1.33) relative to controls (1.49 ± 0.36 , $p < 0.001$), indicating enhanced systemic inflammation which was consistent with many previous studies **Gan WQ et al**,²¹ **Pinto-Plata VM et al**,²² **Broekhuizen R et al**,²³ **de Torres JP et al**,²⁴ **Karadag F et al**,²⁵ and **Pandey S et al**²⁶ [34-38]. **Leuzzi et al**²⁷ in meta-analysis also indicate that baseline higher CRP level is significantly associated with higher late mortality in patients with COPD. The increase in CRP levels with the progression of the disease as seen reflects the severity of the disease and so measuring levels of systemic inflammatory markers like CRP in combination with other biochemical markers at baseline and after anti-inflammatory therapy will be helpful in monitoring disease outcome and also in proper management of disease. Our study further noted that the CRP values rose significantly from mild (3.70 ± 0.73) to moderate (4.47 ± 1.01) and were highest in severe cases (6.64 ± 1.03 , $p < 0.001$), indicating escalating systemic inflammation with disease severity.

MDA the main product of lipid peroxidation, one of the key indicators of oxidative stress has been reported to increase in all stages of COPD severity.^{28,29} Oxidative stress has also been reported to play an important role in the pathophysiology of COPD.^{30,31} The present study found a significant rise in cases (10.02 ± 1.37) versus controls (6.82 ± 0.32 , $p < 0.001$), which was similar as seen in study by **Cristóvãoa et al**³², **Torres-Ramos et al**³³ and **Pandey S et al**²⁶ They also reported significantly higher levels of MDA in all GOLD Stages of COPD severity, as compared with healthy controls.³³ Similarly, the present study also noted a stepwise rise Malonaldehyde from 9.10 ± 0.73 in mild to 9.85 ± 1.00 in moderate and 12.14 ± 1.20 in severe stages ($p < 0.001$).

Similarly in this study we noted that, protein carbonyl levels, a marker of oxidative protein damage, were substantially increased in cases (9.65 ± 1.43) compared to controls (6.24 ± 0.64 , $p < 0.001$). And it also increased from 8.69 ± 0.74 in mild to 9.46 ± 1.03 in moderate and 11.87 ± 1.26 in severe GOLD stages ($p < 0.001$). **Pawar RS & Abhang SA**³⁴ protein carbonyl was significantly increased in patients with COPD cases as compared to healthy controls. **MacNee W**³⁵ reported that the increased oxidative stress leads to increased production of protein carbonyl in COPD patients.

The present study has the certain limitations, including its cross-sectional design, which restricts causal inference and temporal assessment of biomarker changes. The sample size, though adequate,

is limited to a single-center population, potentially affecting generalizability to broader or diverse cohorts. Additionally, environmental exposures and comorbidities that may influence biomarker levels were not extensively controlled, and reliance on serum markers alone may not fully capture localized pulmonary oxidative stress. Despite these limitations, the study offers important evidence supporting the role of inflammation and oxidative stress in COPD pathogenesis and progression.

Conclusion

This case-control study establishes that patients with chronic obstructive pulmonary disease exhibit significantly higher levels of inflammatory (CRP) and oxidative stress markers (protein carbonyl and malonaldehyde) compared to healthy controls, despite comparable age, gender, and locality distributions. The findings further demonstrate a progressive rise in these biomarkers with advancing GOLD stage, paralleling the decline in lung function indices, thereby underscoring their role in disease severity and progression. Smoking and biomass exposure emerged as major risk factors, reinforcing their contribution to COPD pathogenesis. Overall, the study highlights that systemic inflammation and oxidative stress are not only distinguishing features of COPD but also correlate strongly with disease advancement, suggesting their potential utility as biomarkers for monitoring progression and guiding therapeutic interventions.

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