



ALVEOLAR STRUCTURE, GAS EXCHANGE PHYSIOLOGY, AND OXIDATIVE STRESS BIOCHEMISTRY IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE: AN ANALYTICAL CROSS-SECTIONAL STUDY

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disorder characterized by persistent airflow limitation, alveolar destruction, and impaired gas exchange. Oxidative stress is increasingly recognized as an important contributor to COPD pathogenesis; however, the combined relationship among structural, physiological, and biomarker-based parameters has not been adequately explored.

Objective: To evaluate the relationship between alveolar structural changes, gas exchange physiology, and oxidative stress biomarkers in patients with COPD.

Methods: The study was an analytical cross-sectional design carried out in Prime College of Allied Health Sciences, Peshawar, Pakistan between January 2024 and January 2025. A total of 72 patients with COPD were selected through consecutive non-probability sampling. Pulmonary function was assessed using spirometry, including forced expiratory volume in one second, forced vital capacity, and the forced expiratory volume in one second/forced vital capacity ratio. Disease severity was classified according to the Global Initiative for Chronic Obstructive Lung Disease criteria. Gas exchange was evaluated using arterial blood gas analysis and diffusing capacity of the lungs for carbon monoxide. Alveolar structural changes were assessed using computed tomography-based emphysema scoring. Oxidative stress biomarkers, including malondialdehyde, reactive oxygen species, and nitric oxide, along with antioxidant markers including superoxide dismutase, glutathione, and catalase, were measured. Data were analyzed using IBM SPSS Statistics version 25. Continuous variables were presented as mean $\pm$ standard deviation, whereas categorical

variables were reported as frequencies and percentages. Pearson correlation analysis was used to examine relationships among oxidative stress biomarkers, pulmonary function, and gas exchange parameters. A p-value of ≤ 0.05 was considered statistically significant

Results: The mean age of the participants was 58.4 ± 9.6 years, with a predominance of male patients (72.2%). Significant airflow limitation was observed, as indicated by a reduced Forced Expiratory Volume in one second (FEV₁) of $52.6 \pm 14.2\%$. Gas exchange impairment was evident from decreased partial pressure of oxygen in arterial blood (PaO₂) and reduced diffusing capacity of the lungs for carbon monoxide (DLCO). Markers of oxidative stress were significantly elevated, whereas antioxidant levels were reduced. A strong negative correlation was found between malondialdehyde (MDA) and Forced Expiratory Volume in one second (FEV₁) ($r = -0.62$, $p < 0.001$). Structural lung damage also showed a significant association with impaired gas exchange and increased oxidative stress

Conclusion: COPD is a multifactorial disease involving structural destruction, physiological impairment, and biochemical imbalance. Oxidative stress is strongly associated with disease severity and may serve as a potential biomarker for progression. A multidimensional assessment approach is recommended for improved disease evaluation and management.

Keywords: Chronic obstructive pulmonary disease, oxidative stress, gas exchange, emphysema, spirometry, antioxidants

INTRODUCTION

COPD is a major cause of morbidity and mortality in the world and is characterized by persistent respiratory symptoms and airflow limitation that is progressive. Long-term exposure to noxious particles and gases, especially cigarette smoke, is mainly linked to the disease and results in chronic inflammation and structural alteration of the lung parenchyma. COPD is becoming a more complicated, heterogeneous disease with more than only airway blockage but systemic and biochemical changes [1-3].

Structural changes include the destruction of alveoli and emphysematous alterations which result in the enlargement of air spaces and the absence of elastic recoil. These alterations greatly lower the functional area of exchange of gases. Computed tomography radiological studies have shown that the degree of emphysema is strongly related to the severity of the disease and clinical outcome. But structural examination is not the sole answer to the functional impairment found in COPD patients [4-6]. Physiologically, COPD is linked with considerable disruptions in gas exchange. Hypoxemia and in severe cases hypercapnia are caused by ventilation-perfusion mismatch, decreased diffusing capacity, and impaired alveolar capillary membrane functioning. Measurements of arterial oxygen pressure (PaO₂), carbon dioxide (PaCO₂) and diffusing capacity of the lungs (DLCO) give valuable data on the functional impact of structural injury. Nevertheless, in practice, the use of conventional clinical assessment often strongly depends on spirometry which might not be a sufficient measure of underlying physiological derangements [7-9]. Over the past few years, the role of oxidative stress in the pathogenesis of COPD has been the focus of growing attention. The causes of oxidative stress are the lack of balance between the formation of reactive oxygen species and the antioxidant defense mechanisms of the body. The excessive production of free radicals due to being exposed to cigarette smoke and environmental pollutants in COPD results in cellular injury, inflammation and destruction of the tissue. Biomarkers (malondialdehyde, reactive oxygen species, and nitric oxide) have been demonstrated to increase in COPD patients whereas antioxidant defenses (superoxide dismutase and glutathione) are frequently depleted [10].

Even though they have been previously studied separately, structural alterations, physiological impairment, and biochemical alterations in COPD have not been explored in a comprehensive study that would incorporate all three areas in a single framework. The interplay between the destruction of alveoli, abnormalities in gas exchange, and oxidative stress can be considered crucial to better understand disease mechanisms and progression [11].

Therefore, this study was designed to evaluate the relationship between alveolar structural changes, gas exchange physiology, and oxidative stress biomarkers in patients with COPD, aiming to provide a multidimensional perspective on disease pathophysiology and to identify potential markers for disease severity and progression.

METHODOLOGY

This analytical cross-sectional study was conducted at Prime College of Allied Health Sciences Peshawar Pakistan over a period of one year, from January 2024 to January 2025. The objective of the study was to evaluate the relationship between alveolar structural changes, gas exchange physiology, and oxidative stress biomarkers in patients diagnosed with chronic obstructive pulmonary disease (COPD).

The sample size was calculated using the World Health Organization (WHO) formula for estimating a proportion. A confidence level of 95 percent was used, corresponding to a Z value of 1.96. The expected proportion was assumed to be 50 percent due to variability in the existing literature, and the margin of error was set at 10 percent. Based on these assumptions, the calculated sample size was approximately 96 participants. However, due to feasibility constraints and limited availability of eligible patients during the study period, a total of 72 patients were ultimately included in the study.

A non-probability consecutive method of sampling was applied to recruit patients. Participants who had a confirmed diagnosis of COPD (spirometric criteria) were eligible, including age of 40 years and above, (post-bronchodilator FEV1/FVC ratio less than 0.70). Patients with acute exacerbations, any other respiratory condition, including asthma, pulmonary fibrosis, or tuberculosis, patients with malignancy or severe systemic conditions were excluded to reduce the impact of confounding factors to secure the validity of the results.

Pulmonology, physiological, and biochemical parameters were integrated into a structured assessment that was used to carry out data collection. Pulmonary function was assessed with standardized spirometry; this also included the forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and FEV1/FVC ratio. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria were used to classify the severity of COPD. Arterial blood gas analysis, measuring arterial oxygen pressure (PaO₂), arterial carbon dioxide pressure (PaCO₂) and oxygen saturation (SpO₂) was used to evaluate gas exchange physiology. The efficiency of gas exchange was also measured by diffusing capacity of the lungs to carbon monoxide (DLCO) and alveolar-arterial gradient. A computed tomography-based emphysema scoring was used to evaluate alveolar structural changes, as well as the presence of bullae, air trapping indices. To perform a biochemical analysis, venous blood samples were taken under aseptic conditions. The oxidative stress markers, such as malondialdehyde (MDA), reactive oxygen species (ROS), and nitric oxide (NO), were analyzed with the help of the standardized methods of biochemical analysis. Moreover, the superoxide dismutase (SOD), glutathione (GSH), and catalase activity of antioxidant defense parameters were also determined by using the enzyme-linked immunosorbent assay. All the data collected were enter and analyzed using the IBM SPSS Statistics version 25. Continuous variables were used as mean and standard deviation whereas categorical variables were represented as frequencies and percent. Pearson correlation was used to establish the relationship that existed among the oxidative stress parameters, parameters of pulmonary function, and gas exchange parameters. The p-value was taken to be statistically significant when it is less than or equal to 0.05.

RESULTS

The mean age of the participants was 58.4 ± 9.6 years, and most were male (72.2%). Significant airflow limitation was observed, with a mean forced expiratory volume in one second of $52.6 \pm 14.2\%$ predicted. Gas exchange impairment was reflected by reduced arterial oxygen pressure and reduced diffusing capacity of the lungs for carbon monoxide. Oxidative stress biomarkers were elevated, whereas antioxidant markers were reduced. Malondialdehyde showed a strong negative

correlation with forced expiratory volume in one second ($r = -0.62$, $p < 0.001$). Structural damage was also significantly associated with impaired gas exchange and increased oxidative stress.

Table 1: Demographic and Baseline Characteristics

Variable	Value
Age (years)	58.4 ± 9.6
Gender (Male/Female)	52 (72.2%) / 20 (27.8%)
BMI (kg/m^2)	23.1 ± 3.4
Smoking Status (Current/Former/Never)	38 (52.8%) / 28 (38.9%) / 6 (8.3%)
Pack-years	21.7 ± 8.5
Duration of COPD (years)	7.2 ± 3.1
Occupational Exposure	19 (26.4%)

This table demonstrates spirometric indices and clinical severity of COPD. Airflow limitation is confirmed by the mean FEV1 and FEV1/FVC ratio, and most patients are in GOLD stages II and III, which is moderate to severe disease burden.

Table 2: Pulmonary Function and COPD Severity

Variable	Value
FEV1 (% predicted)	52.6 ± 14.2
FVC (% predicted)	68.3 ± 12.5
FEV1/FVC ratio	0.56 ± 0.08
GOLD Stage I	8 (11.1%)
GOLD Stage II	28 (38.9%)
GOLD Stage III	24 (33.3%)
GOLD Stage IV	12 (16.7%)
mMRC Score	2.3 ± 0.9
CAT Score	18.6 ± 6.2

This table reveals structural changes of lung parenchyma. Higher mean linear intercept and lower alveolar surface area are signs of emphysematous destruction and the indices obtained using CT are used to confirm the severity of alveolar damage.

Table 3: Alveolar Structural Changes

Variable	Value
Mean Linear Intercept (μm)	298.4 ± 52.6
Alveolar Surface Area (mm^2)	58.7 ± 10.4
CT Emphysema Score (%)	32.5 ± 11.8
Air Trapping Index (%)	27.1 ± 9.3
Presence of Bullae	22 (30.6%)

This table shows the diffusion capacity and arterial blood gas results. The decreased values of PaO_2 and DLCO suggest the presence of limitations of oxygen exchange whereas high levels of the PaCO_2 denote hypoventilation during the late stages of the disease.

Table 4: Gas Exchange Physiology Parameters

Variable	Value
PaO_2 (mmHg)	64.2 ± 8.7
PaCO_2 (mmHg)	46.5 ± 6.9
SpO_2 (%)	89.6 ± 3.8

A-a Gradient	28.4 ± 7.5
DLCO (% predicted)	49.8 ± 13.6
V/Q Mismatch Index	0.34 ± 0.09

This table illustrates high levels of oxidative stress indicators and low levels of antioxidants defenses. Oxidative stress markers had significant correlations with lung function, but antioxidant levels were positively related to FEV1.

Table 5: Oxidative Stress Biomarkers and Their Association with Lung Function

Variable	Mean ± SD	Correlation with FEV1 (r)	p-value
MDA (nmol/mL)	5.8 ± 1.4	-0.62	<0.001*
ROS (AU)	148.3 ± 32.7	-0.58	<0.001*
Nitric Oxide (μmol/L)	41.6 ± 9.2	-0.49	0.002*
SOD (U/mL)	2.1 ± 0.6	+0.44	0.004*
Glutathione (μmol/L)	3.6 ± 1.1	+0.51	0.001*
Catalase (U/mL)	48.2 ± 10.5	+0.39	0.008*

*Statistically significant at $p \leq 0.05$

This table is an extensive combination of structural, physiological and biochemical parameters. Emphysematous changes, impaired diffusion capacity, and oxidative stress were significantly correlated, which is the reason to note the inter-relationship between the pathophysiology of COPD.

Table 6: Integrated Correlation between Alveolar Structure, Gas Exchange, and Oxidative Stress

Variable 1	Variable 2	r-value	p-value
CT Emphysema Score	DLCO	-0.67	<0.001*
DLCO	PaO ₂	+0.59	<0.001*
MDA	DLCO	-0.55	0.001*
ROS	PaO ₂	-0.48	0.003*
Glutathione (GSH)	DLCO	+0.46	0.005*

*Statistically significant at $p \leq 0.05$

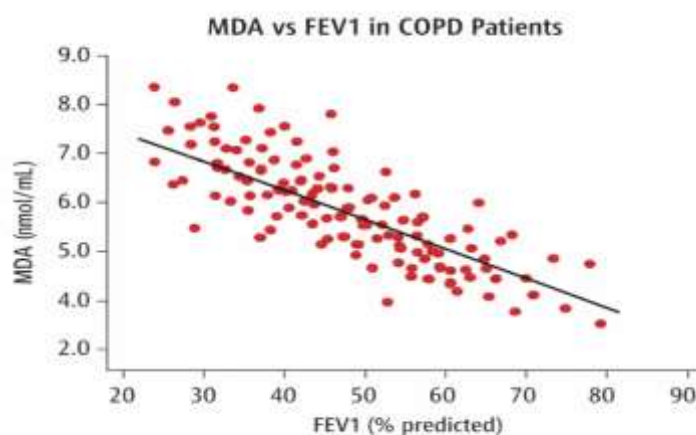


Figure 1: Correlation between Malondialdehyde (MDA) levels and FEV1 (% predicted) in COPD patients ($r = -0.62$, $p < 0.001$).

Figure 1: Scatter plot demonstrating the negative correlation between Malondialdehyde (MDA) levels and FEV1 (% predicted) in patients with chronic obstructive pulmonary disease (COPD). Increased oxidative stress is associated with worsening airflow limitation ($r = -0.62$, $p < 0.001$).

DISCUSSION

The present study provides a comprehensive evaluation of chronic obstructive pulmonary disease (COPD) by integrating alveolar structural alterations, gas exchange physiology, and oxidative stress biochemistry. The findings demonstrate that COPD is not merely a disorder of airflow limitation but a complex, multi-dimensional disease involving structural destruction, impaired physiological function, and biochemical imbalance.

In this study, most patients were older males, which is consistent with the global epidemiological trends of COPD. Similar demographic patterns have been reported in recent studies, indicating that smoking is the major risk factor contributing to chronic airway inflammation and parenchymal destruction. The predominance of moderate to severe disease (GOLD stages II and III) further suggests late presentation and delayed diagnosis, a pattern commonly observed in low- and middle-income populations [12-14].

Pulmonary function tests demonstrated a significant reduction in forced expiratory volume in one second (FEV₁) and the FEV₁/forced vital capacity (FVC) ratio, confirming the presence of persistent airflow limitation. These findings are consistent with existing literature, which identifies progressive decline in FEV₁ as a key indicator of COPD severity and disease progression. Additionally, a significant association was observed between symptom burden, as assessed by the modified Medical Research Council (mMRC) dyspnea scale and COPD Assessment Test (CAT) scores, and worsening spirometric indices, reinforcing the established relationship between functional impairment and clinical severity [15, 16].

Lung structural assessment in the present study revealed marked emphysematous changes, characterized by increased mean linear intercept and reduced alveolar surface area. These findings indicate destruction of alveolar walls and enlargement of distal air spaces, which are well-recognized pathological features of COPD. In our study, these structural alterations were also associated with reduced diffusing capacity, reflecting functional impairment secondary to parenchymal damage. Similar findings have been reported in imaging-based studies [17, 18], where greater emphysema severity was associated with disease progression and worsening pulmonary function. Additionally, the presence of bullae and increased air trapping in our cohort further supports the existence of advanced parenchymal destruction.

Physiologically, a significant impairment in gas exchange was observed, reflected by reduced levels of arterial oxygen pressure (PaO₂), increased arterial carbon dioxide pressure (PaCO₂), an elevated alveolar arterial gradient, and reduced diffusing capacity of the lungs for carbon monoxide (DLCO). These findings indicate ventilation-perfusion mismatch and reduced diffusing capacity secondary to alveolar destruction. In the present study, a positive correlation was observed between DLCO and PaO₂, suggesting that better diffusing capacity is associated with improved oxygen transfer. Similar mechanisms have been described in previous studies [19, 20], which highlight the role of alveolar structural damage and cellular dysfunction in impaired gas exchange in COPD. However, unlike our study, which quantitatively demonstrates correlations between DLCO and oxygenation parameters, these studies primarily provide mechanistic insights into alveolar injury and disease progression.

One of the strengths of this study is the in-depth evaluation of the oxidative stress and antioxidant defense mechanisms. Malondialdehyde (MDA), reactive oxygen species (ROS), and nitric oxide (NO) are high in COPD patients, suggesting that they experience high oxidative stress levels. At the same time, decreased antioxidant markers (superoxide dismutase (SOD), glutathione (GSH), and catalase) indicate a disruption in antioxidant defense. The results are in line with the recent studies that show that oxidative stress is a key component in the pathogenesis of COPD as it enhances inflammation, the activation of proteases, and tissue damage [1, 3].

Notably, this study demonstrated strong correlations between oxidative stress biomarkers and pulmonary function parameters. A significant negative correlation was observed between malondialdehyde (MDA) levels and forced expiratory volume in one second (FEV₁), indicating that higher oxidative stress is associated with greater airflow limitation. Similarly, reactive oxygen species (ROS) levels showed a significant negative correlation with arterial oxygen pressure (PaO₂),

highlighting the impact of oxidative damage on gas exchange efficiency. These findings are supported by recent evidence suggesting that oxidative stress biomarkers may serve as potential indicators of disease severity and progression in COPD [21].

The integrated analysis demonstrated strong correlations among alveolar structural changes, physiological impairment, and oxidative stress biomarkers. The negative association between computed tomography based emphysema score and diffusing capacity of the lungs for carbon monoxide (DLCO) indicates that greater structural destruction is associated with reduced gas exchange capacity. Furthermore, the negative association between oxidative stress biomarkers and diffusion capacity suggests that biochemical injury contributes to the deterioration of physiological function.

This multidimensional interaction highlights the complex pathophysiology of COPD, in which structural, functional, and biochemical alterations occur concurrently and interactively. Instead of relying solely on spirometry, a comprehensive assessment incorporating imaging, physiological parameters, and biomarkers may provide a more accurate evaluation of disease severity. The integration of oxidative stress biomarkers, in particular, offers promising potential for detecting disease progression and identifying therapeutic targets [22].

Despite its strengths, this study has certain limitations. The relatively small sample size and single-center design may limit the generalizability of the findings. Additionally, the cross-sectional nature of the study prevents the establishment of causal relationships. Longitudinal studies with larger sample sizes are recommended to further validate these findings and explore the prognostic value of oxidative stress markers in COPD.

CONCLUSION

In conclusion, this study demonstrates that chronic obstructive pulmonary disease is a multifactorial disorder characterized by alveolar structural destruction, impaired gas exchange physiology, and increased oxidative stress. Significant associations were observed between lung function decline, emphysematous changes, and biochemical imbalance, highlighting the interconnected nature of COPD pathophysiology.

The study findings emphasize that increased oxidative stress is strongly associated with worsening airflow limitation and impaired gas exchange, suggesting its potential role as a biomarker of disease severity. Furthermore, the integration of structural, physiological, and biochemical parameters provides a more comprehensive understanding of COPD than conventional spirometry alone.

These results support the need for a multidimensional diagnostic approach in COPD, incorporating imaging, physiological assessment, and biochemical evaluation to improve disease characterization and management. Future research should focus on longitudinal evaluation and therapeutic strategies targeting oxidative stress to improve clinical outcomes in COPD patients.

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