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COMPARATIVE ANALYSIS OF SERUM CRP, TOTAL CHOLESTEROL, MAGNESIUM, AND URIC ACID LEVELS IN SMOKERS AND NON-SMOKERS WITH COPD: A CROSS-SECTIONAL STUDY

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is a progressive respiratory disorder characterized by airflow limitation and systemic inflammation. Smoking is a major risk factor, but the impact of inflammatory, metabolic, and oxidative stress markers on disease progression in smokers versus non-smokers with COPD remains less explored. This study aimed to assess these biomarkers and their correlation with lung function parameters in both groups.

Materials and Methods: This cross-sectional study included 132 COPD patients (66 smokers and 66 non-smokers) from a tertiary care center. Demographic details, clinical parameters, and spirometric values were recorded. Biomarkers such as C-reactive protein (CRP), total cholesterol, serum magnesium, and uric acid levels were measured. Pearson correlation analysis was performed to assess associations between biomarkers and lung function parameters.

Results: Smokers exhibited significantly lower FEV1 (47.5 ± 11.3% vs. 52.8 ± 10.9%; p = 0.041), FEV1/FVC ratios (63.4 ± 6.5% vs. 67.9 ± 5.8%; p = 0.011), and SpO_2 levels (92.1 ± 3.6% vs. 94.8 ± 2.7%; p = 0.002). Exacerbation frequency was higher in smokers (1.9 ± 1.1 vs. 1.3 ± 0.8; p = 0.017). Biomarker analysis revealed that CRP (r = -0.42; p = 0.001), total cholesterol (r = -0.30; p = 0.007), and uric acid (r = -0.45; p = 0.001) correlated negatively with FEV1, while serum magnesium positively correlated with FEV1 (r = 0.37; p = 0.001). Similar trends were observed with FVC and FEV1/FVC ratios.

Conclusion: Smokers with COPD exhibited greater lung function impairment, higher exacerbation rates, and elevated inflammatory and metabolic markers compared to non-smokers. Elevated CRP, cholesterol, and uric acid levels correlated with worse lung function, while higher serum magnesium levels were protective. These findings emphasize the need for aggressive smoking cessation strategies and targeted biomarker monitoring in COPD management.

Keywords: COPD, Smokers, Inflammatory Markers, Oxidative Stress, Lung Function, C-Reactive Protein, Serum Magnesium.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive respiratory disorder characterized by persistent airflow limitation and chronic inflammation. It is a significant cause of morbidity and mortality, with the World Health Organization (WHO) estimating that COPD accounted for 3.23 million deaths globally in 2019, making it the third leading cause of death worldwide.[1] In India, COPD is particularly prevalent, contributing to 13.2% of all deaths, with a higher burden observed in populations

exposed to tobacco smoke, indoor air pollution, and occupational hazards.[2]

Smoking is one of the most critical risk factors for COPD, contributing to accelerated lung function decline, increased inflammatory response, and systemic complications.[3] It has been shown that up to 50% of smokers may develop COPD during their lifetime, and smokers with COPD experience more frequent exacerbations and faster disease progression than non-smokers.[4] Understanding the biochemical profile differences between smokers and non-smokers with COPD is crucial for targeted disease management.

C-reactive protein (CRP) is a widely recognized inflammatory marker elevated in COPD patients, particularly in smokers. Elevated CRP levels have been associated with increased disease severity, frequent exacerbations, and higher mortality. It is being observed that COPD patients with CRP levels exceeding 3 mg/L had a two times higher risk of hospitalization due to exacerbations.[5] Smokers with COPD tend to exhibit significantly higher CRP levels than their non-smoking counterparts, suggesting that smoking amplifies systemic inflammation.[6]

Total cholesterol levels may also play a role in COPD pathophysiology, especially in smokers who are prone to lipid metabolism disturbances. Research indicates that COPD patients with elevated cholesterol levels have a higher risk of cardiovascular events, a common comorbidity in COPD patients. A study by Bolton et al. reported that individuals with COPD and hypercholesterolemia had a 40% higher risk of cardiovascular-related mortality compared to those with normal cholesterol levels.[7]

Magnesium is an essential mineral involved in bronchial smooth muscle function and respiratory muscle contraction. Magnesium deficiency has been linked to bronchospasm, impaired pulmonary function, and increased COPD exacerbations. COPD patients with low magnesium levels demonstrated significantly lower forced expiratory volume in one second (FEV1) values compared to those with normal magnesium levels.[8] Magnesium depletion may be more common in smokers due to increased oxidative stress and altered nutrient absorption.

Uric acid is a product of purine metabolism that serves as both an antioxidant and a marker of oxidative stress. Elevated uric acid levels are frequently observed in COPD patients, particularly smokers, due to persistent oxidative damage. It is being observed that COPD patients with serum uric acid levels above 6 mg/dL had a around 2 times increased risk of severe airflow limitation compared to those with lower levels.[9]

Given the interplay between inflammation, metabolic dysfunction, and oxidative stress in COPD pathogenesis, this study aimed to assess and compare CRP, total cholesterol, magnesium, and uric acid levels in smokers and non-smokers with COPD. Identifying these differences may provide insights into the role of smoking in COPD progression and help tailor therapeutic strategies to improve patient outcomes.

MATERIALS AND METHODS

Study Design and Setting: This cross-sectional study was conducted at the Department of Biochemistry, a tertiary care center in North India, over a period of 12 months from June 2023 to May 2024. Ethical approval for the study was obtained from the Institutional Ethics Committee (IEC). All participants were informed about the study's objectives, procedures, and potential risks, and written informed consent was obtained before enrollment.

Study Population: The study included patients (aged 40 years or older) diagnosed with chronic obstructive pulmonary disease (COPD) according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. Diagnosis was confirmed based on post-bronchodilator spirometry showing a forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) ratio of less than 0.70. Patients were categorized into two groups based on their smoking status. The smoker group included individuals with a confirmed COPD diagnosis and a history of active or former smoking with a minimum cumulative exposure of 10 pack-years. The non-smoker group consisted of COPD patients with no history of tobacco use or significant exposure to secondhand smoke. Patients were excluded if they had any ongoing acute COPD exacerbation, active infections, chronic inflammatory conditions unrelated to COPD (e.g., rheumatoid arthritis, systemic lupus erythematosus), or malignancies. Additionally, individuals with chronic kidney disease, liver disorders, or those on medications that could significantly alter serum CRP, cholesterol, magnesium, or uric acid levels (such as lipid-lowering agents, magnesium supplements, or uric acid-modifying drugs) were excluded to minimize confounding factors.

Sample Size Calculation: The sample size was determined using the formula for comparing two independent means. Assuming a mean difference of 1.5 mg/L in CRP levels between smokers and non-smokers, with a standard deviation of 2.0 mg/L, a significance level (α) of 0.05, and a power of 80%, the calculated sample size required was 60 participants per group.[10] To account for potential data loss or participant withdrawal, an additional 10% was added, resulting in a final target sample size of 66 participants per group.

Data Collection and Clinical Assessment: Comprehensive demographic data were recorded for each participant, including age, sex, body mass index (BMI), smoking history (pack-years), duration of COPD diagnosis, and comorbidities. A detailed smoking history included information on smoking status (current or former), type of tobacco used, and duration of exposure. Each participant underwent a

detailed clinical examination, and pulmonary function tests were performed using a calibrated spirometer following standard protocols. Spirometry parameters such as FEV1, FVC, and FEV1/FVC ratio were recorded to assess the severity of airflow obstruction. Participants were instructed to withhold bronchodilators for the recommended duration before spirometry to ensure accurate results.

Biochemical Analysis: Blood samples (5 mL) were collected from all participants after an overnight fast of at least 8 hours. Venous blood samples were drawn under aseptic conditions and transferred to plain vacutainer tubes. The samples were allowed to clot at room temperature before being centrifuged at 3000 rpm for 10 minutes to separate the serum. Serum samples were stored at −20°C until analysis to ensure sample stability. Serum C-reactive protein (CRP) levels were measured using a high-sensitivity CRP (hs-CRP) immunoturbidimetric assay, which offers precise detection of low-grade inflammation. The results were expressed in mg/L, with a reference range of <3 mg/L considered normal. Total cholesterol levels were estimated using an enzymatic colorimetric method, ensuring accuracy through standardized reagents. Serum magnesium levels were analyzed via the xylidyl blue colorimetric method, with reference values ranging from 1.7 to 2.3 mg/dL. Serum uric acid was measured using the uricase-peroxidase (POD) method, with a reference range of 3.5 to 7.2 mg/dL for males and 2.6 to 6.0 mg/dL for females. All biochemical analyses were conducted using an automated biochemistry analyzer under stringent quality control protocols to ensure precision and reliability.

Statistical Analysis: Data were analyzed using IBM SPSS Statistics (Version 20.0). Continuous variables such as age, BMI, CRP, cholesterol, magnesium, and uric acid levels were presented as mean ± standard deviation (SD), while categorical variables like smoking status and COPD severity were presented as frequencies and percentages. Group comparisons for continuous variables were conducted using the independent t-test, while categorical variables were compared using the chi-square test. To assess correlations between biochemical markers and spirometry parameters, Pearson's correlation coefficient was applied. A p-value of <0.05 was considered statistically significant.

Ethical Considerations: The study adhered to the principles outlined in the Declaration of Helsinki. All participants provided informed consent prior to enrollment, and confidentiality of patient data was maintained throughout the study. Participants retained the right to withdraw from the study at any stage without consequence. Any adverse events occurring during the study were promptly addressed, and appropriate medical care was provided.

RESULTS

Smokers with COPD had significantly lower FEV1 (% predicted) (47.5 ± 11.3 vs. 52.8 ± 10.9; p = 0.041) and FEV1/FVC ratio (63.4 ± 6.5 vs. 67.9 ± 5.8; p = 0.011) compared to non-smokers. COPD severity was higher in smokers, with more severe cases (34.8% vs. 21.2%) and fewer mild cases (18.2% vs. 30.3%; p = 0.032). Smokers also had a higher heart rate (86 ± 10 vs. 82 ± 9 beats/min; p = 0.041), respiratory rate (22 ± 3.2 vs. 20 ± 2.8 breaths/min; p = 0.012), and lower oxygen saturation (92.1 ± 3.6% vs. 94.8 ± 2.7%; p = 0.002). Additionally, smokers experienced a higher frequency of exacerbations in the past year (1.9 ± 1.1 vs. 1.3 ± 0.8; p = 0.017). Other parameters, including age, BMI, comorbidities, and medication usage, showed no significant differences between groups [Table 1].

Table 1: Comparison of Demographic, Clinical, and Disease Characteristics Between Smokers and Non-Smokers with COPD.

Parameter	Smokers with COPD (n=66)	Non-Smokers with COPD (n=66)	p-value
	Frequency (%)/Mean ± SD		
Age (years)	61.5 ± 8.4	60.2 ± 7.9	0.382
Gender			
Male	54 (81.8%)	49 (74.2%)	0.291
Female	12 (18.2%)	17 (25.8%)	
Body Mass Index (kg/m²)	21.7 ± 3.5	22.9 ± 3.2	0.121
Duration of COPD (years)	9.2 ± 4.1	7.8 ± 3.9	0.089
Pack-years (in smokers)	35.4 ± 12.6	—	—
FEV1 (% predicted)	47.5 ± 11.3	52.8 ± 10.9	0.041
FVC (% predicted)	61.2 ± 9.8	64.5 ± 9.1	0.157
FEV1/FVC Ratio (%)	63.4 ± 6.5	67.9 ± 5.8	0.011
COPD Severity			
Mild	12 (18.2%)	20 (30.3%)	0.032
Moderate	31 (47%)	32 (48.5%)	
Severe	23 (34.8%)	14 (21.2%)	
Comorbidities	36 (54.5%)	29 (43.9%)	0.223
Hypertension (HTN)	22 (33.3%)	19 (28.8%)	0.582
Diabetes Mellitus (DM)	14 (21.2%)	10 (15.2%)	0.441
Ischemic Heart Disease (IHD)	8 (12.1%)	5 (7.6%)	0.421
Systolic Blood Pressure (mmHg)	138 ± 15	134 ± 13	0.097
Diastolic Blood Pressure (mmHg)	86 ± 9	83 ± 8	0.071
Heart Rate (beats/min)	86 ± 10	82 ± 9	0.041

Respiratory Rate (breaths/min)	22 ± 3.2	20 ± 2.8	0.012
Oxygen Saturation (SpO_2 %)	92.1 ± 3.6	94.8 ± 2.7	0.002
Physical Activity Level			
Low	27 (40.9%)	18 (27.3%)	0.178
Moderate	28 (42.4%)	34 (51.5%)	
High	11 (16.7%)	14 (21.2%)	
Medications Used			
Inhaled Corticosteroids (ICS)	29 (43.9%)	21 (31.8%)	0.146
Long-Acting Beta-Agonists (LABA)	37 (56.1%)	45 (68.2%)	
Long-Acting Muscarinic Antagonists (LAMA)	24 (36.4%)	31 (47%)	
Oral Theophyllines	15 (22.7%)	10 (15.2%)	
Exacerbation Frequency in the Past Year	1.9 ± 1.1	1.3 ± 0.8	0.017
Hospitalizations in the Past Year	24 (36.4%)	15 (22.7%)	0.083
Smoking Cessation Status			
Current	45 (68.2%)	—	—
Former	21 (31.8%)	—	—

Smokers with COPD had significantly higher mean C-reactive protein (CRP) levels (5.8 ± 2.3 mg/L vs. 3.7 ± 1.5 mg/L; p = 0.001) and total cholesterol (202.6 ± 28.4 mg/dL vs. 187.4 ± 25.1 mg/dL; p = 0.003) compared to non-smokers. Conversely, serum magnesium levels were significantly lower in smokers (1.69 ± 0.21 mg/dL vs. 1.82 ± 0.19 mg/dL; p = 0.012). Serum uric acid levels were also higher in smokers (6.5 ± 1.3 mg/dL vs. 5.8 ± 1.1 mg/dL; p = 0.024). The prevalence of elevated CRP (≥3 mg/L), cholesterol (≥200 mg/dL), and uric acid (≥6 mg/dL) was notably higher in smokers (74.2%, 56.1%, and 51.5%, respectively) compared to non-smokers (42.4%, 31.8%, and 28.8%, respectively; p < 0.05). Additionally, a significantly higher proportion of smokers had magnesium levels <1.7 mg/dL (43.9% vs. 21.2%; p = 0.011) [Table 2].

Table 2: Comparison of Biomarker Levels Between Smokers and Non-Smokers with COPD.

Biomarker	Smokers with COPD (n=66)	Non-Smokers with COPD (n=66)	p-value
	Frequency (%)/Mean ± SD		
C-reactive protein (mg/L)	5.8 ± 2.3	3.7 ± 1.5	0.001
Total Cholesterol (mg/dL)	202.6 ± 28.4	187.4 ± 25.1	0.003
Serum Magnesium (mg/dL)	1.69 ± 0.21	1.82 ± 0.19	0.012
Serum Uric Acid (mg/dL)	6.5 ± 1.3	5.8 ± 1.1	0.024
CRP ≥ 3 mg/L	49 (74.2%)	28 (42.4%)	0.001
Cholesterol ≥ 200 mg/dL	37 (56.1%)	21 (31.8%)	0.007
Magnesium < 1.7 mg/dL	29 (43.9%)	14 (21.2%)	0.011
Uric Acid ≥ 6 mg/dL	34 (51.5%)	19 (28.8%)	0.016

C-reactive protein (CRP) levels increased progressively with COPD severity, being lowest in GOLD I (3.5 ± 1.4 mg/L) and highest in GOLD IV (7.3 ± 2.5 mg/L; p < 0.001). Similarly, total cholesterol levels rose significantly across stages, from 184.2 ± 23.5 mg/dL in GOLD I to 218.7 ± 30.5 mg/dL in GOLD IV (p = 0.002). Conversely, serum magnesium levels decreased with increasing severity, from 1.85 ± 0.18 mg/dL in GOLD I to 1.61 ± 0.17 mg/dL in GOLD IV (p = 0.012). Serum uric acid levels also showed a significant upward trend, rising from 5.5 ± 1.1 mg/dL in GOLD I to 7.0 ± 1.4 mg/dL in GOLD IV (p = 0.003) [Table 3].

Table 3: Comparison of Biomarker Levels Across Different GOLD Stages in COPD Patients.

Parameter	GOLD I (n=22)	GOLD II (n=39)	GOLD III (n=41)	GOLD IV (n=30)	p-value
	Mean ± SD				
C-reactive protein (mg/L)	3.5 ± 1.4	4.7 ± 1.8	6.1 ± 2.2	7.3 ± 2.5	<0.001
Total Cholesterol (mg/dL)	184.2 ± 23.5	195.6 ± 25.8	206.4 ± 29.3	218.7 ± 30.5	0.002
Serum Magnesium (mg/dL)	1.85 ± 0.18	1.78 ± 0.20	1.69 ± 0.19	1.61 ± 0.17	0.012
Serum Uric Acid (mg/dL)	5.5 ± 1.1	5.9 ± 1.2	6.4 ± 1.3	7.0 ± 1.4	0.003

CRP levels increased significantly with exacerbation frequency, from 3.4 ± 1.2 mg/L in patients with no exacerbations to 7.0 ± 2.3 mg/L in those with ≥3 exacerbations per year (p < 0.001). Total cholesterol levels similarly rose from 182.3 ± 21.6 mg/dL in the no exacerbation group to 210.5 ± 30.2 mg/dL in those with ≥3 exacerbations (p = 0.003). Conversely, serum magnesium levels declined progressively with increasing exacerbation frequency (1.88 ± 0.19 mg/dL in the no exacerbation group vs. 1.62 ± 0.16 mg/dL in the ≥3 exacerbations group; p = 0.002). Serum uric acid levels also showed a significant upward trend, rising from 5.4 ± 1.0 mg/dL in those without exacerbations to 7.2 ± 1.5 mg/dL in those with ≥3 exacerbations (p < 0.001) [Table 4].

Table 4: Biomarker Levels in COPD Patients Stratified by Exacerbation Frequency.

Parameter	No Exacerbations (n=30)	1–2 Exacerbations/ Year (n=50)	≥3 Exacerbations/ Year (n=52)	p-value
	Mean ± SD			
C-reactive protein (mg/L)	3.4 ± 1.2	5.1 ± 1.8	7.0 ± 2.3	<0.001
Total Cholesterol (mg/dL)	182.3 ± 21.6	197.8 ± 27.1	210.5 ± 30.2	0.003
Serum Magnesium (mg/dL)	1.88 ± 0.19	1.73 ± 0.18	1.62 ± 0.16	0.002
Serum Uric Acid (mg/dL)	5.4 ± 1.0	6.1 ± 1.3	7.2 ± 1.5	<0.001

CRP levels exhibited a significant negative correlation with FEV1 (% predicted) (r = -0.42, p = 0.001), FVC (% predicted) (r = -0.36, p = 0.002), and FEV1/FVC ratio (r = -0.48, p = 0.001). Similarly, total cholesterol showed a weaker yet significant inverse correlation with FEV1 (r = -0.30, p = 0.007), FVC (r = -0.28, p = 0.01), and FEV1/FVC ratio (r = -0.33, p = 0.004). Conversely, serum magnesium demonstrated positive correlations with FEV1 (r = 0.37, p = 0.001), FVC (r = 0.34, p = 0.003), and FEV1/FVC ratio (r = 0.40, p = 0.001). Serum uric acid levels were negatively correlated with FEV1 (r = -0.45, p = 0.001), FVC (r = -0.38, p = 0.001), and FEV1/FVC ratio (r = -0.41, p = 0.001), suggesting a consistent association with worsening pulmonary function [Table 5].

Table 5: Correlation of Biomarkers with Pulmonary Function Parameters in COPD Patients.

Biomarker	FEV1 (% predicted)	FVC (% predicted)	FEV1/FVC Ratio (%)
	Pearson correlation coefficient (r), p-value		
C-reactive protein (mg/L)	-0.42; 0.001	-0.36; 0.002	-0.48; 0.001
Total Cholesterol (mg/dL)	-0.30; 0.007	-0.28; 0.01	-0.33; 0.004
Serum Magnesium (mg/dL)	0.37; 0.001	0.34; 0.003	0.40; 0.001
Serum Uric Acid (mg/dL)	-0.45; 0.001	-0.38; 0.001	-0.41; 0.001

DISCUSSION

Our study extensively evaluated inflammatory, metabolic, and oxidative stress markers in smokers and non-smokers with COPD, with additional analysis based on disease severity, exacerbation frequency, and lung function. The findings emphasize the intricate interplay between systemic inflammation, metabolic dysregulation, and oxidative stress in COPD pathogenesis.

Smokers and non-smokers with COPD had comparable demographics; however, smokers exhibited significantly lower FEV1 (47.5 ± 11.3% vs. 52.8 ± 10.9%; p = 0.041) and FEV1/FVC ratios (63.4 ± 6.5% vs. 67.9 ± 5.8%; p = 0.011), indicating greater airflow limitation. These findings align with Oelsner et al., and Strzelak et al., who reported that smoking accelerates lung function decline through sustained airway inflammation and epithelial damage.[11,12] COPD severity was also higher in smokers, with more severe cases (34.8% vs. 21.2%; p = 0.032), consistent with Lai et al., who linked smoking to faster progression to severe COPD.[13]

Smokers showed elevated heart rates (86 ± 10 vs. 82 ± 9 bpm; p = 0.041) and respiratory rates (22 ± 3.2 vs. 20 ± 2.8 breaths/min; p = 0.012), consistent with Duncan et al., who associated these parameters with heightened sympathetic drive and impaired lung mechanics.[14] Smokers also had significantly lower SpO_2 levels (92.1 ± 3.6% vs. 94.8 ± 2.7%; p = 0.002), reinforcing the detrimental impact of smoking on pulmonary gas exchange. Similar trends have been reported by Baqdunes et al., who identified low SpO_2 as a predictor of exacerbations and mortality.[15]

Smokers had a higher exacerbation frequency (1.9 ± 1.1 vs. 1.3 ± 0.8; p = 0.017), aligning with Day et al., who found smoking-associated neutrophilic inflammation increases exacerbation risk.[16] While hospitalization rates were higher in smokers (36.4% vs. 22.7%), the difference was not statistically significant (p = 0.083), potentially reflecting varying healthcare-seeking patterns or comorbidity burdens.

Hypertension, diabetes mellitus, and ischemic heart disease rates were comparable between groups, consistent with previous literature suggesting that these comorbidities may develop independently of smoking status.[17] Nevertheless, smokers' elevated heart and respiratory rates may signal increased cardiovascular risk linked to systemic inflammation and sympathetic activation.[17]

Although smokers had lower physical activity levels, the difference was not significant. Studies by Xiang et al., have shown that physical inactivity correlates with COPD progression and cardiovascular risk.[18] Medication patterns were largely similar, though fewer smokers were on inhaled corticosteroids, despite their higher disease severity, possibly indicating underutilization or reduced adherence.

Our study demonstrated significantly higher CRP levels in smokers with COPD compared to non-smokers (5.8 ± 2.3 mg/L vs. 3.7 ± 1.5 mg/L; p = 0.001). CRP levels also increased progressively with worsening GOLD stages, rising from 3.5 ± 1.4 mg/L in GOLD I to 7.3 ± 2.5 mg/L in GOLD IV (p < 0.001). Furthermore, CRP levels were highest among patients with frequent exacerbations (7.0 ± 2.3 mg/L in those with ≥3 exacerbations vs. 3.4 ± 1.2 mg/L in those without exacerbations; p < 0.001). These findings align with previous studies by Hassan et al., and Leuzzi et al., that have identified CRP as a reliable marker of systemic inflammation in COPD.[19,20]

Elevated CRP levels in smokers may be attributed to chronic exposure to cigarette smoke, which induces oxidative stress and triggers inflammatory cascades involving interleukin-6 (IL-6) and tumor necrosis

factor-alpha (TNF-α), both of which promote CRP synthesis in the liver. Studies by Yang et al., and Lin et al. reported similar associations, confirming that elevated CRP is strongly linked to COPD progression and increased exacerbation risk.[21,22] Elevated CRP levels are particularly concerning because they are not only indicative of systemic inflammation but are also predictive of cardiovascular comorbidities, which are common in COPD patients.

Our study also revealed strong inverse correlations between CRP and pulmonary function markers, including FEV1 ($r = -0.42$, $p = 0.001$), FVC ($r = -0.36$, $p = 0.002$), and FEV1/FVC ratio ($r = -0.48$, $p = 0.001$). This aligns with findings by Song et al., who reported that elevated CRP levels are associated with accelerated lung function decline.[23] Such correlations emphasize that CRP may not only serve as a marker of systemic inflammation but also as a potential predictor of COPD progression and impaired lung function.[23]

Total cholesterol levels were significantly elevated in smokers with COPD (202.6 ± 28.4 mg/dL) compared to non-smokers (187.4 ± 25.1 mg/dL; $p = 0.003$). Moreover, cholesterol levels increased steadily with disease severity, reaching 218.7 ± 30.5 mg/dL in GOLD IV ($p = 0.002$). Patients with frequent exacerbations also had higher cholesterol levels (210.5 ± 30.2 mg/dL in those with ≥3 exacerbations; $p = 0.003$).

Our findings are consistent with previous studies, such as those by Zafirova-Ivanovska et al., which demonstrated elevated cholesterol levels in COPD patients with recurrent exacerbations.[24] The dysregulation of cholesterol in COPD may be explained by systemic inflammation, which alters lipid metabolism and promotes endothelial dysfunction. Smoking-induced oxidative stress may further disrupt lipid profiles by increasing lipid peroxidation, contributing to atherosclerotic changes and cardiovascular risk.[25]

The observed inverse correlations between cholesterol levels and lung function (FEV1: $r = -0.30$, $p = 0.007$) underscore the metabolic component of COPD progression. These results align with Liu et al., who linked dyslipidemia to impaired pulmonary function and heightened inflammatory response. This highlights the potential benefit of lipid management strategies in mitigating COPD-related complications.[26]

Serum magnesium levels were significantly lower in smokers with COPD (1.69 ± 0.21 mg/dL) compared to non-smokers (1.82 ± 0.19 mg/dL; $p = 0.012$). Magnesium levels also decreased with advancing GOLD stages, from 1.85 ± 0.18 mg/dL in GOLD I to 1.61 ± 0.17 mg/dL in GOLD IV ($p = 0.012$), and were lowest among patients with frequent exacerbations (1.62 ± 0.16 mg/dL; $p = 0.002$).

Magnesium plays a crucial role in bronchodilation, muscle relaxation, and immune modulation. Hypomagnesemia has been linked to increased bronchial hyperreactivity and respiratory muscle weakness, which can worsen COPD symptoms. The positive correlations observed between magnesium and lung function (FEV1: $r = 0.37$, $p = 0.001$; FVC: $r = 0.34$, $p = 0.003$; FEV1/FVC: $r = 0.40$, $p = 0.001$) align with studies by Makwana et al. and Kumar et al., who reported that magnesium deficiency is associated with impaired respiratory function and increased exacerbation frequency.[27,28] Given magnesium's involvement in antioxidant defense mechanisms, its depletion may exacerbate oxidative stress in COPD patients, further contributing to lung damage.

Serum uric acid levels were significantly elevated in smokers with COPD (6.5 ± 1.3 mg/dL) compared to non-smokers (5.8 ± 1.1 mg/dL; $p = 0.024$). Uric acid levels increased with advancing GOLD stages, from 5.5 ± 1.1 mg/dL in GOLD I to 7.0 ± 1.4 mg/dL in GOLD IV ($p = 0.003$), and were highest in patients with frequent exacerbations (7.2 ± 1.5 mg/dL; $p < 0.001$).

These findings are consistent with reports by Yang et al., and Büyükbayram et al., which identified elevated uric acid levels as a marker of oxidative stress and hypoxia in COPD patients.[29,30] The significant negative correlations between uric acid and pulmonary function markers (FEV1: $r = -0.45$, $p = 0.001$; FVC: $r = -0.38$, $p = 0.001$; FEV1/FVC: $r = -0.41$, $p = 0.001$) suggest that uric acid may play a detrimental role in disease progression. Elevated uric acid in COPD may arise from enhanced xanthine oxidase activity, a known contributor to oxidative stress and endothelial dysfunction.[30]

The collective findings of our study highlight the interconnected roles of systemic inflammation, lipid imbalance, and oxidative stress in COPD progression. Elevated CRP, cholesterol, and uric acid levels, coupled with decreased magnesium, emphasize the need for a multi-targeted approach in COPD management.[17] Routine monitoring of these biomarkers may provide valuable insights into disease severity, risk of exacerbations, and therapeutic response.[19]

Our study further reinforces the significant impact of smoking in amplifying systemic inflammation and oxidative stress, underlining the need for aggressive smoking cessation strategies. Additionally, the observed correlations between biomarkers and lung function suggest potential avenues for biomarker-guided therapeutic interventions.[22]

Future research should focus on longitudinal studies to establish the predictive value of these biomarkers in COPD outcomes. Interventional studies exploring the role of magnesium supplementation, cholesterol management, and antioxidant therapies may offer novel strategies to improve COPD prognosis and reduce exacerbation frequency.

CONCLUSION

In conclusion, our study highlights distinct biomarker patterns in smokers and non-smokers with COPD, reinforcing the critical role of systemic inflammation, metabolic dysfunction, and oxidative stress in disease

progression. These insights may help improve risk stratification and guide targeted therapeutic approaches for COPD patients.

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