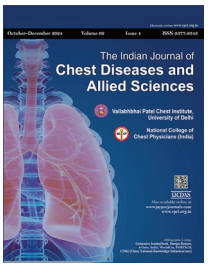
ORIGINAL RESEARCH

To Study the Association of Serum Uric Acid Levels with Severity of Chronic Obstructive Pulmonary Disease



This article is available on www.vpci.org.in

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Received on: 05 July 2024; *Accepted on:* 13 September 2024; *Published on:* 13 February 2025

Abstract

Background: Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory lung disease that causes airflow obstruction which leads to hypoxia. Serum uric acid is increased in hypoxic states as well as in systemic inflammatory conditions. The purpose of the present study was to assess whether the higher value of serum uric acid corresponds with the severity of COPD as per spirometric classification of COPD.

Material and methods: This cross-sectional study included 294 spirometry-diagnosed patients of COPD as per Global Initiative for Chronic Obstructive Lung Disease criteria. Serum uric acid levels were tested on all the patients. The patients with raised serum uric acid levels were further categorized according to severity COPD grade. Reference of normal serum uric acid levels among males was taken as 3.5–8.5 mg/dL and among females as 2.5–6.2 mg/dL.

Results: In the present study of 294 patients, maximum patients, i.e., 59.5%, were in moderate COPD grade. The mean serum uric acid value in male subjects was 5.9 ± 2.066 mg/dL, while in female subjects the mean serum uric acid value was 6.31 ± 1.93 mg/dL. About 85 (22 males and 63 females) had serum uric acid values out of the normal range. In males, maximum (41.6%) were in severe COPD grade, whereas in females maximum (80.8%) were in moderate COPD grade. Severe COPD grade showed statistically significant ($p = 0.037$) association with raised serum uric acid levels in both male and female subjects.

Conclusion: The study concludes that mean uric acid levels progressively increased as the COPD grade increased from I to IV. Since serum uric acid levels were raised in COPD patients mainly in the severe COPD grade, it serves as a useful parameter for assessing disease severity and hypoxemia in known COPD patients.

Keywords: Chronic obstructive pulmonary disease, Serum uric acid, Spirometry.

The Indian Journal of Chest Diseases and Allied Sciences (2024): 10.5005/jp-journals-11007-0136

Abbreviations used in this Article

AECOPD = Acute exacerbation of chronic obstructive pulmonary disease; COPD = Chronic obstructive pulmonary disease; FEV_1 = Forced expiratory volume in 1 second; FVC = Forced vital capacity; GOLD = Global Initiative for Chronic Obstructive Lung Disease; NIV = Noninvasive ventilation; SABA = Short-acting beta-agonist.

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic ailing lung condition consisting of a group of chronic pulmonary symptoms (sputum production, dyspnea, and cough, with or without exacerbations) due to abnormalities of the airways (bronchitis and bronchiolitis) and/or alveoli (emphysema), which cause persistent, progressive, airflow obstruction as per Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines 2024.[1] The increasing incidence of COPD has made it worldwide as one of the biggest contributor of mortality, with 90% fatalities happening in middle- and low-income groups. In 2012, over 3 million individuals lost their lives to COPD, constituting 6% of global deaths. Chronic obstructive pulmonary disease presents a burden, which is both preventable and manageable.[2] By 2030, COPD is expected to rank third in terms of mortality and will rank fifth for types of disease burden. Developing nations will bear a higher burden of COPD-related mortality compared with developed nations.

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How to cite this article: Sarin BC, Grover S, Singh P. To Study the Association of Serum Uric Acid Levels with Severity of Chronic Obstructive Pulmonary Disease. Indian J Chest Dis Allied Sci 2024;66(4):113–117.

Source of support: Nil

Conflict of interest: None

The primary environmental culprits linked to COPD are tobacco smoke and harmful particles and gases exposure in both indoor and outdoor air pollution. Cigarette smoke exposure passively, also known as environmental tobacco smoke, do contribute to respiratory symptoms and COPD, especially after long-term exposure.[3] Biomass like wood, coal, animal dung, and crop residues burned in ineffectual stoves or open fires can generate significant amounts of household air pollution. Exposure to indoor air pollutants like essence sticks and use of liquid-heated mosquito repellents are also linked to the likelihood of developing COPD. Air pollution usually contains particulate matter, heavy metals, greenhouse gases, and oxides of nitrogen or sulfur, and is contributing for high

incidence of COPD worldwide and it contributes to nearly 50% of the all ascribable risk of COPD in the developing countries.[4] The pulmonary risk of air pollution depends on amount of exposure with no apparent "safe" thresholds. It has been observed that in countries with lower air pollution levels, long-duration exposure to dioxides of nitrogen and PM2.5 significantly affects development of lungs in pediatric population and compromises lung function in adults population, thus increasing the risk for COPD.[5] Pulmonary function decreases with long-term exposure to smoke and air pollutants and results in reduced oxygen uptake, thus causing tissue hypoxia in patients of COPD.

The end product of dietary or endogenous purine metabolism is uric acid, which is produced by xanthine dehydrogenase in the liver and intestines. Exogenous purines also significantly contribute to uric acid levels, with about 50% of RNA purines and 25% of DNA purines being absorbed in the intestines and later excreted in urine.[6] Tissue hypoxia has been shown to trigger the breakdown of adenosine, leading to the release of uric acid and purine intermediates. Raised serum uric acid levels are linked to systemic inflammation and increased incidence of cardiovascular risk.[7] In COPD, cigarette smoke leads to oxidative stress and lung inflammation, causing lung tissue damage and decline in pulmonary function. This impaired function decreases oxygen intake, causing more pronounced tissue hypoxia, especially during acute exacerbations of COPD.[8] Serum uric acid is a proposed marker of impaired oxidative metabolism and an independent prognostic marker in various cardiovascular disorders.[8–10]

The aim of the present study was to assess whether the higher values of serum uric acid are associated with the severity of COPD.

Materials and Methods

Study Design

This cross-sectional study was conducted in the Department of TB and Respiratory Diseases from a time period of 1 January 2023 to 31 March 2024 at a tertiary care center of North India.

Inclusion Criteria

Both outpatients and inpatients with a diagnosis of COPD as per GOLD criteria based on spirometry were included in the study. Chronic obstructive pulmonary disease was considered in any patient who had symptoms of chronic cough, dyspnea, and sputum production, with or without a history of exposure to risk factors for the disease. Spirometry findings ensured the diagnosis in this clinical context. A postbronchodilator forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) < 0.70 confirmed the presence of persistent airflow limitation and thus of COPD in patients with significant exposure to noxious stimuli and with appropriate symptoms.[11]

Exclusion Criteria

The subjects with comorbidities which seem to influence serum uric acid levels, such as malignancies, neurological, liver dysfunction, musculoskeletal, and peripheral vascular disease in lower extremities, chronic kidney disease, lung cancer, tuberculosis, unstable angina, pneumonia, and other respiratory diseases, were excluded from the study.

The objectives of the present study were briefed to the participants, and their written consent was documented. The following protocol was followed on all participants: interviews regarding symptomatology, smoking habits, biomass fuel exposure, family history, past history, and risk factors related to COPD using a predefined questionnaire were done. Patient demographics, including weight, height, age, and gender, were recorded. A comprehensive physical examination, encompassing both general and systemic assessments with particular focus on the respiratory system, was performed. Routine laboratory investigations like complete blood count, fasting blood sugar, and chest X-ray were conducted. Spirometry was performed on the patients using ultrasound-based technology EasyOne spirometry machine, and the following key information was documented:

- FVC
- FEV_1
- FEV_1/FVC ratio
- Forced midexpiratory flow rate (25–75%)
- Peak expiratory flow.[12]

Interpretation of spirometry results involved comparing measured values with normal values obtained from healthy individuals, which could vary based on factors such as race, sex, age, height, weight, measurement conditions, and demographic characteristics.

Spirometry was conducted according to national or international guidelines, ensuring that expiratory volume/time curves were smooth and free of irregularities. Additionally, the pause between inspiration and expiration was kept minimal, i.e., less than 1 second. The FVC and FEV_1 values documented for analysis were the largest value obtained from any of three technically satisfactory curves.

Doses that were used were either 400 µg short-acting beta-agonist (SABA) or 160 µg short-acting anticholinergic or both in combination. The FEV_1 was documented 10–15 minutes after SABA was given and 30–45 minutes after short-acting anticholinergic or the combination were given.

The GOLD criteria, which relies on spirometry to assess airflow limitation, was employed to classify COPD patients into different severity grades, as:

- GOLD I: ($FEV_1 \geq 80\%$ predicted) was categorized as mild
- GOLD II: ($50\% \leq FEV_1 < 80\%$ predicted) was categorized as moderate
- GOLD III: ($30\% \leq FEV_1 < 50\%$ predicted) was categorized as severe
- GOLD IV: ($FEV_1 < 30\%$ predicted) was categorized as very severe.

Postbronchodilator ratio of FEV_1 to FVC less than 0.7 was the determinant used for persistent air flow obstruction.[13]

Thereafter, serum uric acid sample of all the study subjects were collected under aseptic conditions. Venous blood sample (2 mL) was drawn from the anterior cubital vein into red-topped vacutainer tubes. Serum was separated by centrifugation at an rpm of 3,500 for 17 minutes after clot retraction. Serum uric acid levels were determined and documented using an enzymatic colorimetric assay performed using a fully automated clinical chemistry analyzer known as Vitros 5,600 employing commercially available kits (Vitros Uric Acid slides).

Reference of normal serum uric acid levels among males was taken as 3.5–8.5 mg/dL and in females the reference value taken was 2.5–6.2 mg/dL.[14]

Statistical Analysis

The recorded data was compiled and documented in a Microsoft Excel 2010 spreadsheet and then analyzed by Statistical Package for the Social Sciences software version 23.0. Descriptive statistics

Table 1: Gender distribution of COPD and its association with severity of disease

	Severity of COPD				
Gender	*Mild*	*Moderate*	*Severe*	*Very severe*	*Total*
Male					
No. of patients	28	98	35	1	162
Percentage of total male	17.3%	60.5%	21.6%	0.6%	100.0%
Female					
No. of patients	35	77	20	0	132
Percentage of total female	26.5%	58.3%	15.2%	0%	100.0%
Total					
No. of patients	63	175	55	1	294
Percentage of total patients	21.4%	59.5%	18.7%	0.3%	100.0%

$\chi^2 = 5.384$; $df = 3$; $p = 0.145$

Table 2: Association of raised serum uric acid levels with grades of COPD of male and female

Severity of COPD	*Raised serum uric acid in males*		*Raised serum uric acid in females*		*Total*	
	No. of patients	*Percentage within the grade*	*No. of patients*	*Percentage within the grade*	*No. of patients*	*p-value*
Mild	2	15.3%	11	84.61%	13	0.347
Moderate	9	19.1%	38	80.8%	47	0.114
Severe	10	41.6%	14	58.3%	24	0.037*
Very severe	1	100%	0	0.00%	1	0.08
Total	22		63		85	

*Statistically significant

included computations of percentages, and means were calculated and analyzed. Analysis of data was done by one-way analysis of variance, Pearson Chi-square test, and Pearson correlation coefficient. In the present study, a p-value < 0.05 was considered as significant statistically.

Results

Demographic Profile and Symptomatology

The present study constituted 294 patients with 162 (55.1%) males and 132 (44.9%) females. In males, maximum patients came in age-group 61–70 years and in females maximum were in 51–60 age-group. Maximum patients were in the fifth decade.

Cough was the commonest symptom present in 219 (74.5%) patients followed by shortness of breath in 217 (73.8%) patients and wheezing in 102 (34.7%) patients.

In the present study, 139 (47.3%) patients had history of biomass fuel exposure, whereas 39 (13.3%) patients had a history of smoking.

As per the GOLD guidelines, COPD patients were categorized according to their severity into mild, moderate, severe, and very severe grades. About 175 (59.5%) patients were in moderate COPD grade followed by 63 (21.4%) patients in the mild COPD grade, while 55 (18.7%) patients were in severe COPD grade, and 1 (0.3%) patient was in very severe COPD grade.

Gender Distribution of COPD and Its Association with Severity of Disease

Out of 162 males subjects, maximum 98 (60.5%) patients were in moderate COPD grade, 35 (21.6%) in severe COPD grade, followed by 28 (17.3%) in mild COPD grade, and 1 (0.6%) in very severe COPD grade, whereas out of 132 females, maximum 77 (58.3%) females were seen in the moderate COPD grade, 35 (26.5%) were in mild COPD grade, followed by 20 (15.2%) in severe COPD grade, and none in very severe COPD grade. The values for the association of COPD patients categorized according to gender and severity of COPD were not statistically significant ($p > 0.05$) (Table 1).

Association of Raised Serum Uric Acid Levels with COPD Severity as per GOLD Guidelines in Males and Females

The mean value of serum uric acid in males was 5.9 ± 2.066 mg/dL, while in female subjects it was 6.31 ± 1.93 mg/dL. In the present study of 294 subjects, 85 patients had serum uric acid values out of the normal range (normal range considered in males was 3.5–8.5 mg/dL and in females normal range was 2.5–6.2 mg/dL). Out of 85 patients who showed raised serum uric acid levels, 22 were male patients and 63 were females. Among these 22 male subjects, 10 (41.6%) were in severe COPD grade, 9 (19.1%) were in moderate COPD grade, 2 (15.3%) were in mild COPD grade, whereas 1 (100%) was in very severe COPD grade, whereas out of 63 females with raised serum uric acid levels, 38 (80.8%) were in moderate COPD grade, 14 (58.3%) were in severe COPD grade, 11 (84.6%) were in mild grade of COPD and none were in very severe grade of COPD.

Raised serum uric acid levels in both male and female subjects showed statistically significant (p-value = 0.037) association with only severe COPD grade. This validates that the raised serum uric acid levels correspond with the increased COPD severity (Table 2 and Fig. 1).

Discussion

Chronic obstructive pulmonary disease is a long-standing lung condition characterized by chronic pulmonary symptoms like cough, dyspnea, and sputum production, with or without

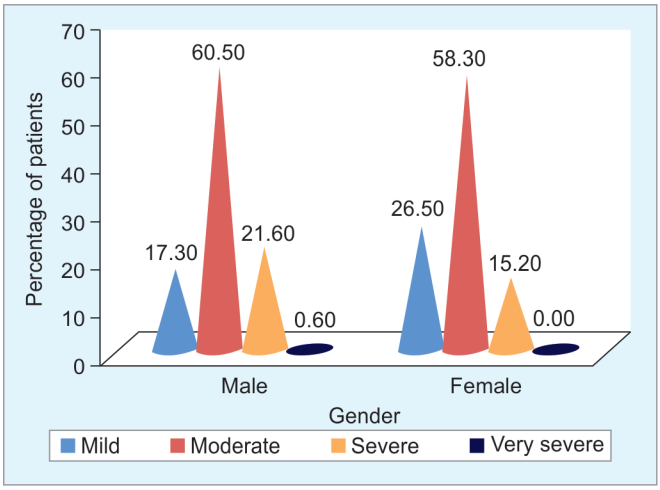

Fig. 1: Gender distribution of COPD and its association with severity of disease

exacerbations. This disease entity has risen to be the leading cause of mortality globally. By 2030, this disease is expected to rank at third position in terms of mortality and rank fifth for types of disease burden.[2] Increasing air pollution, cigarette smoke exposure, and biomass fuel exposure are leading risk factors for COPD.

In clinical practice, cases of COPD most often are treated on the basis of clinical symptomatology, history of the patient, and spirometric values. Chronic obstructive pulmonary disease is diagnosed on spirometry based on postbronchodilation ratio of FEV1/FVC <0.7. Chronic obstructive pulmonary disease is further categorized based on postbronchodilation FEV1 values into different grades according to GOLD 2024 criteria as mild, moderate, severe, and very severe. For confirmation of the diagnosis of COPD, conventional methods include the combination of signs and symptoms, exposure to risk factors along with the spirometric values. Radiological examination is useful as patients usually have hyperinflated lung, flattening of the diaphragm, increased bronchovascular markings, and tubular heart.

A total of 294 patients with COPD (162 males and 132 females) were part of this study. Cough was the commonest symptom present in 219 (74.5%) patients. About 139 (47.3%) patients had history of biomass fuel exposure, whereas 39 (13.3%) patients had a history of smoking.

When the COPD patients were categorized, maximum 175 (59.5%) patients were in moderate COPD grade while only 1 (0.3%) patient was in very severe COPD grade (>0.05). Huijsmans et al. in his study revealed that out of 253 COPD patients, 121 patients were in severe grade, 75 patients were in moderate grade, 57 patients were in very severe grade, and none were in mild COPD grade.[15] In the present study, 85 patients had raised serum uric acid levels. Of these 85 patients with increased serum uric acid levels, 22 were males while 63 were females. Among male subjects with raised serum uric acid levels, maximum belonged to severe COPD grade X (41.6%), whereas out of 63 females with raised serum uric acid levels, 38 (80.8%) were in moderate COPD grade and 14 (58.3%) were in severe COPD grade. In the present study, raised serum uric acid levels showed statistically significant (p-value = 0.037) association with severe COPD grade in both males and females. In the study of 314 consecutive COPD patients who were categorized based on GOLD staging analysis revealed that serum uric acid levels on admission were elevated in patients who had severe airflow limitations. Notably, patients in COPD stages I and II revealed significantly lower levels of serum uric acid when compared with those in COPD stages III and IV ($p < 0.001$). The serum uric acid levels were higher in frequent exacerbators compared with less-frequent exacerbators. Patients with increased levels of serum uric acid exhibited severe airflow obstruction, increased comorbidities, greater dyspnea severity, and impaired oxygenation when compared with those with reduced serum uric acid levels.[16]

A study of 159 subjects aiming to investigate the correlation of elevated levels of serum uric acid levels with the results of patients with COPD in exacerbation revealed that patients with elevated serum uric acid levels exhibited prolonged hospitalization and higher rates of 30-day mortality. Additionally, these patients with elevated serum uric acid levels required noninvasive ventilation (NIV). High serum uric acid levels were found to be associated with more severe airflow limitation (COPD grade).[17] As per literature, serum uric acid levels were higher in frequent exacerbators when compared with less-frequent exacerbators. Patients with increased serum uric acid levels experienced prolonged hospital stays and had higher 30-day mortality rates when compared with those with lower levels. These patients with higher serum uric acid levels required more frequent NIV and prolonged intensive care unit stay.[18] Another study which reciprocates the present study is of 39 cases in which COPD cases exhibited significantly higher levels of uric acid compared with control subjects. Female COPD subjects had higher uric acid levels as compared with males. Furthermore, COPD cases with a disease duration exceeding 10 years had increased uric acid levels in comparison with those with durations of less than 5 years or 5–10 years. Although subjects with very severe grade of COPD tended to have higher uric acid levels, the difference within the different grades was not significant statistically ($p = 0.286$). Among the COPD cases, 13 were smokers and 26 were nonsmokers.[19]

A meta-analysis of seven studies in 2021 of 932 stable COPD patients and 401 healthy control subjects indicated that stable COPD patients showed significantly increased serum uric acid levels when compared with healthy controls. Chronic obstructive pulmonary disease grade I and II subgroups showed significantly lower levels of serum uric acid when compared with COPD grade III and IV subgroups.[20]

A comparative observational cross-sectional study was conducted, involving 25 stable COPD patients and 25 patients experiencing acute exacerbation of COPD (AECOPD), all aged over 40 years. The results revealed that the AECOPD group exhibited highest mean serum uric acid levels. Additionally, significant differences were noted between the stable and AECOPD groups in terms of modified Medical Research Council grading of dyspnea, pack years, pH, pO_2, and pCO_2.[21] As per review of literature, the observations of various studies strongly suggest that serum uric acid levels will serve as a useful marker for assessing severity of disease and hypoxemia in COPD subjects, facilitating early intensive management. Increased serum uric acid levels are indicative of a poor prognosis and a poor state. Since serum uric acid testing is simple, easily available, inexpensive routine laboratory test, it can be a marker for risk stratification in COPD patients and contribute to the early management of this condition. Limitations of the present study was the limited sample size, and one time contact with the

selected patients, so the future of this study is to reciprocate it on a larger group of population and to make it a longitudinal study so that variations in elevated serum uric acid levels can be better documented and comprehended on the utility of it as a prognostic marker.

Conclusion

This study concludes that serum uric acid levels are raised in COPD patients mainly in the severe COPD grade, and so, can serve as a useful parameter for assessment of disease severity and hypoxemia in known COPD patients.

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