

A Study of Serum Uric Acid Levels in Chronic Obstructive Pulmonary Disease

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Abstract :Chronic Obstructive Pulmonary Disease(COPD) is a disease causing limitation of airflow due to inflammation of airways with parenchymal destruction and subsequent emphysema formation.uric acid, the purine degradation product is elevated in conditions associated with hypoxia.This study evaluates serum uric acid levels correlation with disease severity of COPD.The outcome of our study shows 68% subjects had high serum uric acid levels,52% of patients had FEV1 in the range of severe disease, 48% subjects had mMRC grades 3.High serum uric acid levels portends a poor prognosis and also predicts worsening of the stage of the disease from the initial presentation and necessitates early intervention,treatment and rehabilitation to reduce the morbidity and mortality associated with the disease to achieve a good quality of life.

Keywords:acute exacerbation, chronic obstructive pulmonary disease, mortality,uric acid

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I. Introduction

Chronic obstructive pulmonary disease (COPD) is a disease causing limitation of airflow due to inflammation of airways with parenchymal destruction and subsequent emphysema formation. Inflammatory mechanisms are mediated by IL-6,IL-8 and TNF-alpha (SPILL OVER) leads to systemic inflammation and worsening of co morbid illness. So comorbidities need proper evaluation and management as it complicates the treatment of COPD.[1] Associated illness with high morbidity,increased hospital admission,in hospital complications and mortality.[2-3]In 2020 COPD will be the third leading cause of death as per WHO.Prevalence of COPD in India from various meta-analysis suggests that the prevalence of COPD above 30yrs in males is 5% and in females is 2.7%.Uric acid,a final product of Purine metabolism is elevated in hypoxic states.Poor lung functions reduces oxygen uptake causes tissue hypoxia as in COPD causes uric acid elevation due to its release from lungs and peripheral tissue damage.Uric acid levels are associated with systemic inflammation and increased cardio vascular risk. In this study uric acid levels are correlated with COPD as the levels have direct relationship with frequent exacerbations,hypoxia,inhospital morbidity and mortality.

II. Epidemiology

A meta- analysis between 1990-2004 in 28 countries predicted that prevalence was 11% in men,5% in women and 15-21% in smokers and 3.9% in persons who never smoked.Halbert et al concised many prevalence studies from 17 different countries and had conclusion of 4-10% prevalence of COPD. Indian study INSEARCH phase II showed prevalence of COPD in India was 3.7% with 4.5%in males and 2.9% in females.

III. Objectives

To estimate serum levels of Uric acid in patients with COPD.To evaluate the correlation of elevated serum levels of Uric acid with disease severity of COPD patients in Tertiary care centre.

IV. Methodology

4.1 Study design: Analytical study

4.2 Study population: 100 patients of chronic obstructive pulmonary disease.

4.3 Study period: One year.

4.4 Inclusion criteria:

a.Patients diagnosed as COPD age >18 years irrespective of duration of disease according to clinical history and examination.

4.5 Exclusion criteria:

- 1) Age < 18 years.
- 2) Presence of pneumonia.
- 3) With other chronic infections.
- 4) With neoplastic pathologies.
- 5) With other inflammatory diseases.
- 6) With hepatic diseases, renal diseases.
- 7) With excessive alcohol consumption.
- 8) With endocrine diseases.
- 9) With Diabetes Mellitus and Hypertension.
- 10) With myocardial infarction.

V. Observation And Results

In our clinical study where serum uric acid levels are obtained from COPD patients and observed for in hospital morbidity and mortality. The subjects under study had detailed clinical examination and underwent spirometry and serum uric acid levels are studied along with routine investigations. 28% of subjects had adequate oxygen saturation in room air (>90%) and are subjected to 6 minute walk test of which 9 had desaturation and 19% of subjects maintained oxygen saturation. Most of the patient either did not require hospitalization or needed hospitalization for a maximum of 3 – 4 days (74%). Patients with severe grade of COPD had hospitalization more than 5 days (26%). In hospital mortality was 6% with ICU care required for 16% of the subjects, 12% required NIV and 74% of subjects required supplemental oxygen, LTOT required in 12% of subjects. CT chest and Chest x ray were done in all 100 patients in which a combination emphysema and bronchitis dominated with 68% and emphysema dominant in single disease group – 18%. 52% of patients had FEV1 in the range of severe disease, 48% subjects had mMRC grade 3 with 52% subjects had GOLD severe disease. Acute exacerbation of COPD (more than 5 episodes) in 1 year was present in 38% of subjects. Our study included 100 patients among them 8 had mild, 22 had moderate, 52 had severe and 18 had very severe COPD. 68% subjects had high serum uric acid and 32% had low uric acid levels, 24% had low BMI and 60% of the subjects were more than 50 years of age and predominantly males.

Table 1: Exposure To Cotton Dust, Smoking, Ets, Bmf

	yes	no
smoking	64	36
occ.exp	56	44
envexp	36	64
bmf	12	88

ETS –Environmental Tobacco Smoke, BMF –Bio mass Fuel

64% of subjects were smokers and 36% were exposed to environmental tobacco exposure and 56% had occupation exposure to cotton dust with 12% predominantly females exposed to bio mass fuel. Urban population comprised 78% with 46% had duration of illness around 6-10 years

Table 2: Age, Sex Distribution, Duration Of Disease & Place Of Living

	No Of Patients	
Age	<50 Yrs	40
	>50 Yrs	60
Sex	Male	82
	Female	18
Duration	0-5 Yrs	28
	6-10 Yrs	46
	>10 Yrs	26
Place	Urban	78
	RURAL	22

Cough, wheeze and crepitations were the predominant signs and symptoms in the study group and 34% of subjects had fever and 36% had cyanosis with 22% of subjects had loud P2 signifying pulmonary hypertension.

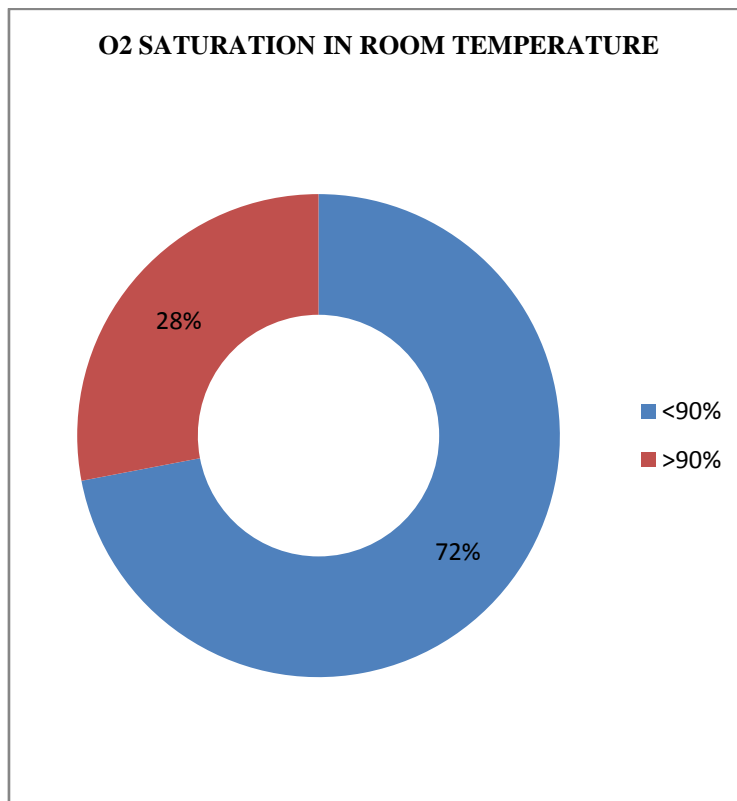
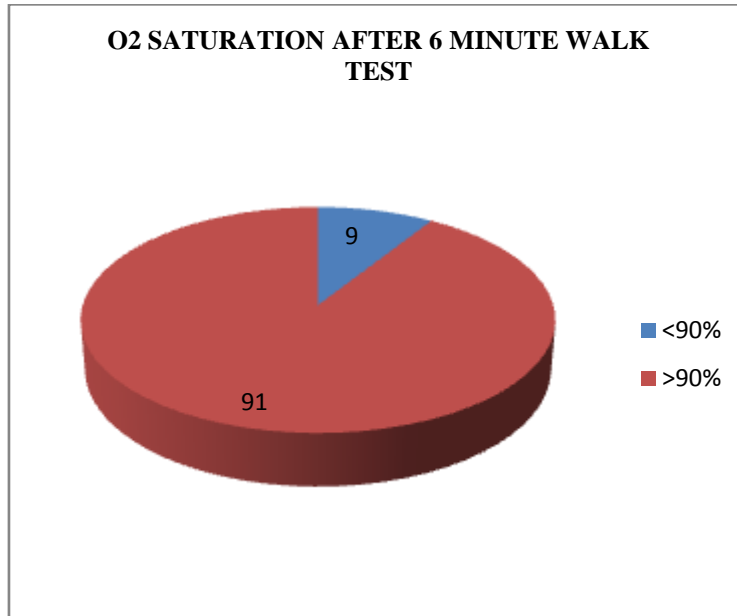
Table 3: Observation Of Signs And Symptoms Presentation

	Signs & Symptoms	
	Present	Absent
Cyanosis	36	64
Clubbing	44	56
Loud P2	22	78

Creptitation	94	6
Wheeze	92	8
Cough	100	0
Fever	34	66

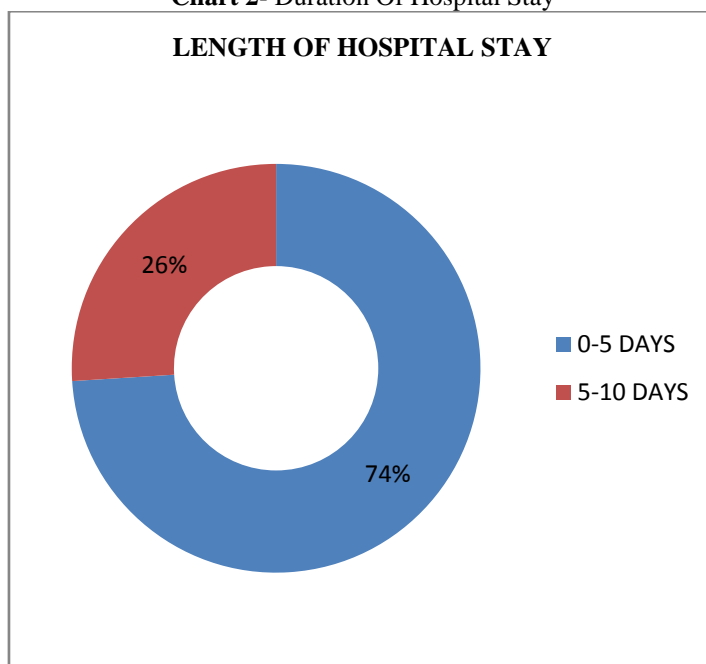
28% of subjects had adequate oxygen saturation in room air(>90%) and are subjected to 6 minute walk test of which 9 had desaturation and 91%of subjects maintained oxygen saturation.

Chart 1-O2 Saturation



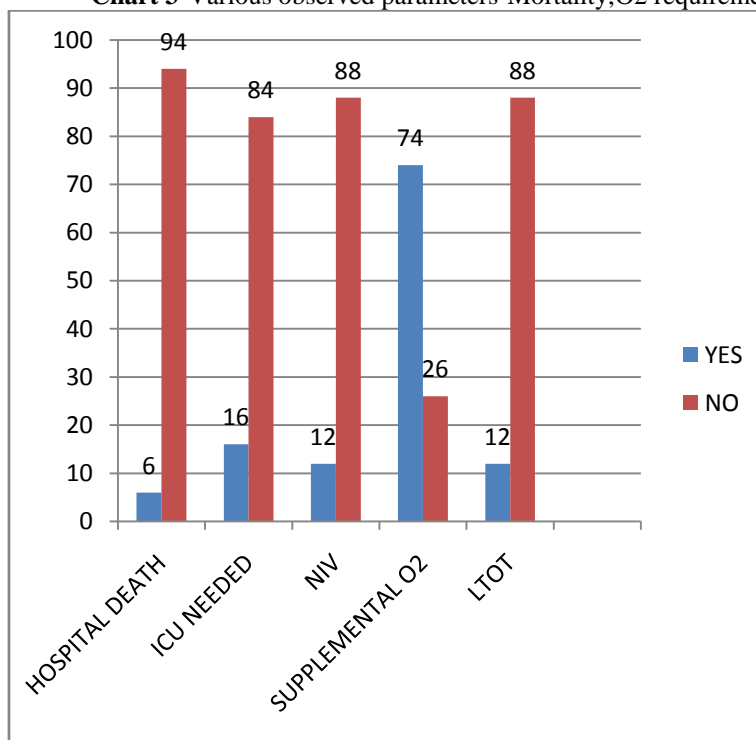
Most of the patients either did not require hospitalization or needed hospitalization for a maximum of 3 – 4 days(74%).

Chart 2- Duration Of Hospital Stay



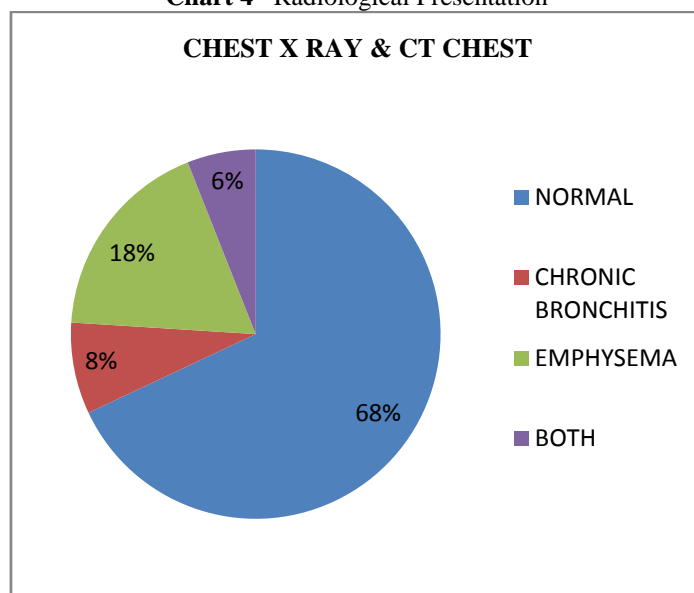
Patients with severe grade of COPD had hospitalization more than 5 days(26%). In hospital mortality was 6% with ICU care required for 16% of the subjects, 12% required NIV and 74% of subjects required supplemental oxygen, LTOT required in 12% of subjects.

Chart 3-Various observed parameters-Mortality,O2 requirement



CT chest and Chest x ray were done in all 100 patients in which a combination emphysema and bronchitis dominated with 68% and emphysema dominant in single disease group – 18%.

Chart 4 –Radiological Presentation



52% of patients had FEV1 in the range of severe disease, 48% subjects had mMRC grade 3 with 52% subjects had GOLD severe disease. Acute exacerbation of COPD (more than 5 episodes) in 1 year was present in 38% of subjects. Mean uric acid level was correlated with each parameter and their results are reviewed. Age and duration of illness correlated with mean serum uric acid levels of 7.6 and 8.1 respectively with statistical significance of p value 0.651 and 0.002 in the age and duration groups. Persons who are smokers, males and from urban population though statistically not significant in correlation with mean serum uric acid levels, urban male patients are more exposed to environmental toxins than their rural counterpart, patients who are smokers in correlation with FEV1, mMRC grades and GOLD severity showed statistical significance (P=0.025).

Table 4 -Uric Acid Correlation With O2 Saturation & Hospital Stay

Parameters		URIC ACID LEVELS		Significance(p value)
		High	Low	
O2 Saturation	Less than 90%	63	9	Significant(0.001)
	More than 90%	5	23	
Length of hospital stay	<5 days	42	32	Significant(0.001)
	>5days	26	0	

Fever, cyanosis, clubbing, crepitations and loud P2(mean serum uric levels-8.87) show statistical significance with p value of 0.001 since cough and wheeze were present in most of the subjects, the p value could not be made nor they are statistically significant. Correlation of occupational exposure and environmental exposure did not show statistical significance but these subjects had high chance of exposure to the above risk factors. Female predominantly exposed to bio mass fuel had mean uric levels of 7.8 had statistical significance with p value=0.441. Correlation with oxygen saturation in room air (mean uric acid -8.01), after 6 minute walk test (mean uric acid level -6.1) (pvalue=0.042), length of stay in the hospital (mean uric acid)-6.9, in hospital death (mean uric acid -8.9), in ICU admission and NIV requirement (mean uric acid levels-9.3,9.4) and requirement of supplemental oxygen (mean uric acid -8.1) showed statistical significance with p value=0.001. Correlation with Long term oxygen therapy (mean uric acid-8.0) did not have statistical significance.

Table 5–Various Paramaters With Uric Acid Correlation

Parameters		URIC ACID LEVELS		Significance(P Value)
		High	Low	
Hospital Death	Yes	6	0	Non Significant(0.083)
	No	62	32	
ICU Admission	Yes	16	0	Significant(0.003)
	No	52	32	
NIV Requirement	Yes	12	0	Significant(0.011)
	No	56	32	

Correlation with chest x ray and ct chest (mean uric acid level-8.2), FEV1 grade of very severe disease (mean uric acid level-8.9), mMRC grade 4 (mean uric acid level-8.9) and GOLD very severe disease (mean uric acid level-9.07) were statistically significant with p value=0.001. Patients with AE COPD had mean serum uric acid level of 8.75 had statistical significance of p=0.003.

VI. Discussion

Uric acid is end product of purine metabolism in humans. Purine nucleotides are metabolised in all the cells of the body, but uric acid is produced due to xanthine oxidase found in small bowel and liver. Enzymes involved in uric acid synthesis are

1. Phosphoribosyl pyrophosphate amidotransferase.
2. Hypoxanthine guanine phosphoribosyltransferase.
3. Xanthine oxidase.

Xanthine oxidase is required to convert xanthine to uric acid. High protein diet increases serum uric acid levels and excretion of uric acid. 700 mg of uric acid is produced in the body daily. 500 mg excreted by kidneys and 200 mg by small bowel. The mean serum levels of uric acid in males and females are 5.3 mg per decilitre and 4.7 mg per decilitre. Hyperuricemia is defined as serum uric acid more than 7 mg per decilitre in males and 6mg per decilitre in females. Due to lack of uricase enzyme in humans, uric acid cannot be converted to urea which in turn, leads to nearly 50 times increased level of Uric Acid in comparison to non primatemammals. Serum uric acid is an important risk factor for systemic hypertension, diabetes mellitus, cardiovascular disease, cerebrovascular accident and metabolic syndrome. Its role as antioxidant and prooxidant is best explained by an ANTIOXIDANT-PROOXIDANT urate redox shuttle operating usually over an atheromatous plaque causing further damage to vascular structures leading on to multiple complications. RNA products of the cells that are released due to oxidative stress from the nuclei of the cells that are exposed, are converted through purine metabolism to uric acid. This forms the basis of uric acid elevation in COPD due to hypoxic damage of the cells of the lungs and has a direct relationship with the worsening symptoms of COPD, with frequent morbidity and mortality. In addition, other demographic and clinical factors, such as gender, BMI, smoking index, and serum glucose levels, are known to be associated with increased serum levels of UA [4]. Therefore, careful consideration of these factors is required when assessing the relationship between pulmonary function and Uric Acid levels. In our study, patients with increased Uric acid levels required more prolonged hospitalisation, as length of stay in the hospital (mean uric acid-6.9), in hospital death (mean uric acid -8.9), in ICU admission and NIV requirement (mean uric acid levels-9.3,9.4) and requirement of supplemental oxygen (mean uric acid -8.1) showed statistical significance with p value=0.001.

These results are comparable with those obtained by Bartziokas *et al.* [5], who assessed serum uric acid, as a predictor of clinically important outcomes in a prospective cohort of patients with COPD. Bartziokas *et al.* study also showed patients with increased UA levels required more prolonged hospitalisation, and required more often use of NIV and ICU admission in 30 days. Studies from Egyptian journal of bronchology (EJB) showed median range of uric acid for severe and very severe disease as 7.6 and 7.9 respectively, studies from European respiratory (ERS) journal showed median serum uric acid levels in severe and very severe disease as 7.5 and 8.6 respectively. In our study the mean uric acid levels in severe and very severe disease were 7.9 and 9.0 respectively. Uric acid levels have been associated with clinical and functional characteristics in patients with COPD in cross-sectional studies conducted in past [6,7,12]. In the present study, High serum uric acid levels are present in patients whose oxygen saturation was <90% at rest. Embarak *et al.* study no such correlation was found, between serum uric acid and arterial oxygen saturation as in other studies [8,9,10].

In a study done by Bartziokas *et al.* Serum UA levels were higher in patients with more severe airflow limitation and in frequent exacerbations. Embarak *et al.* study also showed similar results. Mean uric acid levels in patients with AE COPD were 7.7 and 6.6 in patients with exacerbations more than 5 and less than 5 per year respectively (ERS study). In our study the mean serum uric acid level in AE COPD were 8.75 in frequent exacerbation group and 6.84 in patients with lesser exacerbations in one year which was statistically significant (p value=0.01). Significant associations between serum uric acid and FEV1, Medical Research Council dyspnea scale were reported by Garcia-Pachon *et al.* [6], but they included a small sample of stable COPD patients and no data on the outcomes of those patients were reported. Our study revealed FEV1 grade of very severe disease (mean uric acid level-8.9), mMRC grade 4 (mean uric acid level-8.9) and GOLD very severe disease (mean uric acid level-9.07) were statistically significant with p value=0.001.

Another study done by Sato *et al.* that included 91 COPD outpatients receiving home oxygen therapy, has suggested that serum uric acid/creatinine ratio is related to the survival of such patients [6]. In our study, High serum uric acid levels were present in patients, who needed long term oxygen therapy and supplemental oxygen therapy. Patients with AE COPD had mean serum uric acid level of 8.75 with statistical

significance of $p=0.003$. In contrast, a population-based cross-sectional study by Nicks *et al.* [11] has shown reduced uric acid levels in patients with severe COPD. This discrepancy may be related to the fact that serum uric acid was measured at the time of hospitalization for an AE COPD, in contrast to the stable condition of the patients studied by Nicks. In comparison with our study and SamehEmbarak *et al.* (Egyptian journal of Bronchology), Bartziokas *et al.* the results are as follows

Parameters	Samehembarak Et Al(P Value)	Bartziokas Et Al(P Value)	Our Study(P Value)
Fev1	<0.001	<0.001	0.001
Length Of Hospital Stay	<0.001	<0.001	0.001
Oxygen Saturation	0.99	<0.001	0.001
In Hospital Death	0.09	0.004	0.012
Icu Admission	0.004	0.012	0.001
Niv Requirement	<0.001	<0.001	0.001

VII. Conclusion

High serum uric acid levels had decremental effects in patients with Chronic Obstructive Pulmonary Disease. Serum uric acid levels were elevated in patients with GOLD stage -severe and very severe disease. In hospital morbidity and mortality were increased in patients with elevated serum uric acid levels as evidenced by repeated admissions due to frequent exacerbations of the disease and required more aggressive ICU management and long term oxygen therapy, Non Invasive Ventilation and supplemental oxygen therapy. To conclude, the study signifies that the high serum uric acid levels portends a poor prognosis and also predicts worsening of the stage of the disease from the initial presentation and necessitates early intervention, treatment and rehabilitation to reduce the morbidity and mortality associated with the disease to achieve a good quality of life.

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Conflict of interest

The authors declare that there is no conflict of interest

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