



TO FIND OUT THE CORRELATION OF SERUM URIC ACID AND ASSESS THE PROGNOSTIC ROLE OF SERUM URIC ACID IN ACUTE EXACERBATION OF COPD

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(ABSTRACT) **BACKGROUND AND OBJECTIVE:** various parameters and investigation are use for assessment of severity ,morbidity and mortality in acute exacerbation of COPD, In our study we explore the utility of serum uric acid level in AECOPD,

METHODS: Hospital based descriptive type of observational study of 122 patients of 40-70 years of age group COPD exacerbation . A primary reason for admission other than AECOPD were exclude from study.

RESULTS: In COPD exacerbation mMRC dyspnea grade increase ,the serum uric acid level increase and hospitalisation also increase with high uric acid as compared to low serum uric acid. majority(65.3%) patients of low Uric Acid group having Mean Post-bronchodilator FEV1% was 60.86±14.34while in high uric acid group(60%) patients was 31.78±10.99. Mean pH is low and high CO₂ among also high uric acid patient as compared to low serum uric acid and more

CONCLUSION: Serum Uric Acid level is be a beneficial biomarker in predicting the outcome in COPD patients hospitalized for acute exacerbation.

KEYWORDS :

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases¹.

Based on BOLD study and other large scale studies it is estimated that no of COPD cases was 384 million in 2010 with a global prevalence of 11.7%. By 2030, COPD will occupy fifth rank in terms of burden of disease and third in terms of mortality^{2,3}. Approximately, 30 million people are suffering from COPD in India,⁴ Mortality due to COPD is rising faster; and more even compared to that due to infectious diseases⁵

Table 1: Classification of severity of air flow limitation in COPD as per GOLD criteria

Classification of COPD by impairment of lung function		
Stage	Severity	Spirometry (postbronchodilator)
GOLD 1	Mild	FEV ₁ ≥80% predicted FEV ₁ /FVC <0.7
GOLD 2	Moderate	50% ≤ FEV ₁ < 80% predicted FEV ₁ /FVC <0.7
GOLD 3	Severe	30% ≤ FEV ₁ < 50% predicted FEV ₁ /FVC <0.7
GOLD 4	Very severe	FEV ₁ <30% predicted FEV ₁ /FVC <0.7

COPD exacerbations are complex events usually associated with increased airway inflammation, mucus production and marked gas trapping. increased dyspnea, exacerbations must be dirrerentiated clinically from other events such as acute coronary syndrome, wors ening congestive heart failure, pulmonary embolism and pneumonia⁶.

Exacerbations are mainly triggered by respiratory viral infections although bacterial infections and environmental factors such as pollution. The most common virus isolated is human rhinovirus (the cause of the common cold) and can be detected for up to a week after an exacerbation onset. When associated with viral infections, exacerbations are often more severe, last longer and precipitate more hospitalizations, as seen during winter⁷.

Some COPD patients are particularly susceptible to frequent exacerbations (defined as two or more exacerbations per year) and these

patients have been shown to have worse health status and morbidity than patients with less frequent exacerbations. Patients at high risk of frequent exacerbations can be recognized across all disease severity groups. The exact reason for an individual's increased susceptibility to exacerbation symptoms remains largely unknown.

The strongest predictor of a patient's future exacerbation frequency remains the number of exacerbations they have had in the prior year⁷. Other factors that have been associated with an increased risk of acute exacerbations and/or severity of exacerbations include an increase in the ratio of the pulmonary artery to aorta cross sectional dimension (i.e., ratio > 1) a greater percentage of emphysema or airway wall thickness measured by chest CT imaging and the presence of chronic bronchitis⁸.

Serum Uric Acid, the final product of purine degradation, has been shown to increased in the hypoxic state including patients with COPD and has been proposed as a marker for impaired oxidative metabolism^{9,10}.

An increase in serum uric acid occurs as a result of purine catabolism secondary to tissue hypoxia^{11,12}. It is to be expected that patients with worse pulmonary function and more dyspnea represent a group of COPD patients with a higher risk of hypoxia and impaired oxidative metabolism³, especially during acute exacerbation. Serum uric acid has been studied in several conditions associated with hypoxic states and results consistently show that this parameter reflects a worse situation or a worse prognosis.

mechanisms may be involved in the presence of high uric acid levels in AECOPD. First, prolonged hypoxemia may result in increased pulmonary artery pressures, which promotes purine degradation through increased xanthine oxidase activity¹⁴. Finally, COPD is characterized by systemic inflammation and elevated uric acid levels have been associated with increased levels of inflammatory markers¹⁵, few studies have evaluated the role of uric acid levels on admission for acute exacerbations of COPD on the outcome of exacerbation and the long term survival and exacerbation frequency of COPD patients. The aim of the present study was to evaluate the possible role of serum uric acid as a biomarker for the prediction of the outcome of patients hospitalised for AECOPD

MATERIALS AND METHODS

The study was undertaken in Department of Respiratory medicine, Patients attending OPD and Emergency department and admitted in

Department with Acute Exacerbation of COPD. Hospital based descriptive type of observational study.

INCLUSION CRITERIA:

Those who gave informed consent, and age group was 40-70 years, Diagnosed case of COPD in exacerbation condition,

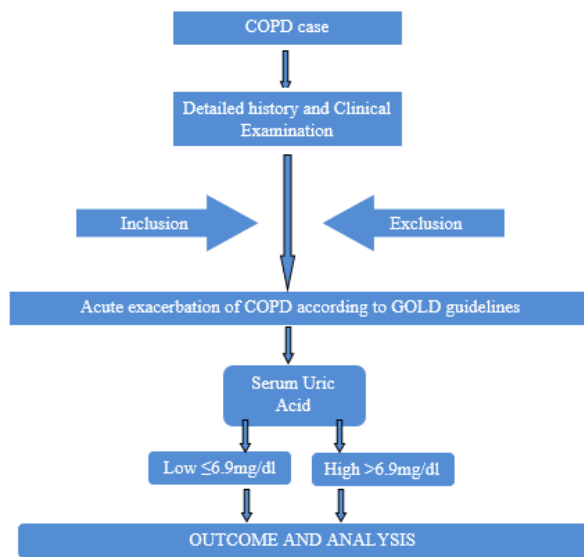
EXCLUSION CRITERIA:

A primary reason for admission other than AECOPD, A history of respiratory disorders other than COPD, Conditions affecting levels of uric acid – PAH, Diabetes mellitus, gout and Drugs affecting levels of serum uric acid if taken.

STATISTICAL ANALYSIS:

Data was entered in MS Excel sheet and was subjected for statistical analysis. Data was presented as n (%) for categorical variables, mean ±SD for normally distributed values and median (interquartile range (IQR)) for skewed numerical variables. Comparisons between groups were performed using Chi-square test and unpaired t-test or Mann–Whitney U-test. The significance level for tests were determined as 95% (P<0.05). MED CALCI 12.2.1.0 Version software was used for statistical calculation.

FLOW CHART



OBSERVATIONS AND RESULTS

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation

The patients were divided in two groups according to Serum Uric Acid levels. Groups were:

1. Low Serum Uric Acid(≤6.9mg/dl)
2. High Serum Uric Acid(>6.9mg/dl)

Table 1. Distribution of patients according to Serum Uric acid levels. (n=122)

Serum Uric Acid	No. of patients	Percentage
≤6.9	72	59.0%
>6.9	50	41.0%
Total	122	100%

Table 1 shows that out of 122 patients of study population, 72(59%) patients were in Low serum Uric Acid(≤6.9mg/dl) group, 50(41%) patients were in High serum Uric Acid(>6.9mg/dl) group

Table 2. Distribution of patients according to age group in relation to Serum Uric acid levels (n=122)

Age group (Yrs)	Serum Uric Acid				Total No.
	Low(≤6.9)		High(>6.9)		
	No.	%	No.	%	
<40	1	1.4%	0	0.0%	1
41-50	8	11.1%	7	14.0%	15
51-60	18	25.0%	13	26.0%	31

Age group	No.	%	No.	%	Total
61-70	45	62.5%	30	60.0%	75
Total	72	100%	50	100%	122

In low and high serum uric acid group, maximum patients 45(62.5%) were in same age group of 61-70yrs ,

Table 3. Distribution of patients according to gender in relation to Serum Uric acid levels (n=122)

Sex	Serum Uric Acid				Total No.
	Low(≤6.9)		High(>6.9)		
	No.	%	No.	%	
Male	59	81.9%	42	84.0%	101
Female	13	18.1%	8	16.0%	21
Total	72	100.0%	50	100.0%	122

In study 72 patients from low serum uric acid group, 59(81.9%) patients were males and 13(18.1%) patients were females. And in high serum uric acid group, 42(84.0%) patients were males and 8(16.0%) patients were females

Table 4. Distribution of the patients according to symptoms (n=122)

Symptoms	No. of patients	Percentage
Breathlessness	102	83.6%
Expectoration	75	61.5%
Cough	90	73.8%
Wheezing	22	18.0%
Chest pain	35	28.7%

Table 4 shows that most of patients in ACOPD having Breathlessness and Expectoration with Cough.

Table 5. Distribution of patients according to Smoking status in relation to Serum Uric acid levels.(n=122)

Smoking Status	Serum Uric Acid				Total No.
	Low(≤6.9)		High(>6.9)		
	No.	%	No.	%	
Current Smoker	46	63.9%	30	60.0%	76
Ex Smoker	8	11.1%	5	10.0%	13
Non Smoker	18	25.0%	15	30.0%	33
Total	72	100.0%	50	100.0%	122

Maximum patient were current and ex smoker in both group.

Table 6. Distribution of patients according to Pack years in relation to Serum Uric acid levels.(n=122)

Pack years	Serum Uric Acid				Total No.
	Low(≤6.9)		High(>6.9)		
	No.	%	No.	%	
0-10	20	27.8%	16	32.0%	36
11-20	3	4.2%	1	2.0%	4
21-30	7	9.7%	6	12.0%	13
31-40	21	29.2%	12	24.0%	33
>40	21	29.2%	15	30.0%	36
Total	72	100.0%	50	100.0%	122

Above table shows that maximum smoker in low serum uric acid group were 31 to 40 Pack years while maximum smoker in high serum uric acid group were >40 Pack years .

Table 7. Distribution of according to mMRC dyspnea grade in relation to Serum Uric acid levels (n=122)

mMRC grade	Serum Uric Acid				Total No.
	Low(≤6.9)		High(>6.9)		
	No.	%	No.	%	
0	0	0.0%	0	0.0%	0
1	0	0.0%	0	0.0%	0
2	21	29.2%	9	18.0%	30
3	40	55.6%	15	30.0%	55
4	11	15.3%	26	52.0%	37
Total	72	100.0%	50	100.0%	122

Above table shows that mMRC dyspnea grade 3 having maximum 55.6% of low serum uric acid group, and in high serum uric acid group the maximum 52.0% of patients were in mMRC dyspnea grade 4

Table 8. Distribution of patients according to Cardiovascular Disease in relation to Serum Uric acid levels(n=122)

Cardiovascular Disease	Serum Uric Acid				Total
	Low(≤6.9) n=72		High(>6.9) n=50		
	No.	%	No.	%	No.
Present	9	12.5%	20	40.0%	29
Absent	63	87.5%	30	60.0%	93
p-value	0.0004				

Above table shows that patients from low serum uric acid group 9(12.5%) had cardiovascular disease while from high serum uric acid group 20(40%) patients had cardiovascular disease(p value < 0.001)

Table 10. Distribution of patients according to frequency of admissions in previous year in relation to Serum Uric acid levels (n=122)

Admission in Previous one year	Serum Uric Acid				Total
	Low(≤6.9)		High(>6.9)		
	No.	%	No.	%	No.
0	45	62.5%	12	24.0%	57
1	16	22.2%	24	48.0%	40
2	9	12.5%	10	20.0%	19
≥3	2	2.8%	4	8.0%	6
Total	72	100.0%	50	100.0%	122

Above table shows that from low serum uric acid group 45(62.5%) maximum had no past medical history of previous admission while high serum uric acid group 12(24%) had no past medical history of previous admission in the last year in hospital; 38(76%) had past history of one to three admission in the last year in high serum uric acid level.

Table 11. Distribution of patients according to COPD GOLD staging in relation to Serum Uric acid levels (n=122)

GOLD stage	Serum Uric Acid				Total
	Low(≤6.9)		High(>6.9)		
	No.	%	No.	%	No.
1	10	13.9%	1	2.0%	11
2	47	65.3%	5	10.0%	52
3	13	18.1%	30	60.0%	43
4	2	2.8%	14	28.0%	16
Total	72	100.0%	50	100.0%	122

Above table shows that maximum patients were in GOLD COPD stage 2 and stage 3 (83.4%) in low serum uric acid group, while that maximum patients were in GOLD COPD stage 3 and stage 4 (88%) in high serum uric acid group

Table 12. Distribution of patients according to FEV1% in relation to Serum Uric acid levels(n=122)

FEV1% of predicted	Serum Uric Acid				Total
	Low(≤6.9)		High(>6.9)		
	No.	%	No.	%	No.
< 30%	2	2.8%	14	28.0%	16
30-49%	13	18.1%	30	60.0%	43
50-79%	47	65.3%	5	10.0%	52
≥ 80%	10	13.9%	1	2.0%	11
Total	72	100.0%	50	100.0%	122

Above table shows that patients from low serum uric acid group, FEV1 % of predicted was 30-79% . FEV1 % of predicted was in 60 (83.4%) in high uric acid group 44(88%)patients,

Table 13. Distribution of patients according to pH in relation to Serum Uric acid levels (n=122)

pH	Serum Uric Acid				Total
	Low(≤6.9)		High(>6.9)		
	No.	%	No.	%	No.
≤ 7.30	8	11.1%	7	14.0%	15
7.31-7.35	27	37.5%	20	40.0%	47
7.36-7.40	28	38.9%	18	36.0%	46
>7.40	9	12.5%	5	10.0%	14
Total	72	100.0%	50	100.0%	122

Above table shows that maximum no of patients from in low serum uric acid group had pH between 7.31-7.4, 55(76.4%) and maximum

patients from in high serum uric acid group had pH between <7.30-7.35, 27(44%).

Table 15. Distribution of patients according to PaCO2 in relation to UA levels

PaCO ₂	Serum Uric Acid				Total
	Low(≤6.9)		High(>6.9)		
	No.	%	No.	%	No.
36-45	10	13.9%	5	10.0%	15
46-55	38	52.8%	25	50.0%	63
56-65	20	27.8%	15	30.0%	35
66-75	4	5.6%	3	6.0%	7
≥76	0	0.0%	2	4.0%	2
Total	72	100.0%	50	100.0%	122

Above table shows that maximum patients of PaCO₂ 46-65 level having in of low serum uric acid group is 58(79%), while in high uric acid group maximum patients of PaCO₂46-65 level having is 35(80%).

Table 16. Distribution of patients according to length of hospitalisation in relation to Serum Uric acid levels (n=122)

Length of hospitalization	Serum Uric Acid				Total
	Low(≤6.9)		High(>6.9)		
	No.	%	No.	%	No.
≤ 5	46	63.9%	20	40.0%	66
06-10	26	36.1%	25	50.0%	51
11-15	0	0.0%	5	10.0%	5
>15	0	0.0%	0	0.0%	0
Total	72	100.0%	50	100.0%	122

Above table shows that hospitalisation period is longer in high serum uric acid patients .

Table 18. Relationship between Serum Uric Acid and Smoking in AECOPD

Smoking Status	Serum Uric Acid			
	Low(≤6.9) n=72		High(>6.9) n=50	
	No.	%	No.	%
Smoker	54	75.0%	35	70.0%
Non Smoker	18	25.0%	15	30.0%
p-value	0.54			

In our study there was no statistically significant relationship(p = 0.54) between Smoking and Serum Uric acid levels in patients of Acute Exacerbation of COPD

Table 19. Relationship between No. of hospitalization in previous year and Serum Uric Acid Levels in AECOPD

No. of hospitalization in previous year	Serum Uric Acid	
	Low(≤6.9) n=72	High(>6.9) n=50
Median	0	1
Range(IQR)	0-1	1-2
p-value	0.0004	

Statistically significant relationship(p<0.001) between levels and No. of hospitalization is more in previous year in Serum high Uric acid patients of Acute Exacerbation of COPD

Table 20. Relationship between mMRC dyspnea grade and Serum Uric Acid Levels in AECOPD

mMRC dyspnea grade	Serum Uric Acid	
	Low(≤6.9) n=72	High(>6.9) n=50
Median	3	4
Range(IQR)	2-3	3-4
p-value	0.0009	

In our study there was statistically significant relationship(p<0.001) between Serum Uric acid levels and mMRC dyspnea in patients of Acute Exacerbation of COPD

Table 21. Relationship between FEV₁ % of predicted and Serum Uric Acid Levels in AECOPD

FEV ₁ % of predicted	Serum Uric Acid	
	Low(≤6.9) n=72	High(>6.9) n=50
Mean	60.86	31.78
S.D.	14.34	10.99

p-value	<0.001
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Predicted FEV1 % is much less in Serum Uric acid levels in patients of Acute Exacerbation of COPD (p<0.001)

Table 22. Relationship between COPD GOLD staging and Serum Uric Acid Levels in AECOPD

GOLD stage	Serum Uric Acid	
	Mean	S.D.
1	5.94	0.36
2	6.16	0.38
3	7.65	0.96
4	8.1	0.80
p-value	<0.001	

Relationship (p<0.001) between Serum Uric acid levels and COPD GOLD staging in patients of Acute Exacerbation of COPD

Table 23. Relationship between pH and Serum Uric Acid Levels in AECOPD

pH	Serum Uric Acid	
	Low(≤6.9) n=72	High(>6.9) n=50
Mean	7.36	7.33
S.D.	0.047	0.06
p-value	0.002	

High Serum Uric acid levels having low pH in patients of Acute Exacerbation of COPD

Table 25. Relationship between Length of hospitalization and Serum Uric Acid Levels in AECOPD

Length of hospitalization(days)	Serum Uric Acid	
	Low(≤6.9) n=72	High(>6.9) n=50
Mean	4.55	7.24
S.D.	2.68	3.19
p-value	<0.001	

longer hospitalization in patients of high Serum Uric acid levels in Acute Exacerbation of COPD (p<0.001)

Table 26. Comparison of need for NIV with Serum Uric acid levels (n=122)

Need for NIV within 30 days of admission	Serum Uric Acid				Total
	Low(≤6.9) n=72		High(>6.9) n=50		
	No.	%	No.	%	No.
Present	8	11.1%	18	36.0%	26
Absent	64	88.9%	32	64.0%	96
p-value	0.001				

High serum uric acid group, 18(36%) patients needed more NIV as compare to low serum uric acid group 8(11.1%) (p value=0.001)

Table 28. Distribution of patients according to Mortality within 30 days in relation to Serum Uric acid levels (n=122)

Death within 30 days of admission	Serum Uric Acid				Total
	Low(≤6.9) n=72		High(>6.9) n=50		
	No.	%	No.	%	No.
Present	1	1.4%	9	18.0%	10
Absent	71	98.6%	41	82.0%	112
p-value	0.001				

High serum uric acid group, 9(18%) patients died more within 30 days of admission as compare to low serum uric acid group 1(1.4%) patient. The difference was statistically significant (p value = 0.001)

DISCUSSION

The present study was undertaken to Study the Level of Serum Uric Acid in predicting outcome in patients of Acute Exacerbations of Chronic Obstructive Pulmonary Disease at tertiary care hospital. Patients who were previously diagnosed COPD (as per GOLD Guidelines) and had Acute Exacerbation at the time of admission were included in the study with informed consent

In this Hospital based descriptive type of observational study 122 Patients of COPD with Acute Exacerbation admitted in Department of

Respiratory Medicine., patients with conditions Affecting levels of uric acid^{16,17} – PAH, Diabetes mellitus, gout and patients taking drugs affecting levels of serum uric acid were excluded, 122 patients of study population in which 72(59%) patients had Low serum Uric Acid(≤6.9mg/dl) levels, 50(41%) patients had High serum Uric Acid(>6.9mg/dl) levels. 82.78% patients were male and 17.21% patients were female. The male female ratio was 4.81: 1. This higher incidence of COPD in male can be attributed to smoking¹⁸, from low serum uric acid group, maximum patients 45(62.5%) were of 61-70 yrs of age while Out of 50 patients from high serum uric acid group, maximum patients 30(60%) were of 61-70 yrs of age, 13(26%) patients were of 51-60 yrs of age .

In the present study most common presenting symptoms in AECOPD patients was breathlessness in 102(83.6%) and cough in 90(73.8%), Expectoration in 75(61.5%), chest pain in 35(28.7%) and 22 (18.0%) patients presented with wheezing. serum uric acid level is not much affecting by smoking¹⁹. Patients with high serum uric acid levels had more dyspnea (mMRC) compared with patients with low Serum Uric Acid. The difference was statistically significant (p<0.001). patients with high serum uric acid levels had more (1-2) hospital admissions in previous year compared zero patients with low Serum Uric Acid. The difference was statistically significant (p<0.001). Also serum uric acid levels presented a positive correlation with length of hospitalization in all study population ($r_s = 0.325, P < 0.001$). These are in accordance with many previous studies²⁰. Mean serum uric acid levels on admission were higher in patients with more severe airflow limitation [5.94±0.36, 6.16±0.38, 7.65±0.96 and 8.1±0.8mg/dl for GOLD stages 1-4, respectively; $P < 0.001$]. Bartziokaset *al*²¹ also found higher Median (IQR) serum uric acid levels in patients with more severe airflow limitation. study shows the serum uric acid levels had a significant negative correlation with FEV1 predicted ($r_s = 0.654, P < 0.001$), which is in accordance with many previous reports. Another study by Ergün, Recai&Ergün, Dilek²² also found an inverse relationship between post bronchodilator FEV1 and serum uric acid level. patients with high serum uric acid levels had more higher comorbidity (i.e. cardiovascular disease and arterial hypertension) compared with patients with low serum uric acid levels.. The difference was statistically significant (p<0.001). 12(24%) patients from high serum uric acid (n=50) group and 3(4.2%) patients from low serum uric acid (n=72) group patients had arterial hypertension. The difference was statistically significant (p=0.001). Patients with high serum uric acid levels had more acidemia when compared to patients with low Serum Uric Acid. in patients with high serum Uric Acid levels compared to 7.36±0.04 in patients with low Serum Uric Acid levels. The difference was statistically significant (p=0.002)

But there is also a study by Ergün, Recai&Ergün, Dilek²² which showed insignificant relationship between Serum Uric Acid and Ph. Patients with high serum uric acid levels had more hypercapnia when compared to patients with low Serum Uric Acid. Mean PaCO₂ was 56.22±8.23 in patients with high serum Uric Acid levels compared to 51.63±6.67 in patients with low Serum Uric Acid levels. The difference was statistically significant (p=0.001). patients with increased uric acid levels required prolonged (7.24±3.19) hospitalisation when compared to patients (4.55±2.68) with low Serum Uric Acid. This was statistically significant (p<0.001). patients with increased uric acid levels often required NIV when compared to patients with low Serum Uric Acid, 18(36%) patients from high serum uric acid (n=50) group and 8(11.1%) patients from low serum uric acid group (n=72) needed NIV. The difference was statistically significant (p=0.001). high serum uric acid levels on admission were associated with increased 30-day mortality in patients with AECOPD. 9(18%) patients from high serum uric acid (n=50) group and 1(1.4%) patient from low serum uric acid group (n=72) died within 30 days of admission. The difference was statistically significant (p=0.001). study by Galamay et al²³, Mohamed H. Zidan et al (2015)²⁴ Sontakke et al.²⁵ Another study by Ergün, Recai & Ergün, Dilek²² and study by EmbarakS et al²⁶, Bartziokaset *al*²¹ AtefeVafaei et al²⁷. found the same kind of result.

SUMMARY AND CONCLUSION

SUMMARY:

The 122 patients (82.8% patients were male and 17.2% patients were female)

admitted with COPD A/E. Routine investigations such as CBC, CHEST X-ray, ABG, Serum Uric Acid and Spirometry were done. The

patients were divided in two groups according to Serum Uric Acid levels. Groups are: Low Serum Uric Acid (≤ 6.9 mg/dl) and High Serum Uric Acid (> 6.9 mg/dl). 72(59%) patients were in Low serum Uric Acid (≤ 6.9 mg/dl) group, 50(41%) patients were in High serum Uric Acid (> 6.9 mg/dl) group. Maximum patients (61.5%) were from 61-70 Yrs age group and 1.3% patients were from < 40 Yrs age group. Our study conclude that the mMRC dyspnea grade increase with high serum uric acid level and hospitalisation also increase with high uric acid as compared to low serum uric acid. majority(65.3%) patients of low Uric Acid group having Mean Post-bronchodilator FEV1% was 60.86 ± 14.34 while in high uric acid group (60%) patients was 31.78 ± 10.99 . Mean pH is low and high CO_2 among also high uric acid patient as compared to low serum uric acid and more NIV is required for treatment with high 18(36%) uric acid patients compared with low 8(11.1%) uric acid and ICU admission and death rate is high with high serum uric acid. Also, patients with increased uric acid levels had more co-morbidities.

CONCLUSION:

Serum Uric Acid level is be a beneficial biomarker in predicting the outcome in COPD patients hospitalized for acute exacerbation. Measurement of Uric Acid level is among the routine analyses and it is an easily applicable, cheap and widely available test. Early detection of high-risk patients via Uric Acid measurement would contribute to improved prognosis by leading to more intensive treatment.

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