Elevated levels of serum uric acid and its correlation with unfavorable outcomes in individuals who experience acute exacerbation of chronic obstructive airway disease.

Running Title: Correlation of Serum uric acid level with severity of COPD.

Istikhar Ali Sajjad 1,*, Awais Aslam2. Mehr Muhammad Imran3, Mehvish Aqil4.

ABSTRACT

Objective: To evaluate the correlation between increased levels of blood uric acid and unfavorable outcomes in patients with acute exacerbation of chronic obstructive pulmonary disease.

Methodology: This Prospective Cohort study was conducted at Pulmonology Department of Jinnah Hospital; Allama Iqbal Medical College, Lahore from Dec 2019 to May 2020. Total 142 patients (71 from exposed and 71 from unexposed group) that satisfied the inclusion criteria were studied. Depending upon level of serum uric acid at the time of admission, before initiation of therapy, these patients were considered as exposed and unexposed. Demographics and all-cause mortality, ICU admission, need for non-invasive ventilation (NIV) and length of hospital stay (LOS) for AECOPD within 30 days was logged.

Results: The 95% confidence interval for the relative risk (RR) of all-cause mortality in the exposed group (raised serum uric acid at the time of admission) was 6.50 with a p-value of 0.003. Patients from exposed group also needed to stay in the hospital longer and more frequently, needed noninvasive breathing and ICU admittance at 30 days. There were increased number of exacerbations among exposed group as compared to unexposed (p-value = 0.002).

Conclusion: The raised serum uric acid at the time of admission is linked to higher chance of morbidity and death in patients of AECOPD. This finding may be helpful in identifying high risk patients so that intensive and rigorous treatment may be initiated early.

Key words: COPD, AECOPD, Serum Uric Acid, Chronic Smokers.

Introduction:

Chronic obstructive pulmonary diseases (COPD) is classified as "a preventable and treatable disease state characterized by air flow limitation that is not fully reversible, is usually progressive, and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases primarily caused by cigarette smoking."[1] COPD is only present if there is chronic airflow restriction; chronic bronchitis without chronic airflow obstruction is not considered COPD. In the United States, approximately 10 million people are affected by COPD, which makes it the 4th leading cause of mortality. Chronic obstructive pulmonary disease (COPD) is a major contributor to morbidity and mortality rates, and its prevalence is increasing globally.[2] An acute episode known as an acute exacerbation of COPD (AECOPD) is one that is featured by a patient's respiratory symptoms getting significantly worse and necessitating a change in medicine.[3,4] Some COPD patients are more vulnerable than others to exacerbations, which negatively affects longevity.[5] According to estimates, COPD is projected to become the third leading cause of mortality worldwide by the year 2020.[6]

Published studies have suggested that up to 50% of exacerbations are not reported to the study team, leading to higher exacerbation rates in symptom-based studies compared to event-based studies.[7,8] It is anticipated that patients with COPD may be unaware of their condition or significance of receiving treatment,[9-11] they could be despondent or have limited movement.

Purine breakdown results in the formation of serum uric acid.[12] Purine is broken down by tissue hypoxia, and since uric acid (UA) is a by-product of this biochemical route, it may be a good indicator of how severe the hypoxia is.[13] It is significant to note that serum uric acid is suggested as measure of defective oxidative metabolism and is an independent indicator of poor prognosis in a number of processes such as congestive heart failure, pulmonary thromboembolism, primary pulmonary hypertension, Eisenmenger syndrome, or acute myocardial infarction-related future adverse effects.[14-18]

Pulmonary function impairment can lead to reduced oxygen intake, which often results in tissue hypoxia, especially during acute exacerbation of chronic obstructive pulmonary disease (AECOPD). In a broad community in Japan, serum uric acid levels has been linked to occurrence of airflow obstruction.[19] however, a short cross-sectional research on COPD patients found a substantial correlation between creatinine & serum uric acid ratio, Dyspnoea and spirometry results.[20] Despite the available data, only a limited number of studies have investigated the impact of serum uric acid levels on the prognosis of acute exacerbations of chronic obstructive pulmonary disease (COPD), as well as the long-term survival rates and incidence of future exacerbations in COPD patients.

1: Assistant Prof. Pulmonology. Faisalabad Medical University. Faisalabad.

2: Assistant Prof. Pulmonology. Aziz Fatima Medical College. Faisalabad.

3: Senior Registrar, Pulmonology. Services Hospital. Lahore.

4: Medical Officer, Pulmonology. Faisalabad Medical University, Faisalabad.

***=corresponding author**
dr.istikhar@gmail.com.

One research that looked at whether or not serum uric acid could assist in identifying COPD patients who were more probable to experience adverse effects and might benefit from early, extensive treatment was carried out in Egypt, revealed that patients with AECOPD had a higher 30-day mortality rate when their serum uric acid levels were elevated (6.9 mg/dl) at the time of admission. The area under the receiver operating characteristic curve for serum uric acid as a predictor of 30-day mortality in patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD) was 0.721 (95% CI: 0.63-0.80), with a sensitivity of 0.82 and a specificity of 0.61 for a cut-off point of greater than 6.9 mg/dl. This result was statistically significant (P = 0.021)

Moreover, patients with elevated serum uric acid levels were more likely to require frequent hospitalizations and had a higher likelihood of requiring non-invasive ventilation (NIV) and admission in the ICU within 30 days.[21] A similar study published in the European Respiratory Journal found that elevated levels of serum uric acid (≥6.9 mg/dL) independently were associated with a higher risk of mortality in 30-days in a multivariate Cox regression analysis (HR 1.317, 95% CI 1.011–1.736; P = 0.044). Furthermore, the study revealed that elevated serum uric acid levels were associated with an increased likelihood of acute exacerbations of COPD, hospitalizations, and 30-day mortality during a one-year follow-up period.[22]

However, a study conducted in India showed contradictory results.[23] The study found that compared to other oxidative stress indicators, individuals with chronic obstructive pulmonary disease had low blood uric acid levels, such as ceruloplasmin. This readily accessible, economical biomarker is trustworthy and helpful in identifying individuals with high-risk chronic obstructive pulmonary disease, which benefits from rigorous treatment. Furthermore, identification of a high-risk group of COPD patients through serum uric acid measurements could aid in optimizing future management plans.

Objective:

To evaluate the correlation between increased levels of blood uric acid and unfavorable outcomes in patients with acute exacerbation of chronic obstructive pulmonary disease.

Methodology:

This prospective cohort study was conducted at Pulmonology Department of Jinnah Hospital; Allama Iqbal Medical College, Lahore from Dec 2019 to May 2020. Total 142 patients (71 from exposed and 71 from un-exposed group) that satisfied the inclusion criteria were studied. Depending upon level of serum uric acid at the time of admission, before initiation of therapy, these patients were considered as exposed and unexposed. Demographics and all-cause mortality, ICU admission, need for non-invasive ventilation (NIV) and length of hospital stay (LOS) for AECOPD within 30 days was logged. The sample size was determined using the WHO sample size tool. This was calculated with level of significance as 5%, power of test as 90% and the projected proportion of unfavourable outcomes among those who were exposed was 18%, whereas the expected percentage of ill outcomes among those who were not exposed was 3%.

The study recorded details of patients, including their age, gender, BMI, smoking status, previous therapy. This data was taken alongside with comorbidities before admission, with a focus on CVD such as CAD and hypertension, as well as diabetes mellitus. Upon admission, clinical data such as vital signs and the degree of dyspnoea were also collected. Dyspnoea was assessed using the modified Medical Research Council (mMRC) scale. Before initiating the therapy serum uric acid and lab tests such as CBC, C-reactive protein (CRP), serum creatinine were performed and the blood samples were taken at the time of admission in emergency room. Treatment and release decisions were made by treating doctors who were not engaged in the research, in conformance to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) standard of recommendations. According to GOLD guidelines, post-bronchodilator spirometry in a stable condition was used to diagnose and classify airflow limitation., that is in the next 06 months and 04 weeks before the admission as per the patients' records or one month to two months after discharge.

Within 30 days, all-cause mortality, need for Non-Invasive Ventilation (NIV), ICU admittance and Length of hospital stay (LOS) for AECOPD were all documented. The research authors assessed patients upon admission and discharge and then followed up with telephone conversations for 1 month. An investigator appointed for the study recorded and document the vitals of the patient. For AECOPD, hospitalizations were recorded centered on patient's own-reporting which is then duly scrutinized by the hospital documents as needed. The primary end-point was all-cause mortality at 30 days. In addition, length of hospitalization, need for mechanical breathing, and the incidence of AECOPD episodes in the previous 30 days were all noted. SPSS v25.0 was used to analyze data.

Difference among both groups were compared using Chi-Square test to see association between adverse outcomes and assess its significance. Data was stratified for age, gender, uric acid levels, hospital stay, co-morbidities and post stratification relative risk was calculated. Relative risk of ≥ 1 was taken significant. p-value of ≤ 0.05 was taken as significant.

Results:

During study period, 142 patients presenting with Chronic Obstructive Pulmonary Disease (COPD) were enrolled. Mean age of patients was 57.85±6.48 years, male (n=110, 77.5%) outnumber females (n=32, 22.5%). Most of the patients (n=72, 50.7%) were from low socioeconomic stratum, 40(28.2%) were from middle and 30(21.1%) patients were from high socioeconomic stratum. Among all 84(59.2%) were current smokers and 53(37.3%) were ex-smokers while only 5(3.5%) patients never smoked. Majority of patients (58.5%, n=83) were on irregular treatment, when presented with AECOPD. The mean weight of patients was 65.09±17.245 kg and BMI 25.56±5.47 kg/m2.Based upon the level of serum uric acid, at the time of presentation and before initiation of appropriate therapy, patients were segregated into two groups. Comparison of age between these patients shown in graph no 1. Those having serum uric acid levels ≥6.9mg/dl were labelled as exposed, other having serum uric acid value below 6.9mg/dl were labelled as unexposed. The exposed group had relatively higher number of patients with history of ≥40 pack years of smoking (53.5% vs. 30.9%, p-value=0.031), were more non-compliant with treatment (69% vs. 47.9%, and p-value=0.011), more duration of hospital stay (Chi-square=12.053, p-value = 0.001). The more patients in exposed group had to be treated with NIV (38% vs. 62%) and spent more days on NIV (Chi-square=1.936, p-value=0.164). Similarly, more patients from exposed group required ICU care as compared to unexposed group (Chi-

square= 2.119, p-value=0.145). During 30 days follow up, the patients in exposed were found to develop more exacerbations (Chi-square=12.195, p-value=0.002) and resulted in significantly higher adverse outcome (18.3% vs. 2.8%, RR=6.50, p-value=0.003).

Graph No 1: Age groups comparison for exposed and unexposed

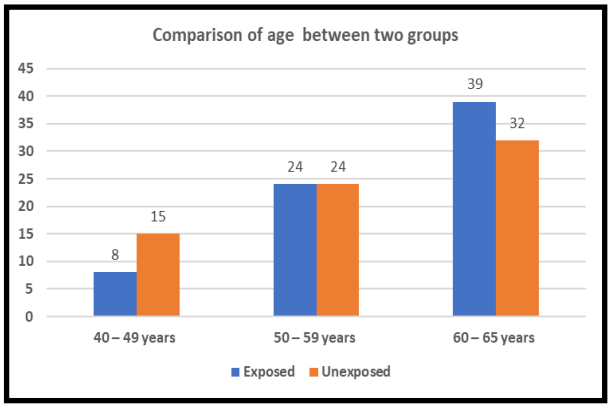

Table No 1: Comparison of condition on discharge of the patients between groups.

Group	Condition On Discharge			Total	p-value
	Stable	Unstable	Died		
Exposed	57	9	5	71	0.084
Unexposed	66	3	2	71	
Total	123	12	7	142	

Table No 2: Comparison of adverse outcome of the patients at follow-up after one month according to exposure.

Group	Adverse Outcome		Total	P-value	Relative Risk
	Yes	No			
Exposed	13	58	71	0.01	6.5
Unexposed	2	69	71		
Total	15	127	142		

Discussion:

Finding of the current study showed that high levels of serum uric acid in patients with AECOPS are associated with high mortality and also with a greater chance to develop AECOPD within 30days of discharge. Additionally, individuals with higher amounts of uric acid needed longer hospital stays & recurrent admissions to intensive care unit (ICU) at 30 days.

There could be number of reasons in AECOPD that cause elevated uric acid levels. First, extended hypoxia that is made worse by AECOPD may contribute to elevated pressures in the pulmonary artery that increase afterload in the right ventricle encouraging the purine degradation by increasing xanthine-oxidase activity.[24] Secondly, a large percentage of COPD patients also have coexisting cardiovascular illness, linked to high uric acid,[25] Supported by higher prevalence of cardiovascular illness in our sample of individuals with elevated uric acid levels. Thirdly, compromised pulmonary function decreases the consumption of oxygen resulting in hypoxic tissues, which is more evident in patients with AECOPD, also lead to increase in uric acid levels as the lungs and peripheral tissues are harmed. Lastly, COPD is featured by systemic inflammation.[26] Higher inflammation markers have been related to elevated uric acid levels. (for e.g. interleukin-6CRP)[27] which impacts on the detection of patients with COPD.[28-29]

Several prior investigations have tried to identify biomarkers that predict mortality in hospitalized AECOPD patients. Several blood biomarkers, serum amyloid-A, tumour necrosis factor, interleukin-6, CRP and fibrinogen, were measured in a research, but they were unable to identify the mortality and morbidity of hospitalized patients of AECOPD.[30] In a Swiss study, Stolz et al[31] Pro-adrenomedullin was found to be an indicator of long-term mortality. A research looked at a variety in clinical characteristics and biomarkers to identify independent determinants of AECOPD hospitalization prognosis and developed the multicomponent DECAF (dyspnoea, acidaemia, consolidation, atrial fibrillation and eosinopenia) score.[32] Uric acid levels previously have been linked to functional and clinical features in COPD patients in cross-sectional research.[33-35] A Spanish research found a link between blood uric acid / creatinine ratio and FEV1, forced vital capacity, & the MRC dyspnoea scale.[35] However, the study only included a limited number of people with stable COPD and no data on their outcomes.

In a extensive community spirometry-based study conducted in Japan, correlations was identified amongst serum uric acid level and spirometry readings.[34] though, none of the research subjects were diagnosed with COPD by a physician.

Another study that examined the correlation between serum uric acid/creatinine ratio and longevity was conducted on 91 COPD patients receiving home oxygen treatment.[33] he authors' conclusions may be limited in terms of generalizability to the broader COPD patient population. Despite fact that previous research demonstrate that uric acid levels grow in more severe disease, Nicks et al[36] conducted a population-based cross-sectional analysis that demonstrated lower amounts of uric acid in people having serious COPD. The differences in the findings between the studies could be due to variations in characteristics of studied population and that the serum uric acid was measured during hospitalization for AECOPD, rather than in stable patients.

On a 30-day follow-up, we discovered that individuals with higher uric acid levels had more exacerbations, contrary to findings of Garcia-Pachon et al.[35] This disparity may be explained by the prospective design of our research. There is evidence to support our observation that frequent exacerbators had higher baseline blood uric acid levels than non-frequent exacerbators in our study.

The ECLIPSE dataset's latest data suggests that severe COPD is more commonly associated with frequent exacerbations.[37] However, finding in the multivariate Cox regression analysis is that in AECOPD serum uric acid levels remained an independent predictor of risk for hospitalizations indicates that this biomarker could be beneficial in identifying individuals who are at high risk for exacerbations.

Fact that blood uric acid is a by-product of purine degradation, which increases in variety of tissue injury and inflammation manifestations in COPD patients, all of which are highly dynamic processes, should be considered.[38-39] Several factors such as CVD, food intake, , renal dysfunction,

and genetic disorders of purine metabolism can influence uric acid levels. In addition, genetics can affect how individuals with COPD respond to inflammation.[40-43]

The current study had some limitations. Firstly, seven patients lost to follow-up after hospital release were excluded from the study. Secondly we were not knowing about the prior existence of AECOPD in our community. The third limitation of our study is related to the research design. We used telephone follow-up, which may have resulted in less reporting of episodes of hospitalization and AECOPD. Based on our results, it appears that blood uric acid levels could be used as a tool for identifying COPD patients who are at a higher risk of experiencing severe outcomes and may require early and intensive therapy. This is particularly noteworthy given that blood uric acid is an easily accessible and low-cost biomarker that can be quickly analysed.

Conclusion:

Elevated serum uric acid levels has an increased risk of morbidity and mortality in patients with COPD.. Uric acid level may therefore help to identify high risk patients and intensive treatment may be initiated at once.

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