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The Relationship between Serum Uric Acid and Severity of Chronic Obstructive Pulmonary Disease (COPD)

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ABSTRACT

Introduction: Some evidence exists about the possible relationship between the serum uric acid (UA) and exacerbation of the chronic obstructive pulmonary disease (COPD). Present study intended to compare the COPD-related variables and the one-year outcome between the two groups of patients with the high and low UA.

Material and Methods: This cohort study consisted of 112 patients with COPD exacerbation. The participants were categorized into low (i.e., <6.5 mg/dL UA, 61 patients) and high (i.e., ≥6.5 mg/dl UA, 51 patients) groups. The variables including: Global initiative for Obstructive Lung Disease (GOLD) classification, oxygen saturation, PCO2, FEV1 (forced expiratory volume in 1 second), trans-thoracic 2D echocardiographic indices, and serum BUN (blood urea nitrogen) and creatinine levels were recorded. Afterwards, the patients were followed up for one year and some other variables such as taking oral antibiotic for respiratory infections, admission to hospital or ICU due to COPD exacerbation, and survival were documented monthly.

Results: The mean serum level of creatinine was significantly higher in the high UA group (1.1±0.4 mg/dL) than the low UA group (1.01±0.1 mg/dL) (P=0.02). No significant difference was observed between the two groups regarding the GOLD classification, FEV1, oxygen saturation, pCO2, and echocardiographic indices. In the one-year follow-up, 42 cases (82.4%) of the high UA group and 39 patients (63.9%) of the low UA group reported taking oral antibiotics, which was indicative of a significant difference (P=0.03). Hospital admission was likewise significantly higher in the high UA group (30 patients, 58.8%) than in the low UA group (23 cases, 37.7%) (P= 0.03).

Conclusion: Those patients with the UA level of ≥ 6.5 mg/dL experienced more hospital admission and were more likely to take oral antibiotics for respiratory infections during a year. However, UA did not correlate with FEV1 or COPD severity.

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Introduction

Chronic obstructive pulmonary disease (COPD) is one of the common chronic respiratory conditions with an estimated prevalence of 5% in the whole population of the US (1). A study performed in the US reported the prevalence of stage 2 or higher COPD as 10% among the middle-aged population (2). COPD encompasses three subtypes of chronic bronchitis, emphysema, and chronic obstructive asthma, all of which being characterized by airflow limitation, breathing

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difficulty, coughing, and other symptoms/signs. It has high morbidity and mortality rates and is the third leading cause of death in the developed countries (3, 4).

Generally, COPD has a poor prognosis (5). Several studies have been done to determine the prognostic factors that can assist in various areas such as grading the severity of the COPD, further managements, predicting lung function decline, clinical practice for educating the patients, and providing the patients with realistic expectations. Decreased forced expiratory volume in one second (FEV1) is a well-established prognostic factor (6) along with variables such as smoking, low body mass index (BMI), exercise capacity, male gender, and comorbid diseases, especially, heart failure (7). The BODE index (Body mass index, airflow Obstruction, Dyspnea, and Exercise) was developed specifically for COPD patients to evaluate mortality and hospitalization risk (8).

Among various categories of predictive and influential factors reported for COPD, inflammatory biomarkers have gained attention recently. For example, C-reactive protein (CRP) is an acute phase reactant, the elevation of which over time has been shown to be associated with declined FEV1 and forced vital capacity (FVC) (9). Serum uric acid level (10-13) and uric acid to creatinine ratio (14) have also been noted in literature as the factors that are associated with poorer prognosis and higher mortality in COPD patients.

Uric acid is the final end product of metabolic degradation of purine nucleotides. Hypoxia, as occurs in the COPD and heart failure, results in depletion of adenosine triphosphate (ATP) and purine nucleotide metabolism activation, which leads into uric acid accumulation and hyperuricemia (15). Uric acid has antioxidant property and is responsible for 60% of the plasma antioxidant capacity (16). In addition, it has pro-inflammatory role in high levels (13, 17, 18).

Present study was conducted due to the important effects noted for uric acid, and since the studies regarding serum uric acid level in COPD patients are limited. There were two main series of objectives. Firstly, we intended to compare the FEV1, echocardiographic indices, and arterial blood gas (ABG) analyses between those with the high and low serum uric acid levels. Secondly, in a 1-year follow-up period, adverse events were compared between the two mentioned uric acid groups.

Materials and Methods

Study Population and Research Design

In this cohort study which lasted from March 2015 to March 2016, the study population consisted of the patients who referred to the Emergency Unit of Vali-e-Asr Hospital, Birjand University of Medical sciences, Birjand, Iran with the diagnosis of acute exacerbation of COPD. The inclusion criteria included both genders at any age for whom the diagnosis of COPD had been made before presentation to the Emergency Department. The exclusion criteria included: 1) history of gout and renal uric acid stones, 2) taking medications such as allopurinol that decrease uric acid level, 3) pulmonary diseases other than COPD, 4) chronic kidney disease (serum creatinine >2 mg/dL), 5) severe hepatic failure, 6) malignant diseases, and 7) taking diuretics and cytotoxic medicines. The included patients were followed for one year and were contacted monthly to assess the outcomes of interest.

Sample Size

Sampling was performed through convenience method. In the previous report regarding the relationship between serum uric acid level and mortality (10), mortality was 14.9% and 3% in the high and low uric acid groups, respectively. Considering α=0.05, power= 80%, and using the following formula, the sample size was calculated as 112 subjects (56 in each groups of the low and high uric acid levels):

$$\frac{\left(z\left(1-\frac{\alpha}{2}\right)\sqrt{p(1-p)}+z(1-\beta)\sqrt{p1(1-p1)+p2(1-P2)}\right)^2}{(p1-p2)^2}$$

Variables

The considered variables included the demographic data, echocardiography indices, emergency department presentation due to COPD exacerbation, admission to hospital or intensive care unit (ICU) because of COPD exacerbation during the follow-up period, mortality, and the need for taking oral antibiotics for respiratory infections. The severity of the disease was graded according to the Global Initiative for Obstructive Lung Disease (GOLD) classification (19).

Data Collection

The demographic data gathered at the first presentation included age, gender, height, and weight. Body mass index (BMI) was calculated. Venous blood sample was obtained from the brachial vein and sent to the laboratory in order to measure the uric acid, creatinine, and blood urea nitrogen (BUN) levels, along with other routine lab tests on the first day of admission. 2D transthoracic echocardiography, spirometry, and ABG analysis were performed at the submission time.

Uric acid-based Classification

According to the assayed uric acid level, the patients were categorized into two groups of uric acid levels of < 6.5 mg/dL and ≥ 6.5 mg/dL.

Statistical Analyses

The data were gathered and entered into the SPSS software (Ver. 16.0). Descriptive indices such as frequency, percentage, mean and standard deviation (±SD) were used to express the data. For comparing the outcomes of interest and the variables between the two studied groups, the Chi-square and Fischer's exact tests were used for categorical variables. The Student's t-test was also used in order to compare the quantitative variables between the two groups. Significance level was considered as P=0.05.

Ethics

The study protocol was approved by the Ethics Committee of Birjand University of Medical Sciences, Birjand, Iran. The study objectives were explained for the patients prior to participation and if agreed, written consents were taken.

Results

The study population consisted of 112 patients, 44 of which were males and 68 were females. Mean (±SD) age of the patients was 67.2 (±12.9) years. Mean (±SD) BMI value was 23.5 (±0.41) kg/m^2.

Analyses at the First Presentation

Regarding the serum uric acid level, there were 61 patients with serum uric acid levels of < 6.5 mg/dL and 51 patients with levels of ≥ 6.5 mg/dL. The number of male patients was 26 (61%) and 18 (29.5%) in the high and low uric acid groups, respectively (P=0.03). The age difference between the high uric acid (65.4±13.1 years) and low uric acid groups (68.9±12.7 years) was not significant (P=0.1).

There were 11 patients with GOLD stage III and 50 with stage IV in the low uric acid group. In the high uric acid group, patients with stages III and IV of GOLD classification were 10 (19.6%) and 41 (81.4%) subjects, respectively. No significant difference was observed between the two groups regarding the GOLD classification. Mean (±SD) uric acid levels in GOLD III and IV stages were 4.1 (±1.7) and 4.8 (±2.2) mg/dL, respectively, and the difference between them was not significant (P=0.2) (Fig. 1).

Table 1 presents comparison of quantitative variables including BMI, serum creatinine, serum BUN, oxygen saturation, pCO2, FEV1, and echocardiographic indices between the low and high uric acid groups. As could be observed, all the variables were comparable between the two groups, except the serum creatinine level, which was significantly higher in the high uric acid group. Systolic heart failure was detected in one patient from the low uric acid group and 2 patients from the high uric acid group (P=0.4). Diastolic heart failure was found in 5 patients among the low uric acid group and in 6 patients among the high uric acid group (P=0.5).

Follow-up Analyses

In the high uric acid group, a higher proportion of the patients (42 cases, 82.4%) reported taking oral antibiotics during the follow-up period compared to the low uric acid group (39 patients, 63.9%) (P=0.03). Table 2 summarizes the data regarding referring to the emergency department due to COPD exacerbation, admission to the hospital or ICU, and hospitalization duration. Significantly more patients in the high uric acid group (30 patients, 58.8%) required hospital admission during the one-year period in comparison to the low uric acid group (23 cases, 37.7%) (P=0.03). No statistically significant difference was observed regarding the number of emergency department visits between the

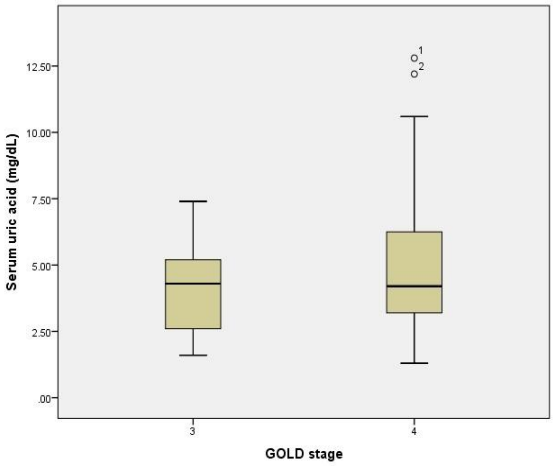

Figure 1. Boxplot showing uric acid level in GOLD stages III (21 patients) and IV (91 patients)

Table 1. Comparison of quantitative variables assessed at the first presentation between the low and high uric acid groups

	Uric acid < 6.5 mg/dL (n= 61)	Uric acid ≥ 6.5 mg/dL (n= 51)	P value[a]
BMI (kg/m^2)	22.7 (2.2)	24.3 (5.8)	0.06
Creatinine (mg/dL)	1.01 (±0.1)	1.1 (±0.4)	0.02
Blood urea nitrogen (mg/dL)	39.9 (±17.01)	45.8 (±25.8)	0.1
Oxygen saturation (%)	79.6 (±13.1)	77 (±18.1)	0.3
pCO2 (mmHg)	51.2 (±14.6)	55.3 (±16.1)	0.3
FEV1 (% predicted)	23.08 (±9.7)	22 (±10.6)	0.5
LVEF (%)	55.4 (±5.6)	54.4 (±4)	0.2
PAP (mmHg)	48.7 (±17)	51.9 (±14.6)	0.2

- Abbreviations: BMI= body mass index; FEV1= forced expiratory volume in one second; LVEF= left ventricular ejection fraction; PAP= pulmonary artery pressure- All the data are presented as mean (±standard deviation)[a] Student's t test

Table 2. Comparison of emergency department visit, hospital admission, hospitalization duration, and ICU admission between the low uric acid (<6.5 mg/dL, N= 61 patients) and high uric acid (≥6.5 mg/dL, N= 51 patients) groups

		Low uric acid	High uric acid	P value
ED visits		7 (11.5%)	12 (23.5%)	0.1[a]
Number of ED visits	Once	6 (85.7%)	9 (75%)	0.58[a]
	Twice or more	1 (14.3%)	3 (25%)	
Hospital admissions		23 (37.7%)	30 (58.8%)	0.03[a]
Number of hospital admissions	Once	15 (65.2%)	29 (66.7%)	0.91[a]
	Twice or more	8 (34.8%)	10 (33.3%)	
Hospitalization duration, day		3.7 (±7)	4.9 (±6.2)	0.3b
ICU admissions		2 (3.3%)	2 (3.9%)	0.8[a]

Abbreviations: ED= emergency department; [a] = Chi-square test; b Student's t test

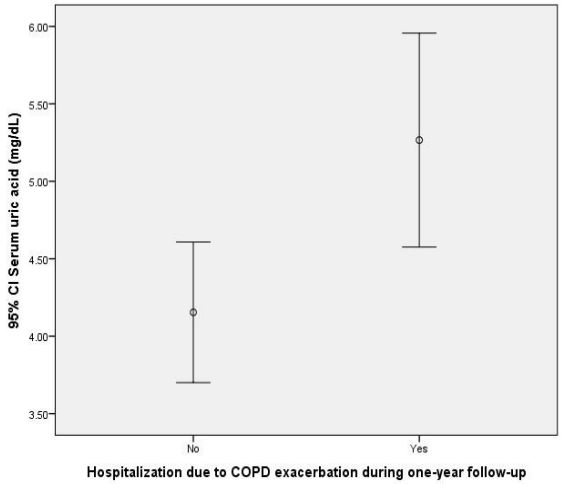

Figure 2. Error bar showing comparison of mean serum uric acid level and its 95% CI (confidence interval) between patients who were admitted to hospital because of COPD exacerbation vs. those not admitted

two groups (P= 0.58). Number of emergency presentations was also higher in the high uric acid group, but the difference was not statistically significant. Mean (±SD) serum uric acid level in those who were hospitalized was 5.2 (±2.5) mg/dL during the follow-up, which was higher than the uric acid concentration during the same period in those who were not admitted to the hospital (4.1±1.7 mg/dL), though the difference was marginally non-significant (P= 0.08) (Fig. 2).

Survival

During the follow-up period, five (8.2%) deaths occurred in the high uric acid group and seven (13.7%) in the low uric acid group, and the difference was not significant regarding this issue (P=0.3).

Discussion

According to our findings, none of the studied variables, including FEV1, oxygen saturation, pCO2, BMI, echocardiographic indices, and COPD severity based on the GOLD classification showed statistically significant difference between the low and high uric acid groups. On the other hand, serum creatinine demonstrated a significant difference between the two study groups. However, in the follow-up, it was revealed that the patients with high uric acid level experienced more hospital admissions due to COPD exacerbation and were more likely to require oral antibiotics for respiratory infections. In contrast, the hospitalization duration and survival were not statistically different between the two uric acid groups.

As stated earlier, uric acid is one of the major anti-oxidants in the body. Respiratory system is extensively exposed to reactive oxygen species; therefore, uric acid and its relationship with respiratory diseases has been the focus of studies in recent years. Serum uric acid can be noted as a marker for impaired oxidative metabolism (14); and it is also believed to play a significant role, besides other factors, in prognosis of respiratory diseases, particularly COPD (17). Moreover, uric acid is detected in high concentrations in the epithelial fluid of both upper and lower respiratory tract and is believed to be an important defense mechanism against oxidants (18). Consequently, higher uric acid levels are expected in more severe hypoxia, which results from more severe COPD state. High serum uric acid has been shown to reflect both worse situation and worse prognosis in conditions with hypoxia such as primary pulmonary hypertension and congestive heart failure (19, 20).

In a previous study, which has considered high uric acid level as concentrations of > 6.9 mg/dL among 214 patients (10), the authors reported results which are similar to the presented findings concerning the one-year mortality. They reported that high uric acid was an independent predictive factor for the 30-day mortality, but not for the one-year survival (10).

Furthermore, they found that high uric acid level was associated with more hospital admissions. In their study, FEV1 was significantly lower in the high uric acid group (10); nonetheless, we did not find any difference regarding FEV1 between the groups. This controversy might be related to several factors including the sample size and different cut-off points for high uric acid.

In another study involving 110 patients with stable COPD and 52 healthy controls, serum uric

acid as well as uric acid/creatinine ratio were not good predictors for exacerbations frequency and COPD severity. However, it should be mentioned that in this study, 47 patients had comorbidities including hypertension and diabetes. Difference of uric acid levels was not statistically significant between those who experienced exacerbation (6 mg/dL) and those who did not experience exacerbation (5.6 mg/dL) more than two times during the preceding 12-month period (11).

In another short-term (30-day) follow-up study (12), 115 patients with acute exacerbation of COPD were included. The patients with higher uric acid level (>6.9 mg/dL) experienced more prolonged hospitalization and were more likely to be admitted to ICU and require ventilation. Also, similar to another study (10), the one-month mortality was higher in the high uric acid group.

In our study, there was no significant difference between the groups regarding heart failure prevalence. Since cardiovascular diseases are mentioned as an important comorbidity that affects the morbidity and mortality in COPD patients (21), we can conclude that this confounder has no influence on the obtained findings. We did not find any difference between the groups concerning the oxygen saturation, which is compatible with the previous studies (12). This might be because several factors affect oxygen saturation including hemoglobin level, cardiac output, and oxygen demands (22).

Here, we measured uric acid upon presentation of patients with acute exacerbation, and all the related studies suggest that uric acid level rises in such conditions. Yet, uric acid level may not rise in the stable COPD. For example, in a study on 367 smokers with COPD, lower uric acid level correlated with more severe COPD (23). We faced some limitations. The follow-up period was relatively short. We suggest that in future studies follow the patients for a longer period. Also, some other laboratory markers such as uric acid to creatinine ratio are useful adjunct prognostic factors in COPD patients. We recommend that the future studies use this marker as well.

The groups studied here were matched regarding the GOLD classification and other comorbidities, such as cardiovascular diseases, which can affect prognosis of COPD. As a result, serum uric acid can be used as an independent factor that can affect COPD exacerbation. Higher mortality in other studies can be due to the associated comorbidities.

Conclusion

Patients with the UA levels of ≥ 6.5 mg/dL experienced more hospital admissions and were more likely to take oral antibiotics for the respiratory infections. However, UA did not correlate with FEV1 or COPD severity.

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Conflict of Interest

The authors declare no conflict of interest.

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