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The Relationship between Serum Uric Acid Levels and Early Mortality in Chronic Obstructive Pulmonary Disease Cases during Exacerbation

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Abstract. *Aim:* In this study, it was aimed to compare the levels of serum uric acid and uric acid/creatinine ratios in patients with COPD during an attack or in stable COPD, and to show whether serum uric acid and uric acid/creatinine ratios are associated with early mortality in COPD patients during an acute attack. *Materials and Methods:* In this study, COPD acute attack (n=155) and stable COPD (n=30) patients were evaluated. The data of these patients were obtained from patient files and computer records. COPD diagnosis and severity assessment were made according to the GOLD 2006 guideline. Participants' age, gender, body mass index, pulmonary function test, arterial blood gas, uric acid, creatinine values and comorbidity information were recorded in the previously prepared Case Data Form. In 2012, when we conducted this study, gold 2006 was taken as the guideline for spirometry measurement, but spirometric measurements determined with reference values determined according to age, height and gender, and FEV1/FVC measurement <70% as diagnostic criteria in acute attack after bronchodilator were the guidelines used later, gold 2017. It is also compatible with gold2020 and gold2021 spirometry criteria. *Results:* It was determined that the uric acid ($p<0.001$) and uric acid/creatinine ($p<0.001$) levels of the patients in the acute attack group were significantly higher than the levels of the patients in the stable group. The attack group was divided into two subgroups according to certain cut-off points for uric acid (>6 mg/dl for women and >7 mg/dl for men) and uric acid/creatinine ratio (median value 7.10). Since the upper limit of the uric acid value measured in the blood is 6 mg/dl in women and 7-8 mg/dl in men, the cut-off points for uric acid (>6 mg/dl for women and >7 mg/dl for men) were determined in our study. According to this categorization, it was determined that there was no statistically significant relationship between uric acid level (odds ratio 2.985 [95% confidence interval 0.618-14,151]) and early mortality risk. *Conclusion:* The results of this study showed that the uric acid and uric acid/creatinine levels in the attack group were higher than the levels in the stable group, but these parameters were not associated with early mortality.

Key words: chronic obstructive pulmonary disease, uric acid, uric acid/creatinine ratio, mortality

1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent respiratory symptoms and recurrent acute exacerbations and severe hypoxemia that develops during these exacerbations, usually due to exposure to harmful particles or gases (1, 2). Chronic obstructive pulmonary disease

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(COPD) is one of the two most common chronic respiratory diseases with asthma, which is characterized by risk factors such as aging and smoking (3). COPD is a health problem characterized by high morbidity and mortality (4, 5). It was determined that hypoxemia and accordingly an increase in uric acid levels were also observed in patients followed up with the diagnosis of COPD, and there was a significant correlation between this increase and the severity of COPD (6 - 8). In addition to COPD, it has been shown that serum uric acid level is increased in diseases such as cyanotic heart disease, heart failure, pulmonary hypertension, and pulmonary thromboembolism in which hypoxemia occurs. Serum uric acid (UA) level is the end product of purine catabolism and conditions that cause hypoxemia are triggers of purine degradation. When correction is made by creatinine ratio to neutralize the effect of possible serum UA level changes due to renal functions, the obtained UA/creatinine (UA/Cr) ratio is sensitive in showing anaerobic changes due to hypoxia. It has been shown that the UA/creatinine ratio is increased in diseases that cause hypoxemia such as uric acid. Studies have shown that the uric acid/creatinine ratio made to neutralize the effect of increased uric acid level is more sensitive than the uric acid level in showing changes due to hypoxia (9, 10). Apart from clinical conditions characterized by hypoxemia, uric acid levels are also affected by factors such as gender, body mass index (BMI) and age. It was found that uric acid levels in men were higher than in women. There was also a correlation between uric acid level and age. It has been shown that conditions with increased body mass index such as visceral obesity are closely associated with uric acid overproduction (11 - 15). In this study, it was aimed to compare the level of serum uric acid and uric acid/creatinine ratios in acute attack or stable COPD cases and to show whether serum uric acid and uric acid/creatinine ratios are associated with early mortality in COPD cases during acute attack.

2. Materials and Methods

After the approval of the ethics committee of the study, the computer records of 2047 patients in total in Erciyes University Faculty of Medicine Hospital Chest Diseases Clinic were examined between March 2008 and May 2011, and those who presented with COPD acute attack, had hypoxemia (SaO_2 <94% or PaO_2 <60 mm-Hg). Anthonisen criteria were used as hospitalization criteria. Patients who met the criteria for increased dyspnea, increased sputum amount and increased sputum purulence were considered. Although increased shortness of breath and increased sputum purulence are considered the most important hospitalization criteria, it is also used as an additional hospitalization criterion in the treatment of comorbidities. (Congestive heart failure, arrhythmias, treatment non-compliance and treatment failure).

In 2012, when we conducted this study, gold 2006 was taken as the guideline for spirometry measurement, but spirometric measurements determined with reference values determined according to age, height and gender, and FEV1/FVC measurement <70% as diagnostic criteria in acute attack after bronchodilator were the guidelines used later, gold 2017. It is also compatible with gold2020 and gold2021 spirometry criteria.

Patients hospitalized due to hypercapnia ($PaCO_2$ >46 mm-Hg) and stable COPD patients evaluated in the outpatient clinic were included in the study. The characteristics of the participants in the acute attack group and stable COPD group, such as age, gender, smoking after a complete physical examination at the time of application; sputum characteristics and exposure to solid waste fuels were recorded. Anthropometric measurement, systolic and diastolic blood pressure arterial values were determined. After the arterial blood gas and biochemical parameter levels were measured, spirometric measurements were made. Electrocardiography and echocardiography were evaluated in all cases.

Exclusion criteria:

- Those with Chronic Kidney Failure (CKD),
- Those with Chronic Liver Disease and/or Failure (Hepatitis B, Hepatitis C, Liver Cirrhosis)
- Those who have malignancy and therefore use cytotoxic drugs,
- Those who have gout and therefore have a history of drug use such as Allopurinol/uricolysis,
- Those who regularly take thiazide diuretics, losartan and similar angiotensin receptor blockers in the last week
- Those with a serum creatinine level above 2-2.5 mg/dl were excluded from the study.

Informed consent forms were obtained from the patients and their relatives before they were accepted into the study.

2.1 Collection of Samples, Laboratory Analysis Methods

Serum uric acid levels and other biochemistry parameters, hemogram measurement, and arterial blood gas were taken with a properly heparinized injector just before the start of treatment. The radial, brachial, or femoral arteries were used when blood samples were taken.

2.2 Statistical Analysis

All data obtained from the study were analyzed using "Statistical Packages for the Social Science" (SPSS) 11.5 on the Windows operating system on the computer. Findings for continuous variables were expressed as mean (mean) ± standard deviation (SD). After descriptive statistical analyzes were made (frequency, percentage distribution, mean±standard deviation), the conformity of the variables to the normal distribution was evaluated with the Shapiro Wilks Test. Continuous variables such as biochemical, complete blood count, spirometric measurement and arterial blood gas parameters of the three groups were compared with the Mann-Whitney U test. Discrete variables were evaluated with Fisher Exact test, Yates Chi-square test, and $p<0.05$ was considered statistically significant.

3. Results

In our study, no significant difference was found between the mean age (p=0.123) and body weight (p=0.975) of the cases in the attack group and the mean age and body weight of the cases in the stable group. The mean height of the cases in the attack group was found to be significantly lower than the average height of the cases in the stable group (p=0.001). The BMI values of the cases in the attack group were found to be significantly higher than the BMI values of the cases in the stable group (p=0.033). Of the cases in the attack group, 38 (30.4%) were female and 87 (69.6%) were male. Of the cases in the stable group, 4 (13.3%) were female and 26 (86.7%) were male. It was determined that there was no significant difference between the gender distributions of the two groups (p=0.097).

There were 56 (45.8%) cases with biomass exposure and 69 (55.2%) cases without biomass exposure in the attack group. In the stable group, there were 10 (33.3%) cases with biomass exposure and 20 (66.7%) cases without biomass exposure. There was no significant difference between the biomass exposure distributions of the two groups (p=0.350). There were 56 (44.8%) cases with pneumonia in the attack group. This may be a relevant confounding factor.

The mean cigarette pack/year (±SD) of the cases in the attack group (n=87) was 40.15±23.79, and the mean cigarette pack/year (±SD) of the cases in the stable group (n=29) was 44.48±21.23. There was no significant difference between the smoking pack-year averages of the two groups (p=0.311). In the attack group, there were 63 (50.4%) smokers who quit, 24 (19.2%) smokers, and 38 (30.4%) non-smokers. In the stable group, there were 19 (63.3%) smokers, 10 (33.3%) smokers, and 1 (3.3%) non-smoker. In the analysis, it was determined that the distribution of smoking history of one group differed significantly from the other group (p=0.007) (Pearson Chi-square test). This significant difference disappeared after the non-smokers with the highest chi-square value were excluded from the analysis (p=0.638). (Yates' Chi-square test). It was found that this significant difference was due to the fact that the rate of non-smokers in the attack group was higher than in the stable group (Table 1). Negative very weak correlation between uric acid values and FEV1 values of all participants (r=-0.186, p=0.021); negative very weak correlation between uric acid values and FEV1% values (r=-0.161, p=0.045); There was a weak negative correlation between uric acid values and FVC% values (r=-0.305, p<0.001). Negative very weak correlation between uric acid/creatinine values and FEV1 values (r=-0.171, p=0.034); negative very weak correlation between uric acid/creatinine values and FEV1% values (r=-0.213, p=0.008); negative weak correlation between uric acid/creatinine values and FVC values (r=-0.277, p<0.001); A weak negative correlation was found between uric acid/creatinine values and FVC% values (r=-0.326, p<0.001). There was no significant correlation between uric acid values and FVC and % FEV1/FVC values (all p values >0.05). No significant correlation was found between uric acid/creatinine values and % FEV1/FVC values (p>0.05 for all correlations) (Table 1).

When the PFT values of the patients in the attack group and the patients in the stable group

Table 1. Relationship between uric acid and uric acid/creatinine values and PFT values of all participants

All participitants (n=155)		**Uric Acid** ***(mg/dl)***	**Uric Acid/ Creatinine** ***(mg/dl)***
FEV_1 *(liter)*	r	**-0.186**	**-0.171**
	p	**0.021**	**0.034**
FEV_1%	r	**-0.161**	**-0.213**
	p	**0.045**	**0.008**
FVC *(liter)*	r	-0.023	**-0.277**
	p	0.778	**<0.001**
FVC%	r	**-0.305**	**-0.326**
	p	**<0.001**	**<0.001**
FEV_1/FVC%	r	0.144	0.046
	p	0.075	0.569

Table 2. Relationship between uric acid and uric acid/creatinine values and PFT values according to partial correlation analysis performed by controlling BMI in all participants

All participants (n=155)		**Uric acid** ***(mg/dl)***	**Uric Acid/ Creatinine** ***(mg/dl)***
FEV_1 *(litre)*	r	**-0.206**	**-0.182**
	p	**0.010**	**0.024**
FEV %	r	**-0.199**	**-0.238**
	p	**0.013**	**0.003**
FVC *(litre)*	r	0.017	**-0.259**
	p	0.832	**0.001**
FVC %	r	**-0.310**	**-0.327**
	p	**<0.001**	**<0.001**
FEV_1/FVC %	r	0.077	-0.001
	p	0.345	0.993

were compared; It was determined that the FEV1 (p=0.002), %FEV1% (p=0.034), FVC (p<0.001) and %FVC (p<0.001) values of the cases in the attack group were significantly lower than the values in the stable group. There was no significant difference between the %FEV1/FVC values of the cases in the two groups (p=0.089) (Table 2). In the partial correlation analysis performed by controlling BMI; negative very weak correlation between uric acid values and FEV1 values of all participants (r=-0.206, p=0.010); negative very weak correlation between uric acid values and FEV1 % values (r=-0.199, p=0.013); There was a weak negative correlation between uric acid values and FVC %values (r=-0.310, p<0.001). Negative very weak correlation between uric acid/creatinine values and FEV1 values (r=-0.182, p=0.024); negative very weak correlation between uric acid/creatinine values and FEV1 %values (r=-0.238, p=0.003); negative weak correlation between uric acid/creatinine values and FVC values (r=-0.259, p=0.001); A weak negative correlation was found between uric acid/creatinine values and FVC % values (r=-0.327, p<0.001). There was no significant correlation between uric acid values and FVC and FEV1/FVC % values (all p values >0.05). No significant correlation was found between uric acid/creatinine values and FEV1/FVC %values (p>0.05 for all correlations) (Table 2).

The uric acid (p<0.001), uric acid / creatinine (p<0.001) and CRP (p<0.001) values of the cases in the attack group were found to be significantly higher than the values of the cases in the stable group. Hemoglobin (p=0.026) values of the cases in the attack group were found to be significantly lower than the hemoglobin values of the subjects in the stable group (Table 3). Negative weak correlation between uric acid values and pH values (r=-0.340, p<0.001) of all participants; A weak positive correlation was found between uric acid values and $PaCO_2$ values (r=0.290, p<0.001). Negative very weak correlation between uric acid values and PaO_2 values (r=-0.229, p=0.004); There was a weak negative correlation between uric acid values and SaO_2 values (r=-0.264, p=0.001). Negative weak correlation between uric acid/creatinine values and pH values (r=-0.263, p=0.001); A weak positive correlation was found between acid/creatinine values and $PaCO_2$ values (r=0.311, p<0.001). Negative very weak correlation between uric acid/creatinine values and PaO_2 values (r=-0.211, p=0.008); A very weak negative correlation was found between uric acid/creatinine values and SaO_2 values (r=-0.158, p=0.049) (Table 3).

In the partial correlation analysis performed by controlling BMI; negative weak correlation between uric acid values and pH values (r=-0.310, p<0.001) of all participants; A weak positive correlation was found between uric acid values and $PaCO_2$ values (r=0.265, p=0.001). Negative very weak correlation between uric acid values and PaO_2 values (r=-0.215, p=0.007); There was a weak negative correlation between uric acid values and SaO_2 values (r=-0.257, p=0.001). Negative very weak correlation between uric acid/creatinine values and pH values (r=-0.243,

Table 3. Relationship between uric acid and uric acid/creatinine values and ABG values of all participants

All participants (n=155)		**Uric Acid** ***(mg/dl)***	**Uric Acid/ Creatinine** ***(mg/dl)***
pH	r	**-0.340**	**-0.263**
	p	**<0.001**	**0.001**
$PaCO_2$ *(mmHg)*	r	**0.290**	**0.311**
	p	**<0.001**	**<0.001**
PaO_2 *(mmHg)*	r	**-0.229**	**-0.211**
	p	**0.004**	**0.008**
SaO_2 *(%)*	r	**-0.264**	**-0.158**
	p	**0.001**	**0.049**

Table 4. Relationship between uric acid and uric acid/creatinine values and FKG values according to partial correlation analysis performed by controlling BMI in all participants

All participants		**Uric Acid** ***(mg/dl)***	**Uric Acid/ Creatinine** ***(mg/dl)***
pH	r	**-0.310**	**-0.243**
	p	**<0.001**	**0.002**
$PaCO_2$ *(mmHg)*	r	**0.265**	**0.295**
	p	**0.001**	**<0.001**
PaO_2 *(mmHg)*	r	**-0.215**	**-0.201**
	p	**0.007**	**0.013**
SaO_2 *(%)*	r	**-0.257**	-0.151
	p	**0.001**	0.062

p=0.002); A weak positive correlation was found between acid/creatinine values and $PaCO_2$ values (r=0.295, p<0.001). There was a very weak negative correlation between uric acid/creatinine values and PaO_2 values (r=-0.201, p=0.013). There was no significant correlation between uric acid/creatinine values and SaO_2 values (p>0.05 for all correlations) (Table 4).

4. Discussion

Serum uric acid (UA) level is the end product of purine catabolism, and conditions that cause hypoxemia are triggers of purine degradation (9, 10). It was found that hypoxemia and accordingly an increase in uric acid levels were also observed in patients followed up with the diagnosis of COPD, and there was a significant correlation between this increase and the severity of COPD (6, 7, 8). In our study, UA and UA/Cr ratios were compared in patients with acute attack and stable COPD, and these values were found to be statistically significantly higher in patients with acute attack. Our study showed that there is a negative correlation between uric acid level and FEV1, %FEV1% and %FVC. In parallel with our study, Aida et al. (2011) showed that forced vital capacity and forced expiratory capacity were associated with serum uric acid levels, and as these values decreased, uric acid levels increased (16). Again, in a study, in which 110 patients with COPD and 52 healthy controls, mean serum uric acid levels and serum uric acid/creatinine ratios were found to be significantly higher in patients with COPD compared to healthy controls, and patients with frequent exacerbations It was found that patients had higher mean serum uric acid levels (17). In another study, serum uric acid level and serum uric acid/creatinine ratio were found to be higher in COPD exacerbation patients (18). In our study, as expected, the uric acid levels of the COPD attack group were found to be higher than the uric acid levels of stable COPD cases.

In this study, we found a negative correlation between uric acid, pH, PaO_2 and SaO_2 levels, and a positive correlation between uric acid and $PaCO_2$ levels in the appearance of those related to arterial blood gas (Table 3).

In studies conducted, there is a relationship between anthropometric parameters such as BMI and the prevalence of hyperuricemia, and conditions with increased BMI, especially visceral obesity, relates to various diseases, interstitial pneumonia and (19) are associated with overproduction of uric acid and deterioration in renal clearance (20).

In our study, without BMI control, there is a negative correlation between uric acid level and FEV1%, FEV1% and FVC%. We found similar results in our study by controlling BMI (Table 2).

The studies report that obesity has negative effects on blood gases (13). In our study, on the other hand, in the analysis we performed by controlling the BMI in the arterial blood gas analysis in which all the participants were evaluated together, we found similar relationships with the study we performed without controlling the BMI (Table 4).

There is ample evidence of associations between uric acid levels and gender. This evidence shows that uric acid levels are higher in men than in women

(16). There is also a relationship between uric acid level and age in order to interact with gender-specific genetic differences (14) There are some reports that uric acid level is higher in elderly patients (21). In our study, we could not find a significant result because the mean age of the patients in the stable group and acute attack group was close to each other. In addition, studies have shown that advanced age and male gender are associated with higher mortality in COPD (15). The relationship between spirometric measurements and uric acid is also significantly affected by factors such as age and gender (16). In our study, there was no significant difference between the mean age and gender distribution of the two groups, and similar to these studies, it was determined that the uric acid level was higher in elderly and male patients.

The results of our study showed that the CRP levels in the attack group were significantly higher than the CRP levels in the stable group. It has been suggested that excessive or decreased production of inflammatory cytokines and chemokines have an effect on the course of COPD (22, 23). It has been determined that local and systemic inflammation increases in COPD attack cases (24), and the inflammatory response is more severe during the attack period (25, 26). In the study conducted by Eagan et al. (2010) (22), it was determined that the CRP levels of COPD cases with frequent exacerbations were higher than in COPD cases without frequent exacerbations. In another study, it was shown that CRP supports the diagnosis of acute exacerbation in COPD based on major exacerbation signs and symptoms (22). Based on these findings, it was determined that the results of our study on CRP were consistent with the results of previous studies.

Anemia is common in COPD, mainly due to blood loss and chronic inflammatory processes, and is often exacerbated during the disease (27). Iron deficiency is associated with hypoxemia, extreme exacerbations and possibly worse exercise tolerance, all of which are predictors of poor prognosis (28). In our study, similar to these publications, we found that the hb values of the patients in the attack group were significantly lower than the hemoglobin values of the patients in the stable group.

In this study, we found a relationship between pneumonia and uric acid level in line with the literature. There were 56 pneumonia patients in the attack group evaluated in our study. COPD exacerbation and infection are two closely related clinical pictures, and uric acid levels are also affected in pneumonia. Although there are two clinical pictures that are closely related to COPD attack and pneumonia (29), Pneumonia is sometimes associated with acute exacerbation of idiopathic interstitial pneumonia as well as high mortality (30). Pneumonia due to frequent viral and bacterial infections was observed in patients at the time of admission (31, 32). As it is, exposure to an air pollutant can cause pneumonia (33). Pulmonary function assessment is recommended when COPD patients are stable and without any signs or symptoms of infection (34). There were 56 pneumonia patients in our study. These patients were in the acute attack group. However, COPD exacerbation and infection are two clinical pictures that are closely related. In addition, uric acid levels are also affected in pneumonia. (35). Since it could not be clearly determined which of the picture belongs to the acute attack of pneumonia and COPD, and all of the pneumonia patients who came in were in the acute attack group, they were considered as the acute attack group without distinction of pneumonia.

The FEV1(p=0.002), %FEV1(p=0.034), FVC (p<0.001) and %FVC(p<0.001) values of the patients in the acute attack group were significantly lower in the attack group than the stable group.. The cut-off value of the uric acid was 6 mg/dl in women (the upper limit of the uric acid value measured in the blood was 6 mg/dl in women), and the cut-off value was 7 mg/dl in men (the upper limit of the uric acid value measured in the blood was 7-8 mg/dl in men), (p<0.001) and uric acid/creatinine (p<0.001) were significantly higher in the attack group. Likewise, the CRP value (p<0.001) was found to be higher in the attack group. Hemoglobin values (p=0.026) were lower in the attack group. Since the ages of the patients in the stable group and acute attack group were close to each other in our study, we could not find any significant results regarding age. In our study, uric acid and uric acid/creatinine ratio, which we found higher in the attack group, has an early mortality risk, (Obsistance ratios of 2.985 (95% CI 0.618-14.15) and 2.346 (95% Confidence), respectively) according to the categorization of the cut -off points for uric acid and uric acid/creatinine ratio range of 0.668-8.238).

There was no difference between the biomass exposure of the attack group and the stable group evaluated in our study. It is known that exposure to

biomass outside the home is important in terms of acute exacerbations of COPD (36). In an animal study conducted by Peckova et al. (37) in 2009, it was shown that controlled biomass exposure increases uric acid levels.

There was no significant difference between the cigarette pack/year averages and smoking cessation distributions of the two groups. Uric acid is the most abundant water-soluble antioxidant in humans and may have a high scavenging capacity for serum free radicals. It also acts as an intracellular free radical scavenger in conditions such as metabolic stress or smoking. Therefore, uric acid, an antioxidant, can be expected to increase in smokers (38, 39). However, in two separate studies, it was reported that uric acid level was found to be lower in regular smokers (40, 41). In our study, we found that the rate of non-smokers in the attack group, where we found high uric acid levels, was higher than the rate in the stable group. In this context, it was determined in our study that the contribution of cigarette smoking to the increase in uric acid level in the attack group should be lower than the stable group.

5. Conclusion

In this study, when the PFT values of the attack group and the patients in the stable group were compared; FEV1 (P=0.002), %FEV1 (p=0.034), FVC (p<0.001) and %FVC (p<0.001) values of the cases in the attack group were found to be significantly lower than the values of the subjects in the stable group. We found similar results in the study performed by controlling BMI. In the analysis of arterial blood gas in this study, we found a negative relationship between uric acid and pH, PaO_2 and SaO_2 values, and a positive relationship between uric acid and $PaCO_2$ values. We found similar results in analyzes of arterial blood gases by controlling BMI.

The uric acid (p<0.001), uric acid/creatinine (p<0.001) and CRP (p<0.001) values of the patients in the attack group were found to be significantly higher than the values of the patients in the stable group. Hemoglobin (p=0.026) values of the patients in the attack group were found to be significantly lower than the hemoglobin values of the patients in the stable group. The rate of non-smokers in the attack group was higher than the stable group. In the attack group, high uric acid or uric acid/creatinine ratio is associated with an early mortality risk (Obsistance ratios of 2.985 (95% CI 0.618-14.15) and 2.346 (95% Confidence), respectively) according to the categorization of the cut-off points for uric acid and uric acid/creatinine ratio range of 0.668-8.238).

CRP value was found to be higher in the attack group. Hemoglobin values were lower in the attack group. Since the ages of the patients in the stable group and acute attack group were close to each other in our study, we could not find any significant results regarding age. In our study, uric acid and uric acid/creatinine ratio, which we found higher in the attack group, has an early mortality risk, according to the categorization of the cut -off points for uric acid and uric acid/creatinine ratio range.

Pulmonary function assessment is recommended when COPD patients are stable and without any signs or symptoms of infection. All 56 pneumonia patients in our study were in the acute attack group. However, COPD exacerbation and infection are two clinical pictures that are closely related. In addition, uric acid levels are affected in pneumonia, similar to that in COPD acute attack, and since all pneumonia patients were in the acute attack group, they were considered as the acute attack group without distinction from pneumonia.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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