

Serum uric acid as a biomarker for prediction of outcomes of patients hospitalized for acute exacerbation of chronic obstructive pulmonary disease

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Background Serum uric acid, the final product of purine degradation, has been shown to be increased in the hypoxic state as well as in systemic inflammation including patients with chronic obstructive pulmonary disease (COPD). The aim of this study was to assess the possible role of serum uric acid as a biomarker for the prediction of outcome of patients hospitalized for acute exacerbation of COPD (AECOPD).

Patients and methods Serum uric acid levels were measured in 115 eligible AECOPD patients on admission. The primary end-point was all-cause mortality at 30 days. The secondary outcomes included the length of hospital stay, need for noninvasive ventilation, or ICU admission within 30 days.

Results Serum uric acid presented an area under the receiver operating characteristic curve of 0.721 (95% confidence interval: 0.63–0.80) for the prediction of 30-day mortality in patients with AECOPD, with a sensitivity of 0.82 and a specificity of 0.61 for the cutoff point greater than 6.9 mg/dl ($P = 0.021$). Also, patients with higher serum uric acid levels required longer hospitalization and more

often required the use of noninvasive ventilation and ICU admission at 30 days. In addition, serum uric acid levels were higher in patients with more severe airflow limitation, patients with cardiovascular comorbidity, and among frequent exacerbators.

Conclusion High serum uric acid levels on admission were associated with increased 30-day mortality in patients with AECOPD. The results of this work suggest a possible role for serum uric acid in the identification of COPD patients at an increased risk of adverse outcomes who may need early intensive management. *Egypt J Broncho* 2014 8:115–120 © 2014 Egyptian Journal of Bronchology.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide and results in an economic and social burden that is both substantial and increasing [1]. An acute exacerbation of COPD (AECOPD) is an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication [1].

Serum uric acid, the final product of purine degradation, has been shown to be increased in the hypoxic state, including in patients with COPD [2–4]. Importantly, serum uric acid has been proposed as a marker for impaired oxidative metabolism and an independent predictor of impaired prognosis in several processes such as congestive heart failure [5], pulmonary thromboembolism [6], primary pulmonary hypertension [7], Eisenmenger syndrome [8], or acute myocardial infarction-related future adverse effects [9].

In COPD, Garcia-Pachon *et al.* [10] assessed the association of serum uric acid and serum uric acid to creatinine ratio with clinical and functional characteristics in stable patients with COPD. However,

few data exist on the significance of serum uric acid in patients with AECOPD. Thus, the aim of this study was to evaluate the possible role of serum uric acid as a biomarker for the prediction of outcome of patients hospitalized with AECOPD.

Patients and methods

Patients

This study was carried out at the Respiratory ICU and Chest Department, Zagazig University Hospitals, during the period from January 2012 to January 2014. It included 115 AECOPD patients. AECOPD was diagnosed according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [1], supported by spirometric evidence of airflow obstruction [forced expiratory volume in 1 s (FEV₁)/forced vital capacity < 0.70] when clinically stable, with clinical criteria of exacerbation including increased dyspnea, increased sputum volume, or sputum purulence. Criteria for exclusion were as follows: previous inclusion in the study; a primary reason for admission other than AECOPD; a history of respiratory disorders other than COPD; patients

without available spirometry data; refusal to participate in the study; or patients with chronic comorbidities that significantly influence uric acid levels (i.e. chronic renal failure, severe liver dysfunction, or malignancies).

Methods

All the patients studied were subjected to the following:

- (1) Thorough assessment of medical history.
- (2) Full clinical examination (general and local examination).
- (3) Plain chest radiography.
- (4) Blood samples were collected from each patient on admission and before the initiation of any treatment for serum uric acid and other routine laboratory investigations including:
 - (a) Complete blood count.
 - (b) Liver functions.
 - (c) Kidney functions.
 - (d) Serum electrolytes (Na, K, Cl).
 - (e) C-reactive protein (CRP).
- (5) Stable-state dyspnea was assessed using the modified Medical Research Council dyspnea scale [1]; this has scores from 0 to 4 according to the patient's severity of dyspnea.
- (6) Arterial blood gases analysis.
- (7) The primary end-point was all-cause mortality at 30 days. The secondary outcomes included the length of hospital stay, need for noninvasive ventilation (NIV), or ICU admission for AECOPD within 30 days.

Decisions on treatment and discharge were made by attending physicians not involved in this study according to the GOLD guidelines [1]. The diagnosis and classification of airflow limitation were based on postbronchodilator spirometry in a stable condition, that is, in the previous 6 months and at least 4 weeks before admission from the patients' records or 4–8 weeks after discharge, according to GOLD guidelines (patients were classified as GOLD stages 1–4 as follows: GOLD 1, $FEV_1 \geq 80\%$ predicted; GOLD 2, $50\% \leq FEV_1 < 80\%$ predicted; GOLD 3, $30\% \leq FEV_1 < 50\%$ predicted; GOLD 4, $FEV_1 < 30\%$ predicted) [1].

Statistical analysis

Statistical analysis was carried out using Epi Info, version 7 and the SPSS version 19 statistical software package (SPSS Inc., Chicago, Illinois, USA). Epi Info™ version 7 (available at: <https://wwwn.cdc.gov/epiinfo/html/downloads.htm>). *P*-value less than 0.05 was considered significant.

Results

This study included 115 patients with AECOPD who

were eligible for inclusion. Patients were divided into two groups according to the presence of serum uric acid levels below or equal to and above the median value (≤ 6.9 mg/dl $n = 65$ or > 6.9 mg/dl $n = 50$, respectively). The demographic data of both groups are presented in Table 1, which showed that patients with high serum uric acid levels had more comorbidity (i.e. cardiovascular disease and arterial hypertension) compared with patients with low serum uric acid levels.

Table 2 shows that patients with high serum uric acid levels had more hospital admissions in previous year, more number of AECOPD in the previous year, more severe airflow obstruction, more dyspnea, more acidemia, more hypercapnia, more hypoxemia, and higher CRP levels compared with patients with low serum uric acid levels.

The median (range) serum uric acid levels on admission were higher in patients with more severe airflow limitation [6.4 (5.9–7.3), 6.6 (5.9–7.5), 7.6 (6.1–10.3), and 7.9 (6.5–11.1) mg/dl for GOLD stages 1–4, respectively; $P < 0.001$] (Fig. 1). Also, serum uric acid levels were higher in frequent ($n = 66$) compared with nonfrequent ($n = 49$) exacerbators [7.4 (6.1–11.1) vs. 6.4 (5.9–7.4) mg/dl, respectively; $P < 0.001$] (Fig. 2).

Figure 3 shows that serum uric acid levels had a significant negative correlation with $FEV_1\%$ predicted ($r_s = -0.57$, $P < 0.001$). Figure 4 shows that serum uric acid levels presented a positive correlation with length of hospitalization in all study population ($r_s = 0.69$, $P < 0.001$).

Table 3 shows a comparison of clinical outcomes at 30 days in patients with low and high serum uric acid levels on admission. Patients with high serum uric acid levels required more prolonged hospitalization and presented higher rates of 30-day mortality compared with patients with low serum uric acid levels. Moreover, patients with high serum uric acid levels required NIV and ICU admission at 30 days more than patients with low serum uric acid levels.

Table 1 Demographic data of all studied patients

Parameters	Low serum uric acid (≤ 6.9 mg/dl) ($n = 65$)	High serum uric acid (> 6.9 mg/dl) ($n = 50$)	<i>P</i> -value
Age (years)	70 (65–76)	71 (66–78)	0.12
Sex (M/F)	52/13	46/4	0.11
Current smokers	20 (30.8)	12 (24)	0.53
BMI (kg/m ²)	24.6 (22.5–28)	25 (19.8–30.3)	0.77
Comorbidity			
Cardiovascular disease	25 (38.5)	40 (80)	<0.001
Arterial hypertension	30 (46.2)	39 (78)	<0.001

Data are presented as median (range) or *n* (%) unless otherwise specified; F, female; M, male.

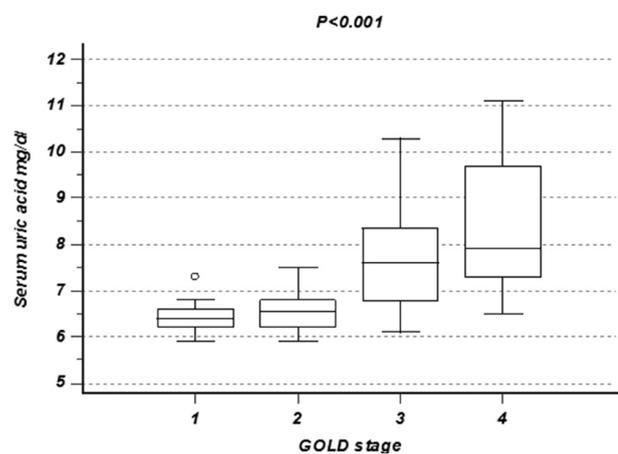
Figure 5 shows the receiver operating characteristic curve evaluating the diagnostic performance of serum uric acid as a predictor of 30-day mortality. In receiver operating characteristic curve analysis, serum uric acid presented an area under the curve of 0.721 (95% confidence interval: 0.63–0.80) for the prediction of 30-day mortality, with a sensitivity of 0.82 and a specificity of 0.61 for the cutoff point greater than 6.9 mg/dl.

Discussion

In the current study, it has been shown that high serum uric acid levels on admission were associated with increased 30-day mortality in patients with AECOPD. Also, patients with increased uric acid levels required more prolonged hospitalization

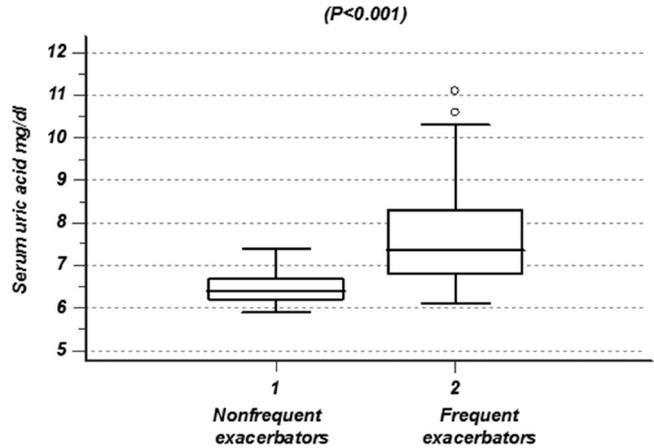
and more often required the use of NIV and ICU admission at 30 days. In addition, serum uric acid levels were higher in patients with more severe airflow limitation, patients with cardiovascular comorbidity, and in frequent exacerbators. These results are comparable and in agreement with those obtained by Bartziokas *et al.* [11], who assessed serum uric acid, the widely available and rapidly measured biomarker, as a predictor of clinically important outcomes in a prospective cohort of patients with AECOPD. Also in agreement with the results of the present work, Lopez [12] evaluated serum uric acid levels among 110 patients with COPD and found a significant correlation between hypoxemia and serum uric acid levels (in stable and exacerbated patients) and between severity of COPD and serum uric acid.

Fig. 1



Serum uric acid levels on admission in all studied patients according to airflow limitation severity [Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 1–4].

Fig. 2



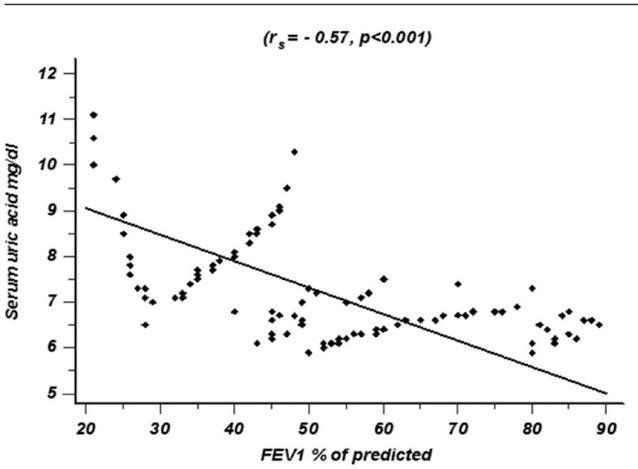
Serum uric acid levels on admission in all studied patients according to exacerbation frequency (nonfrequent = 0–1 events/year vs. frequent ≥ 2 events/year).

Table 2 Clinical and laboratory data of all studied patients

Parameters	Low serum uric acid (≤6.9 mg/dl) (n = 65)	High serum uric acid (>6.9 mg/dl) (n = 50)	P-value
Number of hospital admissions in the previous year	0 (0–1)	1 (0–2)	<0.001
Number of AECOPD in the previous year	1 (1–2)	2 (1–4)	<0.001
mMRC dyspnea scale	3 (2–4)	4 (3–4)	<0.001
FEV ₁ % predicted	60 (32–89)	38 (21–80)	<0.001
GOLD stage			
1	15 (23.1)	1 (2)	<0.001
2	36 (55.4)	8 (16)	
3	13 (20)	28 (56)	
4	1 (1.5)	13 (26)	
Arterial blood gases (on admission)			
pH	7.42 (7.37–7.45)	7.37 (7.28–7.45)	0.001
PaO ₂	65.3 (54.8–75)	60.5 (51–72.3)	0.01
PaCO ₂	40.5 (36.8–50.1)	43.5 (36–56.3)	0.03
Oxygen saturation (%)	92 (87–96)	92 (86–96)	0.99
CRP (mg/dl) (on admission)	3.6 (1–11.1)	8.9 (3–13.9)	<0.001

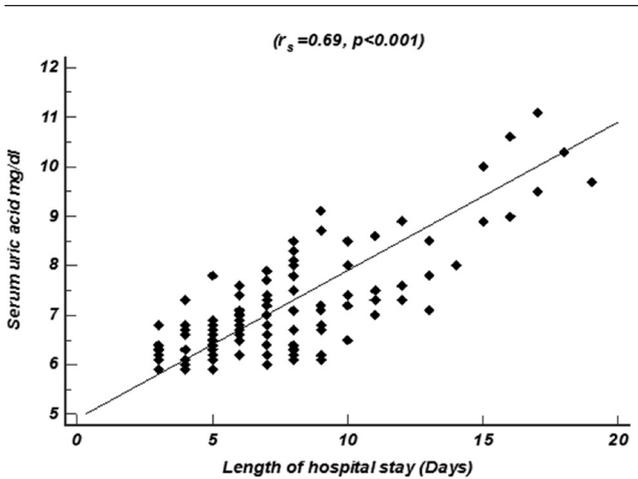
Data are presented as median (range) or n (%) unless otherwise specified. AECOPD, acute exacerbation of chronic obstructive pulmonary disease; CRP, C-reactive protein; FEV₁, forced expiratory volume in 1 s; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, modified Medical Research Council.

Fig. 3



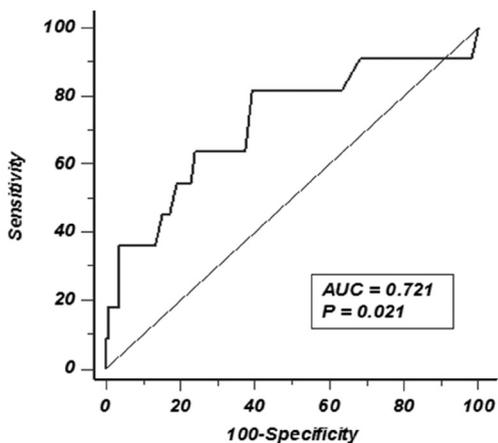
Correlation between serum uric acid levels and FEV₁ % of predicted in the study population. FEV₁, forced expiratory volume in 1 s.

Fig. 4



Correlation between serum uric acid levels and length of hospital stay in the study population.

Fig. 5



Receiver operating characteristic curve evaluating the diagnostic performance of serum uric acid as a predictor of 30-day mortality. AUC = 0.721 (95% confidence interval: 0.63–0.80). AUC, area under the curve.

Table 3 Comparison of clinical outcomes at 30 days with low and high serum uric acid levels

Parameters	Low serum uric acid (≤ 6.9 mg/dl) (n = 65)	High serum uric acid (> 6.9 mg/dl) (n = 50)	P-value
Length of hospital stay (days)	5 (3–8)	8 (5–19)	<0.001
Death within 30 days	2 (3.1)	9 (18)	0.009
ICU admission within 30 days	3 (4.6)	12 (24)	0.004
Need for NIV within 30 days	10 (15.4)	22 (44)	<0.001

Data are presented as median (range) or n (%) unless otherwise specified; NIV, noninvasive ventilation.

An increase in serum uric acid occurs as a result of purine catabolism secondary to tissue hypoxia [13,14]. 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 metabolism [10], 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. Epidemiologic studies have shown that uric acid may be a risk factor for cardiovascular diseases and a negative prognostic marker for mortality in patients with pre-existing heart failure [5]. In patients with pulmonary thromboembolism, serum uric acid increases in proportion to the severity of the embolism [6]. In patients with pulmonary hypertension, serum uric acid has an independent association with long-term mortality [7]. Serum uric acid increases in proportion to hemodynamic severity in adult patients with Eisenmenger syndrome and is associated independently with long-term mortality [8]. Also, serum uric acid level is a suitable marker for predicting acute myocardial infarction-related future adverse effects [9].

Several mechanisms may be involved in the presence of high uric acid levels in AECOPD. First, prolonged hypoxemia that is further increased during AECOPD may result in increased pulmonary artery pressures, leading to increased right ventricular afterload, which promotes purine degradation through increased xanthine oxidase activity [15]. The presence of more hypoxemia in patients with high serum uric acid levels in this study (Table 2) lends support for this mechanism. Also, a considerable proportion of patients with COPD have comorbid cardiovascular disease that may be related to elevated uric acid [16]. This is further supported by the more common cardiovascular disease in patients with increased uric acid levels in our study. Finally, COPD is characterized by systemic inflammation [17], and elevated uric acid levels have

been associated with increased levels of inflammatory markers (e.g. CRP and interleukin-6) [16] that may be important in the outcomes of COPD patients [18,19].

Previous studies have attempted to identify biomarkers that predict clinically relevant outcomes during hospitalization for AECOPD. In a previous study carried out by Koutsokera *et al.* [20], the measurement of several serum biomarkers, including CRP, serum amyloid-A, tumor necrosis factor- α , interleukin-6, and fibrinogen, failed to identify patients with early or late recovery from hospitalization for AECOPD. Stolz *et al.* [21] showed that plasma proadrenomedullin and proendothelin levels were associated with the length of hospitalization, but only proadrenomedullin is a predictor of long-term survival. In addition, in another study by the same investigators, CRP and procalcitonin failed to predict short-term mortality, but increased levels of copeptin were associated with an increased risk of death during hospitalization [22]. In this study, high serum uric acid levels were associated with increased 30-day mortality, suggesting that this easy-to-obtain biomarker may be used to identify high-risk patients with AECOPD who require more intensive treatment. On the basis of these data, serum uric acid may be evaluated as a useful biomarker in a multicomponent score in future studies [11].

In agreement with the current study, uric acid levels have been associated previously with clinical and functional characteristics in patients with COPD in cross-sectional studies [10,23,24]. Significant associations between serum uric acid/creatinine ratio and FEV₁, forced vital capacity and Medical Research Council dyspnea scale were reported by Garcia-Pachon *et al.* [10], but they included a small sample of stable COPD patients and no data on the outcomes of those patients were reported. Another study 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 [24]. In contrast, a population-based cross-sectional study by Nicks *et al.* [25] 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 AECOPD, in contrast to the stable condition of the patients studied by Nicks *et al.* [25].

Cardiovascular disease is associated with increased morbidity and mortality in COPD [26,27]. Elevated uric acid levels were a strong independent marker of impaired prognosis in patients with cardiovascular disease [5,28]. A recent study showed that hyperuricemia is associated with poor outcomes in heart failure patients without chronic kidney disease,

but not in those with chronic kidney disease, suggesting that hyperuricemia may predict poor outcomes when it is related to increased xanthine oxidase activity, but not because of impaired renal excretion of uric acid [29]. The exclusion of patients with chronic renal failure in the present study suggests that the elevated serum uric acid levels may be associated with increased uric acid production in our study population. Some of the patients with cardiovascular comorbidities were receiving medication known to influence uric acid levels, including aspirin or diuretics [30]. However, serum uric acid levels continued to be associated with increased 30-day mortality, even after adjustment for the presence of cardiovascular disease. This further supports the possible role of uric acid as a clinically relevant biomarker in COPD [11].

As in other studies [4,6,7], no correlation was found, in this study, between serum uric acid and arterial oxygen saturation. Tissue hypoxia is determined by the balance between arterial oxygen transport and oxygen demands in tissue, and the lack of correlation between arterial oxygen saturation and markers of tissue hypoxia is not surprising. Oxygen transport is determined not only by oxygen saturation but also by the concentration of hemoglobin, the hemoglobin dissociation curve, cardiac output, the distribution of tissue blood flow, and other factors [4].

It should be taken into consideration that serum uric acid is the end-product of purine degradation, which increases in a very sensitive but nonspecific manner in several forms of tissue damage and inflammation, all of which are very dynamic processes in COPD patients [31,32]. Uric acid levels are influenced by several factors including cardiovascular disease [33], food intake [34], alcohol consumption [35], renal dysfunction, and genetic disorders of purine metabolism [33]. There are also genetic influences in the way in which COPD patients react to inflammation [36], which could play an important role in serum uric acid levels. In the present study, patients with chronic renal failure were excluded, but we cannot exclude other possible confounders that may have influenced the results of this study. However, despite these possible limitations, data from this work provide evidence for a possible role of serum uric acid as a biomarker that is associated with disease severity and may identify patients with worse prognosis in hospitalized patients with AECOPD.

Conclusion

High serum uric acid levels on admission were associated with increased 30-day mortality in patients with AECOPD. The results of the present study,

combined with the fact that serum uric acid is a widely and rapidly available, easy to interpret, low-cost biomarker, suggest a possible role for serum uric acid in the identification of COPD patients at an increased risk of adverse outcomes who may need early intensive management.

Acknowledgements

Conflicts of interest

None declared.

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