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Are Uric Acid and Uric Acid Creatinine Ratio Predictors for Mortality in Acute Exacerbations of Chronic Obstructive Pulmonary Disease?

Kronik Obstrüktif Akciğer Hastalığının Akut Alevlenmesinde Ürik Asit ve Ürik Asitin Kreatinine Oranı Mortalitenin Öngörücüleri midir?

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ABSTRACT

Aim: In the clinical course of Chronic Obstructive Pulmonary Disease (COPD), exacerbations that are defined as worsening of respiratory symptoms (dyspnoea, cough, sputum production) may occur, which causes poor prognosis and require additional treatments. Cost-effective mortality predictors are valuable for the treatment management of COPD. We aimed to investigate whether serum uric acid (UA) and serum uric acid to creatinine ratio (UCR) are predictors of mortality and hypoxemia in patients with acute exacerbations of COPD (AECOPD).

Material and Methods: 105 patients with AECOPD who were hospitalized in a reference chest hospital between January 2014 and December 2018 were evaluated retrospectively in this cross-sectional study. The associations between UA and UCR and long-term mortality, hypoxemia, comorbidity, FEV1 value, and Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease (GOLD) stage were analyzed.

Results: In the present study including 105 patients with AECOPD (97 males, mean age of 65±9 years), a significant correlation was found between hyperuricemia and mortality (95% CI:1.15-10.72, p=0.027; 95% CI:1.16-4.12, p=0.016, respectively), while no correlation was found between UCR and mortality (p=0.051, p=0.053, respectively). Low UA level was associated with hypoxemia significantly (p=0.022), but no association was observed between UCR and hypoxemia (p=0.094).

Conclusion: It appears that UA is more important for predicting long-term mortality in patients with AECOPD than UCR. We suggest that UA can be used as a biomarker of long-term mortality for the identification of high-risk COPD patients that require frequent clinical follow-up and intense treatment management.

Keywords: Serum uric acid, Serum uric acid creatinine ratio, Predictor, mortality, Hypoxemia, Acute exacerbations of COPD

ÖZ

Amaç: Kronik Obstrüktif Akciğer Hastalığı (KOAH) klinik seyrinde, kötü prognoza neden olan, ek tedavi gerektiren, solunum semptomlarında (dispne, öksürük, balgam) kötüleşme olarak tanımlanan alevlenmeler gözlenebilir. Maliyet-etkin mortalite öngörücüleri, KOAH'ın tedavi yönetimi için değerlidir.

Akut KOAH alevlenmeleri olan serum ürik asit (ÜA) ve serum ürik asitin kreatinine oranının (ÜKO) mortalite ve hipoksemi için belirleyici olup olmadığını araştırmayı amaçladık.

Gereç ve Yöntemler: Bu gözlemsel kesitsel çalışmada, Ocak 2014 ile Aralık 2018 arasında bir referans göğüs hastanesinde yatan 105 KOAH alevlenmesindeki hasta retrospektif olarak değerlendirildi. ÜA ve ÜKO ile uzun vadeli mortalite, hipoksemi, komorbidite, FEV1 değeri, KOAH'ın tanı, tedavi ve önlenmesi için küresel strateji (GOLD) evreleri arasındaki ilişkiler analiz edildi.

Bulgular: KOAH alevlenmesindeki toplam 105 hastayı (97'si erkek, ortalama yaş 65±9 yıl) içeren bu çalışmada hiperürisemi ile mortalite arasında anlamlı bir korelasyon bulunurken (sırasıyla, p=0.027; p=0.016), ÜKO ile mortalite arasında korelasyon bulunmadı (sırasıyla, p=0.051, p=0.053). Düşük ÜA seviyesi hipoksemi ile anlamlı olarak ilişkiliydi (p=0.022), ancak ÜKO ile hipoksemi arasında bir ilişki gözlenmedi (p=0.094).

Sonuç: KOAH alevlenmesindeki hastaların uzun vadeli mortalitesini öngörmede serum ÜA'nin ÜKO'na göre daha değerli olduğu görülmektedir. Sık klinik takip ve yoğun tedavi yönetimi gerektiren yüksek riskli KOAH hastalarının tanımlanması için serum ÜA'in uzun vadeli mortalitenin biyobelirteci olarak kullanılabileceğini öneriyoruz.

Anahtar Sözcükler: Serum ürik asit, Serum ürik asitin kreatinine oranı, Prediktör, Mortalite, Hypoksemi, KOAH akut alevlenme

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease that causes the mortality of more than three million people worldwide each year (1). The frequency of the exacerbations increases the severity of the disease, and if a patient has had two or more acute events during the previous year, he or she is considered high risk (1-3). The impact of COPD on the public can be relieved by prevention and appropriate management using methods based on the latest evidence available. Recent studies have focused on easily applicable and cost-effective prognostic biomarkers for COPD.

During exacerbations, there is increased hyperinflation and gas trapping, with the decreased expiratory flow, thus clarifying advanced dyspnoea (4). There is also a worsening of the alveolar ventilation (VA)/perfusion (Q) imbalance that can result in hypoxemia (5). Tissue hypoxia stimulates the degradation of adenosine (6), which causes the excretion of purine intermediates and the end products of purine catabolism such as UA (7).

Seventy percent of UA is excreted by the kidneys, which therefore have a major role in providing UA homeostasis and its serum level. Impaired renal evacuation concludes hyperuricemia (8). Since most UA is excreted from the kidneys, the assessment of its adjusted ratio with creatinine (serum uric acid to creatinine ratio [UCR]) is also significant (9). Kahnert et al. (10) have declared that UA is associated with airway obstruction, cardiovascular comorbidities, exacerbations, and physical capacity, that are the poor prognosis determinants of COPD. Whereas a small cross-sectional study has shown significant associations between UCR and spirometry values and dyspnoea in COPD patients (9). Despite the evidence above, no study has compared UA and UCR for association with long-term mortality and hypoxemia in patients with acute exacerbations of COPD (AECOPD).

The main aim of this study was to investigate whether UA and UCR can be used as cost-effective biomarkers of mortality and hypoxemia in patients with AECOPD. The second aim was to examine the association between UA and UCR values and the inflammatory parameters of leukocyte and CRP, forced expiratory volume in 1-s (FEV1) values, Global Initiative for COPD (GOLD) severity classification of COPD, and comorbidity in patients with AECOPD.

MATERIAL and METHODS

A total of 1642 patients with AECOPD who visited the emergency department (ED) between January 2014 and December 2018 were scanned, and 105 inpatients among these patients, whose research data could be accessed were included in this study. The present single center, cross-sectional study was approved by the ethics commitee of Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital (REC number:2020-16, Date:20.08.2020). Since the study was retrospective, informed consent was not obtained from the patients.

The patient was diagnosed with AECOPD based on the medical history, clinical findings, current symptoms, and the GOLD diagnosis and treatment guidelines by a pulmonologist. The patient with AECOPD whose FEV1/FVC<70% (forced expiratory volume in 1 s / forced vital capacity ratio expressed as a percentage of predicted value) was included in our study.

The exclusion criteria were as follows: (a) patient with hyperuricemia-causing comorbidity (malignancy, gout, liver deficiency, psoriasis, hypercholesterolemia, metabolic syndrome, etc.), (b) patient without UA and creatinine values in the hospital database system, (c) immunosuppressive patient, (d) patient with chronic renal failure and (e) patient who used drugs that increase UA level.

Data of age, gender, comorbid diseases of diabetes mellitus (DM), hypertension (HT) and cardiovascular disease (CVD), physical examination and chest X-ray findings, partial oxy-

gen pressure (pO2-mmHg-) level, CRP (mg/L) value and leukocyte (WBC-mcL-) count at the admission of a patient to the ED were collected from the electronic database of the hospital.

A 2-cc blood sample from the radial artery of a patient with a heparin injector was measured for parameters of ABG (Siemens Rapidlab 348 EX blood gas device) within 30 minutes. Hypoxemia determined in ABG was classified as follows: Those with a pO2 of 60-80 mmHg mildly hypoxemic, those with 40-59 mmHg moderately hypoxemic and those with <40 mmHg severely hypoxemic (11). A sample of venous blood from each patient was evaluated for total blood count and biochemical analyses (Cobas c501 biochemistry device) including CRP, UA (mg/dl), and creatinine (mg/dl).

UA's standard serum value of 6.9 mg/dl was used as the cut-off value of UA. Hyperuricemia was defined as serum UA levels >6.9 mg/dl and hypouricemia was defined as serum UA levels <6.9 mg/dl in patients. UCR cut-off value was calculated by dividing the standard UA value by the standard creatinine value (1.33 mg/dl) and was found to be 5.16. UCR for each patient was calculated separately. A high UCR value was defined as UCR >5.16, on the contrary, a low UCR value was defined as UCR<5.16.

FEV1 (%) value was detected from the results of post-bronchodilator spirometry (Maester Scope PC pulmonary spirometer, Jaeger) performed in a 6-month period before the hospitalization date at the hospital database system. The patient was staged based on the GOLD diagnosis and treatment COPD guidelines as mild (FEV1≥80%), moderate (50%<FEV1<80%), severe (30%<FEV1<50%), and very severe (FEV1<30%) (1).

Survival status was obtained from the death notification system by scanning with identification number of a patient on the date of 31.12.2020. Minimum 2-year (maximum 6-year) survival times of the patients were calculated in months by subtracting the examination date from the date of death and dividing the result by 12.

Statistical Analysis

The IBM SPSS Statistics 24.0 (SPSS Inc., Chicago, IL, USA) program was used to analyse the results. According to the Kolmogorov-Smirnov test of normality results, an unpaired t-test was used to compare normal distribution scales while a Mann-Whitney U test was performed to compare non-normal distribution scales. Since the mortality variable (the dependent variable) is a categorical variable as alive and death; Logistic regression analysis was used to examine the effect of UA, UCR, leucocyte, CRP values on mortality. In the comparision of categorical variables, Chi-square independence test was performed, and Fisher's Exact Test values were used. Cox regression analysis was used to examine the cause and effect between life expectancy and explanatory variables. A p value <0.05 was considered significant.

RESULTS

A total of 105 patients with AECOPD (97 males, with a mean age of 65±9 years) were included in the present study. Fifty (47.6%) of the patients died during the analyzed period.

It was observed that the average age of the 87 patients with a low sUA level was 65.8, while the average age of the 18 patients with a high UA level was 66.4. The average age of the 26 patients with low UCR was found to be 67.2, while the average age of the 79 patients with high UCR was 65.4. GOLD stages and the levels of UA, UCR, inflammatory parameters (WBC and CRP), and pO2 of the patients were summarized in Table 1.

A statistically significant difference was observed between individuals with a UA value below 6.9 mg/dl and those with a UA value above 6.9 mg/dl from the results obtained by COX regression analysis of UA and long-term mortality (p=0.016)

Table 1: Uric acid levels, Uric acid to creatinine ratios, inflammatory parameters, pO2 levels and GOLD stages of Patients with Acute Exacerbations of Chronic Obstructive Pulmonary Disease

		Findings, n (%)
UA (mg/dl)	Low (< 6.9)	87 (82.9)
	High (≥ 6.9)	18 (17.1)
	Total	105 (100.0)
UCR	Low (≤ 5.16)	26 (24.8)
	High (> 5.16)	79 (75.2)
	Total	105 (100.0)
WBC (mcL)	Normal (4-10)	56 (53.3)
	High (> 10)	49 (46.7)
	Total	105 (100.0)
CRP (mg/L)	Normal (≤ 3)	12 (11.4)
	High (> 3)	93 (88.6)
	Total	105 (100.0)
pO2 (mmHg)	< 40	8 (7.6)
	40-59	73 (69.5)
	> 59	24 (22.9)
	Total	105 (100.0)
GOLD stages	Gold 2	11 (10.8)
	Gold 3	42 (41.2)
	Gold 4	49 (48.0)
	Total	102 (100.0)

UA: Serum uric acid, **UCR:** Serum uric acid to creatinine ratio, **n:** Number of patients, **CRP:** C-reactive protein, **pO2:** Partial Oxygen pressure, **GOLD:** Global Initiative for Chronic Obstructive Lung Disease.

(Table 2). Therefore, it was concluded that patients with high UA levels were 2.2 times more likely to die than those with low UA levels (Figure 1). There was no significant difference between patients with a UCR value below 5.16 and those with a UCR value above 5.16 observed in the results obtained from COX regression analysis of UCR and long-term mortality (*p*=0.053*)* (Figure 2).

While a significant correlation between low UA level and low pO2 was found (*p*=0.022), no significant correlation between UCR and pO2 was found (*p*=0.094*)*. There were no influences of UA and UCR on FEV1 (*p*=0.677, *p*=0.571, respectively*)*. UA and GOLD 2, 3, 4 stages were not associated (*p*=0.582, *p*=0.591, *p*= 0.534, respectively). UCR had no influence on GOLD 2, 3, and 4 stages (*p*= 0.537, *p*= 0.278, *p*=0.359, respectively) (Table 3).

Concerning patients' comorbidities, eight (7.6%) of the patients had DM, 24 (22.9%) had HT, and 23 (21.9%) had CVD. Patients without DM, HT, and CVD had low UA and high UCR. There were no significant correlations between UA level and comorbidities such as DM, HT, CVD (*p*=0.136, *p*=0.119, *p*=0.537, respectively).Also UCR with DM, HT, and CVD (*p=0.636, p=* 0.094, *p=0.701, respectively)* (Table 4).

Table 2: Correlation of Uric Acid and Uric Acid to Creatinine Ratio with Mortality in Patients with Acute Exacerbations of Chronic Obstructive Pulmonary Disease

	B	Exp(B)	%95 CI for Exp(B)		p
			Lower	Upper	
UA (mg/dl)	0.782	2.19	1.16	4.12	0.016*
UCR	0.747	2.11	0.99	4.50	0.053

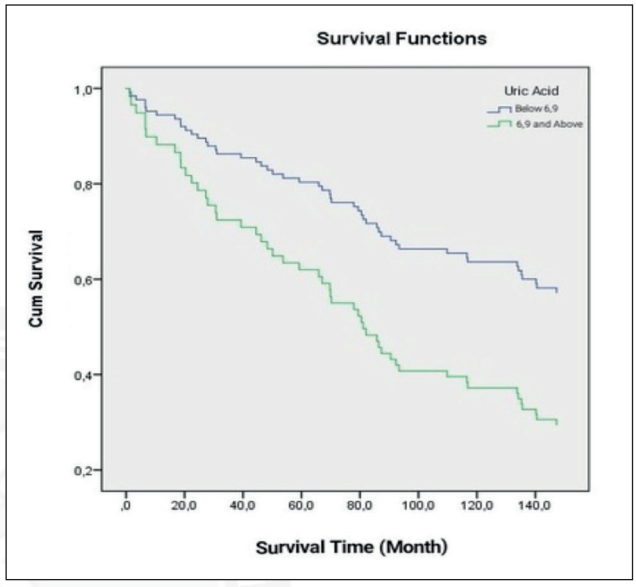

Figure 1: Cox regression analysis of serum uric acid and mortality according to survival time.

Table 3: Comparison of FEV1, GOLD stages and pO2 with serum Uric Acid and Uric Acid to Creatinine Ratio

		UA (mg/L)			UCR		
		Low UA < 6.9	High UA ≥ 6.9	p	Low UCR ≤ 5.16	High UCR>5.16	p
FEV_1 n=104	n (%)	86 (82.7)	18 (17.3)		26 (25.0)	78 (75.0)	
	Avg.	32.97	33.79	0.677	32.01	33.47	0.571_1
	min-max	8.80-77.50	20.80-54.40		13.90-60.40	8.80-77.50	
GOLD 2 n=102	0, n (%)	76 (89.4)	15 (88.2)		22	69 (89.6)	
	1, n (%)	9 (10.6)	2 (11.8)	0.582	3	8 (10.4)	0.537_2
	Total	85 (83.3)	17 (16.7)		25	77 (75.5)	
GOLD 3 n=102	0, n (%)	51 (60.0)	9 (52.9)		17	43 (55.8)	
	1, n (%)	34 (40.0)	8 (47.1)	0.591	8	34 (44.2)	0.278_2
	Total	85 (83.3)	17 (16.7)		25	77 (75.5)	
GOLD 4 n=102	0, n (%)	43 (50.6)	10 (58.8)		11	42 (54.5)	
	1, n (%)	42 (49.4)	7 (41.2)	0.534	14	35 (45.5)	0.359_2
	Total	85 (83.3)	17 (16.7)		25	77 (75.5)	
pO2 (mmHg) n=105	≤ 59, n (%)	71 (81.6)	10 (55.6)		23	58 (73.4)	
	> 59, n (%)	16 (18.4)	8 (44.4)	0.022*	3	21 (26.6)	0.094_2
	Total	87 (82.9)	18 (17.1)		26	79 (75.2)	

UA: Serum uric acid, **UCR:** Serum uric acid to creatinine ratio, **n:** Number of patients, **FEV1:** Forced expiratory volume in 1 second is the volume expired in the first second of maximal expiration after a full inspiration (useful measure of how quickly the lungs can be emptied), **Avg:** Average, **GOLD:** Global Initiative for Chronic Obstructive Lung Disease, **pO2:** Partial Oxygen pressure, p_1**:** Mann Whitney U Testi; p_2**:** Fisher's Exact Test, **p*<0.05: Significant.

Table 4: Comparison of Diabetes Mellitus, Hypertension, Cardiovascular Disease with Uric Acid and Uric Acid to Creatinine Ratio

		UA (mg/dl)			UCR		
		Low UA<6.9	High UA≥6.9	p	Low UCR≤5.16	High UCR>5.16	p
DM n=105	No, n (%)	82 (94.3)	15 (83.3)	0.136	24 (92.3)	73 (92.4)	0.636
	Yes, n (%)	5 (5.7)	3 (16.7)		2 (7.7)	6 (7.6)	
	Total	87 (82.9)	18 (17.1)		26 (24.8)	79 (75.2)	
HT n=105	No, n (%)	70 (80.5)	11 (61.1)	0.119	23 (88.5)	58 (73.4)	0.094
	Yes, n (%)	17 (19.5)	7 (38.9)		3 (11.5)	21 (26.6)	
	Total	87 (82.9)	18 (17.1)		26 (24.8)	79 (75.2)	
CVD n=105	No, n (%)	69 (79.3)	13 (72.2)	0.537	21 (80.8)	61 (77.2)	0.701
	Yes, n (%)	18 (20.7)	5 (27.8)		5 (19.2)	18 (22.8)	
	Total	87 (82.9)	18 (17.1)		26 (24.8)	79 (75.2)	

UA: Serum uric acid, **UCR:** Serum uric acid to creatinine ratio, **DM:** Diabetes mellitus, **HT:** Hypertension, **CVD:** Cardiovascular disease, **n:** Number of patients, ***p:*** Fisher's Exact Test, **p*<0.05: Significant

Table 5: Univariate Logistic Regression Analysis of Inflammatory Parameters with Mortality

Mortality	Exp(B) / OR	95% CI for EXP(B)		p
		Lower	Upper	
UA (mg/dl)	3.51	1.15	10.72	0.027*
Constant	1.39			0.250
UCR	2.55	1.00	6.56	0.051
Constant	0.71			0.155
WBC (mcL)	0.51	0.23	1.11	0.091
Constant	0.89			0.544
CRP (mg/L)	0.76	0.23	2.57	0.662
Constant	0.82			0.519

CI: Confidence interval, **Exp(B):** Adjusted odds ratio, **UA:** Serum uric acid, **UCR:** Serum uric acid to creatinine ratio, **CRP:** C-reactive protein, **p*<0.05: Significant correlation.

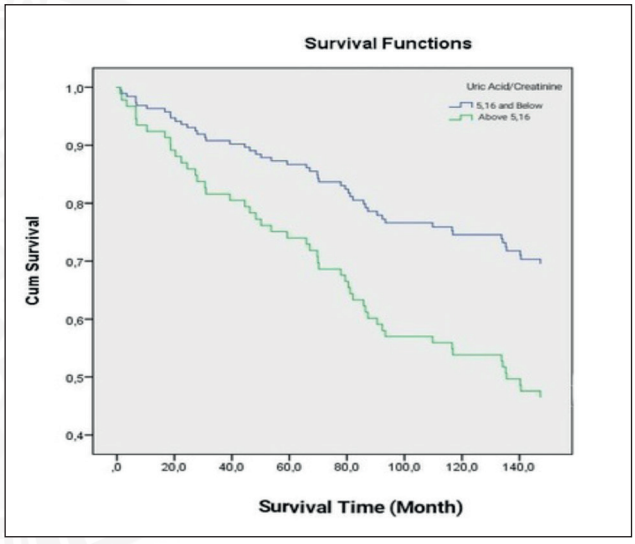

Figure 2: Cox regression analysis of serum uric acid/creatinine and mortality according to survival time.

UA, UCR, WBC, and CRP variables were evaluated as categorical variables. According to the results of the univariate logistic regression analysis of inflammatory parameters with mortality (shown in Table 5), it was observed that the associations between UCR, WBC, CRP variables and mortality were non-significant (p=0.051, p=0.091, p=0.662, respectively), while a high UA level had a significant correlation with mortality (p=0.027).

DISCUSSION

COPD management covers many different approaches such as smoking cessation, physical exercise, vaccinations, patient education, and pharmacological treatment (1). Identification of clinical and laboratory characteristics predicting poor prognosis and mortality is also a guide to improve the benefit of current treatments for an individual patient (12,13).

A significant association between hyperuricemia and long-term mortality (2-6 years) was observed in the present study. Similarly, two previous studies have declared that UA is a predictor for mortality in AECOPD: 30-day mortality predictor in one study (14) and 1-year mortality in the other (15). Moreover, UA level has been determined higher in deceased COPD patients than in survived patients with AECOPD in a recent study (16). In contrast to the four studies mentioned above, hyperuricemia has not shown any significant association with either mortality or risk of future acute exacerbation in a study including 240 male patients (17). Obesity, elder age, and male gender are the factors that increase UA level (18,19). So that, various populations

of the patients (all patients were male in the last sudy) may be responsible for this contrast. However, the clinical states of patients in the first and last-mentioned studies were stable that differs from the other studies.

No significant association between UCR and mortality similar to the outcome of this study was observed in a 2018 study (10). A study conducted in Japan on patients with COPD receiving home oxygen therapy has shown that mortality is significantly higher in those with a higher increase in UCR (20). In another study, UCR was declared as a better COPD predictor than UA, and multiparameter inflammatory models with UCR was declared as better diagnostic characteristics (21). This issue is still controversial in the literature, to which our findings have contributed.

Hyperuricemia is a valuable biomarker for hypoxemia caused by respiratory diseases such as obstructive sleep apnoea syndrome (OSAS) and AECOPD (3, 22). Controversely, hypouricemia was correlated with hypoxemia in this study. UA is an end product of the catabolism of purine nucleotides arising from endogenous (nucleic acids and internal pool of purine nucleotides, mostly adenosine triphosphate [ATP]) and exogenous (dietary purines such as red meat, high-fat dairy, seafood products, and alcohol) sources (23). As mentioned above increased serum UA level is correlated with elder age and male gender (18), but the distribution of age and gender were heterogeneous in the present study. For these reasons, UA level and UCR in patients with AECOPD with hypoxemia might be influenced. Furthermore, we hypothesise that endogenous UA production was decreased in patients with severe exacerbations.

Several researchers suggested using the nocturnal increase in urinary UCR for detection of sleep hypoxemia in both OSAS and COPD according to the results of their studies (24,25). Whereas serum UCR had no significant influence on hypoxemia in this study. Nocturnal desaturation and increased nocturnal hypoxemia can be occurred mostly in patients with COPD in advanced stages (26). But, the UA level used in the calculation of UCR in this study was measured in serum and during daylight and night, which differed from the two studies mentioned.

Hyperuricemia has been associated with HT and both UA and UCR in patients with malignancies have been found significantly higher in a cohort Turkish study including stable COPD patients (27). A Croatian study team (21) has found that COPD patients with CVD have significantly higher UA, but not UCR. Also, they have found that UA and UCR have no correlations with HT. But UA and UCR had no impacts on comorbidities such as DM, CVD and HT in the present study. Higher levels of UA have been associated with higher airway obstructions in terms of FEV_1 and lower physical capacity in terms of 6-min walk distance in a multi-disciplinary approach study (9). Furthermore, UA has been associated with the presence of airflow obstruction in a general population in Japan (28). However, no correlations were found between UA and UCR and FEV1, GOLD stages in this study. The contrast of the present study with other studies on these issues may be due to a small sample of AECOPD patients.

Similar to a previous study (29), levels of CRP and WBC had no prognostic values in severe COPD patients in this study. Also, another study has shown that there is no correlation between CRP and long-term mortality in patients with AECOPD (30). However, a 2006 study with a large patient population has concluded CRP is associated with mortality (31). Today, it is known that CRP is a nonspecific acute phase reactant that increases in a large range of diseases. And one of the causes of AECOPD is pneumonia which may increase CRP and WBC. Additionally, COPD disease also defined as a metabolic syndrome, may accompany many comorbidities that can increase CRP. Based on these, we hypothesize that CRP and WBC show the activity of COPD but can not predict poor prognosis.

The most important limitation of the study was its retrospective design. Patients had a large range of ages (40-86 years), and this study included a small number of female patients (n=8, 6%). Body mass index data were not available in the hospital database system. Additionally, mild and severe COPD patients could not be assessed according to the variables because, as expected the distribution of patients with AECOPD was intensified in advanced stages (GOLD stages 3 and 4). There was no study patient in GOLD stage 1.

UA appeared as a long-term mortality predictor of AECOPD but UCR did not appear as a long-term mortality predictor in this study. UA is a common, inexpensive, and rapid-resulting biochemical serum parameter today. The use of UA as a biomarker for poor prognosis in COPD patients will also provide advantages in these aspects. We suggest that UA can be used cost-effectively to identify high-risk COPD patients who require frequent clinical follow-up and intense management. Prospective studies on this issue should be performed on more homogeneous larger patient populations in terms of weight, age, and gender. And samples of serum should be taken at the same period of the day in order not to be affected by nocturnal increased hypoxemia in patients with COPD.

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Author Contributions

Hulya Abali, Seda Tural Onur, Dilara Demir researched literature and conceived the study. HA was involved in protocol development, gaining ethical approval. **Hulya Abali, Seda Tural Onur, Sinem**

Nedime Sokucu were involved in patient recruitment. **Hulya Abali, Neslihan Boyraci, Seda Tural Onur** were involved in data acqusition. **Hulya Abali, Fatma Tokgoz Akyil,** and **Dilara Demir** contributed to data analysis and interpretation. **Hulya Abali** wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

Financial Support

None to declare.

Ethical Approval

The present single center, cross-sectional study was approved by the ethics commitee of Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital (REC number:2020-16, Date:20.08.2020). Since the study was retrospective, informed consent was not obtained from the patientes.

Review Process

Extremely peer-reviewed and accepted.

REFERENCES

1. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD). Available from: http://www.goldcopd.org/Guidelines/guidelines-resources.html (2021, accessed 1 July 2014).
2. Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998;157(5 Pt 1):1418-1422.
3. Nicks ME, O'Brien MM, Bowler RP. Plasma antioxidants are associated with impaired lung function and COPD exacerbations in smokers. COPD 2011;8(4):264-269.
4. Parker CM, Voduc N, Aaron SD, Webb KA, O'Donnell DE. Physiological changes during symptom recovery from moderate exacerbations of COPD. Eur Respir J 2005;26(3):420-428.
5. Barbara JA, Roca J, Ferrer A, Félez MA, Díaz O, Roger N, Rodriguez-Roisin R. Mechanisms of worsening gas exchange during acute exacerbations of chronic obstructive pulmonary disease. Eur Respir J 1997;10(6):1285-1291.
6. Mentzer RMJr, Rubio R, Berne RM. Release of adenosine by hypoxic canine lung tissue and its possible role in pulmonary circulation. Am J Physiol 1975;229(6):1625-1631.
7. So A, Thorens B. Uric acid transport and disease. J Clin Invest 2010;120(6):1791-1799.
8. Johnson RJ, Kang DH, Feig D, Kivlighn S, Kanellis J, Watanabe S, Tuttle KR, Bernardo Rodriguez-Iturbe B, Herrera-Acosta J, Mazzali M. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? Hypertension 2003;41(6):1183-1190.
9. Garcia-Pachon E, Padilla-Navas I, Shum C. Serum uric acid to creatinine ratio in patients with chronic obstructive pulmonary disease. Lung 2007;185(1):21-24.
10. Kahnert K, Alter P, Welte T, Huber RM, Behr J, Biertz F, Watz H, Bals R, Vogelmeier CF, Jörres RA. Uric acid, lung function, physical capacity and exacerbation frequency in patients with COPD: A multi-dimensional approach. Respir Res 2018;19(1):110.
11. Acıcan T. Arterial Blood Gases. Yoğun Bakım Dergisi 2003;3:160-175.
12. Ryynanen OP, Soini EJ, Lindqvist A, Kilpeläinen M, Laitinen T. Bayesian predictors of very poor health related quality of life and mortality in patients with COPD. BMC Med Inform Decis Mak 2013;13:34.
13. Suissa S, Dell'Aniello S, Ernst P. Long-term natural history of chronic obstructive pulmonary disease: Severe exacerbations and mortality. Thorax 2012;67(11):957-963.
14. Bartziokas K, Papaioannou AI, Loukides S, Papadopoulos A, Haniotou A, Papiris S, Kostikas K. Serum uric acid as a predictor of mortality and future exacerbations of COPD. Eur Respir J 2014;43(1):43-53.
15. Zhang X, Liu L, Liang R, Jin S. Hyperuricemia is a biomarker of early mortality in patients with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2015;10:2519-2523.
16. Ogan N, Günay E, Baha A, Çandar T, Akpınar EE. The Effect of Serum Electrolyte Disturbances and Uric Acid Level on the Mortality of Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease. Turk Thorac J 2020;21(5):322-328.
17. Hwang JJ, Oh YM, Rhee CK, Yoo KH, Park YB, Yoon HI, Lim SY, Lee JH, Kim EK, Kim TH, Lee JH, Lee SD, Lee JS; KOLD Group. Hyperuricemia Is Not Predictive of Long-Term Outcome in Patients with Stable Chronic Obstructive Pulmonary Disease. J Korean Med Sci 2020;35(8):e58.
18. Wang Q, Wang C, Xue J, Chen MM, Sun HW, Jiang M. Characteristics of serum uric acid distribution in occupation, age, gender groups and its influencing factors in physical examination subjects in Nanjing from 2012 to 2016. Zhonghua Nei Ke Za Zhi 2021;60(1):29-34.
19. Klongthalay S, Suriyaprom K. Increased Uric Acid and Life Style Factors Associated with Metabolic Syndrome in Thais. Ethiop J Health Sci 2020;30(2):199-208.
20. Sato N, Kurashima K, Ubukata M, Takayanagi N, Matsushima H, Yanagisawa T, Tokunaga D, Sugita Y, Kanazawa M. Prognostic significance of serum uric acid in patients with chronic obstructive pulmonary disease receiving home oxygen therapy. Nihon Kokyuki Gakkai Zasshi 2003;41(2):74-80.
21. Rumora L, Hlapčić I, Popović-Grle S, Rako I, Rogić D, Čepelak I. Uric acid and uric acid to creatinine ratio in the assessment of chronic obstructive pulmonary disease: Potential biomarkers in multicomponent models comprising IL-1beta. PLoS One 2020;15(6):e0234363.
22. Kadowaki T, Hamada H, Yokoyoma A, Abe M, Nishimura K, Kohno N, Inata J, Kuraoka T, Moritani C, Higaki J. Significance of serum uric acid in patients with chronic respiratory failure treated with non-invasive positive pressure ventilation. İntern Med 2007;46(11):691-697.
23. Maiulo J, Oppedisano F, Gratteri S, Muscoli C, Mollace V. Regulation of uric acid metabolism and excretion. Int J Cardiol 2016;213:8-14.

24. Braghiroli A, Sacco C, Erbetta M, Ruga V, Donner CF. Overnight urinary acid/creatinine ratio for detection of sleep hypoxemia: Validation study in chronic obstructive pulmonary disease and obstructive sleep apnea before and after treatment with nasal continuous positive airway pressure. Am Rev Respir Dis 1993;148(1):173-178.
25. Saito H, Nishimura M, Shibuya E, Makita H, Tsujino I, Miyamoto K, Kawakami Y. Tissue hypoxia in sleep apnea syndrome assessed by uric acid and adenosine. Chest 2002;122(5):1686-1694.
26. Fletcher EC, Miller J, Divine GW, Fletcher JG, Miller T. Nocturnal oxyhemoglobin desaturation in COPD patients with arterial oxygen tensions above 60 mm Hg. Chest 92 1987;92(4):604-608.
27. Durmus Kocak N, Sasak G, Aka Akturk U, Akgun M, Boga S, Sengul A, Gungor S, Arinc S. Serum Uric Acid Levels and Uric Acid/Creatinine Ratios in Stable Chronic Obstructive Pulmonary Disease (COPD) Patients: Are These Parameters Efficient Predictors of Patients at Risk for Exacerbation and/or Severity of Disease? Med Sci Monit 2016;22:4169-4176.
28. Aida Y, Shibata Y, Osaka D, Abe S, Inoue S, Fukuzaki K, Tokairin Y, Igarashi A, Yamauchi K, Nemoto T, Nunomiya K, Kishi H, Sato M, Watanabe T, Konta T, Kawata S, Kato T, Kubota I. The relationship between serum uric acid and spirometric values in participants in a health check: The Takahata study. Int J Med Sci 2011;8(6):470-478.
29. Moberg M, Vestbo J, Martinez G, Lange P, Ringbaek T. Prognostic value of C-reactive protein, leucocytes and vitamin d in severe chronic obstructive pulmonary disease. Scientific World Journal 2014;2014:140736.
30. Stolz D, Christ-Crain M, Morgenthaler NG, Leuppi J, Miedinger D, Bingisser R, Müller C, Struck J, Müller B, Tamm M. Copeptin, C-reactive protein, and procalcitonin as prognostic biomarkers in acute exacerbation of COPD. Chest 2007;131(4):1058-1067.
31. Man SF, Connett JE, Anthonisen NR, Wise RA, Tashkin DP, Sin DD. C-reactive protein and mortality in mild to moderate chronic obstructive pulmonary disease. Thorax 2006;61(10):849-853.