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Original Article

The Effect of Serum Electrolyte Disturbances and Uric Acid Level on the Mortality of Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease

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Abstract

OBJECTIVES: The aim of the study was to determine the prevalence of electrolyte and uric acid disturbances and their effects on mortality in patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD).

MATERIALS AND METHODS: This study included all consecutive AECOPD patients who were managed at our Chest Diseases department between May 2017 and December 2017. Medical records of all the subjects were reviewed, and data were collected retrospectively. Eighty-one patients with AECOPD and 103 subjects in the control group were enrolled retrospectively. The association between the COPD and control groups and biochemical parameters in patients with and without long-term oxygen therapy and noninvasive mechanical ventilation treatment in COPD patients were compared with mortality.

RESULTS: Serum magnesium , phosphorus , potassium , sodium, and calcium (Ca levels were higher in control subjects than in COPD patients (p=0.006, p=0.015, and p<0.001, respectively). While serum levels of Ca and K were significantly lower and serum level of uric acid was higher in deceased COPD patients than in alive AECOPD patients (p=0.023, p=0.001, and p=0.033, respectively), serum levels of Mg, P, and other biochemical parameters were similar.

CONCLUSION: Serum Ca, K, and uric acid levels during the exacerbation period were significant predictors of mortality in COPD patients. In conclusion, the levels of these parameters should be measured and corrected during AECOPD treatment to decrease mortality.

KEYWORDS: Chronic obstructive pulmonary disease, exacerbation, mortality, serum electrolytes, uric acid

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death and a major health problem worldwide [1]. COPD is complicated by acute exacerbations that are associated with healthcare expenditures and high morbidity. Patients with severe COPD exacerbation have factors that influence serum electrolyte imbalance, such as hypoxia, respiratory acidosis, metabolic abnormalities such as serum electrolyte imbalance, uremia, and liver function abnormalities [2]. Serum electrolyte imbalance such as hyponatremia, hypokalemia, hyperbilirubinemia, and elevated levels of transaminases, blood urea, and serum creatinine are either caused by the disease process or the therapy initiated [3].

Electrolyte imbalances can also cause respiratory muscle weakness and impair airway function in this group of patients [4]. Hypercapnia occurs during COPD exacerbations; the sudden decrease in ventilation leads to acute respiratory acidosis or deteriorates pre-existing chronic respiratory acidosis. Owing to the high prevalence of comorbidities [5] and corresponding multi-drug therapies in these patients, mixed acid-base and hydro-electrolyte disorders are becoming increasingly common, particularly in critically ill and elderly populations [6].

Uric acid has a particular importance in the human body owing its antioxidant nature; however, it can have the opposite effect, acting as a proinflammatory factor [7, 8]. A limited number of studies have investigated whether hyperuricemia is associated with a high risk of mortality in patients with COPD [9]. The associations between hyperuricemia and serum electrolyte imbalance and COPD-related mortality are still unclear. Therefore, the aim of the present retrospective study was to evaluate the possible role of serum electrolytes and uric acid levels as a biomarker for the prediction of mortality in patients hospitalized for acute exacerbation of COPD (AECOPD).

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MATERIALS AND METHODS

Between May 2017 and December 2017, 81 patients with acute exacerbation of COPD who were hospitalized after admission to the emergency department or chest diseases department were enrolled retrospectively. Exclusion criteria were as follows: patients who were under the age of 40 years; those with congestive heart failure, renal insufficiency, liver failure, hormonal disease, neuromuscular disease, or active cancer; and those who required mechanical ventilation or intensive care. Data on routine biochemistry, complete blood count (CBC), arterial blood gas (ABG), and pulmonary function tests (PFT) were obtained for all subjects. Data of subjects who underwent long-term oxygen therapy (LTOT) (with oxygen concentrators) and noninvasive mechanical ventilation (NIMV) at home were obtained from medical records. The PFTs were primarily performed during the patient's stable period (obtained from our PFT laboratory recordings). Data regarding PFT results that were consistent with a diagnosis of COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria were obtained as well.. Patients with FEV1/FVC ratios <70% who were reversibility test-negative were diagnosed COPD. Patients were classified into following four groups according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification, exercise capacity (modified Medical Research Council (mMRC) and the British Medical Research Council values) and risk score (exacerbation frequency = EF): stage A (EF ≤2, mMRC≤2); stage B (EF≤2, mMRC≥2); stage C (EF≥2, mMRC≤2); or stage D (EF≥2, mMRC≥2) [1]. Groups of COPD were classified according to GOLD guideline as Group A to D with risk status (exacerbation status and obstruction level and symptom status (mMRC) [1].

Information about the demographic characteristics (including smoking status, cigarette consumption, and exposure to biomass fuels), annual number of exacerbations, history of hospitalization, and dyspnea scores with Medical Research Council (mMRC) were also obtained from the medical history of the subjects. Laboratory data, including CBC, ABG, serum C-reactive protein, glucose, total protein, albumin, sodium (Na), potassium (K), calcium (Ca), magnesium (Mg), phosphorus (P), and uric acid levels and lipid profile, all of which were analyzed on the first day of admission, were evaluated. The study was approved by the Ufuk University Faculty of Medicine and was conducted in accordance with the ethical standards stated in the 1964 Declaration of Helsinki / (20180215/7).

Statistical Analysis

All statistical analyses were performed using the IBM Statistical Package for the Social Sciences for Windows v20.0 (IBM SPSS Corp.; Armonk, NY, USA). Distribution of continuous variables were determined by using the Kolmogorov-Smirnov test. Continuous variables were expressed as mean ± standard deviation SD) or median (min-max) according to the distribution state. Categorical variables were outlined as numbers and percentages. The chi-square test was used to compare proportions in different groups. Student's t-test or the Mann-Whitney U-test was used to compare two independent groups according to the distribution state. Statistical significance was set if two-tailed p values were <0.05.

MAIN POINTS

- Electrolyte imbalances can cause respiratory muscle weakness and impair airway function in COPD patients.
- Serum calcium and potassium levels were lower and uric acid levels were higher in patients with acute exacerbations of COPD who deceased during the admission.
- Serum magnesium, phosphorus, and calcium levels were significantly lower in patients who received long-term oxygen therapy.
- The levels of these parameters should be measured and corrected during AECOPD treatment to decrease mortality.

RESULTS

Totally, 81 AECOPD patients and 103 sex- and age-matched healthy control subjects were included in this study. Demographic characteristics, smoking habits and dyspnea scale evaluated by the mMRC of all subjects and other diseases occurring in all COPD patients are outlined in Table 1. About one-third of the COPD patients were placed in Group C; the rest were in Group D. Dyspnea score and smoking habits were significantly different between the patient and control groups (p=0.015 and p<0.001, respectively) (Table 1).

Serum Mg, P, and Ca levels were higher in control subjects than in COPD patients (p=0.006, p=0.015, and p<0.001, respectively). Total serum protein and albumin levels were significantly higher in control subjects (p<0.001 for both). Renal function was better in control subjects than in COPD patients. The serum lipid profile was significantly lower in control subjects (Table 2). PFT results were outlined. The post-bronchodilator forced vital capacity (FVC), forced expiratory volume at the 1st second (FEV_1), and FEV_1/FVC levels were higher in control subjects. The mortality rate within one month after admission was 18.52% among COPD patients. When we compared laboratory data of all COPD patients who were alive or deceased during the follow-up in our clinic, serum Ca and K levels were significantly lower in deceased COPD patients than in alive COPD patients (p=0.023 and p=0.001, respectively). Serum uric acid levels were significantly higher in deceased COPD patients than in living COPD patients (p=0.033). Serum Mg and P levels and other biochemical parameters were similar between COPD patients. CBC results revealed significantly lower hemoglobin and platelet counts in deceased COPD patients than in alive COPD patients (p=0.002 and p=0.011, respectively). ABG analysis showed higher partial pressure of carbon dioxide ($PaCO_2$) and lower pH in deceased COPD patients than in alive COPD patients (p=0.015 and p=0.021, respectively) (Table 3).

After analyzing laboratory data according to interval limits (higher/normal/lower interval limits) of serum uric acid, K, Ca, and Mg levels, we compared these data between COPD patients and control subjects. Lower than normal intervals of serum K and serum Ca levels were significantly more common in COPD patients than in control subjects (p<0.001 and p<0.002, respectively); other parameters were similar in both

Table 1. Demographic characteristics of COPD patients and control subjects

Characteristics	COPD n=81	Control n=103	p
Age, (year), mean±SD	71.79±9.27	69.31±5.81	0.067
Gender, M, n (%)	67 (82.7)	88 (85.4)	0.615
BMI, (kg/m^2), mean±SD	26.11±5.19	27.00±3.65	0.149
Smoking Habit, n (%)			
Active smoker	59 (72.8)	28 (27.2)	<0.001
Ex-smoker	12 (14.8)	15 (14.6)	
Non-smoker	10 (12.3)	60 (58.3)	
Cigarette consumption, pack-years, mean±SD	51.64±26.13	37.21±12.32	0.015
Biomass, n (%)	51 (63.0)	62 (60.2)	0.702
COPD, (year)	8.0 (1.0-40.0)		
Exacerbation per year	1.0 (1.0-5.0)		
mMRC	2.0 (1.0-4.0)	1 (0-2.0)	<0.001
GOLD group, n (%)			
Group C	29 (35.8)		
Group D	52 (64.2)		

Data are presented as median (min-max), unless otherwise indicated. BMI: body mass index; COPD: chronic obstructive pulmonary disease; mMRC: modified Medical Research Council; GOLD: Global Initiative for Chronic Obstructive Lung Disease

Table 2. Laboratory data of all participants

Laboratory data	COPD n=81	Control n=103	p
Glu, (mg/dL), median (min-max)	100.00 (68.00-268.00)	98.00 (85.00-213.00)	0.814
TP, (mg/dL)	6.57±0.64	7.24±0.48	<0.001
Alb, (mg/dL), median (min-max)	3.10 (2.20-4.50)	4.00 (3.20-4.60)	<0.001
Na, (mEq/L), median (min-max)	137.00 (124.00-149.00)	139.00 (127.00-149.00)	0.016
K, (mEq/L), median (min-max)	3.90 (2.60-5.20)	4.10 (2.90- 5.10)	0.001
Mg, (mg/dL), median (min-max)	0.78 (0.46-1.00)	0.80 (0.66-1.00)	0.006
P, (mg/dL)	3.31±0.59	3.53±0.46	0.015
Ca, (mg/dL)	8.85±0.47	9.38±0.47	<0.001
BUN, (mg/dL)	18.54±5.47	14.62±5.00	0.001
Cr, (mg/dL), median (min-max)	0.80 (0.50-1.70)	0.70 (0.20-1.10)	0.043
UA, (mg/dL)	5.66±1.53	5.29±1.53	0.862
CRP, (mg/L), median (min-max)	33.90 (0.70-209.30)	2.50 (0.10-5.00)	0.036
LDL, (mg/dL)	94.36±35.53	116.90±33.74	0.001
HDL, (mg/dL)	40.63±11.03	51.10±10.18	<0.001
TC, (mg/dL)	164.72±43.57	199.90±42.41	<0.001
Hb, (gr/dL)	13.58±1.62	13.16±1.06	0.309
Plt, (×10^3 µL)	242.61±62.36	271.03±75.45	0.553
ABG			
pH, median (min-max)	7.41 (7.01-7.48)		
$PaCO_2$, (mmHg), median (min-max)	39.70 (25.70-86.00)		
PaO_2, (mmHg)	57.30±11.33		
SaO_2, (%), median (min-max)	89.60 (54.50-97.00)		

Data are presented as mean±SD, unless otherwise indicated. COPD: chronic obstructive pulmonary disease; Glu: glucose; TP: total protein; BUN: blood urea nitrogen; Alb: albumin; Na: sodium; K: potassium; Mg: magnesium; P: phosphorus; Ca: calcium; UA: uric acid; Cr: creatinine; CRP: C-reactive protein; LDL: low density lipoprotein; HDL: high density lipoprotein; TC: total cholesterol; Hb: hemoglobin; Plt: platelet; ABG: arterial blood gas; $PaCO_2$: partial arterial carbon dioxide pressure; PaO_2: partial arterial oxygen; pressure SaO_2: oxygen saturation

Table 3. Comparison of laboratory data between alive and deceased COPD patients

Laboratory data	Alive COPD n=66	Deceased COPD n=15	p
Glu, (mg/dL), median (min-max)	98.50 (68.00-268.00)	123.00 (85.00-197.00)	0.563
TP, (mg/dL)	6.54±0.64	6.77±0.62	0.917
Alb, (mg/dL)	3.15±0.41	3.16±0.57	0.782
Na, (mEq/L), median (min-max)	137.50 (124.00-149.00)	136.00 (129.00-143.00)	0.487
K, (mEq/L), median (min-max)	4.00 (2.70-5.20)	3.30 (2.60-4.30)	0.001
Mg, (mg/dL)	0.77±0.09	0.72±0.12	0.359
P, (mg/dL)	3.35±0.59	3.12±0.61	0.499
Ca, (mg/dL)	8.89±0.42	8.65±0.65	0,023
BUN, (mg/dL)	18.42±5.43	19.17±5.84	0.263
Cr, (mg/dL), median (min-max)	0.80 (0.50-1.20)	0.90 (0.50-1.70)	0.197
UA, (mg/dL)	5.21±1.45	6.43±1.72	0.033
CRP, (mg/L), median (min-max)	33.90 (0.70-209.30)	32.70(3.00-82.50)	0.942
LDL, (mg/dL)	96.03±36.18	86.00±32.20	0.464
HDL, (mg/dL)	40.59±11.03	40.83±11.56	0.777
TC, (mg/dL), median (min-max)	156.50 (94.00-371.00)	170.50 (92.00-222.00)	0.947
Hb, (gr/dL)	13.78±1.58	12.58±1.50	0.002
Plt, ($\times 10^3$ µL)	249.83±61.50	206.47±55.72	0.011
ABG			
pH, median (min-max)	7.41 (7.30-7.48)	7.36 (7.01-7.45)	0.015
$PaCO_2$, (mmHg), median (min-max)	39.00 (25.70-76.70)	52.90 (32.40-86.00)	0.021
PaO_2, (mmHg)	57.65±10.94	55.83±13.24	0.578
SaO_2, (%), median (min-max)	89.30 (62.20-97.00)	90.80 (54.50-94.30)	0.282

Data are presented as mean±SD, unless otherwise indicated. COPD: chronic obstructive pulmonary disease; Glu: glucose; TP: total protein; BUN: blood urea nitrogen; Alb: albumin; Na: sodium; K: potassium; Mg: magnesium; P: phosphorus; Ca: calcium; UA: uric acid; Cr: creatinine; CRP: C-reactive protein; LDL: low density lipoprotein; HDL: high density lipoprotein; TC: total cholesterol; Hb: hemoglobin; Plt: platelet; ABG: arterial blood gas; $PaCO_2$: partial arterial carbon dioxide pressure; PaO^2: partial arterial oxygen pressure; SaO_2: oxygen saturation

Table 4. Distribution of AECOPD patients and control subjects according to normal limits of laboratory data

	COPD n=81	Control n=103	p
Uric acid level*, n (%)			
Lower	1 (1.2)	0 (0)	0.108
Normal	50 (61.7)	77 (74.8)	
Higher	30 (37.0)	26 (25.2)	
Potassium level (3.5-5.5 mEq/L), n (%)			
Lower	18 (22.5)	6 (5.8)	0.001
Normal	63 (77.8)	97 (94.2)	
Calcium level (8.5-10.5 mg/dL), n (%)			
Lower	16 (19.8)	5 (4.8)	0.002
Normal	65 (80.2)	94 (91.3)	
Higher	0 (0)	4 (3.9)	
Magnesium level (1.7- 2.2 mg/dL), n (%)			
Normal	81 (100)	103 (100)	

*Normal uric acid levels are 2.4-6.0 mg/dL (for females) and 3.4-7.0 mg/dL (for males). COPD: chronic obstructive pulmonary disease

Table 5. Deceased and alive AECOPD patients' distribution according to normal interval of laboratory data

	Alive n=66	Deceased n=15	p
Uric acid level*, n (%)			
Lower	1 (1.5)	0 (0)	0.005
Normal	46 (69.7)	4 (26.7)	
Higher	19 (28.8)	11 (73.3)	
Potassium level (3.5-5.5 mEq/L), n (%)			
Lower	9 (13.6)	9 (60.0)	<0.001
Normal	57 (86.4)	6 (40.0)	
Calcium level (8.5-10.5 mg/dL), n (%)			
Lower	9 (13.6)	7 (46.7)	0.004
Normal	57 (86.4)	8 (53.3)	
Magnesium level (1.7- 2.2 mg/dL), n (%)			
Normal	66 (100)	15 (100)	

*Normal uric acid levels are 2.4-6.0 mg/dL (for females) and 3.4-7.0 mg/dL (for males). COPD: chronic obstructive pulmonary disease

Table 6. Comparison of laboratory data of COPD patients according to long-term oxygen therapy (LTOT)

Laboratory data	Receiving LTOT n=55	Not receiving LTOT n=26	p
Glu, (mg/dL), median (min-max)	105.00 (68.00-268.00)	96.00 (74.00-216.00)	0.176
TP, (mg/dL)	6.50±0.64	6.59±0.66	0.582
Alb, (mg/dL)	3.09±0.42	3.29±0.42	0.054
Na, (mEq/L), median (min-max)	137.00 (124.00-144.00)	138.50 (128.00-149.00)	0.440
K, (mEq/L), median (min-max)	3.80 (2.60-4.60)	4.10 (3.30-5.20)	0.006
Mg, (mg/dL), median (min-max)	0.76 (0.46-0.92)	0.80 (0.60-1.00)	0.001
P, (mg/dL)	3.24±0.60	3.53±0.61	0.045
Ca, (mg/dL)	8.76±0.43	9.08±0.56	0.006
BUN, (mg/dL)	18.85±5.96	17.46±4.57	0.296
Cr, (mg/dL)	0.74±0.10	0.81±0.07	0.363
UA, (mg/dL)	5.87±1.73	5.44±1.20	0.260
CRP, (mg/L), median (min-max)	34.20 (0.70-209.30)	23.45 (1.50-85)	0.116
LDL, (mg/dL)	95.74±33.16	100.50±42.23	0.583
HDL, (mg/dL)	40.62±12.84	42.31±11.81	0.574
TC, (mg/dL)	164.76±41.67	177.50±54.00	0.248
Hb, (gr/dL)	13.16±1.75	14.08±1.05	0.016
Plt, ($\times 10^3$ µL)	232.77±63.64	252.38±53.70	0.178
ABG			
pH, median (min-max)	7.40 (7.01-7.47)	7.42 (7.33-7.48)	0.023
$PaCO_2$, (mmHg), median (min-max)	43.30 (26.80-86.00)	37.25 (25.70-46.90)	0.003
PaO_2, (mmHg)	54.46±11.46	63.33±8.48	0.001
SaO_2, (%), median (min-max)	86.00 (54.50-95-60)	92.35 (78.70-97.00)	<0.001

Data are presented as mean±SD, unless otherwise indicated. COPD: chronic obstructive pulmonary disease; LTOT: long-term oxygen therapy; Glu: glucose; TP: total protein; BUN: blood urea nitrogen; Alb: albumin; Na: sodium; K: potassium; Mg: magnesium; P: phosphorus; Ca: calcium; UA: uric acid; Cr: creatinine; CRP: C-reactive protein; LDL: low density lipoprotein; HDL: high density lipoprotein; TC: total cholesterol; Hb: hemoglobin; Plt: platelet; ABG: arterial blood gas; $PaCO^2$: partial arterial carbon dioxide pressure; PaO^2: partial arterial oxygen pressure; SaO^2: oxygen saturation

(Table 4). These data were also analyzed according to the deceased/alive status within COPD patients. Higher than normal interval of serum uric acid level and lower than normal intervals of serum Ca and serum K levels were significantly common in deceased COPD patients (p=0.005, p=0.004, and p<0.001, respectively) (Table 5).

Serum Mg, P, Ca, Na, and K levels were found to be significantly lower in patients undergoing LTOT than in those who did not (p=0.001, p=0.045, and p=0.006, respectively). The same levels were significantly lower in patients undergoing NIMV for chronic respiratory failure (p=0.001) (Table 6).

Among all COPD patients, preadmission usage of LTOT, NIMV, and nebulization therapy at home was significantly higher in the ones who deceased during their hospital admission (p=0.019, p<0.001, and p=0.015, respectively).

DISCUSSION

According to our results, a link between mortality status and serum Mg and P levels hasn't been observed in patients hospitalized for AECOPD. However, serum Ca and K levels were lower and uric acid levels were higher in patients with AECOPD who deceased during the admission, than other patients with AECOPD. Serum Mg, P, and Ca levels were significantly lower in patients who received LTOT than in those who did not. Patients on NIMV had lower serum Mg levels than those who were not.

Hypokalemia is a common electrolyte disturbance in COPD. Serious symptoms, including strokes that lead to respiratory paralysis and tetany, may occur in severe hypokalemia [10]. A study conducted by Goli et al. [2] demonstrated that serum K levels were lower in AECOPD patients than in control subjects, which is consistent with our results. Similarly, a study by Ouf et al. [11] found lower serum K, Na, Mg, Ca, and chlorine levels in patients with AECOPD before treatment than in control subjects and higher $PaCO_2$ and lower pH in COPD patients than in control group. The same study also demonstrated significantly decreased serum Na, K, Mg, and Ca levels in patients who required mechanical ventilation. Among our patients, those previously receiving home LTOT and NIMV had more acidic pH and higher $PaCO_2$ than who did not receive. In addition, significantly more hypokalemia was noted in our AECOPD patients whose hospital admission resulted in mortality. Both Mg and K levels were significantly lower in patients who received LTOT and NIMV than in those who did not. A possible mechanism for this electrolyte imbalance may be the indispensable diuretic treatment given for cor pulmonale, which develops in late COPD. Besides,

beta-agonists, which are used for treating both exacerbations and stable disease, stimulate Na+/K+ ATPase, facilitating intracellular K and Mg uptake [12]. Side effects of systemic corticosteroids that are frequently used to treat attacks may be another explanation for the electrolyte imbalance mechanism [13].

Advanced age, smoking status, inadequate physical activity, and inhaled/systemic corticosteroid treatments are risk factors for osteoporosis in COPD patients [14]. Dimai et al. [15] demonstrated increased bone resorption and bone loss in COPD patients with decompensated respiratory acidosis associated with chronic hypercapnia as well as increased serum calcitonin levels. The authors noted that this might be explained by chronic hypercapnia stimulating osteoclastic resorption. In our study, serum Ca levels were lower in deceased COPD patients than in alive COPD patients. COPD patients with fatal outcomes also had significantly lower blood pH. This acidic environment might have increased the number of ionized Ca fractions, possibly leading to a decrease in protein-bound Ca. Another possible explanation might involve prevention of re-absorption of Ca from renal tubules by systemic corticosteroids used for treating the exacerbation.

Mg is important in bronchodilation and contraction of the smooth muscles of the respiratory system, as well as in mast-cell stabilization, mucociliary clearance, and neurohumoral mediator management [16]. The involvement of Mg in respiratory decompensation has been demonstrated in studies indicating decreased serum Mg levels in patients with severe respiratory disorders [17]. Hypomagnesemia in patients with stable or exacerbating COPD has been associated with the use of steroids, beta-agonists, and diuretics or insufficient dietary intake, but the results are contradicting [18]. Cohen et al. [19] reported that diuretics did not lower the levels of serum Mg. Studies in COPD patients established a positive correlation between serum Mg levels during an attack and annual number of attacks [2, 20]. Comert et al. [21] reported that Mg had beneficial effects on respiratory muscle functions and that it could be used as an add-on to standard therapy as it leads to the recovery of dyspnea in patients during AECOPD. In our study, the serum Mg level was significantly lower in AECOPD patients than in control subjects, but a statistically significant difference was not identified between deceased and alive patients, although the former showed lower serum Mg levels. Moreover, serum Mg levels were within normal laboratory limits in both deceased and alive COPD patients. This could be due to the small number of patients included in this study. Therefore, prospective studies with large populations are required to determine the effects of serum Mg levels on prognosis of AECOPD.

Phosphoproteins, cellular membrane phospholipids, and phosphorus are present in the structure of 2,3-diphosphoglycerate, which helps in the release of oxygen by hemoglobin; all these affect the respiratory tract [22]. Some studies have shown that hypophosphatemia, by depressing diaphragm contraction, results in respiratory failure and makes it difficult to wean the patient from NIMV support. Zhao et al. [4] reported a high rate of failure while weaning COPD patients with hypophosphatemia from mechanical ventilation, which was because of respiratory muscle weakness associated with hypophosphatemia. The likely pathological mechanisms involved in the occurrence of hypophosphatemia in patients with AECOPD include insufficient intake, imbalance between intra- and extra-cellular uptake of serum P, and increased elimination [23]. In our study, we showed that serum P levels were significantly lower in AECOPD patients than in control subjects. Furthermore, serum P levels were lower in patients both receiving LTOT and NIMV than in those who were not; however, there was no difference in mortality. These patients also had lower arterial pH and higher $PaCO_2$. Reduced levels of P in these patients may be due to increased urinary P excretion through inhibition of anaerobic glycolysis by respiratory acidosis.

Uric acid is the end-product of nucleotide catabolism. It accounts for 60% of the plasma antioxidant capacity and is detected at high concentrations in epithelial fluids of the respiratory tract [24]. It is also a proinflammatory factor; tissue hypoxia, chronic inflammation, and oxidative stress seen in COPD lead to elevations in uric acid levels [25]. There are studies indicating a relationship between uric acid elevation and mortality in COPD [9]. Bartziokas et al. [26] study on 314 patients with acute COPD attacks identified decreased uric acid as an independent predictor of 30-day mortality and associated it with acute exacerbation and hospitalization over a one-year follow-up period. NIMV and intensive care need were also high during the 30-day monitoring period. This was attributed to increased xanthine oxidase activity caused by hypoxemia, cardiovascular comorbidity, and damage caused by tissue hypoxia in the lungs and other tissues by increasing circulating levels of uric acid. Vafaei et al. [27] found a significant relationship between high uric acid levels and FEV_1, oxygen saturation, $PaCO_2$, body mass index, echocardiographic changes, and COPD severity. In our study, uric acid levels were significantly higher in deceased COPD patients than in alive COPD patients. A significant difference was also observed in pH and $PaCO_2$ in both groups of patients.

There are some limitations of our study. A small number of subjects made it difficult to interpret the results and arrive at definitive conclusions. Mortality data were also derived from a very small patient group. Another limitation was that we could not compare electrolyte levels during an acute exacerbation and in the stable period of COPD, given the retrospective design of the study. Because our study group included C and D groups of COPD patients who met the criteria of at least one hospitalization, they could not be compared with A and B groups of patients with <1 attack per year. Due to this, the bronchodilators and diuretics they were receiving could not be questioned.

In conclusion, hypocalcemia, hypokalemia, and uric acid elevation were found to be associated with mortality in AECOPD. These parameters should be measured, and electrolyte disturbances should be corrected in patients who were hospitalized for an acute exacerbation to decrease mortality. Furthermore, more comprehensive prospective studies with larger populations are warranted to determine the relationship between these serum biochemical parameters and the prognosis of AECOPD.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Ufuk University (20180215/7).

Informed Consent: Due to the retrospective design of the study, informed consent was not taken.

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