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Original Scientific Paper

THE EFFECT OF URIC ACID LEVEL ON THE SEVERITY OF COVID-19

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SUMMARY – Epidemiological and clinical features of COVID-19 have been reported, but risk factors need to be determined to predict the course of the disease. In our study, we aimed to determine the effect of uric acid level on the severity of the disease. COVID-19 patients who received inpatient treatment between March 11, 2020 and May 30, 2020, and whose uric acid level was measured were included in the study. Demographic characteristics, comorbidities, symptoms, clinical course, laboratory parameters, and treatments were recorded. The study included 83 patients, of these 43 (52%) were males. The mean age was 59±17.1 years. The mean uric acid and albumin levels of the patients who needed oxygen were lower than in those who did not need oxygen (p=0.471 and p=0.057, respectively). There was a significant relationship between the presence of hypouricemia and mortality (p=0.019). In addition, the mean uric acid levels of patients who needed intensive care or died were lower than the mean uric acid levels of patients who did not need intensive care or who lived (p=0.665 and p=0.241, respectively). Oxygen need, intensive care need, and low uric acid level were found to be associated with increased length of hospital stay (p=0.00, p=0.001, p=0.012, and r=-0.276, respectively). Our study results suggest that uric acid levels may be associated with disease severity in the course of COVID-19.

Key words: *COVID-19; Oxygen support; Prognosis; Uric acid*

Introduction

The cause of mysterious pneumonia cases detected since December 2019 in Wuhan, Hubei province of China, was identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) after laboratory studies and virus isolation[1]. Later, the disease caused by SARS-CoV-2 was named by the World Health Organization as coronavirus disease (COVID-19)[2]. The most common symptoms of COVID-19 are fever, cough, and shortness of breath. It may be asymptomatic or cause infection symptoms ranging from mild respiratory tract infection to severe pneumonia. The global mortality rate is about 2.3%[3].

It is recommended to use laboratory parameters such as white blood cell (WBC) count, lymphocyte count, C-reactive protein (CRP), D-dimer, ferritin, and IL-6 to estimate the severity of COVID-19[4,5]. Viral infections cause tissue damage by increasing the formation of reactive oxygen species (ROS)[6-10]. Antioxidant defense systems are activated to control ROS production in response to oxidative stress and cell tissue damage caused by increased ROS[11]. Uric acid is a natural antioxidant with up to 60% of the ROS clearance activity in plasma[12]. SARS-CoV-2 can inhibit reactions that cause oxidative stress and cell damage that occur during infection. In our

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study, we aimed to investigate the effect of uric acid, a physiological antioxidant, on the clinical course of COVID-19.

Materials and Methods

Patients who were diagnosed with COVID-19 and had uric acid level determined in our hospital between March 11, 2020 and May 30, 2020 were included in the study. Real-time reverse transcriptase-polymerase chain reaction test (rRT-PCR) for SARS-CoV-2 was applied in all patients presenting with nasopharyngeal and oropharyngeal sample findings suggestive of COVID-19. All patients with symptoms suggestive of COVID-19 were evaluated by chest computed tomography. The presence of ground glass opacities and areas of consolidation were determined as findings consistent with COVID-19. Patients with positive rRT-PCR test for SARS-CoV-2 and/or typical lung tomography findings for COVID-19 were included in the study.

Data on demographic characteristics (gender, age), chronic diseases (hypertension (HT), diabetes mellitus (DM), chronic kidney disease (CKD), asthma, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF)), coronary vascular diseases (CVD) such as myocardial infarction, angina pectoris and documented coronary heart disease, symptoms at presentation, need of oxygen supply (presence of oxygen saturation in room air <93%), history of secondary infection, need of intensive care, laboratory data (WBC, neutrophil, lymphocyte, platelet, CRP, aspartate aminotransferase test (AST), alanine aminotransferase (ALT), lactic dehydrogenase (LDH), prothrombin time (PT), ferritin, D-dimer, albumin, uric acid), electrocardiogram (ECG), chest tomography, treatments, clinical result (death, recovery), and hospitalization were evaluated.

Based on the normal ranges given at the hospital laboratory, the following parameters were determined: leukocytosis, WBC >10800 μ/L; neutrophilia, neutrophil count >7700 μ/L; lymphopenia, lymphocyte count 1300 μ/L; thrombocytopenia, platelet count <130000 μ/L; and increased CRP >3 mg/L, AST >35 μ/L, ALT >35 μ/L, LDH >247 μ/L, D-dimer >500 μcg/L, ferritin >274 μcg/L, PT >14.8 levels were recorded. In addition, according to the hospital laboratory, the normal range of albumin is defined as 3.5-5.2 g/dL and of uric acid as 3.5-7.2 mg/dL.

The COVID-19 treatment protocol recommended by the Ministry of Health was initiated[13].

Data were analyzed using the SPSS 21.0 statistical program. The level of statistical significance was set at $p<0.05$. Numerical variables were expressed as mean ± standard deviation for normally distributed variables and as median for skewed continuous variables. Categorical variables were expressed as frequency. The χ^2-test was used to evaluate categorical data. In the analysis of continuous variables, independent samples t-test and Pearson correlation analysis were used considering the distribution of data.

This study was approved by the institutional review board and the requirement for informed consent was waived.

Results

The study included 83 COVID-19 patients, 43 (52%) male and 40 (48%) female patients. The mean age was 59±17.1 (median: 63.3) years. Fifty-nine (59%) patients had rRT-PCR positive findings and 82 (99%) patients had computed tomography (CT) findings consistent with COVID-19. On chest tomography, 79 (95%) patients had ground-glass areas compatible with COVID-19, 28 (34%) had areas of consolidation, and 80% of the lesions were bilateral. The most common symptoms were cough (n=48, 58%), fever (n=39, 47%), and weakness (n=24, 29%). There were no patients with conjunctivitis. The most common comorbidities were HT (n=46, 55%), DM (n=43, 52%) and CVD (n=19, 23%).

Elevated WBC was recorded in 14 (17%), lymphopenia in 39 (47%) and thrombocytopenia in 8 (10%) patients. Elevated levels of neutrophils were determined in 16 (19%), CRP in 71 (86%), AST in 38/74 (51%), ALT in 30/74 (41%), ferritin in 11/27 (41%), LDH in 28/62 (45%), D-dimer in 43/60 (72%) (43/60), and PT in 21 (14/66) patients. Low albumin levels were recorded in 20/75 (27%) patients. Low uric acid level (hypouricemia) was found in 22%, normal uric acid level (normal uricemia) in 57%, and high uric acid level (hyperuricemia) in 22% of the patients.

Oxygen support during follow-up was required in 41 (49%) patients, 29 (71%) of them male. Among those that did not need oxygen support, 14 (34%) were male (p=0.001). In addition, 26 of 41 (63%) patients who needed oxygen had DM. DM was present in 15 (36%) of 42 patients who did not need oxygen (p=0.049). Lesions were bilateral on lung tomography in 39 (95%) patients who needed oxygen. Lesions were bilateral on lung tomography in 28 (67%) patients who did not need oxygen (p=0.006).

The mean lymphocyte count was 1100 µ/L, mean platelet count 191146 µ/L, mean CRP 54.5 mg/L and mean ferritin 440.6 µg/L in patients who needed oxygen. In patients not requiring oxygen, the mean lymphocyte count was 1592 µ/L, mean platelet count 222547 µ/L, mean CRP 24.8 mg/L, and mean ferritin 129 µg /L (p=0.007, p=0.042, p=0.007 and p=0.007, respectively). In addition, the mean uric acid was 5.0 mg/dL in patients who needed oxygen and 5.4 mg/dL in patients who did not need oxygen. The mean albumin in patients who needed oxygen was 3.8 g/L *versus* 3.6 g/L in those who did not need oxygen.

Secondary infection developed in 10 (24%) patients who needed oxygen and in one (2%) patient who did not need oxygen (p=0.003).

Eleven (27%) patients who developed need of oxygen also required intensive care. Patients who did not need oxygen did not require intensive care (p=0.00).

Ten of 11 (91%) patients who needed intensive care during follow-up were male, while 33 of 72 (46%) patients who did not need intensive care were male (p=0.008). Secondary infection was present in 45% of patients in need of intensive care. Secondary infection was present in 8% of patients who did not need intensive care. All patients in need of intensive care were given intensive care support, and 4 (36%) patients who received intensive care support during follow-up were lost.

In addition, the mean uric acid level was 4.9 mg/dL in patients who needed intensive care and 5.3 mg/dL in patients who did not need intensive care. In patients that died, the mean uric acid level was 3.9 mg/dL and mean albumin level was 3.6 g/L. In surviving patients, the mean uric acid level was 5.3 mg/day and mean albumin level was 3.7 g/L. Hypouricemia was recorded in 3 (75%) patients that died and in 19% of surviving patients (p=0.019).

The mean hospital stay was 8.1 days. The mean length of hospital stay was 10.7 days in patients who needed oxygen and 5.6 days in patients that did not need oxygen support. The mean hospital stay was 13.1 days in patients that needed intensive care and 7.4 days in patients that did not need intensive care. Hospital stay was longer in those who needed oxygen support and intensive care (p=0.00 and p=0.01, respectively). Also, the uric acid level was inversely related to the length of hospital stay (p=0.012). Considering outcomes, 79 (95%) patients were discharged as cured, and 4 (5%) patients died due to development of acute respiratory distress syndrome (ARDS) and shock.

Demographic characteristics and basic clinical characteristics of the study population according to oxygen needs are detailed in Table 1.

Discussion

The COVID-19 is a new disease worldwide and data on its clinical features are limited. Parameters that can guide the course of the disease are needed. In this article, we present data on the clinical characteristics and course of 83 patients infected with SARS-CoV2 who were diagnosed consecutively in the first 80 days of the pandemic in our country. To date, there are few studies in the literature on the association of COVID-19 and uric acid level[14,15]. Therefore, although the number of patients in this study was limited, it is one of the studies with a relatively high number of patients and may contribute to the limited evidence in this area.

The mean age of patients in our study was 59±17.1 years. The mean age is comparable to other COVID-19 studies (range 51.7-70 years)[16-18]. More than half (52%) of our study patients were male. Gender distribution varies according to studies[19,20]. In many studies involving COVID-19 patients, male gender was found to be associated with the need of intensive care and oxygen support[20-22].

In the first weeks of the outbreak, PCR tests were completed within 48-72 hours due to the limited diagnostic capacity of laboratory testing. Therefore, all patients at our center with suspected COVID-19 symptoms were scanned for faster diagnosis. In addition to studies suggesting that chest tomography is the primary tool in the diagnosis of COVID-19[23], patients with negative PCR tests and CT findings were found to have positive PCR tests during follow-up[24,25]. In our study, most of our patients had findings consistent with COVID-19 in their radiographic images. Consistent with the literature, the findings were bilateral and the presence of consolidation was associated with oxygen demand[24,26-28].

In our study, in accordance with the literature, the most common symptoms of COVID-19 were cough and fever[17,18, 25,29,30], and the most common

Table 1. The features of patients stratified according to the need of oxygen supply during follow-up

Parameter	Need of oxygen supply (+) N=41	Need of oxygen supply (-) N=42	Total N=83	p value
Demographic data				
Age (years)	61.8±16.2	57.4±17.9	59±17.1	0.242
Sex:				0.001
Female, n (%)	12 (29)	28 (67)	40 (48)	
Male, n (%)	29 (71)	14 (33)	43 (52)	
HT, n (%)	22 (54)	24 (57)	46 (55)	0.827
CKD, n (%)	8 (20)	5 (12)	13 (16)	0.380
DM, n (%)	26 (63)	17 (40)	43 (52)	0.030
CHF, n (%)	2 (5)	2 (5)	4 (5)	1
CVD, n (%)	12 (29)	7 (17)	19 (23)	0.260
COLD, n (%)	2 (5)	1(2)	3 (4)	0.616
Asthma, n (%) 0.676		3 (7)	2 (5)	5 (6)
Clinical characteristics				
Dyspnea, n (%)	17 (41)	6 (14)	23 (28)	
Cough, n (%)	22 (54)	26 (62)	48 (58)	
Fever, n (%)	17 (41)	22 (52)	39 (47)	
Nausea, n (%)	5 (12)	2 (5)	7 (8)	
Vomiting, n (%)	2 (5)	1 (2)	3 (4)	
Diarrhea, n (%)	3 (7)	1 (2)	4 (5)	
Abdominal pain, n (%)	6 (15)	1 (2)	6 (7)	
Myalgia, n (%)	3 (7)	7 (17)	10 (12)	
Weakness, n (%)	13 (32)	11 (26)	24 (29)	
Ageusia, n (%)	0	1(2)	1 (1)	
Intensive care need, n (%)	11 (27)	0 (0)	11 (13)	0.000
Treatment regimens				
Hydroxychloroquine, n (%)	41 (100)	42 (100)	83 (100)	
Favipiravir, n (%)	22 (54)	2 (5)	24 (29)	
Secondary infection, n (%)	1 (2)	10 (24)	11 (13)	0.003

Mortality, n (%)	4 (10)	0	4 (5)	0.055
Imaging features				**0.006**
Normal, n (%)	0	1 (2)	1 (1)	
Unilateral, single foci, n (%)	0	9 (21)	9 (11)	
Unilateral, multiple foci, n (%)	4 (10)	2 (5)	6 (7)	
Bilateral involvement, n (%)	39 (95)	28 (67)	67 (81)	
Ground-glass opacities	41 (100)	38 (90)	79 (95)	0.116
Consolidation	14 (34)	14 (33)	28 (34)	1
Discharge time	10.7 ± 5.9	5.6 ± 3.8	8.1 ± 5.1	0.020
Classification by uric acid level	**0.524**			
Normouricemia	22 (54)	25 60	47 (57)	
Hypouricemia	7 (17)	11 26)	18 (22)	
Hyperuricemia	8 (20)	10 (24)	18 (22)	
Laboratory findings				
Hemoglobin, g/dL	13±1.9 (13.6)	12.9 ± 1.7 (12.9)	12.9±1.8 (13)	0.781
WBC, u/L	7160±3538	7064±4121	7112±3821	0.909
Neutrophils, μ/L	5161±3396	4930±3854	5044±3615	0.774
Lymphocytes, μ/L	1100±490	1592±1026	1349±840	0.007
Platelets, μ/L	191146±57559	222547±79483	207036±70875	0.042
CRP, mg/dL	54.5±62.1	24.8±29	39±50.2	0.007
UA, mg/dL	5±2.2	5.4±2.1	5.2±2.2	0.471
D-dimer, μcg/L, λ	1380±1100	894±570	1145±1092	0.947
Ferritin, μcg/L, †	440±4.2	129±8.3	336±374 (168)	0.123
LDH, μ/L, π	296±102	267.2±96.6	283.4±100 (237)	0.209
PT, %, κ	13.7±13.5	22.9±13.1	13.7±1.8	0.800
AST, %, ł	38.4±30	31.6±17.6	34.8±24.4	0.951
ALT, %, ł	40.1±33.7	28.9±23.2	34.2±29	0.752

CHF = congestive heart failure; CKD = chronic kidney disease; CVD = coronary vascular disease; HT = hypertension; COLD = chronic obstructive lung disease; DM = diabetes mellitus; WBC = white blood cell; CRP = C-reactive protein; UA = uric acid; PT = prothrombin time; LDH = lactate dehydrogenase; AST = aspartate aminotransferase; ALT = alanine aminotransferase; † 27 patients; π 62 patients; λ 60 patients; κ 66 patients; ł 74 patients; data are expressed as mean + standard deviation.

accompanying diseases were HT and DM. In addition, the need of oxygen was significantly higher in patients with DM[16-18,31].

We analyzed factors associated with oxygen support, intensive care support, and mortality. In general population studies, severe COVID-19 was found to be associated with leukocytosis, lymphopenia, neutrophil elevation, thrombocytopenia, and high CRP, D-dimer, PT, ferritin, troponin and LDH levels[4,5,18].

High CRP level was the most common abnormal laboratory parameter in our patients. There was no significant correlation between WBC, neutrophil, lymphocyte, platelet, CRP, D-dimer, ferritin, LDH and PT levels in terms of intensive care support and mortality. However, consistent with the literature, there was a significant relationship between lymphopenia, thrombocytopenia, high CRP and ferritin levels, and oxygen demand. The lack of statistical significance was probably due to the low number of patients, which limited the statistical analysis results. Therefore, this issue needs to be clarified in larger studies on COVID-19.

Viral infections trigger oxidative stress by increasing the formation of ROS[6-10]. Oxidative stress resulting from increased ROS causes cell tissue damage[32]. In order to maintain proper cellular redox balance, antioxidant defense systems must control excessive ROS production by clearing or reducing ROS levels[11]. Uric acid, the final breakdown product of purine metabolism, is one of the main antioxidants in plasma[33-36]. It can block reactions that cause cell damage caused by oxidative stress[37]. In addition, it is known that albumin is part of an important antioxidant system in extracellular fluids[38].

The antioxidant system can be weakened by factors such as poor nutrition and nutrient deficiency, pathological conditions, or drug intake.

In our study, patients with hypouricemia had higher mortality. In addition, the mean uric acid and albumin levels were low in patients who needed oxygen and intensive care, and in those that died. This decrease in uric acid level may be due to excessive consumption in antioxidant reactions. Additionally, albumin is one of the main markers used to evaluate nutritional status. Therefore, the decrease in albumin and uric acid levels may be due to malnutrition.

Progressive hypoxemia is often an indicator of poor prognosis in lung diseases, and indicators of hypoxemia are used to assess the severity of COVID-19[16,18,22,28,39-41]. The presence of secondary infection led to an increase in the need of oxygen support and the need of intensive care in our study, as in many studies[20,22,42].

In our patients, the mortality rate in terms of clinical course and outcome was 5%. The overall mortality rate of COVID-19 in the general population has been reported to be approximately 2.3%[3]. In many studies, the presence of comorbidities such as DM and HT and male gender has been associated with increased mortality[16,19,20,43-46]. The high mortality rate in the patients included in our study may be due to the presence of comorbid diseases in 70% of the patients and the high number of male patients.

While the mean length of hospital stay of COVID-19 patients ranged from 10 to 20 days, it was found to be longer in patients with severe symptoms[18,22,43]. In accordance with these studies, hospital stay was longer in patients with severe symptoms in our study. However, when all patients included in the study were taken into account, it was observed that the mean hospital stay was shorter in our patient group. The reason for this may be that patients with comorbid diseases are hospitalized as a central policy. In addition, providing oxygen and intensive care support to all patients may have caused this difference.

Our study had some limitations, e.g., small number of patients and single-center study design. However, few studies have investigated the effect of uric acid on the clinical course of COVID-19 patients. Although the number of patients was small, the information should be given to clinicians interested in managing this patient group. In addition, repeated uric acid measurements could not be performed during the pandemic due to the high patient load.

In conclusion, in our study, it was found that low uric acid levels increased oxygen needs, intensive care needs, and hospital stay of patients. Therefore, low uric acid levels may be associated with severe COVID-19. However, more studies are needed on this subject.

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Sažetak

UTJECAJ RAZINE MOKRAĆNE KISELINE NA TEŽINU INFEKCIJE COVID-19

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Opisana su epidemiološka i klinička obilježja COVID-19, ali preostaje utvrditi rizične čimbenike kojima bi se predvidio tijek ove bolesti. Cilj ovog istraživanja bio je utvrditi učinak razine mokraćne kiseline na težinu bolesti. U istraživanje su bili uključeni bolesnici s COVID-19 koji su liječeni od 11. ožujka 2020. do 30. svibnja 2020. kod kojih je izmjerena razina mokraćne kiseline. Zabilježeni su demografski podaci, supostojeće bolesti, simptomi, klinički tijek, laboratorijski parametri i terapijski podaci. U istraživanje su bila uključena 83 bolesnika, 43 (52%) od njih muškarci. Srednja dob svih bolesnika bila je 59±17,1 godina. Srednje razine mokraćne kiseline i albumina bile su niže u bolenika koji su trebali potporu kisikom nego u onih koji tu potporu nisu trebali (p=0,471 odnosno p=0,057). Zabilježen je značajan odnos između prisutnosti hipouricemije i smrtnosti (p=0,019). Usto, srednje razine mokraćne kiseline bile su niže kod bolesnika koji su trebali intenzivnu njegu ili su umrli u usporedbi s bolesnicima koji tu njegu nisu trebali ili su preživjeli (p=0,665 odnosno p=0,241). Utvrđeno je da su potreba potpore kisikom, potreba intenzivne njege i niska razina mokraćne kiseline povezane s produženim boravkom u bolnici (p=0,00, p=0,001, p=0,012 odnosno r=-0,276). Rezultati ovog istraživanja ukazuju na to da bi razine mokraćne kiseline mogle biti povezane s težinom bolesti tijekom zaraze COVID-19.

Ključne riječi: *COVID-19; Potpora kisikom; Prognoza; Mokraćna kiselina*