URIC ACID AND MORTALITY RELATIONSHIP IN COVID-19

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ABSTRACT

Aim: *The present study aims to investigate and compare the uric acid of the recovered/deceased and ICU/ward COVID-19 patients.*

Method: *The study was conducted with 397 patients with COVID-19 diagnosis. Information about 157 deceased and 240 recovered COVID-19 patients was analyzed retrospectively. Relationship between serum uric acid, Na, K, urea, and creatinine was investigated between patients in the mortal/non-mortal and ICU/ward group.*

Result: *Of the total 397 patients in the study, 158 (39,8%) were female and 239 (60,2%) were male. Statistically significant difference in mortality was found between males and females in order (107-239, 44.8%/50-158,31, 7%; p=0.009). Total mean age (std deviation), was 63.77±16,1, the mean age in the deceased group was 71,41±11, 39, and it was 58.78±16,8 in the survived group and that is statistically significant too (p=0.001). The mean values of Uric acid with order survivor and deceased group ((4,867±1,81 (n=222)-7, 086±3,24(n=148), P=0,000). Mean age in ICU group 69.53±12,52, in the ward group 56.24±17,1 and this age differentiation between two groups is statistically significant (p=0,001), There is a statistically significant difference in ICU care or ward was found between males and females in order (107-239, 44.8%/50-158,31,7%; p=0.009). The mean values of Uric acid with order ICU care and ward group ((6,52 ±3,1(n=217) -4,66±1,46 (n=153), P=0,000)). Serum K+ (Potassium) (4,164±0,5 (n=239)) - 4,357±0,7 (n=157), P=0,002)) levels are higher in deceased groups. The cutoff value of uric acid, which may pose a risk of mortality, was found to be 5,15 mg/dl. And the cutoff value of creatinine, which may pose a risk of mortality, was found to be 0,9 mg/dl.*

Conclusion: *The cutoff value of uric acid, which may pose a risk of mortality, was found to be 5,15 mg/dl and the cutoff value of creatinine, which may pose a risk of mortality, was found to be 0,9 mg/dl. Advanced age, uric acid, creatinine, and potassium increase were found to be associated with mortality.*

Keywords: *Uric acid, Covid-19.*

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Introduction

In December 2019 Covid-19 (Coronavirus disease) outbreak is exposed. WHO declared it as a pandemic on 11 march 2020[(1)]. Coronavirus is actually a well known Rna virus; first publication of related coronavirus was 1949[(2)]. In 2012, the world recalled the coronavirus name loudly with an outbreak called MERS (Middle East respiratory syndrome). MERS caused 858 known deaths in 27 countries[(3)]. Global reported covid-19 case 87,398,390 and mortality rate %2.15 spotted at 07/01/2021[(4)]. Novel coronavirus naturally hosted at-bat but there is a speculating about intermediate hosts such as pangolin[(5, 6)]. Because of transmission from human to human via droplet, aerosol it has been very difficult to handle pandemic situation, it's clear that personal hygiene, and using masks is important to handle viral transmission[(7)]. When we look at the mechanism of novel coronavirus disease a bounding

membrane protein named ACE-2(angio converting enzyme-2) mostly produced by lung, kidney, small intestine and esophageal epithelium[8].

Common clinical symptoms of Covid-19 fever, cough, dyspnea, chest pain, shortness of breath and pneumonia with ground-glass opacities[9]. Some studies showed other symptoms such as gastrointestinal symptoms can be shown in Covid-19 patients[9, 10]. As far as we know COVİD-19 causes kidney failure, impaired coagulation system, cardiac injury, pneumonia and probably most importantly, ARDS(acute respiratory distress syndrome)[11]. İn Covid-19 patients Searching for vaccines and other probable treatments are still undergoing but efficient treatment still can't be found. But we know about Covid-19 disease and how we predict how the disease progresses thanks to some biochemical parameters. Studies have shown higher inflammation markers serum levels such as CRP (C-reactive protein) via severe disease in Covid-19 and also critical CT (Computed tomography) findings so CRP maybe use predict severe illness in Covid-19 patients. With the same result elevated ESR (Erythrocyte sedimentation rate) associated with severe illness in Covid-19[12]. Coagulopathy is a common sign of severe covid-19 patients, micro thrombosis was shown at the performed autopsy[13].

D-dimer is a fibrin degradation product, in-clinic generally used to show thrombosis such as pulmonary thrombosis[14]. İn covid-19 patients' higher D-dimer levels in the admission of hospitals correlate with severity of disease[15]. And studies showed higher serum levels of other biochemical markers such as Troponin, ferritin, LDH (lactate dehydrogenase) or lower levels of lymphocyte count, platelet count are correlated with severity in covid-19 patients[16]. Uric acid is a purine metabolism's final oxidation product and excretion is complete renally[17]. High serum uric acid level related with; acute kidney injury, higher cardiovascular risk, obesity, gout disease and diuretic use especially thiazides[18]. Because of effective treatment or vaccine still undiscovered in covid-19; stratification measures of laboratory findings are still very important. In this study we aim to discover the relationship between severity of covid-19 patients and serum uric acid levels.

Material and methods

Approval of the Sakarya University Medical Faculty Ethics Committee was obtained for this study (27/04/2020-E.4260) This study was conducted on …. of 397 confirmed COVID-19 patients who were hospitalized in the internal medicine clinic due to symptomatic pneumonia between April 15 2020 8 and December 15 2020. Patients with missing laboratory findings were excluded from the study. Also, patients who had already been taken favipiravir before the hospital applied were excluded because favipiravir may affect uric acid metabolism. 225 of 397 patients needed in the İCU (intensive care unit) treatment and 157 patients were deceased. The patients were divided into two groups as survived patients and non-survived patients. Both groups were compared according to demographic features, comorbid conditions, and measurement of the serum uric acid, Na,K, urea, and creatinine laboratory parameters of the patients. Information was recorded from the hospital electronic system.

Statistical analysis

Descriptive analyses were performed to provide information on general characteristics of the study population. Visual (probability plots, histograms) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) were used to determine whether or not they are normally distributed. Descriptive analyses were presented using means and standard deviation for the non-normally distributed variables.

The Independent T-test was used for parametric tests to compare these parameters. The categorical variables were presented as the frequency (% percentage). A p-value<0.05 was considered significant. Analyses were performed using SPSS statistical software (IBM SPSS Statistics, Version 25.0. Armonk, NY: IBM Corp.).

Results

Of the total 397 patients in the study, 158 (39,8%) were female and 239 (60,2%) were male. Statistically significant difference in mortality was found between males and females in order (107-239, 44.8%/50-158,31,7%; p=0.009). Total mean age (std deviation), was 63.77 ±16,1, the mean age in the deceased group was 71,41±11,39, and it was 58.78±16,8 in the survived group and that is statistically significant too(p=0.001). The mean values of Uric acid with order survivor and deceased group ((4,867 ±1,81 (n=222)-7,086±3,24 (n=148), P=0,000)), Creatinine ((1,06±1,2 (n=240)-1,66±1,4(n=157), P=0,000)), Urine (78,97±56,9 (n=225)-89,63±62,2 (n=157), P=0,000)) and K+ (Potassium) ((4,164±0,5(n=239)-4,357±0,7 (n=157), P=0,002)) levels are higher in deceased groups and

all these laboratory findings especially Uric acid levels are statistically significant. (Table 1) When the patients grouped as needed İCU care or ward. Mean age in ICU group 69.53±12,52, in the ward group 56.24±17,1 and this age differentiation between two group is statistically significant (p=0,001), There is a statistically significant difference in ICU care or ward was found between males and females in order (107-239, 44.8%/50-158,31,7%; p=0.009).

The mean values of Uric acid with order ICU care and ward group ((6,52 ±3,1 (n=217)-4,66 ±1,46 (n=153), P=0,000)), Creatinine ((1,52±1,4 (n=225)-1,00±1,02 (n=172), P=0,000)), Urine ((43,27±28,9 (n=225)-38,88±27,0 (n=172), P=0,000)) levels are higher in ICU groups and all these laboratory findings especially Uric acid levels are statistically significant. K+ (Potassium) ((4,28±0,7 (n=224)-4,18±0,49 (n=172), P=0,104)) and Sodium (Na+) ((137,01±6,9 (n=225)-137,14±3,28 (n=172) P=0,820)) levels are higher in the ICU group but its not statistically significant (Table 2). In the comparison of mortality in the ward and intensive care units, while there was 8 (4.7%) deceased out of 172 patients in the ward, there were 149 (66,3%) deceased out of 225 patients in the intensive care unit.

This difference was found to be statistically significant (p=0.003) (Table 1). ROC analysis was performed for the cutoff values of uric acid, urine, creatinine in patients diagnosed with COVID-19 in our center, and the area under the ROC curve, cutoff value, sensitivity and specificity were calculated.

The cutoff value of uric acid, which may pose a risk of mortality, was found to be 5,15 mg/dl (AUC:0.719 %95 CI:0.664-0.775, sensitivity:66, specificity:66, p<0.001), while it was 0.9 mg/dl for creatinine (AUC:0.717 %95 CI:0.664-0.771 sensitivity:66 specificity:66 p<0.001), and 49.5 mg/dl for urine (AUC:0.804 %95 CI:0.760-0.849 sensitivity:70 specificity:73 p<0.001) (Figure 1) (Table 3).

		TOTAL n=397	Survivor n=240	Non Survivor n=157	P
Age mean (std deviation)		63.77 ±16,1 (n=397)	58.78±16,8 (n=240)	71,41±11,39 (n=157)	P=0.001
Gender	Female n(%)	158 (39.8%)	108 (68,3%)	50 (31,7%)	P:0,009
	Male n(%)	239 (60,2%)	132 (55,2%)	107 (44,8%)	
Hospitalization	Ward n(%)	172 (43,8%)	164 (95,3%)	8 (4,7%)	P=0,000
	İCU n(%)	225 (56,2%)	76 (33,7%)	149 (66,3%)	
Uric acid (std deviation, n)		5,754 ±2,7 (n=370)	4,867 ±1,81 (n=222)	7,086 ±3,24 (n=148)	P=0,000
Urine (std deviation, n)		61,6±50,4 (n=397)	43,27±28,9 (n=240)	89,63±62,2 (n=157)	P=0,000
Creatinine(std deviation, n)		1,30±1,3 (n=397)	1,06±1,2 (n=240)	1,66±1,4 (n=157)	P=0,000
Na(std deviation, n)		137,09±5,6 (n=397)	136,74±3,6 (n=240)	137,62±7,7 (n=157)	P=0,130
K(std deviation, n)		4,24±0,6 (n=396)	4,164±0,5 (n=239)	4,357±0,7 (n=157)	P=0,002

Table 1: demographic characteristic and laboratory findings between survivor and non survivor.

		TOTAL n=397	Ward n=172	ICU n=225	P
Age mean (std deviation)		63.77 ±16,1 (n=397)	56.24±17,1 (n=172)	69,53±12,52 (n=225)	P=0.001
Gender	Female n(%)	158 (39.8%)	85 (53,8%)	73 (46,2%)	P:0,001
	Male n(%)	239 (60,2%)	87 (36,5%)	152 (63,5%)	
Uric acid (std deviation,n)		5,754 ±2,7 (n=370)	4,66 ±1,46 (n=153)	6,52 ±3,1 (n=217)	P=0,000
Urine(std deviation,n)		61,6±50,4 (n=397)	38,88±27,0 (n=172)	78,97±56,9 (n=225)	P=0,000
Creatinine(std deviation,n)		1,30±1,3 (n=397)	1,00±1,02 (n=172)	1,52±1,4 (n=225)	P=0,000
Na(std deviation,n)		137,09±5,6 (n=397)	137,14±3,28 (n=172)	137,01±6,9 (n=225)	P=0,820
K(std deviation,n)		4,24±0,6 (n=396)	4,18±0,49 (n=172)	4,28±0,7 (n=224)	P=0,104

Table 2: demographic characteristic and laboratory findings between ICU and ward.

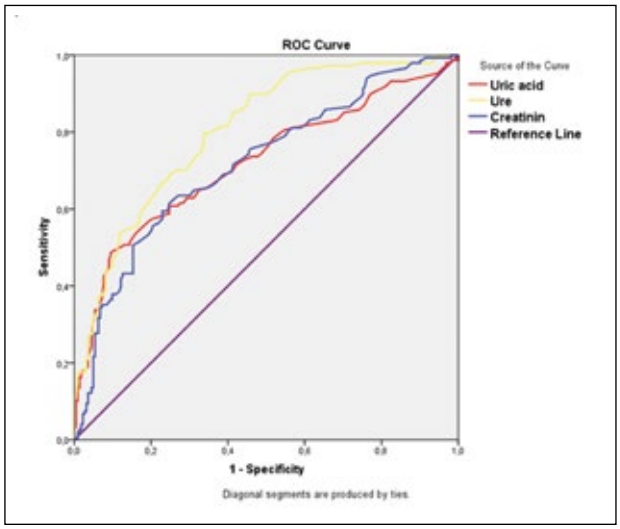

Figure 1: ROC analysis was performed to determine optimal cutoff values of Uric acid, Urine, Creatinine to predict mortality in patients with COVID-19.

RISK FACTOR	AUC (%95 CI)	CUT-OFF	SENSITIVITY (%)	SPECIFICITY (%)	P
Urine	0.804 (0.760-0.849)	49.5	70	73	**0.00**
Creatinine	0.717 (0.664-0.771)	0.9	66	66	**0.00**
Uric Acid	0.719 (0.664-0.775)	5,15	66	66	**0.00**

Table 3: ROC analyses.
AUC: Area under curve, CI: Confidence interval.

Discussion

SARS-CoV-2 virus is the new type of coronavirus that causes Covid-19 outbreak from December 2019. Virus have 3 compartments responsible for virulence Spike (S) glycoprotein lead to attach the cells. What we know about Covid-19 pathogenesis; viruses penetrate the cell with ACE-2 receptors. ACE-2 receptors commonly expressed in lung, respiratory tract cell, kidney, heart tissue, small intestine epitels[19]. Covid-19 affects more than one organ system. Most known and mortal effect of Covid-19 are ARDS(acute respiratory distress syndrome) at the respiratory tract and lungs. Other than ARDS when we look at a wider angle for Covid-19; it is well known that it affects the kidney, coagulation cascade, and heart[20].

Studies showed that; some blood parameters can predict severity and give a physician an idea of the mortality of patients Covid-19. Such as high levels of; Hstni (high sensitive troponin), Ferritin, CRP (C reactive protein), LDH (lactate dehydrogenase), D-dimer or lymphopenia[9]. Many studies have clearly demonstrated that COVID-19 infection has a more severe and fatal course in elderly patients. In a meta-analysis conducted with 36, 470 patients, it was shown that the infection was more severe in patients aged 70 years and over, and this patient group needed more intensive care[21]. Comorbidity, which increases with age, and lower immune system response have been associated with a more severe course in elderly patients[22]. In another study conducted in 3988 intensive care patients in Italy, it was found that advanced age and male gender have a significant relationship with mortality[23]. In another study conducted with patients followed in intensive care in Spain, it was found that patients who died were older patients compared to those who were discharged[23,24]. İn this study; 397 Covid-19 patient's mean age were 63.77±16,1, survivors mean age were 58.78±16,8 (n=240), deceased patient's 71,41±11, 39 (n=157) were spotted. Deceased patient's mean age was higher than the survivor patients and this result was statistically significant. ICU group mean age was 69, 53±12,52 (n=225), ward group mean age was 56.24±17,1 (n=172) spotted. Same as survivor/deceased patients comparison in ICU group mean age was higher than the ward group and this too statistically significant.

Some studies have shown that the immune system has some differences by gender. Female immune systems can produce more CD4+ T cells than male. In infectious situations immunoglobulin production could be more than male in the female patients, same as CD4+ T cells[25, 26]. In China, one study showed that in males COVID-19 infection is more severe and has higher mortality rates than women and also mortality ratio male to female 2,4:1 spotted[27]. In a large meta-analysis conducted with 3,111,714 cases, it has been proven that male COVİD-19 patients have more intensive care needs and higher mortality than the female gender. In this study, no statistically significant difference was found between male and female genders acquired infected with coronavirus, but statistically a significant difference was found in mortality and need for intensive care[28]. In our study; between deceased and survivor groups by gender with statistically significant differences was spotted and this result correlated with that literature. 107 (44.8%) of the patients deceased were male, 50 (31.7%) were female. There was a significant difference in mortality between male and female. Uric acid is well known as an antioxidant molecule and responsible for %50 of total body antioxidation and excreted

completely renal. increased cell turnover(hemolysis, tumor lysis syndrome, or severe sepsis) or decreased excretion of uric acid can cause hyperuricemia[29]. İn clinically; Hyperuricemia is mostly seen with the use of thiazide diuretics and gout disease. But most epidemiological studies show elevated serum uric acid levels correlated with cardiovascular disease, hypertension, atrial fibrillation, non fatty liver disease, chronic kidney disease.

Mechanism of this correlation is unexplained, but experimental studies showed possible mechanisms of elevated uric acid level and these diseases; abnormal antioxidative status, elevated nitric oxide and endothelial dysfunction[30]. İn severe hypoxia serum uric acid levels were found elevated[31] . İn respiratory system disease such as; Chronic obstructive pulmonary disease (COPD), pulmonary hypertension, obstructive sleep apnea uric levels found elevated[32, 33]. Impaired pulmonary function causes more severe tissue hypoxia by reducing oxygen uptake. This can cause both lung and peripheral tissue damage, destruction and an increase in serum uric acid levels[33, 34]. In a study conducted in Italy, it was found that there is a relationship between high serum uric acid levels and increased inflammatory markers, especially elevated İL-6 and CRP levels related with elevated uric acid levels[35]. İn one study conducted with ARDS patients above 8.4 mg/dl uric acid levels related with higher mortality, severe ARDS and patients with multi-system dysfunction serum uric acid levels significantly higher[36]. İn COPD patients elevated serum uric acid levels related to symptoms, severity of disease and exacerbation[37]. In another study by Fabbri et al., It was found that respiratory dysfunction caused significant tissue hypoxia, and serum uric acid levels increased as a result of tissue damage and destruction secondary to hypoxia in peripheral tissues[34].

The mean uric acid of the patients followed in the intensive care unit was found to be 6.52±3.1 (n=217), which was significantly higher than the patients followed in the ward. The mean serum uric acid level of the patients deceased was 7.086±3.24 (n=148), survivıors was 4.867±1.81 (n=222). İn deceased patient's serum uric acid levels significantly higher than survivor patients. İn the ROC analyses, the cutoff value of uric acid, which may pose a risk of mortality, was found to be 5,15 mg/dl. As in other studies, high serum uric acid levels may be associated with severe inflammation, severe hypoxia and associated destruction of peripheral tissues.

In our study, it was concluded that serum uric acid level may be associated with severe and high mortality Covid-19 disease. With this result serum uric acid level can be used as one of the significant parameters in terms of prognosis, but further studies are needed. A meta-analysis conducted in China, biochemical parameters of severe Covid-19 patients and non-severe Covid-19 patient group were compared, and serum creatinine level was found to be higher in the severe patient group, but no significant difference was found in potassium level [38]. In our study, the mean potassium level of patients deceased was found to be 4.357±0.7 (n=157) higher than survivors. The mean serum creatinine level was 1.52±1.4 (n 225) in patients followed in İCU, while it was 1.00±1.02 (n=172) in patients followed in the ward. The creatinine level of the patients followed in the intensive care unit was found to be significantly higher. Mean creatinine level of deceased patients 1,66±1,4 mg/dl (n=157) was spotted and compared with survivor patients significantly higher was found.

İn the ROC analyses, the cutoff value of creatinine, which may pose a risk of mortality, was found to be 0,9 mg/dl. It is thought that the higher average of creatinine and potassium in the patient group followed in the common care and with a mortal course may be related to the more severe course of the disease and the resulting increased cell destruction.

Conclusion

The cutoff value of uric acid, which may pose a risk of mortality, was found to be 5,15 mg/dl and the cutoff value of creatinine, which may pose a risk of mortality, was found to be 0,9 mg/dl. Advanced age, uric acid, creatinine, and potassium increase were found to be associated with mortality.

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