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Is there an association between urine biochemical parameters on admission and the severity OF COVID-19?

Omer Erdogan | Fesih Ok | Serkan Carkci | Emrullah Durmus

Urology Department, Siirt Training and Research Hospital, Siirt, Turkey

Correspondence
Omer Erdogan, Urology Department, Siirt Training and Research Hospital, 56000, Turkey.
Email: eomere86@gmail.com

Abstract

Aim: To determine the importance of urinary biochemical parameters on the severity of coronavirus disease-2019 (COVID-19).

Methods: One hundred and thirty-three patients who were diagnosed with COVID-19 were retrospectively included. Groups were formed according to the severity of their disease (moderate [n = 85], severe [n = 29] and critical = [n = 19]), and an additional control group was created from healthy individuals (n = 50). We investigated the correlation between urine biochemical parameters and the severity of the disease.

Results: Erythrocyturia, proteinuria and glucosuria rates were significantly higher in patients than in the controls. In patients, the median urine specific gravity (SG) was lower ($P < .001$), and the median potential of hydrogen (pH) value was higher compared with the controls ($P < .001$). In correlation analyses, there were strong positive correlations between disease severity and age ($r = 0.545$, $P < .001$), RR ($r = 0.838$, $P < .001$) and proteinuria ($r = 0.462$, $P < .001$), while there was a strong negative correlation with SpO_2 ($r = −0.839$, $P = .001$). On multivariate analysis, age (OR: 1.06, 95% CI 1.03-1.10, $P = .035$), respiratory rate ≥30 breaths/min (OR: 4.72, 95% CI 1.26-6.24, $P < .0031$), SpO_2 ≤ 93% (OR: 3.82, 95% CI 1.18-5.82, $P = .001$) and proteinuria (OR: 1.13, 95%CI 1.02-2.1, $P = .023$) were independent predictive factors for disease severity.

Conclusion: Proteinuria in routine urine analysis, which is one of the parameters that can be easily applied in the application, may be related to the severity of the COVID-19 disease.

1 | INTRODUCTION

In late 2019, a pneumonia epidemic began in Wuhan, China's Hubei Province, with a primarily unknown cause, which is now known to have spread significantly worldwide.[1] The virus that caused the disease was initially named the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and later the World Health Organization described this disease as coronavirus disease-2019 (COVID-19).[2] This disease usually affects individuals between the ages of 30 and 79 years. About half of those with COVID-19 have mild or indeterminate symptoms. Significant symptoms in symptomatic patients include fatigue, fever, cough, muscle pain and shortness of breath.[2,3]

Sometimes, more critical conditions, such as acute respiratory distress syndrome (ARDS) and multi-organ failure can be observed. Patients with these severe conditions often have comorbid diseases, especially hypertension (HT), diabetes mellitus (DM) and heart diseases.[3] Neutrophilia and lymphopenia are the most common laboratory parameters. Abnormal liver function test findings at different rates have also been reported. Serum procalcitonin levels are generally at normal levels, while mild increases in C-reactive protein levels can be seen. Moreover, D-dimer levels are high in 30% of patients.[4,5]

Coronaviruses are enveloped RNA viruses that consist of a single chain and have a positive polarity. Therefore, they do not have RNA-dependent RNA polymerase enzymes, but this enzyme code

has been identified in their genetic makeup. Their surfaces have rod-like extensions.[6]

Urine examinations are fast, convenient and economical. They can be used as an assay to diagnose many diseases, such as urinary tract infections (UTIs), kidney diseases and stone diseases, through the various biochemical parameters of urine.[7-9] So far, one study has been conducted showing the relationship between the biochemical parameters of urine and COVID-19.[10] We aimed to determine the association between the biochemical parameters of urine and COVID-19 disease severity.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

Pre-work permits were obtained by the Turkish Ministry of Health and the local ethics committee of Siirt University (decision no: 2020/05.02). Patients hospitalised in Siirt State Hospital between April and May 2020 and whose COVID-19 polymerase chain reaction (PCR) tests were positive were included in the study. A control group was also formed from 50 healthy individuals. Urine potential of hydrogen (pH), specific gravity (SG), leukocyte, erythrocyte, protein, nitrite, glucose and bacteria were recorded by asking the patients for a full urine examination. In addition, body temperature, respiratory rate (RR), heart rate (HR), mean arterial pressure (MAP) and peripheral capillary oxygen saturation (SpO_2) data were recorded from patients' files. The patients were further sub-divided into four groups (mild, moderate, severe and critical) according to the Diagnostic Treatment Program of New Coronavirus Pneumonia (7th trial version). Patients within the mild group were excluded from the study because they were treated as outpatients.

Patients with chronic renal failure, asthma, hypertension (HT), diabetes mellitus (DM) and chronic obstructive pulmonary disease (COPD) thought to affect the study results were excluded from the study. In addition, the urine of all patient groups was nitrite negative and bacteria were absent. Therefore, patients with urinary tract infections were excluded from the study. In addition, low molecular weight heparin treatment was given prophylactically to all Covid positive hospitalised patients. We compared the patient group with healthy controls. Severe and critical groups in the patient group were combined and defined as severe group and moderate group as non-severe group.

2.2 | Method

After the patients were hospitalised in Siirt State Hospital, about 30 mL of clean mid-flow urine samples were taken from the patients on the same day. A urine sample was taken from critical COVID-19 patients by inserting a catheter. Urinary biochemical parameters, such as urine occult blood, urine glucose, nitrite, SG, pH, proteinuria and leukocytes, were tested using a fully automatic urine biochemical analyser (DIRUI FUS 200/H-800, DIRUI Industrial Co.). Variables

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What is known

- COVID-19 disease is a serious problem in society.
- The severity of the COVID-19 disease varies in patients.
- Laboratory and vital parameters are investigated to predict the course of COVID-19 disease.

What is new

- There is one study that supports our work.
- COVİD-19 disease is a serious social problem and it is important to predict its severity.
- We think that when urine analysis and vital signs are evaluated together, it can be useful in predicting the severity of Covid-19 disease.

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such as proteinuria and erythrocyteuria were used as categorical variables as present or absent. All collected samples were studied within 2 h.

2.3 | Statistical analysis

All statistical analyses were performed using SPSS Statistics software version 26.0 (IBM, Armonk). Continuous variables are expressed as the appropriate means and standard deviations or median and Q1 and Q3. Categorical variables are summarised as the counts and percentages in each category. One-way analysis of variance (ANOVA), Kruskal–Wallis tests, student's t tests and Mann–Whitney U tests were applied to continuous variables, while chi-square and Fisher's exact tests were used for categorical variables. Spearman correlation coefficients were used to describe the association between disease severity and urine and other easily applicable parameters. Binary logistic regression analysis was used to determine the predictive role of clinical and urine biochemical parameters on disease severity. The optimal cut-off value for age was calculated by applying a receiver operating curve (ROC) analysis. A P value <.05 was considered statistically significant.

3 | RESULTS

In our study, there were 85 (63.9%) patients in the moderate group, 29 (21.8%) in the severe group and 19 (14.3%) in the critical group. For the control group, 50 healthy people without COVID-19 were selected.

3.1 | Urine biochemical parameters and vital sign analyses of the patient and control groups

There was no significant difference between the patient and control groups in terms of age (P = .070) or sex (P = .125; Table 1).

The rates of erythrocyturia ($P < .001$), proteinuria ($P = .015$) and glucosuria ($P = .020$) were significantly higher in patients than in the controls. In the patient group, the median SG value was significantly lower than in the control group ($P < .001$). The median pH value was significantly higher in the patient group compared to the control group ($P < .001$; Table 1).

While the mean RR ($P < .001$), HR ($P < .001$) and MAP ($P = .003$) were significantly higher in the patient group than in the control group, the SpO_2 ($P < .001$) was significantly lower (Table 1).

3.2 | Urine biochemical parameters and vital sign analyses of the three patient groups

In terms of SG ($P = .334$) and pH ($P = .229$), there was no significant difference between the three patient groups. Patients in the moderate group had a significantly lower average age than patients in the severe and critical groups ($P < .001$). The rate of proteinuria was significantly higher in patients in the severe and critical groups compared with the moderate group ($P < .001$).

The erythrocyturia ratio was significantly higher in the critical group than in the moderate group ($P < .001$), but there was no significant difference between the severe group and the other two groups ($P > .05$). Proteinuria and glucosuria rates were significantly higher in the severe and critical groups than in the moderate group ($P < .001$).

Proteinuria and glucosuria rates were significantly higher in the critical group than in the severe group ($P < .05$).

There was no significant difference between the patient groups in terms of fever ($P = .098$). The mean RR was significantly higher in the severe and critical groups than in the moderate group ($P < .05$). The mean RR was significantly higher in the critical group than in the severe group ($P < .05$). The mean SpO_2 was significantly lower in the severe and critical groups than in the moderate group ($P < .05$). The mean SpO_2 was significantly lower in the critical group than in the severe group ($P < .05$; Table 1).

3.3 | Correlation and regression analysis between disease severity and easily applicable parameters

The severe and critical groups were classified as severe, while the moderate group was classified as non-severe. Age, RR, SpO_2, erythrocyturia, proteinuria and glucosuria were significantly higher in the severe group than in the non-severe group ($P < .001$; Table 2) On Spearman correlation analysis, there was a strong positive correlation between disease severity and age ($r = 0.545$, $P < .001$), RR ($r = 0.838$, $P < .001$) and proteinuria ($r = 0.462$, $P < .001$), while there was a strong negative correlation with SpO_2 ($r = -0.839$, $P = .001$; Table 3). On multivariate analysis, age (OR: 1.06, 95% CI 1.03-1.10, $P = .035$), respiratory rate ≥30 breaths/min (OR: 4.72,

TABLE 1 The comparison of demographic, clinical and urine biochemical parameters between patient groups and healthy controls

Characteristics	Moderate (n = 85)	Severe (n = 29)	Critical (n = 19)	Total	P value	Control (n = 50)	P value
Age, mean ± SD	47.8 ± 16.2[a,b,*]	66.9 ± 15.6	71.5 ± 12.4	55.3 ± 18.5	**<0.001**	51.6 ± 9.2	.070
Gender, n (%)							
Male	34 (40)	12 (41.4)	9 (47.4)	55 (41.4)	.840	27 (54)	.125
Female	51 (60)	17 (58.6)	10 (52.6)	78 (58.6)		23 (46)	
Fever, n (%)	36 (42.4)	19 (65.5)	9 (47.4)	64 (48.1)	.098	0 (0)	N/A
Respiratory rate, per min, mean ± SD	23.2 ± 2.8[a,b,*]	30.1 ± 0.5[3,*]	33.0 ± 0.8	26.1 ± 4.6	**<.001**	18.6 ± 1.4	**<.001**
Heart rate, per min, mean ± SD	71.3 ± 6.6[b,*]	69.8 ± 7.0[c,*]	80.5 ± 10.6	72.3 ± 8.1	**<.001**	64.6 ± 3.1	**<.001**
MAP, mmHg, mean±SD	76.4 ± 6.2[b,*]	75.1 ± 7.1[c,*]	85.6 ± 9.9	77.5 ± 7.7	**<.001**	75.2 ± 1.9	**.003**
Spo2 (%), mean ± SD	96.3 ± 1.2[a,b,*]	91.2 ± 1.3[c,*]	86.4 ± 1.2	93.7 ± 3.8	**<.001**	95.6 ± 2.1	**<.001**
SG, median (Q1-Q3)	1015 (10)	1015 (11)	1020 (10)	1015 (10)	.334	1020 (9)	**<.001**
pH, median (Q1-Q3)	6 (1)	6 (0.5)	6 (0.5)	6 (0.5)	.229	5.5 (0.5)	**<.001**
Erythrocyturia, n (%)	39 (45.9)[c,*]	20 (69)	17 (89.5)	76 (57.1)	**<.001**	10 (20)	**<.001**
Leukocyturia, n (%)	4 (4.7)	2 (6.9)	3 (15.8)	9 (6.8)	.220	3 (6)	.852
Proteinuria, n (%)	4 (4.7)[a,b,*]	8 (27.6)[c,*]	12 (63.2)	24 (18)	**<.001**	2 (4)	**.015**
Glucosuria, n (%)	6 (7.1)[b,*]	6 (20.7)[c,*]	11 (57.9)	23 (17.3)	**<.001**	2 (4)	**.020**

Statistically significant values are indicated in bold.

Abbreviations: SD, standard deviation; SG, specific gravity; pH, potential of hydrogen; MAP, mean arterial pressure; SpO_2, peripheral capillary oxygen saturation.

[a]Group between moderate disease and severe disease.

[b]Group between moderate disease and critical.

[c]Group between severe disease and critical.

*$P < .05$.

TABLE 2 The comparison of demographic, clinical and urine biochemical parameters between patient groups

Characteristics	Non-severe (n = 85)	Severe (including critical) (n = 48)	P value
Age, mean ± SD	47.8 ± 16.2	68.75 ± 14.5	**<.001**
Gender, n (%)			
Male	34 (40)	21 (43.8)	.673
Female	51 (60)	27 (56.2)	
Fever, n (%)	36 (42.4)	28 (58.3)	.076
Respiratory rate, per min, mean ± SD	23.2 ± 2.8	31.3 ± 1.6	**<.001**
Heart rate, per min, mean ± SD	71.4 ± 6.6	74.0 ± 10.1	.110
MAP, mmHg	76.4 ± 6.2	79.3 ± 9.7	.072
SpO_2 (%), mean ± SD	96.3 ± 1.2	89.3 ± 2.7	**<.001**
SG, median (Q1-Q3)	1015 (10)	1015.5 (11)	0.829
pH, median (Q1-Q3)	6 (1)	6 (0.5)	.089
Erythrocyturia, n (%)	39 (45.9)	37 (77.1)	**<.001**
Leukocyturia, n (%)	4 (4.7)	5 (10.4)	.208
Proteinuria, n (%)	4 (4.7)	20 (41.7)	**<.001**
Glucosuria, n (%)	6 (7.1)	17 (35.4)	**<.001**

Statistically significant values are indicated in bold.

Abbreviations: SG, specific gravity; pH, potential of hydrogen; SD, standard deviation; MAP, mean arterial pressure; SpO_2: peripheral capillary oxygen saturation.

TABLE 3 Spearman correlation analysis between disease severity and easy applicable parameters

Characteristics	Severe disease	
	rho value	P value
Age	0.545	<.001
Respiratory rate	0.838	<.001
SpO_2	−0.839	.001
Erythrocyturia	0.303	<.001
Proteinuria	0.462	<.001
Glucosuria	0.360	<.001

95% CI 1.26-6.24, $P < .0031$), $SpO_2 \leq 93\%$ (OR: 3.82, 95% CI 1.18-5.82, $P = .001$) and proteinuria (OR: 1.13, 95%CI 1.02-2.1, $P = .023$) were independent predictive factors for disease severity (Table 4). The optimum cut-off value of age for predicting severe disease was 53.5 years. The AUC of age was 0.828 (95% CI: 0.756-0.899; $P < .001$). The highest sensitivity and specificity for age were 0.854 and 0.647, respectively (Figure 1).

4 | DISCUSSION

Starting in China in 2019, COVID-19 has spread throughout the world and has been proclaimed by the World Health Organization as a pandemic. This disease comes from an RNA virus known as coronavirus 2 (SARS-CoV-2), which has inflicted an enormous loss of life worldwide. Clinical findings are non-specific, but the disease usually presents with a cough, fever, myalgia, weakness and nausea.[10] In patients with high levels of comorbidity, it may be more severe and cause multi-organ failure.[3]

According to the latest Coronavirus Pneumonia Diagnosis and Treatment Program (7th Edition), patients are divided into four groups as mild, moderate, severe and critical. Clinical findings of patients' blood values, respiratory counts and blood pressures are useful in determining the severity of the disease.[11]

Patients with COVID-19–related pneumonia often do not subjectively appreciate their lung injury. Through the virus's effect on surfactants and the resultant alveolar collapse, patients have a progressive drop in PaO_2 and an incremental increase in their respiratory rate. This process develops over days. The lungs initially remain compliant and patients can effectively ventilate, lowering carbon dioxide partial pressure.[12] They also develop a large right-to-left shunt.[13] Ultimately, the increase in respiratory drive exacerbates both the inflammation and the lung injury caused by the virus itself.[12] The worsening hypoxia increases respiratory rate, and underlying lung damage accelerates overt respiratory failure. Patient deaths are generally caused by acute respiratory failure, cardiac dysrhythmia because of severe hypoxemia and thrombosis.[13] Similarly, we observed that patients with high RR and low SpO_2 at presentation progressively worsened.

In a study that compared the COVID-19 patients and controls, the incidence of protein and erythrocyte in the urine of patients was higher than in the controls ($P < .05$). Furthermore, urine pH and SG were considerably different from the controls. However, the incidence of leukocytes in urine did not differ between the patient and the healthy group. This is because SARS-CoV-2 infection has been linked to non-bacterial.[10] In our study, the positive rates

TABLE 4 The comparison of demographic, clinical and urine biochemical parameters between patient groups and independent predictors of disease severity by univariate and multivariate logistic regression

Characteristics	Univariate model OR (95% CI)	P value	Multivariate model OR (95% CI)	P value
Age	1.08 (1.05-1.12)	**.001**	1.06 (1.03-1.10)	**.035**
Respiratory rate ≥ 30 breaths/min	6.35 (2.23-12.8)	**<.001**	4.72 (1.26-6.24)	**<.001**
SpO$_2$ ≤ 93%	5.24 (1.97-9.8)	**<.001**	3.82 (1.18-5.82)	**.001**
Erythrocyturia	3.96 (1.78-8.80)	**.001**	2.3 (0.86-6.14)	.095
Proteinuria	1.41 (1.12-3.14)	**.001**	1.13 (1.02-2.1)	**.023**
Glucosuria	3.22 (1.60-7.1)	**<.001**	1.12 (0.26-4.83)	.874

Statistically significant values are indicated in bold.
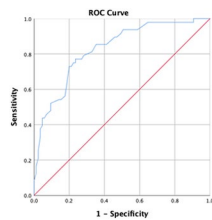
FIGURE 1 The receiver operating characteristic (ROC) Curve analysis of age for COVID-19 disease severity

of erythrocyturia (P < .001), proteinuria (P = .015) and glucosuria (P = .020) were higher in patients than in controls. SG was considerably lower in the patients than in the controls. Moreover, the urine pH value of patients was significantly higher than the controls. However, urine pH and SG values were similar in the patient groups. The average age, RR, MAP, HR, glucosuria, erythrocyturia and proteinuria of severe and critical patients were significantly higher than the moderate group. The mean SpO$_2$ of severe and critical patients was significantly lower compared with the moderate group.

In a study that included 199 SARS-CoV-2 patients, over 65 years of age, presence of CKD (Chronic kidney disease) and levels of serum markers such as albumin and sodium, with independent variables obtained from early urinalysis for COVID-19 acute kidney injury, need for intensive care unit admission and mortality. The predictive model was included and it was shown that LDH can be a useful tool in the management of patients requiring hospitalisation for a SARS-CoV-2 infection.[14] In our study, age (OR: 1.06, 95% CI 1.03-1.10, P = .035), respiratory rate ≥ 30 breaths/min (OR: 4.72, 95% CI 1.26-6.24, P < .0031), SpO$_2$ ≤ 93% (OR: 3.82, 95% CI 1.18-5.82, P = .001) and proteinuria (OR: 1.13, 95% CI 1.02-2.1, P = .023) were independent predictive factors for disease severity.

In another study involving 333 Covid-19 patients, patients with severe or critically ill COVID-19 pneumonia had proteinuria (81.2% and 85.7%, 43.8%, respectively) and haematuria (39.1% and 69.6%, respectively), the incidence of 33.3% has been shown. It was determined that various clinical parameters were associated with proteinuria, haematuria and acute kidney injury in patients with COVID-19 pneumonia.[15] In our study, the rate of proteinuria (4.7%, 27.6%, 63.2%) and haematuria (45.9%, 69%, 89.5%) were found in moderate, severe and critical patients.

COVID-19 is mostly asymptomatic, and symptomatic patients are usually hospitalised and treated. Age, RR and SpO$_2$, proteinuria, which can be easily used in the diagnosis, can provide information about the severity of COVID-19 disease. We believe that it shows acute kidney damage, especially in COVID-19 patients in the severe and critical group. Therefore, urine analysis, which is checked quickly at the time of admission, can also give clues about the severity of the disease. Cytokine storm in COVID-19 patients in the severe and critical group, primarily affecting the kidney can cause multi-organ failure.[16] In the severe and critical group, we believe that kidney damage caused by this mechanism causes proteinuria and erythrocyturia.

This study had some limitations. First, this was a retrospective, single-center clinical trial and, therefore, had a small sample size. In addition, since our study was a retrospective study, it was excluded because the mild patient group included outpatients who did not require hospitalisation.

5 | CONCLUSION

Urine biochemical parameters have no place in the diagnosis of COVID-19 disease, but are important in showing acute kidney damage in the advanced stages of the disease. Therefore, we think that it would be beneficial to routinely examine urine biochemical parameters that are easily applicable and cost-effective in all COVID-19 patients. However, owing to the deficiencies in our study and the small sample size, more comprehensive studies are needed to reach a definite conclusion.

STATEMENT OF ETHICS

All procedures in studies with human participants complied with the Ethical standards of the Corporate Research Committee and the 1964 Helsinki Declaration and subsequent updates.

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CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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