The Role of Urine Biochemical Parameters for Predicting Disease Severity In COVID-19 Patients

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Abstract

Background: We aimed to determine the importance of urinary biochemical parameters in predicting the severity of COVID-19 disease. Methods: Totally 133 individuals diagnosed with COVID-19 in our clinic were included in the study. The groups were formed according to the severity of COVID-19 disease (moderate 85, severe 29, and critical 19), and an additional control group was created from 50 healthy individuals. The correlation between urine biochemical parameters and the severity of disease was investigated. Results: Erythrocyturia, proteinuria, and glucosuria rates were significantly higher in patients than controls. In patients, the median urine specific gravity (SG) value was found to be lower ($p<0.001$), and median potential of hydrogen (pH) value was found to be higher compared to the controls ($p<0.001$). In the severe group age, erythrocyturia, proteinuria, and glucosuria were significantly higher than the non-severe group. On multivariate analysis, proteinuria (OR: 4.66, 95%CI 1.02-21.4, $p=0.047$) and age (OR: 1.06, 95% CI 1.03-1.10, $p<0.001$) were independent predictive factors for disease severity. Conclusion: Some urine biochemical parameters especially proteinuria and advanced age may be useful for predicting the COVID-19 disease severity.

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Running Title: Urine biochemical parameters and COVID-19 disease

Keywords: Urine biochemical parameters, COVID-19, disease severity, coronavirus

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Aim: We aimed to determine the importance of urinary biochemical parameters in predicting the severity of COVID-19 disease.

Methods: Totally 133 individuals diagnosed with COVID-19 in our clinic were included in the study. The groups were formed according to the severity of COVID-19 disease (moderate 85, severe 29, and critical 19), and an additional control group was created from 50 healthy individuals. The correlation between urine biochemical parameters and the severity of disease was investigated.

Results: Erythrocyturia, proteinuria, and glucosuria rates were significantly higher in patients than controls. In patients, the median urine specific gravity (SG) value was found to be lower ($p<0.001$), and median potential of hydrogen (pH) value was found to be higher compared to the controls ($p<0.001$). In the severe group age, erythrocyturia, proteinuria, and glucosuria were significantly higher than the non-severe group. On multivariate analysis, proteinuria (OR: 4.66, 95%CI 1.02-21.4, $p=0.047$) and age (OR: 1.06, 95% CI 1.03-1.10, $p<0.001$) were independent predictive factors for disease severity.

Conclusion: Some urine biochemical parameters especially proteinuria and advanced age may be useful for predicting the COVID-19 disease severity.

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What's known

- COVID-19 disease is a serious problem in society.
- The severity of the COVID-19 disease varies in patients.
- Parameters to predict the severity of the COVID-19 disease are being investigated.
- Urine analysis can be useful in predicting the severity of Covid-19 disease.

What's 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.

Introduction

In late 2019, pneumonia epidemic began in Wuhan, China's Hubei Province, with a primarily unknown cause, which is known to have spread significantly across the World [1]. The virus that caused the disease was initially named as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), and later the World Health Organization described this disease as COVID-19 [2]. The disease usually affects individuals between the ages of 30 and 79. About half of those with COVID-19 disease have mild or indeterminate symptoms. Significant symptoms in symptomatic patients are 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 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 been reported. Serum procalcitonin levels are generally at normal levels, while mild increases in C-reactive protein levels can be seen. D-Dimer levels are high in 30 percent of patients [4,5].

Coronaviruses are enveloped RNA viruses that consist of a single chain and have 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 examination is fast, convenient, and economical. It can be used as an assay to diagnose many diseases such as urinary tract infections (UTI), kidney diseases, and stone diseases by showing biochemical parameters of urine [7,8,9]. So far, one study has been conducted showing the relationship between the biochemical parameters of urine and COVID-19 disease [10]. We aimed to determine the role of biochemical parameters of urine in predicting the COVID-19 disease severity.

Materials and methods

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 hospitalized in Siirt State Hospital between April and May 2020 and whose COVID-19 PCR (Polymerase Chain Reaction) test was positive were included in the study. Also, a control group was 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. The patient group was divided into four (mild, moderate, severe, and critical) groups according to the Diagnostic Treatment Program of New Coronavirus Pneumonia (seventh trial version). Patients with the mild group were excluded from the study because they were treated, outpatient.

Patients who were thought to affect the study results, such as chronic kidney failure, asthma, HT, DM, and chronic obstructive pulmonary disease (COPD) were excluded. Also, all patient groups had nitrite negative in urine and no bacteria. Therefore patients with urinary tract infections were excluded from the study. We compared the patient group with healthy controls. Besides, the severe and critical groups in the patient group were combined to determine the severe group, and the moderate group was defined as the non-severe group.

Method

After the patients were hospitalized 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. Biochemical parameters of urine such as urine occult blood, urine glucose, nitrite, SG, pH proteinuria, and leukocytes were tested using a fully automatic urine biochemical analyzer (DIRUI FUS 200 / H -800, DIRUI IndustrialCo., China). All collected samples were studied within 2 hours.

Statistical Analysis

All statistical analysis was performed out using SPSS Statistics software version 26.0 (IBM, Armonk, NY, USA). Continuous variables were expressed as the appropriate means and standard deviations or medians and interquartile ranges. Categorical variables were summarized as the counts and percentages in each category. One-way analysis of variance (ANOVA), Kruskal–Wallis test, Student's T-test, and Mann Whitney U tests were applied to continuous variables, and chi-square and Fisher's exact tests were used for categorical variables. Binary logistic regression analysis was used to determine the predictive effect of age, proteinuria, and all other significant factors on disease severity. The optimal cut-off value of age was calculated by applying the receiver operating curve (ROC) analysis. A value of $P < 0.05$ was considered statistically significant.

Results

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

Urine biochemical parameters analysis of patients' and control groups

There was no significant difference found between the patients and control groups in terms of age ($p=0.070$) and gender ($p=0.125$) (Table 1).

The rates of erythrocyturia ($p<0.001$), proteinuria ($p=0.015$), and glucosuria ($p=0.020$) were significantly higher in patients than controls. In the patient group, the median SG value was found to be significantly lower than the control group ($p<0.001$). The median pH value was found to be significantly higher in the patient group compared to the control group ($p<0.001$) (Table 1).

Urine biochemical parameters analysis of three patients' groups

In terms of SG ($p=0.334$) and pH ($p=0.229$), there was no statistically significant difference found between the three patients groups. Patients in the moderate group had a significantly lower average age than patients

in the severe and critical groups ($p<0.001$). The rate of proteinuria was significantly higher in patients in the severe and critical groups compared to the moderate group ($p<0.001$).

Erythrocyturia ratio was significantly higher in the critical group than in the moderate group ($p<0.001$), but there was no significant difference found between the severe group and the other two groups ($p>0.05$). Proteinuria and glucosuria rates were significantly higher in severe and critical groups than in the moderate group ($p<0.001$). Proteinuria and glucosuria rates were significantly higher in the critical group than in the severe group ($p<0.05$).

Independent predictive risk factors for disease severity

The severe and critical groups were determined as severe and the moderate group as non-severe. Age, erythrocyturia, proteinuria, and glucosuria were significantly higher parameters in the severe group than the non-severe group ($p<0.001$). On multivariate analysis, proteinuria (OR: 4.66, 95%CI 1.02-21.4, $p=0.047$) and age (OR: 1.06, 95% CI 1.03-1.10, $p<0.001$) were independent predictive factors for disease severity (Table 2). The optimum cut-off value of age for predicting severe disease was 59.5 years. AUC of age was 0.828 [95%CI (0.756-0.899); $P<0.001$]. The highest sensitivity and specificity were 0.771 and 0.765 for age (Figure 1).

Discussion

COVID-19 disease spread throughout the World, starting in China in 2019 and It was accepted by the World Health Organization as a pandemic. It is a RNA virus known as coronavirus 2 (SARS-CoV-2) which causes life losses all over the World. Clinical findings are non-specific and usually include cough, fever, myalgia, weakness, and nausea[2,3]. In patients with high 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 count, and blood pressure are useful in determining the severity of the disease [11].

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 the controls ($p<0.05$). Besides, 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 of erythrocyturia ($p<0.001$), proteinuria ($p=0.015$), and glucosuria ($p=0.020$) were higher in patients than controls. SG was considerably lower in the patients than controls. Besides, urine pH value of patients was significantly higher than controls. However, urine pH and SG values were similar in the patient groups. The average age, glucosuria, erythrocyturia, and proteinuria of severe and critical patients were significantly higher compared to the moderate group.

COVID-19 disease is mostly asymptomatic, and symptomatic patients are treated by hospitalization. In our study, two critical predictive factors, advanced age and proteinuria, were found to be correlated with the COVID-19 disease severity. For this reason, we think that these patients should be hospitalized and closely follow-up even if they are asymptomatic. The frequency of ARDS is observed more frequently in severe patients than non-severe patients [12]. The cytokine storm thought to cause the ARDS table can cause multiple organ failure, affecting the kidney. In the severe and critical group, we believe that kidney damage caused by this mechanism causes proteinuria.

As a result, urine biochemical parameters have no place in the diagnosis of COVID-19 disease but are valuable in terms of the disease's progression. Therefore, we think it would be useful to routinely examine the biochemical parameters of urine that are easily applicable and cost-effective in all COVID-19 patients.

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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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There is no funding source to be declared for this study.

Conflicts of Interest

No conflicts of interest.

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Figure 1. The receiver operating characteristic (ROC) Curve analysis of age for COVID-19 disease severity.**Table 1.** The comparison of demographic and urine biochemical parameters between patient groups and healthy controls.**Table 2.** The comparison of demographic and urine biochemical parameters between patient groups and independent predictors of disease severity by univariate and multivariate logistic regression.

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