

Evaluation of Tubular Dysfunction Using Urine Biomarkers in Children with COVID-19

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What is already known on this topic?

- There is a tubular dysfunction in COVID-19. IL-1 β and IL-6 are elevated in blood biochemistry in COVID-19.

What this study adds on this topic?

- β 2 microglobulin is a simple way to explore tubular dysfunction. IL-1 β and IL-6 levels are high in the urine even in non-critically ill patients.

ABSTRACT

Objective: The coronavirus disease pandemic is a major problem that the world has been facing since December 2019. It mainly affects the respiratory system; however, the disease can affect the kidneys to different degrees. This study aimed to determine the changes in tubular dysfunction and inflammation parameters in children with coronavirus disease using urine biomarkers.

Materials and Methods: We included 36 children who tested positive for severe acute respiratory syndrome coronavirus 2 on real-time reverse transcriptase-polymerase chain reaction using respiratory specimens. Coronavirus disease-positive and -negative period parameters were evaluated. For measurement of interleukin-1 β , interleukin-6, and urine β 2 microglobulin levels, patients' urine samples were collected at diagnosis and 1 month after discharge. Additionally, routine urine and hematological parameters were evaluated concurrently.

Results: For all patients, the median urine β 2 microglobulin, serum urea, and lactate dehydrogenase levels were significantly higher in the coronavirus disease-positive period than in the coronavirus disease-negative period ($P < .05$). Further, serum platelet count was significantly lower in the coronavirus disease-positive period than in the coronavirus disease-negative period ($P < .05$). However, there was no difference in serum creatinine, interleukin-6, or interleukin-1 β levels between the 2 periods ($P > .05$).

Conclusion: Our results suggest kidney involvement and tubular dysfunction in patients with asymptomatic, mild, and moderate infections. Furthermore, interleukin-1 β and interleukin-6 levels were high in the urine, even in non-critically ill patients. We believe that these findings contribute to the accumulation of evidence on continued inflammation in the kidney.

Keywords: COVID-19, interleukins, kidney, proteinuria

INTRODUCTION

The world is currently experiencing the coronavirus disease (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It has been described by the World Health Organization (WHO) as a public health emergency.^{1,2} Coronavirus disease mainly affects the respiratory system, and its clinical spectrum ranges from an asymptomatic state to diffuse alveolar damage leading to acute respiratory distress syndrome (ARDS). It also affects other organs.³ Kidney involvement in critically ill patients with COVID-19 is associated with poor outcomes. Several mechanisms may play a role in kidney injury during COVID-19 infection, including direct invasion of SARS-CoV-2 into the kidney parenchyma, an imbalanced renin-angiotensin-aldosterone system, and microthrombosis.

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In addition, kidney injury secondary to hemodynamic instability, inflammatory cytokines, and the consequences of therapeutics (nephrotoxic drugs and mechanical ventilation) are the other mechanisms. Early detection and specific therapy for renal changes, including adequate hemodynamic support and avoidance of nephrotoxic drugs, may help to improve the condition of critically ill patients with COVID-19.⁴ In a retrospective observational study of 238 pediatric patients with COVID-19 admitted to Wuhan Children's Hospital, the incidence of acute kidney injury (AKI) was 1.2%.⁵ In another study from the United Kingdom, the incidence rate of pediatric AKI was 29%.⁶ The normal urine contains small amounts of interleukin (IL)-1 and many kinds of cytokine inhibitors, including IL-1 inhibitors, sIL-2R, and tumor necrosis factor (TNF)-R.⁷⁻¹¹ In kidney and urinary tract diseases, IL-1, IL-6, IL-8, TNF, and transforming growth factor- β can be detected in the urine.¹²⁻¹⁴

This study aimed to determine the changes in tubular dysfunction and inflammation parameters in children with COVID-19 using urine biomarkers. In addition, we evaluated changes in hematological parameters.

MATERIALS AND METHODS

Patients and Methods

We prospectively evaluated 50 children diagnosed with COVID-19 between May 2020 and August 2020. Clinical and biological variables were also extracted from computer-based medical records. We excluded patients with insufficient data because they did not attend follow-ups and those with chronic diseases. The local Ethical Review Board and Turkey Ministry of Health Committee approved this study (Approval no: 342). We obtained written informed consent from all participants. The study was performed in accordance with the 1964 Declaration of Helsinki and its later amendments.

In total, 36 patients who tested positive for SARS-CoV-2 on real-time reverse transcriptase-polymerase chain reaction using respiratory specimens were confirmed to have COVID-19 by the pediatric infectious department. Suspected cases were diagnosed according to the national COVID-19 guidelines. The criteria were changed intermittently according to changes made by the Coronavirus Scientific Advisory Board in Turkey in response to new data regarding the disease.¹⁵

Patients' urine samples were evaluated for proteinuria at diagnosis and 1 month after discharge. The values were measured using random spot urine samples. The fixed threshold for protein-to-creatinine and albumin-to-creatinine ratios was >0.2 mg/g and >30 mg/g, respectively, based on the current literature.¹⁶ A urine β_2 microglobulin level of ≥ 0.19 mg/L was considered abnormal.¹⁷ Urine β_2 microglobulin, urine albumin, and urine protein levels were determined using commercially available kits via the nephelometric method, immunoturbidimetric method, and benzethonium chloride with turbidimetric method, respectively.

Patients' urine samples for measurement of IL-1 β and IL-6 levels were collected at diagnosis and 1 month after discharge. Urine samples were stored at -80°C until the day of the study. The samples were thawed and centrifuged immediately before analysis. Interleukin (IL)-6 and IL-1 β levels were measured

using enzyme-linked immunoassay (SEA 079 Hu, USCN, Wuhan, Hubei, China and SEA 563 Hu USCN, Wuhan, Hubei, China, respectively). Urine creatinine levels were measured using a Roche Cobas 601 autoanalyzer (Basel, Switzerland). The results are expressed as picograms per millimoles (pg/mmol)-to-creatinine.

Clinical, Biological, and Radiological Parameters

The patients' clinical severity was categorized according to the definitions of Dong et al¹⁸ as follows: (a) asymptomatic infection, including cases with positive diagnoses but without any clinical or radiological findings; (b) mild disease, including cases with acute upper respiratory tract infections but without clinical or radiological pneumonia; (c) moderate disease, including cases with pneumonia and symptoms of respiratory tract infection; (d) severe disease, including cases with progressive respiratory disease, dyspnea, and central cyanosis; and (e) critically ill, including cases presenting with ARDS or respiratory failure, shock, and organ dysfunction (e.g., encephalopathy, myocardial injury, coagulation abnormalities, and AKI).

Data on the following were obtained from electronic medical records at the first hospitalization (COVID-positive period) and 1 month after discharge (COVID-negative period): demographic characteristics (such as age and sex) and laboratory parameters (such as procalcitonin, C-reactive protein [CRP], urea, creatinine, lactate dehydrogenase [LDH], hemoglobin [Hb], white blood cell [WBC] count, lymphocyte count, and platelet count).

In the present study, we included asymptomatic, mild, and moderate cases. We categorized the asymptomatic and mild cases into Group 1 and moderate cases into Group 2. According to the Ministry of Health policy, at the beginning of the outbreak in Turkey, all COVID-19-positive patients with asymptomatic, mild, and moderate diseases were required to be hospitalized.

Statistical Analysis

The Shapiro-Wilk test was used to assess data normality. Distributed data are expressed as means $\pm$ standard deviations (ranges), while non-parametric data are expressed as medians (interquartile ranges) (ranges). Categorical variables are expressed as numbers and percentages. The independent samples *t*-test, Mann-Whitney *U* test, and chi-square test were used to compare independent variables. In addition, the paired samples *t*-tests and Wilcoxon test were used to compare dependent variables. All statistical analyses were performed using the Statistical Package for Social Sciences version 21.0 software (IBM Corp.; Armonk, NY, USA). Statistical significance was set at $P < .05$, and odds ratios and 95% CIs were determined.

RESULTS

Patient Characteristics

Among the enrolled 36 patients, 24 (66.7%) were boys and 12 (33.3%) were girls. The mean age was 11.3 ± 4.8 (2.5-17.5) years. Nineteen (51.4%) patients had an asymptomatic or a mild infection (Group 1), and the remaining 17 (47.2%) patients had a moderate infection (Group 2). For all patients, the mean length of hospital stay was 7.7 ± 2.3 (3.0-13.0) days.

The groups did not differ according to sex (boy-to-girl ratio: 2.8 and 1.25 in Groups 1 and 2, respectively; $P = .24$). There was no significant difference between Groups 1 and 2 in terms of age (8.5 [11] years vs. 14.75 [5.4] years; $P = 0.10$) and length of hospital stay (7.4 ± 2.6 days vs. 7.9 ± 2.7 days; $P = .56$).

Proteinuria, Inflammation, and Hematological Parameters

The mean/median urinary spot β_2 microglobulin, serum procaldonin, CRP, urea, creatinine, LDH, Hb levels; spot protein-to-creatinine, spot albumin-to-creatinine, IL-1 β -to-creatinine, and IL-6-to-creatinine ratios; and WBC, lymphocyte, and platelet

counts in the COVID-positive and -negative periods according to groups (Groups 1 and 2) are summarized in Table 1.

For all patients, the median urine β_2 microglobulin, serum urea, and LDH levels were significantly higher in the COVID-positive period than in the COVID-negative period; serum platelet count was lower in the COVID-positive period than in the COVID-negative period, and this difference was significant ($P < .05$; P1 column). However, there was no difference in serum creatinine, IL-6, or IL-1 β levels between the 2 periods ($P > .05$; P1 column) (Table 1). Further, in Group 1 (P2 column), the median

Table 1. Clinical Characteristics of All Patients and According to the Groups (Group 1 and Group 2)

Characteristics	All Patients (n = 36)			Group 1 (n = 19)			Group 2 (n = 17)			P ⁴	P ⁵
	COVID Positive Period	COVID Negative Period	P ¹	COVID Positive Period	COVID Negative Period	P ²	COVID Positive Period	COVID Negative Period	P ³		
Urinary spot β_2 microglobulin, mg/L (NR: 0-0.3), median (IQR)	0.17 (0.06)	0.17 (0.01)	.01	0.19 (0.08)	0.17 (0.01)	.02	0.17 (0.02)	0.17 (0.01)	.01	.30	.38
Urinary spot protein/creatinine, mg/mg creatinine (NR: <0.2), median (IQR)	0.14 (0.07)	0.14 (0.09)	.71	0.15 (0.06)	0.16 (0.12)	.32	0.12 (0.05)	0.11 (0.10)	.14	.33	.04
Urinary spot albumin/creatinine mg/g creatinine (NR: <30), median (IQR)	5.5 (8.2)	6.0 (8.0)	.68	7.7 (11.4)	4.6 (3.6)	.31	8.2 (10.0)	4.7 (5.5)	.55	.06	.06
Urinary IL-1 β /creatinine pg/mmol creatinine, median (IQR)	4095 (6174)	2298 (3797)	.20	4010 (7318)	2368 (3910)	.33	4668 (3538)	2229 (3997)	.38	.74	.98
Urinary IL-6/creatinine pg/mmol creatinine, median (IQR)	532 (788)	419 (827)	.59	671 (642)	683 (807)	.93	438 (822)	381 (636)	.69	.69	.28
Serum procaldonin μ g/L (NR: <0.5), median (IQR)	0.05 (0.04)	0.04 (0.03)	.78	0.04 (0.06)	0.05 (0.02)	.26	0.05 (0.03)	0.05 (0.07)	.63	.86	.82
Serum CRP mg/L (NR: <5), median (IQR)	0.73 (1.46)	0.55 (0.77)	.08	1.06 (2.60)	0.69 (1.34)	.12	0.64 (0.40)	0.34 (0.59)	.27	.44	.06
Serum urea mg/dL (NR: 18-45), mean $\pm$ SD	26 $\pm$ 6.4	23.6 $\pm$ 7.9	.04	27 $\pm$ 4.1	24.9 $\pm$ 7.3	.32	24.9 $\pm$ 8.3	22 $\pm$ 8.5	.33	.18	.28
Serum creatinine mg/dL (NR: <1.2), mean $\pm$ SD	0.54 $\pm$ 0.19	0.55 $\pm$ 0.2	.42	0.51 $\pm$ 0.24	0.57 $\pm$ 0.24	.06	0.56 $\pm$ 0.12	0.54 $\pm$ 0.16	.42	.06	.64
Serum LDH IU/L (NR: 100-305), median (IQR)	251 (98)	210 (91)	.01	274 (98)	252 (75)	.01	205 (97)	183 (79)	.20	.30	.08
Serum Hb g/dL, mean $\pm$ SD	13.3 $\pm$ 1.40	13.5 $\pm$ 1.30	.22	13.5 $\pm$ 1.05	13.9 $\pm$ 1.2	.06	12.9 $\pm$ 1.74	13 $\pm$ 1.3	.20	.17	.06
Serum WBC/mm ³ , mean $\pm$ SD	6500 $\pm$ 2100	7100 $\pm$ 2150	.19	6500 $\pm$ 1970	7600 $\pm$ 2500	.16	6400 $\pm$ 2270	6500 $\pm$ 1550	.85	.74	.13
Serum lymphocyte count/mm ³ , mean $\pm$ SD	2550 $\pm$ 1150	2700 $\pm$ 850	.29	2800 $\pm$ 1300	2900 $\pm$ 900	.78	2250 $\pm$ 960	2560 $\pm$ 790	.16	.11	.27
Serum platelet count/mm ³ , mean $\pm$ SD	290000 $\pm$ 68000	320000 $\pm$ 70000	.01	280000 $\pm$ 63000	304000 $\pm$ 81000	.03	305000 $\pm$ 71000	334000 $\pm$ 56000	.20	.42	.20

P¹, all patients' COVID positive period versus COVID negative period.

P², Group 1's COVID positive period versus COVID negative period.

P³, Group 2's COVID positive period versus COVID negative period.

P⁴, COVID positive periods Group 1 versus Group 2.

P⁵, COVID negative periods Group 1 versus Group 2.

NR, normal range; IQR, interquartile range; IL-1 β , interleukin-1 β ; IL-6, interleukin-6; CRP, C-reactive protein; LDH, lactate dehydrogenase; Hb, hemoglobin;

WBC, white blood cell.

Bold types indicate the P-value of <.05.

urine $\beta 2$ microglobulin and serum LDH levels were significantly higher in the COVID-positive period than in the COVID-negative period. Further, serum platelet count was lower in the COVID-positive period than in the COVID-negative period, and this difference was significant ($P < .05$; P2 column; Table 1). In Group 2, only spot urine $\beta 2$ microglobulin level was higher in the COVID-positive period than in the COVID-negative period ($P < .05$, P3 column; Table 1).

However, there were no significant differences between Group 1 and Group 2 in terms of urine and serum variables in the COVID-positive period ($P > .05$; P4 column). Furthermore, the urine and serum variables in the COVID-negative period were not significantly different between the groups ($P > .05$; P5 column; Table 1), except urinary spot protein-to-creatinine ratio, which was significantly lower in Group 2 than in Group 1 ($P = .04$; P5 column; Table 1).

DISCUSSION

Coronavirus disease, a major health problem, has been spreading rapidly worldwide, causing a burden on the health systems of countries. Therefore, it is important to evaluate which biomarker is important for diagnosis and follow-up. This study evaluated urine and hematological biomarkers for diagnosis as well as their changes in COVID-positive and -negative periods. To the best of our knowledge, this study is the first to use urine biomarkers to evaluate disease activity in COVID-positive and COVID-negative periods.

Proteinuria is frequently found in patients with COVID-19. In a study by Huart et al.³ proteinuria was of tubular origin, with increased urinary $\alpha 1$ -microglobulin levels. Further, tubular proteinuria was associated with mortality in patients with COVID-19. In another study conducted by Pei et al.¹⁹ 65.8% of patients, mainly severe or critically ill patients, presented with proteinuria. $\beta 2$ microglobulin is an 11 870-Da single-chain polypeptide that is found in almost all nucleated cells. It is a cytokine-inducible protein. A high level of $\beta 2$ microglobulin in the urine is thought to reflect a cytokine storm.²⁰ In our study, spot urine $\beta 2$ microglobulin level was higher in the COVID-positive period than in the COVID-negative period. Some studies have suggested direct virus-mediated tubular injury on kidney biopsies, including electron microscopy.^{21,22} A study conducted by Hoffmann et al.²³ has suggested preferential cellular entry of SARS-CoV-2 in the tubular expression of angiotensin-converting enzyme 2. However, since there were no severe or critically ill patients, we believe that our results could be a possible explanation for the mechanism of kidney injury. Our patients did not take any medications or received only oxygen therapy. In addition, our patients had tubular proteinuria. The design of the current study did not allow the detection of SARS-CoV-2 on kidney biopsies. However, these data could explain the kidney dysfunction caused by SARS-CoV-2 infection or inflammatory cytokines rather than treatment agents.

A study conducted by Yaqinuddin and Kashir²⁴ asserted that IL-1 β is discriminated as a causative factor for cytokine release, similar to IL-6, thereby contributing to the "cytokine storm" of SARS-CoV-2. Furthermore, IL-6 is considered as the most important causative cytokine in "cytokine storm." Therefore, it is thought that the plasma concentration of IL-6 is increased

in patients with ARDS.²⁵ Chen et al.² found that the level of the inflammatory cytokine IL-6 increased significantly in critically ill patients with COVID-19. In our study, although there was a slight decrease in the mean/median urinary IL-1 β -to-creatinine and IL-6-to-creatinine ratios in the COVID-positive period than in COVID-negative period, the ratios did not differ across groups. The normal values of IL-1 β and IL-6 are unknown, but the absence of a significant decrease in urinary IL levels 1 month after diagnosis may be evidence of continued inflammation. In addition, based on the literature, high levels of $\beta 2$ microglobulin were thought to reflect cytokine storm.²⁰ We believe that this supports our opinion.

Several studies have explored the role of different blood biomarkers in the pathogenesis of COVID-19. In their meta-analysis, Henry et al.²⁶ found that patients with severe and fatal diseases had significantly increased WBC counts and decreased lymphocyte and platelet counts compared to non-severe disease and survivors. Furthermore, Kermali et al.²⁷ found that LDH levels and renal markers were elevated in severe disease. Similarly, in our study, serum urea and LDH levels were lower in the COVID-negative period than in the COVID-positive period. Moreover, serum platelet counts were higher in the COVID-positive period than in the COVID-negative period.

Acute kidney injury is an important issue that is closely related to mortality in patients with COVID-19. One possible explanation for AKI is hypovolemia.²⁸ In our study, we found that there was a significant increase in serum urea levels in the COVID-positive period than in the COVID-negative period in all patients. However, we did not find an increase in the serum creatinine level. We believe that an increase in serum urea level without an increase in creatinine level is relevant to a hypovolemic state in our patients.

Our study has limitations. First, the confounding factors were associated with a limited number of patients. Second, because of the lack of a control group, we could not compare the results of IL levels. Finally, there were no severe and critically ill patients at the beginning of the pandemic.

In conclusion, we compared the urine and blood biomarkers of COVID-positive and COVID-negative periods. We found that there is a tubular dysfunction in COVID-19, and $\beta 2$ microglobulin is a simple way to explore the tubular dysfunction. In addition, the IL-1 β and IL-6 levels were high in the urine, even in non-critically ill patients. We believe that these findings contribute to the accumulation of evidence on continued inflammation in the kidney.

Ethics Committee Approval: This study was approved by Ethics committee of Ankara Training and Research Hospital, (Approval No:342).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer Review: Externally peer-reviewed.

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E.Ç.S.; Data Collection and/or Processing – L.D., E.Ç.S.; Analysis and/or Interpretation – N.T., K.A.; Literature Search – N.T., B.C.C.Y.; Writing Manuscript – N.T., A.U.G.; Critical Review – K.A., M.Ş.

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