Original Article – General Urology
Grand J Urol 2023;3(2):54-9
DOI: 10.5505/GJU.2023.50470

Comparison of Pre-COVID-19, COVID-19, and Post-COVID-19 Urinalysis Parameters and Assessment of Their Relationships with Renal Functions

Pre-COVID-19, COVID-19 ve Post-COVID-19 Ürinanaliz Parametrelerinin Karşılaştırılması ve Böbrek Fonksiyonları ile İlişkilerinin Değerlendirilmesi

Leyla Ozturk Sonmez[1], Hulya Vatansev[2], Gokhan Ecer[3], Mehmet Giray Sonmez[4]

[1]Department of Emergency Medicine, University of Health Sciences, Beyhekim Training and Research Hospital, Konya, Türkiye
[2]Department of Chest Diseases, Necmettin Erbakan University Meram School of Medicine, Konya, Türkiye
[3]Department of Urology, University of Health Sciences, Konya Training and Research Hospital, Konya, Türkiye
[4]Department of Urology, Necmettin Erbakan University Meram School of Medicine, Konya, Türkiye

Cite as: Ozturk Sonmez L, Vatansev H, Ecer G, Sonmez MG. Comparison of pre-COVID-19, COVID-19, and post-COVID-19 urinalysis parameters and assessment of their relationships with renal functions. Grand J Urol 2023;3(2):54-9.

Submission date: 04 April 2023 **Acceptance date:** 09 May 2023 **Online first:** 12 May 2023 **Publication date:** 19 May 2023

Corresponding Author: Leyla Ozturk Sonmez / University of Health Sciences, Beyhekim Training and Research Hospital, Department of Emergency Medicine, Konya, Türkiye / ozturkleyla@gmail.com / ORCID ID: 0000-0003-0201-4468

Abstract

Objective: This study compared the pre-COVID-19, COVID-19, and post-COVID-19 periods of the patients in terms of urinalysis parameters and assessed the relationships between the changes in these parameters and renal functions.

Materials and Methods: Four-hundred-eighty-two moderate and severe COVID-19 patients who had the data of urinalysis performed in the pre-COVID-19 period at most three months before the onset of COVID-19 diagnosis, during COVID-19 disease, and 15 days after they completely recovered from the COVID-19 disease were included in the study. Parameters of bilirubin, erythrocyte, leukocyte, protein, glucose, acidity (pH), and density were analyzed in urine samples, and the results were recorded.

Results: CRP, e-GFR, fibrinogen and D-dimer values were found to be significantly different between the three groups (for all parameters p<0.05). A negative correlation was found between e-GFR and both CRP (p<0.001, r:-0.289) and D-dimer (p:0.02, r:-0.129) values of the patients during COVID-19. Urine pH, presence of leukocyturia, presence of microscopic hematuria and presence of proteinuria were found to be significantly different between the three groups (for all parameters p<0.05). It was determined that these four parameters increased significantly during the COVID-19 period and decreased in the post-COVID-19 period. A negative correlation between urine density and e-GFR (p:0.04, r:-0.175) and a positive (p:0.02, r:0.195) correlation between urine density and CRP were detected during COVID-19.

Conclusion: The significant presence of hematuria and proteinuria during COVID-19 disease in line with the literature data supports the opinion that the disease causes renal involvement. The tendency of the parameters on the post-COVID 15th day to return to normal ranges shows that the effects of the inflammation are reversible after the patients recover from the disease.

Keywords: COVID-19, e-GFR, hematuria, proteinuria, urinalysis

Öz

Amaç: Bu çalışmada hastaların Pre-COVID-19, COVID-19 ve Post-COVID-19 dönemlerinde idrar parametrelerinin karşılaştırılması ve bu değişimin böbrek fonksiyonları ile ilişkisi değerlendirilmiştir.

Gereçler ve Yöntemler: Pre-COVID-19 dönemde 3 ay öncesine kadar, COVID-19 hastalık döneminde ve COVID-19 hastalığından tamamen iyileştikten 15 gün sonra ürinanaliz yapılmış olan 482 orta ve şiddetli COVID-19 hastası çalışmaya dahil edilmiştir. İdrar örneklerinde bilirubin, eritrosit, lökosit, protein, glukoz, asidite (pH) ve dansite parametreleri incelendi ve sonuçlar kaydedildi.

Bulgular: CRP, e-GFR, fibrinojen ve D-dimer değerleri üç grup arasında anlamlı olarak farklı bulundu (tüm parametreler için p<0,05). COVID-19 döneminde e-GFR'nin CRP (p<0.001, r:-0,289) ve D-dimer (p:0.02, r:-0,129) ile negatif korelasyona sahip olduğu bulundu. İdrar pH'ı, lökositüri varlığı, mikroskobik hematüri varlığı ve proteinüri varlığı üç grup arasında anlamlı olarak farklı bulundu (tüm parametreler için p<0.05). Bu dört parametrenin de COVID-19 döneminde anlamlı artış gösterdiği, post-COVID-19 dönemde de azalma gösterdiği saptandı. COVID-19 döneminde idrar dansitesinin e-GFR ile negatif (p:0.04, r:-0,175) CRP ile pozitif (p:0.02, r:0,195) korelasyona sahip olduğu tespit edildi.

Sonuçlar: Literatür verileri ile uyumlu olarak COVID-19 hastalığı sırasında anlamlı hematüri ve proteinüri varlığı, hastalığın böbrek tutulumuna neden olduğu görüşünü desteklemektedir. Post-COVID-19 15. günde ölçülen parametrelerinin normale dönme eğilimi göstermesi enfeksiyon dönemi geçtikten sonra inflamasyonun etkilerinin geri dönüşümlü olabileceğini göstermektedir.

Anahtar kelimeler: COVID-19, e-GFR, hematüri, proteinüri, ürinanaliz

ORCID ID: **H. Vatansev** 0000-0002-8382-3904 **G. Ecer** 0000-0002-2805-8664 **M.G. Sonmez** 0000-0003-4615-7348

Introduction

Coronaviruses mainly cause respiratory tract infections and gastrointestinal infections in humans [1]. World Health Organization (WHO) named the infectious pneumonia disease caused by SARS-CoV-2 virus as coronavirus disease 2019 (COVID-19) [2]. Hypoxia, dyspnea, acute respiratory distress syndrome (ARDS), septic shock, and multiple organ failure can also be seen in severe and critically ill COVID-19 cases [3]. But most of the SARS-CoV-2 cases remain asymptomatic after vaccination [4]. Many studies revealed that urinary system involvement is prevalent in patients infected with SARS-COV-2. Only limited number of studies showing a correlation between urinary biochemical parameters and SARS-COV-2 are available in the literature [5,6].

Urinalysis covers quick, economical, useful, and noninvasive tests which provide detailed information on urine. These data can aid in the diagnosis of many diseases including urinary tract infections and can also be used in the monitorization of the outcomes of the treatment used for these diseases [7,8].

The effects of SARS-CoV-2 on urinary biochemical parameters were analyzed through comparing patient and control groups or based on the severity of the disease in previous studies but no research has yet been made both on the effect and change in urinary parameters in periods before, during, and 15 days after recovery from COVID-19 disease and also on the relationship between the change in these parameters and renal function tests and inflammatory markers. This study compared the parameters of urinalysis in periods before, during, and after recovery from pre-COVID-19 disease, and assessed the relationships between the changes in these parameters and renal functions.

Material and Methods

The protocol of the study was approved by the Institutional Ethics Committee of Necmettin Erbakan University (NEU: 2020/2835). Nine hundred ninety-seven patients hospitalized due to COVID-19 disease between January 2020 and January 2022 were evaluated. Demographic data and comorbid conditions of the patients were recorded. Four hundred eighty-two moderate and severe COVID-19 inpatients who complied with the inclusion criteria and had the data of urinalysis performed in a maximum of three months before the diagnosis of COVID-19 disease, during the course of COVID-19 disease, on the 1st day of hospitalization, and on the 15th day of their discharge were included in the study.

RT-PCR-positive oropharyngeal and nasopharyngeal swabs prepared for the detection of SARS-CoV-2 infection revealed the diagnosis of COVID-19. Following the diagnosis of Sars-Cov-2 infection, 15-30 mL clean, middle-flow urine samples were collected for the patients. After the recovery, once the first negative RT-PCR result of these patients was obtained, urinalysis was re-taken on the post-discharge 15th day. Urine samples were drawn from the urinary catheters of the critically ill patients. Urinary parameters of bilirubin, erythrocyte, protein, glucose, acidity (pH), and urine density were analyzed semi-quantitatively on Dirui- H800 FUS-2000 (Dirui Industrial Co. Ltd., China) urine biochemical analysis device, digital imaging and automatic particle definition method microscopically and the results were recorded.

Peripheral venous blood samples (5 mL) were drawn into serum separator tubes (Vacuette, Greiner Bio-One, Kremsmuenster, Austria) in the morning between 9:00 am and 10:00 am after 8 hours of fasting. Serum samples were set aside for 30 to 60 minutes to allow the formation of clots prior to centrifugation at 1500G for 10 minutes at room temperature. Results of routine biochemical, hematological, and urine analyzes were obtained by reviewing patients' records. Hematological analyses were performed using XN-1000 Sysmex (Sysmex Corporation, Kobe, Japan) hematology analyzer. All biochemical parameters were analyzed using Abbott kits (Abbott Laboratories, Chicago, IL, USA), which are manufactured for use with an Architect c16000 Auto-Analyzer.

Exclusion Criteria

Patients with underlying chronic diseases such as hypertension, diabetes mellitus, chronic heart failure, patients with urinary system oncological and stone disease, mild COVID-19 that did not require hospitalization, and critically ill COVID-19 patients that required intensive care unit care were excluded from the study.

Statistical Analysis

The data were encrypted and entered SPSS (Version 23) software (IBM, SPSS Inc., Chicago, Illinois, USA). The categorical values of the patients were expressed as numbers and percentages and analyzed with a chi-square test. Continuous variables were presented as mean and standard deviation (SD). Friedman and Cochrane Q-tests were used for the statistical analysis of the three groups. $P<0.05$ was considered statistically significant.

Results

Mean age of 482 patients included in the study was 51.1 ± 20 years and 54% of the patients were male. A significant difference was found among the three groups in terms of hematological parameters of e-GFR, CRP, fibrinogen, and D-dimer values. (For all parameters: $p<0.05$). There was no difference among the three groups regarding the remaining hematological parameters. In the post-COVID-19 period of the patients, renal function tests such as eGFR, creatinine, and urea had turned back to their baseline values. Details of demographic and hematological parameters are available in **Table 1**. In the correlation analysis a negative correlation was found between e-GFR and both CRP ($p<0.001$, r:-0.289 and D-dimer (p:0.02, r:-0.129) during the course of the COVID-19 disease (**Figure 1**).

Urinalysis parameters of pH value, leukocyturia, microscopic hematuria, and proteinuria differed among the three groups (for all parameters $p<0.05$). These three parameters had a significant increase during the COVID-19 disease and decreased in the post-COVID-19 period. No difference was detected between other urinalysis parameters. Details of urinalysis parameters are available in **Table 2**. The correlation analysis showed a negative correlation between urine density and eGFR (p:0.04, r:-0.175), and a positive (p:0.02, r:0.195) correlation between urine density and CRP (**Figure 2**).

Table 1. Details of pre-COVID-19, COVID-19, and post-COVID-19 15th day demographical and hematological parameters

Parameters n=482	Pre-COVID	COVID	Post-COVID 15th day	P
Demographical parameters				
Age (year) mean ± SD	51.1 ± 20			-
Sex M/F %	54 /46			-
Hematological parameters				
e-GFR (mean± SD)	92.1 ± 33.2	88.69 ± 33.5	90 ± 37.7	**0.03**
Urea (mean± SD)	33.9 ± 21.9	46.9 ± 50	41.08 ± 30.4	0.39
Creatinin (mean± SD)	1.17 ± 0.5	1.36 ± 1.37	1.1 ± 0.3	0.8
CRP (mean± SD)	23 ± 67	69 ± 89	35 ± 57	**0.001**
Fibrinogen (mean± SD)	290 ± 140	373 ± 219	335 ± 151	**<0.001**
D-dimer (mean± SD)	287 ± 600	655 ± 2180	452 ± 798	**<0.001**
Uric acid (mean ± SD)	6.1 ± 3.4	5 ± 1.9	5.5 ± 2.7	0.15
Sodium (mean± SD)	138.4 ± 3.4	138.1 ± 5.2	138.2 ± 5.6	0.06
Potassium (mean± SD)	4.4 ± 0.5	4.32 ± 0.6	4.2 ± 0.7	0.32
Calcium (mean± SD)	9.1 ± 1.2	9.01 ± 0.7	9 ± 1.04	0.2
LDH (mean± SD)	235 ± 112	259 ± 218	250 ± 196	0.31
CPK (mean± SD)	88 ± 61	122 ± 195	85 ± 73	0.7

eGFR: estimated glomerular filtration rate; SD: standard deviation; CRP: C- reactive protein; LDH: lactate dehydrogenase; CPK: creatine phosphokinase

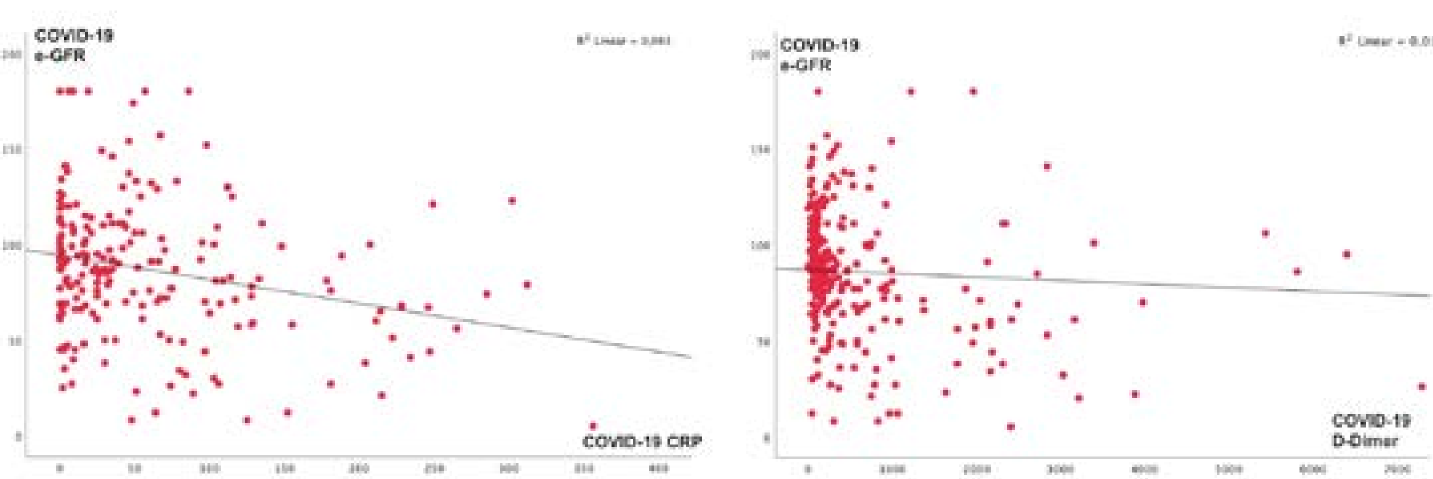

Figure 1. Correlation analysis of e-GFR with CRP and D-dimer

Table 2. Details of pre-COVID-19, COVID-19, and post-COVID-19 15th day urinalysis parameters

	Pre-COVID	COVID	Post-COVID 15th day	P
Urine density (mean± SD)	1016.61 ± 8.4	1017.02 ± 48.7	1015.1 ± 6.4	0.15
Urine pH (mean± SD)	5.88 ± 1.2	6.04 ± 1	6.2 ± 0.7	**0.04**
Urine bacterial microscopy (Number of cells) (mean ±SD)	1.97 (0-10)	2.04 (0-25)	2 (0-20)	0.58
Urine leukocyte microscopy (Number of cells) (mean ±SD)	3.77 (0-5)	9.67 (0-664)	7.67 (0-365)	**0.04**
Urine erythrocyte microscopy (Number of cells) (mean ±SD)	3.15 (0-5)	29.83 (0-488)	7.75 (0-388)	**0.01**
Bilirubinuria + %	5.6	1.5	0.5	0.36
Proteinuria + %	2.2	3.3	0.7	**0.01**
Glucoseuria + %	6.8	8.8	5.6	0.44

SD: sandard deviation

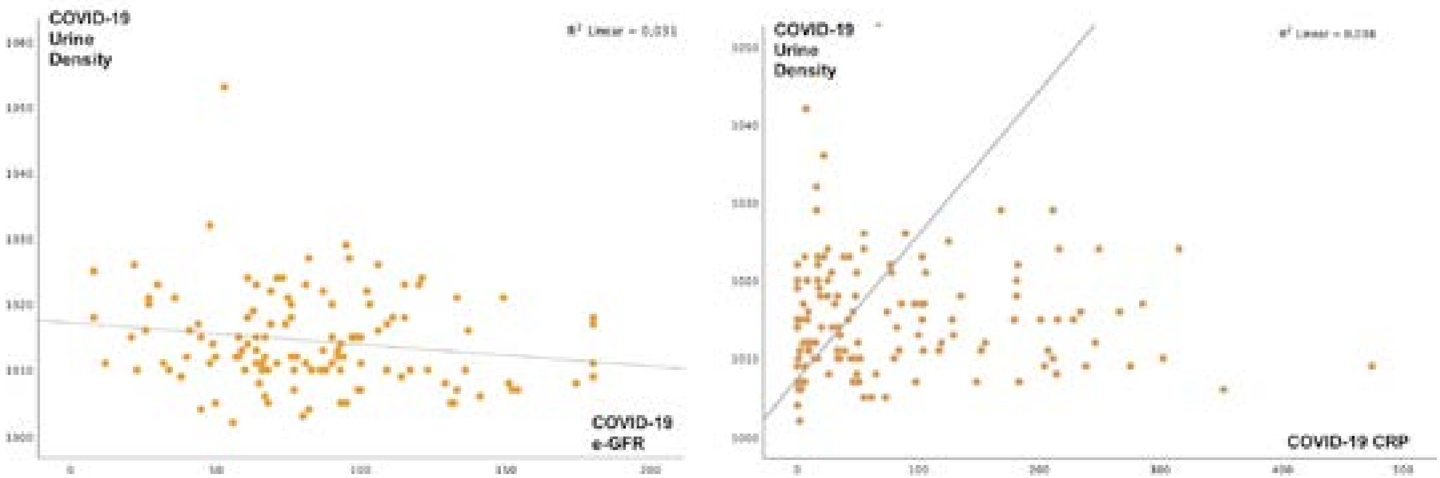

Figure 2. Correlation analysis of urine density with e-GFR and CRP

Discussion

Urine biochemical parameters can be used for the diagnosis of urinary tract infections, and other systemic diseases, and in the follow-up of treatment effects. Urinalysis can reveal these parameters and is also extremely useful as it provides easy sampling, cost efficiency, and quick results [8].

A limited number of studies in the literature have shown the relationship between COVID-19 and urinary parameters. Current studies were conducted through the comparison of Sars-COV-2 positive and negative patients. Our study stands unique as it shows the changes in urine biochemistry in patients before the diagnosis of COVID-19 disease, during, and after recovery from this epidemic. Liu et al. reported higher urine protein, pH values, and erythrocyte counts, but lower urine density in the COVID-19 group compared to the control group [9]. Another study reported kidney involvement in 75% of COVID-19 patients, and 65.8% of these patients had proteinuria and 41.7% had hematuria [10]. Murgod et al. detected a higher rate of hematuria and proteinuria in COVID-19 patients compared to healthy controls and a significant increase in both parameters as the severity of the infection increased [6]. Demirelli et al. assessed 120 COVID-19 patients, and categorized these patients based on the severity of the disease. Respective percentages of these patients had glucosuria (6.7%), proteinuria (13.4%), urobilinogen positivity (5.8%), leukocyturia (8.3%), and hematuria (9.2%) [11].

In our study patients, we detected a significant increase in the rates of proteinuria, hematuria, and leukocyte counts during COVID-19 disease compared to the pre-COVID-19 period and a significant decrease in these parameters after recovery from the disease ($p<0.05$, for all parameters). Additionally, urine pH levels increased in the COVID-19, and post-COVID-19 periods of the patients. As reported in the studies, we think that the presence of proteinuria and hematuria in our study is related to renal involvement in COVID-19. Contrarily, the detection of leukocyturia associated with COVID-19 can be related to the worsening of infection or the change of bladder flora due to the medications used in hospitalized patients.

Pei et al. reported that proteinuria and microscopic hematuria were more significant in critically ill COVID-19 patients and acute kidney injury was seen at a rate of 42% among these patients while at a rate of 4.5% in the COVID-19 population in general [10]. Bonetti et al. studied the urine samples of 226 patients admitted to the emergency department and proteinuria, and microscopic hematuria were detected in 89%, and 72% of the patients, respectively. They reported that high urea and creatinine values were related to increased mortality rates and analysis of urine sediment was regarded as a useful prognostic test [5]. In their logistic regression analysis, Morell-Garcia et al. reported that among urinalysis parameters microscopic hematuria was a risk factor for acute kidney injury (AKI), intensive care requirement, and mortality [12]. Yıldırım et al. reported the presence of AKI in 4.5% of COVID-19 patients and rates of proteinuria and hematuria were 64% and 64% vs 4.8% and 43% in patients with and without AKI, respectively. Additionally, significantly higher creatinine, CRP, fibrinogen, and D-dimer levels were detected in AKI patients [13].

In this study, we aimed to statistically evaluate the change in kidney function tests in our patients during, and after recovery from the COVID-19 disease. As a matter of fact, it was determined that creatinine values increased and eGFR values decreased (1.17 ± 0.5 vs 1.36 ± 1.37, 92.1 ± 33.2 vs 88.69 ± 33.5 respectively) during COVID-19 disease compared to the pre-COVID-19 period. Although creatinine elevation occurred in most of the patients, this increase could not be described as evidence of renal failure. As a matter of fact, it has been determined that the results of kidney function tests such as eGFR, creatinine, and urea tend to return to pre-COVID-19 values after recovery from this disease. While urea, creatinine, and eGFR levels tend to decrease during COVID-19 disease, they tend to normalize in the post-COVID-19 period, but the change is significant only for eGFR (p:0.03). Although these findings support the claim that COVID-19 negatively affects renal function, our data has shown lack of any permanent change that can cause permanent kidney failure. This study has also showed a negative correlation between levels of some markers of inflammation including eGFR, CRP, and D-dimer ($p<0.001$, $p=0.02$ respectively). These findings have indicated that the severity of infection and inflammation may aggravate the adverse effects on kidney functions. Additionally, urine density during COVID-19 disease had a negative correlation with eGFR and a positive correlation with CRP. This fact can be an indicator of the relationship between infection and urine parameters.

Failure to analyze urinary sediment, urine creatinine, and electrolyte values and non-categorization of the severity of COVID-19 disease in our patients are the main limitations of this study.

Conclusion

This study detected a significant decrease in eGFR, and increase in infection parameters of CRP and D-dimer during the COVID-19 disease. Thus, attention should be paid to kidney failure during the COVID-19 disease, especially in patients with critical kidney function test results and it should be emphasized that the condition may get more severe due to the severity of the infection. The significant presence of hematuria and proteinuria during the COVID-19 disease supports the idea that the disease also affects kidneys in line with the literature data. The tendency of the parameters to return to their normal ranges 15 days after recovery from COVID-19 disease indicates that the effects of the inflammation are reversible after the resolution of the infection. Highly detailed studies including greater number of subgroups investigating changes in urinary findings for a longer period should be conducted.

Ethics Committee Approval: All procedures performed in this study involving human participants were conducted in accordance with the ethical standards of the institutional and/ or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Consent according to the Helsinki declaration was taken from local ethics committee before the study (NEU: 2020/2835; date: 27.01.2021; decision #: 88).
Informed Consent: An informed consent was obtained from all the patients.
Publication: The results of the study were not published in full or in part in form of abstracts.
Peer-review: Externally peer-reviewed.
Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept – L.O.S., M.G.S.; Design – L.O.S., M.G.S.; Supervision – L.O.S., H.V., M.G.S.; Resources – L.O.S., H.V., G.E., M.G.S.; Materials – L.O.S., H.V., G.E., M.G.S.; Data Collection and/or Processing – L.O.S., H.V., G.E., M.G.S.; Analysis and/or Interpretation – L.O.S., M.G.S.; Literature Search – L.O.S., H.V., G.E., M.G.S.; Writing Manuscript – L.O.S., M.G.S.; Critical Review – L.O.S., M.G.S.
Conflict of Interest: The authors declare that they have no conflicts of interest.
Financial Disclosure: The authors declare that this study received no financial support.

References

[1] Fung TS, Liu DX. Human Coronavirus: Host-Pathogen Interaction. Annu Rev Microbiol 2019;73:529-57. https://doi.org/10.1146/annurev-micro-020518-115759

[2] World Health Organization. WHO Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020. https://www.who.int/dg/speeches/detail.Published February 11, 2020.

[3] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506. https://doi.org/10.1016/S0140-6736(20)30183-5

[4] Kostoff RN, Briggs MB, Porter AL, Spandidos DA, Tsatsakis A. COVID-19 vaccine safety. Int J Mol Med 2020;46:1599-602. https://doi.org/10.3892/ijmm.2020.4733

[5] Bonetti G, Manelli F, Bettinardi A, Borrelli G, Fiordalisi G, Marino A, et al. Urinalysis parameters for predicting severity in coronavirus disease 2019 (COVID-19). Clin Chem Lab Med 2020;58: e163-165. https://doi.org/10.1515/cclm-2020-0576

[6] Murgod P, Doshi P, Nimbargi R. Urine Biochemical Parameters in Predicting Severity of SARS-CoV-2 Infection: an Experience in Tertiary Care Centre in Western India. Iran J Pathol 2021;16:304-9. https://doi.org/10.30699/IJP.2021.136576.2496

[7] Berger RE. The urine dipstick test useful to rule out infections. A meta-analysis of the accuracy. J Urol 2005;174:941-2. https://pubmed.ncbi.nlm.nih.gov/16093998/

[8] Erdman P, Anderson B, Zacko JC, Taylor K, Donaldson K. The accuracy of the Sysmex UF-1000i in urine bacterial detection compared with the standard urine analysis and culture. Arch Pathol Lab Med 2017;141:1540-3. https://doi.org/10.5858/arpa.2016-0520-OA

[9] Liu R, Ma Q, Han H, Su H, Liu F, Wu K, et al. The value of urine biochemical parameters in the prediction of the severity of coronavirus disease 2019. Clin Chem Lab Med 2020;58:1121-4. https://doi.org/10.1515/cclm-2020-0220

[10 Pei G, Zhang Z, Peng J, Liu L, Zhang C, Yu C, et al. Renal Involvement and Early Prognosis in Patients with COVID-19 Pneumonia. J Am Soc Nephrol 2020;31:1157-65. https://doi.org/10.1681/ASN.2020030276

[11] Demirelli E, Sönmez MG, Tok DS, Çetin S, Öğreden E, Usta M, et al. The impact of Coronavirus Disease 2019 (COVID-19) on urinalysis parameters. Minerva Urol Nephrol 2021 Jun 22. Online ahead of print. https://pubmed.ncbi.nlm.nih.gov/34156201/

[12] Morell-Garcia D, Ramos-Chavarino D, Bauça JM, Argente Del Castillo P, Ballesteros-Vizoso MA, García de Guadiana-Romualdo L, et al. Urine biomarkers for the prediction of mortality in COVID-19 hospitalized patients. Sci Rep 2021;11:11134. https://doi.org/10.1038/s41598-021-90610-y

[13] Yildirim C, Ozger HS, Yasar E, Tombul N, Gulbahar O, Yildiz M, et al. Early predictors of acute kidney injury in COVID-19 patients. Nephrology (Carlton) 2021;26:513-21. https://doi.org/10.1111/nep.13856