Original Article

Are Patients with Covid-19 at Risk of Long-Term Chronic Kidney Disease?

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Abstract

Background: The relationship between Coronavirus Disease 2019 (COVID-19) and acute kidney injury (AKI) is well-established. However, a comprehensive evaluation of kidney outcomes in the long-term course of COVID-19 is not yet been performed. The aim of this study is to investigate whether chronic kidney disease (CKD) develops within six months after hospital discharge in COVID-19 patients who did not have kidney damage at the time of admission to the hospital. **Patients and Methods:** This single-center retrospective study investigated a total of 1008 participants selected from 7500 COVID-19 patients with real-time reverse transcription-polymerase chain reaction (RT-PCR) positivity. All patients had mild/moderate or severe COVID-19. Patients were randomly selected from inpatient and outpatient settings. Critical COVID-19 patients were not included. **Results:** The mean age of the patients was 56.57 ± 16.30 years, and 69.9% of them were male. The comorbidity percentages of the participants were as follows; 19.5% coronary artery disease (CAD), 28.6% diabetes mellitus (DM), 36.2% hypertension (HT), 3.1% cerebrovascular obstruction (CVO), 1.7% malignancy, 2.6% chronic obstructive pulmonary disease (COPD), 9.4% asthma, % 1.7 dementia, 9.9% hyperlipidaemia, and 1.7% hepatitis B virus (HBV). Kidney function tests of these patients at first admission and 6 months later were compared to reveal the relationship between COVID-19 and CKD. Serum glucose, sodium estimated glomerular filtration rate (eGFR), and uric acid levels were found to be high in the post-COVID-19 period (P = 0.001). However, there were a decrease in serum albumin, potassium, alanine aminotransferase (ALT), C-reactive protein (CRP), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and gamma-glutamyl transferase (GGT) levels (P = 0.001). The difference between the first measurement of serum urea and creatinine (Cr) levels and the measurement 6 months later was not statistically significant (P = 0.102 and P = 0.300, respectively). **Conclusions:** Those who survived the mild/moderate and severe clinical manifestations of COVID-19 did not exhibit any risk of kidney outcomes after the acute phase of the disease, suggesting that the kidney can protect itself over a long period of time.

Keywords: *Chronic kidney disease, coronavirus disease 2019, kidney function tests, mild COVID-19, moderate COVID-19, severe COVID-19*

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Introduction

After infiltrative COVID-19 infects the lungs, it can enter the bloodstream and reach the kidneys. It can accumulate in the resident cells of the kidney and damage them. Therefore, the kidney is one of the most

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frequently involved extrapulmonary organs. Patients are more prone to kidney damage in the severe form of COVID-19.[1] COVID-19 is related to acute (short-term) mortality and morbidity.[2] Evidence shows that, apart from acute illness, patients recovering from COVID-19 may practice post-acute sequelae, also colloquially term as "long COVID", which involves the extrapulmonary and pulmonary organ manifestations, which include kidneys.[3]

Chronic kidney disease is described in the existence of decreased kidney function (measured by eGFR) or signs of kidney damage persisting for >3 months (increased albuminuria, abnormal urinary sediment, and kidney structural abnormalities even at normal eGFR) and has health implications.[4] İn the United States (US), CKD, an epidemic influencing 12% of total adults, heralds brutal progression for many patients, often leading to cardiovascular death or kidney failure.[5,6] It is crucial to uncover whether COVID-19 has contributed to this increasing CKD population.

The relationship between AKI and COVID-19 is well known. Most studies have addressed the severe/critical COVID-19 group and AKI. There are only a few studies on COVID-19 and CKD. Nevertheless, a comprehensive evaluation of kidney outcomes in individuals surviving COVID-19 is not available yet. These studies are essential, especially in patients with mild/moderate and severe COVID-19, which constitute the largest population of COVID-19. Therefore, we conducted this study.

Materials and Methods

This single-center, retrospective study was designed in accordance with the Declaration of Helsinki, with the approval of the ethics committee. The requirement for informed consent was waived, since the data used in the study were anonymous, and data were gathered from patients' files and the hospital database.

The files of approximately 7500 COVID-19 patients who applied to Batman Education and Research Hospital were reviewed, and 1008 patients were found eligible for the study. Patient inclusion criteria were RT-PCR positivity and the presence of laboratory data at the time of admission to the hospital and 6 months later. Demographic and laboratory data were obtained from patient files. Demographic characteristics include age, gender, and history of comorbidity (DM, CAD, HT, CVO, cancer, asthma, COPD, dementia, hyperlipidaemia HBV). Laboratory parameters include eGFR and kidney, and function tests.

Inclusion criteria: RT-PCR positive COVID-19 participants (both outpatients and inpatients discharged from the hospital); those with normal kidney function at hospital admission (confirmed twice by laboratory analysis); those with severe COVID-19 and mild/moderate; those between the ages of 18-85 were included.

Exclusion criteria: AKI, CKD, kidney transplant patients, and dialysis patients (hemodialysis and peritoneal dialysis) were excluded. Those with a history of haematuria and proteinuria; those who had COVID-19 (even if they had mild-moderate or severe) but did not apply to our hospital after 6 months; those who were PCR negative and had thorax computerized tomography (CT) involvement; those with critical COVID-19 were excluded.

Following the interim guidelines of the World Health Organization, the diagnosis of COVID-19 was made based on laboratory positivity for severe respiratory syndrome coronavirus-2 (SARS-CoV-2).[7] eGFR calculation was done by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[8]

Patients were divided into four groups according to the clinical severity of COVID-19 (determined according to the basic clinical findings at the time of admission), as mild, moderate, severe, and critical. The following criteria were also taken into account while creating the patient groups. 1. Mild: Patients without pneumonia. 2. Moderate: Patients with respiratory symptoms and pneumonia not accompanied by hypoxia. 3. Severe: Patients with an oxygen saturation <94%, respiratory rate ≥30/min, pulmonary infiltration >50% (pulmonary infiltration or ground-glass opacities in thorax CT, involvement of more than 50% of the lung parenchyma area in total), PaO2/FiO2 <300 and dyspnoea. 4. Critical: Patients with septic shock, multi-organ failure requiring mechanical ventilation, and respiratory failure.[9]

Based on this severity grouping of COVID-19, individuals with mild/moderate and severe COVID-19 were included in the study, while critical cases were excluded.

Laboratory tests: Routine laboratory and demographic data were obtained from the files in the hospital registry system. After 12 hours of fasting, serum samples were taken. Biochemical parameters such as uric acid, urea, Cr, eGFR, albumin, LDH, sodium, potassium, ALT, AST, GGT, CRP, and glucose, were tested using Beckman Coulter Chemistry Analyzer AU5800 Device (Beckman Coulter Mishima K.K., Tokyo, Japan).

Both sputum (secretory) and nasopharyngeal (with swab) specimens were taken from total participants. Patients were analyzed with RT-PCR using the PowerChek

2019-nCoV real-time polymerase chain reaction kit (Bioeksen R and D Technologies Inc. Comp., Istanbul, Turkey).

Statistical analysis: The results obtained in the research were evaluated with the Statistical Package for Social Sciences (SPSS) for IBM 25 software package. The data in the personal information form was evaluated using descriptive statistical methods (percentage, number, standard deviation, and mean). A t-test was also applied to dependent groups. A level of $P < 0.05$ was considered statistically significant.

Results

The mean age of the participants was 56.57 ± 16.30 years, and 30.1% were female. Of the participants, 25% were outpatients, and 75% were inpatients. The percentages of comorbidities were 28.6% DM, 19.5% CAD, 36.2% HT, 3.1% CVO, 1.7% malignancy, 9.4% asthma, 2.6% COPD, 1.7% dementia, 9.9% hyperlipidemia, and 1.7% HBV [Table 1].

Laboratory parameters at the time of hospital admission due to COVID-19 and 6 months after surviving COVID-19 were compared. Serum glucose, sodium, uric acid levels, and eGFR values were statistically significantly different (P = 0.001). In other words, glucose, eGFR, sodium, and uric acid levels were high in the post-COVID-19 period. Serum albumin, ALT, AST, GGT, and LDH levels were also statistically significantly different (P = 0.001). In the post-COVID-19 period, decreases were observed in serum albumin, potassium, CRP, ALT, AST, GGT, and LDH levels. Serum urea and Cr levels were statistically notably different [Table 2].

Discussion

There were no COVID-19-related abnormalities in kidney functions (urea, Cr, and eGFR) in the 6 month follow-up of any of our patients who had COVID-19 and survived. There was an increase in eGFR. Glucose, sodium, and uric acid levels were high in the post-COVID-19 period (P = 0.001). However, serum albumin, potassium, CRP, ALT, AST, GGT, and LDH levels were reduced (P = 0.001). Our data exhibited that patients had no signs of chronic liver disease after COVID-19 and also suggested the possibility that high glucose level poses a risk for DM disease.

There is no detailed and comprehensive evaluation of renal outcomes after the acute post-COVID-19 stage still. A better understanding of kidney outcomes after acute COVID-19 will guide the development of care strategies to enrich the health and well-being of individuals with long-term COVID-19.[10] We conducted this study to shed light on these unknowns. Besides, most of the studies in the literature have focused on critical patients and patients with AKI. In particular, we did not observe any studies on the post-COVID-19 sequelae of mild/moderate and severe COVID-19 individuals. Our study will be the first in this aspect.

New data report that severe acute respiratory syndrome coronaviruses (SARS-CoV and SARS-CoV-2) can

Table 1: Patients' demographic characteristics

Age (years)		
(Min-max)	(18-102)	
Mean±SD	56.57±16.30	
Variables	***n***	**%**
Gender		
Male	437	69.9
Female	571	30.1
Follow-up		
Outpatient	252	25
Inpatient	756	75
DM		
Yes	288	28.6
No	720	71.4
HT		
Yes	365	36.2
No	643	63.8
CAD		
Yes	179	19.5
No	811	80.5
CVO		
Yes	31	3.1
No	977	96.9
Malignancy		
Yes	17	1.7
No	991	98.3
Asthma		
Yes	95	9.4
No	991	90.6
Dementia		
Yes	17	1.7
No	991	98.3
Hyperlipidaemia		
Yes	100	9.9
No	908	90.1
HBV		
Yes	17	1.7
No	991	98.3
COPD		
Yes	26	2.6
No	982	97.4

DM, Diabetes mellitus; HT, Hypertension; CAD, Coronary artery disease; CVO, Cerebrovascular obstruction; HBV, Hepatitis B virus; COPD, Chronic obstructive pulmonary disease

Table 2: Comparison of patients' laboratory parameters

Parameter	Initial measurement	Measurement after 6 months	Sig. (2-tailed)	Sig. (2-tailed)
Glucose (70-110 mg/dL)	153.14±81.11	141.04±74.31	*t*=5.021	0.01
Urea (17-43 mg/dL)	34.20±16.23	33.45±14.38	*t*=1.636	0.102
SCr (0.5-1.2 mg/dL)	0.71±0.41	0.70±0.34	*t*=1.038	0.300
Sodium (136-146 mEq/L)	136.53±5.52	138.41±7.46	*t*=-6.300	0.01
K (3.5-5.1 mEq/L)	3.97±0.94	3.83±1.41	*t*=2.528	0.01
CRP (0-5 mg/L)	36.70±26.90	10.80±20.90	*t*=19.03	0.01
eGFR mL/min/1.73 m^2	94.25±23.32	97.81±25.29	*t*=-6.025	0.01
Albumin (3.5-5.2 g/dL)	34.14±11.42	37.8 4±12.22	*t*=-6.288	0.01
ALT (0-35 U/L)	34.12±45.43	23.79±33.15	*t*=6.411	0.01
GGT (0-38 U/L)	57.82±69.85	37.34±57.08	*t*=7.551	0.01
AST (0-35 U/L)	38.19±28.57	24.79±32.06	*t*=10.501	0.01
LDH (0-247 U/L)	301.45±114.09	235.00±73.92	*t*=14.663	0.01
Uric acid (2.6-6 mg/dL)	4.38±2.18	4.59±2.13	*t*=-2.203	0.02

SCr, Serum creatinine; K, Potassium; CRP, C-reactive protein; eGFR, Estimated glomerular filtration rate; ALT, Alanine aminotransferase; GGT, Gamma-glutamyl transferase; AST, Aspartate aminotransferase; LDH, Lactate dehydrogenase

insert islet cells through angiotensin-converting enzyme-2 (ACE-2) receptors and give rise to reversible β-cell injury and temporary hyperglycemia. There have been assumptions about new-onset Type 1 DM triggered by COVID-19.[11] In our patients, hyperglycemia was detected in the biochemical analysis performed both at the time of acceptance to the hospital and 6 months later (P = 0.01), suggesting that COVID-19 may be associated with diabetes.

In a recent study on 1100 Chinese COVID-19 patients, Boddu SK *et al*.[12] documented that high serum AST levels were observed in 18% of non-severe and 56% of severe ones. In the same study, elevated serum ALT levels were observed in 20% of non-severe and 28% of severe patients. In these studies, ALT and AST elevations were detected during an acute episode of COVID-19. To the best of our knowledge, there are no serum ALT and AST studies after post-acute COVID-19. Our study determined that liver enzymes 6 months after surviving COVID-19 were within the normal range. The serum albumin level after 6 months was also in the normal range, and increased compared to the previous serum level (P = 0.001), while the serum ALT, AST, and GGT levels were within the normal range and decreased compared to the previous serum level (P = 0.001). COVID-19 is not associated with chronic liver disease.

Although the mechanisms primary the development of AKI are not known, it is thought that kidney involvement may be a manifestation of acute tubular necrosis (ATN). ATN is caused by shock associated with multi-organ failure, sepsis, and COVID-19 infection.[13] It is unclear whether the influences of COVID-19 are matchless or like to those observed in individuals with other infections and sepsis. Early reports propose that post-COVID-19 sequelae are like those that occur in survivors of sepsis and acute respiratory distress syndrome.[14] In addition, the risk of CKD in patients hospitalized with COVID-19 is like that of patients hospitalized with influenza.[15] A US study using Veterans Health Administration health electronic records to implement a detailed post-COVID-19 evaluation presented that COVID-19 increases the risk of CKD, and this risk is highest among those with severe illness. Even after the first 30 days following the diagnosis of COVID-19, adverse kidney manifestations (AKI, CKD, and urinary tract infections,) arise among hospitalized patients.[3] Hultström M *et al*.[16] reported the prevalence of CKD 3-6 months after discharge in a cohort of COVID-19 intensive care unit (ICU) patients. They included a total of 122 participants in the ICU. Then they excluded 3 COVID-19-negative individuals, 33 who died, and 26 who refused follow-up or did not have a serum Cr test, leaving 60 participants to be analyzed in their study. Critical COVID-19 advances along with the progression of CKD in a great number of patients. The progress in the CKD phase was related to acute kidney disease, described as more than 7 days of AKI, and KDIGO phase 3 AKI at the ICU. As these studies suggest, the AKI or CKD state in COVID-19 is like a part of the septic manifestation. All causes of infection can cause it. In COVID-19, like other viral infections, the septic presentation, when severe, can cause AKI. As the patient heals or recovers from sepsis, the injury to the kidney, like other organs affected by the septic condition, may become chronic or improve. Patients with sepsis are generally those who stay in the ICU and are connected to a mechanical ventilator and have critical COVID-19. Critical COVID-19 is likely to cause both AKI and CKD. This is in the nature of all infections. COVID-19 can cause as much CKD as other viral infections will cause CKD. Groups other than critical

COVID-19 (mild/moderate and severe COVID-19) are not related to CKD.

There are very few studies in the literature on CKD, which is a long-term sequela of COVID-19. We would like to mention a few of them. Jansen J *et al*.[17] reported that 35% of the patients had decreased renal function (eGFR < 90 ml/min/1.73 m^2) 6 months after hospitalization with COVID-19. İnterestedly, during follow-up, 13% of patients who did not have AKI in the course of hospitalization demonstrated a decrease in eGFR. Our study, however, found a significant increase instead of a decrease in eGFR ($P = 0.01$). Another study reported that SARS-CoV-2 infects tubular epithelium and podocytes in human renal and is related to kidney damage and fibrosis, which can express the development of CKD after COVID-19.[17,18] SARS-CoV-2 has been shown to cause a molecular transition in kidney cells by inducing profibrotic signaling and then tissue damage. Since organoids deficiency perfusion and immune cells, they proposed a model in which kidney damage caused by SARS-CoV-2 is partly independent of ICU treatment or the systemic effects of the disease and rather represents a direct effect of the virus. Therefore, virus infection can directly trigger acute damage and fibrotic remodeling (with this model, renal function declines, and CKD occurs).[17] This is a comment study defending the thesis that COVID-19 causes CKD in the long term. All the pathological findings mentioned are general statements and are observed in the process of all infections. We assume that these pathological findings were obtained from COVID-19 and AKI studies. We found no evidence that the findings were derived from CKD studies.

Bowe B *et al*.[10] showed that those who survived 30 days after COVID-19 had a higher risk of AKI, eGFR reduction, end-stage renal disease, and major adverse kidney events compared to those who were not infected with COVID-19. Greater longitudinal loss of eGFR was detected in COVID-19 survivors compared to uninfected controls. The risk of adverse kidney outcomes increased with the severity of the acute infection represented by the care setting (hospitalized, non-hospitalized, and admitted to ICU). Evidence reports a risk of significant kidney outcomes in patients with COVID-19 and highlights the need to integrate a component of kidney care into acute post-COVID-19 care pathways. Our study found a significant increase instead of a decrease in eGFR ($P = 0.01$). Serum urea and Cr levels were not statistically significant ($P = 0.102$ and $P = 0.300$, respectively). The study mentioned above emphasized that the kidney has adverse effects in those who have had COVID-19. These kidney outcomes were based on laboratory data. The emergence of CKD after COVID-19 and its association with COVID-19 need to be proven by kidney biopsy studies (experimental animal studies, autopsy, and human studies), just as it has been proven by renal biopsy studies that diseases such as DM and hypertension cause CKD.[19,20] Co-morbidity, polypharmacy, a decrease in eGFR over time, and acute addition of different diseases constitute an overlap for CKD, especially in the majority of patients affected by COVID-19. Therefore, comprehensive kidney biopsy studies are required to clarify the relationship between COVID-19 and CKD or long-term adverse kidney outcomes.

The uniqueness of both the design of our study and the results of our study add strength to our study in two ways. There is no other study in the literature similar to our research.

Limitations

First, a definitive diagnosis to determine whether participants have kidney involvement due to COVID-19 is made by renal biopsy. However, we performed clinical and laboratory analyses rather than invasive interventions. We thought that was enough. Second, we wanted to include all COVID-19 patients admitted to the outpatient clinic during our research period. However, we could not include all of them due to missing data. Despite this, we think that the number of our patients is sufficient. Third, the findings of kidney disease include proteinuria and haematuria. These data were not available in the files of the patients 6 months later. Besides, none of our patients had these findings at the time of admission to the hospital.

Conclusion

In the 6-month follow-up after mild, moderate, and severe COVID-19, no kidney disease was detected with or without comorbidity, inpatient, or outpatient follow-up. Likewise, liver function tests were detected within the normal range. Diabetes is likely to occur after having COVID-19. According to our data, COVID-19 is not associated with CKD. However, comprehensive kidney biopsy studies are required to clarify the relationship between COVID-19 and CKD.

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Conflicts of interest

There are no conflicts of interest.

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