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Research Article

Long Term Effects of COVID-19 on Kidney Function

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Keywords

- COVID-19
- CKD
- AKI

Abstract

Back ground: We aimed to represent the effects of SARS Co V -2 on kidney functioning during the COVID-19 pandemic in patients of varied baseline GFR values staged into renal categories of one to five.

Methods: We conducted a single-center, retrospective study using data of patients hospitalized for COVID-19 with acute kidney injuries. Demographic characteristics, clinical findings, laboratory parameters [glomerular filtration rate (GFR), Creatinine, Blood urea nitrogen (BUN)] of pre covid, during covid, post-COVID infection, were reviewed. Predicted changes in the GFR were analyzed. The study's primary outcome was a predicted decline in GFR observed during the covid infection period compared to pre covid. The secondary outcome was predicted improvement in GFR after resolution of infection or covid -19 tested negative.

Results: The study included one hundred patients (mean age: 57.35+/- 17.5 years). The odds ratio of multivariate logistic regression analysis shows the association of kidney functioning during the pre-covid period with an odds ratio of 1.699 (95% CI- 1.299 to 2.551), during COVID with an odds ratio of 0.5404 (95% CI- 0.3620 to 0.7025), and post-covid with an odds ratio of 0.98 (CI- 0.9646 to 1.000). A decrease in GFR from Pre-COVID to during-COVID was observed with the estimated odds ratio of 1.001 (CI-0.9999 to 1.002, z- value 1.795, p-value-< 0.001). The positive and negative predictive powers were 92.86% and 96.67%, respectively. An association of an improvement in GFR was observed during the post-covid infection period with an odds ratio of 0.999 (CI-0.99-1.002, p-value-0.79). Indeed, the average decrease in GFR was prominent in second renal category patients, and the white race showed a 75% mortality rate, 14% in African Americans, and 11% in other races.

Conclusion: COVID-19 can cause acute ischemic kidney injury. Patients with CKD stage 3A are most affected. Patients who had longer lengths of stay in the hospital had greater severity of acute kidney injury. We found a higher mortality ratio in patients assigned to renal categories 2 and 3.

ABBREVIATIONS

AKI: Acute Kidney Injury, CKD: Chronic Kidney Disease; RC: Renal Category; LOS: Length of Stay; ESRD: End Stage Renal Disease; MU-IRB-University Of Missouri-Institutional Review Board

INTRODUCTION

The COVID 19 pandemic has brought waves of epidemiological research, case studies, and meta-analyses on signs and symptoms of the virus in the context of specific patient populations and organ systems, including the kidneys. Comorbidities generally portend a worse prognosis in patients with COVID 19 than previously healthy patients, and guidelines have been proposed on treating hospitalized COVID 19 patients with comorbidities [1,2]. Most sources also show higher mortality rates for patients who have various subcategories of kidney disease at the time of SARS CO-v infection [3,4]. Mechanisms of Immediate injury by Covid 19 to the kidneys have also been previously proposed. Previous studies have discovered that SARS COV2 can directly attack renal podocytes and proximal epithelial cells via ACE2 receptors, in addition to causing prerenal AKI in hospitalized patients [5-9]. Other studies suggest that mechanisms of kidney injury in COVID could also be secondary to massive cytokine release from primary pulmonary inflammation, as well as general hypoxia and hypercoagulability. We also know that patients with AKI due to COVID were shown to have higher mortality rates than those who did not suffer an AKI during COVID-related hospitalization. However, not much detail is known about the specific recovery of kidney function in hospitalized COVID 19 patients with preexisting kidney injury [10]. Mortality rates have been calculated, but we still lack information about morbidity associated with infection [11]. This study aims to quantify the effects of COVID 19 in recovery of kidney function in 5 patient populations: patients with a normal GFR prior to COVID 19 infection, patients with GFR >45, patients with GFR <45, patients with ESRD or dialysis-dependent, and patients with renal transplant [3,12,13].

MATERIALS AND METHODS

The Missouri university hospitals provide patient care services for a diverse population. The University of Missouri institutional review board approved the retrospective research study as minimal risk research using data collected from hospital electronic medical records and waived for informed consent. The patients affected with covid -19 infection confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), infection by a nasopharyngeal sample's positive polymerase chain reaction testing [14]. Patients were admitted to university hospitals of Missouri between March 1st 2020, to April 31st 2021.

Inclusion & exclusion criteria

Patients were included to study if they were admitted to the hospital (inpatient, observation or short stay) with a COVID-19 diagnosis (ICD-10 code U07.1) (Flow Chart 1). It was confirmed with positive results of SARS Co V -2 infection at the hospital, which was performed based on WHO criteria and confirmed by RT-PCR of nasopharyngeal specimens. This research study was conducted after receiving written approval from MU-IRB due to the retrospective nature of the analysis. We excluded patients with unknown pre-covid kidney functioning status also with unknown pre and post COVID test results.

Data Collection

Patient data was collected through electronic medical records of the university hospital of Missouri. The patient data includes demographics, diagnosis codes (International Classification of Diseases 9/10 Clinical Modification [ICD-9/10-CM] codes), and renal categories, along with laboratory measurements and documented during admission registration. Patient characteristics included age, sex, race, length of stay (LOS), renal categories (Table 2). We looked for laboratory values of blood urea nitrogen, creatinine, glomerular filtration rate that are obtained at 3 stages of COVID-19 infection as pre, during and post periods.

Baseline characteristics

Demographics:

1. Age — 57.35
2. Race — 72W, 21AA, 3-UA
3. COVID -19 — 463 +ve, 837 -ve
4. Length of stay — Max- 60, Min- 1

Renal Categories:

Category 1:	GFR>90 mL/min.	23
Category 2:	GFR 45-90mL/min.	53
Category 3:	GFR <45mL/min	15
Category 4:	ESRD or DIALYSIS	8
Category 5:	Post-transplant kidney	1

Lab parameters:	Pre -COVID-19	COVID-19
1. BUN	+/-18	27.95+/-21.2
2. Creatinine	+/-2.5	2.394+/-3
3. GFR	+/-28	58.31+/-28.8

Flow Chart 1: Baseline characteristics .

Definitions of renal categories and outcomes

The definition of established comorbidity as the presence of ICD-9/10-CM codes association of renal diseases is performed as per AHRQ comorbidities via ICD10 codes. Renal categories are defined based on the 2012 kidney disease improving global outcomes.

According to Chronic kidney diseases (KDIGO-CKD) classification, the patients were distributed into renal categories one to five based on their normal or basal GFR indicating the level of kidney functioning. Renal categories from one to five includes a normal GFR, CKD stage 3A (GFR>45), CKD 3B GFR (<45), ESRD or who are on dialysis, and post renal transplant patients respectively (Table 1).

To determine the predicted average decline in glomerular filtration rate (GFR) in patients during covid infection as the primary outcome of the study. Also, the predicted average increase in GFR after tested negative for covid was considered a secondary outcome of the study.

Literature search Criteria

PubMed, Scopus databases were searched using the following search builder: (COVID-19 AND kidney functioning OR renal damage AND SARS CoV-2, COVID-19 CKD/ AKI). Reports published in a peer-reviewed journal with kidney dysfunctions during COVID-19 and their outcomes were included in this paper.

Statistical analysis

Continuous variables such as age, lab parameters, length of stay are reported as mean ± standard deviation (SD). The GFR values of these patients with underlying comorbidities were further decreased during the COVID-19 infection period, which

Table 1: Mortality rate in different age groups.

Race	All ages	<40 years	40-70yrs	70-99yrs
White	75%	6%	25%	45%
African Americans	14%	0%	6%	14%
Others	11%	0%	12%	0%

Table 2: percentage of population distribution in different renal categories.

	Age <40years	40-70yrs	70-99yrs
Renal category1	26%	61%	13%
Renal category2	16%	54%	28%
Renal category3	13%	53%	34%
Renal category4	0	75%	25%
Renal category5	100%	0%	0%

was analyzed by multivariate logistic regression analysis. Multivariate logistic regression analyses were used to estimate adjusted odds ratios (ORs), decrease in GFR during COVID-19 and increase in GFR after the post-covid-19 period with 95% confidence intervals (CIs), in these hospitalized patients. The analysis results of t-tests for continuous data (age, length of stay) in association with kidney dysfunction showed significant results. Statistical analyses were carried out with Graph pad prism version 9. A p-value <0.05 was considered statistically significant.

RESULTS

We identified a total of 1307 patients with positive COVID-19 infection, but we included only 463 patients who have had acute kidney injuries. However, due to the lack of pre and post covid lab values, we included 100 patients as the study group. Each patient's length of stay is also represented in this study.

In this study, 23 patients were distributed into renal category one with normal kidney function (GFR >90 mL/min). Renal category two consists of those with GFR 60-89 mL/min includes 53 patients. Renal category 3 with GFR 30-59 mL/min includes 15 patients, renal category 4 with GFR 15-30 mL/min has 8 patients, and renal category 5 includes patients with GFR <15 mL/min includes 1 patient (Figure 4).

The multivariate logistic regression analysis determined the significant association of kidney dysfunction due to covid infection. The GFR values of each patient collected during pre-covid, peak covid and post covid were analyzed and compared to determine the outcomes of acute kidney injuries that occurred due to covid infection. The analysis has confirmed a significant association of a decline in GFR during the peak covid period. The model explained between 58% (Cox-Snell's R squared) and 80% (Nagelkerke's R squared), of the variance in the dependent variable (GFR outcome) and correctly classified in 94% of the cases. All consecutive patients GFR values are analyzed as pre-covid (OD-1.699, 95% CI- 1.299 to 2.551), during COVID (OD-0.5404, 95% CI- 0.3620 to 0.7025), post covid (OD- 0.98, CI-0.9646 to 1.000).

A significant decline in GFR rate was observed with the estimated odds ratio 1.001 (CI-0.9999 to 1.002, z- value 1.795, p-value-< 0.001) in covid infected patients compared with their baseline GFR during pre-covid for each patient. A decrease in GFR from Pre COVID to peak COVID indicates the decline in kidney functioning during this pandemic associated with infection. The deterioration of kidney function confirms that the covid infection affects the healthy kidney and patients with underlying chronic kidney diseases who belong to different renal categories. In our study, the significant decline in GFR confirmed a positive predictive power of 92.86% and a negative predictive power of 96.67%. Furthermore, the area under the receiver operating curve (Figure 1) shows the predictive efficacy of the outcome as a decrease in GFR with COVID -19 infection as 0.9822 (95% CI-0.9578 to 1.000, p-value: <0.0001) shows a significant association of the COVID-19 infection with acute renal injuries.

According to the Hosmer-Lemeshow hypothesis test, the statistics (895.2, a p-value of <0.0001) shows significant results for infection associated acute changes in the kidney with a Log-likelihood ratio (84.83, P<0.0001). A predicted improvement in GFR during the period of post covid has shown significant association with an estimated odds ratio of 0.999 (CI-0.99-1.002, p-value-0.79) It indicates the effect of covid infection on recovery, and it was expected secondary outcome of the study.

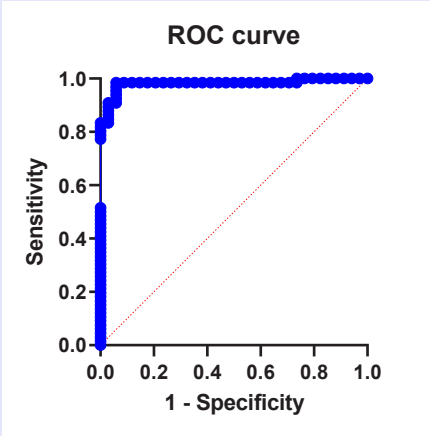


Figure 1 It shows receiver operative curve indicating the efficacy of outcomes of decreased kidney function with covid-19 infection.

Correlation of kidney functioning according to the Age, renal categories and length of stay at hospital

An analysis of t-tests showed a significant association between the length of stay and age. The average age of the study population was 57 (CI-51.42 to 43.08), with a mean length of stay of 10.10 days. The elderly patients stayed longer in comparison to others. The study includes 80% category three kidney dysfunction patients were aged more than 50 years. In this study, patients with longer LOS in the hospital were seen in renal category (Figure 2). Patients in this category two showed a more decline in average GFR compared to other renal category patients. We found that patients with longer LOS and older patients showed a high decline in GFR, indicating the worst renal dysfunction among COVID-19 patients.

Our study found that 38% of patients aged between 60-69 had end-stage renal disease staged into renal category 4. Interestingly, most patients who experienced renal dysfunction in renal category 2 are patients of age above 70 years. Patients who had longer lengths of stay had greater severity of acute kidney injury, and patients who belonged to renal category two stayed longer in the hospital.

Study outcomes

The significant decline in average GFR was observed more in renal category 2 during the time period of the pre-covid to peak-covid (Figure 3). The mortality ratio (Figure 5), was higher in patients with renal category 1 and 5 compared to others. We found higher mortality ratio in patients who had normal baseline GFR previously during pre-covid and also in patients with end stage renal disease and who were on dialysis. The observed mortality rates are 75% in white race, 14% in African Americans and 11% in others (Table 1).

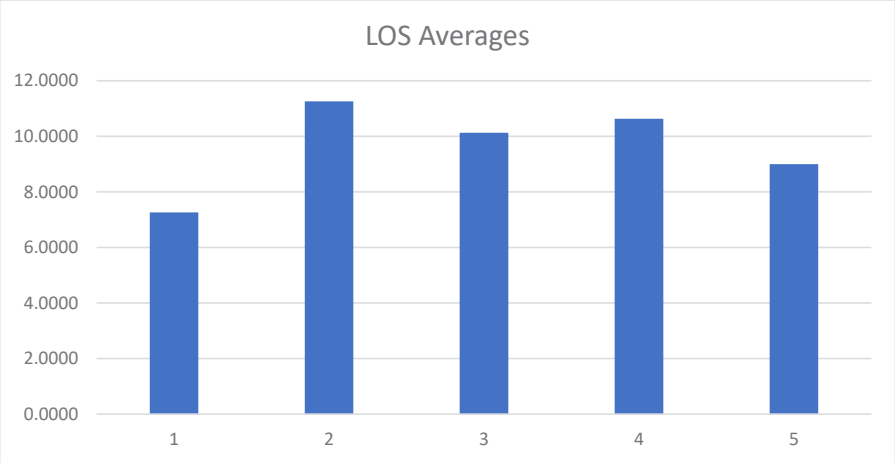
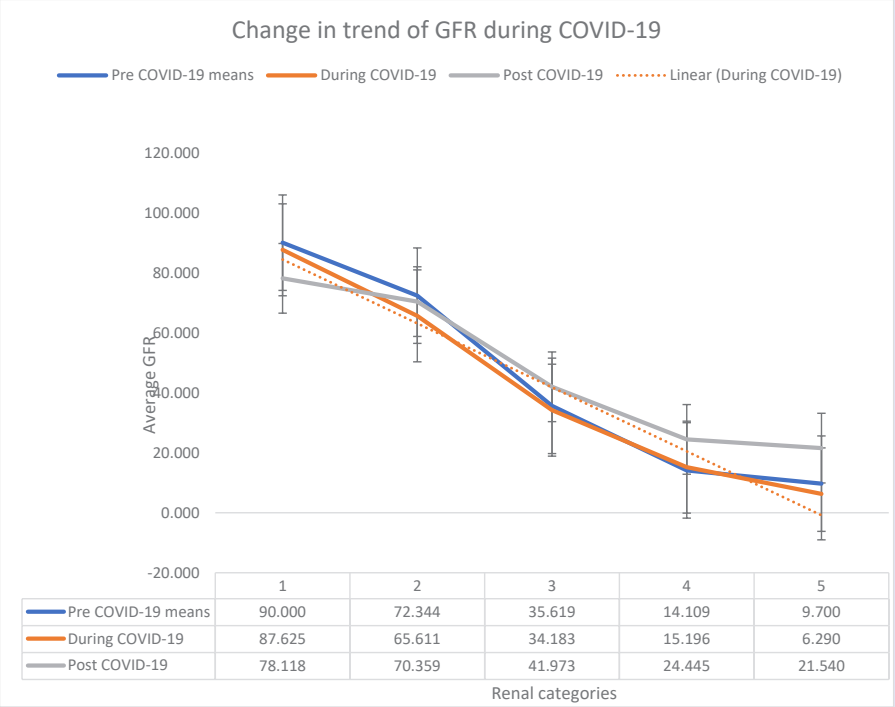


Figure 2 It indicates Renal categories Vs LOS in the hospital.



	1	2	3	4	5
Pre COVID-19 means	90.000	72.344	35.619	14.109	9.700
During COVID-19	87.625	65.611	34.183	15.196	6.290
Post COVID-19	78.118	70.359	41.973	24.445	21.540

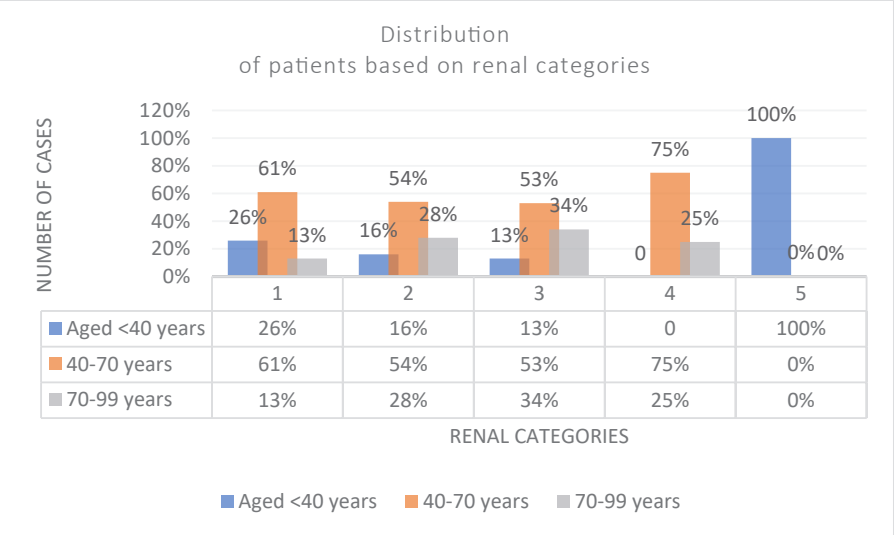
Figure 3 It indicates the decline in GFR in different renal categories during covid-19.

DISCUSSION

The research is primarily as SARS-CoV-2-induced renal dysfunction, its association with change in lab parameters that indicate kidney function in a hospital-based retrospective observational study. As discussed previously regarding the definitions of renal categories, the impact of SARS CoV-2 infection on renal function was assessed in 5 renal categories. Acute changes were seen in patients with both normal kidney functioning and patients with chronic kidney disease, evidenced by abnormal lab values of blood urea nitrogen, creatinine, glomerular filtration rate [15-17]. Similarly, a recent meta-analysis, proved that a significant effect of infection in causing acute renal dysfunction in all renal categories and these patients were progressing to the worst outcomes [18]. In addition, severe renal damage led to the renal transplantation and extensive hemodialysis [19].

COVID-19 increased risk of acute kidney injury (AKI)

SARS CoV-2 infection-associated sepsis, cardiogenic shock, hypercoagulation, small vessel injuries, immune-mediated injury together can cause compromised hemodynamics and induces acute kidney dysfunction in the form of prerenal ischemia [20]. Hypercoagulation leading to microthrombi formation due to immune-mediated cell reactions presenting with hematuria and proteinuria could be the major risk factor for mortality during the



	1	2	3	4	5
Aged <40 years	26%	16%	13%	0	100%
40-70 years	61%	54%	53%	75%	0%
70-99 years	13%	28%	34%	25%	0%

Figure 4 It Indicates distribution of patients into renal catteries one to five based on their baseline GFR.

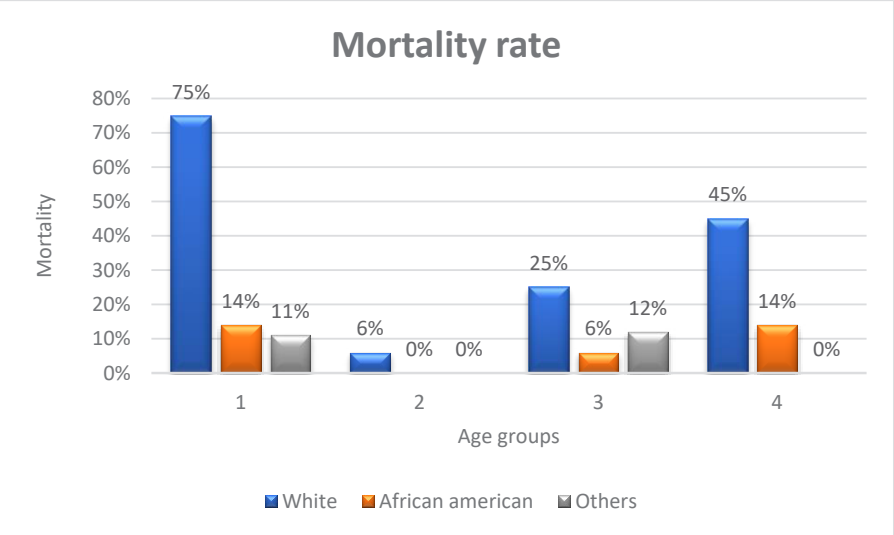


Figure 5 Covid-19 induced mortality observed in different races in the study.

COVID-19 pandemic, especially in critical care admitted patients and requires mandatory renal replacement therapy [15,21].

In COVID, acute tubular necrosis can occur due to cytokine storm, via an angiotensin-converting enzyme 2 (ACE2) pathway, or due to the virus causing direct toxicity to podocytes and proximal tubular cells. COVID-19 related kidney dysfunction can be predicted with a decrease in GFR and abnormal creatinine and BUN levels [8]. Increase in creatinine and blood urea nitrogen along with a decrease in GFR were associated with increased length of stay at the hospital due to delay in recovery from COVID-19 infection [22].

Acute tubular injury occurring to the proximal tubules has been the primary anatomical area of study during COVID-19 [23]. Furthermore, covid infected patients were also shown nephropathy with worsening focal segmental glomerular disease due to damage to podocytes and endothelial cells in minority of the patients along with acute changes in the renal function [24].

Age is a factor that naturally contributes to worsening renal dysfunction, and so contributes the renal dysfunction imparted by infection with COVID-19 [1]. A recent systematic review subgroup analysis characterized the influence of age on incidence of AKI, which helps to appreciate the significance of age on the kidney dysfunction during COVID-19 [25]. Similar to our study, the previously published studies revealed that acute worsening of kidney function was observed more commonly in elderly with end stage renal disease (ESRD), and also in kidney transplanted patients [26-28]. Immediate volume replacement may decrease the prevalence of acute kidney injury but should be

done cautiously to avoid hypervolemia which leading to respiratory compromise. New approaches have emerged targeting treatment of renal transplant patients to tailor their immunosuppressants while treating COVID-19 with antivirals [29-31].

Chronic kidney diseases during COVID-19

Mechanism of infection of the kidneys with COVID-19 involves renal angiotensin aldosterone system activation through ACE2 receptors, which are located on various organs in the body including tissues like type 2 alveolar cells of lung epithelium and renal tubular epithelial cells [12,32-34]. The ACE 2 converts angiotensin II to angiotensin, and is responsible for systemic vasoconstriction. By altering this mechanism, coronavirus causes systemic vasodilation and inflammation which further complicates the kidney function in CKD patients [35,36].

We have obtained results of greater decline in average GFR in renal category 2 than renal category 1 significantly during infection period. In contrast to our study, a recent study [34], demonstrated a greater decline in kidney function in renal categories 1 and 3 than renal category 2. Of note, that study included large population of only patients admitted to hospital ICU and it was a retrospective single centered observational study. Similar to our study, a multicentered study conducted by Gasparini, M et al. observed severity of infection was higher in renal categories 1 and 3 compared to other renal categories [25].

We observed a greater decline in average GFR in CKD 3A (GFR >45 mL/min) also in severe CKD patinets. Also, Huart et al., revealed the acute kidney injuries are associated more common in patients with renal categories 2 and 3 compared to the renal category of 1. Although the referenced proteinuria as a measure of kidney dysfunction, their study has been biased in nature with less significant results compared to our study [33].

The renin-angiotensin-aldosterone system inhibitors have shown beneficence in hypertensive patients and kidney functioning even though there was a dilemma on taking these medications during this pandemic [37-40]. Kidney transplanted patients are on immunosuppressive medication which further compromises the immune system and exposes them to early infection and results in worse outcomes [3,41-43].

LIMITATIONS

This study has few limitations; the first limitation is the study's retrospective nature. Second, we have got the less significant results for the improvement in GFR during the post-covid period, which could be due to the median duration of follow-up being relatively short. The third limitation is that this study was done in a single center, which leads to bias during selection.

CONCLUSIONS

CoVID-19 can cause acute ischemic injury to the kidney due to SARS-CoV-2 associated complications via either direct or indirect pathways. We found a higher mortality ratio in renal category two patients.

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We would like to submit the manuscript title entitled "Long term effects of COVID-19 on kidney function" to be considered for publication as an article in the "Journal of clinical nephrology and research".

We declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere.

FINANCIAL DISCLOSURE OR FUNDING & CONFLICT OF INTEREST

We know of no conflicts of interest associated with this publication, and there has been no significant financial support for this work that could have influenced its outcome. As the corresponding author, I confirm that the manuscript has been read and approved for submission by all the named authors.

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