Original Article

COVID-19 in CKD Patients: Report from India

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Abstract

Background: COVID-19 is a novel acute infection that is mainly manifested as acute respiratory disease. Information on coronavirus disease-2019 (COVID-19) in CKD patients who are not on dialysis is very limited. We are reporting a single-center observational study on the effect of COVID-19 in CKD patients. **Methods:** A single-center retrospective study with consecutive patients who had eGFR <60 mL/min/1.73 m^2 (CKD-EPI) admitted with COVID-19, from April to July 2020 were included. **Result:** A total of 30 patients were included in the study. Patients of CKD stage 5, 4 and 3 were 50%, 13.3%, and 36.6%, respectively. The mortality rate was 53.3%. Category wise, 9 were in mild; 3 in moderate, and 18 were in the severe COVID category. Twenty-five patients (83.3%) developed acute on CKD. Twenty patients (67%) required renal replacement therapy (RRT). The prognosis of patients who required RRT was poor. High LDH and IL-6 were significantly associated with mortality. Lymphopenia, present in 50% of cases was associated with fatal outcome. There was a 100% survival rate in mild to moderate cases and 11% in severe cases. **Conclusion:** Mortality among hospitalized CKD patients is high.

Keywords: *AKI, CKD, Coronavirus, Covid19, SARSCoV2*

Introduction

COVID-19 is increasing in India at an unprecedented rate and is at number three in the top 10 countries affected by COVID-19 with more than 50 lakhs patients and deaths of more than 90,000 at the time of this report. Delhi was one of the first states to be hit hard by the Covid-19, with a total caseload around two lakhs and the death of more than 4500 patients.[1] COVID-19 is an acute infection that is mainly manifested as acute respiratory diseases characterized by acute interstitial and alveolar pneumonia. With the passage of time, novel manifestations of the disease were started to be reported. At present, almost all organ systems have been reported to be involved even in patients without an overt MODS.[2]

Renal involvement has been documented in various studies ranging from Acute tubular necrosis to TMA and collapsing FSGS.[3] It has been observed that virus-like particles are present in podocytes and renal tubular epithelial cells by electron microscopy, and SARS-CoV-2 nucleoprotein antibody-stained renal tubular epithelia positive, but the specificity of the antibody used needs to be established.[4] Although various observational studies have analyzed the clinical spectrum and outcome among patients with chronic illnesses, very few studies have specifically studied the outcome among the pre-dialysis CKD patients.[5,6] Here, we are reporting a single-center observational study on the effect of COVID-19 in CKD patients who were on conservative management.

Material and Methods

A single-center retrospective study was conducted at Sir Ganga Ram Hospital, New Delhi, India. We identified consecutive patients who had eGFR <60 mL/min/1.73 m^2 (CKD-EPI) on two occasions before 3 months of admissions, admitted in our center with COVID-19, from April to July 2020. The demographic details, history, comorbidities, clinical course during admission, and follow-up were obtained from the medical record department. We also recorded the total admissions and mortality among Covid 19 patients in this hospital at the same time. The study was conducted in a multi-specialty tertiary care center in the national capital with a total bed capacity of more than 650. A total of 320 beds were allocated to COVID cases. Out of these, 61 beds were ICU with ventilators, and

How to cite this article: Pawar N, Tiwari V, Gupta A, Bhargava V, Malik M, Gupta A, *et al.* COVID-19 in CKD patients: Report from India. Indian J Nephrol 2021;31:524-30.

Received: 25-09-2020
Revised: 24-10-2020
Accepted: 03-11-2020
Published: 09-11-2021

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Access this article online

Website: www.indianjnephrol.org

DOI: 10.4103/ijn.IJN_460_20

Quick Response Code:

103 beds were ICU without a ventilator. Twelve dialysis machines and 4 CRRT machines were allocated in the COVID unit. For managing outpatient and inpatients for dialysis for COVID 19 patients, we followed the guidelines for dialysis published in the Indian Journal of Nephrology.[7] COVID- 19 was detected by nasopharyngeal swab and tested by RT-PCR. The treatment protocol was based upon the latest evidence and guidelines from the ministry of family health and welfare.[8]

Category of disease

We have divided the initial presentation of the disease as per 3 categories of disease defined by the Ministry of Health and family welfare, India.[8] Mild disease was defined as patients who are positive for COVID-19 without any evidence of pneumonia or hypoxia. Moderate disease was defined as patients with pneumonia secondary to COVID-19 with SpO2 ≥90% on room air. Severe disease was defined as adults with severe pneumonia (pneumonia plus any 1 of the following: SpO2 <90% on room air, respiratory rate >30 breaths/min or severe respiratory distress).

The data was entered in Microsoft excel 2007 and was analyzed using IBM SPSS version 20.0. Qualitative data was analyzed by using frequency and percentage and quantitative data by the mean and standard deviation. Association between two qualitative data was done by the Chi-square test, and comparison of mean values of quantitative data was done by unpaired t-test. A *P* value of less than 0.05 was considered significant.

Result

The total number of Covid 19 patients admitted to the hospital is shown in Table 1. For comparison, we have also included the total cases and deaths in India and Delhi. Consecutive 30 CKD (not on dialysis) patients with COVID-19 were included in the study. The median age of patients was 65 years. Of these, majority were male (76.6.%). The baseline characteristics of these patients are mentioned in Table 2. All patients were symptomatic on admission and details of symptoms are shown in Table 3. AKI developed in 25 (83.3%) patients. On analyzing cases requiring renal replacement therapy (RRT), 55% of the patients belonged to CKD stage 5, and 30% were from CKD stage 3. 70% of patients who required RRT had a fatal outcome. Patients who recovered from AKI, at 14 days from admission, 44.4% had reached their baseline creatinine while the rest had a declining trend or stable but higher creatinine from the baseline.

Three patients had a urine analysis after undergoing urinary catheterization. Proteinuria was present in 17 (56.7%) at the time of admission. Trace proteinuria was present in 2 (6.6%), 1 + in 10 (33.3%) and 2+ in 5 (16.6%). Hematuria was present in 6 patients (20%). On evaluation, urinary abnormalities including proteinuria did not show any significant relationship between death or survival (p-value 0.96). Mean serum sodium was 136.5 mEq/L (133.3-140 mEq/L). Hyponatremia was present in 11 (36.6%) cases, while it was present in 4 (25%) out of 16 cases who died. There was no significant relationship between mortality and hyponatremia (p vaue-0.22).

Secondary sepsis was assessed in all these cases by serum procalcitonin and blood culture testing. Serum procalcitonin was raised in 13 (43.3%) patients. Of these, 8 (61%) patients died. Blood culture was positive (*Klebsiella pneumonia*) in only one patient. There was no significant relationship between mortality and raised procalcitonin (p value-0.45). Raised blood sugar level (random blood sugar >200 mg/dl) was found in 76% of cases. The majority of the patient (67%) were diabetic. All diabetic patients received regular or ultra-short acting insulin. Two of the three non-diabetic patients also required regular insulin (18 ± 4.4 U/day) to achieve euglycemic status. All patients who had raised blood sugars were receiving steroids. None of the patients developed any complications due to increased blood sugars.

Inflammatory parameters

Biochemical parameters, including inflammatory markers, are shown in Table 3. On subgroup analysis of patients who died (group A) and survived (Group B), LDH and IL-6 were significantly increased in group A (p-value 0.02 and 0.01, respectively). On the contrary, ferritin and CRP did not show any significance. Lymphopenia was present in 15 (50%) cases [Table 3]. Out of these, 11 (73.3%) had a fatal outcome, while four patients (26.6%) survived. Patients with lymphocyte more than 1000/uL had better results as 10 (66.6%) patients survived, and five patients (33.3%) died. The mean lymphocyte count in group A was 853/uL, which was lower than group B (mean lymphocyte count- 1101.5/uL). The mean neutrophil lymphocyte Ratio (NLR) of group A (11.05) was significantly higher than that of group B (3.3; *P* value 0.002).

Table 1: Total number of cases and mortality in India, Delhi and, admissions in Hospital during April-July

Month	Total Cases		Admissions		Mortality			
	India	Delhi	Total	CKD	India	Delhi	Total (Hospital)	CKD
April	33,610	3439	39	0	1,075	56	2 (5%)	0 (0%)
May	1,82,143	19,844	340	2	5,164	473	7 (2%)	2 (100%)
June	5,66,840	87360	662	21	16,893	2742	81 (12%)	8 (39%)
July	16,38,870	135598	380	7	35,747	3963	65 (17%)	6 (86%)

Table 2: Baseline characteristics of CKD with COVID patients

General characteristics	Total	Outcome		*P*
		Group A (Death)	Group B (Recovered)	
n, (%)	30	16 (53.3%)	14 (46.6%)	
Age in years, Median, (IQR)	65 (58-68)	65 (58.7-68.2)	62 (52.7-67.5)	NS
Gender, Male, *n* (%)	23 (76.6%)	12 (40%)	11 (36.6%)	NS
Female, *n* (%)	7 (23.3%)	4 (13.3%)	3 (10%)	NS
Diabetes, *n* (%)	20 (66.6%)	13 (43.3%)	7 (23.3%)	NS
Hypertension, *n* (%)	28 (93.3%)	15 (50%)	13 (43.3%)	NS
Cardiac condition, *n* (%)	11 (36.6%)	6 (20%)	5 (16.6%)	NS
COPD/OSA	5 (16.6%)	4 (13.3%)	1 (3.3%)	NS
Kidney disease				
Diabetic kidney disease *n* (%)	20 (66.6%)	13 (43.3%)	7 (23.3%)	NS
Chronic glomerulonephritis *n* (%)	5 (16.6%)	2 (6.6%)	3 (10%)	NS
Chronic interstitial disease *n* (%)	4 (13.3%)	1 (3.3%)	3 (10%)	NS
SLE nephritis *n* (%)	1 (3.3%)	0	1 (3.3%)	NS
Stage of CKD				
CKD-III, *n* (%)	11 (36.6%)	7 (23.3%)	4 (13.3%)	NS
CKD-IV, *n* (%)	4 (13.3%)	3 (10%)	1 (3.3%)	NS
CKD-V, *n* (%)	15 (50%)	6 (20%)	9 (30%)	NS

Chest X-ray was done in all the patients. The majority of cases (73%) showed abnormalities in the form of bilateral infiltrate. It was more common in group A than group B. Abnormal chest X-ray was significantly associated with mortality [Table 3].

COVID 19 specific therapy

The patient received treatment in the form of inj. Tocilizumab, inj Remdesvir, convalescent plasma therapy, steroids, tab azithromycin, Hydroxychloroquine, bronchodilators, and other supportive management [Table 3]. Steroids, HCQ, and azithromycin were available from the beginning. Convalescent Plasma and Tocilizumab were available from the 2nd week of May. Hence, majority who had moderate and severe covid disease received the therapy. Remdesivir was available in the last week of June. However, in view of its contraindication in compromised renal function, it was given to only one patient (eGFR >45 mL/min/1.73 m^2) in the usual dose 200 mg on day 1 followed by 100 mg/day for 4 days. All the patients in the severe category received convalescent plasma therapy (12 patients-single volume 200 mL, six patients-double volume 400 mL), steroids (10 patients-dexamethasone, eight patients- methylprednisolone), seven patients received a single dose of tocilizumab (8 mg/kg; maximum 600 mg). On analyzing it in groups A (survived) and B (expired), none of the therapy showed significance in survival.

Most of the patients (60%) had severe disease at the baseline [Table 3]. Respiratory failure and mechanical ventilation was required in around 80% of the severe category patients. The mean time from symptoms onset to mechanical ventilation was 7.2 days, and from admission to intubation was 4.3 days. At 21 days, there was a 100% survival rate in mild and moderate cases, but only two cases in severe cases (11% of severe cases) survived. This result was significant, with a *P* value < 0.05. The median time of hospitalization in group A was ten days, and group B was 8 [Table 3].

Discussion

COVID-19 has put tremendous pressure on the already frail healthcare facilities in the country. CKD is one of the significant causes of non-communicable disease and health burden in India.[9] Thus, we are reporting a small observational study on 30 CKD patients, not on any RRT admitted to our center with COVID.

As we have shown in Table 1, the number of cases and mortality increased as the case load increased in the country and Delhi. In July, admissions reduced by almost 50%; however, the number of deaths remained same. This could be due to most patients with mild disease were either home isolating themselves or getting admitted into COVID care centers and, only patients with moderate and severe disease were getting hospitalized. Among the CKD patients, mortality was low in June as compared to April and July. This again was due to the fact that most patients who were admitted in June were having a milder disease and similar patients were home isolated in July rather than getting hospitalized.

AKI was common among CKD patients, with an incidence of 83% of the patients. In the study by Cheng Y *et al*., the incidence of AKI was 12% among CKD patients, whereas 4% among patients with normal baseline creatinine.[6] The very high incidence of AKI in the present study is surprising. As the AKI is common among patients in CKD,[10] the severe degree of renal insufficiency along with more severe infection in the cohort can account for

Table 3: Clinical features, severity, management in COVID 19 infected CKD patients

Symptoms	Total	Outcome		*P*
		Group A (Death)	Group B (Recovered)	
Fever, *n* (%)	29 (96.6%)	15 (50%)	14 (46.6%)	NS
Cough, *n* (%)	23 (76.6%)	14 (46.6%)	9 (30%)	NS
Shortness of breath, *n* (%)	24 (80%)	15 (50%)	9 (30%)	NS
Diarrhea, *n* (%)	8 (26.6%)	4 (13.3%)	4 (13.3%)	NS
Vomiting, *n* (%)	10 (33.3%)	7 (23.3%)	3 (10%)	NS
Headache, *n* (%)	19 (63.3%)	16 (53.3%)	3 (10%)	NS
Body-ache, *n* (%)	30 (100%)	16 (53.3%)	14 (46.6%)	NS
X- ray abnormality, *n* (%)	22 (73.3%)	16 (53.3%)	6 (20%)	0.003
Biochemical parameters, (Mean), (1st and 3rd interquartile range)				
Serum Creatinine at presentation, mg/dl	4.83 (2.35-7.5)	3.5 (2.4-6.8)	4.9 (2.4-7.6)	NS
Hemoglobin gm/dl	9.8 (8.32-11.47)	9.5 (8.2-11)	10.4 (8.7-11.7)	NS
Lymphocyte count/uL	993 (847-1344)	853 (413-1050.2)	1101.5 (986.7-1697.2)	0.04
Neutrophil to lymphocyte ratio	6.1 (2.77-13.27)	11 (5.3-21.3)	3.3 (2-6.2)	0.002
LDH, U/L	346 (276-460)	421 (321.7-580)	290 (241-342)	0.02
CRP, mg/dl	71 (34.4-128.7)	86 (62.5-137)	37 (24.2-110.7)	NS
IL-6, pg/mL	83.8 (37.2-274.7)	240 (83.5-723)	45.5 (27.2-113)	0.01
Ferritin, ng/mL	1080 (610-1993.2)	1455.5 (717.5-2545.7)	836 (464-1242)	NS
Proteinuria, *n* (%)	17 (56.7%)	9 (30%)	8 (26.6%)	NS
Hematuria, *n* (%)	6 (20%)	3 (10%)	3 (10%)	NS
Severity				
Mild, *n* (%)	9 (30%)	0	9 (30%)	NS
Moderate, *n* (%)	3 (10%)	0	3 (10%)	NS
Severe, *n* (%)	18 (60%)	16 (53.3%)	2 (6.6%)	0.02
Oxygen therapy, *n* (%)	22 (73.3%)	15 (50%)	7 (23.3%)	0.03
Mechanical ventilator, *n* (%)	15 (50%)	14 (46.6%)	1 (3.3%)	0.006
Decreased urine output, *n* (%)	19 (63.3%)	13 (43.3%)	6 (20%)	0.01
Normal urine output, *n* (%)	11 (36.6%)	3 (10%)	8 (26.6%)	0.04
Renal replacement therapy				
Conservative, *n* (%)	10 (33.3%)	2 (6.7%)	8 (26.6%)	0.02
Intermittent Hemodialysis, *n* (%)	17 (56.6%)	11 (36.6%)	6 (20%)	0.04
CRRT, *n* (%)	3 (10%)	3 (10%)	0	0.02
Treatment				
Hydroxychloroquine, *n* (%)	30 (100%)	16 (53.3%)	14 (46.6%)	NS
Azithromycin, *n* (%)	30 (100%)	16 (53.3%)	14 (46.6%)	NS
Remdesvir, *n* (%)	1 (3.3%)	1 (3.3%)	0	NS
Steroids, *n* (%)	26 (86.6%)	16 (53.3%)	10 (33.3%)	NS
Tocilizumab, *n* (%)	14 (46.6%)	10 (33.3%)	4 (13.3%)	NS
Plasma therapy, *n* (%)	18 (60%)	14 (46.6%)	4 (13.3%)	NS

this finding. Around 55% of patients had their baseline eGFR <30 mL/min/1.73 m^2, and 60% had a severe category of disease as compared to the Cheng Y *et al*. study where mean eGFR was 48 min/min/1.73 m^2. Probable etiology for an exacerbation is uncertain in most cases and most likely due to the interaction of multiple factors like the synergistic effect of virus-induced direct cytotoxic effect causing direct tubular injury and cytokine-induced systemic inflammatory response.[11] It is more pronounced in patients with moderate to severe disease, acute respiratory distress syndrome (ARDS), and those requiring ICU admission. Other possible mechanisms of AKI could be from ischaemic tubular injury due to multiorgan failure and shock and possible prerenal etiology from volume depletion secondary to decreased oral intake and high fever. Drug toxicity and hemodynamic insult can also play a role.[12]

Rhabdomyolysis is an important cause of AKI among COVID 19 patients.[13-16] Actual incidence of AKI due to COVID 19 associated rhabdomyolysis is largely unknown. In a study from China, kidney abnormalities were studied among 26 autopsies of patient. Clinically, 9 patients had features of kidney involvement.[4] Histopathological study of the renal tissue revealed features suggestive of AKI due to rhabdomyolysis in 3 patients (33%). As observed in other viral myositis, direct muscle invasion and inflammation mediated injury may have a role in SARS-CoV2 associated

rhabdomyolysis. In our study, none of the patient had rhabdomyolysis.

The relationship between developing respiratory failure and requiring RRT is intriguing as out of 15 (50%) patients who required mechanical ventilation, 12 of 15 patients (80%) required dialysis. 10 of the 12 patients required RRT within 12 hours of intubation and were on vasopressors. The most common indication of initiating HD was anuria or oliguria. A significantly increased requirement of RRT among COVID 19 patients may be multifactorial. Firstly, our cohort already had compromised renal function, and AKI is common among CKD patients.[10] Secondly, most patients required RRT after intubation and were on vasopressors and in majority, shock preceded AKI, suggesting the hemodynamic origin of the worsening of renal function. In a meta-analysis of 31 studies, it was found that mechanical ventilation increases the risk of AKI by three folds.[17] Thirdly, there could be an increased propensity of COVID19 patients towards renal failure.[18] One of the hypotheses to explain the apparent 'Nephrotropism' in COVID-19 is that the ACE2 receptor, which acts as the entry portal into the cells, is also found in the proximal tubular cells of the nephron, and viral nucleocapsid protein has been observed in PCT and urine.[11,19-20]

In the present study, it was observed that patients with CKD 3-4 who required RRT had worse outcomes (100% mortality) compared to patients who were already at stage 5 CKD (45% mortality). The reason for higher mortality in the relatively less severe CKD group is not entirely apparent. One hypothesis is that patients who required dialysis with initial CKD stages may be a surrogate marker of more severe disease when compared to the patient who already has severely compromised renal function, and even a milder COVID-19 precipitated the complete renal failure.

Laboratory parameters at the time of admission, especially Ferritin, CRP, IL-6, showed a trend of progressive derangement from mild to severe category. Similar to the general population, these markers can serve as prognostication markers in severe disease, alerting the clinician to be more vigilant in cases with raised inflammatory markers. In the present study, increased IL-6 and LDH were significantly associated with mortality ($p < 0.05$) compared to ferritin and CRP in CKD patients, which is consistent with other studies on CKD V.[21] Our study showed significantly high NLR in fatal cases compare to survived patients (p-value 0.002). Around 73.3% of the lymphopenic patients died while only 26.6% of patients survived. The poor prognosis of lymphopenic patients in COVID 19 was also observed in a meta-analysis of 23 studies.[22]

There is a scarcity of knowledge regarding the efficacy of various therapies against COVID19 in CKD patients. In our study, patients received various treatment in the form of Tocilizumab, plasma therapy, steroids, and Remdesivir, but none of the treatment was proven significant for survival. However, given a small number of patients, results cannot be generalized. In a study by Li L *et al*., a RCT was performed to evaluate the efficacy of Plasma therapy among the severe COVID 19 infected patients.[23] Around 4% of the patients had kidney disease at baseline. The study did not find any significant benefit in the outcome of the patients.

Mortality among renal disease has been reported to be higher than patients without renal disease. For the patients who are undergoing dialysis, mortality is around 30%.[22,24-26] In a recent study from India by Trivedi M, 38% of the patient on MHD expired. In an unpublished study (n-40) from our institute, 12.5% of dialysis patients succumbed to the infection. A similar trend is seen among the transplant patients with death reported in the 0-33%.[27-29] In two unpublished studies from our institute, mortality was 23.5% among transplant of >6 months (n-30) and 10% among recent transplant (n-49) (<1 month). The mortality among CKD patients (53%) was similar to the critically ill patients admitted in ICU (22-61%).[30-33] Only one study has evaluated the outcome of COVID 19 among CKD patients. In the study by Cheng Y *et al*., 101 patients had raised serum creatinine among 701 Covid-19 patients admitted in the hospital in China, the mortality among patients with raised creatinine was significantly higher (33%) than in patients with normal renal function (13%),[6] although this study failed to differentiate CKD from AKI at the time of admission (only 9% were actually known CKD patients). As CKD patients are heavily burdened with other comorbidities, higher mortality than the non-CKD population is expected as COVID 19 associated mortality has been shown to be more among the patients with chronic illness.[34] In an analysis of over 7000 in the US, CKD patients were 12 times more frequent ICU requiring and nine times more frequent in hospitalized, non-ICU COVID-19 patients than in those not hospitalized.[34]

As we have shown in our report, CKD patients are a vulnerable group of patients with a dismal outcome. We, therefore, suggest that CKD patients should take extra precautions to prevent COVID infection. CKD exposed and suspected individuals should be on the high priority for testing and, subsequently, hospitalization if needed. Admissions of moderate-severe patients should be done in facilities where there is the easy availability of dialysis facilities.

Our study has a few limitations. First, it is a single-center, small sample size study. Second, laboratory tests like IL-6, ferritin, CRP were not repeated in every patient, so the trend of these inflammatory markers was not evaluated. Third, it is difficult to ascertain the incidence of COVID 19 among CKD patients as only admitted patients were included in the study. Additionally, this study may overestimate mortality in CKD patients as this is a hospitalized cohort only.

In conclusion, mortality among hospitalized CKD patients is high. Laboratory parameters, especially IL-6, LDH may serve as important prognosticating markers in CKD, similar to the general population. AKI is common, especially in patients with moderate and severe infection. The incidence of dialysis requirement is significant among patients who are on mechanical ventilation.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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