Original Article

COVID-19 Infection in Renal Transplant Patients: Early Report From India

Gaurav Bhandari, Vaibhav Tiwari, Anurag Gupta, Vinant Bhargava, Manish Malik, Ashwani Gupta, Anil Kumar Bhalla, Devinder S. Rana

Department of Nephrology, Sir Ganga Ram Hospital, New Delhi, India

Abstract

Introduction: COVID –19 has gripped the whole world and patients with comorbidities especially kidney ailments are at higher risk of developing severe disease. Among kidney disease, transplant patients are the most vulnerable group. Information on coronavirus disease 2019 (COVID-19) in kidney transplant patients is very limited. **Methods:** An observational study was conducted on 20 kidney transplant patients who tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by polymerase chain reaction from April to June 2020. **Results:** The majority of cases were males (85%). The median age of the patients was 50 years (interquartile range [IQR] 40.75–60.75). Diabetes and hypertension were present in 55% and 95% of patients, respectively. Coronary artery disease was present in three patients (15%). The median time from transplant to COVID-19 testing was 54 months (IQR 36–105). Chronic allograft nephropathy was found in 35% of patients. The mean baseline creatinine was 1.71 mg/dL. The most common symptom was fever (80%). Acute Kidney Injury was seen in 60% of patients with a mean creatinine of 2.60 mg/dL. Based on severity, 50% of patients had mild disease, 25% moderate disease, and the remaining 25% had severe disease. All 20 patients were on oral steroids, calcineurin inhibitors (18 on tacrolimus and two on cyclosporine), and antimetabolite (19 on mycophenolate mofetil and one on azathioprine). Antimetabolite agents were stopped in all patients and tacrolimus was stopped in severe cases (25%). Hydroxychloroquine was given in 15 patients (75%). Fifteen patients (75%) recovered while five (25%) died. **Conclusion:** Kidney transplant recipients infected with COVID-19 have high mortality.

Keywords: *AKI, COVID-19, kidney transplantation*

Introduction

The first case of the novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was found in the city of Wuhan, China.[1] It has spread out from Wuhan to the entire world, causing a global pandemic. Information on coronavirus disease 2019 (COVID-19) and the clinical course in kidney transplant recipients is very limited.

Considering the immunity of transplant patients, they might be at a higher risk of COVID-19 disease with poor prognosis. However, only a few case reports have been published in the literature on COVID-19 disease in kidney transplant patients, and none have been published from India to our knowledge. Herein, we report our experience of COVID-19 in kidney transplant patients based on clinical features, treatment, and outcomes of the disease.

Materials and Methods

A single-center observational study was conducted. All consecutive kidney transplant patients with COVID-19 infection from April to June 2020 were included in this study. COVID-19 was detected by taking a nasopharyngeal swab, and testing was done through a reverse transcription-polymerase chain reaction (RT-PCR) kit.

Category of disease

We divided the initial presentation of the infection as per the three categories of disease as defined by the Ministry of Health and Family Welfare, India.[2]

Mild

Patients who were positive for COVID-19 without any evidence of pneumonia or hypoxia.

Moderate

Patients with pneumonia secondary to COVID-19 with SpO2 ≥90% on room air.

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Address for correspondence:
Dr. Vaibhav Tiwari,
Old Rajinder Nagar,
New Delhi - 110 060, India.
E-mail: drvt87@gmail.com

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Severe

Patients with severe pneumonia (pneumonia plus any 1 of the following: SpO2 <90% on room air, respiratory rate >30 breaths/min, or severe respiratory distress)

All patients who were asymptomatic for more than 3 days with the total duration of disease from onset of symptoms exceeding 10 days underwent repeat RT-PCR test for COVID-19. A negative test was treated as recovery from infection.

Results

A total of 20 patients were included in this study for over 3 months. The baseline characteristics of the patients are shown in Table 1. All patients were live-related allograft recipients and 3 patients had undergone an ABO-incompatible transplant. The majority of patients were male with a median age of 50 years. Coronary artery disease was present in three patients of which one patient had undergone coronary artery bypass grafting (CABG) surgery 6 years back while the remaining two had undergone stent placement 4 and 3 years back. The majority of the patients were symptomatic (95%), with fever as the most common manifestations in 80% of the patients. Fever with diarrhea was present in two patients. The severity of COVID-19 infections in the patients is mentioned in Table 2. Laboratory parameters, including inflammatory markers, are mentioned in Table 3.

All patients had received anti-thymocyte globulin (ATG) as an induction agent and were taking triple-drug immunosuppression at the time of diagnosis of infection. Antimetabolite was stopped in all the patients. Calcineurin inhibitors were stopped in all severe patients. Oral steroids were stopped in patients with moderate-to-severe disease (50%) and were started on injection methylprednisolone 20 mg twice daily. In mild cases (50%), oral steroids were continued. Hydroxychloroquine (HCQ) was given in 15 (75%) patients. Electrocardiogram (ECG) was done to look for QT prolongation before starting HCQ. Antibiotics were given in 90% of the patients; Azithromycin was given in nine patients (45%), and the rest 45% of patients received parenteral antibiotics like meropenem or piperacillin/tazobactam. Two patients (mild category) did not receive any antibiotics. All patients in the moderate-to-severe disease category received anticoagulation (enoxaparin 40 mg OD). Tocilizumab in the dose of 8 mg/kg with a maximum dose of 800 mg was given to 3 patients; one in the moderate category and two patients in the severe category. Convalescent plasma therapy was given to 5 patients; one in the moderate category and 4 in the severe category. None of our patients received remdesivir.

Serum creatinine (s.cr) ≥1.5 times higher than the baseline was found in 12 patients. The majority of patients in the mild category (8 patients) and 3 patients in the moderate category achieved their baseline creatinine at the time of discharge from the hospital. One patient in moderate category had a stable creatinine value of 2.4 mg/dL (baseline s.cr-1.5 mg) and another one had declining value 2.7 mg/dL (baseline s.cr-1.9 mg/dL). Among the severe category, 2 patients were anuric and initiated on continuous renal replacement therapy (CRRT).

Fifteen patients (75%) recovered from COVID-19 disease while 5 (25%) died. Mortality was 100% in the severe disease category. Patients with mild and moderate disease recovered fully. When baseline characteristics were compared among the deceased and alive patients [Table 1], deceased patients had significantly higher mean creatinine. There was no statistically significant difference in age, duration of transplantation, and comorbidities between the two groups. Similarly, deceased patients had significantly higher creatinine at admission. The severity of disease and COVID-specific therapy were not significantly associated with the outcome.

Discussion

The whole world is facing a COVID-19 pandemic. Cases of COVID-19 are increasing in India and is at number

Table 1: Baseline characteristics of transplant patient with COVID-19

General characteristics		Outcome		*P*
		Death	Recovered	
Number, *n*	20	5	15	
Age in years, median, (IQR)	50, (40.75-60.75)	48, (38.5-51.5)	53, (40-61)	NS
Gender, Male%	17 (85%)	4 (20%)	13 (65%)	NS
Diabetes, *n* (%)	11 (55%)	1 (5%)	10 (50%)	NS
Hypertension, *n* (%)	19 (95%)	4 (20%)	15 (75%)	NS
Coronary artery disease, *n* (%)	3 (15%)	2 (10%)	1 (5%)	NS
Transplant-related characteristics				
Transplant duration in months, median, (IQR)	54, (36-105)	38, (32-54)	70, (36-110)	NS
Chronic allograft nephropathy, *n* (%)	7 (35%)	4 (20%)	3 (15%)	NS
H/O rejection, *n* (%)	2 (10%)	-	2 (10%)	NS
Baseline creatinine (1 month before the COVID-19 infection), mg/dL (mean)	1.71	2.52	1.53	0.04

Table 2: Clinical features, severity, management, and outcomes in COVID-19 infected renal transplant patient

Variable	Total	Outcome		*P*
		Death	Recovered	
Symptoms				
Fever, *n* (%)	16 (80%)	13 (65%)	3 (15%)	NS
Sore throat, *n* (%)	2 (10%)	2 (10%)	0	NS
Dyspnea, *n* (%)	8 (40%)	3 (15%)	5 (25%)	NS
Diarrhea, *n* (%)	2 (10%)	1 (5%)	1 (5%)	NS
AKI, *n* (%)	12 (60%)	6 (30%)	6 (30%)	NS
Serum creatinine at presentation, mg/dL (mean)	2.60	1.81	3.79	0.006
Immunosuppression status at the time of diagnosis of infection				
Number of patients on steroids, *n* (%)	20 (100%)	15 (75%)	5 (25%)	NS
Number of patients on Tacrolimus, *n* (%)	18 (90%)	14 (70%)	4 (20%)	NS
Number of patients on Cyclosporine, *n* (%)	2 (10%)	1 (5%)	1 (5%)	NS
Number of patients on Mycophenolate, *n* (%)	19 (95%)	14 (70%)	5 (25%)	NS
Number of patients on Azathioprine, *n* (%)	1 (5%)	1 (5%)	0	NS
Immunosuppression management after the diagnosis of infection				
Stoppage of antimetabolites (Mycophenolate/Azathioprine), *n* (%)	20 (100%)	15 (75%)	5 (25%)	NS
Continuation of steroids, *n* (%)	20 (100%)	15 (75%)	5 (25%)	NS
Stoppage of CNI (Tacrolimus/Cyclosporine), *n* (%)	5 (25%)	0	5 (25%)	NS
COVID-19 specific treatment				
HCQ, *n* (%)	15 (75%)	10 (50%)	5 (25%)	NS
Azithromycin, *n* (%)	9 (45%)	4 (20%)	5 (25%)	NS
Tocilizumab, *n* (%)	3 (15%)	0	3 (15%)	NS
Convalescent plasma therapy, *n* (%)	5 (25%)	0	5 (25%)	NS
High-dose steroids, *n* (%)	10 (50%)	5 (25%)	5 (25%)	NS
Severity of infection at the time of admission				
Mild, *n* (%)	10 (50%)	10 (50%)	0	NS
Moderate, *n* (%)	5 (25%)	5 (25%)	0	NS
Severe, *n* (%)	5 (25%)	0	5 (25%)	NS
Outcome of the COVID-19 infection at 21 days	20 (100%)	15 (75%)	5 (25%)	

Table 3: Laboratory parameters in a renal transplant patient with COVID-19 infection at the time of admission

Parameters	Overall	Clinical severity		
		Mild	Moderate	Severe
IL-6, pg/mL (median)	75	23	45	166
CRP, mg/dL (median)	21	3.8	23	34
Ferritin, ng/mL (median)	366	231	311	567
D-Dimer, µg/mL (median)	1.5	0.22	1.6	1.6
Lymphocyte, cell/mm^3 (median)	1100	1500	1100	650

four in the top 10 countries affected by COVID-19 with cases of more than 6.5 lacs and deaths of more than 18,000.[3] Kidney transplant patients are at risk for COVID-19 infection. Thus, we present an observational study of 20 COVID-19 positive kidney transplant patients. Although the sample size is small, COVID-19 has a varied presentation in the general population, and the prognosis is different in each kidney transplant case depending on the severity of COVID-19 disease.

The most common presentation was fever, which was seen in 80% of patients. This is following the general population and kidney transplant patients having fever as the commonest presentation of COVID-19 disease.[4,5] Pneumonia was present in 50% of patients. Around 10% of patients had diarrhea, and AKI was seen in 60% of patients with a mean creatinine of 2.60 mg/dL at presentation. Disease severity was also variable. In our study, 50% of patients had mild disease, 25% had moderate disease, and the remaining 25% had severe disease. None of the patients admitted with the mild disease had worsening of their symptoms. One patient was managed at home. Another patient who recently had transplantation (1 month back) was found to be COVID-19 positive when he was planned for double J-stent removal. He was admitted to a dedicated COVID center. Although a study from China showed that patients with mild disease had zero mortality and such patients can be managed with supportive care and adjustment of immunosuppressants,[5] we recommend that transplant patient are high-risk group, therefore, if home isolation is opted, discussion regarding the red flag signs, active monitoring of temperature and oxygen saturation, and facility to shift to hospital in an emergency should be available. All patients who had severe disease, to begin with, had death as their outcome. All these patients were

directly admitted into the ICU. The mean duration of symptoms in these patients was 4.2 days. Time from onset of symptoms to death was 11.2 days, and from intubation to death was 4.8 days. A study from Wuhan, China, is consistent with the above findings showing that all COVID-19 patients who died had a severe disease in the form of acute respiratory distress syndrome (ARDS).[6]

Laboratory parameters at the time of admission, especially ferritin, C-reactive protein **(**CRP), interleukin 6 (IL-6), and lymphocyte count, showed a trend of progressive derangement from the mild-to-severe category [Table 3]. 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.

Although there is no conclusive evidence regarding the discontinuation of immunosuppressive agents in COVID-19 infection, the European group has recommended to discontinue the antimetabolite drugs in mild cases and additionally to stop calcineurin inhibitors (CNIs) in severe cases.[7] We agree with these recommendations, but additional factors regarding the comorbidities, especially high-risk patients for rejection, preexisting lung diseases, or any other significant comorbidities, should be considered before deciding the modification of immunosuppression. Regarding the reinitiating of immunosuppression, seven of the 10 mild cases and two of the moderate cases were restarted on antimetabolite after 14 days of their negative RT-PCR test in half the initial dose.

Regarding the use of specific therapy in kidney transplant recipients, no recommendations are available. HCQ has been proven to have antiviral activity and it inhibits T-cell activation, thereby decreasing cytokine storm and attenuating the severity of the disease.[8] HCQ reduces viral load which is reinforced by azithromycin.[9] Oral or i.v. dexamethasone also reduces death in severe disease.[10] None of the therapy had any significant impact in this study. Recently, the Food and Drug Administration (FDA) approved the use of a novel antiviral agent, Remdesivir in COVID-19. Few studies have shown that Remdesivir can shorten the time to recover in patients with pneumonia due to COVID-19, however, another report has found no clinical benefit.[11-13] Its use is not recommended in patients with estimated glomerular filtration rate (eGFR) <30/mL/min/1.73 m^2. As such, no clinically important drug interaction is anticipated between Remdesivir and immunosuppressive medication, however, due to lack of evidence, no recommendation is available regarding its use in transplant patients[14]

Acute kidney injury (AKI) is a relatively common finding among patients hospitalized with COVID-19.[15] This has been attributed to the angiotensin-converting enzyme 2 (ACE2) receptors, which acts as the entry portal into the cells, and are found in the proximal tubular cells. In a recent study, the incidence of AKI in the general population was

Table 4: Various case series of renal transplant patient with COVID-19 infection

Country	United States[17]	United States[18]	United Kingdom[19]	China[8]	India (present study)
Number of patients	36	10	7	5	20
Patient characteristics					
Age	60	57	57	45	50
Sex (male%)	72%	60%	57%	80%	85%
Diabetes	36%	80%	43%	20%	55%
Hypertension	29%	100%	85%	40%	95%
Other comorbidities	17%	20%	-	20%	15%
Transplant-related characteristics					
Live donor recipient, %	-	50%	29%	0%	100%
Cadaveric donor recipient, %	75%	40%	71%	100%	0%
Duration, mean	-	7.7 years	5.9 years	1.5 years	5.4 years
COVID-related characteristics					
Symptoms					
Fever	58%	80%	85%	100%	80%
Dyspnea	44%	30%	100%	0%	40%
Diarrhea	22%	20%	14%	0%	10%
AKI	-	50%	57%	20%	60%
Renal replacement therapy	21%	-	42%	0%	10%
Treatment given					
HCQ	86%	90%	-	-	75%
Azithromycin	46%	90%	-	-	45%
Leronlimab	21%	-	-	-	-
Tocilizumab	7%	-	-	-	15%
Mortality	27%	33%	14%	0%	25%

found to be 23% and in patients with various comorbidities as high as 60%.[16] In this study, the incidence of AKI was also 60%. The study by Banerjee *et al*. also found a similar incidence of 57%, which reinforces the fact that transplant patients are at higher risks of AKI than the general population.

Till date, there is only a few case series of COVID-19 infection in renal transplant patients published in the literature [Table 4]. Mortality has ranged from 14–33%, which is substantially high when compared to the general population of 1–5%. This is well expected considering the immunosuppressed status as well as other frequent associated comorbidities.

Conclusion

In conclusion, renal transplant patients are at higher risk of mortality, especially when the initial presentation is of severe category. Deranged laboratory parameters at baseline, especially high creatinine, ferritin, CRP, and lymphopenia have a worse prognosis. AKI is common among these patients than the general population.

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Conflicts of interest

There are no conflicts of interest.

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