Original Article

COVID-19 Infection in Kidney Transplant Recipients: A Single Centre Study from Northern India

Abstract

Introduction: Coronavirus disease 2019 (COVID-19) has resulted in significant morbidity and mortality worldwide. The pre-immunosuppressed state along with other existing co-morbidities can influence the outcomes of COVID-19 in transplant patients **Material and Methods:** This was a single centre prospective cohort study done in kidney transplant recipients (KTRs), who underwent kidney transplantation (from December 2012 to November 2020), who were actively followed up at our centre and were diagnosed with COVID-19 disease between 1 April and 30 November 2020. **Results:** A total of 62 kidney-transplant recipients tested positive for COVID-19. Their median age was 39 (19–61). Males were predominantly infected (87.1%). Fever was the most common symptom (77.42%). Thirteen (20.9%) had mild form of disease, 32 (51.6%) had moderate form and 17 (27.4%) had severe disease. Based on initial symptom, 18 (29.03%) were given home treatment, 29 (46.7%) were treated in isolation wards and 15 (24.1%) were treated in intensive care unit. Decrease in the dose of immunosuppressant (anti-metabolites in 67.7%, calcineurin inhibitor in 22.5%) was predominantly carried out as the initial mode of treatment. Remdesivir in 64.5% and anticoagulant therapy in 54.84% were given as a modality of treatment. Mortality rate in our study was 14.5%. **Conclusions:** Patients of kidney transplant are at high risk of getting infected with COVID-19, due to their immunosuppressed state. Initial symptoms in KTRs with COVID-19 are similar to that of the general population. Mortality rate is comparatively higher in KTRs as compared to general population.

Keywords: *COVID-19, immunocompromised, immunosuppression, kidney transplant recipient, morbidity, mortality*

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Introduction

The novel coronavirus(severe acute respiratory syndrome coronavirus-2) was first identified toward the end of 2019 in Wuhan, Hubei province of China, as the cause of a new viral respiratory illness, designated as coronavirus disease 2019 (COVID-19).[1] Despite the worldwide effort to contain COVID-19, new cases were identified all over the world by January 2020 and the World Health Organization designated COVID-19 as a pandemic in March 2020.[2] The first case of COVID-19 in India, which originated from China, was reported on 30 January 2020.[3] On 12 March, a 76-year-old man, with a travel history to Saudi Arabia, became the first COVID-19 fatality of India.[4]

The number of patients has, since then, exponentially risen all over the country. As the COVID-19 pandemic progresses, evidence of high morbidity is emerging daily, reflected by elevated hospitalization rates in intensive care units (ICUs) resulting in excessive mortality rates. Solid organ transplant patients including kidney transplant recipients (KTRs) are at a uniquely increased risk of serious complications from COVID-19 because of immunosuppressive (IS) medication use and pre-existing co-morbidities like diabetes, hypertension and cardiovascular diseases.

Methods

This is a prospective cohort study, which included all patients who underwent kidney transplantation at our hospital from December 2012 to November 2020 and were diagnosed with COVID-19 disease between 1April and 30 November 2020. This study aimed to evaluate prevalence, demographics, co-morbidities, clinical and functional parameters associated with

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COVID-19 disease and survival in a population of kidney recipients. COVID-19 positivity was defined as a positive result on real-time polymerase chain reaction (PCR) assay of nasal and/or pharyngeal swab specimens. In the case of a first negative quantitative RT-PCR, if the patient had a clinical presentation or radiologic images compatible with COVID-19 infection, a second nasopharyngeal swab was performed. Depending on the severity of the initial presentation, patients were either hospitalized or were given home treatment.

All charts were manually reviewed for demographics, history of recent exposure, immunosuppression changes, clinical signs and symptoms, and laboratory findings. Patients were graded as mild, moderate, severe and critical as per the standard definition of WHO and baseline characteristics are compared between them. Following inclusion and exclusion criteria were followed.

Inclusion criteria: (1) All living and deceased donor KTRs. (2) Age >18 years. (3) All KTR patients who were on active follow-up. (4) Patients who were admitted with COVID-19 disease and patients who opted home treatment for the same.

Exclusion criteria: We excluded patients with graft failure and return to dialysis.

Results

At our hospital, we identified 62 consecutive adult kidney transplant recipients who tested positive for COVID-19 between 1 April and 30 November 2020. Demographic details and immunosuppression used in patients are shown in Table 1. One recipient was not given any induction therapy. Of the 62 recipients, 16 recipients had diabetes mellitus, 10 recipients had hypertension, 6 had obesity, 1 had chronic liver disease and 1 had hypothyroidism. COVID-19 disease was of mild grade in 13 (20.9%) recipients, moderate grade in 32 (51.6%) recipients and severe grade in 17 (27.4%) recipients. Seven patients who developed severe disease had diabetes mellitus. Among the patients who had obesity, three of them developed severe COVID-19 disease. A total of 44 patients got admitted, while 18 of them opted for home quarantine and were regularly monitored through telephonic consultation and video call services.

Table 1: Factors associated with COVID-19 disease in kidney transplant patients

Recipient characteristics	Total patients (*n*=62)
Age (years) [median range]	39 years (19-61)
Sex Male (%)	54 (87.1%)
Cause of ESRD	
a) CGN (presumed)	39 (62.9%)
b) CTIN (presumed)	8 (12.9%)
c) Diabetic nephropathy	8 (12.9%)
d) Hypertensive nephropathy	6 (9.6%)
e) Others	1 (1.61%)
Donor relation	
Living donor	59 (95.16%)
Deceased donor	3 (4.84%)
Induction therapies	
a) ATG	49 (79.03%)
b) Basilixumab	12 (19.35%)
c) Nil	1 (1.61%)
ABO incompatible	5 (8.06%)
SWAP transplant	5 (8.06%)
Episodes of rejection	10 (16.12%)
Co-morbidities	
a) Diabetes	16 (25.8%)
b) Hypertension	10 (16.12%)
c) Obesity	6 (9.6%)

Table 2: Clinical feature of kidney transplant recipients with COVID-19 disease

	All patients (*n*=62)
Clinical presentation no.	
Fever	48 (77.42%)
Cough	44 (70.97%)
Anosmia	7 (11.29%)
Dyspnoea	15 (24.19%)
Diarrhoea	6 (9.68%)
Myalgia	16 (25.81%)
Laboratory test	
WBC (lymphopenia)	45 (72.5%)
CRP (increased)	41 (66.1%)
Serum procalcitonin (increased)	10 (16.1%)
IL-6 level	24 (38.7%)
CT chest (CT severity score)	
Mild	38
Moderate	15
Severe	9

Clinical presentation

Clinical features and investigations of the patients are shown in Table 2. Fever was the most common symptom developed in 48 recipients, out of whom 17 had high-grade fever, 20 had fever of moderate grade and 11 had low-grade fever. Cough was present in 44 recipients. Dyspnoea was the main complaint in 15 recipients and they were managed in ICU. A total of 45 (72.5%) patients were lymphopenic. The C-reactive protein level was >10 mg/dl in 41 patients (66.1%), procalcitonin level was >0.2 ng/ml in 10 patients (16.1%) and 24 (38.7%) had a serum interleukin-6 (IL-6) level >60 pg/ml.

Treatment perspective

Although effective treatment of COVID-19 is currently unknown, anti-COVID-19 treatment which is recommended worldwide was started in all recipients. Remdesivir, an RNA polymerase inhibitor, was administered in 40 out of 62 patients which included moderate-to-severely

ill patients; anticoagulant in the form of enoxaparin/unfractionated heparin/oral anticoagulant was administered in 34 out of 62 patients, tab azithromycin was given in all 62 patients and hydroxychloroquine was given in 5 out of 62 patients.Immunosuppressant dose was modified in 55 recipients, while in 7 recipients, dose was not changed. Immunosuppression management included decreasing dose of an antimetabolite (mycophenolate mofetil/mycophenolic acid/azathioprine) by 50% in 42 (67.7%) mild-to-moderate cases, while in 11 (17.7%) severely ill patients, antimetabolites was completely stopped.

In addition, tacrolimus dose was also decreased in 12 (19.3%) severely ill patients along with stoppage of antimetabolite. In 2 patients, tacrolimus dose was decreased, without changing the dose of antimetabolite, who had mild-to-moderate symptoms. Tacrolimus doses were titrated to a target trough of 3–5 ng/ml. Steroid dose was unchanged in patients with mild–moderate disease in our study. In those with critical disease (Acute respiratory distress syndrome (ARDS) or requiring mechanical ventilation, oral steroid was changed to intravenous methylprednisolone, dexamethasone or hydrocortisone in an attempt to suppress cytokine release syndrome.

Tocilizumab was given in 2 severely ill patients, whose IL-6 levels were raised but serum procalcitonin level was normal, both responded to treatment and recovered. Intravenous antibiotics were also given in patients, whose serum procalcitonin levels were raised, indicating secondary sepsis and those who required invasive ventilation. Convalescent plasma was given in four patients in the early phase of infection; when they started to deteriorate, all four of them showed improvement in symptoms.

Clinical outcomes

Mean value of baseline serum creatinine before developing COVID-19 was 1.74 mg/dl. Mean value of serum creatinine at the time of admission was 2.22 mg/dl. Mean value of serum creatinine at the time of discharge was 1.84 mg/dl. Forty-seven patients out of 62 developed acute kidney injury (AKI) and their serum creatinine levels increased after developing COVID-19 compared to serum creatinine levels before developing COVID-19 infection. All 47 patients recovered from AKI during the course of the disease or after recovery from COVID-19. As per KDIGO classification of AKI, 39 recipients developed stage 1 AKI while 8 recipients developed stage 2 AKI. One patient who had an increase in serum creatinine levels required renal replacement therapy during the COVID-19 infection period.

A total of 21 recipients required oxygen support who had moderate-to-severe symptoms, out of which 4 recipients needed non-invasive mechanical ventilation in the form of C-PAP/BIPAP and 8 recipients required invasive ventilation and were managed in ICU. A total of 15 sick recipients required ICU care out of which 8 required ventilators, 4 required CPAP/BIPAP and 3 required high flow oxygen support. A total of seven recipients required ionotrope support, six of them required noradrenaline support and one of them required noradrenaline and vasopressin support. All eight recipients on ventilator succumbed to COVID-19 and its complication of which six required ionotrope support. Mean duration of eight recipients on ventilator was 15.75 h. Mean duration of ICU stay of all 15 recipients was 3 days.

One of the patients who had chronic allograft nephropathy due calcineurin inhibitor (CNI) toxicity with a baseline serum creatinine of 3.4 mg/dl, after developing COVID-19, had graft dysfunction because of secondary sepsis, thus requiring multiple ionotropes and haemodialysis. Eventually the patient succumbed to COVID-19. Nine of the 62 patients who were COVID-19-positive died during this period. All of them were severely ill and required mechanical ventilation. Mortality rate in our study was 14.5%.

Radiological findings

All 62 recipients had their chest CT scan done. Based on the CT severity score grading, the extent of lesion was classified into mild (0–8), moderate (9–15) and severe (16–25). Out of 62 recipients, 38 of them had mild lesions, 15 had moderate lesions and 9 of them had severe lesions. Fifty of them had bilateral lesions and 12 had unilateral lesions.

Complications

All the recipients were regularly followed up till now. Out of 62 recipients, only one of the recipients developed decreased vision, which was due to vitreous haemorrhage. No other complications were noted in any other recipients. Complications related to mental health, such as anxiety and depression, were not seen in any of our patients' post-recovery. Table 3 shows treatment and outcomes in kidney transplant recipients with COVID-19 disease

Discussion

This prospective study, conducted at our hospital, provides a broad understanding of COVID-19 disease in post-renal allograft recipients who are basically immunocompromised. Our study identifies obesity, diabetes and hypertension as factors independently associated with COVID-19 disease in patients with kidney transplants. Similar findings were also observed in other studies across the world.[5] These risk factors were associated with COVID-19 disease in general population also.[6] COVID-19 disease in our study was not related to any particular age group, sex, ABO blood group and tobacco consumption, which was similar in comparison to other studies.[5] But in other studies related to general population, COVID-19 disease was more in certain blood group individuals.[7]

We observed that patients with COVID-19 are more frequently recipients from living donors (95.1%), mainly

Table 3: Treatment and outcomes in kidney transplant recipients with COVID-19 disease

Treatment and outcomes	All patients (*n*=62)
Type of treatment	
Home-based therapy no.(%)	18 (29.03%)
Treatment in isolation ward no.(%)	29 (46.7%)
Treatment in ICU no.(%)	15 (24.1%)
Change in immunosuppression no (%)	
MPA/MMF (dose decreased)/Withheld	42 (67.7%)/11 (17.7%)
CNIs (dose decreased)	14 (22.5%)
Anti-COVID-19 therapies	
Hydroxychloroquine no.(%)	5 (8.06%)
Tocilizumab	2 (3.2%)
Anticoagulation	34 (54.84%)
Convalescent plasma	4 (6.45%)
Remdesivir	40 (64.5%)
Oxygen therapy	
Oxygen required no.(%)	21 (33.8%)
Non-invasive mechanical ventilation	11 (17.74%)
Invasive ventilator (yes/no)	8 (12.9%)
Outcomes	
Creatinine on admission or COVID positive (mg/dl) (mean)	2.22 (mg/dl)
Creatinine on discharge or COVID negative (mg/dl) (mean)	1.84 (mg/dl)
RRT required no.(%)	1
Recovery no.(%)	53 (85.4%)
Died no.(%)	9 (14.5%)
Complications	
Graft dysfunction	1 (1.61%)

because in our region and also in our country, deceased donor transplantation is less in number as compared to living donor. In contrast, KTRs from deceased donors were more in number in studies done at Columbia (80%),[8] Paris (97%) and New York (77%),[9] who got infected with COVID-19, while in Nair *et al.*,[10] living donors were 50% and deceased donors were 40% in number.

Males were predominantly affected in our study (87%). In other studies, also males were mainly affected.[5,8,9,11] The 62 patients included in our study had a median age of 39 (interquartile range19–61) years. In recent other studies, median age varied between 50 and 60 years.[5,8,9-12] In our study, 70.9% were given treatment in hospital, based on their initial symptoms. Similar rates of hospital admissions were also seen in other studies,[11-13] while in a study done in Paris (91%), patients were hospitalized based on their initial symptoms.[5] Hundred percent of patients were hospitalized in Fernandez-Ruiz,[14] Nair *et al.*[10] and The Columbia University Kidney Transplant Program.[8]

The most common presenting symptom we observed was fever, followed by cough, similar to other studies related to KTRs.[5,8,10,11,14,15] Fever was reported in less number of patients as an initial symptom in one study.[13] AKI developed in 75.8% of our patients, which was quite higher in number. AKI has been described in other studies also as 57%,[12] 50%,[10] 42%,[5] 40%[8] and 23%,[9] respectively.

In our study, KTRs developed symptoms ranging from mild-to-severe grade. Similar range of symptoms was also seen in other larger studies.[8,11,12,14,16] Severe disease was seen in 27.4% of patients, in our study. Compared to other studies from New York by Pereira *et al.*,[11] 44% of 46 KTRs had severe and 34 (54%) had mild-to-moderate disease, while in other study from New York (27%), Paris (22%) developed severe COVID-19 disease and required intubation[8] which was similar to our study.

Management of COVID-19 in KTRs has been somewhat complex because appropriate choice or optimal dosing of individual IS agents remains mostly incomprehensible. Optimizing dose of IS has been subjective, every institute followed their own algorithm. At our institute, we decreased the dose of antimetabolite by 50% in 67.7% of mild-to-moderate cases. In severe cases, we stopped antimetabolite in 17.7% of cases and decreased the dose of CNIs by 50% in 19.3% of severe cases. In comparison to Pereira *et al.*,[11] antimetabolite dose was reduced or held in 87%. In Akalin *et al.*[13], withdrawal of antimetabolites was done in 67% and withdrawal of tacrolimus in 17% cases. At the Columbia University Kidney Transplant Program[8] study also, withdrawal of antimetabolite was done in 71% cases. In Nair *et al.*[10] also, withdrawal of antimetabolite was done in 89%. In Fernandez-Ruiz[14], withdrawal of antimetabolite was done in 80%. In Azzi *et al.*[9], antimetabolite was stopped in 94% of cases.

In our study, we decreased the dose of CNIs by 50% in 19.3% of severe cases. In comparison to Pereira *et al.*[11], CNI's dose was decreased or held in 18%. In Akalin *et al.*[11], withdrawal of tacrolimus was done in 17% cases. In the Columbia University Kidney Transplant Program[8], tacrolimus and mycophenolate mofetil (MMF) were replaced with prednisolone in 7% cases. In Nair *et al.*[10], tacrolimus was discontinued in 9% cases, while in Fernandez-Ruiz[14] study, reduction in tacrolimus was done in 6/7 (86%). In Banerjee *et al.*[12] also, reduction of tacrolimus dose was done. No change in immunosuppression was done in 11.29% cases in our study, while in Nair *et al*.,[10] in 10% cases, immunosuppression was not changed and in the Columbia University Kidney Transplant Program[8] study immunosuppression was not changed in 7% of cases. In contrast to our study, several other studies steroids dose was decreased like Pereira *et al.*[11] and the Columbia University Kidney Transplant Program.[8]

Remdesivir was one drug which was used extensively in our study owing to the results seen in general population. It was used in 64.5% of cases in mostly moderate-to-severe grade. Its use was increased as pandemic progressed. In other studies, it was less commonly used. In Pereira *et al.*,[11] it was used in only 3% cases. In Azzi *et al.*,[9] it was given in 8% of cases. Tocilizumab was given in 3.2%

cases in our study. In comparison to this in Pereira *et al*.,[11] it was given in 20% of cases, in Alberici *et al*.[17] it was given in 30% of cases, whereas in Akalin *et al*.[13] it was in 5% of cases. In a study from Paris, it was given in only 2% of cases.[5] Difference in number of cases in which it was given can be due to the specific indication of its usage.

At the start of pandemic, hydroxychloroquine was given in almost all of the cases who tested positive for COVID-19 but later on its use was decreased gradually as per the series of reports published on its benefit in the disease. In our study, it was given in 8.06% of cases. Almost similar to our finding, a study done in Paris, hydroxychloroquine was given in 11% of cases.[5] But in studies such as Pereira *et al*.,[11] Alberici *et al*.[17] and Akalin *et al*.,[13] it was given in 91%, 95% and 67% of cases, respectively.

Patients who needed ICU admissions in our study were 15 (24.1%). Similar rates of ICU admissions were noted in other studies as well and varied between 20% and 30%.[10-13,17] In our study, mortality in KTR's developing COVID-19 was 14.5%. Four studies from New York in kidney transplant patients reported a mortality of 13%,[8] 28%,[13] 30%[10] and 35.4%.[9] Another report from Italy in transplant recipients with COVID-19 described an overall mortality rate among admitted patients of 25%.[17] In a study in Paris,[5] mortality rate was 24%. One study from the United Kingdom had mortality rate (14%) similar to our study.[12]

Conclusion

Transplant patients constitute a population more vulnerable to develop COVID-19. We are of the opinion that KTRs infected with COVID-19 should be monitored closely in the light of lowered immunosuppression. Presenting symptoms are similar to those of non-transplant individuals. Case by case must be evaluated carefully and managed according to age, risk factors, severity of infection, IS regimen, immune status and side effects.

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Conflicts of interest

There are no conflicts of interest.

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