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The Impact of COVID-19 on Renal Transplant Recipients in a Tertiary Care Centre in Tamilnadu

Martin Sebastian*, Poongodi Annadurai, Srinivasaprasad Nagalakshmi Dhanapal, Gokul Prasannan, Arjun Lal, Sujit Surendran, Edwin Fernando Merin and Thirumal Valavan Kalaiperumal

Department of Nephrology, The Tamil Nadu Dr. M.G.R. Medical University, Chennai, India

Corresponding author: Martin Sebastian, Department of Nephrology, Govt Stanley Medical College, The Tamil Nadu Dr. M.G.R. Medical University, Chennai, Inida, E-mail: martin00007@gmail.com

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Abstract

Background: The COVID-19 pandemic created havoc for all disciplines in medicine. Nephrologists, their patients and renal transplant recipients faced unique and challenging problems.

Aim: We aimed to study the epidemiology and short-term follow-up of COVID-19 positive renal transplant patients admitted to our hospital.

Methods: This was an observational study of 51 COVID positive renal transplant patients admitted in our center from the period of March 2020 to June 2021. Short-term follow-up of the survivors at 4 weeks of discharge was also done.

Results: Mean age was 40 yrs. Most common comorbidity was diabetes (17.6%); presenting symptom was fever (96.1%). Clinical severity of pneumonia ranged from asymptomatic (4%), mild (23%), moderate (4%) and severe (69%). Graft dysfunction was seen in 96.1%. Mortality was 33.3%. Altered mental status at presentation and severe COVID pneumonia was associated with mortality (p-value<0.005). Remdesivir therapy and immunosuppressant regimen change had significant effect on survival (p-value<0.005). At 4 weeks after discharge, 44% had persistent graft dysfunction.

Conclusion: Mortality was high in renal transplant recipients infected with COVID-19. Graft dysfunction was also common during COVID-19 infection in this population.

Keywords: Renal transplant; COVID-19; Graft dysfunction; Immunosuppressant regimen; Remdesivir therapy; Pneumonia

Introduction

The novel corona virus 2019 infection, which originated in the city of Wuhan, in Hubei province, China, in December 2019 shares close similarities in its genomic structure with the severe acute respiratory syndrome corona virus (SARS-CoV) that caused the SARS global pandemic in 2003 and the Middle East Respiratory Syndrome (MERS) epidemic in 2012 (MERS-CoV) and even closer similarities to bat SARS-like beta corona virus [1]. It has resulted in significant morbidity and mortality worldwide. Due to its widespread nature, COVID-19 was declared as a pandemic by World Health Organization on March 11, 2020.

In the general population, the median incubation period is estimated at 5.1 days and 97.5% of those who develop symptoms will do so within 11.5 days of infection. Nasopharyngeal swab samples appear to be more sensitive for diagnosis than oropharyngeal and sputum samples; given sensitivity limitations, multiple negative assays are often used for rule outs. Viral shedding may persist for weeks (~20 days). Nosocomial transmission is common. Ro (transmission kinetics) is ~2; this means that, without physical separation, 50% of the population must become immune to prevent spread in the community [2].

Transplant patients are particularly at a higher risk of contracting COVID-19 because of their immunosuppressed state and comorbidities [3]. For now the experience in the management of COVID-19 in the post-transplant population is limited. There are only few single center studies about this population from south India. We present an observational study of 51 COVID-19 RT PCR positive renal transplant patients admitted in a tertiary care center in south India.

Aim

We aimed to study the epidemiology and short-term follow-up of COVID-19 positive renal transplant patients admitted to our hospital.

Materials and Methods

The clinical study was approved by the ethics committee based on international standards of good clinical practice per local laws and regulations (Transplant Human Organ Act, India). Our study also abided by the declaration of Helsinki and

declaration of Istanbul principles. Written informed consent was obtained from all recipients. The diagnosis of COVID-19 was confirmed by real-time Reverse Transcription Polymerase Chain Reaction (RT-PCR) from nasopharyngeal (nasal) swab. Adult KTRs with COVID-19 (age >18 yrs) who were admitted were included in the study. Detailed clinical histories including co morbidities were recorded. Laboratory and radiological data were collected. Clinical severity and assessment parameters were divided the pneumonia into;

Mild

KTRs with mild symptoms including fever, cough, without shortness of breath or hypoxia and uncomplicated upper respiratory tract infections.

Moderate

Patients demonstrated clinical features of pneumonia including fever, cough, dyspnea, hypoxia with oxygen saturation (SpO2) <94% (range 90%-94%) on room air and respiratory rates of 24-30/min.

Severe

Patients had advanced signs of clinical pneumonia plus 1 of the following clinical criteria: Respiratory rate >30/min, severe respiratory distress and SpO2 <90% on room air.

Statistical analysis was performed using the Statistical Package for Social Science (SPSS) version 23. Continuous data are presented as median and Interquartile Ranges (IQRs) and mean SD; t tests were used to compare 2 groups. Categorical data were compared using χ^2 test. A P-value<0.05 indicated statistical significance. A Cox regression model was performed for multivariate analysis.

Results

There were a total of 51 COVID-19 positive renal transplant patients in the study. The mean age of this cohort was 41.4 years. There were 43 males (84.3%) and 8 females (15.7%). The median duration from transplant to the diagnosis of COVID-19 was 4 years. The baseline characteristics are shown in **Table 1.**

Table1: Demographics of study population. (Mean or n).

Variables	Total (n=51)	Survivors (n=33)	Non survivors (n=18)	p-value
Age	40	39	41.5	0.71
Male	43	26	17	0.23
Female	8	7	1	
Living donor	38	26	12	0.5
Deceased donor	13	7	6	
Induction agent				
No induction	24	18	6	0.302
Basiliximab	15	9	6	
ATG	12	6	6	
Comorbidities				
DM	9	8	1	0.04
HTN	3	3	0	
ACEI/ARB use	6	5	1	0.3
Recent rejection treatment	10	4	6	0.06

There were 13 deceased donor renal transplant recipients and 38 live related renal transplant recipients. The severity of COVID-19 infection is mentioned in **Table 2**. 10 patients had history of treatment for graft rejection recently. 9 patients had diabetes (17.6%). Most common presenting symptoms was fever (96.1%) followed by cough (90.2%) and breathlessness (72.5%). 4 patients had diarrhea as their presenting symptom (8%). 47 out of 51 patients had history of contact with COVID positive cases. Clinical severity of COVID-19 pneumonia ranged from asymptomatic (4%), mild (23%) and moderate (4%) to severe (69%). Oxygen therapy was required for 76% patients. Strategies to modify immunosuppressant's included discontinuation of anti-metabolites, reducing dose of CNI and stopping all immunosuppressant drugs in very sick cases. Discontinuation of

anti-metabolites without changes in calcineurin inhibitors and steroids was done in 45% patients. On recovery, the steroid was changed to the original dose and anti-metabolite was reintroduced at reduced doses in the first week after discharge. Remdesivir was given for 38 (75%) patients. 3 patients developed mucormycosis.

Table 2: Laboratory and therapy related data. (Mean or n).

Variables	Total (n=51)	Survivors (n= 33)	Non survivors (n= 18)	p-value
Clinical symptoms				
Fever	49	31	18	0.28
Cough	46	30	16	0.8
Breathlessness	37	20	17	0.01
Altered sensorium	4	0	4	0.005
Diarrhea	4	0	4	0.005
S. Creatinine				
Best SCr	1.1	1.2	1.1	0.59
SCr prior to COVID	2.4	1.8	3.3	0.012
SCr during COVID	3.7	2.4	5.9	0.003
Clinical severity				
Asymptomatic	2	2	0	0.005
Mild	12	12	0	
Moderate	2	2	0	
Severe	35	17	18	
AKI	49	31	18	0.28
Remdesvir	38	20	18	0.002
Oxygen therapy	39	21	18	<0.0001
Immunosuppressant drug change	38	20	18	0.002

Overall patient mortality was 33.3% (17 of 51). It was 100%(17 of 17) in patients requiring invasive ventilator support. Altered metal status at presentation and severe COVID pneumonia were significant risk factors for mortality. Immunosuppressant drug regimen change, Remdesivir and oxygen therapy had significant effect on survival. Demographic and therapy related data of survivors is mentioned in **Table 3.**

Table 3: Demographic and therapy related data of survivors. (Mean or n).

Variables	Total (n=33)	Graft recovered (n=18)	Persistent graft dysfunction (n=15)	p-value
Age	39	42.8	38.9	0.23
Male	26	13	13	0.312
Female	7	5	2	

Living donor	26	14	12	0.87
Deceased donor	7	4	3	
Induction agent				
No induction	18	8	10	0.443
Basiliximab	9	6	3	
ATG	6	4	2	
Co morbidities				
DM	8	4	4	0.96
HTN	3	2	1	
ACEI/ARB use	5	3	2	0.79
Recent rejection treatment	4	0	4	0.019
S. Creatinine				
Best SCr	1.2	1.04	1.3	0.06
SCr prior to COVID	1.9	1.6	2.12	0.11
SCr during COVID	2.5	1.9	3.02	0.005
Clinical severity				
Asymptomatic	2	1	1	0.018
Mild	12	10	2	
Moderate	2	2	0	
Severe	17	5	12	
Oxygen therapy	21	9	12	0.266
Immunosuppressant drug change	20	8	12	0.037

Graft dysfunction was seen in 96.1% of patients. 7 patients developed oliguric renal failure requiring dialysis of which 2 expired later in the course of disease. No significant risk factors were identified for graft dysfunction. Of the 34 patients who survived, 15 had persistent graft dysfunction after 4 weeks of follow-up. Severity of pneumonia, recent treatment for rejection and immunosuppressant drug change were risk factors for persistent graft dysfunction at 4 weeks. Severity of COVID-19 was an independent risk factor for mortality as per multivariate analysis.

Discussion

COVID-19 is a rapidly evolving disease with a high transmission rate and has changed our lives in an unprecedented way. The transplant patients are a special group that needs collaborative effort amid this global health crisis. Mortality was higher in transplant recipients infected with prior corona virus outbreaks [4]. The illness from COVID-19 in renal transplant recipients ranged from mild to severe and few patients presented with atypical symptoms [5].

The most common presentation was fever, which was similar to what was seen in 96.1% of the patients in our study. Zang et al., had shown that in general population and kidney transplant patients fever is the commonest presentation of COVID-19 disease [6]. Disease severity was also variable. In our study, 4% were asymptomatic, 23% of patients had mild disease, 4% had moderate disease and the remaining 69% had severe disease. 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 immunosuppressant's, 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 [6,7].

In the absence of a definite therapy or guidelines, the modification of immunosuppressant's and continuation of steroids along with other COVID-19 management strategies are recommended for KTRs [8,9]. The other COVID-19 treatment used in KTRs includes anti-virals, hydroxychloroquine, macrolides and Remdesivir. However, there are equivocal results for COVID-19 outcomes with these drugs in the general population and KTRs [10,11].

The reported incidence of AKI and abnormal renal parameters in COVID-19 patients in the general population is 3%-9% [12], while the risk of development of AKI in KTRs with COVID-19 is very high (42%) [13]. In our study we found that approximately 96.1% of KTRs with COVID-19 developed AKI. 36.7% of patients who developed AKI expired. 7 patients had oliguric renal failure requiring hemodialysis. They also succumbed to their illness. Severe pneumonia with hypoxia was the cause of death in all of them. Acute kidney injury in COVID-19 has been attributed to various factors including direct injury due to SARS-CoV-2, hemodynamic insults, cytokine related injury and coagulation dysfunction [14]. Histological lesions described in the native kidneys are acute tubular injury, pigmented tubular casts, focal segmental glomerulosclerosis (collapsing variant) and segmental glomerular fibrin thrombi and "viral-like" particles in the glomerulus and tubules [15]. The kidney allograft is at an additional risk of AKI due to the above COVID-19 related factors and transplant related factors like graft rejection and CNI toxicity. Histological data from allograft biopsies is lacking. Clinical features of acute tubular injury were seen in all of our patients in varying degrees. Evidence of graft rejection episodes in recipients with COVID-19 is lacking with only two studies have reported an incidence of 1% and 8% [16,17].

The four reported outcomes of COVID-19 in literature in KTRs are: (i) Uneventful asymptomatic disease, (ii) complete disease recovery, (iii) recovery with sequalae and (iv) death (due to active disease or sequalae) [18]. In our study mortality was 33%. Significant mortality was observed in mechanically ventilated patients in our study. 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) [7].

We did a short term follow-up of the survivors. Of the 34 patients who survived, 15 (44%) had persistent graft dysfunction. There is evidence suggesting that kidney function may not completely recover after COVID-19 in the general population. In a cohort of 1655 US veterans with AKI because of COVID-19, 47% did not recover to baseline by discharge [19]. Our data are in contrast with Paula et al., who reported 3-month outcome of 26 kidney transplant recipients with AKI during COVID-19, with all patients recovering to baseline at the end of follow-up [20]. In our study, recovery of kidney function was not associated with baseline co morbidities, use of renin angiotensin inhibitors, baseline immunosuppression, the severity of COVID-19, Remdesivir and presence of diarrhea during presentation. A study had shown the safety of Remdesivir in AKI and CKD population [21]. The persistent graft dysfunction in our study highlights the need for close monitoring of graft function in such patients. Transplant programs should do a case-by-case evaluation when carrying out a transplant surgeries [22].

We understand that our study has limitations as there was no uniform treatment protocol for COVID-19 positive patients and that treatment continued to evolve based on new evidence and new data from the growing number of COVID-19 published reports. It is possible that our data shows an underreporting of COVID-19 in transplant recipients as patients were treated at home with tele-consultation for mild febrile illness. Our report also focused on hospitalized patients and thus conclusions may not be broadly applicable to all patients diagnosed and managed in the outpatient setting. Our study could act as data of COVID positive renal transplant patients from south India and could add on to our knowledge in this cohort.

Conclusion

The COVID-19 pandemic has been challenging for kidney transplantation programs around the world, with a big impact on transplant policies and in the management of infected and uninfected patients. These patients have higher incidence of acute kidney injury and mortality compared to general population. Our study stresses on monitoring serum creatinine of the survivors as there was a high incidence of persistent graft dysfunction in them. Registries of COVID positive renal transplant patients could help us to understand and study this population better.

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