

Impact of Covid-19 on Survival among Kidney Transplant Patients in a Tertiary Care Centre in North Kerala – A Longitudinal Study

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ABSTRACT

BACKGROUND

In this study we wanted to measure the prevalence of Covid-19 disease among patients of renal transplant. The secondary outcome was to determine the demographic, clinical profile, and functional parameters of renal function and co morbidities associated with outcome in Covid-19 disease and to determine the predictors of mortality in patients who are post kidney transplant.

METHODS

A longitudinal study of 19 post-transplant patients with Covid-19 infection was conducted in our institute. The inclusion criteria included those patients who were post-transplant with age more than 18 years. The exclusion criteria were patients with graft failure and return to dialysis. The impact of Covid-19 on transplant patients was assessed. Various parameters including age, date of transplant, related or unrelated transplant, change in immunosuppression, comorbidities, graft function, radiological findings of Covid-19, dialysis requirement, and mortality was assessed. The data was analysed using PASW 18 statistical software. Qualitative variables were expressed in frequency and percentage. Quantitative variables as mean and standard deviation.

RESULTS

Mortality rates of patients with post renal transplant who developed Covid-19 infection was 23 %. The incidence of Covid-19 among transplant population was 3.8 %. In our series most of our patients had live related kidney donor transplantation. And the incidence of co morbidities like hypertension and diabetes was 57 % and 47 % respectively. The factors that was responsible for poor prognosis among transplant patients was graft dysfunction at the time of presentation and the presence of co morbidities. There was worsening of the mean graft functioning after the patient had recovered from Covid, and the mortality of patients on renal replacement therapy and patients on mechanical ventilation was very high.

CONCLUSIONS

Mortality rates among transplant patients was higher than the general population, and the factors responsible was graft dysfunction and co morbidities.

KEY WORDS

Covid-19, Post-Transplant, Mortality

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DOI: 10.14260/jemds/2022/21

How to Cite This Article:

Puthiyottil NT, Krishnan JE, Meleamadathil

S. Impact of Covid-19 on survival among

kidney transplant patients in a tertiary

care centre in North Kerala – a

longitudinal study. J Evolution Med Dent

Sci 2022;11(01):109-114, DOI:

10.14260/jemds/2022/21

Submission 12-07-2021,

Peer Review 20-07-2021,

Acceptance 22-01-2022,

Published 27-01-2022.

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BACKGROUND

The need for the study is that renal transplant patients are at high risk for developing Covid-19 infection due to chronic immunosuppressive treatment and associated factors like age, graft dysfunction, smoking and cardiovascular problems.

The novel coronavirus 2019 disease which first originated in the city of Wuhan, in China has infected more than 190 million people and caused more than 4 million deaths worldwide. There are multiple studies addressing the risk factors, clinical features, and prognosis of the disease have been published in the general population. With around 20 % of Covid cases having moderate to severe clinical manifestation and 5 % progressing to critical illness. The case fatality rates ranged in different studies, ranging from 1 % to 7 % in the general population. The presence of comorbidities such as old age, diabetes, hypertension, coronary artery disease, chronic lung disease, obesity have been identified as major risk factors for severe disease in the general population. However, the diagnosis and clinical course of the disease in kidney transplant recipients may differ from the general population due to the chronic immunosuppressed state and coexisting conditions. There is very little studies on the infectious course of Covid-19 in the kidney transplant recipient population. The prevalence of Covid-19 in the transplant population, when compared to the general population, the impact of co morbidities in these population and the progression of the disease in the same group of patients needs to be further analysed. The severity of the disease at the time of presentation and the impact of patient outcome in the change in immunosuppression are not defined in this specific group of patients. The outcome of patients with graft dysfunction at the time of presentation and the severity of the disease needs to be analysed. In this study, our intention was to analyse these important questions in this group of patients, from a single centre perspective and to correlate the same with the general population.

Objectives

1. To estimate the prevalence of Covid-19 infection in kidney transplanted recipients.
2. To determine the factors associated with outcome and mortality in Covid-19 disease.

METHODS

This longitudinal study was conducted in a single tertiary care centre of Northern part of Kerala. Renal transplant patients with age more than 18 years who attended the Nephrology OPD from March 2020 to December 2020 were enrolled and patients with graft failure and return to dialysis were excluded from the study.

Screening for Covid-19 was performed in symptomatic patients only. RT-PCR or antigen test was used for diagnosis. All Covid-19 positives were registered and monitored. Depending upon the severity of symptoms, patients were either admitted in hospital or managed on outpatient basis. All patients were systematically screened for clinical and biological parameters of Covid-19 infection, age, sex, time

after transplantation, body mass index, tobacco consumption, coexisting disease like diabetes, hypertension, asthma, COPD, cardiovascular diseases, post-transplant rejection episodes and current graft function and current immunosuppression. For patient with Covid-19 disease data collection included initial clinical manifestation, laboratory tests, CT scan of chest, concomitant diagnosis during hospital course, patient medication like antiviral therapy, immunosuppressive modification, oxygen support, invasive ventilation and KRT. The functional status was assessed by the renal function test.

Primary outcome was to measure the prevalence of Covid-19 disease among patients of renal transplant.

The patients were interviewed in the OP or in the Covid ward during admission, their progress noted, consent of patients was obtained during admission and ethical committee clearance obtained and convenient sampling taken.

The secondary outcome was to analyse the factors associated with Covid-19 and patient survival during the course of infection.

Statistical Analysis

Descriptive statistics were used to assess the baseline characteristics of the data. Qualitative variables were expressed in frequency and percentage. Quantitative variables as mean and standard deviation. Data was entered in MS Excel and analysed using PASW 18 statistical software.

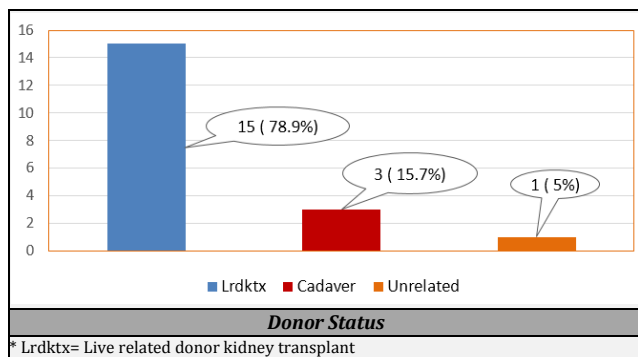
RESULTS

Renal transplant patients are at higher risk for critical Covid-19 infection, in view of chronic immunosuppressive therapy and co existing co morbidities. Here at Calicut Medical College, we identified 19 consecutive adult post-transplant patients who tested positive for Covid-19 either via an RTPCR or antigen test.

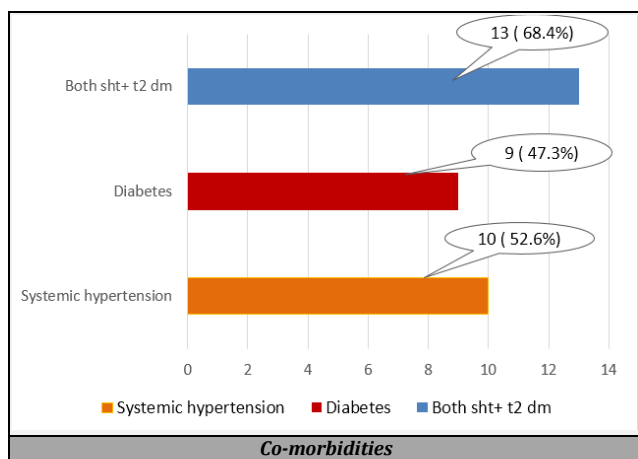
Of the 19 patients 17 were males (89.4 %) with a median age of 41.3 years, and age ranging from 23 to 61 years.

Of the 19 patients, 15 patients about 79 % had live related transplants. 3 patients about 15 % had cadaveric transplant. One patient had an unrelated transplant.

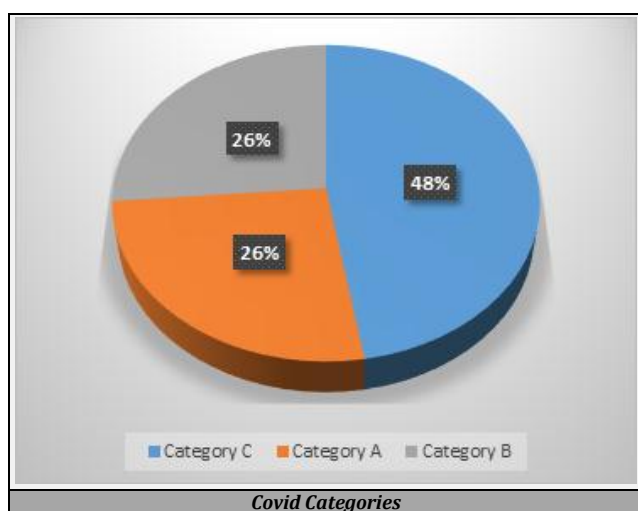
Predictor Variables	Outcomes of Covid-19	Survived	Died	(P - value)
Gender	M :17	12 (70.58 %)	5 (29.4 %)	
	F: 2	2 (100 %)	0	
Comorbidities	Yes 13	10 (76.9 %)	3 (23 %)	
	No 6	4 (66.6 %)	2 (33.3 %)	
Category based on severity	Category A + B 10	10 (100 %)	0	p value - 0.0530
	Category C 9	4 (44.4 %)	5 (55.5 %)	
Donor status	Live related kidney transplant 15	10 (66.6 %)	5 (33.3 %)	p value - .5304
	Unrelated + diseased Donor 4	4 (100 %)	0	
Graft dysfunction	No dialysis 13	12 (92.4 %)	1 (7.6 %)	
	Yes 10	5 (50 %)	5 (50 %)	p value - .0325
Required haemodialysis	No 9	9 (100 %)	0	
	Yes 6	2 (33.3 %)	4 (66.7 %)	p value - .0173
Required invasive ventilation	No 13	12 (92.4 %)	1 (7.6 %)	
	Yes 6	1 (16.6 %)	5 (83.3 %)	p value - 0.0005
Predictors and Outcomes of Post-Transplant Patients with Covid-19				



Of the total patients 57 % had hypertension and 47 % had diabetes mellitus. 68 % had both diabetes and hypertension.

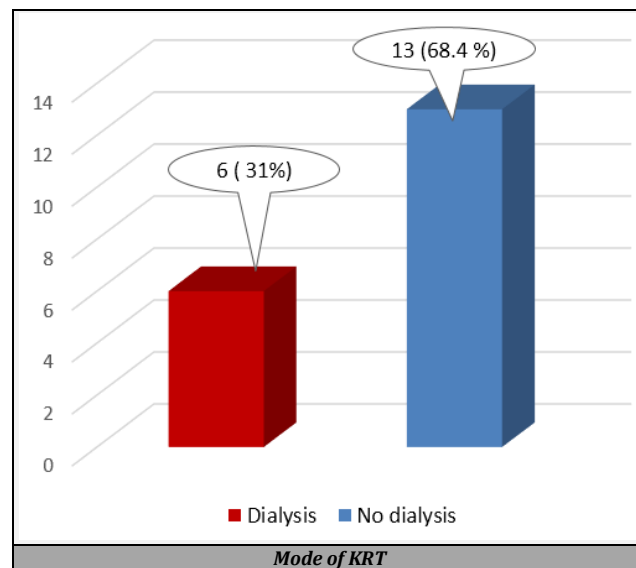


Out of the 19 patients, 48 % patients presented with severe symptoms, which was categorised as Cat C Covid, requiring either oxygen therapy or invasive / non-invasive ventilation. While 26 % had only mild symptoms and 26 % had no symptoms.



Among 19 patients who were included only 7 had radiology done in the form of chest x ray. Of these 7 patients 6 of these patients had significant x ray findings.

Of the 19 patients 6 required kidney replacement therapy which accounted for around 30 % of the patients and all of them had intermittent haemodialysis as the form of kidney replacement therapy.



5 of the patients expired following Covid related complications and all of them required mechanical ventilation before their death.

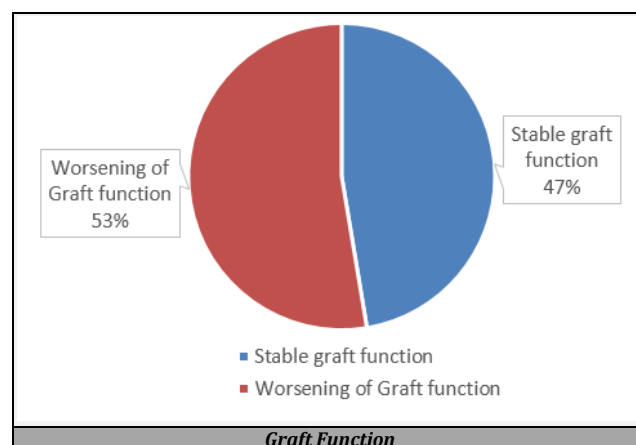
50 % of patients were on triple drug regimen with steroids, tacrolimus, and mmf. 3 patients with cadaver transplants had anti thymocyte globulin as an induction therapy. 3 patients were on steroids, aza and cyclosporine. 1 patient was on wysolone and tacrolimus, this patient had to stop mmf prior to Covid in view of gastrointestinal side effects. 1 patient was only on azathioprine and one patient was on steroid, mmf and everolimus.

Of the 19 patients 8 patients had stopped mmf during the course of Covid infection. The rest of them continued the original immunosuppressive therapy.

Of the 19 patients diagnosed with Covid-19, RTPCR was used as a diagnostic tool in 5 patients while antigen was used in the remaining 14 patients.

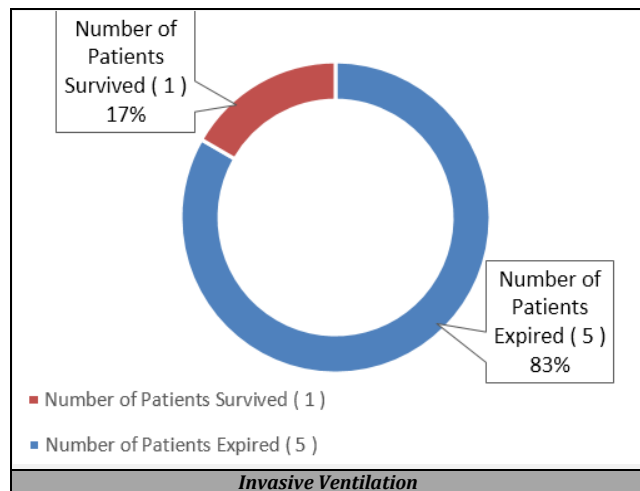
For one patient the duration of treatment required was around 1 month. 4 patients had a treatment duration greater than 10 days. While rest 14 patients turned antigen negative by day 10.

Normal graft function was seen in 9 of our 19 transplant patients which accounted for 47 % of the total patients. While the remaining 53 % of patients had graft dysfunction.

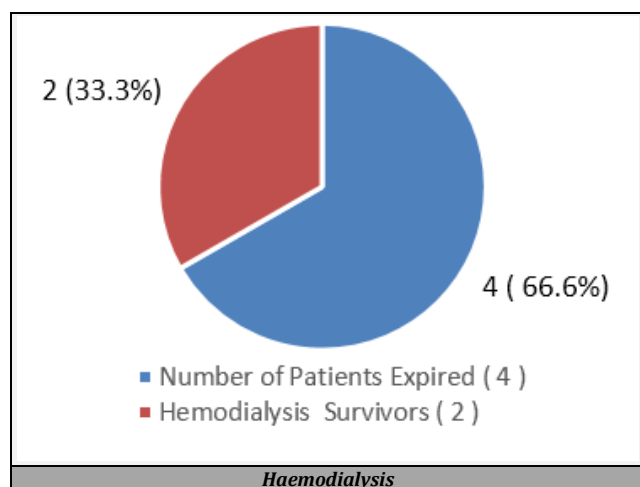


Of the 19 patients 6 required invasive ventilation i.e., around 31 % of total patients. Among them 5 patients

expired, which means around 83 % of ventilated patients expired. Only one patient survived invasive ventilation.



Renal replacement therapy in the form of haemodialysis was required in 6 patients. This accounted for around 31 % of the total patients. Of the 6 patients 4 expired. This accounted for 66 % of all patients who required haemodialysis.



So, to summarise, of the 5 patients who expired out of 19 patients, around 80 % that is 4 patients required haemodialysis. All of them required mechanical ventilation. All of the patients had graft dysfunction and all of them were males. All the patients had live related donor transplantation. None of the cadaver patients in our series expired and only one patient was diabetic, while 3 had hypertension as a co morbidity.

DISCUSSION

A study in France by Michelle Elias¹ et al. published in JASN on July of 2020, actively followed up 1216 patients from 2 hospitals. Of whom 66 patients around 5 % were identified as Covid positive, this was higher than in the general population which was around (0.3 %). Of the 66 patients 64 patients had diseased donor transplantation. 16 patients of the 66 who had Covid-19 expired, which accounted for about 24 % of patients. Mortality was higher in the invasive ventilation

group. 73 % of the invasive ventilation group and 10 % of the non-invasive ventilation group expired. Diabetes mellitus was seen in 12 out of 66 patients which accounted for 18 % of the population. 7 patients required RRT and all of them were mechanically ventilated. Prior graft dysfunction was not evaluated in the study.

In another study published in New England Journal of Medicine, by Enver Akalin² et al. in Montefiore Medical Centre, it was identified that 36 transplant recipients were Covid-19 positive. Of whom 27 recipients had deceased donor transplantation which is around 75 %. 8 patients who were in stable condition without major symptoms around (22 %) and 28 (78 %) patients were admitted in hospital. 27 of the hospitalised patients (96 %) had radiological findings of viral pneumonia and 11 (39 %) received mechanical ventilation. 6 patients (21 %) received renal replacement therapy.

At a median follow up of 21 days 10 of the 36 patients (28 %) and 7 of the 11 patients who were intubated (64 %) had died. 34 recipients (94 %) had hypertension, 25 (69 %) had diabetes mellitus, 13 (36 %) had a history of smoking tobacco or were current smokers, and 6 (17 %) had heart disease as co morbidities. Graft dysfunction prior to the recent Covid infection was not analysed in this study.

In a case report by Muhammed Ahmed Elhadeedy³ et al. from Sheffield kidney Institute, of 8 cases of Covid-19 infection of patients who were post-transplant two patients had acute kidney injury and one of them required haemodialysis as a form of renal replacement therapy. One patient was managed at home and 7 required admission and of the 7 patients admitted one patient required intensive care admission, where she required mechanical ventilation. Of these patients 4 had hypertension, one had diabetes mellitus, one had bronchial asthma and one patient had a history of malignancy. There was no mortality in this study.

In a cohort of 13 transplant centres in India which include 250 covid positive transplant recipients by Vivek B.Kute⁴ et al. 226 of them were living donor transplants and 24 was deceased donor transplants. Most common comorbidities included 210 patients (84 %) with arterial hypertension and 80 patients (32 %) with diabetes. The clinical severity ranged from asymptomatic 15 patients (6 %), mild symptoms in 150 patients (60 %), moderate symptoms in 50 patients (20 %) and severe symptoms in 35 patients (14 %). Risk factor for mortality included older age, dyspnoea, severe disease, obesity and allograft dysfunction. Overall patient mortality was 29 patients (11.6 %). Mortality rates increased to 47 % (25 of 53) for patients in the Intensive Care Unit and 96.7 % (29 of 30) for patients on mechanical ventilation.

In another study published in March 2020 in Kidney International by Debasish Banerjee et al.⁵ 7 cases of Covid-19 kidney transplant recipients, 2 patients were managed on an outpatient basis, but the remaining five required admission and 4 in intensive care unit. 3 patients with severe disease were diabetic. There was one mortality in this study.

In another study by Ozgur Akin⁶ Oto et al. published in BMC Nephrology predicting the outcome of Covid-19 infection in kidney transplant recipients among 109 patients, males: females were 63: 46. Acute kidney injury developed in 46 patients with Covid-19 accounting for about 42 % patients and 4 of these patients 3.7 % required renal replacement therapy. A total of 22 patients that is around 20.2 % patients were admitted in the Intensive Care Unit, and 19 patients that

is around 17.4 % required invasive mechanical ventilation and 14 patients around 12.8 % died. Patients admitted in the intensive care unit were significantly older above the age of 60 years. Multivariate analysis identified presence of ischemic heart disease and initial serum creatinine levels as independent risk factors for mortality, whereas age over 60 and initial serum creatinine levels were independently risk factors for Intensive Care Unit admission.

In a study by Alina Dacianaelec⁷ et al. published in International Journal of Infectious Diseases, in which 42 transplant recipients with Covid-19 were reviewed, some of them were receiving antiretrovirals with $n = 8$ or remdesivir of $n = 10$. Most patients were males around 71 % and their median age was 52 years. The median glomerular filtration rate in these patients as 56 ml / min. Regarding disease severity 36 % had mild disease, 19 % had moderate disease, 31 % had severe disease and 12 % had critical disease. Seven patients around 16.6 % died during hospitalisation. Acute kidney injury was found in 24 % of kidney transplant recipients at admissions. Upon discharge estimated glomerular filtration rate increased in 32 % and decreased in 39 % of kidney transplant recipients compared with the admission rate. The decrease was more prevalent in the remdesivir group compared with kidney transplant recipient without any antiviral treatment. Most patients 62 % returned to baseline glomerular filtration rate values one month of discharge. The proportion was similar between the patients receiving antiviral treatment and those not receiving this treatment.

In our study, we followed up 500 post-transplant patients over our study period, we identified 19 patients who suffered from Covid-19. The study found a mortality of 5 patients which was 26.3 %. In our series 15 patients (79 %) had live related kidney donor transplants and 3 patients (15 %) had diseased donor transplant and one patient had an unrelated donor transplant. In this study the percentage of diseased donor transplants were much lower than other comparable studies. The co morbidities were hypertension in (57 %), diabetes in (47 %) and 68 % had both the co morbidities. 47 % of patients had severe symptoms, 26 % had mild symptoms and another 26 % were asymptomatic. Normal graft function was seen in 9 out of 19 patients, which accounted to 47 % of the total patients, while 53 % of the patients had graft dysfunction. 6 patients required invasive ventilation of which 5 patients expired amounting to (83 %). While one patient survived. Renal replacement therapy was required in 6 patients of whom 4 patients expired (66 %). Mean graft function before Covid was 1.93 ± 0.837 with a range between 1 to 4. After Covid the mean graft function worsened to 3.88 ± 2.87 with a range between 1 to 11. In our study the factors that led to mortality were severe Covid-19 infection, requirement of mechanical ventilation and graft dysfunction were observed in all the deceased. Renal replacement therapy requirements were seen in 4 of the 5 and co morbidities were seen in 3 of the 5 patients (60 %).

Covid-19 poses multiple challenges in patients who are kidney transplant recipients. Post transplantation the recipients are at increased risk for acquisition of Covid-19 because they are in an immuno-compromised state and they are also at an increased risk of transmitting the disease to their care givers and health care providers. The clinical manifestations of Covid-19 in kidney transplant recipients is

variable and generally similar to those observed in the non-immuno-compromised patients. The approach to diagnosis is also similar to the general population where rapid antigen testing or polymerase chain reaction being used. In transplant patients the signs and symptoms may be subtle, with rapid progression of the disease requiring mechanical ventilation and renal replacement therapy in a greater proportion of patients than in the general community. The approach to management that is the use of anti-virals and supportive care was similar to the general population although careful attention should be paid to potential drug-drug interaction and the effect of immunosuppressive regimen. Changes in the immunosuppressive regimen are generally individualised based upon the disease severity and specific regimen used, the severity of covid infection and the risk of acute allograft rejection. Some kidney transplant recipients recover without reduction in immunosuppression, while others with severe disease may progress to death even with reduction of immunosuppression. In our centre antimetabolites were stopped in patients with severe Covid disease. Patients with co morbidities like hypertension and diabetes mellitus were at a higher risk of progression of Covid-19 disease, and the need for invasive ventilation and renal replacement therapy was more in this subgroup of patients. General measures in the form of cleaning hands often, coughing or sneezing in your bent elbow, avoid touching your eyes, nose and mouth, limiting social gathering and time spent in crowded places, avoiding close contact with someone who is sick, and clean and disinfect frequently touched objects and surfaces and to wear masks while in public, and other prevention strategies that are applicable for the general population are also advised to patients who are post renal transplantation. The control of comorbidities is also recommended as there is higher risk of progression of disease with Covid-19 patients who have co morbidities. All transplant recipients are eligible for vaccination, unless contraindicated in the setting of hypersensitivity to the vaccine or to its components. The ideal timing for vaccination remains uncertain as of now.

CONCLUSIONS

The incidence of Covid-19 among patients in the transplant population was around 3.8 % while the average prevalence of Covid-19 in India is around 2.3 %. The patients who had complications of Covid-19, had graft dysfunction at the time of presentation, or had co morbidities. Mortality rates was around 23 % while in the general population the mortality rates among Covid-19 patients was around 1 %. The immunosuppressive medications need to be adjusted depending on the severity of the disease. Antimetabolites like MMF and azathioprine in patients with severe disease were stopped. General Covid-19 appropriate behavioural measures recommended, in the form of cleaning hands often, coughing or sneezing in your bent elbow, avoid touching your eyes, nose and mouth, limiting social gathering and time spent in crowded places, avoiding close contact with someone who is sick, clean and disinfect frequently touched objects and surfaces, to wear masks while in public, control of co morbidities, and tele consultations on follow up whenever possible so as to reduce risk of contamination.

Limitations

Our study had several limitations. It was a single centre study, which did not allow us to broaden the horizon of this study to other centres. The study period was short and there was no follow up of patients after discharge from the hospital and hence it did not depict the complete course of the disease. Our study was a longitudinal study and changes in immunosuppression are not a part of randomised trials, and the therapeutic interventions were only descriptive in nature.

Data sharing statement provided by the authors is available with the full text of this article at jemds.com.

Financial or other competing interests: None.

Disclosure forms provided by the authors are available with the full text of this article at jemds.com.

REFERENCES

- [1] Elias M, Pievani D, Randoux C, et al, Covid-19 infection in kidney transplant recipients: disease incidence and clinical outcomes. *J Am Soc Nephrol* 2020;31(10):2413-23.
- [2] Akalin E, Azzi Y, Bartash R, et al. Covid-19 and kidney transplantation. *Engl J Med* 2020;382(25):2475-7.
- [3] Elhadey MA, Marie Y, Halawa A. Covid-19 in renal transplant recipients: case series and a brief review of current evidence. *Nephron* 2021;145:192-8.
- [4] Kute VB, Bhalla AK, Guleria S, et al. Clinical Profile and Outcome of Covid-19 in 250 Kidney Transplant Recipients: A Multicenter Cohort Study From India. *Transplantation* 2021;105(4):851-60.
- [5] Banerjee D, Popoola J, Shah S, et al. Covid-19 infection in kidney transplant recipients. *Kidney Int* 2020;97(6):1076-82.
- [6] Oto OA, Ozturk S, Turgutalp K, et al. Predicting the outcome of Covid-19 infection in kidney transplant recipients. *BMC Nephrol* 2021;22(1):100.
- [7] Elec AD, Oltean M, Goldis P, et al. Covid-19 after kidney transplantation: Early outcomes and renal function following antiviral treatment. *Int J Infect Dis* 2021;104:426-32.