ORIGINAL ARTICLE

A Single Centre Case-Series of Covid-19 Infection in Kidney Transplant Recipients

Tushar D, Bavikar P, Shinde N, Wakhare P, Bale C, Sajgure A
Dr D.Y Medical College, Hospital and Research Institute, Sant Tukaram Nagar, Pimpri, Pune, Maharashtra, India.

ABSTRACT

INTRODUCTION: Severe acute respiratory syndrome coronavirus (SARS-CoV) has mutated over time, affecting its virulence, pathogenicity and disease severity. In December 2019, a new coronavirus (SARS-CoV-2) has emerged causing a disease known as coronavirus disease (COVID-19). The COVID-19 has a broad spectrum of severity ranging from an asymptomatic to a severe acute respiratory syndrome requiring mechanical ventilation. COVID-19 is often more severe in people aged 60 years or more, or those with health conditions like lung or heart disease, diabetes, or conditions that affect the immune system including kidney transplant recipients. In this case series, we presented our experience with 17 kidney transplant recipients who had COVID-19 infection. In India, COVID-19 peaked twice: once between August and November 2020, and again between March and June 2021. Thus, there was paucity of COVID-19 data in kidney transplant recipients in India during these times. **MATERIAL AND METHODS:** Our case series constituted a retrospective observational study involving 17 kidney transplant recipients who experienced COVID-19 infection from November 2020 to September 2021 at a solitary tertiary care center in Pune. Within our institution, the nephrology team assessed kidney transplant recipients with COVID-19 for appropriate immunosuppression dosing, renal drug clearance when deemed necessary, and overall well-being. Treatment for COVID-19 adhered to institutional protocols. **RESULTS:** In our case series, majority of the patients (n=13) had COVID-19 in March 2021 to July 2021 and the commonest presenting symptoms were fever and cough. Out of 17 kidney transplant recipients included in this case series, 13 patients survived while 4 patients succumbed to infection. **CONCLUSION:** An individualized, case-based approach to managing transplant recipients with COVID-19 is crucial for achieving favorable clinical outcomes.

Keywords
COVID-19 infection, kidney transplant recipients (KTRs), India

Corresponding Author
Dr. Purva Bavikar
Dr D.Y Medical College, Hospital and Research Institute, Sant Tukaram Nagar, Pimpri, Pune, Maharashtra, India, 411018.
Email: 3purva@gmail.com

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INTRODUCTION

Kidney transplantation recipients are one of the most adversely affected group due to COVID-19 pandemic. As per the government of India advisory, the transplant program was suspended during the national lock down between March 23, 2020 until July 31, 2020. Pune was amongst the worst-hit metropolitan cities of India during COVID-19 pandemic which witnessed a staggering 19,525 number of deaths due to COVID-19 as of October 13, 2021.[1] The approach to COVID-19 infection evolved rapidly worldwide from early 2020 until late 2021. Our institute protocols were largely based on "Revised Guidelines on Clinical Management of COVID-19"[2] published on March 31, 2020 by Government of India, Ministry of Health and Family Welfare and "Maharashtra COVID-19 Task Force Recommendations for the management of hospitalized COVID-19 patients"[3] published on March 23, 2021. This case series provided a retrospective analysis of clinical data of kidney transplant recipients suffering from COVID-19 and managed at a tertiary care centre in Pune. We reported a total of 17 RT-PCR (Real time reverse transcription polymerase chain reaction) confirmed COVID-19 positive kidney transplant recipients (KTRs) and their clinical outcomes.

MATERIAL AND METHODS

Our study was a retrospective observational, case series of 17 KTRs with COVID-19 infection describing their clinical presentation, graft function, immunosuppression dosing, treatment given and clinical outcomes. Patient medical records between November 1, 2020 to September 30, 2021 were obtained from Medical Records Department of the hospital. Kidney transplant recipients, who either visited the outpatient department or admitted at a tertiary care centre in Pune with COVID-19 infection confirmed by RT-PCR were included in this case series. We also reviewed the non-contrasted high resolution computed tomography (HRCT) thorax findings report as per the 25 point- CT-severity scoring system (chest), described by Ghufran Araf Saeed.[4]

All KTRs in the study underwent investigations like COVID-19 RT-PCR, hemogram, serum urea, creatinine, electrolytes, blood gas analysis, urine dipstick, urine protein creatinine ratio, liver function tests, prothrombin time, activated partial thromboplastin time (aPTT), serum lactate dehydrogenase, D-dimer and ferritin levels, ultrasonography of abdomen and chest X-ray. Special investigations like Interleukin-6 (IL-6) levels, graft vessel doppler, HRCT chest, echocardiography, blood and urine cultures were done as per treating physician's discretion. Data was compiled and analysed on MS Office Excel Sheet (v 2019, Microsoft Redmond Campus, Redmond, Washington, United States). Data of 17 KTRs were analysed with respect to their age, clinical presentation, presence of diabetes, baseline creatinine, organ donor (live -related or deceased), timing of COVID-19 infection post kidney transplant, graft function during the infection, immunosuppression dose-modification, need for ventilation support, admission to intensive care unit and clinical outcomes.

RESULTS

We classified KTRs with COVID-19 infection as per disease severity into mild, moderate and severe. KTRs with fever and/or upper respiratory tract infection (URTI) symptoms without hypoxia were either isolated at home or admitted in COVID-19 ward (n=9). KTRs with a respiratory rate of 24 breaths per minute or more, or hypoxia (SpO2 less than 85%) were admitted in a step-down critical care unit (n=2). The critically ill KTRs requiring non-invasive ventilation (BiPAP), or mechanical ventilation were hospitalized in the intensive care unit of COVID-19 (n=6). The COVID-unit ward and step-down critical care unit were located on the same floor. In addition, the COVID-19 RT-PCR positive KTRs indicated for hemodialysis were dialyzed at the bedside in our institute as there were two portable dialysis water systems with a storage capacity of 200 litres reserved for the usage of COVID-19 patients. A new dialyzer was used for each hemodialysis session. In our case series, the median age of KTRs was 35 years and majority of the KTRs were male (14 subjects).

Majority of our studied KTRs received allograft from a living-related-donor (13 KTRs) whereas only 4 received graft from deceased-donor. The minimum duration of onset of COVID-19 infection post kidney transplant was three months and the maximum was 180 months, with a median duration being 27 months and an average of 49.41 months. Out of 17 studied COVID-19 KTRs, thirteen survived and four succumbed. Out of 13 survived KTRs, four were dialysis dependent whereas nine recovered from the illness and successfully discharged from the hospital. All relevant clinical data of all KTRs has been tabulated in Table I Clinical (Profile of KTRs Succumbed to COVID-19 Infection), Table II (KTRs Requiring Hemodialysis) and Table III (KTRs Managed Conservatively).

Out of four KTRs who died due to COVID-19, three patients were living-donor recipients who deceased at 3, 35 and 55 months respectively after the kidney transplant whereas one deceased-donor-renal-allograft recipient died at 19 months post kidney transplant. Intravenous (IV) injection Remdesivir was given to three KTRs; 200 mg on day 1 followed by 100 mg for the next 3 days with the 4th and the 5th dose given on alternate days.

Patient 1: A 35 year-old, male with end stage renal disease (ESRD) requiring maintenance hemodialysis with double vessel coronary artery disease (2VD) who were managed with percutaneous coronary artery stenting one year prior to kidney transplantation. In February 2021, the patient

Table I: Clinical profile of Kidney Transplant Recipients Succumbed to COVID-19

Patient	1	2	3	4
Age (years)	35	41	51	33
Sex	Male	Male	Male	Male
Donor	Mother	Deceased	Wife	Father
Comorbidities	Ischemic Heart Disease, post PTCA	Hepatitis C (HCV Positive)	Diabetes	Hypertension
Cause of End stage renal disease	?Chronic Glomerulonephritis	Chronic tubulointerstitial disease	ADPKD, Post B/L Nephrectomy with old abdominal Tuberculosis	FSGS (biopsy proven)
Presentation of COVID-19 infection	Fever, Dyspnea	Fever, dry cough,	Fever, cough, dyspnea	Fever, epistaxis, dyspnea
(COVID-19) Time since transplant	3 months	19 months	35 months	55 months
Month of COVID-19 infection	May 2021	April 2021	October 2021	December 2020
No. of days from presentation to death	6	7	15	21
Steroid	IV Methylprednisone at 80 mg/d	IV Methylprednisone at 80 mg/d	Prednisolone 5 mg/d. On day 7 switched to inj Hydrocortisone 300 mg/d	Inj Methyl-prednisone 80 mg/d, switched to Hydrocortisone 300 mg/d on day 6
Tacrolimus	6 mg/d	4 mg/d	1 mg/d	2.5 mg/d
Mycophenolate sodium	discontinued on day 2	discontinued on day 3	halved to 360 mg/d until day 7, stopped on Day 7	Stopped on Day 7
If RRT (Hemodialysis) needed	No	No	No	No
Baseline Creatinine (mg/dL)	1.7	1.7	0.55	2.8
Graft function (Sr Creatinine [mg/dL]) on COVID-19	3	2.9	1.78	3.1
Days from onset of illness, needing Ventilatory support	Limited Oxygen supply. Referred to higher centre, got intubated and put on Mechanical ventilation on Day 6	Limited Oxygen supply. Referred to higher centre, got intubated and put on Mechanical ventilation on Day 7	Day 9 - started on NIV Day 13 - Mechanical Ventilation	Day 3 - High flow Oxygen Day 10 - NIV Day 12 - mechanical ventilation

ADPKD - Autosomal dominant polycystic kidney disease
FSGS - Focal segmental glomerulosclerosis
NIV - Non invasive ventilation
PTCA - Percutaneous trans-luminal coronary angioplasty

underwent kidney transplantation with his mother as the donor. A month post transplantation, he developed acute coronary syndrome and was successfully discharged after being managed conservatively with heparin injection and antiplatelet therapy. In April 2021 he developed COVID-19 infection requiring mechanical ventilation. His serum creatinine increased to 3 mg/dL during infection and mycophelonate sodium was discontinued on day 2 of hospitalization as per institute protocols. The patient was transferred to another hospital which had ventilator support, as he required mechanical ventilation. He did not undergo any form of renal replacement therapy during the course of hospitalization. The patient succumbed on Day 6.

Patient 2: A 41-year-old male with a history of ESRD on maintenance hemodialysis since 2017 who underwent deceased donor kidney transplantation in 2019. He was a known case of hepatitis C (HCV) and his HCV viral load tested two months prior to COVID-19 infection as per routine protocol was undetectable. He presented to the emergency room with 3-days history of fever with dry cough and dyspnea. On presentation his vitals were stable with SpO2 under room air of 92%, serum creatinine of 2.9 mg/dL and a urine output of 3-4L/day. He was transferred to critical care unit which had availability of ventilator as his condition worsened within 6 hours of admission.

He was on non-invasive ventilation (NIV) for the first 2 days, mycophenolate sodium was reduced to 180 mg/day from 720 mg/day. On Day 3, mycophenolate sodium was discontinued and antibiotics were stepped up. On day-7 of admission, he had a emergency mechanical ventilation. However, despite of all supportive measures his clinical condition deteriorated and pronounced death on the same day.

Patient 3: A 51-year-old-male with autosomal dominant polycystic kidney disease and abdominal tuberculosis who had bilateral nephrectomy and underwent spousal kidney transplant in 2018. He was on triple immunosuppression maintenance dose as described in Table I and was also taking short acting insulin for post-transplant diabetes mellitus. He presented to outpatient department in September 2021 with a 1-day history of fever. Initially he was admitted to the COVID-19 ward as he was comfortable under room air. On day 4 of admission his SpO2 dropped to 88% and 6L/min oxygen was administered. However, his condition progressively worse. On day 9 of admission, he was put on BiPAP mode of ventilation and on day 13, he was electively ventilated with mechanical ventilation. He was previously taking 720 mg/ day mycophenolate sodium which was reduced to 360 mg/ day on day 4 and discontinued on day 7. Tacrolimus was discontinued on day 13. Serial monitoring of LDH, D-dimer, IL-6 and ferritin, were suggestive of a cytokine storm. On day 14, he was anuria on triple inotropic support and mechanical ventilation. His condition rapidly deteriorated and was pronounced death on day 15 of admission. Throughout hospitalization his graft function was satisfactory until day 14 when he became anuric and his serum creatinine had risen to 1.5 mg/dL (baseline creatinine - 0.55 mg/dL).

Patient 4: A 33-year-old-male with ESRD secondary to biopsy-proven focal segmental glomerulosclerosis (FSGS) on maintenance hemodialysis and a history of father-to-son kidney transplantation done in 2015. The patient presented with history of fever, cough, dyspnea and epistaxis in December 2020. He required 15L/min oxygen by day 3 of admission followed by BiPAP mode of NIV on day 10 and mechanical ventilation on day 12 and continued to be on mechanical ventilation for total of 9 day-7 of admission, mycophenolate sodium was discontinued. His graft function was optimal throughout his 21-day period of hospitalization. On day 21, he was pronounced death after developed septic shock and cardiac arrest. Amongst KTRs who survived, the median age was 41 years and the median duration of presentation post-transplant was 27 months. As described in Table II and III, four KTRs developed graft dysfunction requiring maintenance hemodialysis whereas 13 KTRs were conservatively managed with good graft function.

Table II: Clinical Profile of Kidney transplant recipients who were dialysis dependant during or after COVID-19 infection

Patient	5	6	7	8
Age (years)	17	32	32	46
Sex	Male	Female	Male	Female
Donor	Grandmother	Mother	Mother	Father
Cause of End stage renal disease	Nephronophthisis	Nephrolithiasis (calcium	? Chronic glomerulonephritis	FSGS, biopsy proven
Graft biopsy	prior to COVID-19 : Crescentic glomerulonephritis	Not done	post COVID-19 : Acute tubular injury with the background of chronic allograft nephropathy	prior to COVID-19 : active antibody mediated rejection
Presentation of COVID-19 infection	Fever, cough, dyspnea, hemoptysis	Fever, cough, oliguria,	Fever, diarrhea, nausea, vomiting	Fever, cough, dyspnea
(COVID-19) Time since transplant	27 months	29 months	22 months	25 months
Month of COVID-19 infection	November 2020	April 2021	May 2021	September 2021
Steroid dose during COVID-19	Prednisolone 15mg (switched to MPS	Inj MPS 80 mg/d	Prednisone 15 mg/d	Prednisone 20 mg/d
Tacrolimus dose during COVID-19	3 mg/d	Cyclosporine 50 mg/d	2 mg/d	1 mg/d
Mycophenolate dose during COVID	360 mg/d	Stopped	Stopped	Stopped
If RRT (Hemodialysis) needed	3 months post COVID 19 infection	During COVID-19	2.5 months post COVID-19	During COVID-19 infection
Baseline Creatinine (mg/dL)	2.4	0.8	2.4	1.2
Sr Creatinine (mg/dL) during	3.44	7.4	3.2	8.4

FSGS - Focal segmental glomerulosclerosis
MPS - Methylprednisone
RRT - Renal replacement therapy

Patient 5: A 17-year-old-male with history of kidney transplantation in 2018 in which his grandmother being renal allograft donor. In November 2020, he presented with 3-day history of high grade fever, cough, breathing discomfort. He was admitted to COVID-19 ward for 10 days when his COVID-19 RTPCR was noted to be positive. His baseline creatinine since transplantation was 2.4 mg/dL which rose to 3.4 mg/dL during the admission. His mycophenolate sodium was reduced to 360 mg/day whereas prednisone and tacrolimus were continued. He received treatment as per institutional protocol and was discharged on day 10.

One month later he developed hemoptysis and was managed conservatively. Since then he had a rising trend of serum creatinine. In February 2021, his serum creatinine rose to 5.4 mg/dL despite on low dose maintenance of triple immunosuppression. He then developed clinical features suggestive of fluid overload and was started on maintenance hemodialysis twice weekly. Prior to developing COVID-19 his allograft biopsy in September 2021 was suggestive of crescentic glomerulonephritis and he had undergone five sessions of plasmapheresis.

Patient 6: A 32-year-old-female with history of kidney transplant in 2017 was admitted in April 2021 after being tested positive for COVID-19 when she presented with fever, diarrhea, vomiting and oliguria. Her serum creatinine was 7.4 mg/dL and blood urea of 170 mg/dL. On day-2 of admission, she was started on hemodialysis. Her serum creatinine performed six months prior to COVID-19 infection was recorded as 0.8 mg/dL. During COVID-19 infection, mycophenolate sodium was discontinued, cyclosporine was reduced to 50 mg/day and steroid was continued. An allograft biopsy was not done due to financial constraints. She continued on twice weekly hemodialysis and on regular follow-up.

Patient 7: A 32-year-old-male with history of kidney transplantation in 2018 was tested positive for COVID-19 RTPCR in 2021. He presented with nausea, vomiting and diarrhea and was advised for home management. He was advised for supportive care and adequate hydration. His creatinine during COVID-19 infection was 3.2 mg/dL and he remained asymptomatic. In June 2021, 2-months after tested positive for COVID-19 during his follow up in our institute, his serum creatinine increased to 6.4 mg/dL and urine output decreased to 2 litre/day. After 3-days of pulse -therapy with 500 mg/day methylprednisolone and adequate hydration his creatinine decreased to 4 mg/dL. He underwent allograft biopsy which was suggestive of acute tubular injury with a background of chronic allograft nephropathy. In July 2021, he was started on twice weekly maintenance hemodialysis due to persistent decline in renal function.

Patient 8: A 46-year-old female with biopsy-proven focal segmental glomerulosclerosis (FSGS) causing ESRD had kidney transplantation in 2019. In August 2021, she was diagnosed to have active antibody mediated rejection. She underwent five sessions of plasmapheresis and immunosuppression dose modification after which her creatinine plateaued to 5 mg/dL. In September 2021 she was tested positive for COVID-19 RTPCR when she presented with fever, cough, dyspnea. Her serum creatinine was 8.8 mg/dL and she had severe metabolic acidosis.

She underwent three sessions of acute hemodialysis and was continued on twice weekly maintenance hemodialysis. Clinical analysis of KTRs with COVID-19 infection managed conservatively is described in Table III. Mean age of this category of KTRs was 39.2 years with minimum age 21 years and maximum age 60 years. Out of 9 KTRs managed conservatively majority were male (8 KRTS) and received allograft from live related-kidney donors (8 KRTS). Among the 9 KRTS, one of them had a history of diabetes before undergoing transplantation. Table III describes patient-wise immunosuppression modification.

DISCUSSION

This case series provides a thorough retrospective analysis of 17 RT-PCR positive COVID-19 of kidney transplant recipients (KRTs). From the observation, majority of the cases in our institution were affected during year 2021 than 2020. In India, COVID-19 vaccination roll out programme was started on January 16, 2021. Thus, all patients in the study had not received the COVID-19 vaccination. The mean duration of COVID-19 infection

Table III: Clinical Profile of Kidney transplant recipients with COVID-19 infection, who were managed conservatively

Patient	9	10	11	12	13	14	15	16	17
Age (years)	22	53	21	34	44	49	60	28	42
Sex	Male	Male	Male	Male	Male	Male	Female	Male	Male
Donor	Mother	Deceased	Mother	Brother	Mother	Mother	Mother	Grandfather	Mother
Diabetes	No	Yes	No	Yes	No	No	No	No	No
Cause of End stage renal disease	NSAID Nephropathy	Diabetic Nephropathy	Chronic Glomerulonephri-tis	Unknown	Unknown	Unknown	Unknown	Unknown	?Chronic Glomerulonephri-tis
Graft Biopsy	3 months post COVID-19	Not done	Not done	Not done	Not done	Not done	Not done	Prior to COVID 19	Not done
Presentation of COVID-19 infection	Fever, cough, sore throat, diarrhoea,	Fever, dyspnea, epistaxis, hemoptysis	Fever, cough	Fever, cough, sore throat	Fever, dyspnea, cough,	Fever	Fever, cough	Fever, dyspnea, cough,	Fever, cough, dyspnea
(COVID-19)	5 months	19 months	24 months	25 months	39 months	45 months	180	144 months	144 months
Month in which	May 2021	March 2021	April 2021	July 2021	April 2021	April 2021	April 2021	April 2021	April 2021
Baseline Creatinine (mg/	0.6	1	0.95	1.2	1.75	1.2	0.8	4	1.3
Sr Creatinine	2.3	1.15	1.77	1.2	2.6	1.8	1.14	7	1.73
CT severity score	Not done	12 / 25	6 / 25	6 / 25	12 / 25	Not done	Not done	16 / 25	9 / 25
Least recorded	92%	93%	96%	96%	86%	90%	96%	78%	85%
Oxygen required	4L/min	No	No	No	10 L/min	3 L/min	No	15L/min	15L/min
Steroid	Prednisone 10 mg/d	Prednisone 20 mg/d	Prednisone 5 mg/ d	Prednisone 5 mg/d	MPS 80 mg/d	Prednisolone 5 mg/d, increased to 10 mg/d	Predni-sone 5 mg/d	Hydrocortisone 100 mg q4h/d	MPS 40 mg/d
Tacrolimus	5 mg/d	2 mg/d	5 mg/d	6 mg/d	1 mg/d	1.5 mg/d	1 mg/d	Stopped	NA
MMf	Reduced from 1440 mg/d to 720 mg/d	Stopped	Stopped	1440 mg/d	Reduced from 720 mg/d to 360 mg/d	Reduced from 1080 mg/d to 540 mg/d	1080 mg/d continued	Stopped	Reduced from 500 mg/d to 250 mg/d
Other	No	No	No	No	No	No	No	No	Sirolimus 1 mg/d
Remdesivir	No	Yes	No	No	No	No	Yes	Yes	Yes
RRT	No	No	No	No	No	No	No	Yes	No
Day of Discharge	7 days	17 days	7 days	5 days	10 days	7 days	5 days	21 days	26 days

ATIN - Acute tubule-interstitial nephritis
MPS - Methylprednisone
MMf - Mycophenolate mofetil
NSAID - Non steroidal anti-inflammatory drugs
RRT - Renal replacement therapy

after kidney transplant in this study was 49.411 months. Four KTRs were diabetic, of which three had post-transplant diabetes while one was diabetic prior to transplant. Injection of Remdesivir, which was then considered to be beneficial was administered to 12 KTRs including 4 patients who succumbed to COVID-19. Immunosuppression in COVID-19 is beyond the scope of this article, hence discussion shall be limited to our experience. At present, there are no guidelines regarding immunosuppression in kidney transplant recipients with COVID-19. Out pf 17 KRTs, 11 of them had received anti -thymocyte globulin as immunosuppression induction agent during kidney transplantation whereas 2 did not receive any induction and medical records on the other KRTs were unavailable. During presentation, all patients (17 KRTs) received Prednisone and mycophenolate whereas 15 KRTs received tacrolimus and another 2 KTRs were on either cyclosporine or sirolimus respectively. The decision to alter the dosing of immunosuppression was individualised according to the severity of presentation and laboratory investigations after daily reviews.

Limitations

The study sample size was small. Hence statistical analysis could not be applied. As it was a retrospective analysis of patients during a pandemic some data were missing. Hence it was not discussed.

Future Prospects

Our case series has opened several avenues for research. We are yet to standardize protocols and establish guidelines on approach to case management and curtailing the severity of infection in high-risk patients. As the KRTs population was small, a multi-centre study addressing certain aspects of COVID-19 in transplant recipient would definitely contribute to significant data.

CONCLUSION

Kidney transplant recipients in our case series, had a similar clinical presentation compared to general population. The cause of death in KTRs in our series was multi-factorial with immunosuppression being an additional risk factor. Whether the natural course of COVID-19 in transplant recipient population is different from the general population, it cannot be extrapolated. A case based, individualized approach in managing transplant recipients with COVID-19 is the key to clinical outcome. Anti-proliferative agents like mycophenolate and calcineurin inhibitors like tacrolimus, and cyclosporin remain to be the cornerstone for transplant maintenance immunosuppressive regimens. It would be premature to deduce whether dose modification of these agents, alters the course of COVID-19 infection while striking a balance for prevention of graft-rejection due to small size of study population. Apart from the rapidly evolving treatment options available from country to country, mandatory use of face-masks, social distancing, home-isolation, hydration, adequate nutrition and vaccination are fundamental in this pandemic.

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