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Original Article

Internal Medicine Section

Clinical Course and Outcome of COVID-19 in Kidney Transplant Recipients: A Single-centre Retrospective Observational Study

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ABSTRACT

Introduction: Solid Organ Transplants (SOT) is at increased risk of Coronavirus Disease 2019 (COVID-19) infection, which may result in acute graft dysfunction and even death. While the disease has been well studied in the general population, it is not the case in renal transplant recipients. The poor immunological response of the vaccine in post renal transplant patients, the emergence of newer strains, and the possibility of a third wave in India, makes it even more important to know more about the course and outcome of the disease in post renal transplant patients.

Aim: To evaluate the demographics, clinical presentation, biochemical profile, course of hospitalisation in post kidney transplant patients with COVID-19.

Materials and Methods: This retrospective observational study study with 18 patients was conducted in Madurai Medical College, Tamil Nadu, India for duration of four months, from May 2021 to August 2021 and data collection from May 2021 to July 2021 and data analysis in August 2021. All post kidney transplant patients having evidence of COVID-19 were included. Detailed clinical history, biochemical profile, radiological findings, treatment, and final outcomes were collected and compared. Non parametric statistical tests were used, in addition to Chi-square test and odds ratio. Kaplan-Meier plot was used for survival analysis.

Results: The most common presentation was fever 15 (83.3%), followed by cough 10 (55.6%). C-reactive Protein (CRP) {65 mg/L (11.48-94.48)}, D-dimer {0.72 mcg/mL (0.59-1.1)}, serum creatinine {3.5 mg/dL (2.12-5.93)}, and platelet count {200,000 cells/cu.mm (1.75-2.22)} and showed statistically significant ($p<0.05$) association with the outcome. About 15 (83.3%) patients developed Acute Kidney Injury (AKI). Seven patients (38.9%) had stage three AKI necessitating haemodialysis, of which six did not survive. The median survival time was 22 days, with 95% confidence interval (19.792-24.208), with case fatality rate of 33.3%

Conclusion: Post kidney transplant patients are at high risk of contracting COVID-19. CRP, D-dimer, serum creatinine, platelet counts, and arterial oxygen saturation may serve as prognostic markers. Dialysis may be required in view of high incidence of AKI and acute graft dysfunction, though the outcome seems dismal in such patients. Hence, the need for early hospitalisation and more effective treatment protocol is essential to improve outcome.

Keywords: Acute graft dysfunction, Biopsy, Coronavirus disease 2019, Dialysis, Immunosuppressives, Rejection

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the virus responsible for the COVID-19, is responsible for an everlasting worldwide pandemic. The country has witnessed two horrendous waves of the disease and is standing at the brink of a third one. The high rate of transmissibility in the asymptomatic phase has facilitated the virus to spread globally with catastrophic outcomes [1]. It has posed as a great challenge for clinicians all over the world. Though, it may cause a mild disease in some, it has led to millions of deaths worldwide [1].

The SOT recipients are vulnerable to many respiratory viral infections due to a weakened T-cell mediated immune response [2]. SOT recipients have been classified as having high risk for severe illness due to SARS-CoV-2 by the Centers for Disease Control and Prevention (CDC) [3]. There is still paucity of data on the natural course of the disease, the treatment regime to be used, the effect of the immunosuppressive drugs, the risk factors and many more in the SOT recipients. Interestingly, an immunocompromised state has yet not been proven to have a worse clinical outcome [4]. A Chinese meta-analysis proposed that risk factors such as hypertension, chronic respiratory disorders, cardiovascular diseases, older age, but not immunosuppression as predictors of severe COVID-19 disease [5]. Another study pointed out that viruses that belong to the same coronavirus family, as Middle East Respiratory Syndrome (MERS) and SARS-CoV-2 have not been shown to have an increased risk or worse outcome in immunocompromised patients [6]. Immunosuppression on the background of hyperinflammation may prove to be even beneficial, by blunting down the cytokine release, as postulated by Mehta P et al., [7]. In contrast, a review article by Lai Q et al., found a mortality of 23.1% and a need for invasive ventilation in 23.9% of SOT recipients [8]. The expert American Association of the Study of Liver Disorder (AASLD) consensus also pointed out that immunosuppressed patients are at higher risk for severe illness from COVID-19 [9].

There have been numerous case series on COVID-19 in SOT recipients from all over the world. But the evolving variants of coronaviruses are still posing a danger to the community. The Centre for Disease Control and Prevention (CDC) has declared the recent omicron variant (B.1.1.529) as a variant of concern [10]. The recent surge of Omicron cases is worrisome and may present as the third wave in the Indian subcontinent. The effectiveness of full vaccination in SOT recipients is also dismal. A study done in Israel showed seroconversion after vaccination in only 37.5% in kidney transplant recipients, as compared to 100% in the controls [11].

The treatment protocol of COVID-19 among these transplant patients is also different from the general population. Complex decisions regarding the tapering of immunosuppressives have to be taken. The immunosuppressives used in renal transplant recipients were found to have anti-viral properties. Corticosteroids may be beneficial in the treatment [12]. Mycophenolate Mofetil (MMF) was shown to have antiviral properties against MERS, but in SARS-CoV-2, it has been shown to do more harm than benefit in in-vivo studies [13]. Therefore,

its use is not recommended. Calcineurin inhibitors have been shown to have anti-viral properties, but still needs more research [14]. There are limited data on the clinical courses and outcome of COVID-19 in renal transplant recipients from South India.

This study presents an analysis of the data on COVID-19 in renal transplant patients. It aimed to evaluate the demographics, clinical presentation, biochemical profile, and course of hospitalisation in renal transplant patients with COVID-19.

MATERIALS AND METHODS

This was a retrospective observational study. conducted at Madurai Medical College, Tamil Nadu, India for a duration of four months, from May 2021 to August 2021 and data collection from May 2021 to July 2021 and data analysis in August 2021. This study was approved from the Institutional Ethics Committee (CDSCO: Reg no. ECR/1365/Inst/TN2020). A written informed consent was obtained from all the participants of this study.

Inclusion criteria: The inclusion criteria comprised all post kidney transplant patients (both live and deceased donor) having evidence of COVID-19 (either Reverse Transcription Polymerase Chain Reaction (RT-PCR) positive or evidence of COVID-19 pneumonia on Computed Tomography (CT) chest).

Exclusion criteria: The exclusion criteria included all patients with chronic graft dysfunction.

Study Procedure

A total of 18 patients were evaluated in this study. Data regarding the clinical history, routine blood investigations complete blood count, renal function tests, liver function tests, serum ferritin, D-dimer), radiological findings- Ground Glass Opacities (GGO), lobar consolidation, oxygen requirement, treatment and final outcomes were collected and compared.

Lymphopenia was defined as Absolute Lymphocyte Count (ALC) <1000 cells/cumm [15]. Oxygen requirement was classified as: no oxygen needs; low oxygen requirement (nasal cannula, venturi mask with FiO_2 of 0.5); high oxygen requirement (venturi mask with FiO_2 of >0.5, reservoir mask with oxygen at 15 L/min and high -flow nasal ventilation); non invasive ventilation; and mechanical ventilation [16].

The AKI was defined and classified according to Acute Kidney Injury Network (AKIN) criteria [17]. An institutional protocol was devised for managing immunosuppression in post-transplant COVID-19 patients after referring the European Renal Association-European Dialysis and Transplantation Association Developing Education Science and Care for Renal Transplantation in European States (ERA-EDTA DESCARTES) expert opinion [18]. Anti-proliferative agents (MMF and Azathioprine) were reduced. Of the patients taking Calcineurin inhibitors cyclosporin A was continued at the same dose and Tacrolimus dose was reduced. The dose of prednisolone was increased to 20 mg once daily. For patients with severe COVID-19 pneumonia, all immunosuppressants except low dose steroids were withdrawn.

The CRP was checked for all patients and patients were divided into having mild, moderate, or severe inflammatory reaction {CRP (mg/L) 10-50-mild; 50-100-moderate; >100-severe}.

Patients were treated with Intravenous (IV) steroids (either dexamethasone 6 mg BD or methyl prednisolone 40 mg twice a day (BD) depending on their inflammatory status [19,20]. In such patients, oral steroids were withheld.Underlying procoagulant risk was determined according to D-dimer values {D-dimer (mcg/mL) <0.5-mild; 0.5-1.0-moderate; >1.0-severe}. All patients with mild risk were started on once daily, and all patients with moderate to severe risk were started on twice daily subcutaneous enoxaparin.

All patients were treated with hydroxychloroquine, vitamin C, zinc and ivermectin. Remdesivir was started for patients who had SpO_2 level <85%. It was administered as an intravenous infusion of 200 mg on day one followed by 100 mg as infusion once daily for four more days [21]. Final outcome was classified as either recovery, death or recovery from the illness, but still on dialysis (graft loss).

STATISTICAL ANALYSIS

All data was compiled in Microsoft Excel, and statistical analysis done using Statistical Package for the Social Sciences (SPSS) v16. Normality tests (Shapiro Wilk, assessment of skewness and kurtosis) revealed non parametric data. Non parametric statistical tests were used, in addition to Chi-square test and odds ratio. Kaplan-Meier plot was used for survival analysis. The p-value <0.05 was considered statistically significant, and 95% confidence intervals were used.

RESULTS

Total of 18 patients were studied (14 male and four female). The mean age was 40.389±11.3 years. Most of the patients had associated co-morbidities, the most common of which were diabetes and systemic hypertension (8 out of 18 each). Two patients had chronic Hepatitis C Virus (HCV) infection, one had chronic Hepatitis B Virus (HCB) infection, two had a history of coronary artery disease, and one had a recent history of acute graft dysfunction. The demographic variables and co-morbidities of the study population are shown in [Table/Fig-1].

Variables	Total patients n=18	Survivors n=12	Non survivors n=6	p-value	Odds ratio (95% CI)
Age (years) mean (range)	40 (33.75-50)	42 (24.75-49.75)	40 (37-52)	0.573*	
Sex					
Male	14 (77.8%)	9 (75%)	5 (83.3%)	0.688+	1.667 (0.135-20.578)
Female	4 (22.2%)	3 (25%)	1 (16.7%)		
Type of transplant					
Deceased	10 (55.6%)	9 (75%)	1 (33.3%)	0.710+	
Alive	8 (44.4%)	3 (25%)	5 (83.3%)		
Time since transplant (Months)	37 (23.5-111.25)	37 (24.25-98.25)	17 (12.75-39)	0.705+	
Co-morbidities					
DM	8 (44.4%)	4 (33.3%)	4 (66.7%)	0.180+	4 (0.5-31.981)
NODAT	4 (22.2%) 50% of DM	2 (16.7%) 50% of DM	2 (33.3%) 50% of DM	0.423+	2.5 (0.256-24.375)
SHTN	8 (44.4%)	4 (33.3%)	4 (66.7%)	0.180+	4 (0.5-31.981)
CAD	2 (11.1%)	2 (16.7%)	0	0.289+	
HCV	2 (11.1%)	1 (8.3%)	1 (16.7%)	0.596+	2.2 (0.113-42.735)
HBV	1 (5.6%)	0	1 (16.7%)	0.146+	
Recent graft dysfunction	1 (5.6%)	1 (8.3%)	0	0.506+	

Baseline serum creatinine (mg/dL)	1.45 (1.3-1.88)	1.4 (1.3-1.98)	1.5 (1.3-1.92)	0.711*	
Baseline immunosuppression					
CNI (Tac/Cy A)	12/3 (66.7%/16.7%)	8/2 (66.7%/16.7%)	4/1 (66.7%-16.7%)	1.000+	
MMF	16 (88.9%)	10 (83.3%)	6 (100%)	0.289+	
mTORi	1 (5.6%)	1 (8.3%)	0	0.467+	
AZA	1 (5.6%)	1 (8.3%)	0	0.467+	

[Table/Fig-1]: Demographic variables and co-morbidities of the study population.
DM: Diabetes mellitus; NODAT: New onset diabetes after transplantation; SHTN: Systemic hypertension; CAD: Coronary artery disease; HCV: Hepatitis C virus; HBV: Hepatitis B virus; CNI: Calcineurin inhibitors; MMF: Mycophenolate mofetil; mTORi: mammalian target of rapamycin inbitors, AZA: Azathioprine; Mann whitney U test to calculate p-value*; Chi-square test/Fisher's exact test used to calculate the p-value+

The median time since transplant was 37 (IQR 23.5-111.25) months. The median duration of hospital admission was around 13.5 (IQR 7-20.25) days {10 (IQR 7-15.75) days in survivors vs 20.5 (IQR 11.75-22.5) days in non survivors, p-0.004}. The baseline creatinine was 1.45 (IQR 1.3-1.88) mg/dL. The baseline immunosuppressive used was calcineurin inhibitors in 15 patients, Mycophenolate Mofetil (MMF) in 16 patients, Azathioprine in one patient and mTOR inhibitors in one patient. Five patients were on double immunosuppression and 13 patients were on triple immunosuppression.

The symptomatology, laboratory investigations and radiographic findings of the patients are shown in [Table/Fig-2]. The most common symptom was fever. One patient presented with an acute anterior wall myocardial infarction. During further evaluation, two patients had diabetic ketoacidosis, one patient had emphysematous pyelonephritis. Three patients showed rejection [Table/Fig-3].

Features at diagnosis	Total patients	Survivors	Non survivors	p-value	Odds ratio (95% CI)
Clinical presentation					
Fever	15 (83.3%)	9 (75%)	6 (100%)	0.180+	
Cough	10 (55.6%)	6 (50%)	4 (66.7%)	0.502+	2 (0.26-15.381)
Dyspnea	8 (44.4%)	3 (25%)	5 (83.3%)	0.019+	15 (1.215-185.198)
Gastrointestinal symptoms	3 (16.7%)	3 (25%)	0	0.180+	
Myalgia	9 (50%)	6 (50%)	3 (50%)	1.000+	1 (0.141-7.099)
Pharyngitis	4 (22.2%)	4 (33.3%)	0	0.109+	
Angina	1 (5.6%)	1 (8.3%)	0	0.467+	
Laboratory tests on diagnosis					
Hb (gm/dL)	11.6 (10.42-12.8)	12.15 (10.9-13.7)	10.5 (6.75-12)	0.055+	
TC (cells/cumm)	7.65 (6.15-9.975)	8 (6.457-11.9)	5.65 (3.37-7.2)	0.388*	
ALC (cells/cumm)	830 (570-1555)	940 (555-1870)	677.5 (455.5-825)	0.242+	
Incidence of lymphopenia	12 (66.7%)	7(58.3%)	5 (83.3%)	**<0.001***	
CRP (mg/L)	65 (11.48-94.48)	19.5 (9.22-78.5)	85.5 (75.5-108.25)	**0.012***	
D-dimer (mcg/mL)	0.72 (0.59-1.1)	0.625 (0.557-0.79)	1.0 (0.8-1.4)	**0.03***	
Peak serum creatinine (mg/dL)	3.5 (2.12-5.93)	2.55 (1.52-3.70)	6 (4-7.25)	**0.001***	
Peak serum urea (mg/dL)	88 (48.5-150)	62 (33.5-123.5)	140 (90.25-157)	0.096*	
Platelet count (cells/cumm)	2.0 (1.75-2.22)	2.1 (1.86-2.62)	1.72 (1.22-2.14)	**0.02***	
CT-chest findings					
Multifocal/Bilateral GGO (with GGO%)	14 (77.8%) 22.5 (8.5-47.5)	9 (75%) 10 (5-25)	5 (83.3%) 45 (26.25-58.75)	**0.02**+	
Lobar opacities	2 (11.1%)	1 (8.3%)	1 (16.7%)	0.596+	
No acute findings	2 (11.1%)	2 (16.7%)	0	0.289+	
Swab positivity	12 (66.6%)	7 (58.3%)	5 (83.3%)	0.289+	3.571 (0.313-40.751)
SpO_2(%)	94.5 (82.25-97)	96 (93.75-97)	79 (75-84.5)	0.001*	

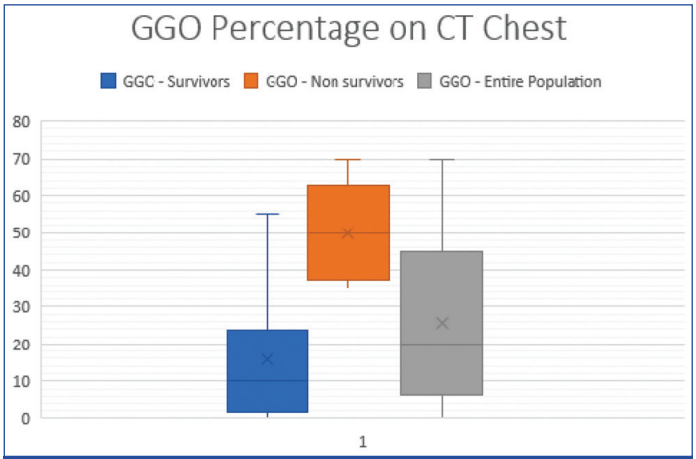
[Table/Fig-2]: Clinical presentation, laboratory investigations and radiographic findings.
TC: Total count; ALC: Absolute lymphocyte count; Hb: Haemoglobin; CRP: C-reactive protein; Total patients: 18; Survivors: 12; Non survivors: 6; Mann Whitney U test to calculate p-value*; Chi-square test/Fisher's exact test used to calculate the p-value+

Pt	Sex	Age (yrs)	Time since transplant (months)	Transplant Type	Maintenance IS	Baseline SCr (mg/dL)	Presentation	CRP at presentation (mg/L)	SCr at presentation (mg/dL)	Biopsy	Treatment	Outcome
1	F	20	16	Deceased	T/M/P	1.3	Fever, Myalgia	62	5.2	ACMR	P-Increased Haemodialysis	Recovered Haemodialysis-dependant
2	M	34	24	Deceased	T/M/P	1.8	Fever, Myalgia, Cough	104.9	7.8	Mixed ACMR and ABMR	T and M-Decreased, P-Increased Plasmapheresis Haemodialysis	Death
3	M	40	15	Live	T/M/P	1.4	Fever, Myalgia, Cough, Dyspnea	78	8.2	ACMR	T and M-Decreased, P-Increased Haemodialysis	Death

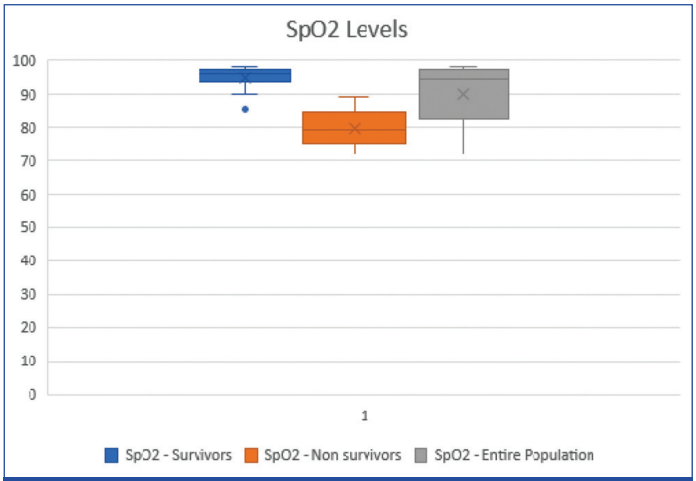
[Table/Fig-3]: Biopsy findings in patients with acute graft dysfunction.
T: Tacrolimus; M: Mycophenolate mofetil; P: Prednisolone; ABMR: Antibody mediated rejection; ACMR: Acute cell mediated rejection; SCr: Serum creatinine; IS: Immunosuppressants; CRP: C-reactive protein

The median WBC count was 7650 cells/cu.mm. The incidence of lymphopenia was 66.67%. The median Absolute Leukocyte Count (ALC) was less in non survivors. Similarly, the median platelet count was also low in non survivors. Though the baseline creatinine was almost same in both survivors (1.4 mg/dL) and non survivors (1.5 mg/dL), the peak creatinine during in hospital admission was higher in non survivors, which also had a prognostic effect on the survival (p-0.001). The median CRP in survivors was low in comparison to non survivors. Quite similarly, D-Dimer was also low in survivors. Both CRP and D-Dimer were statistically significant with respect to the outcome.

Total 12 out of 18 patients had nasopharyngeal swab RT-PCR positivity. Fourteen patients had multifocal/bilateral GGOs and the average GGO involvement was 22.5%. Two patients had lobar opacities and two had no acute radiographic findings. [Table/Fig-4] represents the Box and Whisker plot of the quantum of GGOs of survivors and non survivors. Non survivors had a relatively poor oxygenation status {SpO_2-79% vs 96% in survivors, p-0.001]. Box and Whisker plot of oxygen saturation of survivors and non survivors is shown in [Table/Fig-5].



[Table/Fig-4]: Box and Whisker plot for percentage of GGOs on CT chest.



[Table/Fig-5]: Box and Whisker plot for SpO_2 levels at time of admission.

Two patients were treated with i.v. Remdesivir and 16 patients were treated with oral antivirals (Oseltamivir in 12 and Favipiravir in 4 patients).

Immunosuppressives were tapered on a case to case basis. For three patients MMF, Tacrolimus were decreased, and Prednisolone was increased. All immunosuppressives, except low dose steroids were stopped for one patient. All these four patients did not survive irrespective of these drastic measures. Six patients did not need any change in the immunosuppressive regimen, all of whom survived. Details regarding the treatment (including tapering of immunosuppressive drugs and ventilation requirement) are shown in [Table/Fig-6].

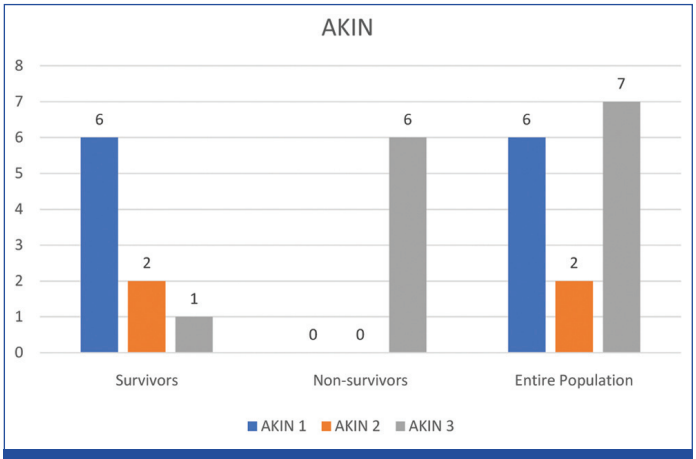
Four patients needed invasive ventilation, two needed non invasive ventilation, and three needed low flow nasal oxygen, while nine patients were oxygen independent.

Treatment	All patients	Survivors	Non survivors	p-value
Change in immunosuppressive drug				
- Tacrolimus decreased	1 (5.6%)	1 (8.3%)	-	0.467+
- MMF decreased	5 (27.8%)	4 (33.3%)	1 (16.7%)	0.457+
- Prednisolone increased	8 (44.4%)	6 (50%)	2 (33.3%)	0.502+
- Azathioprine discontinued	1 (5.6%)	1 (8.3%)	-	0.467+
- All immunosupressants discontinued	1 (5.6%)	-	1 (16.7%)	0.146+
- No change in immunosuppression	6 (33.3%)	6 (50%)	-	0.034+
- MMF and tacrolimus decreased, prednisolone increased	3 (16.7%)	-	3 (50%)	0.007+
Intravenous steroids				0.087+
- IV Methylprednisolone	5 (27.8%)	3 (25%)	2 (33.3%)	0.710+
- IV Dexamethasone	7 (38.9%)	3 (25%)	4 (66.7%)	0.084+
Anticoagulants	17 (94.4%)	12 (100%)	5 (83.3%)	0.146+
Anti-viral				0.126+
- Remdesivir	2 (11.1%)	2 (16.7%)	0	0.223+
- Oseltamivir	12 (66.7%)	6 (50%)	6 (100%)	**0.034+**
- Favipiravir	4 (22.2%)	4 (33.3%)	0	0.109+
Ventilation requirements				
- No oxygen	9 (50%)	9 (75%)	0	**0.001+**
- Low oxygen requirement	3 (16.7%)	3 (25%)	0	
- High oxygen requirement	0	0	0	
- Non invasive ventilation	2 (11.1%)	0	2 (33.3%)	
- Invasive ventilation	4 (22.2%)	0	4 (66.7%)	
Hospitalisation duration (days)	13.5 (7-20.25)	10 (7-15.75)	20.5 (11.75-22.5)	**0.044***
Haemodialysis initiation (day of hospitalisation)	6 (4-7)	0* (0-7)	4.5 (3-8.5)	**0.001***

[Table/Fig-6]: Treatment protocol (including ventilation and haemodialysis requirement). Low oxygen requirement- nasal cannula, venturi mask with FiO_2 of 0.5; High oxygen requirement- venturi mask with FiO_2 of >0.5, reservoir mask with oxygen at 15 L/min and high-flow nasal ventilation; *-only 1 in the survivors (1 of 12 patients) underwent haemodialysis on the day 7 of hospitalisation; MMF: Mycophenolate mofetil; Mann whitney U test to calculate p-value*; Chi-square test/Fisher's exact test used to calculate the p-value+

The incidence of AKI was remarkably high 15 (83.3%) with stage 3 AKIN being the most common finding 6 (38.9%) [Table/Fig-7,8]. All these six patients underwent haemodialysis, out of which 5 patients died, and one had a graft loss and is still on haemodialysis. The median time of initiation of haemodialysis in non survivors was five days with 95% confidence interval (2.841-7.159). All patients with AKIN 1 and 2 survived without the need of haemodialysis.

Six patients died (case fatality rate- 33.3%). One patient recovered from the illness but had graft loss and is continuing dialysis



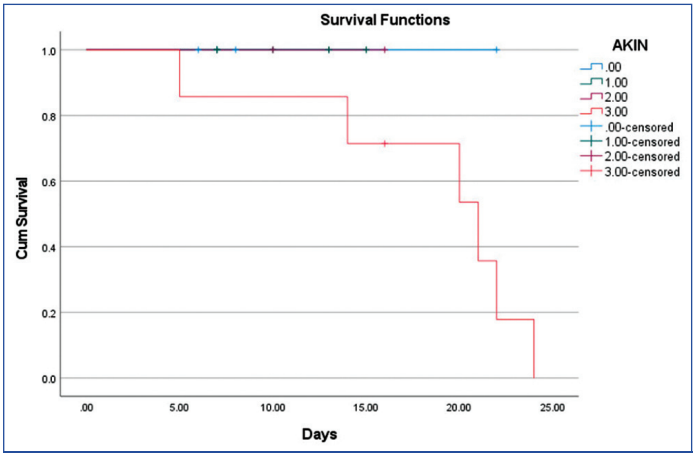
[Table/Fig-7]: Incidence of AKI.

[Table/Fig-8], at the time of reporting the study. The most common cause of death was respiratory failure 3 (50%), followed by sepsis 2 (33.3%), and sudden cardiac arrest 1 (16.7%) [Table/Fig-8].

Outcome	All patients	Survivors	Non Survivors	p-value
Normal graft function	3 (16.7%)	3 (25%)	0	
Acute kidney injury	15 (83.3%)	9 (75%)	6 (100%)	**0.003**+
AKIN 1	6 (33.3%)	6 (50%)	0	
AKIN 2	2 (11.1%)	2 (16.7%)	0	
AKIN 3	7 (38.9%)	1 (8.3%)	6 (100%)	
AKI recovered				**0.001**+
With RRT	6 (33.3%)	1 (8.3%)		
Without RRT	9 (50%)	9 (75%)		
Graft loss	1 (5.6%)	1 (8.3%)	-	0.506+
Died	6 (33.3%)	0	6 (100%)	
Cause of death				
- Respiratory failure	3 (16.6%)		3 (50%)	
- Sepsis	2 (11.1%)		2 (33.3%)	
- Sudden cardiac arrest	1 (5.6%)		1 (16.7%)	

[Table/Fig-8]: Outcome and cause of death.
AKI: Acute kidney injury, RRT: Renal replacement therapy; p-values are for the comparisons between survivors and non survivors; Data Representation: n (%) or median (IQR: Inter quartile range); Chi-square test/Fisher's exact test used to calculate the p-value+

The Kaplan-Meier survival analysis is shown in [Table/Fig-9]. It shows the probability of the event (death) at specific intervals in the study population. The median survival time was 22 days (19.792-24.208) with 95% confidence interval. There was no difference in the type of transplant (live or deceased) on the overall survival.



[Table/Fig-9]: Kaplan-Meier survival analysis.

DISCUSSION

There are still many uncertainties regarding the recent COVID-19 pandemic in kidney transplant patients in terms of clinical symptomatology, patient and graft outcomes, the effect of immunosuppression and the role of anti-virals. This study has discussed the demographics, clinical presentation, biochemical profile, and course of hospitalisation in kidney transplant recipients with COVID-19.

Most of the patients presented with fever and cough, like the study done in Columbia University, in which 87% patients had fever and 60% had cough [22]. An Italian study showed similar results [16]. This is in contrast to another study done in the same geographical region, in which cough was the predominant symptom [23].

Three patients presented with only diarrhoea. Interestingly, diarrhoea was a common symptom in a Spanish study where four of 18 patients had diarrhoea whether post-transplant immunosuppression may modify the clinical presentation of COVID-19, making SOT recipients more prone to gastrointestinal symptoms compared to non transplant patients, remains to be confirmed [24].

One patient presented with an acute anterior wall myocardial infarction. Myocardial injury has been demonstrated to be around 7% in a review article by Uriel N et al., [25]. In a case series from Italy, 24 of 28 COVID-19 patients with myocardial infarction had chest pain as their first symptom [26]. Acute Coronary Syndrome (ACS) either due to plaque rupture demand ischaemia or vasospasm is certainly conceivable [27]. Activated macrophages secrete collagenases that degrade collagen, a major constituent of the fibrous capon atherosclerotic plaques, which can lead to plaque rupture [28]. Activated macrophages also secrete tissue factor, a potent procoagulant that triggers thrombus formation when the plaque ruptures [28]. Given haemodynamic changes and exaggerated inflammatory response frequently seen with COVID-19, risk for ACS is higher.

Further evaluation revealed that two patients had diabetic ketoacidosis, one of whom also developed emphysematous pyelonephritis and succumbed. Study done in India by Pal R al., concludes that Diabetic ketoacidosis is not uncommon in COVID-19 patients with pre-existing diabetes mellitus and portend a poor prognosis with a mortality rate of nearly 50% [29].

The radiological findings were variable with the most common finding being bilateral/multifocal GGOs (77.8%), two patients had lobar consolidation and two patients had normal CT findings. This finding was comparable to the study done in Columbia university, where about half of the patients had bilateral/multifocal opacities, 13% had lobar opacities and 33% had unremarkable radiographs [22].Another study done in Wuhan, China showed a similar finding, with GGOs being the most common radiological abnormality [30].

The incidence of lymphopenia was more in non survivors (83.3% vs 58.3% in survivors). The median ALC was also lower in non survivors, though not statistically significant. This is in contrast with the study done in New York, where the lowest lymphocyte count had a prognostic significance on the outcome [31].However, the median platelet count which was also lower in non survivors had a statistical correlation with the outcome, similar to the New York study [31]. This could be explained by the possible occurrence of Disseminated Intravascular Coagulation (DIC) with COVID-19, which is more common in non survivors [32].

Many patients also had elevated D-dimer level, which in the absence of any obvious thromboembolic events, also favours the occurrence of microvascular thrombosis or DIC. A study done in China postulated that higher D-dimer levels are associated with a severe infection [33].

The median CRP value was also comparatively higher in non survivors which could reflect an exaggerated inflammatory response. Both CRP and D-dimer were significantly associated with the overall survival.

The AKI was described in 57% transplant patients as compared to 29% in general population in a Chinese study [34]. In another study, 40% post-transplant patients developed AKI [22]. In this study, fifteen (83.3%) patients developed AKI, out of which 7 (38.9%) patients had AKIN stage 3. Around 6 (33.3%) patients needed renal replacement therapy in the form of haemodialysis. In the study done in New York by Azzi Y et al., 23% needed RRT [31]. Angiotensin- Converting Enzyme (ACE-2) and dipeptidyl peptidase, which are expressed in proximal tubule cells, have been identified as receptors for coronavirus [35,36]. Uptake of SARS-CoV-2 virus into the proximal tubular epithelium is a possible explanation for AKI. In addition, microangiopathy mediated by complex inflammatory processes has also been suggested [37].

Three patients underwent biopsy for acute graft dysfunction, out of which two had TCMR and one had co-existent ABMR and TCMR [Table/Fig-3]. They were treated with high dose steroids (including plasmapheresis for the patient with co-existent ABMR and TCMR). In a study by Kudose S et al., on biopsy findings in COVID-19, out of three allograft biopsies, one patient had TCMR, one had cortical necrosis and one had Acute Tubular Injury (ATI) [38]. Out of these three, two patients recovered and one continued to be dialysis

dependent. In contrast, in this study, all the three patients had a poor outcome. Two of these patients did not survive. One had a graft loss and is continuing dialysis. In addition to the above described mechanisms for AKI in COVID-19, other mechanisms like acute rejection from under suppression, or CNI toxicity through drug-drug interaction may play a role in transplant kidneys [39]. Also, the inflammatory milieu surrounding COVID-19 may trigger or exacerbate immune-mediated processes in transplant patients like development of acute T-cell mediated rejection in a patient with preformed donor-specific antibodies [38]. Supporting this hypothesis is the fact that all the 3 patients who had graft rejection had markedly high CRP.

Regarding ventilation requirements, 4 (22.2%) patients were intubated and mechanically ventilated. All those who were required mechanical ventilation did not survive. This is similar to the finding in an American study where 23 out of 28 intubated patients did not survive and the need for intubation was thus, concluded as a marker of poor prognosis [31]. All the intubated patients had severe disease, thus the high mortality in them. A Korean study compared mortality between early intubated patients and patients managed conservatively [40]. Early intubation was not found to offer any survival benefit.

Managing immunosuppression in these patients is challenging and should be decided after considering the patient age, severity of COVID-19 infection, associated co-morbidities, and time post-transplant. In milder forms of disease, the usual practice is to continue the same dose of immunosuppression, but this approach might favour high mortality in COVID-19 infection. It has been suggested in a study by Banerjee D et al., that Anti-proliferative agents (MMF or Azathioprine) should be stopped, the dose of prednisolone be increased, and the dose of Tacrolimus be reduced [41]. An evident risk with such an approach is rejection but given the high mortality risk, the clinician's main goal should be to focus on keeping the patient alive, with a careful assessment of risks versus benefits of continuing immunosuppression. Regarding adjustment of immunosuppression, 6 (33.3%) patients with milder form of the disease were managed on the same immunosuppressive dosage, all of whom survived with normal graft functions. One patient, who was on azathioprine developed severe persistent leukopenia and thus, azathioprine was stopped. He was suspected to have CMV viremia, but his WBC count improved with mere stoppage of azathioprine. Patients on cyclosporine A were continued on the same dose, since it has been shown to have an inhibitory effect on proliferation of coronaviruses through its impact on cyclophilin A and B [14].

The optimal timing of the reintroduction of the original immunosuppressive is also still questionable. There are reports that viral shedding can occur for up to 2 weeks, but a maximum period of 37 days has also been observed [42,43]. There is also an association between the severity of the infection and the peak viral loads, which may influence the duration of subsequent viral shedding [44]. Thus, given the uncertainty, the protocol followed, was to start the immunosuppressive dosage to preinfection level at either the time of discharge or to delay to a maximum of two weeks, given the risk that prolonged reduction of immunosuppression may trigger an episode of rejection.

All the patients received either oral antivirals (Oseltamivir or Favipiravir) or i.v. Remdesivir. Reports have suggested a role for Hydroxychloroquine (HCQ) in reducing the viral load [45]. Invariably, all patients were treated with HCQ, in the absence of QT prolongation. Patients, who had high TC, were also treated with i.v. antibiotics and oral doxycycline. All except one patient who had severe thrombocytopenia due to underlying TMA, were treated with subcutaneous enoxaparin. The RECOVERY trial demonstrated mortality benefit in treatment with dexamethasone [19]. In steroids-SARI (Glucocorticoid Therapy for Novel Coronavirus Critically Ill Patients with Severe Acute Respiratory Failure), i.v. methyl prednisolone was used, which also had a mortality benefit [20]. The WHO subsequently recommended the use of systemic corticosteroids in severe cases [46]. In this study, 12 out of 18 patients received i.v. steroids in the form of either dexamethasone (five patients) or methylprednisolone (seven patients), though their use did not have any mortality benefits.

Nine patients recovered, six patients died (case fatality rate 33.3%) and one patient is still on dialysis. The mortality rate is comparable to other studies done in post-transplant COVID-19 patients [24,31].

The cause of death was extrapulmonary in 50% of the patients [Table/Fig-8]. Similar finding was observed in another study, where one of the seven patients studied, expired of a possible bowel infarction or intraabdominal sepsis. They concluded that mortality in critically ill patients with COVID-19 infection could be due to extrapulmonary causes like myocarditis or bowel involvement [41]. As described earlier, the median platelet count, peak creatinine value, CRP value and the D-dimer value had a statistical correlation with the mortality.

Limitation(s)

The sample size was small, long term follow-up was not done and proteinuria was not evaluated. Biopsy could also not be done in all patients due to logistic reasons.

CONCLUSION(S)

All transplant patients are at a higher risk of getting COVID-19 owing to their underlying immunosuppressed state. Varied presentation may occur with significant chest radiograph findings. The CRP, D-dimer, admission creatinine and platelet, arterial oxygen saturation are overall prognostic markers. They are also at a remarkably high risk of developing AKI, including acute graft rejection and a significant proportion may even need renal replacement therapy. In addition to anti-virals, the treatment also includes careful alteration of immunosuppression. The case fatality rate is also higher suggesting the need of stringent management, early hospitalisation, and more effective treatment protocol.

More studies are needed to know better about the course and outcomes of COVID-19 in transplant patients. It is therefore suggested, all countries should start maintaining a record of COVID-19 infections in kidney transplant patients. Analysis of this data may help clinicians make informed decisions about the management of these patients in these uncertain and rapidly evolving times.

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