



Impact of COVID-19 on renal transplant recipients



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Abstract

Introduction: It was essential to explore immunosuppressant management strategies and potential clinical variables associated with COVID-19 related mortality in order to provide insight for clinicians attempting to manage kidney transplant recipients during the ongoing severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) pandemic.

Objectives: The aim of the study was to assess the impact of COVID-19 on post-transplant renal function and outcome of immunosuppressant management on COVID-19.

Patients and Methods: This is a cross sectional observational study conducted from March 2020 to January 2022 in a tertiary care hospital in South India. Baseline characteristics, comorbidities, history of graft dysfunction, symptoms and immunosuppressant modification was noted. Outcomes of COVID-19 such as acute kidney injury (AKI), need for dialysis and post COVID-19 complications were noted. The statistics were expressed as percentage for categorical variables and mean \pm SD for continuous variables.

Results: Out of 400 renal transplant patients on regular follow up, 28 patients developed COVID-19. The incidence of AKI was 64.2%. Immunosuppressant dose modification was done in majority of patients [mycophenolate mofetil (28.5%), steroids (53.5%) and tacrolimus (39.2%)]. Outcomes included recovery from AKI in 61.1%, recovery from oxygen dependence in 100% patients with an overall mortality rate of 7.1% patients. About 17.8% patients developed post-COVID-19 complications.

Conclusion: Immunosuppressant dose modification during COVID-19 could play a role in development of AKI; infection being an independent risk factor. Patients should be monitored for development of post-COVID-19 complications.

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Introduction

Mortality of renal allograft recipients with COVID-19 is around 22% to 28% among hospitalized patients (1-3). Risk factors such as elderly age, comorbidities, and malignancy; have been associated with severe COVID-19; the role of immunosuppression still remains controversial (4,5). We explore immunosuppressant management strategies to provide insight for clinicians attempting to manage renal transplants during the pandemic. The study aims to assess the impact of COVID-19 on graft function and vice versa.

Objectives

- To assess the clinical and biochemical profile of COVID-19 positive renal transplant recipients
- To establish the outcome of COVID-19 in renal transplant recipients
- To establish the effect of immunosuppressant modification on COVID-19 and graft function

Patients and Methods

Study design

Patients aged more than 18 years, who have been diagnosed with COVID-19 with reverse transcription-polymerase chain reaction (RT-PCR) after undergoing renal transplantation, who were either home quarantined or isolated in facility, were considered for study. Patients who have undergone renal transplantation and tested negative for COVID-19 were excluded from study.

This study was a cross-sectional observational study that was conducted from March 2020 to January 2022 in a tertiary care centre in South India. We screened 400 renal transplant recipients and identified 28 post-transplant patients in our centre who developed COVID-19. Patients who satisfied the inclusion criteria were considered for this study.

Basic patient characteristics such as age, gender, type of transplantation, duration since transplantation, comorbidities,

Key point

Immunosuppressant modification is an important strategy in management of renal transplant recipients infected with COVID-19. Patients with high computerized tomography (CT) severity score of the lungs and history of chronic graft dysfunction must be monitored closely for development of acute kidney injury. It is crucial to watch for post COVID-19 complications in transplant recipients.

previous history of graft dysfunction/rejection, cause of end stage renal disease, induction agents used at the time of transplantation, history of COVID-19 contacts, COVID-19 vaccination status, last tacrolimus levels were noted either from medical records or direct enquiry on outpatient department follow-up. Patients were enquired about clinical symptoms such as cough, fever, gastrointestinal discomfort, shortness of breath, acute kidney injury (AKI) at presentation, asymptomatic infection and oxygen requirement. Investigation details such as computerized tomography (CT) severity score of the lungs, D-dimer, C-reactive protein (CRP), total leukocyte count, ferritin, lactate dehydrogenase (LDH), serum creatinine was collected. Information regarding COVID-19 management strategies used such as medications including hydroxychloroquine, steroids (oral or intravenous), antibiotics, remdesivir, tocilizumab, anticoagulation, plasma therapy, anti-fungals), proning strategies, oxygen therapy (including face mask, non-invasive and invasive mechanical ventilation) was obtained. Immunosuppressive medications received prior to COVID-19 along with dose modifications of immunosuppressive (such as mycophenolate mofetil, cyclosporine/tacrolimus and prednisolone) made during COVID-19 therapy and continuation of post-transplant prophylaxis was monitored. Outcomes such as recovery from AKI, need for renal replacement therapy, recovery from oxygen dependence, overall mortality and post COVID-19 complications were noted.

Statistical analysis

Descriptive statistics were expressed as percentage and mean. Chi-square test for associations was applied to ascertain the association between chronic graft dysfunction and AKI, however, could not be applied to find the significance of dose modification in causing AKI due to low numbers. Fischer's exact test was applied to analyse the significance of inflammatory markers in AKI. Kruskal Wallis test was applied to compare CT severity scores with inflammatory markers. Results with $P < 0.05$ were considered to be significant. The data collected were noted and analysed using Statistical Package for Social Sciences (SPSS) software.

Results

Out of 400 renal transplant recipients screened, 28 patients developed COVID-19. Most patients belonged to the age

group of 30 years-49 years (13 patients in age group 30 years to 39 years and 10 patients in the age group 40 years to 49 years) with male predominance (86%). Ninety two percent of patients had hypertension as their comorbidity. Forty two percent patients had chronic glomerulonephritis and 39% patients had chronic interstitial nephritis as their native kidney disease. B positive blood group was the predominant blood group category (43%) among the patients considered for study. Duration since transplantation was three to five years in ten patients and five to ten years in 9 patients (Figure 1).

Eighty-two percent of patients underwent live related renal transplant and 17.8% patients underwent deceased donor renal transplant. Pre-existing chronic graft dysfunction was present in 60.7% patients. Immunosuppressant induction was given in 57.1% patients, of which 87.5% received anti-thymocyte globulin (ATG) and the remaining 12.5% received basiliximab as the induction agent. COVID-19 positivity rate was predominantly higher during second wave (64.2%) in comparison with first wave (28.5%) and third wave of COVID-19 (7.1%). Only two patients who turned positive had received the first dose of COVID-19 vaccination. Household contact history for COVID-19 was found in 25% patients. Twenty-eight percent patients were isolated at home and 71.4% were quarantined in Institution. Only one patient was asymptomatic and 27 patients developed overlapping symptoms, predominantly gastrointestinal discomfort (57%), other symptoms included fever (46%), cough (35%) and shortness of breath (35%).

AKI was found in 64.2% patients overall, 55.5% patients with AKI had a history of chronic graft dysfunction. Seven patients (41.1%) with chronic graft dysfunction did not develop AKI. The average creatinine in patients with AKI was 2.21 mg/dL (among those without chronic graft dysfunction) and 3.01 mg/dL (among those with chronic graft dysfunction). The average creatinine in patients without AKI was 1.06 mg/dL (among those without

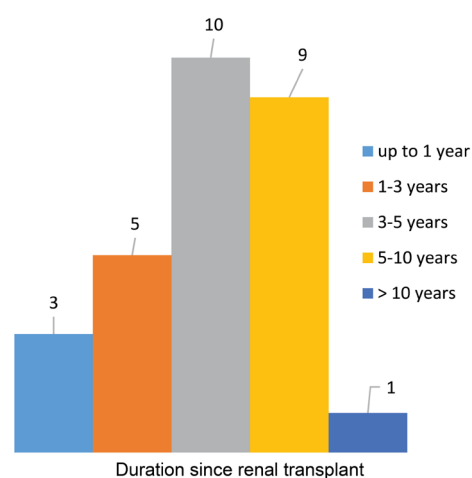


Figure 1. Distribution of patients according to duration since transplantation

chronic graft dysfunction) and 1.62 mg/dL (among those with chronic graft dysfunction). Although the incidence of AKI was higher among patients with chronic graft dysfunction, the findings were not statistically significant ($P=0.6$)

Oxygen was required in 42.8% patients, of which only one patient required invasive ventilation. Prone strategies were adopted in 16.6% patients among those who required oxygen support.

Computerized tomography (CT) scan was performed to assess the severity index and extent of lung involvement. COVID-19 infection was categorized into 3 categories based on the CT severity scores. 50% patients had mild infection (CT score <8), 25% patients had moderate infection (CT score between 8 to15) and 25% patients had severe (CT score >15) infection. AKI was observed in 28.5% patients among mild infection and 100% patients among moderate and severe infections.

Mean total leukocyte count, CRP, ferritin, lactate dehydrogenase (LDH) and D-dimer in patients with COVID-19 was 6180 cells/mm³, 27.1 mg/dL, 956.9 µg/L, 311 units/L, 3.62 mg/L respectively. Each parameter was further sub-categorized for the ease of comparison with AKI, as depicted in Table 1.

No significant association was found between incidence of AKI and the inflammatory markers, except serum ferritin ($P<0.05$), however a significant association was found between CT severity score and CRP ($P=0.005$), ferritin ($P=0$), LDH ($P=0.012$), D-dimer ($P=0.003$).

Average tacrolimus trough level noted in patients with AKI was 6.58 ng/mL versus 5.74 ng/mL in those without AKI. Mean tacrolimus levels in patients with mild COVID-19 (CT score <8) was 5.75 ng/mL, moderate

COVID-19 (CT score of 8 to 15) was 7.67 ng/mL and severe COVID-19 (CT score >15) was 5.95 ng/mL. Ninety-six percent patients received tacrolimus prior to COVID-19. Dose reduction was done in 40.7% patients who received tacrolimus, of which 81.8% patients developed AKI and 54.5% patients required oxygen support. Among patients without dose reduction, 12.5% patients developed AKI and 31.2% required oxygen support (Table 2, Figures 2 and 3).

Mycophenolate mofetil (MMF) was given in 85.7% patients prior to COVID-19 infection. The drug was withheld or dose was reduced in 33.3% patients. Relationship between dose of MMF and incidence of AKI is as depicted in Table 2 and Figure 3. Oxygen support was required in five patients on same dose of MMF in comparison with five patients on modified dose of MMF (or dose withheld) (Figure 2).

Steroid use was noted in terms of prednisolone equivalents. All patients received steroids prior to COVID-19. During COVID-19, same dose was continued in 46.4% patients, dose reduction was conducted only in one patient (3.5%) and dose was increased in 50% patients. Among those patients in whom same dose was continued, 30.7% patients developed AKI and 15.3% patients required oxygen support. Among patients with decreased steroid dose, 100% patients developed AKI, however without oxygen requirement. In patients with higher dose of steroids, 92.8% patients developed AKI and 71.4% patients required oxygen support (Table 3).

Other supportive measures like anticoagulation were given in 50% patients, of which 100% patients developed AKI and 78.5% required oxygen support. Remdesivir was administered to 35.7% patients at dosage adjusted to creatinine clearance, of which 100% patients developed

Table 1. Inflammatory markers in COVID-19 positive renal transplant recipients

Inflammatory markers (units)	Description	Count	AKI Count	AKI %	P value
WBC (cells/cubic mm)	<5000	11	8	72.73%	0.39
	5000-10000	15	8	53.33%	
	>10000	2	2	100.00%	
CRP (mg/L)	<10	16	7	43.75%	0.07
	10-50	6	5	83.33%	
	50-100	3	3	100.00%	
	>100	3	3	100.00%	
Ferritin (µg/L)	<200	3	1	33.33%	<0.05
	200-500	11	2	18.18%	
	500-1000	9	9	100.00%	
	>1000	6	6	100.00%	
LDH (units/L)	<300	15	8	53.33%	0.47
	300-500	10	8	80.00%	
	>500	3	2	66.67%	
D-dimer (mg/L)	<0.5	3	2	66.67%	0.19
	0.5-5	20	8	40.00%	
	>5	4	4	100.00%	

WBC: White blood cell count, CRP: C-reactive protein, LDH: Lactate dehydrogenase, AKI: Acute kidney injury.

Table 2. Relationship between immunosuppressant dose reduction and graft function

	Patients receiving pre-COVID-19	Dose reduction	AKI	% AKI	O2 requirement	%O2 requirement
MMF	24	8	8	100%	5	63%
TAC	27	11	9	82%	6	55%
Cyclosporine	1	1	1	100%	1	100%
Azathioprine	3	2	2	100%	2	100%
Everolimus	1	0	0	0%	0	0%
	Patients receiving pre-COVID-19	Dose maintained	AKI	% AKI	O2 requirement	%O2 requirement
MMF	24	16	7	44%	5	31%
TAC	27	16	2	13%	5	31%
Cyclosporine	1	0	0	0%	0	0%
Azathioprine	3	1	0	0%	0	0%
Everolimus	1	1	0	0%	0	0%

MMF, Mycophenolate mofetil; TAC, tacrolimus; AKI, acute kidney injury.

both AKI and required oxygen support (Table 4).

Outcomes of COVID-19 on renal transplant recipients was noted as patient’s recovery from AKI (61.1 %), those patients with AKI requiring renal replacement therapy (RRT) (11.1%), recovery from oxygen dependence (100%), mortality rate (7.1%) and post COVID-19 complications

(17.8%). The COVID-19 complications observed, includes mucormycosis, new onset diabetes, delayed recovery beyond 1.5 months with prolonged COVID-19 positivity state, pancreatitis and nephrotic syndrome and dialysis dependence after COVID-19 (Table 5).

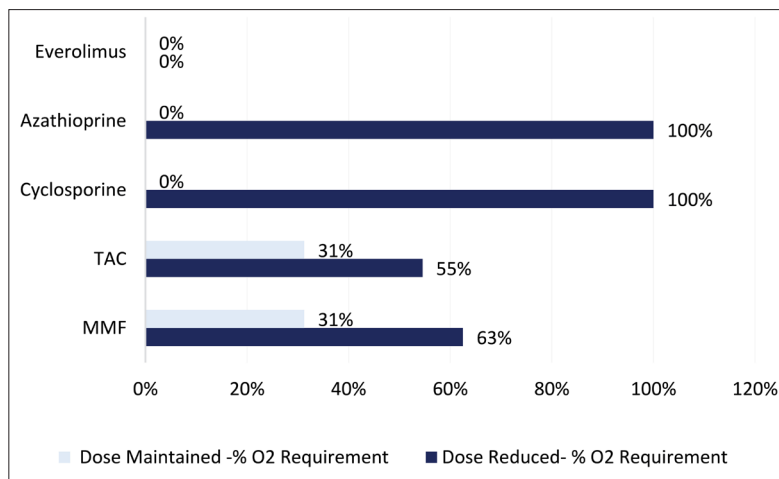


Figure 2. Influence of immunosuppressants on oxygen requirement.

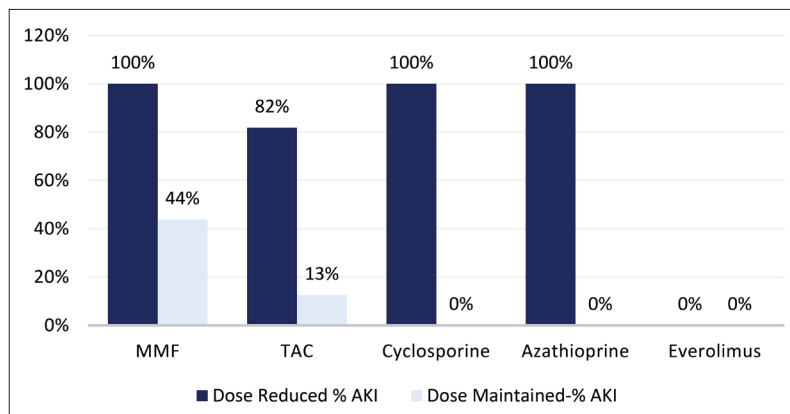


Figure 3. Influence of immunosuppressants on AKI.

Table 3. Relationship between steroid dose modification with graft function and COVID-19 severity

	No of patients who received pre-COVID-19	Dose Modified in	AKI	% AKI	O2 Requirement	% O2 Requirement
Steroid	28					
Dose increased		14	13	93%	10	71%
Dose reduced		1	1	100%	0	0%
Dose maintained		13	4	31%	2	15%

Table 4. Effect of other supportive COVID-19 management therapies on graft function and disease severity

Medications	Patients who received	AKI	AKI %	O2 Requirement	% O2 Requirement
Anticoagulation	14	14	100%	11	79%
Hydroxychloroquine	1	1	100%	1	100%
Ivermectin	0	0	0%	0	0%
Antibiotic cover	25	18	72%	12	48%
Remdesivir	10	10	100%	10	100%
Antifungals	1	1	100%	1	100%

Table 5. Outcomes of COVID-19 on renal transplant recipients.

Treatment outcomes	No of patients
Recovery from AKI	11
Requiring renal replacement therapy during infection	2
Relieved of oxygen dependence	12
Overall mortality	2
Post-COVID-19 complications (mucormycosis, diabetes, nephrotic syndrome and pancreatitis, dialysis dependence, prolonged viral shedding >1.5 months)	5

Discussion

The lungs are the most commonly affected organ by COVID-19, followed by the kidneys. Infection with SARS-CoV-2 not only causes new renal damage but also increases the difficulty of treatment of patients with underlying renal disease. Renal involvement mainly manifests as renal tubular injury. Renal complications must be given increased attention in the diagnosis and treatment of COVID-19 (6). The impact of direct virus injury complicated by dysregulated hyperimmune response with release of various cytokines in COVID-19 contributes to complexity of management. The largest concern at present being, measures to tailor the immunomodulating agents during active viral infection (7).

The incidence of COVID-19 in renal transplant patients was found to be 7% in this study in comparison with 5.2% in the study by AlOtaibi et al in Kuwait where 2000 patients post renal transplant were screened, of which 104 developed COVID-19. Most of them were males aged around 49 years, similar to this study (8).

The median time from transplant to onset of infection was around 5 years, similar to our observation. GI discomfort (57.1%) and fever (46.4%) were the most common symptoms as per our study in comparison with

study by Santeusano et al (9), conducted in New York in a tertiary care centre where respiratory symptoms were predominant. 82% patients in this study were those who underwent live related renal transplant in comparison with 44.7% in the above study (9), probably due to increased prevalence of live related transplants in India and demand versus supply gap.

Sixty-four percent patients developed AKI in the current study in comparison with 33% in a study by Bossini et al conducted in Italy on 53 renal transplant recipients (10). This difference could be attributed to higher incidence of AKI among moderate and severe COVID-19 as per CT severity score in this study. As per a literature review by Imam et al (11), AKI was observed in 34.1% patients. Chronic graft dysfunction was noted in 85% patients in comparison with 60.7% in the present study, probably due to difference in sample size. However, incidence of AKI was more commonly observed in patients with increased baseline creatinine (58.8%) and this was in concordance with the literature review (11).

Inflammatory markers such as total leucocyte counts (WBC), CRP, ferritin and D-dimer were studied and were found to be >10000 cells/cubic mm, >50 mg/dL, >500 µg/L, >5 mg/L, respectively among patients who

developed AKI. However, other studies have compared the relationship between the above-mentioned parameters with acute respiratory distress syndrome and mortality (10,11), but not with the incidence of AKI. Hence further research with larger sample size is required to establish specific cut-offs to alert the clinician to vigilantly watch for development of AKI.

In the study by Santeusano et al (9), 78.9% patients with COVID-19 received lymphocyte depleting agents and 7.9% received IL2 inhibitors as induction agents compared to 87.5% (n=14 out of 16 induced patients) ATG and the remaining 12.5% (n=2) received basiliximab as the induction agent in this study. Immunosuppressant reduction was not associated with graft rejection or improved survival among patients studied by Santeusano et al (9). Conversely, both higher incidence of AKI and increased oxygen requirement was found among patients with reduced dose of immunosuppressants (tacrolimus, MMF, cyclosporine and azathioprine). However, high incidence of AKI and higher oxygen requirement was observed among patients who received higher than usual dose of steroids, which was warranted due to the disease severity itself (secondary to cytokine storm). As per the TANGO Consortium (12), that observed 144 patients, the incidence of AKI was 52.1% with tacrolimus reduction in 22.9%, MMF reduction in 67.9% and increased dose of steroids in 66%. This was in accordance with the current study, where overall incidence of AKI was 64.2%, with tacrolimus reduction in 40.7%, MMF dose reduction in 33.3% and increased dose of steroids in 50% patients.

The study by Favà et al (13) conducted in Spain on 104 patients, the overall mortality ranged around 27%, in comparison with 14% in current study, as majority of those patients were elderly and suffered from pre-existing pulmonary disease. These figures were close to those obtained in New York (28.9%) (9) and 33% in Italy (10) with the discrepancy being attributed to smaller sample size of the current study. Gasparani et al stated (14) that 20% patients with acute on chronic kidney disease were dialysis dependent after recovery from COVID-19 as compared to 11.1% patients in current study, although not many studies indicate RRT dependence among transplant patients after recovery from COVID-19. A literature review (11), stated that 62% had complete clinical recovery similar to present study (61%).

We acknowledge that there are limitations when we attempt to extrapolate our findings as this was a relatively small patient cohort at a single transplant centre and was not adequately powered to detect small differences in patient characteristics that may influence patient outcomes. Additionally, although patient management and treatment selection were guided by institutional protocols, these protocols were subject to individual clinical judgement and evolved over the course of the pandemic as further data became available.

Conclusion

- Patients with higher CT severity score, and those with pre-existing chronic graft dysfunction should be closely monitored for development of AKI.
- Markers such as total count >10000 cells/mm³, serum CRP >50 mg/L, ferritin>500 µg/L, LDH of 300-500 units/L and D-dimer >5 mg/L, requires high vigilance for development of AKI.
- Incidence of AKI was found to be higher on reduction of immunosuppressant doses, however, larger numbers are required to establish a significance.
- Patients should be followed up for post COVID-19 complications.

Limitations of the study

This study infers from results obtained from a small cohort of COVID-19 positive renal transplant recipients in a single tertiary care centre in South India. However, larger numbers are necessary to ascertain the effect of immunosuppressant modification on graft function and course of the infection.

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Author's contribution

Conceptualization: Ganesan Geethanjali, Elumalai Ramprasad.

Data curation: Ganesan Geethanjali.

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Ethical issues

This study was conducted according to ethical standards of human experimentation in accordance to the Helsinki Declaration. The institutional ethical committee at Sri Ramachandra Institute of Higher Education and Research (SRIHER) University approved all study protocols (IEC ethical code# CSP-MED/21/SEP/71/128), CTRI No.CTRI/2021/09/036848. The study was exempted from written consent by the institutional ethics committee as it was a retrospective observational study. Ethical issues including plagiarism, data fabrication, double publication have been completely observed by the authors.

Conflicts of interest

The authors declare that they have no competing interests.

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None. All investigations done were a part of basic standard of

treatment and the patients incurred no extra costs due to the study.

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