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COVID-19 Infection in Renal Transplant Recipients: Experience from a Tertiary Care Center in Nepal

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ABSTRACT

Introduction

COVID-19 pandemic has challenged the health system globally specially the low to middle income countries. Renal transplant recipient is at risk due to immunosuppressed state. The course of the disease and its outcome is not completely known and there is scarcity of information from developing world.

Methods

The study was carried out at Tribhuvan University Teaching Hospital, Kathmandu from May 2020 till May 2021. All of the renal transplant recipients infected with COVID-19 virus were included in the study. Duration of transplantation, recipient's comorbidities, clinical presentation including laboratory investigations and outcome in terms of hospitalization, need of intensive care, and need of mechanical ventilation, organ failure and mortality were studied.

Results

There were 71 patients (male/female: 60/11, mean age 42.6±10.4) were included in the study. 72% patients (n=51) required hospitalization. There were 15 patients (21%) who expired. Patients requiring mechanical ventilation were 14 (19.7%), 24 (33.8%) required intensive care, 10 (14%) required hemodialysis support during admission. A prior history of rejection, presence of diabetes, graft dysfunction at baseline, and a higher creatinine at baseline was associated with mortality. Hypoxia, leucopenia, lymphopenia was predictive with mortality. Raised inflammatory markers as d-Dimer, LDH, development of acute kidney injury was associated with mortality. Presence of acute kidney injury was associated with increased risk of mortality, need of intensive care and prolonged hospitalizations.

Conclusion

COVID-19 infection in renal transplant recipients carries a high risk for mortality. The factors that correlated with risk for mortality were hypoxia, leucopenia, high inflammatory markers and need of mechanical ventilation.

Keywords
COVID-19, mechanical ventilation, mortality, renal transplantation

INTRODUCTION

Corona virus disease (COVID-19) is caused by the single stranded RNA virus called Severe Acute Respiratory corona virus 2 (SARS CoV 2).[1] Since the first reports of cases from Wuhan, a city in Hubei province of China in the end of 2019, cases have been reported in all continents.[2] The disease has infected more than a quarter of billion people worldwide, the biggest pandemic the world has seen in more than a century.

The clinical presentation of COVID-19 infection is highly varied up to 33 percent not developing symptoms.[3] A report of 44,500 confirmed infection showed mild, severe and critical disease have been reported to occur in 81%, 14% and 5% respectively.[4] Similarly an extensive report of 1.3 million cases revealed a hospitalization rate of 14% with 2% admissions to intensive care unit.[5,6]

Nepal has faced two waves of the disease and an ordering of national lockdown by the government. More than 8,00,000 cases have been reported in the country with a high infection rate per population,[7] with the pandemic causing exhaustion of available resources and divergence of medical personnel to care of covid infected patients.

Renal transplant recipients represent a unique vulnerable population owing to their immunosuppressed states, multiple comorbidities and frequent contact with the health care system. Information about the manifestations, evaluation and treatment of the disease in this group is constantly evolving. Data from developing countries are still lacking.

METHODS

We performed this study with the aim to assess the outcome of COVID-19 infection in transplant recipients. Our study is a retrospective cross-sectional study conducted at Tribhuvan University teaching hospital, Kathmandu, Nepal, a tertiary referral center in the country. All the renal transplant recipients who developed COVID-19 infection during the period of May 2020 to May 2021 were included in the study.

The diagnosis of patients was based on clinical signs symptoms and radiological findings and confirmed with a positive real time polymerase chain reaction (RT-PCR) from a nasopharyngeal and/ or an oro-pharyngeal swab. Patients with lack of data on survival and discharge were excluded from the study.

Patient's pre-transplant demographics, comorbidities, baseline immunosuppression, prior events were recorded from patient's record file kept at department of nephrology and transplantation. Patient's clinical symptoms, signs, vitals, laboratory investigations, complications encountered, therapeutic measures and interventions provided and clinical outcome were reviewed and recorded by the investigators.

As dictated by institutional protocol the severity of illness was divided into four categories.

- Mild COVID-19 - have symptoms of covid pneumonia (fever, cough, and myalgia) but no dyspnea or abnormal chest imaging or hypoxia.
- Moderate COVID-19 - have symptoms including clinical evidence of lower respiratory disease or abnormal chest imaging but pulse oximetry less than or equal to 94% on room air (90-94%)
- Severe COVID-19 - Pulse oximetry is less than 90% on room air, respiratory rate > 30 bpm or lung infiltrates > 50%
- Critical COVID-19 - In respiratory failure, septic shock and/or multiple organ dysfunctions with need or impending need for invasive ventilation

Patients with mild disease with no complications were evaluated and sent for self-quarantine/ home isolation as dictated by national protocol at the time. These patients were reviewed daily and closely monitored. Patients with higher severity of disease, complicated course and requiring oxygen therapy were admitted to ward or intensive care as their clinical condition dictated. Patients who were not able to isolate/ quarantine due to various reasons were admitted in the hospital as well.

Patient's treatment was dictated by their severity of infection. Out patients were managed symptomatically and their immunosuppression were not modified. Antimetabolite was decreased or reduced in patients with moderate, severe and critical disease or in mild cases that did not show an improvement in first few days. Calcineurin inhibitor (CNI) was adjusted according to severity of the illness to target trough level of tacrolimus of 4-6 ng/ml with levels <4 ng/ml preferred for patients with critical disease. Hypoxic patients were treated with bolus of corticosteroids either dexamethasone or methylprednisolone or an increased dose of prednisolone. All modifications were made after review in department of nephrology and transplantation. Use of covid specific therapies as remedesivir, convalescent plasma etc. was determined by institutional protocol, availability at the time of treatment and patient's illness features. The primary outcome was in hospital mortality. The secondary outcome included need of intensive care, development of acute kidney injury and duration of hospitalization.

The analysis was performed using IBM SPSS statistics for windows version 25.0. Descriptive statistics was summarized as numbers, percentages for categorical variables and mean, median standard deviation, interquartile range (IQR) for continuous variables where necessary. Categorical variables

were compared with the chi square test or Fisher's exact test. Non parametric variables were analyzed with student's t test or Mann-Whitney-U-Test in case of abnormal distribution of the data. A p- value of <0.05 was considered significant.

RESULTS

We enrolled consecutive renal transplant recipients with confirmed COVID-19 infection that came under our care. There were a total of 71 cases living related kidney transplants recipients of confirmed COVID-19 positive infection who came under our care. Fifty-one (72%) of them were hospitalized while 20 (28%) patients were managed under self-isolation and home quarantine. Sixty (84%) patients were male 11 (16%) patients were female. The mean age of patient population was 42.6±10.4years.

The presenting category of illness severity (n= 71) was mild 25 (35%), moderate 11 (15%), severe 35 (50%). Among the admitted patients (n=51), the worst severity of illness was mild 1(2%), moderate 10(20%), severe 23(45%), and critical 17(33%).

Mean duration from transplantation was 67.7±44.4 months. Forty nine (96%) patients received induction by a rATG (anti thymocyte globulin) while 2(4%) patients received basiliximab. Prior history of graft rejection was present in 14 (27%) patients, native kidney disease recurrence in 11(22%). Hypertension was present in 44 (86%) patients, Diabetes in 16(32%) patients. Use of an ACE inhibitor or an ARB was seen in 25(49%) patients. The immunosuppressive regimen consisted CNI, antimetabolite and prednisolone. Mean baseline serum creatinine was 141.6±86.4 millimol/l. The baseline characteristics of the patients are presented in Table 1.

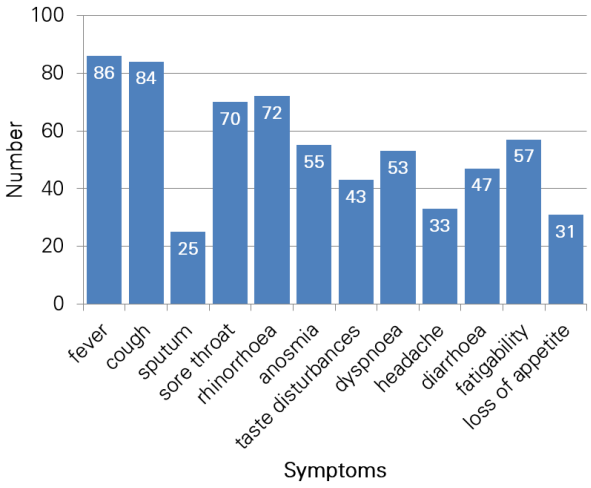

Figure 1. Frequencies of various symptoms

All but 3(4%) patients were symptomatic. Fever (86%) and cough (84%) were the most frequent presenting features on presentation (Figure 1). The mean days of symptoms prior to testing were 4.86±2.5 days. The mean days of symptoms prior to admission were 11.39±5.8 days with more than 6 days passing between time to diagnosis and time to admission.

There were 45(88%) patients requiring oxygen at presentation with 77% of these patients requiring oxygen more than 2 L/min. There were 22(43%) patients having saturation of O_2 at or above 90% while 29(57%) had saturation below 90%. The severity of the disease at presentation was varied. Of them 5 (10%), 11 (22%) and 35 (68%) patients presented with mild, moderate and severe disease respectively. We noticed that the severity of illness deteriorated during hospitalization in many patients.

Table 1: Transplant demographics of the infected patients

Pre-illness demographics	Total		Expired		Improved		p value
	%/median	%/IQR	%/median	%/IQR	%/median	%/IQR	
Age	40	13	41	15	39	17.75	0.27
Female	7	13.7	2	13.3	5	13.9	1
Male	44	86.3	13	86.7	31	86.1	
Rejection in 1 year	3	5.9	1	6.7	2	5.6	1
Rejection ever	14	27.5	7	46.7	7	19.4	0.047
Disease recurrence	11	21.6	5	33.3	6	16.7	0.35
prior graft dysfunction	25	49.0	11	73.3	14	38.9	0.03
DM	16	31.4	8	53.3	8	22.2	0.03
HTN	44	86.3	15	100.0	29	80.6	0.09
ACEI/ARB use	25	49.0	8	53.3	17	47.2	0.69
Duration from Tx	67.7	44.4	78	81	48	60.75	0.058
Prior Creatinine µmol/l	71	100	129	92	109	31.5	0.009

DM: Diabetes mellitus, HTN: hypertension, ACEI: Angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker

Table 2. Laboratory parameters among the admitted patient

Investigations	Total		Expired		Improved		p value
	%/median	%/IQR	%/median	%/IQR	%/median	%/IQR	
Hb (g/dl)	13.5	2.8	13.7	3.5	13.2	2.825	0.94
WBC (/mm^3)	4700	3000	3900	2100	4700	3777.5	0.049
ANC (/mm^3)	3300	2900	2900	1800	3400	3050	0.09
ALC (/mm^3)	900	500	700	300	1100	575	0.009
Platelets(/mm^3)	147000	95000	145000	98000	163000	93000	0.57
Creatinine (umol/L)	159	106	187	156	133.5	102.75	0.10
albumin(g/L)	38	20	36	8	38	6.5	0.19
D-dimer (mcg/ml)	1.25	1.25	2.31	1.2	0.935	0.6725	0
ALP (U/L)	184	57	200	26	170	57.5	0.06
ALT (U/L)	48	33	68	27	45	22.5	0.03
AST(U/L)	59	36	78	28	51	37	0.03
Ferritin (ng/ml)	485	436	496	303	477	516	0.11
LDH (U/L)	480	231	642	275	476	159.75	0.03
Creatinine at outcome	136	273	392	258	119	64.25	0

Hb: hemoglobin, WBC: white blood cell count, ANC: Absolute neutrophil count, ALC: Absolute lymphocyte count, ALP: Alkaline phosphatases, ALT: Alanine transferase, AST: Aspartate transferase, LDH: Lactate dehydrogenase

The worst category on admission was 1 (2%), 10(20%), 23(45%), 17(33%) mild, moderate, severe, and critical illness respectively. It was observed that worse category of illness during the course of illness rather than the presenting category was associated with a worse prognosis.

Mean hemoglobin concentration was 13.5 g/dl. Leucopenia was observed frequently, in 22 patients (43%). Acute kidney injury, cytopenia and acute liver dysfunction were observed frequently among admitted patients. Thirty-three (65%) patients had acute kidney injury in view of raised creatinine and 42(83%) had some degree of proteinuria observed in urinalysis. Ten patients (14%) required hemodialysis support during their illness period. Cytopenia was observed in 22(43%) patients and transaminitis was seen in 20(39%) patients. Inflammatory mediators like hypoalbuminemia, ferritin and LDH were raised in many patients. (Table 2).

There were 23 (45%) patients managed in the general ward while 28 (55%) patient required close monitoring with 19 (37%) patients required intensive care support. Noninvasive ventilation (NIV) was required by 18(35%) patients while Mechanical ventilation was required for 14 (28%) of patients and none of them survived.

CNI was adjusted in 25 (49%) of the patients. Target trough level of 4-6 ng/ml was maintained. Antimetabolite were adjusted in all (100%) admitted patients. 13 (25.5%) patients had a decrease in their dose while 38 (74.5%) patients had their drug stopped completely. Forty-nine (96.9%) admitted patient received steroid boluses with dexamethasone (74.5%) methylprednisolone (9.8%) and raise in dose of oral prednisolone (11.8%). Forty four (86.3%) patients received prophylactic anticoagulation. Forty eight (94.1%) received antibacterial antibiotics, most frequently azithromycin. Of them 26 patients received anti-viral remedesivir as a 200 mg bolus on day 1 and 100 mg once a day for next 5 days. It was used in 13 (86.7%) patients who expired and among 13 (36%) among patients who survived. Convalescent plasma was used in 10 patients (19.6%) (Table 3).

There were a total of 15 mortalities (21%) among the infected cohort and represents 2.5% of overall transplant recipients. All of the expired patients were hospitalized. None of the patients who were kept in quarantine/isolation required hospitalization. Presence of a prior history of rejection, history of prior graft dysfunction, diabetes and hypoxia during presentation were statistically significant for mortality. Mean baseline serum creatinine was 141.6±86.4 among the entire cohort with the expired group having a higher baseline creatinine than improved group (187.1±112 vs 133.5±102.7). Leucopenia and lymphopenia were significantly more severe among the expired cohort. Raised inflammatory markers like ferritin, LDH and d-Dimer were significantly higher in patients who expired. Worse the severity of illness worse was the prognosis. A total 17 had critical illness and only 3 survived. All the patients who presented with mild symptoms all survived. None of the patients who required mechanical ventilation (14) survived. Out of 19 patients who required ICU admission only 4 survived. Acute kidney injury was seen in 33 (65%) patients. Ten of these patients (14%) required hemodialysis. Presence of acute kidney injury was significantly associated with mortality, need of intensive care and prolonged hospitalizations.

Table 3. Clinical features and hospital course of admitted patients

Investigations	Number (%)	Expired		Improved		p value
		n/Median	%/IQR	n/Median	%/IQR	
Admission Days						
<7 days	13 (25.5)	4	26.7	9	25.0	0.16
7-14 days	26 (51.0)	5	33.3	21	58.3	
>14 days	12 (23.5)	6	40.0	6	16.7	
O_2 requirement at presentation						
10l	11 (21.6)	7	46.7	4	11.1	0.003
15l	3 (5.9)	2	13.3	1	2.8	
5l	21 (41.2)	6	40.0	15	41.7	
2l	10 (19.6)	0		10	27.8	
SpO_2 at presentation						
>90	22 (43.1)	2	13.3	20	55.6	0.006
<89	29 (56.9)	13	86.7	16	44.4	
Highest temperature						
36-37	4 (7.8)	0	6.7	4	11.1	0.03
37-38	15 (29.4)	1	33.3	14	38.9	
38-39	14 (27.5)	5	40.0	9	25.0	
39-40	14 (27.5)	6	20.0	8	22.2	
40-41	4 (7.8)	3		1	2.8	
Category at ER						
Mild	5 (9.8)	0	6.7	5	13.9	0.05
Moderate	11 (21.6)	1	93.3	10	27.8	
Severe	35 (68.6)	14		21	58.3	
Worst category during admission						
Critical	17 (33.3)	14	93.3	3	8.3	<0.001
Mild	1 (2.0)	0		1	2.8	
Moderate	10 (19.6)	0		10	27.8	
Severe	23 (45.1)	1	6.7	22	61.1	
Highest care needed						
HDU	9 (17.6)	0	100.0	9	25.0	<0.001
ICU	19 (37.3)	15		4	11.1	
Ward	23 (45.1)	0		23	63.9	
Ventilatory support						
NIV required	18 (35.3)	14	93.3	4	11.1	<0.001
MV required	14 (27.5)	14	93.3	0		<0.001
Need of intensive care	24 (47.1)	15	100.0	9	25.0	<0.001
Complications						
AKI	33 (64.7)	15	100	18	50.0	<0.001
Cytopenia	22 (43.1)	11	73	11	30	0.012
Acute liver dysfunction	20 (39.2)	10	66.6	10	27.7	0.013
Secondary infections	20 (39.2)	10	66.6	10	27.7	0.013

SpO_2: saturation of oxygen, HDU: high definition unit, ICU: intensive care unit, NIV: non invasive ventilation, MV: Mechanical ventilation, AKI: Acute kidney injury

Table 4. Results of multivariate analysis

Characteristics	p value	Odds ratio	95% Confidence interval for OR	
			Lower	Upper
Age	0.99	0.052	0.36	1.155
baseline creatinine	1	0.981	0	4.326
Diabetes mellitus	0.99	0.078	0.980	4.86
Prior history of rejection	0.99	1.143	0.47	3.72
Total leucocyte count	0.99	0.97	0	3.882
Absolute neutrophil count	0.99	1.042	0	3.462
Creatinine at outcome	0.02	1.01	1.002	1.02
Absolute lymphocyte count	0.99	1.105	0	7.032
Lactate dehydrogenase	0.049	0.967	0	1.68
D-dimer	0.004	10.04	2.05	49.17
Aspartate transaminase	0.99	23.573	0.87	2.98
Alanine transaminase	0.99	0.036	0	4.23
Secondary infections	0.54	0.432	0.029	6.475
Acute kidney injury	0.99	32.54	0.03	4.89

Patients presenting with atypical symptoms like diarrheal illness were frequently complicated by development of AKI. Among patients who survived 18(50%) patients attained their previous baseline creatinine by discharge. Presence of other complications like cytopenia, acute transaminitis, and secondary infection were also associated with mortality and need of intensive care support. (Table 3).

Multivariate analysis showed that raised levels of d-Dimer and lactate dehydrogenase were significantly associated with mortality (Table 4).

DISCUSSION

Our study showed a mortality rate of 21% among the infected cohort and 29.4% among hospitalized patients. Among all the transplanted patients (n=601) mortality rate comes at 2.5% and the infectivity rate comes at 11.8%. These report are high compared to general population of the country, with infection rate of 2.8% in the population with death rates of 0.4%.[7] The higher infection rate may be linked to multiple factors like chronically immunosuppressed state, presence of multiple comorbidities and lack of self-care, social distancing, and lack of an accessible health facility. Infection transmission from an asymptomatic care giver was also reported. Similarly study conducted in two transplant centers in France, revealed high infectivity in transplanted patients compared to general population, 5% incidence in transplant population compared to 0.3% in general population.[8] But a retrospective analysis conducted in Romania in single center revealed a lesser infectivity rate of only 2.86%.[9]

Varying mortality rates have been reported among various studies ranging from 11% to 46%.[10–13] The rate in our study is higher than in other studies. We took data from patients who presented to a tertiary care center, and the patients were comparably sicker and had severe illness. There could me asymptomatic cases that did not come under our care and recovered elsewhere, this probably reflects in the higher mortality present in our study.

Risk factors for mortality like older age, lymphopenia, raised inflammatory markers (ferritin, LDH, d-Dimer, CRP, and procalcitonin) previous rejection episodes, higher baseline serum creatinine, higher plasma viral load, need of mechanical ventilation, presence of multiple comorbidities and concomitant infections have been shown in multiple studies.[10–14]

Similar risk factors were also present in our study; interestingly age was not associated with mortality among our cohort. Our transplant cohort had a lower age compared to the studies presented from developed world reflecting the difference in the native kidney disease as cause of chronic kidney disease.

Acute kidney Injury was a frequent complication in our study with 33 patients (65%) and one third of these patients (10) progressed to require renal replacement therapy in form of hemodialysis. Development of AKI and need of RRT or associated with worse outcome in our study. Similar findings have been reported in various other studies too.[15] The cause of acute kidney injury are many and probably represent a complex interaction among various factors. Kidney transplant recipients have a solitary functioning kidney, with use of CNI, a higher prevalence of hypertension, diabetes, use of ACE inhibitors and Angiotensin receptor blockers puts the recipient at higher risk of developing acute

kidney injury.[16] Our study reported a slightly higher rate of AKI than other studies.[17] Diarrheal illness was a frequent presenting symptom. Volume depletion and development of pre renal aki probably attributed to this. Among the 18 patients with Aki and had survived only 9 patients (50%) had completely recovered from AKI by the time of discharge from the hospital probably reflecting the time required for recovery of AKI. We did not perform routine biopsies in our patients. Fifty percen of the patients with AKI who survived had resolution of their AKI at the time of discharge probably attributed to acute tubular injury. One of our patients was biopsied due to rising creatinine and increasing proteinuria and revealed antibody mediated rejection. Contributory factors could be the covid infection and modification of immunosuppression regimen. Various pathological entities have been described in Covid patients with AKI; Acute tubular injury, collapsing glomerulopathy, thrombotic microangiopathy present in kidney biopsies and antibody and T-cell mediated rejection in allografts.[18,19]

Our study was not designed to review the effect of various treatment modalities on the consequences of infection. It was seen that treatment with remedesivir, convalescent plasma was more frequently used among patients in intensive care and those who expired but its effect on disease course could not be obtained. Our cohort of patients had a longer duration of symptom onset and hospitalization (mean days 7.4 days SD 2.5); explained by various factors like unavailability of specialist care, difficult travel due to lockdown and financial constraints which probably caused a delay. It probably reflects the progression of the viral infection to a later stage and clinical benefit that could be expected from the treatment was not seen.

Our study does have limitations. We conducted a single center study in a tertiary referral center. Small sample size and retrospective nature of the study was not powered to evaluate the effect of various treatment modalities on outcome of the disease. Although the immunogenicity and efficacy of COVID-19 vaccines are uncertain in transplant recipients, our cohort of patients reported to us before vaccination program was available in the nation, hence we could not assess the effect of vaccination in these patients.

CONCLUSION

The infectivity rate and mortality rates are higher in the Transplant recipients when compared to general population of the country. Covid 19 infection in renal transplant recipients frequently leads to AKI requiring renal replacement therapy.

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CONFLICT OF INTEREST

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