

RESEARCH PAPER

Outcome of Kidney Transplant Recipients During Covid-19 Pandemic

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Abstract

Background: Kidney recipients constitute a vulnerable group of population and may have high risk of morbidity and mortality when infected with COVID-19.

Objective: To assess the overall outcome as well as the incidence and impact of COVID-19 among recipients who underwent transplantation during the pandemic

Methods: A pre-designed follow up protocol was set to prospectively analyse the data obtaining from the recipients who underwent renal transplantation since 8 March 2010, the first appearance of COVID-19 in Bangladesh till 31 December, 2020. Outcome parameters were renal functional status; surgical, urological, immunological and medical complications; and incidence of COVID-19 and its outcome during the first 12 weeks post-transplant period.

Results: Out of 100 patients, 82.0% were male and 18.0% were female. Serum creatinine levels ($\mu\text{mol/L}$) at 4, 8 and 12 weeks post-transplant were 200 in 6.0%, 5.0% and 6.0% respectively. Graft nephrectomy was done in 3 cases due to vascular complications. Five (5.0%) patients presented with symptoms of COVID-19, among them, 2 cases were confirmed with RT-PCR. There were 6 death cases, and septicaemia was the most common cause of death. The overall mortality rate was 6.0% in our study population but in COVID-19 confirmed cases it was 50.0%.

Conclusion: During this pandemic, the overall outcome of renal transplantation was excellent and the incidence of symptomatic COVID-19 among transplant recipients was not higher than the incidence observed in general population of Bangladesh. But among the COVID-19 confirmed recipients, mortality rate was significantly higher.

Keywords: Kidney transplant, Kidneys transplant recipients, Impact of COVID-19, Serum creatinine

Introduction

COVID-19 (coronavirus disease 2019) has been declared as a global pandemic on 11 March, 2020 by WHO and people of every corner of the globe are affected by it.¹ Social distancing is a very important factor and is recommended to prevent the spread of this deadly virus. ESRD patients on renal replacement therapy needs frequent hospital visits to get their life saving treatment and it is a very difficult routine for them to maintain social distancing and other precautions. During this pandemic, Center for Kidney Diseases and Urology Hospital, Dhaka is providing all types of services of renal replacement therapy

including kidney transplantation thrice per week, without stopping activities for a single day.

Kidney transplant recipients are definitely in high risk group and may suffer from severe illness of COVID-19 as they are getting immunosuppressive and highly likely to be associated with other comorbidities such as diabetes, hypertension, cardiovascular disease etc. It has been suggested that some immunosuppressive drugs that are routinely used in post-transplant period such as prednisolone and mycophenolate may have beneficial effects in patients with COVID-19.² Similar mode of presentation and early recovery of kidney transplant recipients with COVID-19 as seen in general population has been reported in some studies.³⁻⁵ However, the magnitude of COVID-19 pandemic is progressing and mortality is increasing daily with evidence of high mortality rates among vulnerable groups.

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Different studies from Montefiore Medical Center and Columbia University, USA, St. George's University Hospital National Health Service Foundation Trust, UK and Spedali Civili University Hospital, Italy have shown high mortality rate, ranges from 20% to 28%, among renal transplantation patients with COVID-19, whereas only 1% to 5% mortality rate among general patients infected with COVID-19.⁶⁻⁹ Among general population, male sex, age, smoking, hypertension, diabetes carry poor outcome but there is a lack of evidence of risk factors and high mortality rate among COVID-19 infected kidney transplant recipients.¹⁰

Since the start in 2007, a total of 850 cases of live related renal transplantation were performed in this hospital. The first reported case of COVID-19 in Bangladesh was on the 8th March, 2020 and during the pandemic more than 100 cases of kidney transplantation has been done. Here, a single-centre experience at Center for Kidney Diseases and Urology Hospital, Dhaka, Bangladesh; was described regarding early overall outcome as well as the incidence and outcome of symptomatic COVID-19 in renal transplant recipients during this pandemic. The study was aimed to assess outcome of kidney transplant recipients during COVID-19 pandemic.

Materials and Methods

Study population and data collection: In this prospective study, all the consecutive recipients prior selected by multidisciplinary team and who underwent live related renal transplantation at Center for Kidney Diseases and Urology Hospital, Dhaka, Bangladesh between March and December 2020 were included in the study. All patients were under active follow up protocol for 12 weeks from the date of transplant. No patient was excluded from this study because post-transplant patient recovery and graft function and all urological, medical and immunological complications including graft failure were considered as outcome and none was lost for follow up. Informed written consent was obtained from all patients prior to this study.

Study design and clinical characteristics: This prospective study was conducted between 8 March and 31 December, 2020. All the demographic and clinical characteristics of every recipient candidate were recorded before transplantation. No patient underwent RT-PCR for COVID-19 test as a routine workup unless clinical features and/or biochemical markers are

suggestive of it. After surgery, close monitoring was done in intensive care unit with recording of all clinical and biochemical parameters. Patient was discharged home between 10-14 post-operative days with the advice of follow up at weekly for 4 weeks then bi-weekly for next 6 weeks. During this 12 week period, any patient presents with symptoms of COVID-19 underwent RT-PCR test for confirmation, only COVID-19 confirmed recipients got admitted in hospital but all the symptomatic patients either RT-PCR positive or negative for COVID-19 were considered as COVID-19 positive individual and treated according to updated national and WHO guidelines. There was no dosage modification of maintenance immunosuppression in COVID-19 positive recipients. All clinical, biochemical, radiological parameters and ultimate outcomes were recorded. Additionally, a hotline was established to guide the patients regarding pandemic and to answer any other health related questions.

Demographic and clinical characteristics include age, sex, BMI, Blood group, smoking, associated comorbidities (diabetes, cardiovascular disease, hypertension, chronic respiratory disease), prior transplant, duration of dialysis before transplant and maintenance immunosuppressive drugs.

Main outcome variables: Outcome variables were graft function (serum creatinine), delayed graft function, rejection episode, vascular complications such as dissecting aneurysm, renal arterial thrombosis, disruption, stenosis or aneurysm; renal vein thrombosis or disruption; urological complications such as ureteral fistula/stenosis, pelvic haematoma/lymphocele, scrotal abscess/hydrocele, inguinal or incisional hernia; wound complications such as infection, dehiscence; and medical complications such as bacterial, viral or fungal infection especially COVID-19 infection.

Patients who were diagnosed with COVID-19 infection, collected data included time of infection since transplant, initial presenting features, biochemical markers, computed tomographic findings of chest, renal function during hospital course, medications specific for COVID (support of oxygen, invasive ventilation, antiviral therapy, immunosuppression and renal replacement therapy) and outcomes (cure of infection, readmission and mortality).

Statistical analysis: Statistical analysis was done using SPSS version 26 with fisher exact test and student's t test.

Results

Baseline demographic and clinical characteristics

Active follow-up of 100 consecutive recipients was performed who underwent live related transplantation since 8 March to 3 December, 2020 in Center for Kidney Diseases and Urology Hospital, Dhaka, Bangladesh. The mean age was 35.6±9.7 years, 82.0% were male and 18.0% were female. One patient had the history of prior live related renal transplantation. The mean

BMI of all patients was 22.1±3.1 kg/m². The most common blood group in this study was ‘O’ (35.0%). Thirty-two percent patients had the history of prior smoking. HTN was the most common comorbidities (79%). Sixty-nine (69.0%) patients had received maintenance hemodialysis for less than one year (table I). The induction and maintenance immunosuppression included prednisolone, tacrolimus and mycophenolate.

Table I: Baseline demographic and clinical characteristics of patients underwent live related kidney transplantation (n=100)

Characteristics	Total	Alive	Death	Symptoms related to COVID-19		
				Total PCR-ve	RT-PCR +ve	RT-
Number, n (%)	100(100)	94(94)	6(6)	5(5)	2(2)	3(3)
Age, yr ± SD	35.6±9.7	35.2±9.8	38.7±5.2	30.8±8.3	31±9	30.7±7.8
Sex, n (%)						
Male	82(82)	77(81.9)	5(83.3)	4(80)	2(100)	2(66.7)
Female	18(18)	17(18.1)	1(16.7)	1(20)	0	1(33.3)
BMI, kg/m ² ± SD	22.1±3.1	22.8±3.1	24.1±1.7	20.8±3.2	23±0.2	19.1±3.2
Blood group, n (%)						
A	26(26)	24(92.3)	1(3.8)	2(7.7)	1(3.8)	1(3.8)
B	34(34)	32(94.1)	2(5.9)	2(5.9)	0	2(5.9)
O	35(35)	32(91.4)	3(8.6)	1(2.9)	1(2.9)	0
AB	5(5)	5(100)	0	0	0	0
Smoking, n (%)						
Current	1(1)	1(100)	0	0	0	0
Prior	32(32)	27(84.4)	5(15.6)	3(9.4)	2(6.3)	1(3.1)
Never	67(67)	66(98.5)	1(1.5)	2(2.9)	0	2(2.9)
Comorbidities, n (%)						
DM	4(4)	3(75)	1(25)	1(25)	1(25)	0
HTN	79(79)	73(92.4)	6(7.6)	5(6.3)	2(2.5)	3(3.8)
Prior transplant, n (%)	1(1)	0	1(100)	0	0	0
Donor type, n (%)						
Mother	34(34)	34(100)	0	3(8.8)	1(2.9)	2(5.9)
Father	13(13)	13(100)	0	0	0	0
Wife	31(31)	28(90.3)	3(9.7)	1(3.2)	1(3.2)	0
Daughter	2(2)	2(100)	0	0	0	0
Sibling	16(16)	14(87.5)	2(12.5)	1(6.3)	0	1(6.3)
Aunt/Uncle	4(4)	3(75)	1(25)	0	0	0
Duration of dialysis before transplant, n (%)						
<1 year	63(63)	63(100)	0	3(4.8)	1(1.6)	2(3.2)
1-2 years	19(19)	17(89.5)	2(10.5)	1(5.3)	1(5.3)	0
>2 years	18(18)	14(77.8)	4(22.2)	1(5.6)	0	1(5.6)

Post-transplant renal functional status

On discharge, 7% patients had reached serum creatinine level within normal limit. At the end of 12 weeks follow up the patients who had serum creatinine ($\mu\text{mol/L}$) within normal limit (<120) and between 121 and 150 ($\mu\text{mol/L}$) were 19.0% and 46.0% respectively (figure 1 and figure 2). Two (2.0%) patients had returned to dialysis as graft nephrectomy was done due to renal arterial aneurysm. Patients who infected with COVID-19 developed mild rise of serum creatinine during infective period but two weeks after recovery it returned to almost baseline, 121-150 $\mu\text{mol/L}$ in 25.0% and 151-200 $\mu\text{mol/L}$ in 75.0% cases.

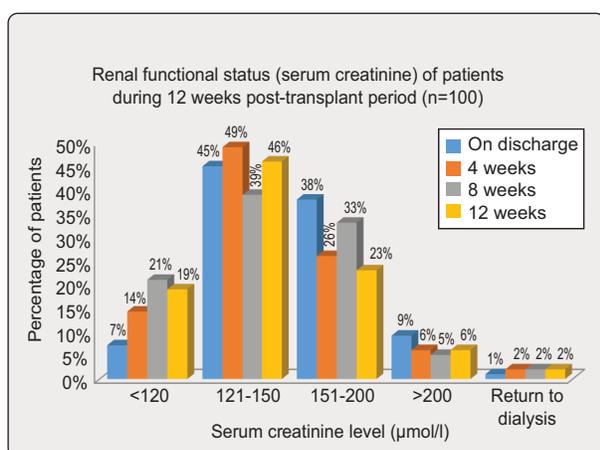


Figure 1: Renal functional status (serum creatinine) of patients during 12 weeks post-transplant period (n=100)

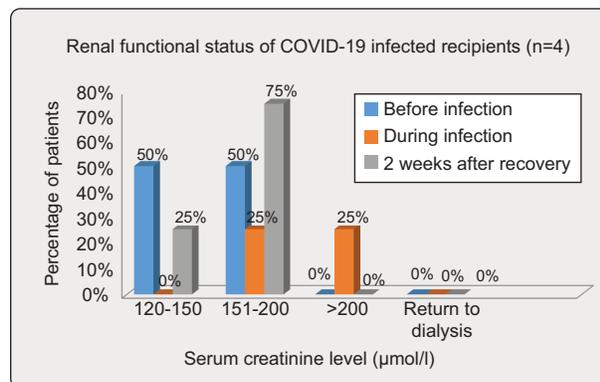


Figure 2: Renal functional status (serum creatinine) of COVID-19 infected transplant recipients (n=4)

Post-transplant complications

During the study period, 6 (6.0%) cases of mortality were noticed, 3 cases due to septicemia; and one of each due to atrial fibrillation, post-COVID-19

complications and arterial anastomotic disruption (figure 3). Two patients developed renal arterial thrombosis, out of them one could maintain renal function avoiding dialysis as thrombosis occurred in one out of two renal artery and another case underwent graft nephrectomy. Two cases developed renal artery aneurysm and underwent graft nephrectomy. One patient developed atrial fibrillation, got admitted in ICU and died. A total of 5 (5.0%) patients presented with symptoms of COVID-19 disease, out of them 2 were confirmed with RT-PCR. Among two confirmed COVID-19 cases, one fully recovered and one died due to post COVID-19 complications. Diabetes Mellitus was developed in 19 (19.0%) recipients.

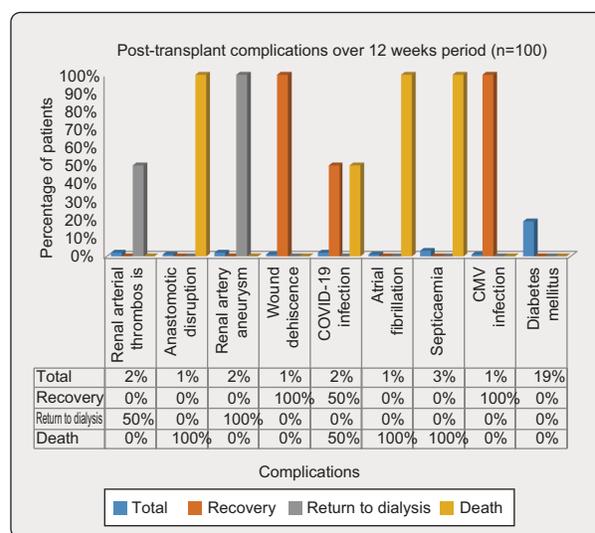


Figure 3: Post-operative complications and outcome of patients during 12 weeks post-transplant period (n=100)

Presenting features and outcomes of COVID-19 infected kidney recipients

A total of 5 (5.0%) patients presented with symptoms of COVID-19 but only 2 (2.0%) cases were confirmed as COVID-19 positive with RT-PCR. The common presenting symptoms were fever, sore throat and cough in 100.0%, 60.0% and 80.0% of patients respectively. On presentation mean SPO₂ and body temperature ($^{\circ}\text{F}$) were 95.6 ± 1.9 and 101.4 ± 1.1 respectively (table II). Blood markers were elevated in all the suspected COVID-19 recipients including RT-PCR for COVID-19 positive and negative cases. Among COVID-19 positive cases, one patient showed up to 50.0% of lung opacities on chest CT. Maintenance immunosuppression was not changed in any cases.

One patient needed invasive mechanical ventilation and developed AKI that required haemodialysis and ultimately died. Out of five suspected cases of COVID-19, four (80.0%) patients were fully recovered.

Outcome related risk factors analysis in COVID-19 infected recipients

Most of the COVID-19 infected recipients were in the age range of between 31-40 years (60.0%), male sex (80) and had the BMI (kg/m²) of 21-25 (60.0%). 'A'

and 'B' blood group individuals were predominantly infected, and 60.0% patients had the history of prior smoking (table III). HTN was the most common comorbidity among affected recipients (100.0%) and duration of dialysis before transplant was less than one year in 60.0% of the patients. The patient who died of COVID-19 was male and had the age range of between 31-40 years, of 'O' blood group, history of prior smoking, diabetes and hypertension with up to 2 years of haemodialysis before transplantation.

Table II: Presentation, treatment and outcomes of transplants recipient infected with COVID-19

Characteristics	Total suspected patients, n=5	RT-PCR for COVID-19 positive patients, n=2	RT-PCR for COVID-19 negative patients, n=3
Clinical symptoms, n (%)			
Fever	5(100)	2(100)	3(100)
Sore throat	3(60)	2(100)	1(33.3)
Headache	2(40)	1(50)	1(33.3)
Cough	4(80)	2(100)	2(66.7)
Dyspnea	1(20)	1(50)	3(100)
Vital parameters (mean ± SD)			
SPO2	95.6(1.9)	94(2.0)	96.7(0.5)
Respiratory rate, /min	25.6(5.4)	30(6.0)	22.7(1.7)
Temperature, 0F	101.4(1.1)	102(1.0)	101(1.0)
Pulse, beats/min	112.4(14.9)	130(6.0)	100.7(2.5)
Systolic BP, mmHg	152.8(13.2)	168(3.0)	142.7(5.4)
Diastolic BP, mmHg	92(4.9)	97(1.0)	88.7(3.3)
Blood markers (mean ± SD)			
Total WBC count, /μL	5620(1256.0)	4650(350.0)	6266.7(1360.8)
Lymphocyte, %	14.6(4.1)	10(2.0)	17.7(1.2)
C-reactive protein, mg/L	20.8(9.3)	30(8.0)	14.7(2.5)
Serum ferritin, μg/L	484(213.2)	715(155.0)	330(21.6)
D-Dimer, ng/mL	324(74.9)	405(55.0)	270(8.2)
Chest CT scan, n (%)			
No findings	3(60)	0	3(100)
Opacities <20%	1(20)	1(50)	0
20-50%	1(20)	1(50)	0
Maintenance immunosuppression, n (%)			
No change	5(100)	2(100)	3(100)
COVID-19 drug treatment			
Favipiravir	5(100)	2(100)	3(100)
Ivermectin	5(100)	2(100)	3(100)
Anti-platelet	5(100)	2(100)	3(100)
Mechanical ventilation, n (%)			
Invasive	1(20)	1(50)	0
Noninvasive	1(20)	1(50)	0
Outcomes, n (%)			
AKI/ Dialysis required	1(20)	1(50)	0
Recovery	4(80)	1(50)	3(100)
Mortality	1(20)	1(50)	0

Table III: Factors and comorbidities related outcome analysis in transplant recipients infected with COVID-19 (n=5).

Factors and comorbidities	Total, n (%)	Alive, n (%)	Dead, n (%)	P Value
Age, year				
≤30	2(40)	2(100)	0	1
31-40	3(60)	2(66.7)	1(33.3)	
Sex Men	4(80)	3(75)	1(25)	1
Women	1(20)	1(100)	0	
BMI, kg/m ²				
≤20	2(40)	2(100)	0	1
21-25	3(60)	2(66.7)	1(33.3)	
Blood group				
A	2(40)	2(100)	0	0.20
B	2(40)	2(100)	0	
O	1(20)	0	1(100)	
Smoking				
Prior	3(60)	2(66.7)	1(33.3)	1
Never	2(40)	2(100)	0	
Comorbidities				
DM	2(40)	1(50)	1(50)	0.523
HTN	5(100)	4(80)	1(20)	
Duration of dialysis before transplant, year	0.4			
<1	3(60)	3(100)	0	
1-2	1(20)	0	1(100)	
>2	1(20)	1(100)	0	

Discussion

End stage renal disease (ESRD) is a serious health issue that needs high costs for treatment. Over the last ten years the incidence and prevalence of ESRD is increasing.^{11,12} Although, the exact underlying causes are not identified, several medical conditions like hypertension, diabetes, obesity etc. may be the aetiological factors. Worldwide the most common cause of ESRD is glomerulonephritis.^{13,14} Underlying causes of ESRD in transplant recipients were not mentioned in this study.

Among different types of renal replacement therapy, renal transplantation is the best treatment option for ESRD patients. It increases the life expectancy of 3-17 years when compared with haemodialysis receiving patients.¹⁵ In this study, all patients underwent live related transplantation as deceased donor transplantation has not yet started in Bangladesh. Living donor graft survival rate is found higher than

that of deceased graft on literature review.¹⁵⁻¹⁸ This study revealed that 12 weeks graft survival rate was more than 95.0% and serum creatinine level was used as an indicator of graft function.

The mean age of the recipients in present study was 35.6 (±9.7) years and 82.0% was male. Observation suggests that these groups can manage a donor with a bit easier way than others as there is huge crisis of donor in Bangladesh. In this study, most of the donor were mother (34.0%) followed by spouse (31.0%). Donor for the older age group of patients with ESRD does not meet the criteria either medically, legally or emotionally.

Hypertension was the most common associated morbidity and majority of the patients who had received haemodialysis for up to one year due to long waiting for transplantation. All patients were evaluated by multidisciplinary team for medical fitness and for

ethical clearance. RT-PCR for COVID-19 of every recipient was not performed as a routine protocol unless symptoms suggested and no recipient was detected as COVID-19 positive during the hospital admission period of two weeks.

Out of 100 patients, six mortality cases were observed during the follow-up of 12 weeks and the most common cause was septicaemia (3 cases). Following renal transplantation mortality risk is increased in early post-transplant period when compared with dialysis and becomes equal after 12-15 weeks, and subsequently there is significant survival benefit in the long-term.¹⁹ Cardiovascular cause followed by infections (commonly urinary tract infection) is the most common cause of mortality in post-transplant period.²⁰ Septicaemia is the most common cause of mortality in this study.

This study also tried to find out the incidence of symptomatic COVID-19 infection among renal transplant recipients and its outcome. Out of 100 patients, total 5 patients were suspected as COVID-19 disease, among them 2 patients were confirmed as positive with RT-PCR but all 5 cases were treated as positive cases. There was one mortality (50.0%) out of two COVID-19 confirmed cases. Symptomatic COVID-19 infection rate was found to be much lower than that reported in Bangladesh among general population (2% vs. 15%). These may not reflect the actual scenario due to small sample size and during follow up period no RT-PCR for COVID-19 was done in any asymptomatic individuals. Several steps were taken to protect these immunocompromised groups, such as follow up in outpatient department on a fixed date and time separated from other patients with isolated and easy access to pathology and radiology section, hotline services, instruction to maintain restricted lifestyle etc.

It is necessary to understand the course of COVID-19 and which group can be managed safely at home and which group needs close monitoring in HDU or ICU. One of COVID-19 infected recipients safely managed at home isolation with smooth recovery. Dosage of immunosuppressive drugs was not changed in patients during the infective course. Wide range of testing related to COVID-19 disease may enable better understanding of the natural history of coronavirus infection in kidney transplant recipients. This will lead to improved overall management of these patients by increasing case detection rate and implementing

patient stratification.

Limitations of this study include small sample size and single centre study. Furthermore, only the patients who presented with symptoms of COVID-19 were identified and reported but screening of whole study population was not conducted where asymptomatic COVID-19 might be present. Also comparison was not made between the clinical courses of COVID-19 between recipient groups with COVID-19 infected general population. Further large scale study is needed to reach in a decision regarding appropriate management of COVID-19 in this vulnerable population.

Conclusion

The incidence of symptomatic COVID-19 among transplant recipients was lower than that of general population in Bangladesh but the mortality rate was significantly higher. Escaping conventional, regular hospital visits by providing dedicated services with hotline communication, isolated follow-up protocol in reserved outpatient department and restricted lifestyle can reduce hospital-acquired COVID-19 infection in these patients. Good overall outcome provides encouragement and enthusiasm to continue transplantation programme during this pandemic.

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