

Review Article

Renal Transplants in Covid-19 Pandemic

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Abstract

Coronavirus Disease 2019 (COVID-19) is a global public health crisis and a pandemic of international concern. The delivery of transplant care worldwide is severely challenged by the COVID-19 pandemic. Along with the inherent risks of immunosuppression, kidney transplant recipients are also at higher risk of getting infected with the coronavirus. The clinical manifestations, treatment, and prognosis of COVID-19 pneumonia in these patients may differ from the general population which poses a challenge to the clinicians in the transplant setting. The transplant community is at crossroads in choosing between the lesser of two evils: continuing immunosuppression and accepting a detrimental outcome when a transplant recipient develops COVID-19 infection versus postponing transplantation operation to a safer period.

Keywords: COVID-19; Pandemic; Renal Transplantation

Introduction

Several coronaviruses are known to cause respiratory infections ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). The novel coronavirus Severe Acute Respiratory Syndrome Coronavirus 2 [SARS CoV 2] is the cause of Coronavirus Disease-19 (COVID-19). This novel virus and disease were unknown before the outbreak was first reported in December

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2019 from Wuhan city, Hubei province in China. COVID-19 is now a pandemic affecting many countries globally [1]. Over 215 countries, areas or territories have been affected and as on 13th May 2020, 4,139,794 persons have tested positive and 285,328 persons have succumbed to the disease [2].

Fever, dry cough and malaise are the most common symptoms of COVID-19. Other less common symptoms include aches and pains, nasal congestion, headache, conjunctivitis, sore throat, diarrhea, loss of taste or smell, or a rash on skin or discoloration of fingers or toes [1]. A majority of infected people (about 80%) recover from the disease without needing hospital care. Around 20% COVID-19 infected individuals become seriously ill and develop breathlessness. Older people, and those with underlying medical comorbidities like hypertension, cardiac ailments and respiratory disease, diabetes mellitus, or cancer, are at higher risk of developing a serious illness [1].

Kidney Transplant Recipients are at Risk

Akalin et al. [3], reported that kidney-transplant recipients appeared to be at predominantly higher risk for critical corona viral illness due to chronic immunosuppression and comorbidities. They identified 36 successive adult transplant recipients who tested positive for Covid-19 “between” 16th March to 1st April 2020. A total of 26 transplant recipients (72%) were male with the median age of 60 years. Twenty-seven recipients (75%) had received a deceased-donor kidney; 34 recipients (94%) had hypertension, 25 (69%) had diabetes mellitus, and 6 (17%) had cardiac disease. The number of patients receiving tacrolimus, prednisone and mycophenolate mofetil or mycophenolic acid was 35 (97%), 34 (94%), and 31 (86%), respectively. The most frequent initial symptom was fever (58%), and diarrhea (22%). Eight stable patients (22%) were monitored at home, and 28 patients (78%) required hospital admission. Twenty-seven of the hospitalized patients (96%) had radiographic findings that were consistent with viral pneumonia, and 11 (39%) patients with respiratory failure needed mechanical ventilation in the intensive care unit. Six patients (21%) received renal replacement therapy. At a median follow-up of 21 days (range, 14 to 28 days), 10 of the 36 kidney-transplant recipients (28%) and 7 of the 11 patients who were managed on ventilator support (64%) had succumbed to the disease. Two of the eight patients (25%) who were monitored at home, died. Both the patients had received Anti-Thymocyte Globulin (ATG) therapy within the previous 5 weeks. The results of this study indicated a very high early mortality among kidney-transplant recipients with Covid-19; 28% at three weeks as compared with the reported 1 - 5% mortality among the general population infected with COVID-19. The mortality rate amongst patients who were older than 70 years was reported in the range of 8 to 15%.

Similarly, Banerjee et al. [4], described seven cases of COVID-19 infection in kidney transplant recipients from three South London Hospitals over a six-week period. Two of seven patients presented within three months of transplantation. Overall, two were managed on an outpatient basis, but the remaining five required hospital care, four

in Intensive Care Units (ICU). All patients had fever and exhibited classic respiratory symptoms. Other clinical features included hypoxia, chest crepitation; blood biochemistry tests revealed lymphopenia and high C-reactive protein levels. Immunosuppression was modified in six of the seven patients. Three patients with severe disease also had diabetes. During a three-week follow up one patient recovered, and another patient died. The authors concluded that COVID-19 infection in transplant patients could be severe, requiring ICU admission. The symptoms were predominantly respiratory and associated with fever. Most patients needed modified immunosuppressive regimen and along with supportive therapy.

The Columbia University Kidney Transplant Program [5], reported on 15 kidney transplant recipients who required hospitalization for confirmed COVID-19. Patients presented most often with a fever (87%) and/or cough (67%). Initial chest radiograph most commonly showed bilateral infiltrates. Patients were managed with immunosuppression reduction and the addition of hydroxychloroquine and azithromycin. Although 27% of their patients needed mechanical ventilation, over 50% were discharged home by the end of follow-up.

Kidney Transplant Programs

Martino et al. [6], expressed their concern about kidney transplant programs during the coronavirus disease pandemic. Everyone recognizes the importance of kidney transplants for patients undergoing dialysis. However, one cannot ignore the potential safety issues during this pandemic. They reported on other concerns they had regarding the transplant programs, such as the limited accuracy of the RT-PCR test, which could lead to under-diagnosis of infection with the corona virus. The weaknesses in the detection of the corona virus could be due to faulty collection, handling, transport and storage, and timing of the test in the pre-analytical phase and due to viral recombination, assay quality, harmonization, and instrument performance in the analytical phase [7]. All these factors could result in a high risk of false-negative test results [8].

A Chinese study of chest Computed Tomograms (CT) reported positive RT-PCR assays in only 601 (59.3%) of 1014 patients with suspected infection [9]. Among the 308 patients with initial negative RT-PCR, 147 (47.7%) were re-evaluated after the test as highly probable cases, and 103 (33.4%) as likely cases (based on symptoms, CT scan, and subsequent swab test). Only 58 (18.8%) patients were found to be true negative cases. This high rate of negative results from RT-PCR in patients with radiological features typical of COVID-19 pulmonary infection raises serious concerns about sensitivity of this test in asymptomatic patients.

COVID-19 infection could be missed before transplant procedure both in donors and recipients who are asymptomatic owing to the sensitivity issues with the RT-PCR test. Transplanted patients have increased susceptibility to coronavirus infection in the immediate postoperative period and after hospital discharge, owing to induction therapy and immunosuppressive treatment. Apart from the sensitivity issues with the RT-PCR test, the transplant program might face other challenges in the form of scarce resources (beds, operating theatres, medics, and nurses). Apart from this, the transplant teams could themselves be involved in the care of COVID-19 patients. Moreover, a logistical difficulty also exists in the form of ensuring clean and microbiologically safe pathways within hospitals for transplant patients. Martino et al. [6], do not consider kidney transplantation as a safe procedure in COVID-19 pandemic areas.

In certain conditions such as, cases with no vascular access, unfeasible dialysis, or a hyper-immune state, the benefits of a kidney transplant definitely outweigh the risks. Decisions regarding operations must be made on a case to case basis. European Association of Urology [10], has put down specific guidelines concerning renal transplantation during the COVID-19 pandemic. Our institutional transplant committee has made specific recommendations (Table 1) based on this to function during this crisis.

Priority Category	Low Priority	Intermediate Priority	High Priority
Definition	Safely Deferred for 6 Months	Safely Deferred for 3 Months	To Perform on an Urgent Basis or within 4 Weeks
	<ul style="list-style-type: none"> Non-urgent renal transplantation with living donor. Renal transplantations in complex medical situations and patients with multiple comorbidities. Paediatric renal transplant with living donor. 	<ul style="list-style-type: none"> Creation of AV-Fistula for Haemodialysis access. Peritoneal dialysis catheter placement. Eligible candidate for renal transplant with expected long-time in the waiting list subject to availability of deceased donor. 	<ul style="list-style-type: none"> Urgent transplant in patient with dialysis access failure. Combined Transplant (Heart; Liver; Pancreas and Kidney).
Recommendations	<ul style="list-style-type: none"> Postpone transplant 	<ul style="list-style-type: none"> Perform procedure or transplant after case-based discussion. Obtain high-risk written-informed consent 	<ul style="list-style-type: none"> Perform Transplant after appropriate counselling of both donor and recipient with their families. High-risk written-informed consent to be taken

Table 1: Recommendations from KLES kidney foundation transplant committee for renal transplantation during COVID-19 pandemic.

Note: Evaluation of a prospective donor for COVID-19: There are no specific recommendations at present as the living-related donor transplant is on temporarily suspended till further orders from higher government authorities.

There is no evidence base concerning the likely impact on clinical outcomes for making further recommendations. Clinicians working in the Transplantation settings should be directed by their local experience and available health-care resources during the COVID-19 pandemic.

Immunosuppression

Management of the patient's immunosuppression remains a challenge given the lack of data particular to COVID-19. Decisions relating to the use of immunosuppression must be considered on a case by case basis bearing in mind factors such as patient age, presence of donor-specific antibodies, time since transplantation, prior episode of rejection, and baseline graft function. There is a need to keep a right equilibrium between controlling infection and maintaining allograft function. Reduction in the dose of immune-suppressants may lead to acute rejection. In the setting of COVID-19, it would further complicate the patient's progress and force the clinician to make difficult decisions regarding the treatment of acute rejection versus losing the allograft. Immunosuppressive medications may increase the patient's risk of infection and the risk of more life-threatening disease. With past experience of other viral infections, a 50% reduction in dose or

termination of antimetabolite medications on the initial diagnosis of COVID-19 seems to be an appropriate strategy [11]. Tacrolimus dose should be adjusted to achieve a trough of 4-6 ng/ml., so as to reduce hyper-inflammatory response [11].

Renal Transplant at our Center During COVID-19 Pandemic

The 1st case of COVID-19 was reported in India on the 30th of January 2020, since then the number has gradually progressed to the present number of 74,983 cases [12]. Our hospital is situated in Belagavi district of Karnataka, South India. The total number of COVID-19 cases as of 13th May 2020 is 113. All these patients have been admitted to the District Hospital for isolation and observation. This facility is situated at a distance of 1 km from our hospital designated to care for non-COVID related illnesses.

During the period from 1st Jan 2020 till date, we have performed only four renal transplantation operations (Table 2) as the Indian Society of Organ Transplantation suggested a temporary suspension of the living-related kidney transplant program. This recommendation was in line with the Ministry of Health and Family Welfare’s advisory for hospitals and medical facilities dated 3rd March 2020 [13]. Thirty-six kidney transplant recipient patients are living in the vicinity (radius of 50 km) of our hospital; they have been taking the usual immunosuppressive drugs at regular doses. None of these patients have reported to the hospital with any signs of upper respiratory infection during the past 12 to 16 weeks. All the patients have been counselled regarding lifestyle modification measures such as frequent hand-wash with soap and water or use of alcohol-based sanitizers, maintain respiratory hygiene, wearing N95 masks, frequent gargling with lukewarm water and to eat a balanced meal freshly cooked at home. They are also advised to avoid unnecessary travel, avoid crowded places, and to maintain social distancing whenever appropriate.

Months	Living-related Kidney Transplant	Deceased-donor Kidney Transplant
Jan-2020	01	00
Feb-2020	03	00
March-2020	00*	01

Table 2: Renal Transplantation Programme at our centre.

Note: *As per Indian Society of Organ Transplantation; the living donor transplant programme may be temporarily suspended in line with the MoHFW’s advisory for Hospitals and Medical Institutions dated 3rd March 2020.

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Conflict of Interest

Authors declare conflict of Interest as None.



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