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RESEARCH ARTICLE

COVID- 19 and Transplantation in India

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ABSTRACT

COVID 19 pandemic had a major impact on solid transplantation worldwide. This impact was felt more severely in resource constrained countries like India. In the initial phase of the pandemic, transplantation activities were halted. This was because of increased strain on the healthcare facilities by the pandemic and all non-urgent surgeries were disrupted. Also, there was concern among physicians about the risk of immunosuppression during the ongoing pandemic. After receiving guidance from national health authorities, transplantation activities were cautiously restarted. With increasing understanding about the pathophysiology of the viral infection transplantation activity increased over the months and both COVID- 19 infected individuals were accepted as donor and recipients. This was done after a thorough clinical, microbiological and radiological evaluation. Vaccination was made available early in India and guidelines for vaccination were adopted for all kidney transplant recipients. Like everywhere else, it was noted that vaccine efficacy was suboptimal in transplant recipients and breakthrough infections were common. COVID-19 associated mucormycosis was a unique feature during the second wave of the pandemic in India. It almost manifested as an epidemic and had devastating consequences in our country. This review aims to look at the response of Indian transplant physicians combating the COVID-19 pandemic in the last two years. Mention is also made about the mucormycosis infections (an epidemic within the pandemic) which was an important issue during the second wave of the pandemic.

## Introduction

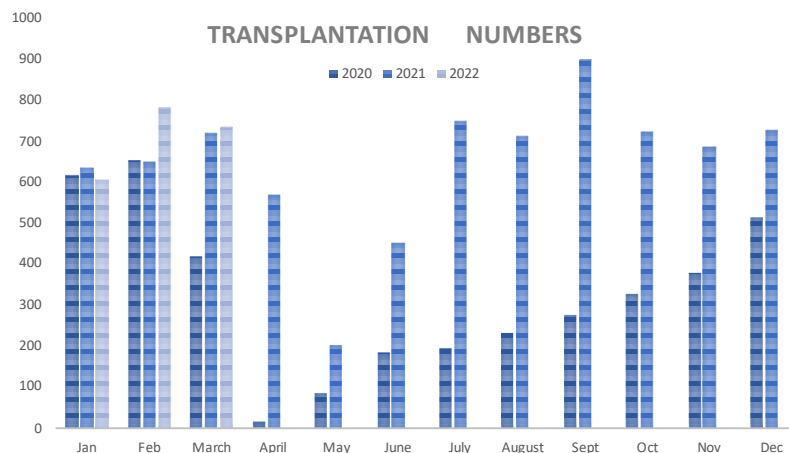
Since the first description of the severe acute respiratory syndrome (SARS) following a new coronavirus in 2019, (1) the world has been grappling with a pandemic impacting more than 220 countries and territories worldwide. The virus, designated as COVID-19 by WHO, has as of now, affected more than 520 million people with more than 6.2 million dying of this infection. The Indian subcontinent has also seen the devastating impact of this virus with more than 4 million infections till date. Not just socio-economic activities were impacted, healthcare also came under severe strain and many non-emergent activities were suspended during the pandemic. Also, patients could not access healthcare services because of various difficulties during the early stages of lockdown. (2) Besides, there were challenges in continuing transplantation activities in a resource constrained country like ours. Not only there were lack of regulatory guidelines and infrastructure shortages (adequate testing facilities, transplant nurses etc.) there was concerns about exposing our chronic kidney disease patients to immunosuppression during a raging viral pandemic. Transplant physicians got together and started collaborative work understanding and defining protocols that will prevent disruptions in

transplantation activities in our country. This review discusses the challenges faced by healthcare professionals involved in transplantation services during the pandemic in India.

## Transplantation activity during the pandemic

In the early part of the pandemic, transplant physicians in India were hesitant to expose patients to high doses of immunosuppressives with the COVID -19 virus running amok throughout the country. Transplantation activities were suspended in many parts of the country. The effect was seen mostly on the waitlisted programs of public sector hospitals. (3)

Our concerns were reinforced by the data emerging from the western world. In one of the earliest studies from Spain COVID -19 infection in kidney transplant recipients (KTR) was associated with higher incidence of acute respiratory distress syndrome (ARDS), acute kidney injury (AKI) and death. (4) Many other earlier studies showed poorer outcomes of COVID-19 infection in kidney transplant recipients. (5,6, 7). In India transplantation activity almost came to a standstill in the month of April 2020. It slowly picked up over the next few months but did not reach the pre-covid levels in 2020. (Figure 1)



**Figure 1:**Transplantation activities from January 2020 till April 2022. Transplantation activities were severely curtailed in the early months of 2020 (March 2020-August 2020). Transplantation continued with some restrictions during the second wave in India May 2021-August 2021)

With better understanding of the pathophysiology, development of guidelines for kidney transplantation activity during the pandemic, (8,9) and studies showing comparable outcomes, (10,11) transplant activities restarted in India, albeit at a lesser frequency.

Studies from India reported results comparable to that reported from other developed countries. In KTRs who developed early COVID - 19 infection, the mortality was comparable. On the other hand, severity of COVID-19 infection and mortality was significantly higher in waitlisted patients on dialysis. (12) Overall, in another study from India, transplantation outcomes were comparable during the pandemic. COVID -19 infection was noted in 13.4% patients. (13) COVID- 19 related mortality in these transplant patients was 14.6 % similar to that noted in another study. (14)

### **Transplantation involving COVID 19 recovered recipients and donors**

During the latter half of 2020 and the first six months of 2021, India was reporting one of the highest number of cases. The case positivity rate was more than 20% in many states. This led to the detection of COVID- 19 infection (mostly asymptomatic) in many donors and recipients being evaluated for living donor transplantation. Because of this, many living donations were cancelled throughout the country. And there were no guidelines as to when these COVID positive donors and recipients could be reconsidered for donor nephrectomy/transplantation. To address this issue, a country wide collaborative study looked into the safety of COVID- 19 positive donors offering their kidneys after four weeks (minimum) of symptom resolution. This study confirmed the safety of proceeding with kidney transplantation with asymptomatic COVID -19 positive donors who were clinically, virologically and radiologically free of infection. No recipient developed clinical evidence of COVID- 19 infection in the immediate post operative period. All the recipients were COVID-19 rt-PCR negative at the time of discharge. (15) A similar study was conducted to see whether a COVID 19 infected recipient can undergo kidney transplantation after 4-6 weeks following recovery from the viral infection. In the initial study, safety of transplantation was confirmed in these patients. Early patient and allograft survival was 100%. Approximately 5% of patients developed acute rejection which responded to intravenous methylprednisolone therapy. No patient had any

evidence of recurrence of COVID-19 infection in the immediate post- transplant period. (16) This was further expanded with data from 372 patients from all over India. The results were similar to that of the earlier paper. With careful evaluation kidney transplantation was safe in COVID-19 recovered recipients. In our study, patients with radiological sequelae but with-out any clinical evidence of infection also did well. There were very few surgical issues which was gratifying as some studies have reported increased peri-operative complication in patients undergoing surgery with COVID-19 infection. (18)

### **COVID-19 Infection in Kidney Transplant Recipients**

In the initial phases of the pandemic itself many studies suggested that the kidney transplant recipients were particularly vulnerable and often developed severe COVID 19 infection and had unfavorable outcomes. These patients had higher incidence of hospitalizations, acute kidney injury (AKI) and death. (19) However, with increasing experience with the use of corticosteroids it was noted that the solid organ transplant status did not behave differently from other critically sick COVID- 19 patients. The twenty-eight - day mortality in hospitalized organ transplant recipient did not vary from other critically sick patients. Also, duration of intensive care unit stay, incidence of ARDS, coagulation abnormalities, hemodynamic instability, ventilatory status and secondary infections were similar to other critically sick patients. (20) The mortality varied between 10-33% depending on the severity of COVID- 19 infection. (21,22,23) Some studies have reported a higher incidence of acute kidney injury (AKI) in transplant recipients. (20) Kidney transplant recipients have more than 30% higher risk of developing AKI. (7) The mechanisms of AKI in transplant recipients include direct viral infection of the tubular cells through angiotensin converting enzyme 2 dependent pathway. Endothelial dysfunction also contributes to the development of microthrombi. (24) Calcineurin inhibitors can also increase the risk of endothelial injury.

In a study from India severe COVID -19 infection was seen in about 50% of the patients. About 28% of these patients developed AKI stage 3. Kidney biopsy revealed acute tubular injury in 9/11 patients, acute cellular rejection in 2/11 patients and 3 patients had chronic antibody mediated rejection. Complete recovery of graft function was

seen in 40.5% of patients. Worsening proteinuria following COVID- 19 infection was noted in 37.5% of patients. Graft failure was seen in 14.3 %. This study underlined the fact that even though mortality outcomes are similar to that in the general population, graft function is impacted unfavorably following COVID- 19 infection. (25) Non-recovery of allograft function and development of antibody mediated rejection was also noted in another report from India.(26)

### **Vaccination in Kidney transplant recipients**

With the advent of safe and immunogenic vaccines against COVID-19, (27,28) vaccination as a mitigation measure for COVID-19 infection became an important strategy in India. A national program was rolled out initially for the healthcare workers and then the vulnerable groups of the population (elderly, immunocompromised patients etc.) The national organ transplant and tissue organization (NOTTO) published its guidelines regarding vaccination in kidney transplant recipients. (29) These guidelines suggested that not only the transplant recipient, but all the household members should be vaccinated expeditiously. Patients scheduled for a transplant should receive their vaccination 2 weeks pre or six months post transplantation. Transplant recipients who had previous COVID-19 infection and or, have antibodies against COVID-19 were also required to be vaccinated. The government did not advise checking of antibody levels before vaccination. Transplant recipients were advised to undergo the entire schedule of vaccination with only one type of vaccine.

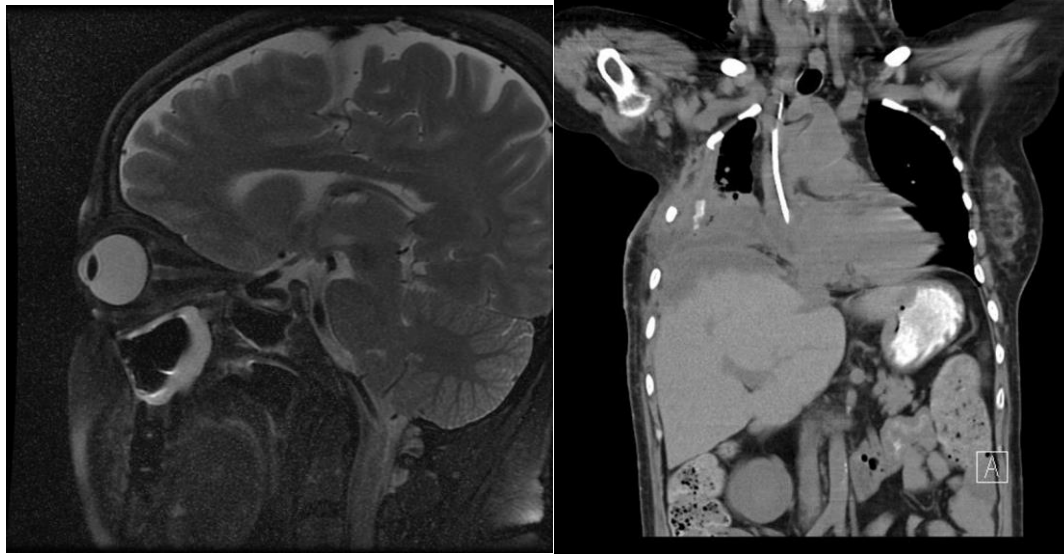
Early on, it became increasingly clear that transplant recipients do not mount adequate immune response (both B cell and T cell) against COVID-19 vaccines. (30) This suboptimal response in transplant recipients is not entirely unexpected as these patients are on immunosuppressive medications which does not allow them to have sufficient protective response against COVID- 19 infection. Patients who have a previous infection may have a better protection after vaccination compared to COVID- 19 naïve KTRs. (31) A study

from India showed despite completing two doses of vaccination, four KTRs developed breakthrough COVID- 19 infection. In this cohort, only one had a seroconversion and had detectable anti-spike antibodies. (32). As is the norm in the developed world currently, the government of India is also advising three doses of anti-COVID 19 vaccines for all transplant recipients.

### **Mucormycosis in the second wave of the pandemic**

With increasing knowledge about management COVID -19 infection, there was an improvement in outcomes in COVID-19 infected patients in India. The complications including AKI reduced significantly in the second wave of the pandemic not only in India but worldwide. (33) Clinicians were able to handle COVID -19 infection better. However, the flip side of this story was the indiscriminate use of steroids in our country, which led to the emergence of mucormycosis in our patients. The second wave of the pandemic in India saw an upsurge of mucormycosis infections in COVID-19 infected patients. COVID-19 associated mucormycosis attained epidemic proportions in India with at least 14,872 cases as of May 28, 2021. The state of Gujarat contributed to the maximum number of cases followed by Maharashtra. (34)

High incidence of mucormycosis was also reported in immunocompromised renal transplant patients. In a study which collected many centers from India, showed that the incidence of COVID associated mucormycosis in KTRs was 4.4%. In the majority of these patients (59.1%) mucormycosis was diagnosed after discharge from their COVID- 19 hospitalization. Ninety one percent of the patients had rhino-orbital-cerebral mucormycosis. Pulmonary involvement often was associated with extensive rib destruction. (Figure 2a and b) The risk factors for development of this fungal infection included older age, obesity, and severe COVID- 19 infection (requiring high flow oxygenation /ventilation) and delay in treatment. The overall mortality was 26.7%. There was 100% mortality in all the pulmonary mucormycosis patients. (35)



**Fig 2:** Rhinocerebral involvement (a) and extensive rib destruction (b) in two cases of COVID-19 associated mucormycosis.

### Conclusion

COVID- 19 infection had a devastating impact on kidney transplant recipients in India. Even though overall mortality was comparable, allograft rejection and unresolved acute kidney injury were more frequent in this cohort of patients. The response to vaccination was inadequate, making

this group of patients more vulnerable to re-infections. COVID -19 associated mucormycosis was a major feature during the second wave of the pandemic. This infection almost attained epidemic proportion. Mucormycosis also affected a large number of transplant recipients with a high mortality rate.

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