

# Heart transplantation in the time of COVID-19 pandemic

Debabrata Dash<sup>1\*</sup>, Rohit Mody<sup>2</sup>, Naveed Ahmed<sup>1</sup> and Sreenivas Reddy<sup>3</sup>

<sup>1</sup>Department of Cardiology, Aster Hospital, Dubai, UAE

<sup>2</sup>Department of Cardiology, Max Super Specialty Hospital, Bathinda, India

<sup>3</sup>Department of Cardiology, Government Medical College and Hospital, Chandigarh, India

## Abstract

The outbreak of novel Coronavirus disease 2019 (COVID-19) has appeared as a global pandemic and a public health crisis. COVID-19 is the clinical manifestation of infection with Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). Although it is predominantly a respiratory illness, there is growing awareness of the cardiovascular manifestations of COVID-19 disease. This global pandemic has unique implications for heart transplant patients, including those on the waiting list and transplant recipients. These populations are exposed to increased risk for both acquisition of COVID-19 infection and progression to severe disease given multiple healthcare contacts, underlying comorbidities and immunosuppression; and targeted prevention and treatment strategies are needed. This review summarizes on the implications of COVID-19 for heart transplantation.

## Introduction

The healthcare professionals across the world are confronted with unprecedented challenges due to the emergence of coronavirus disease 2019 (COVID-19). High infectivity, ability to get transmitted even during asymptomatic phase and relatively low virulence have resulted in rapid transmission of this deadly virus beyond geographic regions, leading to a pandemic. It appears that preexisting cardiovascular (CV) disease and CV risk factors enhance vulnerability to COVID-19. Further, COVID-19 can worsen underlying CVD and even precipitate de novo cardiac complications.<sup>1</sup> One area of cardiovascular medicine that remains especially vulnerable in such pandemics is that of heart transplantation (HT). The donors, recipients and those awaiting HT are at increased risk. The eminent risk for the recipients is more obvious owing to their immunocompromised state.

## Clinical features relevant to HT physicians

Our knowledge of COVID-19 is still evolving. Past experience with prior coronavirus epidemics such as SARS (Severe Acute Respiratory Syndrome) and MERS (Middle East respiratory syndrome) demonstrated that transplant patients had similar presentations to the general population [1,2]. Data is rapidly accumulating on the impact of COVID-19 within the transplant community. CV disease is a well-known factor for increasing the risk of contracting this deadly virus. The risk is compounded even more among patients with heart failure who receive a transplanted heart. Recipients of HT may be at an increased risk for infection and adverse outcomes with COVID-19 infection because of a number of comorbidities that are common following HT, including hypertension, diabetes, and cardiac allograft vasculopathy [3]. Imaging displays pneumonia in the majority of hospitalized (75-100%) patients. Patients with less severe infections may have lower rates of abnormalities. Mortality appears to be age dependent, with the highest rates among older adults (Age 50-59: 1.3%, 60-69: 3.6%, 70-79: 8%, 80+: 14.8%) [4]. It appears to be highest in lung transplant recipients and lowest in the liver and HT populations. There is a paucity of data on mild and asymptomatic infections which might alter these estimates.

In the current pandemic, a case study described the clinical courses of two HT recipients from China who presented with fevers and had laboratory and CT scans that were similar to nonimmunosuppressed individuals with bilateral ground glass opacities in a peripheral distribution. One had relatively mild disease, while the other required hospitalization needing supplemental oxygen. Both were managed by withholding baseline immunosuppressive regimens and treating with high dose steroids, intravenous immunoglobulin, and antibiotics, and both survived without evidence of allograft rejection [5,6]. A recently published survey of 87 heart transplant recipients during this pandemic in China demonstrated that these patients had a low rate of infection with SARS-CoV-2, and transition to COVID-19, as long as they practiced social distancing [7]. Only four patients had upper airway infections and three of them tested negative for SARS-CoV-2 while the fourth patient recovered well without needing any testing.

A recent single center study looked at a case series consisting of 28 patients who received HT between March 1, 2020, and April 24, 2020. Patients from that center who were followed up who were later infected with COVID-19 were included in the analysis. According to the study results, the median age of the patient population was 64.0 years, with a median time of 8.6 years between HT and COVID-19 treatment. Overall, 25% of these patients died. Hypertension, diabetes, and cardiac allograft vasculopathy appeared in 71%, 61%, and 57%, respectively. Other common comorbidities included obesity (body mass index > 30 kg/m<sup>2</sup>) in 28%; stage IV or greater chronic kidney disease in 36%, with 18% on hemodialysis; and preexisting allograft dysfunction in 14%. In addition, 79% had to be hospitalized for COVID-19, of whom 25% required mechanical ventilation in the intensive care

\*Correspondence to: Debabrata Dash MD, DM, Department of Cardiology, Aster Hospital, Kuwait Road, PO Box: 119428, Dubai, UAE, E-mail: dr\_dash2003@yahoo.com

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unit, 21% were treated as outpatients, and 32% expired. None of them however, manifested signs of organ rejection.<sup>8</sup> The researchers also noted that HT patients with COVID-19 tended to have more intense immunosuppression than other organ transplant recipients [8].

## Implications down the road

### HT Donors

The safety of patients awaiting HT has also been jeopardized by the COVID-19 pandemic due to potential transmission from the donor to the recipient. Although very little is known about this novel virus to reliably estimate the risk of transmission through donor organs, RNAemia was reported in at least 15% in one case series [9]. Knowledge of local epidemiology plays an important role. Although household members of Covid-19 patients have obviously been “exposed”, persons who work in or frequent places known to be part of Covid-19 clusters should also be considered exposed. All healthcare professionals involved in organ procurement should keep abreast of such epidemiological developments in their community. One must be vigilant in choosing uninfected donors, recognizing that many may be asymptomatic carriers and that current testing has limitations. Chest computed tomography needs to be done to exclude radiographic pneumonia. In discussing donor offers with listed patients, expanded consent should include the potential risks of a COVID-19 positive donor, despite procedures in place to mitigate risk. It is equally important to protect procurement teams. Major societal recommendations include avoiding donors with known or suspected COVID-19 and if a donor had COVID-19, they should be COVID-19 free (by PCR) for at least 14 days (Table 1) [10,11]. In a country with widespread community transmission, temporary suspension of the deceased donor program should be considered, especially when resources at the transplant center may be constrained. In countries where the chains of transmission can be defined, eg, because of excellent contact tracing and transparent public reporting of clusters, transplantation may be considered. Beyond donor suitability, the considerations of ICU beds and transplant surgeons in the recipient hospital are also critical beyond donor suitability.

### HT recipients

Many HT recipients have medication-induced lymphopenia. Particularly close attention should be paid to such patients with suspected or confirmed COVID-19 infection demonstrating lymphopenia. Such attention may include admission in the hospital and paying careful heed to oxygen saturation. Patient-to-patient, and patient-to-healthcare worker infection have been described and human-to-human transmission has been confirmed [12,13]. As such, strict infection prevention practices are of paramount importance [14]. The mainstay of diagnostic testing is the use of PCR to identify viral presence in samples collected from the respiratory tract of persons under investigation. Negative testing may occur early with asymptomatic patients [15].

Since these initial reports, a growing number of solid organ transplant (SOT) recipients have been hospitalized for COVID-19 in different places. Irrespective of transplant status, in-hospital disease transmission is increasing, with hospitals increasingly admitting COVID-19 patients in separate intensive care units and wards. Specific to HT recipients, manifestations of myocarditis (with high troponin levels, ECG changes) and new LV dysfunction may mimic rejection. Yet, endomyocardial biopsy is being restricted due to risks of exposure. The current epidemic raises the concerns about rapidly progressive disease leading to morbidity and mortality [16].

Important decisions have already come pertaining to actively listed patients. In-hospital patients waiting for HT are at increased risk for contracting the virus compared to others waiting at home. Upon subsequent infection with COVID-19, they are at risk for more severe infection (or co-infection) due to their underlying health conditions, and risk delisting. Nurses who treat COVID-19 patients should not be assigned to patients awaiting HT. However, with the surge in such cases, this may not be practical. The transplant centers should highlight the waitlist mortality risk-benefit ratio and disseminate important institutional updates to all listed patients (no matter whether they are hospitalized or at home) by telephonic conversation or mail (Table 1).

The hospital may reduce HT volume in a staged manner to meet ICU bed, staffing and medical equipment needs of the majority non-transplant population. The center may reserve active transplant status for only those with likely to have waitlist mortality of 1-2 weeks, thus limiting transplant to patients in tiers 1 or 2 of the new heart allocation policy [17]. Restrictions need to be in place for highly sensitized patients requiring intensive peri and postoperative care and prolonged immunosuppression and with the need for frequent biopsy surveillance. Left ventricular assist device (LVAD) implantation is likely to serve as a bridge to transplant to get at-risk patients out of the hospital, minimizing their exposure to COVID-19 (Table 1). The clinician should stay away from implanting LVAD in elective cases, due to resource constraints and potential for nosocomial infection.

### Post HT management

Extra precautions should be taken to mitigate the risk of post-operative exposure. This extends to visitors, nurses, physiotherapists, and other ICU staff. They should be assigned to negative pressure ventilation room with airborne isolation. Nurses who treat COVID-19 patients should refrain from caring post HT. Recipients should be re-tested prior to discharge and receive focused education around disease prevention at home. The current pandemic also affects the post-HT ambulatory population.

Multidisciplinary HT teams must counsel patients and families regarding appropriate preventative measures including frequent hand-washing and social distancing. The study by Ren, *et al.* [7] suggests HT recipients do not have a substantially higher rate of COVID-19 infection compared to the general population. This finding is not surprising because immunosuppressive treatment used in these patients favors specific viral infections such as cytomegalovirus or herpes simplex virus infections much more than community-acquired respiratory viruses. Additionally, 97% patients adopted prevention and quarantine measures. The threshold for telemedicine and virtual medicine should be low in order to minimize in-person contact with the healthcare system, reducing patient risk of exposure. The patients should go for laboratory work at a local laboratory or using home services rather than at the hospital to minimize exposure. Right heart catheterization and endomyocardial biopsy, if deemed non-urgent, are delayed (Table 1). For monitoring rejection in stable outpatients, non-invasive monitoring with echocardiography, gene profiling (for acute cellular rejection), or donor-derived cell free DNA (for antibody-mediated rejection) may be useful [18].

Managing HT recipients with COVID-19 has increased complexity because they have more intense immunosuppression than many other SOT recipients, combined with the potential for the virus to cause both primary and secondary myocardial injury [2]. The authors recommend that patients who have received HT are treated at a transplant center while infected with COVID-19. Furthermore, these patients may need

**Table 1.** Suggested recommendations pertaining to heart transplant during COVID-19 pandemic

Transplant Area	Recommendations
Donor	<ul style="list-style-type: none"> <li>• Covid-19-focused travel and social history</li> <li>• Exclusion of donors at risk of other disease transmission( HIV, HPB, HCV etc)</li> <li>• Exclusion of marginal donors having mild LVH and/or LV dysfunction</li> <li>• Donor contract tracing</li> <li>• Availability and rapid turn-around of PCR assay for donor</li> <li>• At least 2 tests to increase sensitivity and specificity</li> <li>• COVID-19 free interval of 14 days</li> <li>• Chest CT for exclusion of pneumonia</li> <li>• Separate consent for potential COVID-19 donors</li> </ul>
Recipient	<ul style="list-style-type: none"> <li>• COVID-19 free environment</li> <li>• Staying away of nurses who attend COVID-19 patents from patients awaiting HT</li> <li>• Exclusion of hospital-acquired infection by PCR</li> <li>• Telephonic and/or mail communication regarding expected delay and organizational changes</li> <li>• Lower threshold for LVAD as a bridge to transplant</li> <li>• Reduction of overall transplant program activity</li> </ul>
Post transplant	<ul style="list-style-type: none"> <li>• Negative pressure ventilation room with airborne isolation</li> <li>• Staying away of nurses who attend COVID-19 patients from post-transplant patient</li> <li>• Reduction of staff contact and outside visitors</li> <li>• Stress on patient/family hygiene and social distancing</li> <li>• Prompt testing and diagnosis of patients with symptoms related to rejection</li> <li>• Delaying elective testing, Echocardiography, RHC and EMB</li> <li>• Adherence to local laboratory or home service for the tests</li> </ul>
Transplant patients infected with COVID-19	<ul style="list-style-type: none"> <li>• Reduction of dose of calcineurin inhibitor</li> <li>• Reduction or withhold of mycophenolate mofetil/azathioprine dose</li> <li>• Ruling out other bacterial, fungal infection</li> <li>• Monitoring for viremia</li> <li>• Monitoring for drug-drug interactions</li> <li>• Continuation of statins unless contraindicated</li> <li>• IL-6 inhibitors for cytokine storm?</li> <li>• Monitoring for allograft dysfunction</li> </ul>

COVID-19: coronavirus disease 2019; CT: computerized tomography; EMB: endomyocardial biopsy; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; IL: interleukin ; LVAD: left ventricular assist device; LV: left ventricular ; LVH: left ventricular hypertrophy ; PCR: polymerase chain reaction; RHC: right heart catheterization.

ongoing monitoring in the recovery phase as an immunosuppression regimen is reintroduced and the consequences to the allograft itself become apparent. Recommended management of transplant recipients infected with COVID-19 is primarily supportive care and continuation of immunosuppression for mild COVID-19 with reduction of the anti-metabolite (mycophenolate or azathioprine) and further treatment based on disease severity [2]. Several of the proposed drugs for COVID-19 infection have significant interactions with calcineurin blockers. Azithromycin and hydroxychloroquine are CYP3A4 inhibitors and significantly increase serum concentration of cyclosporine [19]. Lopinavir/ritonavir association is a strong CYP3A4 inhibitor that can raise serum concentrations of both tacrolimus and cyclosporine [20]. Wishful thinking and watchful monitoring of calcineurin blocker levels are thus necessary if these drugs are used. However, these need to be tested in further clinical trials before treatment algorithms are promulgated widely, with particular attention to drug-drug interactions and QT prolongation.

## Conclusion

Our knowledge of COVID19 pandemic and its CV implications is getting enhanced every day. The ongoing pandemic has raised the question of whether to continue offering HT because of concerns regarding a risk for exposure to COVID-19 during hospitalization, as well as challenges in curbing the infection with high levels of immunosuppression. There is paucity of data on optimal treatment protocols and none have been clearly shown to optimize outcomes. While considering potential therapies, it would be critical to recognize drug-drug interactions and the risk of rejection. There may be a surge in LVAD implantations as bridge to transplantation until our understanding of the risk of transmission is more robust, or we have a evidence based definitive treatment for this novel virus, or until this pandemic has gone. There are some limitations regarding

the management of HT patients during the current pandemic. First, symptom-based screening alone sometimes fail to detect a high proportion of infected patents. Second, interpretation of radiological findings in patients with preexisting cardio-pulmonary conditions may appear to be difficult. Third, rate of false negative nasopharyngeal swab results may be significant. Therefore, to repeat the test seems to be of paramount importance. However, the optimal number and the timing of repeating samples have to be established. In addition, reliability and role of serological assays in this setting have to be investigated yet.

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