REVIEW ARTICLE

LUNG TRANSPLANT IN COVID 19 – THE IMPENDING NEED OF SALVAGE THERAPY

Dhiraj Bhambhani[1], Suresh Bhambhani[2], Garima Bhambhani[3], Ajay Goenka[4], Jyotsna[5], Riddhi Tondon[6]

ABSTRACT :

A worldwide pandemic of unparalleled scope in the last century has been brought on by the coronavirus illness of 2019 (COVID-19). The current review demonstrated that, in certain patients with severe, persistent COVID-19-associated ARDS, lung transplantation is the only viable alternative for survival. Carefully chosen patients can undergo the surgery successfully, with favourable early post-transplant outcomes.

KEYWORDS: COVID 19, respiratory, lung transplant, pulmonary FIbrosis.

INTRODUCTION :

Various end-stage lung disorders can be treated by lung transplantation; however, individuals who have had an acute lung damage from an infectious source are often not candidates for the procedure.[1] Although there have been a few isolated cases of lung transplantation for COVID-19 associated acute respiratory distress syndrome (ARDS),[2-4] there is not enough information to guide the selection of suitable recipients, the timing of the transplant, or the results of the transplant. Lung transplantation as a treatment for individuals with severe ARDS related to COVID-19 is also constrained by a number of unresolved issues. For instance, the allograft lung may experience a recurrence of the SARS-CoV-2 or superinfecting pathogens linked to viral pneumonia in the native lung. The SARS-CoV-2 infection may cause severe pleural and pulmonary hilar inflammation, which might provide technical challenges for the transplant surgery and result in longer ischemia times, the requirement for intraoperative blood transfusions, and post-transplant graft failure. Additionally, post-transplantation recovery may be hampered and results may beworsened by the severe de-conditioning brought on by protracted mechanical breathing, sedation, and neuromuscular blockade.

Corresponding Author : Dr. Dhiraj Bhambhani

[1]MBBS, People's College of Medical Sciences, Bhopal

[2]Assot. Prof., Department of Medicine, Chirayu Medical College , Bhopal,

[3]Reader, Dept. of Public Health Dentistry, People's College of Dental Sciences and Research Centre

[4]Director, Chirayu Medical College and Hospital, Bhopal

[5]MBBS

[6]Junior Resident, MIMSRC, Bhopal

COVID 19 - Facts and figures:

India recorded more than 35 million cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as of January 1, 2022, second only to the United States prior to the current surge brought on by the Omicron strain. A COVID death rate of 345 per million people is inferred by India's official cumulative COVID death count of 0.48 million, which is roughly one-seventh of the US mortality rate. Due to insufficient COVID death certification, chronic disease misattribution, and the fact that the majority of fatalities occur in rural regions frequently without medical assistance, it is commonly thought that India's reported COVID death total sare underreported.[5]

COVID 19 - Disease progression

Coronavirus disease 2019 is the phrase used to describe the clinical appearance of SARS-CoV-2 infected individuals (COVID-19). After the first illness phase, which is characterised by viral reaction symptoms and signs including fever, dry cough, and lymphopenia, the majority of patients (about 80%) experience mild to moderate symptoms and recover. However, during the initial period of dyspnea and hypoxemia, a sizable portion of patients experience worsening host infiammatory response symptoms, which can range from life-threatening organ dysfunction including acute respiratory distress syndrome, shock, and heart failure. In the general

population as well as in specific lung disorders,protracted disease courses and chronic physical and psychological damage are extensively recognised.[6] According to Jan C. Kamp et al observations, several patients had clinical conditions that appeared stable for up to 10 days following the commencement of SARS-CoV-2 symptoms. Following this, they noticed a fast decline in respiratory function or even a drop in oxygen saturation without shortness of breath, which in many cases necessitated the need for critical care. Silent hypoxemia, a well-described characteristic of COVID-19, is the phrase used to characterise an asymptomatic reduction in oxygen saturation.

Contemplation and consideration for lung transplant:

Cypel M and Keshavjee S7 outlined 10 factors that should be carefully taken into account when determining whether a patient with COVID-19-associated Acute Respiratory Distress Syndrome (ARDS) is a candidate for lung transplantation. The likelihood of a favourable outcome is likely to be increased by the following elements.

1. Candidates must first be under 65 years old. Existing data from ECMO bridge to lung transplantation reveals that older patients had worse results.
2. Transplant candidates should only have single-organ dysfunction.
3. Enough time should be given for the healing of the lungs. Given the poor long-term survival chances of lung transplantation, it is desirable for the patient to be able to survive without a transplant (about 60 percent at 5 years). After several weeks to months on extracorporeal membrane oxygenation (ECMO) and total organ failure, prior investigations have demonstrated that lungs severely damaged by infiuenza or bacterial pneumonia can recover to maintain life with non-limiting function. It is uncertain if COVID-19 will recover at a slower rate than other infectious agents. According to French data, individuals with COVID-19-related ARDS on ECMO had a recovery rate that is comparable to those with ARDS from other causes. Despite the lack of a current guideline, in our opinion, transplantation should not be considered before 4-6 weeks have passed from the onset of the first clinical indications of respiratory failure.
4. Fourth, there should be radiological evidence of advanced fibrosis or significant bullous destruction, both of which are indicators of irreversible lung illness.
5. The patient has to be awake and able to talk about the transplant. In patients with ARDS, transplantation frequently takes place without first-person permission. Patients must be aware of how a transplant affects their quality of life. Acute respiratory sickness can be psychologically distressing and often impossible to overcome, as can waking up after a lung transplant with a life of immunosuppression and problems.
6. While they are waiting for a transplant, patients should be able to take part in physical therapy. The outcomes of these patients have clearly improved, according on data from ECMO bridge to transplant.
7. Patients must meet the remaining standard requirements for transplantation, such as a sufficient body mass index and the absence of any other significant comorbidities, including severe coronary artery disease.
8. The patient must have recently negative SARS-CoV-2 PCR results or deep respiratory tract sample infectivity testing demonstrating the absence of a live virus. Evidence suggests that PCR-positive individuals, including those who are asymptomatic, have a considerably greater death rate following surgical treatments.
9. The transplant centre has to have extensive knowledge in high-risk transplantation. Some of the most difficult and riskiest operations include lung transplantation in patients who are bridging ECMO for ARDS. As a result, only facilities with extensive ECMO bridging experience ought to provide the technique. In order to do this, patients with COVID-19 who undergo lung

transplantation may benefit significantly from referral to a small number of specialised centres.

10. There should be a large donor pool available to the centre, as well as a low waiting list death rate. This element will keep donor organ allocation fair and equitable and give patients who are more likely to survive the chance to receive a life-saving organ transplant.

Lung injury and COVID 19:

Unknown but likely multifactorial, the mechanisms by which SARS-CoV-2 produces lung damage include the cytokine release syndrome that follows, ventilator-induced lung damage, drug-induced pulmonary toxicity, subsequent nosocomial pneumonia, and thrombosis.[8]

Literature evidence for Outcome:

In an editorial by Amy Roach et al9, the authors reported that the average number of lung transplants per centre for respiratory failure caused by Covid-19 was 2.5 (with a range of 1 to 25). A total of 214 lung transplants were performed, of which 197 (92.1%) were bilateral lung transplants (including 2 heart-lung and 5 lung-kidney transplants) and 17 (7.9%) were single-lung transplants (including 1 lung-kidney transplant). The authors believed that lung transplantation may be an appropriate therapy for certain patients with irreversible respiratory failure caused by Covid-19 since the 3-month survival rate among these patients approximated that of individuals who received lung transplantation for reasons other than Covid-19.

The outcomes of lung transplantation in three patients with respiratory failure linked to COVID-19 that is not resolving were reported by Ankit Bharat et al[10]. In order to find SARS-CoV-2 RNA in explanted lung tissue from the three patients as well as in extra control lung tissue samples, they used single-molecule fiuorescence in situ hybridization (smFISH). On the explanted lung tissue from the three transplant recipients as well as the warm postmortem lung biopsies from the two patients who had passed away from pneumonia caused by COVID-19, they performed extracellular matrix imaging and single-cell RNA sequencing. SARS-CoV-2 was not found in the lungs of these five patients with protracted COVID-19 disease, according to smFISH, but histology revealed substantial signs of damage and fibrosis that matched end-stage pulmonary fibrosis. In order to find parallels in gene expression across cell lineages, they used machine learning to compare single-cell RNA sequencing data from the lungs of patients with late-stage COVID-19 to those from the lungs of patients with pulmonary fibrosis. According to their research, some COVID-19 patients experience severe fibrotic lung disease, making lung transplantation their sole chance for life.

Ankit Bharat et al[11] conducted a multicentric trial among severe COVID cases. At six high-volume transplant centres in the USA (eight recipients at three centres), Italy (two receivers at one centre), Austria (one recipient), and India (one recipient), 12 patients with COVID-19-associated ARDS had bilateral lung transplantation between May 1 and September 30, 2020. (one recipient). Prior to transplantation, chest imaging revealed substantial lung damage that did not get better in spite of extracorporeal membrane oxygenation and protracted mechanical breathing. Due to extensive pleural adhesions, hilar lymphadenopathy, and increased intraoperative transfusion needs, the lung transplant process was technically difficult. The explanted lungs' pathology revealed significant, persistent acute lung damage with signs of lung fibrosis. SARS-CoV-2 didn't reappear in the allografts. All COVID-19 patients were able to wean themselves off extracorporeal life support, and their short-term survival rates were comparable to those of transplant recipients who did not have the virus.

At Temple University Hospital, Norihisa Shigemura et al.12 conducted an analysis of prospectively collected data from lung transplant recipients who had pneumonia caused by the COVID-19 virus and patients who were being evaluated for lung transplantation for COVID-19 sequelae. There were 8 fatalities out of 511 lung transplants from 2016 to 2019 and 5 deaths out of 131 lung transplants in

2020, for a total mortality rate of 25% (13/52) among lung transplant recipients with COVID-19 pneumonia (1.6 percent). Three of the five recipients of transplants who passed away afterward were infected with COVID-19 while hospitalised in the ICU after the transplant process and died of progressive septic shock despite receiving all possible therapies, including ECMO. The recipient's age above 70, the presence of stage 3 or worse chronic renal disease, and higher sequential organ failure assessment (SOFA) and 4C scores at the time of admission were all revealed by multivariate analysis as significant risk factors for death (P 0.05).

Ryoung-Eun Ko et al[13] is to summarised the collective experience of Lung transplant (LT) for patients in Korea who have severe COVID-19-related ARDS. In South Korea (June 2020-June 2021) a countrywide multicenter retrospective observational research was conducted with subsequent LT for severe COVID-19-related ARDS. Prior to LT, all 11 patients had rehabilitation while being maintained by venovenous ECMO. After ECMO cannulation, patients underwent transplantation at a median time of 49 days (IQR, 32-66). Within 72 hours following LT, two people experienced primary graft malfunction (18.2 percent). One patient passed away 4 days after LT from sepsis, while another required retransplantation owing to graft failure. Ten patients are still alive and doing well after a median follow-up of 322 days (IQR, 299-397). Post-transplant results were comparable across the two groups when compared to previous LTs following bridging with ECMO (n=27).

Despite the above said evidence, a lot of doubt around the possibility of lung recovery and the reversibility of lung damage, the purpose and timing of Lung transplantation for respiratory distress due to COVID 19 remains unclear. A recent analysis14 of the United Network for Organ Sharing (UNOS) database revealed a total of 63 patients who were listed for LTx from May 2005 to December 2018 with a primary diagnosis of nonCOVID-19-associated ARDS. 39 of the 63 people on the waiting list who requested a lung transplant did so. 16.7% of the 24 patients who remained on the waitlist but did not receive a lung transplant had their names removed owing to clinical progress.

Factors affecting Lung transplant outcome:

Previous research revealed a link between pre-LT physical function and post-transplant morbidity and death.[15-17] Patients with severe COVID-19-related ARDS also experienced ICU-acquired weakness, much like other ARDS patients.[18] To avoid patient-ventilator dyssynchrony and ventilator-induced lung damage as well as lengthy stays in the intensive care unit, these patients frequently underwent severe sedation. Therefore, when treating ARDS caused by COVID-19, ICU-acquired weakness might get worse.

CONCLUSION:

In conclusion, when therapy has been escalated to extended to hospitalisation due to disease severity, lung transplantation has a therapeutic function for carefully chosen patients with COVID-19. Despite receiving several weeks of the best medical care, patients who still require mechanical ventilation or ECMO, have advanced disease severity, radiological signs of irreversibility, and a high risk of developing life-threatening complications should only be given consideration for lung transplantation. A minority of individuals who experience severe COVID-19-related chronic pulmonary fibrosis may also be candidates for lung transplantation. To identify individuals who are likely to develop irreparable lung disease and could benefit from early lung transplantation, further research is required. It becomes necessary to navigate such a difficult technique successfully in order to rescue more people even with a shortage of donor organs and medical experts during the pandemic as the disease spreads without showing any signs of stopping. To that purpose, it is important to carefully develop lung transplantation in patients with post-COVID lung failure, and we also need to pay attention to the existing mortality of patients infected after lung transplantation.

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