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Lung Transplantation for COVID-19 patients and COVID-19 in Lung Transplant Recipients

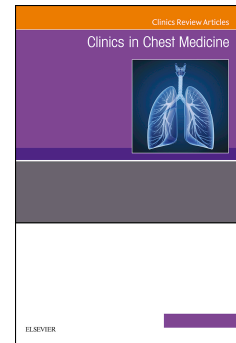
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## **Lung Transplantation for COVID-19 patients and COVID-19 in Lung Transplant Recipients**

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### **Synopsis**

Lung transplant is a life-saving treatment for carefully selected patients with respiratory failure related to the infection with COVID-19. Despite a complex pre-transplant medical course, the post-transplant outcomes are excellent when performed by experienced centers.

**Keywords:** Lung, transplant, COVID-19, ARDS, ECMO.

**Key points:** Respiratory failure, COVID-19 infection, ARDS, ECMO, Lung transplantation

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## Background

COVID-19 infection has affected millions of people, resulting in a wide spectrum of manifestations ranging from self-limited disease to severe acute respiratory distress syndrome (ARDS) requiring hospitalization and respiratory support, which, in some cases, can progress into lung fibrosis. For the most severe forms of the SARS-CoV-2 infection resulting in ARDS, modalities of respiratory support include mechanical ventilation and extracorporeal membrane oxygenation (ECMO). After initiation of respiratory support, a certain percentage of patients will not recover sufficient lung function to remain free from mechanical respiratory support. Additionally, certain patients infected with COVID-19 will develop long-lasting deterioration in their respiratory function, oxygen dependence, and overall deterioration in their performance due to the development of pulmonary fibrosis. Although these patients remain free from respiratory support, their quality of life is significantly affected, similar to patients with chronic respiratory diseases. Additionally, they may be at risk for the development of secondary pulmonary hypertension and cardiac dysfunction<sup>1,2</sup>. Lung transplantation for respiratory complications secondary to COVID-19 infection has been performed in over 200 patients in the United States with outcomes comparable to transplants performed for the traditional indications of chronic lung diseases<sup>3</sup>. Table 1 summarizes the relevant literature related to the lung transplantation in patients with respiratory failure secondary to COVID-19 infection.

Determination of the transplant candidacy for patients with respiratory failure secondary to COVID-19 requires careful consideration. Prior reports have used lung transplantation for

COVID-19 in patients who are younger and with less comorbidities, have had excellent performance status before the onset of COVID-19. However, prolonged hospitalizations, dependence on the ventilator, recurrent infections, malnutrition, physical deconditioning, and other respiratory complications, such as hemothorax and pneumothorax, make the transplant evaluation and the procedure quite challenging. It is imperative that the patients and their caregivers be provided with a clear understanding of the potential complications associated with changes in lifestyle and the need for lifelong immunosuppressive medications following transplantation.

### **Selection of candidates for lung transplantation**

Approximately 5% of patients infected with COVID-19 develop a severe form of the disease<sup>4</sup> although this is expected to reduce with the vaccination and now less common with the most prevalent Omicron variants (BA.2, BA.4 and BA.5). The mortality of patients with severe disease is close to 30%<sup>5,6</sup> despite optimized medical care. The number of patients with severe disease or long-term sequelae after a COVID-19 infection is substantial when considering the number of patients infected with COVID-19. However, there is still a lack of strong data demonstrating the long-term course of the disease. The course of the disease differs significantly between patients that remain free of mechanical ventilation since the development of symptoms or after a period of mechanical respiratory support and the patients that cannot be weaned from ventilator support or ECMO.

In a Spanish study that investigated the incidence of COVID-19 infection in Catalonia, 1.83% of the patients had an outpatient COVID-19 diagnosis and mortality was 3.01%. In the same

study, the patients that required hospitalization for COVID-19 represented 0.3% of the population but the mortality in this group was 19.16%<sup>7</sup>. Other studies have reported a decrease in the functional respiratory reserve demonstrated by a reduction in the pulmonary function testing and exercise tolerance as well as radiographic evidence of lung fibrosis after 3 to 4 months of initial symptoms of COVID-19 infection<sup>8,9</sup>. However, there is a lack of understanding of the implications of these findings in the long term.

Radiographic findings after COVID-19 infection include ground glass opacities (GGO), frank lung consolidation, and atelectasis. These findings are considered early manifestations and do not necessarily represent signs of irreversible damage. However, the GGOs can represent fibrosis, particularly when they present late in the course of the disease and other signs of lung fibrosis are present simultaneously. Traction bronchiectasis, honey combing, and subpleural fibrosis are more definitive signs of lung fibrosis and irreversible changes<sup>9,10</sup>; however, anecdotally some patients have demonstrated resolution of similar radiographic findings. The development of pleural effusions represents a unique challenge, particularly in coagulopathic patients and patients receiving therapeutic anticoagulation and ECMO support due to spontaneous bleeding in the pleural cavity and bleeding associated with placement of chest tubes. Spontaneous pneumothorax is another frequent complication of COVID-19 infection more frequently seen in patients who are receiving mechanical ventilation likely related to the effects of positive pressure ventilation on a fibrotic, stiff lung parenchyma. Lung expansion after placement of thoracostomy tubes is frequently incomplete with persistent air in the pleural spaces and prolonged air leaks. However, the development of lung fibrosis after COVID-19 infection is not uniform in all hospitalized or

ventilated patients and has been associated with advanced age, history of COPD and IPF, alcoholism, smoking, prolonged mechanic ventilation, and length of ICU stay<sup>11</sup>.

The COVID-19 findings closely resemble the course of the disease seen in patients with other coronavirus infections such as Middle East Acute Respiratory Syndrome (MERS) and severe acute respiratory syndrome (SARS). In patients with SARS and MERS, the majority recovered from their symptoms after two weeks, but about one third of the patients developed severe respiratory complications, including pneumonia and acute respiratory distress syndrome (ARDS), and a subgroup of patients developed chronic lung fibrosis<sup>12,13</sup>.

Waiting a reasonable period of time for the lungs to recover coupled with optimal respiratory care to maximize the chances of lung recovery is recommended before considering a patient for a lung transplant. Patients should be referred for a lung transplant evaluation after a multidisciplinary team with experience in the management of ARDS and lung transplant patients determines if there is: (i) no recovery after 4-6 weeks from the onset of symptoms of COVID-19, (ii) significant respiratory deterioration from base line and (iii) the need for oxygen supplementation, mechanical ventilation or extracorporeal life support. Contraindications for a lung transplant, such as an active or recent malignancy, severe chest wall deformities, irreversible bleeding disorders, compromise of other major organ systems, active substance abuse, inability to comply with a complex medical regimen, lack of adequate financial, or social support, should be ruled out first. Based on initial reports from our center and others, it is recommended that patients who undergo lung transplantation for COVID-19 include those younger than 70 years old, have been cleared of COVID-19 infection, single organ failure, no permanent neurologic damage, and a body mass index below 35<sup>14,15,16,17</sup>.

Once a patient has been deemed a suitable candidate for transplantation, any decision related to timing of the transplant should include several factors. The ideal time to perform a lung transplant in patients with lung disease after COVID-19 is determined by a combination of reasonable evidence indicating that the lung changes are irreversible, the physiologic reserve of the patient is adequate, and the physical deconditioning and complications associated with the disease have not placed the patient at too high a risk of death and complications – thus, reducing the benefit of a transplantation. For patients with significant functional limitations due to the COVID-19 infection or who require mechanical respiratory support, the risk of developing further complications affecting other organ systems, increasing physical deconditioning, and malnutrition should be considered. In such patients, there should be an emphasis on decreasing sedation, increasing the patients' involvement in their care, optimizing nutritional support, and minimizing threats to other systems. Judicious management of fluids is critical to improve the respiratory function without compromising other organ systems.

Approximately one-third of the patients admitted to the hospital for COVID-19 infection developed acute kidney injury and approximately 15% required renal replacement therapy<sup>18,19</sup>. Hospitalized patients requiring high ventilator support for a prolonged period have a low likelihood of recovery. In our series, without a lung transplant, there was a near 100% mortality rate for patients who required more than seven days of mechanical ventilation for COVID-19 ARDS<sup>20</sup>. Therefore, an early preliminary evaluation for lung



transplantation candidacy of these patients before starting mechanical life support is recommended to help tailor individual therapy.

For patients who are not admitted to the hospital, a standard evaluation for lung transplantation should be performed. A sufficient time for recovery of 4 weeks, or ideally 8 weeks, from the beginning of COVID-19 symptoms is recommended before considering lung transplantation. Recently published high-quality studies support the use of extracorporeal membrane oxygenation (ECMO) for ARDS, and large multicenter studies have reported good outcomes with the use of ECMO for COVID-19-associated ARDS. Considering this evidence, prolonged ECMO support, extending past 28 days, may be necessary to bridge some patients with COVID-19-associated ARDS to recovery, instead of bridging to lung transplant<sup>21</sup>. A complete standard evaluation is recommended, including all the physiologic and socioeconomic factors used for the evaluation of all patients considered for lung transplantation. To date, in the United States, patients who have received lung transplants for COVID-19 are younger than patients receiving lung transplants for other indications<sup>17,3</sup>

Demonstration of eradication of the COVID-19 infection is critical before performing a lung transplantation. Strong immunosuppression, needed immediately after the lung transplant, can be detrimental in patients with a persistent COVID-19 infection. We recommend that patients receive two negative PCR tests 24 hours apart performed using samples obtained from the distal airways with a bronchoalveolar lavage, as those areas have a higher viral load and have a lower false negative rate in comparison to the upper airway. When the patient is

not intubated, we recommend two negative PCR tests from samples obtained from the upper airway at least 24 hours apart<sup>17,15</sup>.

### **Intraoperative considerations during transplant**

To date, most transplanted patients for COVID-19 ARDS have received a double lung transplant as the most common procedure for any lung transplant recipient with acute respiratory failure requiring MV or ECMO support, and also in part due to the high prevalence of severe pulmonary hypertension<sup>3,17</sup>. However, a few single lung transplants in patients with respiratory disease secondary to COVID-19 infection have been performed successfully<sup>3</sup>. Many COVID-19 patients develop structural abnormalities such as cavitary lesions and recurrent pleural infections with recurrent bacterial infections. The presence of persistent infections or structural abnormalities, such as large cavities that could be potential sources of infection in the postoperative period, pose a high risk for patients' undergoing a single lung transplant for respiratory disease secondary to COVID-19 infection. As such, single lung transplantation should be considered on a case-by-case basis and mostly reserved for patients with long-term COVID-19 fibrosis rather than ARDS.

Due to the high incidence of pulmonary hypertension and right ventricular dysfunction, in addition to the higher incidence of severe pleural adhesions, the use of intraoperative venoarterial (VA) ECMO support is highly recommended. As many of these patients are already on peripheral venous-venous (VV) ECMO support, it is important to consider conversion to VA ECMO for a better hemodynamic support. Pneumonectomies also pose significant challenges because of the presence of adhesions between the lungs and the pleura

and mediastinum. In these patients, the dissection planes are frequently altered, and bleeding is often significant. Surgical teams, as well as perfusion and anesthesia teams, should be aware of this and prepare to transfuse and support the patient. The chest cavities are often small, requiring caudad retraction of the diaphragm to facilitate the operation. As expected, the operative time and organ cold ischemic time is longer in COVID-19 patients, as is the requirement for transfusion of blood products in comparison with other pathologies<sup>17</sup>.

A unique challenge in COVID-19 ARDS patients is the presence of diaphragmatic dysfunction. In a recent study, 76% of patients discharged to rehabilitation after severe COVID-19 ARDS had sonographic evidence of diaphragm dysfunction<sup>22</sup>. The mechanisms associated with the diaphragmatic dysfunction in these patients include critical illness myopathy, ventilator-induced diaphragmatic dysfunction, iatrogenic injury of the phrenic nerve during placement of central lines, post-infectious inflammatory neuropathy of the phrenic nerve, and direct neuromuscular involvement of the COVID-19 virus. Peripheral nerves and muscles express Angiotensin-converting enzyme 2 receptor to which viral structural proteins bind. Autopsy studies have demonstrated diaphragmatic fibrosis and a unique myopathic phenotype compared to other ICU patients<sup>23,24,25</sup>.

The prevalence and impact of these findings in transplanted patients is unknown, but they play a role in the increased number of complications, need for ventilator support, and ICU stay. A diaphragmatic and phrenic nerve evaluation with bedside ultrasound is a useful tool in ventilated patients to assess the function of the diaphragm longitudinally and detect improvement or deterioration of the diaphragmatic function. Although to date there are no

studies evaluating the effect of any therapeutic intervention for diaphragmatic dysfunction after lung transplants for respiratory disease after COVID-19 infection, some transplant centers advocate for the early use of diaphragmatic pacing in a selected group of patients. However, the short and long-term results of this intervention are unknown. Nonetheless, these findings stress the importance of protecting the phrenic nerve during the conduction of the operation minimizing trauma or traction of the nerves.

### **Postoperative care of the transplanted patients**

Postoperative care in the intensive care unit involves respiratory support with mechanical ventilation and extracorporeal life support with VV and VA ECMO. The length of stay in the hospital and in the ICU after a lung transplant for COVID-19 has been reported to be almost twice as long for patients receiving lung transplants for other reasons. In our series, the median length of stay for COVID-19 transplant patients versus other lung transplant patients was 28.5 vs 16 days in the hospital and 6.5 vs 2 days in the ICU. The need for care in the ICU was largely determined by the need for mechanical ventilation. Analysis of the UNOS database for patients receiving transplants related to COVID-19, indicate that over 70% of such patients have needed mechanical ventilation for at least 48 hours after the transplant<sup>3</sup>. In our series, the median time on a ventilator was 6.5 days<sup>17</sup>. Additionally, according to the UNOS database, approximately 12.3% of patients needed postoperative ECMO<sup>3</sup>, and there was a 30-day mortality of 2.2 % (4 of 183 patients analyzed) and a 6-month survival rate of 92%.

In our series, one-year survival rate after transplantation of 30 patients for COVID-19 was 100% after a median follow up of 351 days in comparison with 83.3% survival of patients that received transplants for a different pathology. Thirty percent of the patients needed ECMO support after transplant<sup>17</sup>. The difference in the need for ECMO support post-transplant is likely explained by institutional preferences in the postoperative management of these patients and the heterogeneity in patient complexity. The causes of early, postoperative deaths include respiratory failure, rejection after transplant, gastrointestinal infection, hyperammonemia, and COVID-19 infection. Other frequent postoperative complications after lung transplant for COVID-19 include primary graft dysfunction, stroke, acute renal failure and transplant rejection, and pleural effusions.

Renal dysfunction occurs more frequently in patients with COVID-19. This is true also for patients after lung transplants due to COVID-19 in comparison with patients undergoing lung transplants for other reasons. Approximately 30% of patients hospitalized with COVID-19 develop kidney injury, and 50% of COVID-19 patients in the ICU with kidney injury require dialysis. Vascular endothelial injury associated with COVID-19 infection, hemodynamic instability, tissue inflammation, and immune infiltration may play a role in the origin of kidney injury<sup>26</sup>. Even though the long-term outcomes are unknown, patients with COVID-19 infection and renal failure have higher mortality and worse outcomes. Approximately 5% of COVID-19 patients who have received a lung transplant needed dialysis before transplantation<sup>3</sup>. In comparison with non-COVID-19 patients, the rate of permanent hemodialysis after lung transplant is significantly higher in COVID-19 patients (13.3% vs 5.5%). Of note, a similar percentage of COVID-19 patients that received a lung

transplant (10%) required only temporary postoperative dialysis<sup>20</sup>. However, it is unclear what percentage of patients that had renal failure before transplant required permanent dialysis after lung transplant. Some centers have performed simultaneous lung and kidney transplants when the potential of recovery of kidney function was deemed low.

The degree of primary graft dysfunction (PGD) after transplant is not clearly understood. In our series, 70% of the patients had some degree of primary graft dysfunction. However, their rate of acute rejection or development of donor specific antibodies was zero in comparison with a 12% in non-COVID-19 patients. A potential explanation for the low rate is the dilution of HLA antibody titers due to a higher rate of bleeding and transfusions<sup>17</sup>. The impact of these findings in the development of chronic allograft dysfunction in these patients is unknown. Despite the higher frequency of PGD, the patients that received a lung transplant for respiratory diseases after COVID-19 infection had more significant improvement in their performance in comparison with the non-COVID-19 patients<sup>20</sup>. This is not surprising considering the more critical condition of the COVID-19 patients at the time of the transplant relative to the non-COVID-19 patients as well as the younger age and healthier base line of such patients before COVID-19 infection.

With the high prevalence of COVID-19 infection, a particular subject with impactful implications for the future is the selection of lungs from donors that could have had infection for COVID-19. The current recommendation from the UNOS is to obtain samples from the lower respiratory tract from donors and analyze those by PCR for COVID-19, due to the higher frequency of the viral receptor ACE2 in the lower respiratory tract and because the

viral testing in samples obtained from bronchoalveolar lavage remains positive for a longer period in comparison to samples obtained from the upper respiratory tract<sup>27</sup>. However, to maximize the use of the organs and decrease the false positive rates of COVID-19 tests, if a positive test is found and the clinical probability of a positive infection is low, it is recommended to repeat the test in samples obtained from the distal airways. In donors with a history of infection of COVID-19 more than 21 days before the lung procurement, the likelihood of active COVID-19 infection and transmissibility is extremely low. The assessment of the organ at the time of procurement also provides valuable information about the condition of the organ. Evaluation of the donor lungs with a CT scan looking for fibrotic changes, persistent hypoxia in central and selective arterial gases sampling, thick and rigid lungs at in situ palpation of the organs, and reduced lung compliance in the ventilator are all indicators of fibrotic changes in the lung. Figure 1 shows an algorithm for evaluating the donor lungs in the setting of a potential history of COVID-19<sup>28</sup>.

In conclusion, lung transplant is a life-saving treatment for carefully selected patients with COVID-19 associated respiratory failure. Despite a complex pre-transplant medical course, the post-transplant outcomes are excellent when performed by experienced centers.

Table 1. Relevant published articles on Lung transplantation for severe COVID -19 infection

|   |  |
|---|--|
| Demonstration of need and feasibility of lung transplantation for severe COVID-19 infection | Lung transplantation for patients with severe COVID-19. Bharat, A. et al. <i>Sci Transl Med.</i> 2020. <sup>16</sup> |
|---|--|

|  |   |
|--|---|
| Early recommendations of criteria for lung transplantation in patients with COVID-19 infection   | When to consider lung transplantation for COVID-19. Cypel, M. <i>Lancet Respir Med.</i> 2020. <sup>14</sup>   |
| Multi-institutional international early experience and outcomes of lung transplantation for severe COVID-19 infection                                | Early outcomes after lung transplantation for severe COVID19: a series of the first consecutive cases from four countries. Bharat, A. et al. <i>Lancet Respir Med.</i> 2021. <sup>15</sup>        |
| Larger, single institutional experience with lung transplantation for COVID-19 associated ARDS   | Clinical Characteristics and Outcomes of Patients With COVID-19–Associated Acute Respiratory Distress Syndrome Who Underwent Lung Transplant. Kurihara, C et al. <i>JAMA.</i> 2022. <sup>17</sup> |
| Experts' opinions on approaching lung transplantation for patients with COVID-19 infection   | Lung transplantation for patients with COVID-19. King, C., et al. <i>Chest,</i> 2022. <sup>29</sup>   |
| Reported national outcomes for patients that underwent lung transplantation for respiratory failure secondary to COVID-19; analysis of the UNOS data | Lung transplantation for COVID-19 related respiratory failure in the United States. Roach, A., et al. <i>NEJM.</i> 2022. <sup>3</sup>   |



## Clinics Care Points

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## Figures

**Figure 1.** Institutional practice for assessment of lungs from donor with historic COVID-19. From Querrey M, Kurihara C, Manerikar A, et al. Lung donation following SARS-CoV-2 infection. *Am J Transplant.* 2021;21(12):4073-4078. <sup>27</sup>.

**Pre-Donation Imaging**

1. Chest Radiograph and Computed Tomography
  - No evidence of pulmonary fibrosis or interstitial lung disease
2. Transthoracic ECHO
  - No evidence of pulmonary hypertension or right ventricular dysfunction

**Preoperative Assessment**

- No concerns for poor lung compliance or gas exchange due to a sequela of COVID-19

**Intraoperative Assessment\*\*\***

- Manual palpation and recruitment of lung demonstrating normal compliance and no gross fibrosis
- Satisfactory pulmonary venous sampling from all four veins\*\*\*\*

\*Onset defined as a positive PCR or symptom onset if PCR not performed. Use of PCR is suggested since determination of symptom-onset could be unreliable when obtaining history from the donor family

\*\*>60 day duration since positivity is selected as presence of replication-competent virus is unlikely after 60 days

\*\*\*Intraoperative frozen section could be utilized in centers when sufficient expertise and data is available

\*\*\*\*While selective venous gases may be useful, it can be avoided if there are no concerns for COVID-19 related lung damage based on other parameters or when hemodynamic instability precludes this assessment

