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Lung Transplantation for COVID-19–related Lung Disease: Clinical Experience and Call for a Global Registry

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Coronavirus disease 2019 (COVID-19) has caused a global pandemic of unprecedented magnitude. Among hospitalized patients, about a third develop adult respiratory distress syndrome (ARDS) with an average mortality rate of 16%.[1] This is often difficult to manage, requiring unusually high levels of sedation, paralytics, and support with extracorporeal membrane oxygenation (ECMO). In selected cases, lung transplantation can be a viable treatment option for patients with irreversible lung damage who would otherwise inevitably face death.

Since the onset of the pandemic, the volume trend for lung transplant because of COVID-19–related lung disease (CRLD) has shifted with an uncertain trajectory. Initially, rapidly increasing number of lung transplants for COVID-19–related ARDS was observed.[2] With the arrival of COVID-19 vaccines, an increasing numbers of therapeutics to treat COVID-19 infection, and the emergence of less virulent variants of COVID-19, the transplant volume for COVID-19–related ARDS has declined. Additionally, there is increasing evidence that patients with severe COVID-19–related ARDS who require prolonged support with invasive mechanical ventilation or ECMO have the potential to recover without lung transplantation.[3,4] How many survivors of severe acute respiratory syndrome coronavirus 2 may need lung transplantation for fibrotic lung disease in the future is currently unclear. The United Network of Organ Sharing, which collects and reports data on transplant volumes in the United States, established COVID-19–related ARDS and COVID-19–related pulmonary fibrosis as listing diagnoses in their database in October of 2020. Since then, a total of 364 lung transplants for COVID-19 have been reported to date, 223 for COVID-19–related ARDS and 141 for COVID-19–related fibrosis, accounting for almost 10% of the entire US lung transplant volume in 2021, making it the third most common indication after interstitial lung disease and emphysema in that year (https://optn.transplant.hrsa.gov/data, last accessed June 6, 2022). Despite this, the body of literature to guide practice remains sparse and is largely limited to short-term follow-ups and single-center experiences.

Most available case reports on lung transplant for CRLD were published in the early phase of the pandemic, and the majority of recipients had COVID-19–related ARDS. Early reports highlight concerns regarding disease transmission and reactivation of severe acute respiratory syndrome coronavirus 2 in the allograft. Although successful lung transplantation has been reported in a patient with a positive COVID-19 polymerase chain reaction (PCR) at the time of transplant,[5] most centers mandate 2 negative COVID-19 PCRs at least 24 h apart before listing for transplant. To our knowledge, no cases of COVID-19 reactivation have been reported in lung transplant recipients. Since donor-derived COVID-19 infection of a lung transplant recipient and participating operating room personnel has been reported even in the setting of negative COVID-19 PCR testing from the upper respiratory tract,[6] potential lung donors in the United States are now required to undergo nucleic acid testing from the lower respiratory tract (optn.transplant.hrsa.gov).

The timing of transplant in patients with COVID-19–related ARDS is highly challenging and has varied from 41 d[7] to 6 mo[8] from the time of diagnosis in the published literature. The potential for delayed recovery has to be weighed against the risk of complications from prolonged critical illness. Experts suggest a minimum of 4 to 6 wk

Received 20 April 2022. Revision received 13 June 2022.

Accepted 19 July 2022.

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M.G.I. reports research support, paid to Northwestern University, from AiCuris, GlaxoSmithKline, Janssen, and Shire; he is a paid consultant for Adagio, AlloVir, Celltrion, Cidara, Genentech, Roche, Janssen, Shionogi, and Viracor Eurofins; he is also a paid member of Data and Safety Monitoring Boards from Janssen, Merck, SAB Biotherapeutics, Sequiris, Takeda, and Vitaeris; and he also receives royalties from UpToDate. S.A. is a consultant BioMx, Phico, Merck (honoraria), and Gilead (honoraria). M.M.W. is an unpaid consultant for LifeNet Health.

M.G.I. received support provided by National Center for Advancing Translational Sciences grant UL1TR001422. S.A. received support from the Cystic Fibrosis Foundation (ASLAM20A0-I 2021), National Institute of Health/National Center for Advancing Translational Sciences grant (UL1TR001442), and National Institute of Health/ National Institute of Allergy and Infectious Diseases grant (AI571981).

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ISSN: 0041-1337/20/1071-18

DOI: 10.1097/TP.0000000000004327

between the onset of COVID-19 ARDS and consideration for lung transplant and recommend additional evidence of irreversible structural lung damage.[9] This time frame may be insufficient in some patients who have the potential for delayed recovery.[3,4]

Most evaluations for lung transplant candidacy occur on relatively stable patients in the outpatient realm. In contrast, transplant evaluations for potential candidates with CRLD frequently occur in an intensive care environment in patients with very high acuity and dependence on life support. These circumstances can necessitate significant variance to the transplant evaluation and interfere with the reliability and accuracy of neurocognitive and psychosocial assessments. In most case reports where such information was provided, patients were able to give consent, but it remains questionable how much critical illness affected patients' ability to understand the complexities and risks that were involved in a transplant for CRLD. Inability to provide consent should be regarded as an absolute contraindication to the procedure unless there are exceptional circumstances. Limited data suggest that patients with CRLD who are unable to consent may be more prone to posttransplant depression, especially in cases of a prolonged and difficult recovery.[7] Noncompliance may complicate the posttransplant course, especially in patients without prior medical history and need for long-term follow-ups.

Deconditioning and frailty as a result of prolonged critical illness are common barriers to transplant candidacy in patients with CRLD and have previously been associated with adverse outcomes in lung transplant recipients.[10] Mobilizing critically ill patients with CRLD is highly resource and labor intensive, requires expertise of the care personnel, and may be unfeasible in patients who are too unstable. Ability to participate in physical therapy is generally considered essential to consider a patient with CRLD as a transplant candidate, but the degree of physical impairment in reported cases is highly variable. Many of the reported recipients were not ambulatory at the time of surgery,[8,11] which is likely a major contributor to prolonged recovery times in these patients. Awake rehabilitation and the ability to maintain ambulation have previously been associated with improved outcomes in non-COVID patients requiring ECMO as a bridge to lung transplantation.[12-14]

Frequently, requests to evaluate patients with CRLD for lung transplant originate from hospitals without transplant capabilities. The majority of referrals will not be suitable for transplantation, and selecting appropriate candidates for transfer to a transplant center can be very challenging, especially if the patient requires additional life support to facilitate a safe transport. Several centers have proposed a protocolized interdisciplinary approach incorporating telemedicine assessments before accepting a patient for transfer.[15]

Most of the available literature commented on the unique intra operative challenges in patients with CRLD. The severe parenchymal destruction, extensive pleural involvement, and reactive lymphadenopathy often result in very difficult mobilization of the native lungs, resulting in longer surgery and cold ischemia times, increased need for intraoperative blood products, and a higher incidence of primary graft dysfunction.[16] Secondary colonization or infection with bacterial or fungal organisms is a common complication of prolonged critical illness, mechanical ventilation, and pleural instrumentation. It is largely unclear how this affects posttransplant outcomes, although some cases of postoperative morbidity and mortality related to bacterial[17] and fungal sepsis[16] have been reported.

Most of the early available case reports only document short-term posttransplant outcomes on single patients or case series.[7,8,11,16-18] Very recently, analyses of larger patient cohorts over a longer time span have been published: A retrospective analysis of the United Network of Organ Sharing database reported outcomes on 214 patients who received lung transplantation for COVID-19–related respiratory failure in the United States[2] with a median follow-up of 1.9 mo. Patients were relatively young (mean age 52 y) and predominantly male (79.2%), and included a high percentage of patients of Hispanic origin (36.6%), consistent with reports that have identified a higher risk of COVID-19–related respiratory failure in this group. Almost two thirds of the patients required ECMO before lung transplant. The mean lung allocation score was 87.5, indicating very high priority for donor lungs. The reported 30-d survival was 97.8% and approached that of patients who were transplanted for other indications. Another report summarized the experience of 30 consecutive patients who received lung transplantation for COVID-19–related ARDS at a single center and compared it to 72 patients with non-COVID-19–related end-stage lung disease in the same time period.[19] Patients in the COVID-19 group were younger (53 versus 62) and had higher lung allocation scores (85.8 versus 46.7), shorter time on the transplant waitlist (11.5 versus 15 d), higher need for intraoperative blood transfusions (6.5 units of packed red blood cells versus 0), higher incidence of primary graft dysfunction (70% versus 20.8%), and need for permanent renal replacement therapy (13.3% versus 5.5%). Impressively, all 30 patients in the COVID-19 group were still alive at the time of the report with a median follow-up of 351 d.

The amount of available literature on lung transplantation for CRLD remains sparse. Limited experience exists in regard to patients who survive COVID-19 but develop pulmonary fibrosis necessitating consideration for lung transplantation at a later time.[20] Even less is known about patients with preexisting lung disease, where COVID-19 exacerbates respiratory failure and leads to potential transplant candidacy.

The existing transplant registries are designed to capture demographics, clinical variables, and transplant-related outcomes for all organ donors and recipients. The International Society of Heart and Lung Transplantation is the only organization that tracks lung transplant–related outcomes globally. In the United States, transplant centers are required to report their outcomes to the Scientific Registry of Transplant Recipients. Both registries do not address many of the unique challenges in lung transplantation for CRLD regarding candidate selection, pretransplant functional status and comorbidities, and infectious complications and postoperative complications. For instance, duration of mechanical ventilation and ECMO support—both important metrics that can affect posttransplant outcomes in these patients—are not monitored by existing transplant registries. The global registry that is maintained by the

Extracorporeal Life Support Organization has tracked outcomes of COVID patients who require ECMO support, but the database is lacking specifics about patients that proceed to lung transplantation (www.elso.org). However, adding variables to the existing databases to capture the circumstances of lung transplants for CRLD more accurately has limited relevance for other disease groups and is likely not feasible.

Given the above, our group has created a global database to obtain detailed clinical information on lung transplants that have been performed for CRLD. It is administered by the Northwestern University Feinberg School of Medicine and has received Internal Review Board approval. The database is open access, and transplant centers across the world have been invited to submit retrospective cases electronically. Because no protected health information is obtained, institutions should not require permissions from their home Internal Review Boardss or data usage agreements before entering cases. Most of the requested information is specific to the diagnosis of CRLD, including details on COVID-19 therapy before transplant, duration of ECMO and ventilator support, functional status, patient ability to consent, intraoperative requirements, secondary infections, and postoperative complications and outcomes (https://www.feinberg.northwestern.edu/sites/nutorc/Lung%20Transplant%20Registry/index.html). As of mid-May of 2022, a total of 89 cases have been entered into the registry: 75 from the United States, 10 from Europe, and 4 from South America. We believe that capturing the experience of lung transplant programs of different sizes from different countries offers important perspectives and will help guide clinical practice for this patient population in the future and encourage transplant centers to share their expertise in transplanting patients with this challenging condition.

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