



Lung Transplantation for Patients with COVID-19 Acute Respiratory Distress Syndrome

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Patients with severe coronavirus disease 2019 (COVID-19) acute respiratory distress syndrome (ARDS) may exhibit pulmonary fibrosis after the viral illness resolves. Some of these patients may experience severe functional lung impairment, and thus require transplants to prevent death or maintain a tolerable quality of life. Considering the reversibility of COVID-19 ARDS, lung transplant candidates are observed for 1–2 months and must be selected very carefully before transplantation. As the short-term outcomes of such patients are comparable to those of patients with other indications for transplantation, lung transplantation should be actively considered.

Keywords: COVID-19, Acute respiratory distress syndrome, Lung transplantation

Introduction

Lung transplantation has been considered the last resort for patients with various end-stage lung diseases. Transplantation is indicated for patients with refractory chronic lung diseases such as idiopathic pulmonary fibrosis, idiopathic pulmonary hypertension, and chronic obstructive pulmonary disease [1]. As outcomes have improved over time, the number of transplantations has rapidly increased [2]. In Korea, the number of lung transplantations has increased in recent years; more patients who urgently require transplants are now receiving them [3,4].

Previously, mechanical support was associated with poor post-transplant outcomes. However, with the advent of extracorporeal membrane oxygenation (ECMO), critically ill patients with chronic end-stage lung disease could be bridged to transplantation. Recent advances in ECMO have allowed long-term patient support [5]. Traditionally, patients with acute respiratory distress syndrome (ARDS) were not indicated for lung transplantation for various reasons. First, the reversible nature of ARDS limits the need for transplantation. ARDS survivors experience only trivial sequelae (such as mild physical impairment), and ARDS does not compromise long-term survival [6,7]. In addition, some ARDS patients are too fragile or critically ill for lung

transplantation.

Respiratory failure was reported as the cause of death in 13%–19% of ARDS patients [8]. The use of ECMO has recently facilitated long-term survival in ARDS patients, although injured lungs may undergo fibrotic changes. If these changes are unlikely to be reversible, lung transplantation may be an option [9–11]. However, patients must be carefully selected for ECMO-bridged lung transplantation. In this review, the author discusses the practical issues that must be considered when considering lung transplantation for patients infected with coronavirus disease 2019 (COVID-19).

Indications for lung transplantation in patients with COVID-19 ARDS

During the last 2 years of the COVID-19 pandemic, the clinical features of patients with COVID-19 ARDS who underwent lung transplantation were described in many case reports and retrospective analyses. According to the United Network for Organ Sharing registry, approximately 7% (214) of all lung transplantations performed nationwide in the United States from August 2020 to September 2021 were for patients with respiratory failure caused by COVID-19, including 140 (4.6%) with ARDS and 74 (2.4%) with



pulmonary fibrosis [12]. Preoperatively, 97 (53.0%) of the patients received mechanical ventilation, while 118 (64.5%) received ECMO and 9 (4.9%) underwent dialysis. Of the 214 lung transplantations, 197 (92.1%) were bilateral and 17 (7.9%) were unilateral [12]. The International Society for Heart and Lung Transplantation recommends lung transplantation only for a small minority of patients with COVID-19 [13]. Lung transplants for otherwise healthy patients with COVID-19-related respiratory failure should be considered only when the following conditions are met: at least 28 days have elapsed since the onset of severe lung injury, 2 polymerase chain reaction tests for severe acute respiratory syndrome coronavirus 2 conducted at least 24–48 hours apart are negative, only 1 organ has failed, the patient has good nutritional status and rehabilitation potential, and center-specific criteria are fulfilled.

Outcomes of lung transplantation in Korean COVID-19 ARDS patients

Early data indicated that the post-transplantation outcomes of COVID-19 ARDS patients were comparable to those of patients with chronic lung disease previously indicated for transplantation [14–16]. In the United States, the postoperative death rate was only 4.2% over a median of 1.9 months [12]; causes of death included COVID-19 infection (n=1), respiratory failure (n=3), anoxia (n=1), transplant rejection (n=2), gastrointestinal infection (n=1), and hyperammonemia (n=1). The 30-day mortality rate was 2.2% (n=4) and the 3-month survival rate was 95.6%. Complications included stroke in 6 of 183 patients (3.3%), the need for additional ECMO in 8 of 65 patients (12%), and transplant rejection in 11 of 183 patients (6.0%). In Austria, 19 patients underwent transplantation to treat COVID-19 ARDS; the 30-day mortality rate was 0%. After a median follow-up of 134 days (range, 47–450 days), 14 of the patients were still alive [17]. Given that the 3-month survival was comparable to that of patients with other diseases in whom lung transplantation is indicated, COVID-19 ARDS may be an appropriate indication for lung transplantation if ongoing irreversible injury or post-ARDS lung fibrosis is likely. However, the long-term efficacy of lung transplantation and the reversibility of COVID-19 ARDS are still matters of debate.

A few Korean case reports on lung transplantation for COVID-19 ARDS patients have appeared. Given the relatively successful national quarantine policy, the incidence of COVID-19 infections was low before the emergence of the Omicron variant. Therefore, few lung transplantations

were performed, although a report of 11 cases was published in 2021. The early outcomes were acceptable—that is, they were comparable to those of patients with other indications for transplantation [18]. Primary graft dysfunction developed in 2 patients (18.2%), of whom 1 died of sepsis 4 days after transplantation and 1 underwent retransplantation after initial graft failure. After a median follow-up of 322 days (range, 299–397 days), 10 patients were alive and in good condition. The Omicron variant was first reported in Korea in March 2022. Additional transplantations would thus be expected [12], but further research is needed to confirm this possibility.

Disease reversibility and optimal timing

Based on patients with post-ARDS fibrosis, it is reasonable to perform lung transplantation in COVID-19 ARDS patients dependent on high oxygen concentrations or who cannot be weaned off mechanical ventilation. An early report described post-COVID-19 lung fibrosis; some patients exhibited significant and persistent functional lung impairments [19]. The most important question is whether the COVID-19 ARDS patient has an irreversible lung condition. Lung transplantation should be considered when the life-expectancy benefit outweighs the risk. However, data on the long-term outcomes of COVID-19 ARDS survivors are lacking. In an Austrian case, a patient was observed for 52 days before being scheduled for lung transplantation [16]. In another case series from China, 2 patients were scheduled for lung transplantation at an earlier stage (i.e., on days 27 and 33) [20].

If the sequelae of COVID-19 ARDS are similar to those of ARDS of other causes, it is not certain that survivors will benefit from lung transplantation. As mentioned above, most ARDS survivors exhibit only mild physical impairment at the 1-year follow-up [6]. However, the long-term sequelae of COVID-19 infection may differ. A longitudinal follow-up study of COVID-19 ARDS survivors found that 4.9% exhibited significant oxygen desaturation (<88%) during the 6-minute walk test [21]. In addition, a substantial proportion of COVID-19 survivors are discharged to nursing or rehabilitation facilities; 60 days after discharge, 6.7% of hospital survivors and 10.4% of intensive care unit survivors had died [22]. COVID-19 ARDS requiring ECMO support would be expected to be associated with serious physical or lung impairment. In a meta-analysis, the mortality rate of COVID-19 ARDS was 39% [23]. In ARDS cases requiring ECMO, the 90-day

mortality was <40%, as revealed by analysis of an international ECMO registry [24]. Therefore, some COVID-19 ARDS survivors may develop end-stage lung conditions; the viral damage is irreversible. This emphasizes that candidates for lung transplantation must be selected very carefully.

Unfortunately, it is almost impossible to optimally time transplantation. Cypel and Keshavjee [25] suggested ways to evaluate the possible benefit of lung transplantation for COVID-19 ARDS candidates. It was suggested that registration on the transplant wait-list should be delayed by at least 4–6 weeks because the lung may recover without severe functional limitations. In another study, all COVID-19-associated ARDS candidates were observed for 1–2 months before transplantation [26]. Clinical problems include irreversible lung damage, donor shortages, and the loss of the transplant opportunity for other potential recipients. Multidisciplinary data to guide clinical decision-making are still lacking. In particular, the absence of COVID-19 should be confirmed in all candidates to prevent viral reactivation or transmission during or after lung transplantation.

Conclusion

Patients with severe COVID-19 ARDS may exhibit pulmonary fibrosis after the viral illness resolves. Some of these patients may exhibit severe functional lung impairment, and thus require transplants to prevent death or maintain a tolerable quality of life. Such patients have received lung transplants over the past 2 years of the pandemic [14,27], but the long-term benefits remain unknown. The long-term outcomes and pathophysiology of COVID-19 ARDS remain under investigation. Nevertheless, the decision to perform a lung transplant decision for a very ill COVID-19 ARDS patient should not be delayed. As the short-term outcomes of such patients are comparable to those of patients with other indications for transplantation [12]; lung transplantation should be actively considered.

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Author contributions

All work was done by Woo Hyun Cho.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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