JCS Journal of Chest Surgery
https://doi.org/10.5090/jcs.22.055
pISSN: 2765-1606 eISSN: 2765-1614
J Chest Surg. 2023;56(1):6-13

Clinical Research

Early Outcomes of COVID-19 Lung Transplantation Recipients in Korea: A Single-Center Study

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ARTICLE INFO
Received July 11, 2022
Revised September 26, 2022
Accepted October 23, 2022

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Background: Coronavirus disease 2019 (COVID-19) has been found to cause life-threatening respiratory failure, which can progress to irreversible lung damage. Lung transplantation can be a life-saving treatment in patients with terminal lung disease (e.g., acute respiratory distress syndrome caused by infection). This study aimed to present the clinical course and results after initial lung transplantation in patients with severe COVID-19 who did not recover even with optimal medical care.
Methods: From August 2019 to February 2022, this study enrolled 10 patients with COVID-19 (5 men; median age, 55.7 years) who underwent lung transplantation at a single center in Korea. All patients' characteristics, clinical pathway, overall survival, complications, and operative data were collected and analyzed.
Results: Veno-venous extracorporeal membrane oxygenation or an oxygenator in a right ventricular assist device circuit was applied to 90% of the patients, and the median length of extracorporeal life support before operation was 48.5 days. There were no cases of mortality after a median follow-up of 372.8 days (interquartile range, 262.25–489 days). The major complications included the requirement for postoperative extracorporeal membrane oxygenation support in 2 cases (20%), re-transplantation in 1 case (10%), and re-exploration due to bleeding in 2 cases (20%). During the follow-up period, 3 out of 10 patients died.
Conclusion: Excellent early outcomes were observed for patients who underwent lung transplantation. Thus, lung transplantation can be an effective and feasible treatment for patients with end-stage lung disease caused by COVID-19.

Keywords: Lung transplantation, COVID-19, Surgical outcome

Introduction

Coronavirus disease 2019 (COVID-19) can cause numerous complications, especially irreversible damage to pulmonary function [1]. According to the World Health Organization, there have been more than 510,000,000 confirmed cases of COVID-19 globally, including 6,200,000 deaths, as of May 2022. During the same period, more than 17,400,000 people (approximately 28% of the population) were infected in Korea, and more than 23,000 of these patients died [2]. In particular, there was a rapid increase in the number of patients with COVID-19 who showed fibrotic changes and impaired lung function and who required mechanical ventilation [3,4]. Some of these patients required extracorporeal membrane oxygenation (ECMO), and their 90-day mortality was 38% [1]. Although lung transplantation has been performed for patients who did not recover from pulmonary damage, there are few reports of lung transplantation for COVID-19 patients with end-stage lung disease. Lung transplantation is considered a life-saving treatment in patients with terminal lung disease. Several studies have reported that ECMO could be a bridge to lung transplantation with feasible early outcomes [5,6]. However, as there have been no previous reports from this high-volume center in South Korea, the purpose of this study was to review the surgical strategy, clinical course, and results after initial lung transplantation in patients with severe COVID-19 infection who did not recover despite optimal medical care.

Methods

Patient information and data collection

We retrospectively identified 10 patients with COVID-19 who were registered on a lung transplantation waiting list and underwent transplantation between May 2020 and February 2022. Perioperative medical treatment was provided as part of the routine protocol for lung transplantation in consultation with intensive care unit (ICU) pulmonologists. We collected and analyzed perioperative demographic and clinical data on overall survival, the basic underlying disease before transplantation, ECMO application during the perioperative period, ICU stay dates, and major postoperative complications. The patients were followed up during the period from the operation date to the date of discharge or to the date of their most recent outpatient visit.

The study protocol was approved by the institutional review boards of Asan Medical Center (IRB registration no., 2021-1847). The requirement for informed consent from individual patients was omitted because of the retrospective design of this study. All processes related to the donors, transplant orders, and matching followed the guidelines of the Korea Organ Donation Center.

Surgical strategy

Including respiratory rehabilitation, perioperative management was performed by a specialist in pulmonology. In accordance with the recommendations of the International Society of Heart and Lung Transplantation, patients with potential for lung transplantation were selected as candidates. Every step was approved by the institutional ethics committees and communicated to the multidisciplinary team, which included thoracic surgeons, anesthesiologists, pulmonologists, pathologists, and perfusionists. The multidisciplinary lung transplant committee confirmed the suitability of candidates by reviewing the medical records of end-stage lung disease patients. For patients with COVID-19, since their clinical features and prognosis were unknown, transplant recipients were selected after serious consideration and analysis with experts. Once the selected patient information was communicated to the Korean Network for Organ Sharing, patients were ranked for donor lung allocation according to their urgency, and the most urgent priority was given to patients requiring mechanical ventilation or ECMO. In patients with severe right ventricular dysfunction, our strategy was to switch to an oxygenator in a right ventricular assist device circuit (Oxy RVAD) to maintain cardiopulmonary function. Patients before and after surgery were regularly re-evaluated by the Lung

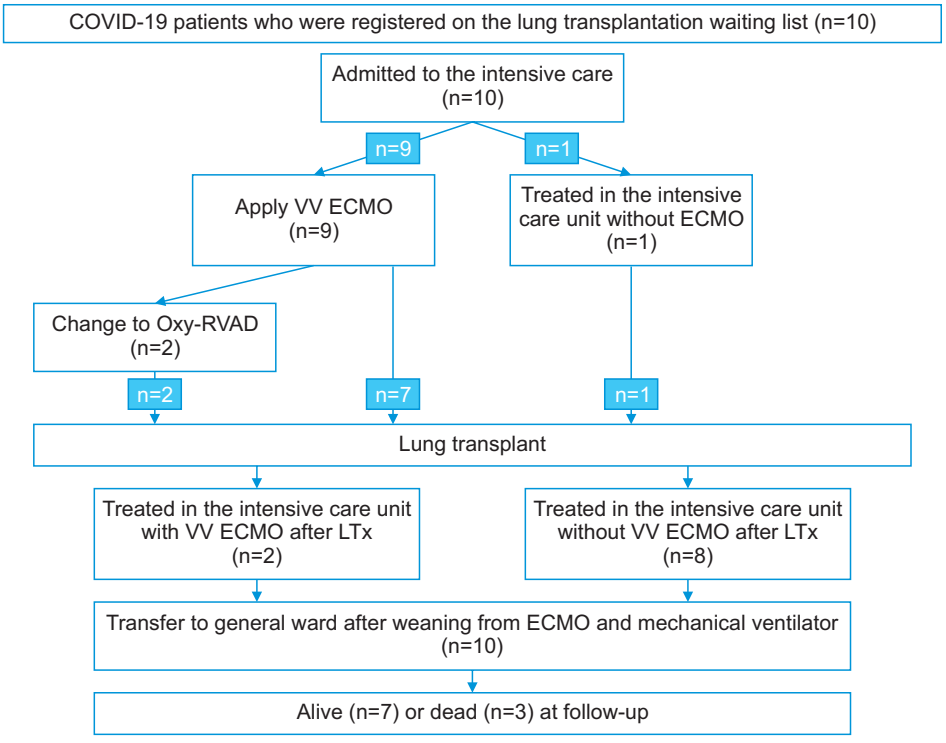

Fig. 1. Treatment process of coronavirus disease 2019 (COVID-19) patients who underwent lung transplantation. VV ECMO, veno-venous extracorporeal membrane oxygenation; Oxy RVAD, right ventricular assist device with an oxygenator; ECMO, extracorporeal membrane oxygenation; LTx, lung transplantation.

https://doi.org/10.5090/jcs.22.055

Transplantation Committee at least once a month (Fig. 1).

At the time of surgery, recipients arrived at the operating room early, considering age, disease state, and the possibility of adhesions, and were transported to the operating room 4 hours before the arrival of the donor lung. The surgical procedure was performed under ECMO and began approximately 1 hour before the donor lungs arrived. This cannulation procedure was assisted by a cardiac surgeon. An important but small step that determines postoperative blood loss and ischemic time is meticulous bleeding control.

Statistical analysis

Clinical information through September 2022 was retrieved from institutional electronic medical databases and electronic chart reviews. Categorical variables were presented as percentages (%) and frequencies. Continuous variables were expressed as means±standard deviations or medians with the 25%–75% interquartile ranges (IQRs). Analyses were performed using R statistical software ver. 3.4.00 (The R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/).

Results

Patient characteristics

From August 2019 to February 2022, a total of 92 lung transplants were performed at Asan Medical Center. Ten of these patients underwent lung transplantation because of COVID-related acute respiratory distress syndrome (ARDS). The characteristics of the patients are shown in Table 1. The mean age of the patients who underwent surgery was 55.7 years, and 5 (50%) were men. After the patients were diagnosed with COVID-19, it took an average of 6.6 days for them to be admitted to the ICU, 9.5 days until intubation for mechanical ventilator support, and 76.2 days to undergo transplantation. The patients were on the waiting list of the organ transplant center for an average of 16.8 days before receiving a transplant. All patients underwent a tracheostomy at the time of transplant listing. Nine patients (90%) were supported with veno-venous (VV) ECMO before transplantation; of these, 2 patients (20%) were switched to an Oxy RVAD after 21 days and 64 days, respectively, due to right ventricular dysfunction. Only 1 patient did not receive preoperative VV ECMO.

The clinical characteristics of each patient are described in Table 2. Age, underlying medical conditions, and body surface area were included by default. In addition, the time intervals from the diagnosis of COVID-19 to undergoing lung transplantation and from being included on the waiting list to receiving the transplant are shown. Eight patients (80%) presented with comorbidities, such as hypertension, diabetes, hyperlipidemia, tuberculosis, and gout. The remaining 2 patients (20%) had no comorbidities. All patients received ICU rehabilitation during their ICU stay, and 3 patients are currently undergoing inpatient treatment. The remaining patients were identified and marked for follow-up from the date of the surgery to the date of the last outpatient visit.

Table 1. Patient characteristics of the lung transplantation recipients with COVID-19 (n=10)

Characteristic	Value
Age (yr)	55.7±7.51
Sex	
Male	5 (50)
Female	5 (50)
Height (cm)	163.88±11.39
Weight (kg)	58.83±9.34
Body surface area (kg/m^2)	1.63±0.17
Blood type	
A	2 (20)
B	3 (30)
O	2 (20)
AB	3 (30)
Time from COVID-19 diagnosis to ICU admission (day)	6.6±5.64
Time from COVID-19 diagnosis to intubation (day)	9.5±6.93
Time from COVID-19 diagnosis to operation (day)	76.2±23.24
Time on the waiting list (day)	16.8±9.55
Status at the time of operation	
Tracheostomy	10 (100)
ECLS	
VV ECMO	7 (70)
Oxy RVAD	2 (20)
No ECLS	1 (10)
Length of ECLS support at the time of listing (day)	48.5±26.32
Hypertension	5 (50)
Diabetes mellitus	1 (10)
Hyperlipidemia	4 (40)
Echocardiography	
Left ventricular ejection fraction	60.6±3.46
Right ventricular dysfunction	5 (50)
Left ventricular dysfunction	0
Pulmonary hypertension	5 (50)

Values are presented as mean±standard deviation or number (%), unless otherwise indicated.
COVID-19, coronavirus disease 2019; ICU, intensive care unit; ECLS, extracorporeal life support; VV ECMO, veno-venous extracorporeal membrane oxygenation; Oxy RVAD, right ventricular assist device with an oxygenator.

Table 2. Characteristics of the individual transplant recipients

Patient	Age (yr)	Comorbidities	BSA (kg/m^2)	Time from COVID-19 diagnosis to LTx (day)	Time on waiting list to LTx (day)	ECLS before LTx	Time on ECMO at time of LTx (day)	Total pump time (min)	Time in ICU after LTx (day)	Time in hospital after LTx (day)	Date of follow-up (day)	Alive or dead
Patient 1	57	None	1.64	87	33	VV ECMO	49	238	14	88	733	Alive
Patient 2	64	Bronchiectasis	1.78	52	14	VV ECMO	49	432	38	146	593	Alive
Patient 3	61	Rheumatic arthritis	1.57	54	24	Oxy RVAD	24	242	19	90	536	Alive
Patient 4	43	HTN, hyperlipidemia	1.41	76	14	VV ECMO	60	261	37	161	246	Alive
Patient 5	54	None	1.62	70	10	None	0	276	22	99	348	Alive
Patient 6	64	DM, HTN, hyperlipidemia	1.5	46	5	VV ECMO	21	227	29	155	321	Alive
Patient 7	56	HBV	1.83	108	29	VV ECMO	80	385	39	127	315	Death
Patient 8	58	HTN, hyperlipidemia, TB (40 years ago), gout, HBV	1.65	108	22	Oxy RVAD	82	372	27	199	311	Alive
Patient 9	59	HTN, hyperlipidemia	1.36	105	15	VV ECMO	79	333	27	179	179	Death
Patient 10	41	HTN	1.96	56	2	VV ECMO	42	303	62	145	145	Death

Values are presented number or mean, unless otherwise indicated.
BSA, body surface area; COVID-19, coronavirus disease 2019; LTx, lung transplantation; ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; VV ECMO, veno-venous extracorporeal membrane oxygenation; Oxy RVAD, right ventricular assist device with an oxygenator; HTN, hypertension; DM, diabetes mellitus; HBV, hepatitis B virus; TB, tuberculosis.

Intraoperative characteristics

The surgical profile of lung transplantation is detailed in Table 3. All lung transplantation operations were performed via bilateral lung transplantation with the support of veno-arterial ECMO, through a clamshell incision. During surgery, the patients received a transfusion of packed red blood cells of 12.6 units, as well as fresh frozen plasma and platelet concentrate transfusions (average, 6.3 units and 8.8 units, respectively). The mean operation time was 616.2 minutes, the average total pump time was 306.9 minutes, and ischemic times were 287 minutes and 304 minutes for the left and right sides, respectively.

Postoperative outcomes

The post-lung transplantation course is shown in Table 4. Two patients (20%) were maintained on ECMO because of low cardiac output syndrome after surgery; they underwent ECMO weaning within a week after the transplant operation. The patients received mechanical ventilation assistance after transplantation for a median of 22.3 days (IQR, 10–26.75 days). The median durations of postoperative intensive care in the ICU and hospital stay were 32.2 days (IQR, 23.25–37.75 days) and 138.9 days (136.0–159.5 days), respectively.

The major postoperative complications were acute kidney injury (1 patient, 10%), neuropathy (3 patients, 30%), seizure (1 patient, 10%), and complicated pleural effusion (3 patients, 30%). Four cases (40%) underwent reoperation: 2 (20%) for bleeding control, 1 (10%) for delayed sternal closure, and 1 (10%) for re-transplantation due to severe graft

Table 3. Operative profile of lung transplant recipients with COVID-19 (n=10)

Outcomes	Mean±SD
Intraoperative pRBC (unit)	12.6±7.85
Intraoperative FFP (unit)	6.3±5.78
Intraoperative PC (unit)	8.8±9.93
Transplantation	
Total operation time: skin to skin (min)	616.2±72.06
Total pump time (min)	306.9±67.14
Total ischemic time: left lung (min)	287±98.68
Total ischemic time: right lung (min)	304.6±71.72
Anastomosis time: left lung (min)	64.6±10.51
Anastomosis time: right lung (min)	57.5±10.93

COVID-19, coronavirus disease 2019; SD, standard deviation, unless otherwise indicated.
pRBC, packed red blood cell; FFP, fresh frozen plasma; PC, platelet concentrate.

https://doi.org/10.5090/jcs.22.055

Table 4. Overall clinical outcomes of lung transplant recipients with COVID-19 (n=10)

Outcomes	Value
Post-transplant hospital course	
Postoperative prolonged ECMO	2 (20)
Length of mechanical ventilation after LTx (day)	22.3 (10–26.75)
Length of stay in ICU after LTx (day)	32.2 (23.25–37.75)
Length of stay in hospital after LTx (day)	138.9 (136–159.5)
No. of patients still in hospital	0
Follow-up after LTx (day)	372.7 (262.25–489.00)
Post-transplant complications	
AKI/CVVH	1 (10)
Bleeding requiring reoperation	2 (20)
Reoperation for delayed sternal closure	1 (10)
Critical illness neuropathy	3 (30)
Seizure	1 (10)
Complicated pleural effusion	3 (30)
Re-transplantation (heart-lung transplantation)	1 (10)
Overall survival	
Alive	7 (70)
Dead	3 (30)

Values are presented number (%) or median (interquartile range), unless otherwise indicated.
COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; LTx, lung transplantation; ICU, intensive care unit; AKI, acute kidney injury; CVVH, continuous veno-venous hemofiltration.

failure. In the re-transplantation case, severe graft failure occurred on the second day after surgery, and heart-lung re-transplantation was performed 5 days later. The median follow-up period for all patients was 372.7 days (IQR, 262.25–489 days). During the follow-up period, 3 out of 10 patients died.

Discussion

It is clear that the most irreversible complication of COVID-19 is severe respiratory failure, even though its symptoms are diverse. Lung transplantation is clearly the sole therapy for patients progressing to end-stage pulmonary dysfunction [4,5,7,8]. The progression of patients with COVID-19 was similar to that observed for other ARDS patients undergoing lung transplantation [9-11]. Ten cases of lung transplantation were reported in this single-center retrospective study. There were 3 deaths after an average of 372.7 days of observation. All patients except for 1 received assistance via ECMO before surgery. They underwent postoperative management and active rehabilitation in the ICU after surgery. Our institution has performed the most transplantations in Korea. Therefore, a notable strength of this paper is that it describes many cases reported for the first time from a single institution.

As reported previously, the first lung transplantation of a COVID-19 patient in Korea, a Korean living in Mexico, was also performed at this center [12]. The patient's respiratory symptoms and desaturation gradually worsened. After a thorough discussion of the patient's characteristics and condition, it was decided to transfer him to Korea for surgery via an air ambulance. After a successful operation, he was discharged without major complications, and planned to return to Mexico. The course of most patients was similar to that of this first case. As mentioned before, experiences with dual organ transplantation for patients with COVID-19 are limited [13]. One of our cases had simultaneous lung and heart transplantation; this 64-year-old male patient was the only case with rejection immediately after surgery. Two days following surgery, as oxygen demand increased and bilateral lung consolidation on chest X-ray examinations deteriorated rapidly, acute rejection was considered. Heart-lung re-transplantation was performed 5 days later. Twenty-five days after re-transplantation, the patient was transferred to the ward and discharged 146 days after the first operation, without any complications.

Three patients died after surgery, at 315 days, 179 days, and 145 days after the operation, respectively. First, a patient was discharged without any specific complications after surgery, but 40 days after discharge, he was admitted to the emergency room due to pneumonia. He had convulsive seizures during treatment for pneumonia, and brain magnetic resonance imaging showed a fungal infection, including angioinvasive aspergillosis, in the left temporal lobe. He died on the 41st day of readmission due to progressively worsening symptoms of brain infection and sepsis. The second patient was transferred to the general ward without any specific complications on the 27th day after lung transplantation. During rehabilitation treatment at the Department of Rehabilitation Medicine, he died from sepsis due to a Permcath infection with bacteremia and aggravated pneumonia. The last patient underwent percutaneous transhepatic gallbladder drainage due to a common bile duct stone and cholecystitis on the 25th day after transplantation. The infection became progressively worse, and biliary-origin sepsis deteriorated. The patient died of sepsis. All the patients who died after lung transplantation died from sepsis because an infection could not be controlled. When we consider ways to reduce postoperative mortality, postoperative infection control is important in transplant patients taking immunosuppressive drugs.

Hawkins et al. [1] analyzed 140 papers and reported the results of 21 cases in which patients with COVID-19 received transplantation; 66% of these cases were in the United States. In addition, Roach et al. [8] reported that, from August 2020 to September 2021, 214 cases of lung transplantation (7.0% of a total of 3,039 lung transplants) were performed for lung diseases related to COVID-19. Comparing the data from these 2 papers with our data revealed that the average ages of the transplant recipients were 55, 52, and 55.7 years, respectively. The average waiting period from diagnosis to transplantation was 76.2 days at our center, whereas in the paper by Hawkins et al. [1], the average waiting time was reported to be 70.8 days. The proportions of patients who received ECMO were 85% (17/21), 64.5% (118/183), and 90% (9/10), respectively. The heterogeneity of those findings could be attributed to differences in the pretransplant procedures. Although, in general, the results from those 3 papers are not substantially different, our study is meaningful in that it reports surgery performed with the same infrastructure and strategy at a single institution in Korea. In particular, the lung transplantation process in Korea is different from that in America or Europe, from patient matching to postoperative management. Thus, this article makes a substantial contribution by dealing with the overall process of lung transplantation in Korea for patients with COVID-19.

Another previous study analyzed the short-term outcomes of lung transplantation in COVID-19 patients in Korea [10]. Ko et al. [10] described the results of 11 lung transplantation patients in Korea from a medical point of view, and 3 of the early cases presented herein were included. Our article meaningfully builds upon that study by showing expanded results with the addition of the results of 7 additional cases conducted over the following 1 year. This study included more than half of the transplantations for patients with COVID-19 performed in Korea during the study period. In addition, this report emphasized the treatment strategy, with a particular focus on the surgical aspect. Because the results were from a single institution, it is possible to clearly see aspects of management that may be ambiguous due to differences in surgical strategies, facilitating the suggestion of a good treatment strategy by showing the results obtained when using the indications and treatment principles of this center.

Data and experience with lung transplantation in patients with acute respiratory failure (e.g., ARDS) associated with COVID-19 infection are still limited. Overall, previous studies suggest that lung transplantation may be considered in carefully selected patients with ARDS [7,13,14]. However, since Korea uses a system that allocates lungs according to the urgency of lung transplantation, there are differences from the data from other countries. A high priority in lung transplantation in Korea is determined by whether ECMO or mechanical ventilation is applied, which is calculated regardless of the likelihood of survival after transplantation [9,10,15]. It should be taken into account that physical function before lung transplantation is associated with mortality and morbidity. This underscores the need to carefully select transplant recipients through a multidisciplinary approach in Korea, especially in patients with COVID-19.

In our center's strategy, among patients with COVID-19-related ARDS, the most important and difficult problem in selecting lung transplant recipients was determining the reversibility of impaired lung function. Whether lung function could be restored in patients with COVID-19 was a point of considerable debate, and this question was intensively discussed when deciding to perform a lung transplant for each patient, with the consultation of several experts to elicit their opinions. Particular caution was taken regarding changes in lung parenchyma caused by COVID-19 infection because not much was known about these changes. Most of the patients in our study received mechanical ventilation for at least 2 weeks, but showed no clinical improvement, and the parenchymal infiltration throughout the chest computed tomography (CT) did not show clear improvements. Pulmonary compliance was also severely reduced, suggesting that irreversible pulmonary parenchymal changes, such as extensive fibrosis, had occurred. These criteria were not significantly different from the beneficiary selection criteria of non-COVID-19 patients with ARDS who underwent lung transplantation at our hospital [16].

In patients with acute lung disease caused by COVID-19 infection, it has been incompletely described at what point lung transplantation will have the best prognosis. Although respiratory experts recommend that performing a lung biopsy would help with the decision, this remains a difficult issue because insufficient data have been reported on the pathological findings of the lungs of patients with COVID-19 infection, and it is unclear whether a lung biopsy can be representative of the condition of the entire lung. Ultimately, even though high-quality medical support and supplies were guaranteed at our center, it was important to make a decision based on lung imaging (e.g., CT) and epidemiological considerations in determining the reversibility of impaired lung function in lung transplant recipients.

Bilateral lung transplantation should be considered when

the treatment of patients with COVID-induced, secondary end-stage lung failure is extended to long-term mechanical ventilation or ECMO. Transplantation serves a therapeutic role with effective short-term outcomes in a carefully selected group of these patients. Severe COVID-19 infection may progress to irreversible lung damage, and these patients may benefit from early lung transplantation [7-9]. It is also important to implement optimal treatment and perioperative preparation for these patients using a multidisciplinary approach. Although the long-term results of lung transplantation in severe patients with COVID-19 remain to be determined, it is also necessary to share experiences from different regions around the world to establish standardized treatments and protocols. As the global COVID-19 pandemic continues, lung transplant surgery will play an increasingly important role in the treatment and management of these complex patients.

This article provides important information from a single-center study of patients with COVID-19 who received lung transplantation for ARDS. However, there are several limitations to this study. First, this was a retrospective study. In addition, although this may be the largest number of cases in a single Korean institution, the sample size is still small, even when considering the number of lung transplants performed at our institution. Second, as this study focused only on patients with COVID-19, an objective comparison with patients undergoing lung transplantation for other common reasons was not possible. This must be addressed in future research. Third, the timing of ECMO application in this study followed the protocol of the center. These processes also affect the priorities for allocating lungs at organ transplantation centers in Korea. This makes it difficult to compare our findings with US or European data.

In conclusion, bilateral lung transplantation is a feasible treatment option for patients with COVID-19 with irreversible damage, with excellent early outcomes. The patients who are considered for lung transplantation should be limited to those who require mechanical ventilation or ECMO despite optimal medical management. A multidisciplinary approach will be required to optimize perioperative management and the transplant process.

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Conflict of interest

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

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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