Lung transplantation for severe COVID-19-related ARDS

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Abstract

Background: Lung transplantation (LT) is the gold standard for various end-stage chronic lung diseases and could be a salvage therapeutic option in acute respiratory distress syndrome (ARDS). However, LT is uncertain in patients with coronavirus disease 2019 (COVID-19)-related ARDS who failed to recover despite optimal management including extracorporeal membrane oxygenation (ECMO). This study aims to describe the pooled experience of LT for patients with severe COVID-19-related ARDS in Korea.

Methods: A nationwide multicenter retrospective observational study was performed with consecutive LT for severe COVID-19-related ARDS in South Korea (June 2020–June 2021). Data were collected and compared with other LTs after bridging with ECMO from the Korean Organ Transplantation Registry.

Results: Eleven patients with COVID-19-related ARDS underwent LT. The median age was 60.0 years [interquartile range (IQR), 57.5–62.5; six males]. All patients were supported with venovenous ECMO at LT listing and received rehabilitation before LT. Patients were transplanted at a median of 49 (IQR, 32–66) days after ECMO cannulation. Primary graft dysfunction within 72 h of LT developed in two (18.2%). One patient expired 4 days after LT due to sepsis and one patient underwent retransplantation for graft failure. After a median follow-up of 322 (IQR, 299–397) days, 10 patients are alive and recovering well. Compared with other LTs after bridging with ECMO ($n = 27$), post-transplant outcomes were similar between the two groups.

Conclusions: LT in patients with unresolving COVID-19-related ARDS were effective with reasonable short-term outcome.

Keywords: COVID-19, extracorporeal membrane oxygenations, frailty, lung transplantation, treatment outcome

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Background

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 has spread worldwide. COVID-19 mainly affects the respiratory system with some patients rapidly progressing to acute respiratory distress syndrome (ARDS) where up to 33% may require mechanical ventilation (MV).[1–3] Among the patients with COVID-19-related ARDS who require MV, some patients progress to the fibrotic phase of ARDS, which is associated with prolonged ventilator support and increased mortality.[4,5] Based on the experience obtained during previous respiratory virus outbreaks,[6–9] therefore, extracorporeal membrane oxygenation (ECMO) could be used to bridge such patients to recovery or lung transplantation (LT).[10–13]

Although LT has been suggested as a salvage therapy for carefully selected patients with ARDS,[12–14] there is limited experience on this potentially life-saving procedure for COVID-19-related ARDS. In addition, several concerns including recovery of lung injury, concomitant infections, and uncertainty

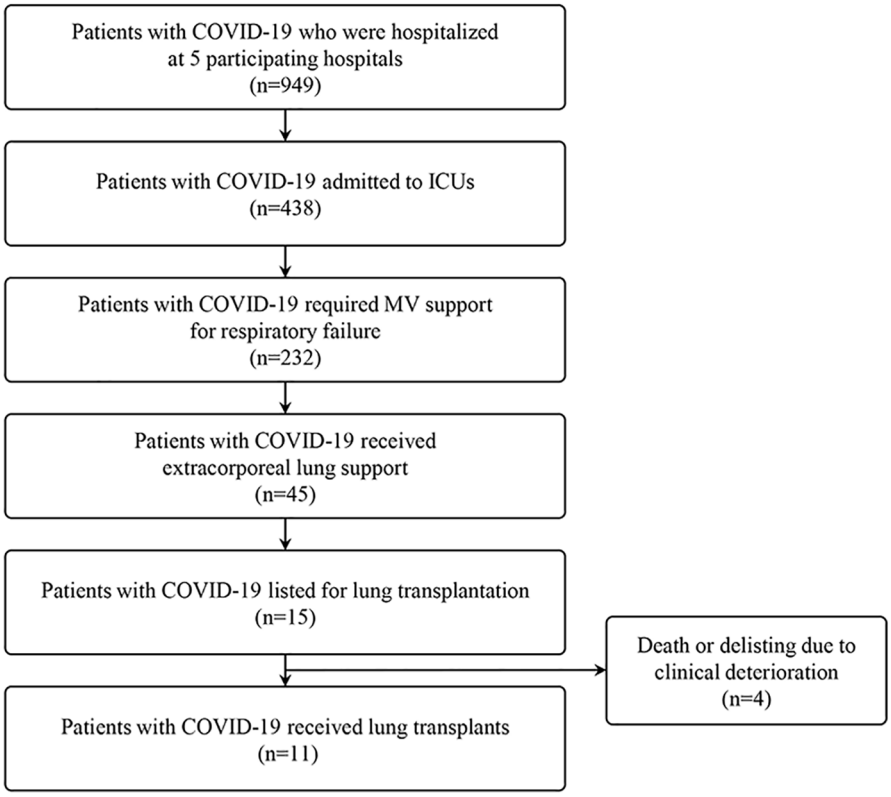

Figure 1. Study flow.

of long-term outcomes limit the use of LT as a salvage therapy for patients with severe COVID-19-related ARDS. Nonetheless, sporadic cases of LT for patients with COVID-19-related ARDS have been reported.[15] In addition, a case series of patients with COVID-19-related ARDS who were bridged to LT by ECMO at high-volume centers in four Western countries shows that LT could be done successfully with good early post-transplantation outcomes.[16] However, no case series from Asia has been reported.

This study aims to describe the pooled experience of LT for patients with severe COVID-19-related ARDS in Korea. In addition, mortality and short-term outcomes were compared with other LTs after bridging with ECMO from the Korean Organ Transplantation Registry data.[17]

Methods

Study design and population

A nationwide multicenter retrospective cohort study was conducted by the Korean LT Study Group. Five of the eight LT centers in Korea performed LT in patients with severe COVID-19-related ARDS and participated in this study. The institutional review boards at each participating hospital approved this study and waived the requirements for informed consent owing to the noninterventional observational nature of the study.

Eleven consecutive LTs for patients with severe COVID-19-related ARDS between June 2020 and June 2021 were enrolled in the study (Figure 1). The patients were followed up until the date of hospital discharge or the date of the latest visit to the outpatient clinics.

COVID-19 care and consideration for LT

The patients received treatment for severe COVID-19-related ARDS following the institutional standard of care for each institution. Moreover, the multidisciplinary COVID-19 care team at the respective institutions, which includes infectious disease physicians, pulmonary and critical care physicians, and cardiologists, conducted

medical care for patients with severe COVID-19-related ARDS. LT was discussed with the multidisciplinary LT team at least 4 weeks after onset of ARDS for patients with no evidence of lung recovery. Some patients precluded LT evaluation after discussion with the multidisciplinary LT team. Common reasons for preclusion were multiorgan failure, secondary complications (e.g. sepsis or stroke), and general contraindications relevant to LT. Frailty alone was not considered to be exclusive because these patients had been healthy before the onset of COVID-19-related ARDS.

Data collection

Information about LTs, donors, transplantation operations, and postoperative results was retrospectively collected. Data for LTs including pre-COVID-19 demographic information, pre-transplantation status, and donor characteristics were collected. Chest computed tomography (CT) features were classified based on the previous report on the CT finding of COVID-19 pneumonia.[18] Frailty before COVID-19 infection was assessed by the clinical frailty scale.[19] Donor lung score was calculated by Oto *et al.*'s[20] donor score. Before transplantation, all patients underwent panel reactive antibody (PRA) screening tests for HLA class I and class II antibodies. Calculated panel reactive antibody (cPRA) was measured using the cPRA calculator for anti-HLA antibodies greater than 1000 mean fluorescence intensity (MFI). Transplant surgery data include unilateral or bilateral LT, operation time, ischemic time, and transfusion requirement. Post-transplantation outcome data including primary graft dysfunction (PGD), complication, and mortality were also collected.

The Korean Organ Transplantation Registry data, described in a previous study, was used to compare LTs for severe COVID-19-related ARDS with other LTs after bridging with ECMO.[17]

Statistical analysis

Data were summarized using descriptive statistics as median and interquartile ranges (IQR) for continuous variables and as numbers and percentages for categorical variables. To assess the difference between LTs for severe COVID-19-related ARDS and other causes after bridging with ECMO, data were compared using the Mann–Whitney *U* test and Fisher's exact test for continuous and categorical variables, respectively. Data were analyzed using R Statistical Software (Version 3.2.5; R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

Fifteen patients with severe COVID-19-related ARDS were on the waiting list for LT. However, three patients expired awaiting LT, and one patient was delisted for multiorgan failure (Figure 1). The baseline characteristics of the 11 patients who had LT for severe COVID-19-related ARDS and their clinical characteristics are shown in Tables 1 and 2. Six (54.5%) patients were male, and the median age of all patients was 60.0 (IQR, 57.5–62.5) years. The median clinical frailty scale was 1.0 (IQR, 1.0–2.0). Three (27.3%) patients had comorbidities (e.g. chronic lung disease, diabetes mellitus, or high-dose or long-term steroid use). The patients had a median of 8.0 (IQR, 4.0–10.0) days from diagnosis to intensive care unit (ICU) admission and 8.0 (IQR, 4.5–11.0) days from diagnosis to MV support. COVID-19-specific medical treatments included corticosteroid ($n=9$; 81.8%), remdesivir ($n=4$; 36.4%), hydroxychloroquine ($n=1$; 9.1%), lopinavir/ritonavir ($n=1$; 9.1%), and ivermectin ($n=1$; 9.1%).

The patients had a median of 54.0 (IQR, 40.0–63.0) days from COVID-19 diagnosis to listing. At lung transplant listing, 10 (90.9%) and eight (72.7%) patients had a tracheostomy and became negative for COVID-19, respectively. However, the three COVID-19 positive patients were also tested negative for COVID-19 while waiting for LT, and eventually all patients were tested negative for COVID-19 before LT. All patients, including vein–pulmonary artery cannulation in one (9.1%), were supported with venovenous ECMO. The median time from MV to ECMO was 6.0 (IQR, 1.0–32.0) days. Of the 11 patients, five (45.5%) were awake while on ECMO. Three (27.3%) were on continuous renal replacement therapy and four (36.4%) recovered from acute kidney injury. Pulmonary ($n=7$) and catheter-related ($n=4$) superinfections occurred before LT. Nine (81.8%) patients were suffered from sepsis. Nosocomial pathogens were observed in pulmonary and catheter-related infections as follows: methicillin-resistant *Staphylococcus aureus*, extended-spectrum β-lactamase-producing *Klebsiella pneumoniae*, *Corynebacterium striatum*, *Burkholderia*

Table 1. Clinical characteristics of the study cohort.

Characteristics	Patients with COVID-19-associated ARDS (*N* = 11)
Gender, male	6 (54.5)
Age, years	60.0 (57.5–62.5)
Body mass index, kg/m^2	23.7 (20.4–25.3)
Blood group	
A	2 (18.2)
B	3 (27.3)
O	1 (9.1)
AB	5 (45.5)
Clinical frailty scale	1.0 (1.0–2.0)
Comorbidity	
Chronic lung disease	1 (9.1)
Diabetes mellitus	1 (9.1)
High- or long-term corticosteroid use	1 (9.1)
Time from COVID-19 diagnosis to ICU admission, days	8.0 (4.0–10.0)
Time from COVID-19 diagnosis to intubation, days	8.0 (4.5–11.0)
Antiviral medication for COVID-19	
Remdesivir	4 (36.4)
Steroid	9 (81.8)
Others[a]	3 (27.3)
Time from COVID-19 diagnosis to listing, days	54.0 (40.0–63.0)
At the time of listing	
Venovenous ECMO	11 (100)
Time from intubation to ECMO, days	6.0 (1.0–32.0)
Awake ECMO bridging	5 (45.5)
Mechanical ventilation support[b]	11 (100.0)
Continuous renal replacement therapy	3 (27.3)
Normal left ventricular ejection fraction	11 (100.0)
Evidence of pulmonary bacterial superinfection	7 (63.6)
Evidence of fungal colonization	1 (9.1)
Chest CT findings at the time of listing	

(Continued)

Table 1. (Continued)

Characteristics	Patients with COVID-19-associated ARDS (*N* = 11)
Distribution	
Peripheral	1 (9.1)
Both central and peripheral	10 (90.9)
Opacity	
Ground-glass	1 (9.1)
Ground-glass and consolidation	9 (81.8)
Consolidation	1 (9.1)
Crazy-paving pattern	8 (72.7)
Interlobar septal thickening	9 (81.8)
Fibrous stripe	8 (72.7)
Air bronchogram	9 (81.8)
Number of patients recovered from acute kidney injury	4 (36.4)
Number of patients recovered from sepsis	9 (81.8)
Highest ICU rehabilitation stage on the waiting list	
Passive range of motion	3 (27.3)
Active range of motion	2 (18.2)
Sitting on edge of bed	3 (27.3)
Sit to stand	3 (27.3)

COVID-19, coronavirus disease 2019; ARDS, acute respiratory distress syndrome; CT, computed tomography; ICU, intensive care unit; ECMO, extracorporeal membrane oxygenation.
Values are presented as median (interquartile range) or number (%).
[a]Others included one hydroxychloroquine, one ivermectin, and one lopinavir/ritonavir.
[b]Ten were tracheostomized patients.

contaminans, *Citrobacter freundii*, carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant *Enterobacteriaceae*, vancomycin-resistant *Enterococci*, and candida species.

All patients received ICU rehabilitation during the waiting list for LT. The duration of ICU rehabilitation was a median of 28.0 (IQR, 17.5–43.0) days before LT (Table 1).

Intraoperative and donor characteristics

The intraoperative characteristics of the LTs are shown in Table 3. All patients underwent bilateral LT through the clamshell incision. The median time on the waiting list was 26.0 (IQR, 9.0–38.0) days. The median operation time of all patients was 510.0 (IQR, 446.5–541.0) min. Total ischemic time for the right and the left lung was 199.0 (IQR, 142.0–291.5) and 319.0 (IQR, 222.0–350.5) min, respectively. Blood transfusion was required in all patients with a median of 10.0 units of packed red blood cells (IQR, 3.5–12.5) and 2.0 units of fresh frozen plasma (IQR, 1.0–6.5).

The median age of donors was 51.0 (IQR, 40.5–58.0) years and 72.7% were male. The median predicted total lung capacity ratio was 1.0 (IQR, 1.0–1.1). Lung donor score was a median of 5.0 (IQR, 3.0–6.5). All organs were from deceased

Table 2. Characteristics of individual transplant recipients.

	Age, years	Center	Comorbidities	Time from MV to LT, days	Tracheostomy	Time on ECMO at time of LT, days	Awake during bridging	Rehabilitation before LT, days	Class I cPRA, %	Class II cPRA, %	Time from LT to ventilator weaning, days	Time in ICU after LT, days	Time in Hospital after LT, days	Follow-up after LT, days	Alive or expired
Patient 1	63	A	No	56	Yes	56	Yes	28	Negative	Negative	18	32	51	417	Alive
Patient 2	62	A	No	75	Yes	73	Yes	43	4%	Negative	9	13	165	294	Alive
Patient 3	60	A	No	83	Yes	34	Yes	12	Negative	Negative	2	13	Still admitted	299	Alive
Patient 4	56	B	No	84	Yes	49	No	16	91%	96%	9	15	88	476	Alive
Patient 5	65	B	Yes	50	Yes	49	No	9	61%	Negative	28	38	146	336	Alive
Patient 6	62	B	No	53	No	24	No	19	Negative	Negative	12	19	90	300	Alive
Patient 7	51	C	No	112	Yes	111	Yes	54	Negative	Negative	102	239	239	559	Alive
Patient 8	63	C	No	133	Yes	133	Yes	94	98%	17%	-	4	4	4	Expired
Patient 9	59	D	Yes	36	Yes	30	No	32	Negative	Negative	5	7	97	224	Alive
Patient 10	59	D	No	67	Yes	59	No	43	Negative	Negative	7	10	124	338	Alive
Patient 11	55	E	Yes	64	Yes	6	No	24	Negative	Negative	7	13	35	308	Alive

cPRA, calculated panel reactive antibody; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; LT, lung transplantation; MV, mechanical ventilation.

donors and the most common causes of brain death were brain hemorrhage (36.4%) and hypoxic brain damage (36.4%).

Post-transplantation outcomes

Post-LT course and outcomes are presented in Table 4. PGD developed in two patients (18.2%) within 72 h after LT, and one patient received retransplantation for severe graft failure at 6 days. Ten (90.9%) patients had complications, and the most common complication was infection ($n = 7$, 63.6%) followed by critical illness polyneuromyopathy ($n = 5$; 45.5%). All except one patient received rehabilitation after transplantation. Three patients who received renal replacement therapy before LT recovered from renal failure after LT. One patient in the current series expired due to *K. pneumoniae* bacteremia 4 days after LT, which was not isolated from the donor lung. The median days from LT to ventilator weaning was 9.0 (7.0–16.5) days. From transplantation to ICU discharge, the median time was 13.0 (IQR, 11.5–25.5) days. Of the nine patients discharged from the hospital following LT, seven (77.8%) required re-hospitalization for the management of new infections, wound problems, or airway procedures. After a median follow-up of 322 (IQR, 299–397) days, 10 patients are alive and recovering well.

The study patients were compared with 27 patients who received LT for other causes after bridging with ECMO (Table 5). The duration from MV to LT (67 *versus* 18 days; $p < 0.001$) and from ECMO to LT (49 *versus* 11 days; $p < 0.001$) was prolonged in patients with COVID-19-related ARDS. Post-transplant outcomes including the prevalence of PGD, post-transplant acute kidney injury, post-transplant bleeding, and airway complication were similar between the two groups. However, infection was more frequent in patients with COVID-19-related ARDS (63.6% *versus* 14.8; $p = 0.005$). Finally, hospital mortality was not significantly different between the two groups (9.1% *versus* 25.9%; $p = 0.395$).

Discussion

This multicenter retrospective observational study reported 11 lung transplants for severe COVID-19-related ARDS in Korea. Patients were very fit before being affected with COVID-19-related ARDS. All patients were supported by ECMO at

Table 3. Characteristics of lung transplantation.

Characteristics	Patients with COVID-19-associated ARDS (*N* = 11)
Time on the waiting list, days	26.0 (9.0–38.0)
Intraoperative support	
Venoarterial ECMO	7 (63.6)
Venovenous ECMO	3 (27.3)
Cardiopulmonary bypass	1 (9.1)
Operation time, min	510.0 (446.5–541.0)
Total ischemic time, right, min	199.0 (142.0–291.5)
Total ischemic time, left, min	319.0 (222.0–350.5)
Number of intraoperative packed red blood cell	10.0 (3.5–12.5)
Number of intraoperative fresh frozen plasma	2.0 (1.0–6.5)
Donor characteristics	
Gender, male	8 (72.7)
Age, years	51.0 (40.5–58.0)
Body mass index, kg/m^2	23.3 (21.2–25.1)
Predicted TLC ratio	1.0 (1.0–1.1)
Smoker	2 (18.2)
Lung donor score	5.0 (3.0–6.5)
PaO_2 at FiO_2 100%	504 (379–540)
Donor cause of brain death	
Brain hemorrhage	4 (36.4)
Suicide	3 (27.3)
Hypoxic brain damage	4 (36.4)

COVID-19, coronavirus disease 2019; ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; TLC, total lung capacity; PaO_2, partial pressure of oxygen in arterial blood; FiO_2, fraction of inspired oxygen. Values are presented as median (interquartile range) or number (in percentage).

the time of listing, and most patients had recovered from acute kidney injury or sepsis. They received ICU rehabilitation before and after LT. No significant differences in the intraoperative management and immediate outcomes of lung transplants were found for severe COVID-19-related ARDS compared with other lung transplants for other causes after bridging with ECMO. Only one patient was lost in the early postoperative period, resulting in a hospital mortality rate of 9.1%.

Data and experience regarding LT in patients with acute respiratory failure (e.g. ARDS) are still limited. Several case reports and case series currently presented acceptable LT outcomes in carefully selected ARDS patients.[12–14] Chang *et al.*[12] showed a single-center experience of 14 lung transplants for ARDS over 5 years. They reported acceptable outcomes with a 3-year survival rate of 78%. Frick *et al.*[13] presented post-transplant outcomes of ARDS patients from three high-volume European transplant centers with 13 patients over

Table 4. Post-lung transplantation course and outcomes.

	Patients with COVID-19-associated ARDS (*N* = 11)
Induction therapy	10 (90.9)
Postoperative prolonged ECMO	4 (36.4)
PGD at 72 h	
PGD 0	9 (81.8)
PGD 1	0 (0.0)
PGD 2	1 (9.1)
PGD 3	1 (9.1)
Complications	
Acute kidney injury required renal replacement therapy	3 (27.3)
Bleeding requiring chest reopening	2 (18.2)
Bleeding managed by medical management	2 (18.2)
Infection	7 (63.6)
Airway complication	3 (27.3)
Critical illness neuropathy	5 (45.5)
Complicated pleural effusion	3 (27.3)
Rehabilitation after transplantation	10 (90.9)
Highest rehabilitation stage	
Passive range of motion	1 (10.0)
Active range of motion	1 (10.0)
Sitting on edge of bed	0 (0.0)
Sit to stand	3 (30.0)
Walking in place	5 (50.0)
Length of stay in ICU, days	88.0 (75.0–98.5)
Length of hospital stay, days	156.0 (137.0–191.3)
Time from transplantation to ICU discharge, days	13.0 (11.5–25.5)
Number of patients still in hospital[a]	1 (10.0)
Overall survival	
Alive	10 (90.9)
Expired	1 (9.1)
Follow-up after transplantation, days	322.0 (299.3–397.3)

COVID-19, coronavirus disease 2019; ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; PGD, primary graft dysfunction; ICU, intensive care unit.
Values are presented as median (interquartile range) or number (in percentage).
[a]Patients in hospital as of December 31, 2021.

Table 5. Comparison of clinical characteristics and outcomes between COVID-19 patients and other causes patients who received extracorporeal membrane oxygenation as a bridge to lung transplantation.

	Patients with COVID-19-associated ARDS (*N* = 11)	Control (*N* = 27)	*p*
Gender, male	6 (54.5)	21 (77.8)	0.238
Age, years	60.0 (57.5–62.5)	58.0 (53.0–62.0)	0.287
Body mass index, kg/m^2	23.7 (20.4–25.3)	21.4 (18.7–23.4)	0.122
Comorbidity			
Cardiovascular disease	0 (0.0)	1 (3.7)	1.000
Chronic lung disease	1 (9.1)	21 (77.8)[a]	<0.001
Diabetes mellitus	1 (9.1)	3 (11.1)	1.000
Normal left ventricular ejection fraction	11 (100.0)	25 (92.6)	1.000
Time from intubation to LT, days	67.0 (54.5–83.5)	18.0 (7.0–26.5)	<0.001
Time from listing to LT, days	26.0 (9.0–38.0)	27.0 (10.5–40.5)	0.961
Time from ECMO to LT, days	49.0 (32.0–66.0)	11.0 (6.0–18.0)	<0.001
Characteristics of LT			
Bilateral lung transplantation	11 (100.0)	26 (96.3)	1.000
Operation time, min	510 (447–541)	575 (474–690)	0.097
Total ischemic time, right, min	199 (142–292)	280 (231–363)	0.053
Total ischemic time, left, min	319 (222–351)	331 (250–372)	0.384
Number of intraoperative packed RBC	10.0 (3.5–12.5)	9.0 (6.5–12.0)	0.821
Number of intraoperative FFP	2.0 (1.0–6.5)	3.0 (0.0–6.0)	0.961
PGD at 72 h			
PGD 0	9 (81.8)	25 (92.6)	0.435
PGD 1	0 (0.0)	0 (0.0)	
PGD 2	1 (9.1)	2 (7.4)	
PGD 3	1 (9.1)	0 (0.0)	
Complications			
Acute kidney injury required renal replacement therapy	3 (27.3)	7 (25.9)	1.000
Bleeding requiring chest reopening	2 (18.2)	6 (22.2)	1.000
Bleeding requiring medical management	2 (18.2)	1 (3.7)	0.196
Infection	7 (63.6)	4 (14.8)	0.005
Airway complication	3 (27.3)	2 (7.4)	0.134
Postoperative prolonged ECMO	4 (36.4)	8 (29.6)	0.714
Length of stay in ICU, days	88.0 (75.0–98.5)	33.0 (23.0–43.5)	<0.001
Hospital survival			0.395
Alive	10 (90.9)	20 (74.1)	
Expired	1 (9.1)	7 (25.9)	

COVID-19, coronavirus disease 2019; ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; FFP, fresh frozen plasma; ICU, intensive care unit; LT, lung transplantation; PGD, primary graft dysfunction; RBC, red blood cell.
Values are presented as median (interquartile range) or number (%).
[a]Twenty-one patients (13 idiopathic pulmonary fibrosis, 5 connective tissue disease–related interstitial lung disease, 2 bronchiolitis obliterans, and 1 emphysema).

22 years, and these patients revealed a 30-day and 1-year survival rate with 92.3% and 71.6%, respectively. Harano *et al.*[14] analyzed the United Network for Organ Sharing database and presented outcomes of 39 lung-transplanted ARDS patients. They compared postoperative outcomes of ARDS patients with restrictive lung disease patients. The ARDS patients received more ECMO bridging to LT, but survival time and in-hospital mortality rates were not significantly different. Overall, previous studies have shown that LT could be considered in carefully selected ARDS patients. Recent case series of LT for severe COVID-19-related ARDS show similar results with previous studies of ARDS patients.[15,16,21] In addition, these studies emphasized a multidisciplinary approach to selecting suitable candidates for LT for severe COVID-19. Moreover, a multidisciplinary approach to selecting suitable COVID-19-related ARDS patients for LT also proceeded. However, the median age of lung transplants was higher than those of other reports.[14,15] This may be due to the Korean lung allocation system which is primarily based on the urgency of a transplant.[22] According to the Korean lung allocation system, patients with ECMO on the waiting list had the highest priority for transplantation, regardless of the probability of post-transplant survival. However, the results of this study provide additional information on LT in relatively old patients with COVID-19-related ARDS because the disease is more progressive in older patients.[23,24]

Previous studies showed that physical function before LT was associated with morbidity and mortality after transplantation.[25–27] Similar to other ARDS patients, patients with severe COVID-19-related ARDS were also affected by ICU-acquired weakness.[28] These patients often received deep sedation to prevent patient-ventilator dyssynchrony and ventilator-induced lung injury and also required long ICU stay. Therefore, ICU-acquired weakness may be aggravated during the course of managing COVID-19-related ARDS. All patients in this study received rehabilitation during their ICU stays, and 45.5% were awake while on ECMO. The awake ECMO has several benefits for physical function such as reduced sedatives and active rehabilitation.[29–31] In addition, patients who were treated with the awake ECMO as a bridge to transplantation and active rehabilitation would have better outcomes than patients who received MV as a bridge to transplantation.[25] These results suggest that considering the availability of active rehabilitation with awake ECMO may be a key factor for selecting suitable patients for LT. Considering the patient's physical function and frailty when deciding on LT in COVID-19-related ARDS patients is important based on these experiences with ARDS patients.

Although the results of this study provide important information about the outcome of LT in patients with severe COVID-19-related ARDS, the study has several limitations that should be acknowledged. First, this retrospective study was limited to a small number of patients and was associated with the inherent shortcomings of the study design. Second, the relatively elderly patients bridged with ECMO in this study may reflect the Korean lung allocation system based first on transplant urgency, which is different from the US and the European lung allocation score system based on the expected benefit after LT as well as the disease severity. Therefore, this result has limited generalization with other countries. However, acceptable results also can be obtained even in relatively elderly COVID-19 patients if the physical function before transplantation is good. Finally, COVID-19-related ARDS patients could not be compared with other causes of ARDS because a small number of patients were registered in the KOTRY and a few patients received LT for other causes after bridging with ECMO. Further systematic studies that could directly compare the outcomes of LT between COVID-19-related ARDS and other cases of ARDS are needed.

In conclusion, LT in patients with COVID-19-related ARDS leads to acceptable short-term outcomes. LT could be considered only for patients who are carefully selected with physical function as experienced from previous ARDS patients.

Author contributions

Ryoung-Eun Ko: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Writing – original draft; Writing – review & editing.

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Young Tae Kim: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Resources; Writing – review & editing.

Kyeongman Jeon: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Supervision; Writing – original draft; Writing – review & editing.

Conflict of interest statement

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References

1. Richardson S, Hirsch JS, Narasimhan M, *et al.* Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA* 2020; 323: 2052–2059.
2. Buckner FS, McCulloch DJ, Atluri V, *et al.* Clinical features and outcomes of 105 hospitalized patients with COVID-19 in Seattle, Washington. *Clin Infect Dis* 2020; 71: 2167–2173.
3. Wunsch H. Mechanical ventilation in COVID-19: interpreting the current epidemiology. *Am J Respir Crit Care Med* 2020; 202: 1–4.
4. Lim ZJ, Subramaniam A, Ponnapa Reddy M, *et al.* Case fatality rates for patients with COVID-19 requiring invasive mechanical ventilation. A meta-analysis. *Am J Respir Crit Care Med* 2021; 203: 54–66.
5. Auld SC, Caridi-Scheible M, Blum JM, *et al.* ICU and ventilator mortality among critically ill adults with coronavirus disease 2019. *Crit Care Med* 2020; 48: e799–e804.
6. Davies A, Jones D, Bailey M, *et al.* Extracorporeal membrane oxygenation for 2009 influenza A(H1N1) acute respiratory distress syndrome. *JAMA* 2009; 302: 1888–1895.
7. Pham T, Combes A, Rozé H, *et al.* Extracorporeal membrane oxygenation for pandemic influenza A(H1N1)-induced acute respiratory distress syndrome: a cohort study and propensity-matched analysis. *Am J Respir Crit Care Med* 2013; 187: 276–285.
8. Alshahrani MS, Sindi A, Alshamsi F, *et al.* Extracorporeal membrane oxygenation for severe Middle East respiratory syndrome coronavirus. *Ann Intensive Care* 2018; 8: 3.
9. Choi WS, Kang CI, Kim Y, *et al.* Clinical presentation and outcomes of middle east respiratory syndrome in the Republic of Korea. *Infect Chemother* 2016; 48: 118–126.
10. Barbaro RP, MacLaren G, Boonstra PS, *et al.* Extracorporeal membrane oxygenation support in COVID-19: an international cohort study of the Extracorporeal Life Support Organization registry. *Lancet* 2020; 396: 1071–1078.
11. Ramanathan K, Shekar K, Ling RR, *et al.* Extracorporeal membrane oxygenation for COVID-19: a systematic review and meta-analysis. *Crit Care* 2021; 25: 211.
12. Chang Y, Lee SO, Shim TS, *et al.* Lung transplantation as a therapeutic option in acute respiratory distress syndrome. *Transplantation* 2018; 102: 829–837.
13. Frick AE, Gan CT, Vos R, *et al.* Lung transplantation for acute respiratory distress syndrome: a multicenter experience. *Am J Transplant* 2022; 22: 144–153.
14. Harano T, Ryan JP, Chan EG, *et al.* Lung transplantation for the treatment of irreversible acute respiratory distress syndrome. *Clin Transplant* 2021; 35: e14182.

15. Hawkins RB, Mehaffey JH, Charles EJ, *et al.* Lung transplantation for severe post-coronavirus disease 2019 respiratory failure. *Transplantation* 2021; 105: 1381–1387.

16. Bharat A, Machuca TN, Querrey M, *et al.* Early outcomes after lung transplantation for severe COVID-19: a series of the first consecutive cases from four countries. *Lancet Respir Med* 2021; 9: 487–497.

17. Ko RE, Lee JG, Kim SY, *et al.* Extracorporeal membrane oxygenation as a bridge to lung transplantation: analysis of Korean Organ Transplantation Registry (KOTRY) data. *Respir Res* 2020; 21: 20.

18. Fu F, Lou J, Xi D, *et al.* Chest computed tomography findings of coronavirus disease 2019 (COVID-19) pneumonia. *Eur Radiol* 2020; 30: 5489–5498.

19. Rockwood K, Song X, MacKnight C, *et al.* A global clinical measure of fitness and frailty in elderly people. *CMAJ* 2005; 173: 489–495.

20. Oto T, Levvey BJ, Whitford H, *et al.* Feasibility and utility of a lung donor score: correlation with early post-transplant outcomes. *Ann Thorac Surg* 2007; 83: 257–263.

21. Chen JY, Qiao K, Liu F, *et al.* Lung transplantation as therapeutic option in acute respiratory distress syndrome for coronavirus disease 2019-related pulmonary fibrosis. *Chin Med J* 2020; 133: 1390–1396.

22. Yu WS, Kim SY, Kim YT, *et al.* Characteristics of lung allocation and outcomes of lung transplant according to the Korean urgency status. *Yonsei Med J* 2019; 60: 992–997.

23. Grasselli G, Greco M, Zanella A, *et al.* Risk factors associated with mortality among patients with COVID-19 in intensive care units in Lombardy, Italy. *JAMA Intern Med* 2020; 180: 1345–1355.

24. Zhou F, Yu T, Du R, *et al.* Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; 395: 1054–1062.

25. Fuehner T, Kuehn C, Hadem J, *et al.* Extracorporeal membrane oxygenation in awake patients as bridge to lung transplantation. *Am J Respir Crit Care Med* 2012; 185: 763–768.

26. Singer JP, Diamond JM, Gries CJ, *et al.* Frailty phenotypes, disability, and outcomes in adult candidates for lung transplantation. *Am J Respir Crit Care Med* 2015; 192: 1325–1334.

27. Singer JP, Diamond JM, Anderson MR, *et al.* Frailty phenotypes and mortality after lung transplantation: a prospective cohort study. *Am J Transplant* 2018; 18: 1995–2004.

28. Van Aerde N, Van den Berghe G, Wilmer A, *et al.* Intensive care unit acquired muscle weakness in COVID-19 patients. *Intensive Care Med* 2020; 46: 2083–2085.

29. Crotti S, Iotti GA, Lissoni A, *et al.* Organ allocation waiting time during extracorporeal bridge to lung transplant affects outcomes. *Chest* 2013; 144: 1018–1025.

30. Biscotti M, Gannon WD, Agerstrand C, *et al.* Awake extracorporeal membrane oxygenation as bridge to lung transplantation: a 9-year experience. *Ann Thorac Surg* 2017; 104: 412–419.

31. Na SJ and Jeon K. Extracorporeal membrane oxygenation support in adult patients with acute respiratory distress syndrome. *Expert Rev Respir Med* 2020; 14: 511–519.