Outcomes of perioperative extracorporeal membrane oxygenation use in patients undergoing lung transplantation

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Background: The aim of this single-center study is to review the transplant outcomes of patients receiving lung transplantation (LTx) using intraoperative extracorporeal membrane oxygenation (ECMO) according to the perioperative use of ECMO.

Methods: We retrospectively reviewed the transplant outcomes of 107 consecutive patients who underwent LTx using intraoperative ECMO between March 2013 and August 2016 at Severance Hospital of Yonsei University (Seoul, Korea).

Results: Patients were divided into the following three groups according to the use of perioperative ECMO: only intraoperative ECMO (n=47) or extended post-operative ECMO but no bridging and no postoperative ECMO re-implantation (secondary ECMO; n=28) as Group A (n=75); bridging ECMO without secondary ECMO (n=14) as Group B; and secondary ECMO with (n=7) or without (n=11) bridging as Group C. Baseline demographics were comparable among the three groups. The mean duration of preoperative ECMO bridging was 16.4±15.6 (n=21). After a median of 17.7 months (range, 3.1–40.9 months) for survivors, the one year overall survival (OS) rates after LTx for the three groups were 76.3%±5.2% for Group A, 59.9%±14.3% for Group B, and 14.0%±9.0% for Group C (P<0.0001). The secondary ECMO (Group C) was established a mean of 7.9±5.3 days after LTx. The main cause of secondary ECMO was acute respiratory failure from pneumonia, and the main cause of death was infection-related events.

Conclusions: Our data suggests that the use of perioperative ECMO, including its extended postoperative use during LTx, is feasible and has favorable outcomes. However, as shown by the poor survival outcome after secondary ECMO, the development of solid strategy to reduce the need for secondary ECMO implantation after LTx seems important.

Keywords: Extracorporeal membrane oxygenation (ECMO); lung transplantation (LTx); intraoperative ECMO

Introduction

Following pivotal progress in technical improvements and safety as demonstrated in the CESAR trial (1) and other recent encouraging survival data (2), extracorporeal membrane oxygenation (ECMO) is now considered in a broader spectrum of adult patients with respiratory failure, and the feasibility and advantages of its use as a bridge to lung transplantation (LTx) have been suggested by an increasing number of encouraging findings (3). Moreover, there has been a notable paradigm shift from intraoperative cardiopulmonary bypass (CPB) to ECMO for intraoperative cardiopulmonary support during LTx. In line with several theoretical advantages of ECMO compared with CPB, including a miniature circuit requiring a closed circulation circuit with no cardiotomy suction and enhanced biocompatibility leading to lesser anticoagulation requirement that potentially lowers the activation of the coagulation cascade and inflammatory system (4), increasing data on the comparison of intraoperative ECMO with CPB favors the use of ECMO (5-9). We have recently reported our experience of the transition to routine use of intraoperative venoarterial ECMO (vaECMO) from CPB with encouraging results. The purpose of this single-center study was to review the transplant outcomes of patients receiving LTx using intraoperative ECMO according to the perioperative use of ECMO.

Methods

Patients

Intraoperative cardiopulmonary support using vaECMO has been used routinely for all patients undergoing LTx at our institution since March 2013 (10). We conducted a retrospective review of clinical data on 107 consecutive adult patients (>18 years of age) who underwent LTx with intraoperative vaECMO between March 2013 and August 2016 at Yonsei University Severance Hospital (Seoul, Korea). Pre-, intra-, and post-operative data and laboratory and respiratory data were obtained at the initiation and during ECMO therapy using a retrospective review of the prospectively recorded registry database and electronic medical records. This study was approved by the Institutional Review Board of Yonsei University Health Service at Severance Hospital and complied with the Declaration of Helsinki.

Definition

Extended ECMO use was defined if the patient left the operative room with a running ECMO system, and secondary ECMO use was defined if the patient required re-insertion of ECMO after decannulation (5). Bridging ECMO use was defined if the patient received a bridging therapy with ECMO before LTx. Primary graft dysfunction (PGD) was assessed and graded according to the International Society for Heart and LTx lung transplant injury grades (11), after excluding other potential diagnoses as previously reported (12). We considered PGD recorded between 48 and 72 hours after LTx for the analysis.

LTx and ECMO technique

The operative technique and general principle for LTx have previously been described (10,12). Briefly, the surgical approaches were either bilateral anterolateral thoracotomy preferably in the fourth intercostal space for single- (n=8) and double- (n=99) LTx. All patients received standard triple immunosuppressant consisting of calcineurin inhibitor (cyclosporine or tacrolimus), mycophenolate mofetil, and methylprednisolone. All intraoperative cardiopulmonary support was performed via vaECMO, while those who were initially on bridging veno-veno ECMO (vvECMO) required a change to vvaECMO (veno-veno-arterial ECMO). vaECMO was established during anesthesia induction or after open-chest or hilar dissection. Following a heparin infusion of 2,000 units, patients were cannulated peripherally, centrally, or a combination of both. The target activated clotting time was 150–180 seconds during ECMO. Protamine was used only on weaning from intraoperative ECMO. Other institutional procedures regarding ECMO techniques were performed as described previously (10).

Statistical analysis

Continuous variables were compared using the Kruskal-Wallis test and shown as the median with interquartile range (IQR). Categorical data were analyzed using Fisher's exact test or Pearson's χ^2 test, depending on the distribution, and these data are shown as absolute frequencies and percentages. The overall survival (OS) curve after LTx was plotted using the Kaplan-Meier method, and differences were compared using the log-rank test. All statistical analyses were performed using Statistical Package for the
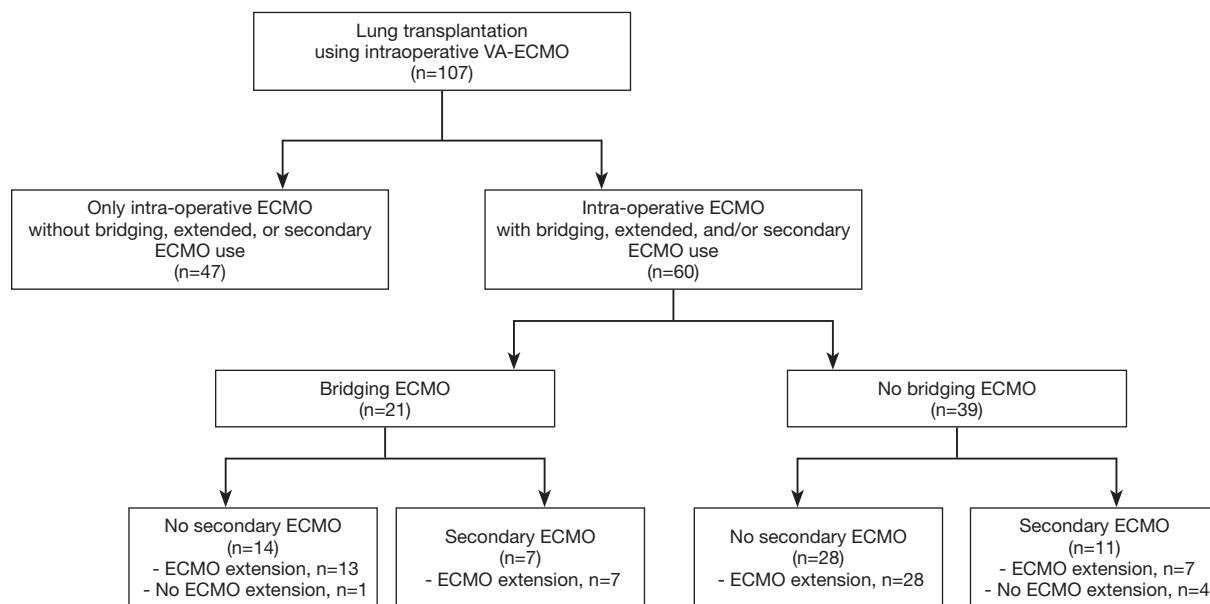
Figure 1 Patient subgroups according to the perioperative use of ECMO for lung transplantation. ECMO, extracorporeal membrane oxygenation.

Social Sciences version 16.0 software (SPSS Inc., Chicago, IL, USA).

Results

Patient demographics

During the study period, a total of 107 adult patients (median age 55 years, range, 18–75 years; male sex, n=64) were transplanted using ECMO for intraoperative cardiopulmonary support. Indications for LTx were idiopathic pulmonary fibrosis (IPF; n=62), connective tissue disease ILD (n=9), COPD (n=6), bronchiectasis (n=5), bronchiolitis obliterans syndrome after allogeneic stem cell transplantation (n=12), acute interstitial pneumonitis (n=4), pulmonary hypertension (n=3), lymphangioleiomyomatosis (n=3) and other indications (n=3).
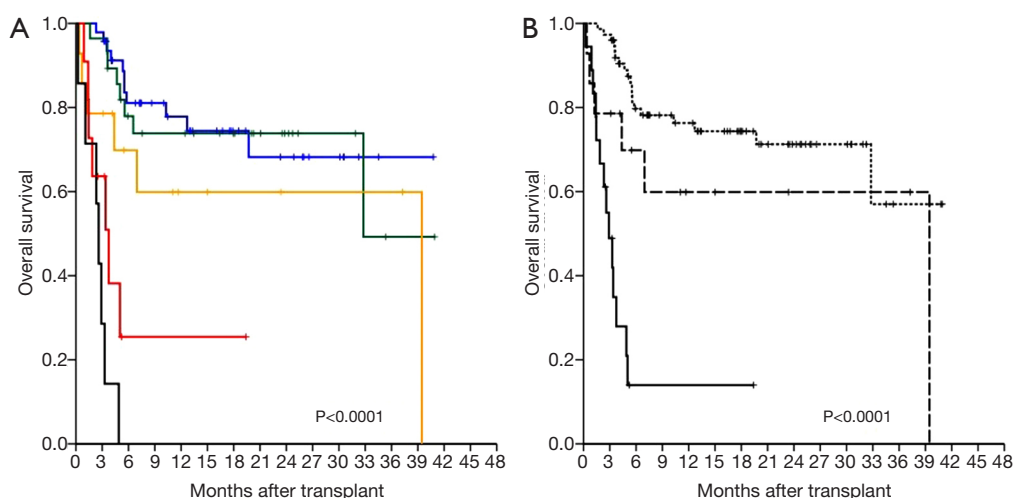
Perioperative use of ECMO support

The patient population was grouped as summarized in *Figure 1*. Of 107 patients undergoing LTx using an intraoperative ECMO, 60 (56.1%) patients received additional ECMO support. That is, 21 of these 60 patients (35%) were on ECMO for a bridging therapy before transplant and 18 patients (30.0%) required a secondary use of ECMO support after decannulation; whereas, in

55 of the patients (91.7%), ECMO support was extended into the postoperative period with a configuration change from vvaECMO to vvECMO. The remaining 47 patients received ECMO support only intraoperatively (43.9%) and were weaned off from ECMO in operation room.

Survival according to the perioperative use of ECMO support

We first analyzed the OS according to the perioperative uses of ECMO, arbitrary divided into five clinical situations: (I) 47 (43.9%) patients receiving only intraoperative ECMO use; (II) 28 (26.2%) patients with extended use of ECMO but without bridging ECMO nor second ECMO; (III) 14 (13.1%) patients receiving bridging ECMO with (n=13) or without (n=1) extended ECMO but not requiring a second ECMO; (IV) 11 (10.3%) patients receiving a second ECMO with (n=7) or without (n=4) extended ECMO but no bridging ECMO; (V) 7 (6.5%) patients with bridging and secondary ECMO (all required extended use). After observing the OS of each group [1 year OS, group (I): 77.8%±6.6%; group (II): 73.8%±8.5%; (III): 60.0%±14.3%; (IV): 25.5%±15.1%; (V): 0%] as shown in *Figure 2A*, we merged the patients into three arbitrary groups: Group A (n=75, 70.1%), patients receiving only intraoperative ECMO or extended ECMO but no bridging nor second ECMO [(I) + (II)]; Group B (n=14, 13.1%), patients

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Figure 2 Kaplan-Meiers OS curves according to the perioperative uses of ECMO. (A) OS arbitrary divided into 5 clinical situations: blue line indicates patients receiving only intraoperative ECMO, green line for patients with intraoperative ECMO extension but without bridging nor secondary ECMO, yellow line for those receiving bridging ECMO but without secondary ECMO, red line for patients requiring secondary ECMO but not having received bridging ECMO, and black line indicates patients receiving both bridging and secondary ECMO; (B) OS arbitrary divided in to 3 clinical situations: Group A (dotted line), merging of the two subgroups indicated by blue and green lines; Group B (dashed line), patients indicated by yellow line; Group C (solid line), merging of the two subgroups indicated by red and black lines. OS, overall survival; ECMO, extracorporeal membrane oxygenation.

receiving bridging ECMO but no second ECMO (III); and Group C (n=18, 16.8%), patients receiving a second ECMO with (n=7) or without (n=11) a bridging ECMO [(IV) + (V)].

Comparisons of clinical characteristics and transplant outcomes in Group A, B, and C

Baseline demographics of patients and donors were similar among the three groups, as summarized in *Table 1*. Patients who required re-implantation of secondary ECMO after LTx (Group C) showed male predominance and higher body mass index, while patients in Group A, who did not receive bridging ECMO nor secondary ECMO, had donors with higher PaO_2 values compared to Groups B and C. The waiting time was longer in Group A, as compared with Groups B and C (mean, 113 *vs.* 59 *vs.* 84 days; *Table 1*).

PGD score grade 3 (n=14), which was assessed at the time period between 48 and 72 hours after transplant, was more frequently observed in Group B (21.4%) and in Group C (22.2%) when compared with that in Group A (9.3%), without a statistical significance (*Table 2*). On the other hand, 13 of 14 patients (92.9%) with PGD score grade 3 had intraoperative ECMO extension, while 45.2% of the remaining non-PGD-grade 3 patients (42/93)

required ECMO extension (P=0.001; data not shown). With regard to early post-LTx outcomes, when compared with Groups B or C, patients in Group A had a significantly shorter duration of intraoperative ECMO extension (mean, 2.8 *vs.* 4.3 *vs.* 4.5 days; P=0.005), shorter intensive care unit (ICU) length of stay (LOS; mean, 13.4 *vs.* 44.6 *vs.* 52.1 days; P<0.0001), and shorter hospital LOS (mean, 59.6 *vs.* 79.3 *vs.* 80.9; P=0.003).

After a median of 17.7 months (range, 3.1–40.9 months) for survivors, the one year OS rates after LTx according to the three groups were 76.3%±5.2% for Group A, 59.9%±14.3% for Group B, and 14.0%±9.0% for Group C (P<0.0001; *Figure 2B*). Mortality rates at 1, 3, and 6 months after LTx were significantly higher in Group C (*Table 2*). The characteristics of each patient in Group C who received re-implantation of secondary ECMO are summarized in *Table 3*. The most common cause of second ECMO was acute respiratory failure (n=12; 67%), and the mean number of days from LTx to implantation of the second ECMO was 7.9±5.3 days. Successful weaning from the second ECMO was observed in nine patients; however, five of these patients did not survive (*Table 3*). The time from LTx to secondary ECMO was longer for the patients with weaning failure when compared with those who were

Table 1 Baseline demographics

Characteristics	Group A	Group B	Group C
No. of patients	75	14	18
Age, years, median [IQR]	55 [45–62]	54 [46–59]	59 [48–63]
Male, n [%]	41 [55]	8 [57]	15 [83]
Body mass index (kg/m^2), median (IQR)	19.7 (18.2–23.3)	20.5 (14.8–23.8)	23.3 (19.5–25.2)
Smoking history, n [%]	37 [49]	6 [43]	13 [72]
LTx indication, n [%]			
IPF	44 [59]	6 [43]	12 [67]
BO after allogeneic SCT	9 [12]	2 [14]	1 [5.5]
CVD-related ILD	7 [9]	1 [7]	1 [5.5]
COPD	5 [7]	0	1 [5.5]
Bronchiectasis	5 [7]	0	0
AIP	0	2 [14]	2 [11]
PHT	2 [2]	0	1 [5.5]
LAM	3 [4]	0	0
Others*	0	3 [22]	0
Donor variable			
Age, years, median [IQR]	46 [32–51]	35 [24–55]	46 [40–50]
Male, n [%]	44 [59]	9 [64]	15 [83]
Body mass index (kg/m^2), median [IQR]	22.5 (20.5–24.8)	23.8 (21.4–25.3)	22.4 (20.0–24.0)
Smoking history, n [%]	32 [43]	8 [57]	10 [56]
Pre-operative ventilation, days, median [IQR]	142 [74–183]	186 [129–229]	125 [63–211]
PaO$_2$ (100% FiO$_2$, mmHg) , median [IQR]	467 [387–513]	407 [333–469]	423 [351–475]
Bridging ECMO (n=21)	–	14	7
VA, n [%]	–	2 [14]	1 [14]
VV, n [%]	–	12 [86]	6 [86]
Waiting time (days), mean ± standard deviation	113±145	59±74	84±114

*, hypersensitive pneumonitis (n=1); bronchiolitis obliterans organizing pneumonia (n=1); ventilator-induced lung injury (n=1). AIP, acute interstitial pneumonia; BO, bronchiolitis obliterans; COPD, chronic obstructive lung disease; CVD-ILD, collagen vascular disease related interstitial lung disease; ECMO, extracorporeal membrane oxygenation; FiO$_2$, fraction of inspired oxygen; IPF, idiopathic pulmonary fibrosis; IQR, interquartile range; LAM, lymphangioleiomyomatosis; LTx, lung transplantation; PaO$_2$, partial pressure of arterial oxygen; PHT, pulmonary hypertension; SCT, stem cell transplantation; VA, veno-arterial; VV, veno-venous.

successfully weaned (57.0±44.8 *vs.* 30.0±35.8; P=0.101). Causes of mortality are summarized in *Table S1*. In our cohort, infection was the most common cause of death: Group A, n=12 of 19 deaths (63%); Group B, n=3 of 6 deaths (50%); and Group C, n=11 of 14 deaths (79%), and the most common pathogen were *Acinetobacter baumannii*

(n=11), followed by *Pseudomonas aeruginosa* (n=6) and *Klebsiella pneumonia* (n=5; *Table S1*). The ICU LOS and hospital LOS were significantly longer for the 27 patients with infection-related deaths, when compared with that of the other patients (n=81; mean for ICU LOS, 52.6 *vs.* 14.8 days, P<0.0001; mean for hospital LOS, 96.5 *vs.*

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Table 2 Intra- and post-operative data

Characteristics	Group A	Group B	Group C	P value
No. of patients	75	14	18	
Transplant type, n (%)				0.141
Double	70 (93.3)	14 (100.0)	15 (83.3)	
Single	5 (6.7)	–	3 (17.7)	
Ischemic time (minute), mean ± standard deviation				
Right	246±88	257±66	221±71	0.344
Left	329±83	341±78	305±67	0.629
Single	201±88	N/A	204±14	1.000
PGD score grade 2–3, n [%]	30 (40.0)	7 (50.0)	8 (44.0)	0.765
PGD score grade 3, n [%]	7 (9.3)	3 (21.4)	4 (22.2)	0.237
ECMO extension into postoperative care, n (%)	28 (37.3)	13 (92.9)	14 (77.8)	<0.001
Duration of ECMO extension	2.8±3.5	4.3±4.7	4.5±3.8	0.005
Mortality, n [%]				
1 month	0	2 (14.3)	2 (11.1)	0.006
3 months	2 (2.7)	3 (21.4)	9 (50.0)	<0.0001
6 months	14 (18.7)	4 (28.6)	14 (77.8)	<0.0001
1 year	16 (21.3)	5 (35.7)	14 (77.8)	<0.0001
ICU LOS (days), mean ± standard deviation	13.4±10.6	44.6±56.4	52.1±50.7	<0.0001
Hospital LOS (days), mean ± standard deviation	59.6±53.4	79.3±53.1	80.9±40.5	0.003

ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; LOS, length of stay; PGD, poor graft dysfunction.

55.9 days, P<0.0001).

Clinical characteristics and transplant outcomes of patients with pretransplant bridging ECMO

Regarding 21 patients with preoperative bridging ECMO (all 14 patients in Group B and 7 patients of Group C), the type of ECMO was VA-ECMO in 2 patients and VV ECMO in the remaining 19 patients. The mean duration of preoperative ECMO bridging was 16.4±15.6 (IQR, 5.5–19.5), whereas the mean waiting time was significantly shorter for patients with bridging ECMO (63.2±95.4 days; IQR 7.0–78.5), compared with those without bridging ECMO (110.1±140.3 days; IQR 23.3–142.3; P=0.022). The most common indication of LTx in the 21 patients with bridging ECMO was IPF (n=9, 42.9%), followed by AIP (n=4, 19.0%). ECMO support was extended postoperatively in all but one patient with bridging ECMO, whereas PGD grade 3 was observed more frequently in patients with bridging

ECMO when compared with the others (28.6% *vs.* 9.3%; P=0.030). The mean ICU LOS and hospital LOS for the pretransplant ECMO group were significantly longer than for the other patients (mean for ICU LOS, 57.7±56.1 *vs.* 15.7±18.6 days, P<0.0001; mean for hospital LOS, 86.6±48.7 *vs.* 60.7±51.6 days, P=0.002). While the OS at 1 year was 38.9%±11.4% for all 21 patients with pretransplant ECMO, there was a significant difference in OS for patients without requiring (Group B, n=14; 60.0%±14.3%) versus those with (7 of 18 patients in Group C; all died within a year after LTx) secondary ECMO support (P=0.003; *Figure 2A*).

Discussion

Recently, increasing experience of ECMO has been gained in terms of pre-, intra-, and postoperative cardiopulmonary support for patients undergoing LTx, with favorable results. Regarding intraoperative ECMO during LTx, Ius *et al.* demonstrated lower blood product transfusion

Table 3 Characteristics of patients with implantation of secondary ECMO (Group C)

No.	Age/sex	LTx indication	Bridging ECMO	Extended ECMO	Causes of second ECMO	Time from LTx to second ECMO	Duration of second ECMO (days)	Weaning of Second ECMO	Survival Outcome	Cause of death
1	68/M	IPF	No	Yes	Sepsis (A. baumannii, K. pneumoniae)	POD 146	8	Failed	Died	Sepsis (A. baumannii, K. pneumonia)
2	60/M	IPF	No	No	Pneumonia	POD 26	3	Failed	Died	Pneumonia (Burkholderia cepacia, MRSA)
3	62/M	IPF	No	No	Sepsis (A. baumannii, VRE)	POD 101	3	Failed	Died	Pneumonia
4	67/M	IPF	No	Yes	Bronchopleural fistula	POD 23	2	Successful	Survived	–
5	63/M	IPF	Yes	Yes	Pneumonia	POD 7	16	Successful	Died	Pneumonia (P. aeruginosa, A. baumannii)
6	59/M	IPF	No	No	Acute pulmonary edema	POD 54	4	Failed	Died	Enteral bleeding
7	18/M	BO	Yes	Yes	Pulmonary hemorrhage, pneumonia	POD 21	13	Failed	Died	Sepsis (A. baumannii)
8	58/M	IPF	No	Yes	Pneumonia	POD 12	4	Successful	Survived	–
9	63/M	IPF	No	No	Pneumonia, acute pulmonary edema	POD 95	11	Successful	Died	Bowel perforation
10	52/M	IPF	No	Yes	Cardiac arrest	POD 31	8	Successful	Died	Bleeding
11	49/F	AIP	Yes	Yes	Pulmonary hemorrhage	POD 78	11	Failed	Died	Pulmonary hemorrhage
12	59/M	IPF	Yes	Yes	Pulmonary hemorrhage	POD 87	12	Successful	Died	Sepsis (A. baumannii)
13	61/M	IPF	No	Yes	Bronchopleural fistula, pneumonia	POD 27	18	Failed	Died	Sepsis (A. baumannii)
14	46/M	AIP	Yes	Yes	Acute pulmonary edema	POD 5	7	Successful	Died	Sepsis (P. aeruginosa, VRE)
15	25/F	PHT	Yes	Yes	Pulmonary hemorrhage	POD 54	18	Failed	Died	Sepsis (A. baumannii, K. pneumonia)
16	64/M	IPF	Yes	Yes	Sepsis (A. baumannii)	POD 6	2	Failed	Died	Sepsis (A. baumannii)
17	44/F	CVD-ILD	No	Yes	Portal vein obstruction, pneumonia	POD 5	9	Successful	Survived	–
18	51/M	COPD	No	Yes	Right heart failure	POD 5	12	Successful	Survived	–

A. baumannii, Acinetobacter baumannii; AIP, acute interstitial pneumonia; BO, bronchiolitis obliterans; COPD, chronic obstructive lung disease; CVD-ILD, collagen vascular disease related interstitial lung disease; ECMO, extracorporeal membrane oxygenation; F, female; IPF, idiopathic pulmonary fibrosis; K. pneumoniae, Klebsiella pneumoniae; LTx, lung transplantation; M, male; MRSA, methicillin-resistant Staphylococcus aureus; P. aeruginosa, Pseudomonas aeruginosa; PHT, pulmonary hypertension; POD, postoperative day; VRE, vancomycin-resistant enterococci.

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requirements and improved survival in the ECMO group, when compared with the CPB group (8); whereas Aigner *et al.* suggested that the versatility of ECMO allows maintaining ECMO utilized intraoperatively can be extended in the postoperative period (5). However, data regarding the optimal approach of ECMO support in the postoperative period of LTx remain limited, heterogeneous in the setting of its use, and with varying success in results (13-16). Following the routine use of intraoperative VA-ECMO in our institution (10), this present study examined our single-center experience of transplant outcomes in 107 patients undergoing an LTx with the use of ECMO support in the perioperative period as a bridge to transplant, as an intraoperative cardiopulmonary support, and/or as a postoperative bridge to recovery.

Postoperative extended ECMO support was not used electively in any of our patients, and one can expect that the patients who did not require additional ECMO support other than ECMO as intraoperative cardiopulmonary support would show the best clinical outcomes. By separately considering those with pretransplant ECMO support or posttransplant secondary ECMO implantation, we demonstrated that the patients with extended use of the intraoperative ECMO had similar (P=0.856) survival rates compared with the patients with intraoperative ECMO only, with respective OS rates at 6-month and 1-year of 81% *vs.* 78% and 78% *vs.* 74%, respectively. Previous studies reporting outcomes of post-LTx ECMO support have typically dealt with ECMO as a rescue strategy that is mainly utilized for early severe PGD. Moreover, before intraoperative ECMO was widely accepted, post-LTx ECMO support meant that the implantation of ECMO devices was required after LTx and that the best time to start post-LTx ECMO had to be determined. According to the study by Hartwig *et al.*, 28 of 498 (6%) study patients undergoing LTx required VV-ECMO implantation for severe PGD after transplant, and 96% of these patients were successfully weaned with one year OS of 64% (14). Initiation of postoperative ECMO was considered when mechanical ventilator requirements reached peak inspiratory pressures of 35 cm H_2O and the fraction of inspired oxygen content surpassed 0.60 in their study (14). In contrast, Bermudez *et al.* reported that 67% (n=39) of 58 patients who required early (0 to 7 days after lung or heart-lung transplant) ECMO support after LTx for PGD were successfully weaned with one year OS of 59%. In their cohort, ECMO was usually initiated when PaO_2 was <60 mmHg with a FiO_2 >80% (13). While there is

a possibility that earlier institution of post-LTx ECMO support could favorably affect LTx not using intraoperative ECMO, recent reports showed that the prevalence of PGD and the need for secondary ECMO implantation could be reduced by continuing intraoperative ECMO support postoperatively (8,17). In our study, 53 of 55 patients (96%) were successfully weaned from the extended use of intraoperative ECMO support, although 14 of these patients (26%) eventually required a secondary ECMO after a mean of 32±39 days (IQR 3–55; data not shown).

On the other hand, the clinical outcomes of secondary use of postoperative ECMO support were significantly worse than the other subgroups of patients in our study. The main indication of secondary ECMO implantation after LTx in our cohort was pneumonia or sepsis, which is in agreement with a recent study by Marasco *et al.* (16). In their cohort, the indications for early ECMO (<7 days posttransplant) were primary graft failure, whereas the postoperative ECMO later than 7 days after LTx were established for infection and non-specific graft failure (16). Additionally, as suggested in the study by Harwig *et al.* in which blood stream infections appeared to be the main source of morbidity and mortality in patients with LTx, not using intraoperative ECMO, who required posttransplant ECMO support, the main causes of death was infection in our cohort (14). Mason *et al.* also identified that the only risk factor of mortality in their 22 patients who required post-LTx implantation of ECMO was the establishment of ECMO for sepsis or pneumonia (18). Moreover, multidrug-resistant organisms, including *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and extended-spectrum β-lactamase (ESBL)—producing or carbapenemase-producing Enterobacteriaceae (such as *Klebsiella pneumoniae*), were the main sources of sepsis or pneumonia in our study. It is not surprising that hospital-acquired infections in the ICU would be a significant obstacle for patients requiring a second ECMO implantation (19). Alternatively, Marasco *et al.* suggested that the innate disease processes determine the poor results seen for late secondary ECMO after LTx (16).

Waiting time before LTx is an important risk factor for transplant outcomes in patients awaiting LTx, particularly in cases at high risk of acute clinical decompensation that inevitably require prolonged mechanical ventilation prior to LTx (20,21). Owing to technical advancements (3) and promising results from the adoption of "awake ECMO" (22,23), pretransplant bridging ECMO for patients waiting for an available donor lung is now no longer an independent risk factor for mortality, although current

recommendations regarding its indication are still based on institutional experience (3). Moreover, the implementation of the Lung Allocation Score led to improvement in waiting list mortality rates (24) and has given priority to patients undergoing pretransplant bridging ECMO because of their higher scores. In our cohort, ~20% of the patients were on ECMO preoperatively, suggesting the severity of these high-risk patients. In line with previous reports, our patients with bridging ECMO had significantly higher rates of PGD grade 3 (29% *vs.* 9%) and longer mean ICU (58 *vs.* 16 days) and hospital LOS (87 *vs.* 61 days). While the one year OS in all 21 patients with pretransplant bridging ECMO was relatively lower (~40%) than other recent reports (25), those who did not require a secondary ECMO showed an OS reaching 60%.

Limitations of this study include the retrospective nature of the analyses with a single center data and the unavailability of the data regarding parameters reflecting transplanted lung function. Moreover, decisions on the extension of intraoperative ECMO or the initiation of secondary ECMO were made on an individual basis, thus lacked predetermined criteria.

In conclusion, our data showed that the postoperative extended use of intraoperative ECMO during LTx is feasible and provides favorable survival outcomes similar to uncomplicated LTx with intraoperative ECMO only. However, poor survival outcomes shown for patients who required a secondary ECMO indicate that development of a solid strategy to reduce the need for secondary ECMO implantation after LTx seems important.

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Table S1 Causes of death

Characteristics	Group A	Group B	Group C
No. of patients	75	14	18
No. of deaths (%)	19 (25%)	6 (43%)	14 (78%)
Causes of death			
Infection	12	3	10
Sepsis (*Acinetobacter baumanii*)	2	–	3
Sepsis (*Acinetobacter baumanii*, *Klebsiella pneumoniae*)	–	–	2
Sepsis (*Klebsiella pneumoniae*)	1	–	–
Sepsis (*Klebsiella pneumoniae*, *Candida glabrata*)	1	–	–
Sepsis (*Vancomycin-resistant enterococcus*, *Candida albicans*)	–	1	–
Sepsis (*Pseudomonas aeruginosa*)	–	2	–
Sepsis (unknown pathogen)	1	–	–
Pneumonia (*Acinetobacter baumanii*)	1	–	1
Pneumonia (*Acinetobacter baumanii*, *Klebsiella pneumoniae*)	1	–	–
Pneumonia (*Acinetobacter baumanii*, *Pseudomonas aeruginosa*)	–	–	1
Pneumonia (*Pseudomonas aeruginosa*)	2	–	–
Pneumonia (*Pseudomonas aeruginosa*, vancomycin-resistant enterococcus)	–	–	1
Pneumonia (*Burkholderia cepacia*, methicillin-resistant *Staphylococcus aureus*)	–	–	1
Invasive pulmonary aspergillosis	1	–	–
Pneumonia (unknown pathogen)	2	–	1
Hemorrhage	1	–	3
Arrhythmia/cardiogenic shock	1	1	–
Thrombus	1	–	–
Thrombotic thrombocytopenic purpura	1	–	–
Myocarditis	1	–	–
Hepatic failure	1	–	–
Bowel perforation	–	–	1
Hemophagocytic lymphohistiocytosis	1	–	–