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Beneficial effects of extracorporeal membrane oxygenation over cardiopulmonary bypass in living-donor lobar lung transplantation

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living-donor lobar lung transplantation;
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extracorporeal membrane oxygenation;
cardiopulmonary bypass;
primary graft dysfunction

BACKGROUND: Extracorporeal membrane oxygenation (ECMO) has been frequently used instead of cardiopulmonary bypass (CPB) as extracorporeal circulatory support during cadaveric lung transplantation. This study compared the outcomes of intraoperative CPB or ECMO in living-donor lobar lung transplantation (LDLLT).

METHODS: CPB and ECMO were performed in 23 and 53 patients, respectively, who underwent initial bilateral LDLLT in our institution from 2008 to 2019. We retrospectively compared the short- and long-term outcomes between the 2 groups.

RESULTS: Patient background, graft size-matching data, operation time, extracorporeal circulation time, and bleeding amount were not significantly different in the 2 groups. However, the CPB group required more transfusion than the ECMO group (6,860 vs 3,840 ml, respectively; $p = 0.002$). The rate of increase in body weight through LDLLT was 7.4% and 4.9% in CPB and ECMO groups, respectively ($p = 0.040$), and primary graft dysfunction scores were significantly worse in the CPB group. Postoperative ECMO support was required in 4 cases, and hospital death occurred in 1 patient exclusively in the CPB group. Chronic lung allograft dysfunction (CLAD) was diagnosed in 43.5% and 17.0% of patients in the CPB and ECMO groups, respectively ($p = 0.021$), and the 5-year CLAD-free survival was 55.8% and 72.7% of patients, respectively ($p = 0.013$).

CONCLUSIONS: Intraoperative ECMO reduced primary graft dysfunction, possibly due to the lower requirement for intraoperative transfusion and less intraoperative weight gain causing systemic edema.

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The beneficial effect of ECMO in the early phase may result in less CLAD development in the long-term follow-up after LDLLT.

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Background

Bilateral living-donor lobar lung transplantation (LDLLT) is an acceptable option for critically ill patients who are unable to wait for grafts from deceased donors.[1] The operation is performed under the use of extracorporeal circulatory support (ECS). Cardiopulmonary bypass (CPB) used to be the standard method for intraoperative ECS during cadaveric lung transplantation (CLT). However, an increasing number of lung transplant centers have recently employed extracorporeal membrane oxygenation (ECMO) to replace CPB. This replacement is attributed to less bleeding, reduced inflammatory response, and lower grade of pulmonary graft dysfunction (PGD) associated with the former procedure.[2-7] The influence of intraoperative CPB and ECMO on the postoperative course in CLT has been previously reported.[2-8] However, its effect on LDLLT has not been evaluated thus far. In LDLLT, recipients are critically ill and receive relatively small grafts from healthy donors under ECS with short ischemic time. This allows comparison of 2 types of ECS less influenced by factors of donors. Thus, the aim of this study was to investigate the effects of intraoperative CPB and ECMO on the short- and long-term outcomes of LDLLT.

Materials and methods

Patients

A total of 227 consecutive patients underwent lung transplantation (135 CLTs and 92 LDLLTs) at Kyoto University Hospital between June 2008 and December 2019. Among them, only those undergoing bilateral LDLLT were included in this study. From 2008-2011, we routinely employed CPB in patients undergoing LDLLT. Since 2012, we have been using ECMO in most LDLLT procedures, while CPB has been selectively employed in pediatric and complicated cases requiring cardiac repair (Figure 1).

We retrospectively evaluated the clinical characteristics of patients (i.e., age, sex, body weight, indications for lung transplantation, donor's age, and donor's smoking history) which may influence PGD.[9,10] We also evaluated the graft size-matching data using forced vital capacity (FVC)[11] or 3-dimensional computed tomography (CT) volumetry,[12] because under-sized grafts may be susceptible to PGD. In addition, we compared perioperative factors and short-term outcomes, including delayed chest closure, between the CPB and ECMO groups. Delayed chest closure is required due to oversized grafts or PGD manifesting as hypoxia, pulmonary hypertension, and lung edema. We also investigated renal function and any perioperative increase in body weight as a possible indicator of systemic edema. Acute kidney injury is diagnosed when the serum creatinine level increases by 0.3 mg/dl or more or increases by 1.5 times or more compared to the preoperative level.[13] PGD was evaluated using arterial blood gas and chest X-ray pulmonary edema during the first 3 days after surgery according to the consensus established by the International Society for Heart and Lung Transplantation.[14] Moreover, the requirement for postoperative ECMO with bilateral infiltration on X-ray denoted PGD grade 3. The ventilator-dependent period was defined from the date of the LDLLT to that of complete withdrawal from mechanical ventilation. The development of acute rejection, postoperative pneumonia, and chronic lung allograft dysfunction (CLAD) was also evaluated. The observation period of CLAD-free survival spanned from the date of LDLLT to that of last follow-up, CLAD development, or death. CLAD was diagnosed based on the definition provided in the International Society for Heart and Lung Transplantation consensus report.[15] The overall and CLAD-free survival rates were also calculated and compared between the CPB and ECMO groups. The follow-up period for LDLLT was censored at the time of retransplantation. The study protocol (R2389-1) was approved by the Ethics Committee of Kyoto University, Kyoto, Japan. All patients provided written informed consent for the use of these data.

CPB and ECMO at bilateral LDLLT

Surgical procedures were performed as previously described.[16] In the CPB group, full heparinization was achieved and activated clotting time was maintained > 400 seconds. The ascending aorta and the right atrium were cannulated, and the patient was placed on standard CPB. Under full CPB, ventilation was terminated. Bilateral pneumonectomy was performed, followed by bilateral lobar implantation. Subsequently, both lobar grafts were simultaneously reperfused and reventilated.

In the ECMO group, the activated clotting time was maintained at approximately 180 seconds through administration of the minimum dose of heparin. The ascending aorta was cannulated for infusion. Two drainage cannulas were placed, one in the right atrium via the right femoral vein and the other in the superior vena cava via the right atrium. Next, central ECMO was established. We maintained 1-lung ventilation using a double lumen endotracheal

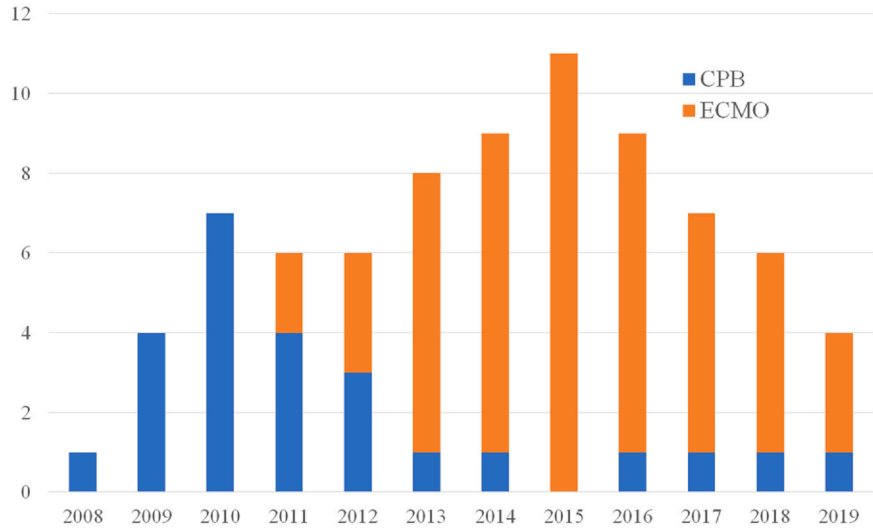


Figure 1 Ratio of intraoperative extracorporeal circulatory support in single or bilateral LDLLT. Since 2012, ECMO has been preferably used compared with CPB. CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; LDLLT, living-donor lung lobar transplantation.

tube, ensuring that the ECMO flow could be controlled at approximately 70% of the full flow to avoid the risk of massive air entrainment. The right graft was initially implanted after right pneumonectomy, followed by reperfusion and reventilation. Similarly, the left graft was implanted after left pneumonectomy, followed by reperfusion and reventilation.

There have been no major changes in organ preservation methods or surgical techniques during the observation period in this report. Regarding immunosuppressive regimens, Azathioprine had been changed to Mycophenolate mofetil around 2009, and Cyclosporine had been changed to Tacrolimus around 2013.

Statistical analysis

Results are presented as the median (range), unless otherwise stated. For survival analysis, the rate of survival without transplantation up to 5 years was recorded. Univariate Cox proportional hazards modeling was performed to investigate the relationship between intraoperative CPB and ECMO and clinical outcomes. Multivariate Cox proportional hazard modeling was used to investigate the relationship between clinical measurements and mortality. Clinical measurements were defined as continuous variables, with the exception of sex, donor's smoking status, and types of primary underlying diseases. The Kaplan-Meier method and log-rank test were used for the evaluation of mortality in the CPB and ECMO groups.

Comparison between 2 groups was performed using Fisher's exact test for the categorical data and the Mann–Whitney U test for nonparametric variables. The p-values < 0.05 denoted statistically significant differences. Statistical analyses were performed using the statistical software EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

Results

Patients

Among 227 cases, 78 cases of bilateral LDLLT were identified. One patient receiving bilateral middle lobe transplantation and another who developed severe graft dysfunction due to difficult vascular anastomosis were excluded. Therefore, a total of 76 cases were included in the analysis (Figure 2). All patients received LDLLT under intraoperative ECS; intraoperative CPB and ECMO were used in 23 and 53 patients, respectively.

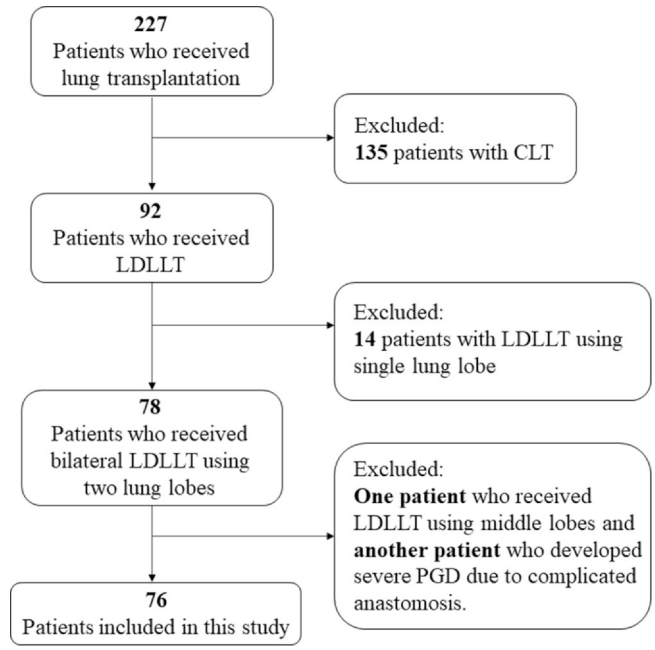


Figure 2 A flowchart with inclusion and exclusion criteria. CLT, cadaveric lung transplantation; LDLLT, living-donor lung lobar transplantation; PGD, primary graft dysfunction.

Table 1 Baseline Characteristics of Patients Undergoing Bilateral Living-Donor Lobar Lung Transplantation Using CPB or ECMO

	CPB ($n = 23$)	ECMO ($n = 53$)	p
Median age, years (range)	44 (8-64)	37 (12-64)	0.808
< 15 years, n (%)	5 (21.7%)	5 (9.4%)	0.159
Females, n (%)	13 (56.5%)	28 (52.8%)	0.807
Body weight before LTx, kg (range)	45.0 (16.3-66.3)	43.4 (21.6-73.8)	0.672
BMI, kg/m^2 (range)	18.0 (11.1-20.4)	17.2 (9.9-25.9)	0.968
Donor age, years (range)			
Right donor	42 (20-67)	38 (21-59)	0.830
Left donor	42 (22-60)	45 (21-60)	0.743
Donor, smoking history, n (%)	11 (47.8%)	25 (47.2%)	1
FVC size match,[a] % (range)	66.4 (45.7-109.4)	63.1 (36.9-112.0)	0.830
CT volumetry size match,[b] % (range)	88.7 (28.6-189.0)	92.4 (41.7-230.9)	0.684
Native lung-sparing LTx, n (%)	2 (8.7%)	9 (17.0%)	0.488
Right-to-left inverted LTx, n (%)	0	15 (28.3%)	0.004
Diseases, n (%)			0.523
ILD	10 (45.5%)	23 (43.4%)	
Post-HSCT lung injury	9 (39.1%)	23 (43.4%)	
PAH	3 (13.6%)	2 (3.8%)	
Others	1 (4.5%)	5 (9.4%)	

BMI, body mass index; CPB, cardiopulmonary bypass; CT, computed tomography; ECMO, extracorporeal membrane oxygenation; FVC, forced vital capacity; HSCT, hematopoietic stem cell transplantation; ILD, interstitial lung disease; LTx, lung transplantation; PAH, pulmonary arterial hypertension.
Data are presented as number (%) or median value (range).
[a]Predicted vital capacity of recipient/FVC of donor.
[b]Total volume of recipient's right and left thoracic spaces/grafts' volume of 2 donors.

Among them, 11 patients underwent LDLLT with single or bilateral upper lobes of the recipient spared as previously described (2 patients with CPB and 9 patients with ECMO).[17] Since 2014, 15 patients in the ECMO group have undergone right-to-left inverted LDLLT because right lower lobe is approximately 25% bigger than left lower lobe.[18] The baseline characteristics of the CPB group ($n = 23$) and ECMO group ($n = 53$) are presented in Table 1. Age, sex, body weight prior to lung transplantation, and body mass index were not significantly different between the 2 groups. Regarding the characteristics of donors, age and the proportion with smoking history were similar between the 2 groups. In addition, the FVC size match was not significantly different (median: 66.4% [45.7%-109.4%] and 63.1% [36.9%-112.0%] in the CPB and ECMO groups, respectively; $p = 0.769$). Similarly, the CT volumetry size match was not significantly different (median: 88.7% [28.6%-189.0%] and 92.4% [41.7%-230.9%], respectively; $p = 0.667$). The distribution of diseases was similar in both groups; only one patient in the CPB group required cardiac repair due to an atrial septal defect with idiopathic pulmonary arterial hypertension (PAH).

Short-term outcomes after LDLLT

Perioperative parameters and short-term outcomes are shown in Table 2. The operation time and extracorporeal circulation time were not significantly different. Graft ischemic time was within 3 hours in both groups; the right graft ischemic time was longer in the CPB group vs the ECMO group (162 [96-282] vs 116 [38-293] minutes, respectively, $p < 0.001$), while the left graft ischemic time was similar in both groups (132 [75-223] vs 135 [58-250] minutes, respectively, $p = 0.919$) because of the difference in reperfusion sequence as described in the method section. The amount of intraoperative blood loss in the CPB and ECMO groups was 3,483 (800-14,358) and 2,490 (0-18,686) ml, respectively ($p = 0.328$). The CPB group was associated with significantly more intraoperative transfusion of red blood cells, fresh frozen plasma, and platelet concentrate compared with the ECMO group (4,200 [990-10,360] vs 2,520 [840-12,880] ml, $p = 0.005$; 1,800 [240-4,700] vs 960 [0-5,180] ml, $p = 0.002$; and 500 [250-1,200] vs 400 [0-1,450] ml, $p < 0.001$, respectively). The amount of total transfusion was also greater in the CPB group vs the ECMO group (6,860 [1,630–12,080] vs 3,840 [1,320–19,130] ml, respectively, $p = 0.002$). The frequency of reoperations due to hemorrhage and delayed chest closure was not significantly different between the CPB and ECMO groups (8.7% vs 5.7%, $p = 0.635$; 8.7% vs 1.9%, $p = 0.216$, respectively). The increase in body weight, measured at the time of admission to the intensive care unit (ICU), compared with the preoperative body weight was significantly greater in the CPB group vs the ECMO group; that is, the body weight was increased by 7.4 ([–4.7] to 30.9)% vs 4.9 ([–5.5] to 23.6)%, respectively ($p = 0.040$). A postoperative creatinine increase during 48 hours after LDLLT was 0 (–0.1 to +0.9) in the CPB group and –0.02 (–0.37 to +0.45) in the ECMO group ($p = 0.0465$). No significant difference was noted in the development of acute kidney injury (5 cases in the CPB group and 4 cases in the ECMO group, $p = 0.119$).

PGD grade 3 was significantly more frequent in the CPB group compared with the ECMO group at ICU admission (3 [13.0%] vs 0 [0%], respectively; $p = 0.025$). Postoperative

Table 2 Intraoperative and Postoperative Parameters Between Two Groups Using Intraoperative CPB or ECMO

	CPB ($n = 23$)	ECMO ($n = 53$)	p
Operation time, minutes (range)	475 (350-712)	498 (210-898)	0.249
Extracorporeal circulation time, minutes (range)	225 (182-405)	243 (185-369)	0.070
Ischemic time (right graft), minutes (range)	162 (96-282)	116 (38-293)	< 0.001
Ischemic time (left graft), minutes (range)	132 (75-223)	135 (58-250)	0.919
Intraoperative blood loss, ml (range)	3,483 (800-14,358)	2,490 (0-18,686)	0.328
Intraoperative RBC transfusion, ml (range)	4,200 (990-10,360)	2,520 (840-12,880)	0.005
Intraoperative FFP transfusion, ml (range)	1,800 (240-4,700)	960 (0-5,180)	0.002
Intraoperative PC transfusion, ml (range)	500 (250-1,200)	400 (0-1,450)	< 0.001
Intraoperative total transfusion, ml (range)	6,860 (1,630-12,080)	3,840 (1,320-19,130)	0.002
Reoperation due to hemorrhage, *n* (%)	2 (8.7%)	3 (5.7%)	0.635
Delayed chest closure, *n* (%)	2 (8.7%)	1 (1.9%)	0.216
Weight increase at ICU admission, kg (range)	2.8 ([−2.5] to 12.1)	2.0 ([−2.5] to 9.1)	0.099
Weight increase ratio at ICU admission, % (range)	7.4 ([−4.7] to 30.9)	4.9 ([−5.5] to 23.6)	0.040
Acute kidney injury, *n* (%)	5 (21.7%)	4 (7.5%)	0.119
PGD 3 at ICU admission after LTx, *n* (%)	3 (13.0%)	0 (0%)	0.025
PGD 3 on postoperative day 1 after LTx, *n* (%)	3 (13.0%)	1 (1.9%)	0.080
PGD 3 on postoperative day 2 after LTx, *n* (%)	3 (13.0%)	3 (5.7%)	0.359
PGD 3 on postoperative day 3 after LTx, *n* (%)	2 (8.7%)	5 (9.4%)	1
Postoperative ECMO support, *n* (%)	4 (17.4%)	0 (0%)	0.007
Tracheostomy performed			
Preoperatively/postoperatively/none, *n*	0/10/13	4/21/28	0.553
Ventilator dependent period, days (range)	12 (3-79)	11 (3-138)	0.493
ICU stay, days (range)	14 (4-28)	12 (5-133)	0.281
Hospital death, *n* (%)	1 (4.3%)[a]	0 (0%)	0.303
Acute rejection, *n* (%)	12 (52.2%)	31 (58.5%)	0.624
Postoperative pneumonia, *n* (%)	6 (26.1%)	11 (20.8%)	0.765
Chronic allograft dysfunction, *n* (%)	10 (43.5%)	9 (17.0%)	0.021
Cause of death during 5 years after LTx, *n*			0.242
Chronic allograft dysfunction	4	1	
Infection	2	4	
PTLD	0	1	
Malignant tumor	0	1	

CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; FFP, fresh frozen plasma; ICU, intensive care unit; LTx, lung transplantation; PC, platelet concentrate; PGD, primary graft dysfunction; PTLD, post-transplant lymphoproliferative disorder; RBC, red blood cell.

Data are presented as number (%) or median value (range).

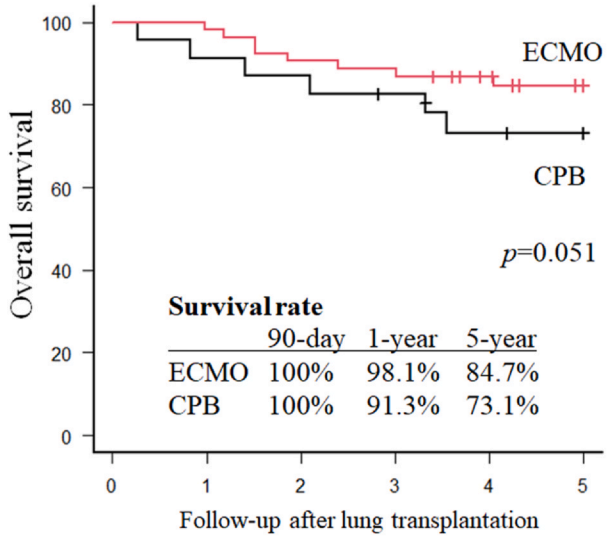
[a]One patient expired due to aspiration pneumonia.

ECMO support was required in 4 and 0 cases in the CPB and ECMO groups, respectively ($p = 0.007$). The frequency of postoperative tracheostomy was similar in these 2 groups. The durations of postoperative mechanical ventilation and ICU stay were similar (12 [3-79] vs 11 [3-138] days, $p = 0.493$; and 14 [4-28] vs 12 [5-133] days, $p = 0.281$, respectively). One patient (4.3%) in the CPB group expired during the in-hospital period on postoperative day 98 due to aspiration pneumonia. The 90-day mortality rate in both groups was 0%. Regarding 3 patients who developed PGD grade 3, the duration of ICU stay was longer than that of patients who did not develop PGD grade 3 (19 days vs 12 days, $p = 0.045$), and the duration of mechanical ventilation tended to be longer (23 days vs 11 days, $p = 0.081$).

No significant difference was noted in the 12 patients of the CPB group and 31 patients of the ECMO group who received treatments, including a corticosteroid pulse for acute rejection ($p = 0.624$). In addition, no significant difference was observed with regard to postoperative pneumonia (6 patients in the CPB group, and 11 patients in the ECMO group, respectively, $p = 0.765$).

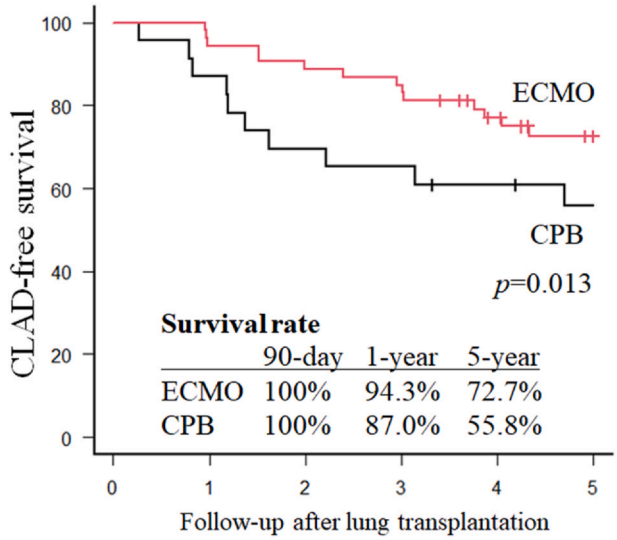
Long-term outcomes after LDLLT

The median follow-up period was 98 months (3-163 months) in the CPB group and 80 months (12-136 months) in the ECMO group. One patient in the CPB group underwent retransplantation with ECMO from living donors due to CLAD 34 months after the initial LDLLT; the follow-up period was censored at the time of retransplantation. CLAD was diagnosed in 10 patients (43.5%) in the CPB group and 9 patients (17.0%) in the ECMO group ($p = 0.021$). Thirteen patients (6 and 7 patients in the CPB and ECMO groups, respectively) expired within 5 years after LDLLT. Regarding the cause of death, 4 and 1 patients in the CPB and ECMO groups, respectively, expired due to CLAD; 2 and 4 patients, respectively, expired due to infection; 1 patient in the ECMO group



	0 year	1 year	2 years	3 years	4 years	5 years
ECMO group						
Number at risk	53	52	48	47	42	37
Upper 95% CI		1.00	0.96	0.95	0.94	0.92
Lower 95% CI		0.87	0.79	0.77	0.74	0.72
CPB group						
Number at risk	23	21	20	18	15	13
Upper 95% CI		0.98	0.96	0.93	0.87	0.87
Lower 95% CI		0.70	0.65	0.60	0.50	0.50

Figure 3 Kaplan-Meier curve for overall survival comparing intraoperative ECMO with CPB. The ECMO group showed a better survival rate vs the CPB group, although the difference was not statistically significant ($p = 0.051$). CI, confidence interval; CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation.



	0 year	1 year	2 years	3 years	4 years	5 years
ECMO group						
Number at risk	53	50	47	45	37	31
Upper 95% CI		0.98	0.95	0.92	0.86	0.83
Lower 95% CI		0.84	0.77	0.72	0.63	0.58
CPB group						
Number at risk	23	20	16	15	13	11
Upper 95% CI		0.96	0.84	0.81	0.77	0.73
Lower 95% CI		0.65	0.47	0.42	0.38	0.33

Figure 4 Kaplan-Meier curve for CLAD-free survival comparing intraoperative ECMO with CPB. The ECMO group showed a significantly better survival rate vs the CPB group ($p = 0.013$). CI, confidence interval; CLAD, chronic lung allograft dysfunction; CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation.

expired due to post-transplant lymphoproliferative disorder; and 1 patient in the ECMO group expired due to a malignant tumor. The 1- and 5-year overall survival rates were 91.3% and 73.1% in the CPB group, and 98.1% and 84.7% in the ECMO group, respectively. The survival tended to be better in the ECMO group; however, the difference did not reach statistical significance ($p = 0.051$; Figure 3). The 1- and 5-year CLAD-free survival rates were 87.0% and 55.8% in the CPB group, and 94.3% and 72.7% in the ECMO group, respectively. The CLAD-free survival was significantly better in the ECMO group ($p = 0.013$; Figure 4). Regarding pediatric cases, no significant difference was noted in the frequency of acute rejection and CLAD between patients aged < 15 years and ≥15 years ([2 out of 10 vs 18 out of 66, $p = 1$], and [6 out of 10 vs 37 out of 66, $p = 1$], respectively). The ratio of PGD grade 3 at ICU admission was found to be significantly higher in patients < 15 years of age compared to patients ≥15 years of age (2 out of 10 vs 1 out of 66, $p = 0.044$).

Donor-specific antibody after LDLLT developed within 5 years in 3 patients in the CPB group, 2 of which developed CLAD. Donor-specific antigen developed in 3 patients in the ECMO group, none of which developed CLAD within 5 years. Two patients in the CPB group and 8 patients in the ECMO group had less than 5 years of follow-up at the time of publication. Even limited to cases aged 15 years or older, 9 out of 18 CPB cases and 9 out of 48 ECMO cases developed CLAD ($p = 0.027$).

Regarding the primary underlying diseases, the 5-year CLAD-free survival rates were 83.7% in patients with lung injury after hematopoietic stem cell transplantation (post-HSCT lung injury) ($n = 32$), 60.0% in patients with PAH ($n = 5$), 56.9% in patients with interstitial lung disease, and 50.0% in patients with other diseases ($n = 6$), respectively ($p = 0.214$) (Figure S1). The 5-year CLAD-free survival rate of patients with post-HSCT lung injury was significantly better than those of patients with the other diseases (83.7% vs 56.3%, $p = 0.037$) (Figure S2).

Univariate Cox proportional hazards analysis regarding CLAD-free survival revealed that age, post-HSCT lung injury, FVC size match, CT volumetry, intraoperative CPB (vs ECMO), operation time, extracorporeal circulation time, intraoperative blood loss, intraoperative transfusion, ischemic time (right graft) were the significant factors (Table 3). Multivariate Cox proportional hazard analysis was performed using these factors (age, post-HSCT lung injury, CT volumetry, intraoperative CPB, operation time, and intraoperative transfusion) as explanatory variables. Age, intraoperative CPB, and operation time were significantly related to CLAD-free survival (hazard ratio [HR] = 03, $p = 0.03$; HR = 3.89, $p = 0.002$; and HR = 1.01, $p = 0.009$, respectively) (Table 4).

Table 3 Univariate Cox Proportional Hazards Analysis on CLAD-Free Survival in 76 Patients Who Underwent Living-donor Lung Transplantation

Characteristics	HR	95% CI	*p*-value
Sex, men	1.59	0.78-3.25	0.20
Age, years	1.03	1.00-1.05	0.01
BMI, kg/m^2	1.06	0.97-1.16	0.21
Post-HSCT lung injury, *n*	0.43	0.19-0.97	0.04
FVC size match, %	0.98	0.95-1.00	0.04
CT volumetry size match, %	0.99	0.98-1.00	0.03
Intraoperative CPB (vs ECMO), *n*	2.44	1.18-5.03	0.02
Operation time, minutes	1.00	1.00-1.01	0.004
Extracorporeal circulation time, minutes	1.01	1.01-1.02	0.001
Ischemic time (right graft), minutes	1.01	1.00-1.02	0.002
Ischemic time (left graft), minutes	1.01	1.00-1.01	0.32
Intraoperative blood loss, ml	1.00	1.00-1.00	0.03
Intraoperative RBC transfusion, ml	1.00	1.00-1.00	0.04
Intraoperative FFP transfusion, ml	1.00	1.00-1.00	0.003
Intraoperative PC transfusion, ml	1.00	1.00-1.00	0.08
Intraoperative total transfusion, ml	1.00	1.00-1.00	0.02
Weight increase at ICU admission, kg	1.10	0.99-1.22	0.07
Weight increase ratio at ICU admission, %	1.02	0.98-1.07	0.29
PGD grade 3 at 48-72 hours after LTx	0.45	0.11-1.89	0.28
Acute rejection	1.57	0.73-3.35	0.25

BMI, body mass index; CI, confidence interval; CLAD, chronic lung allograft dysfunction; CPB, cardiopulmonary bypass; CT, computed tomography; ECMO, extracorporeal membrane oxygenation; FFP, fresh frozen plasma; FVC, forced vital capacity; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit; LTx, lung transplantation; PC, platelet concentrate; PGD, primary graft dysfunction; RBC, red blood cell.

Table 4 Multivariate Cox proportional hazards analysis to analyze the relationship between clinical measurements and CLAD-free survival in patients undergoing living-donor lung transplantation.

Characteristics	HR	95% CI	*p*-value
Age, years	1.03	1.00-1.06	0.03
Post-HSCT lung injury, *n*	0.83	0.32-2.17	0.70
CT volumetry size match, %	0.99	0.98-1.00	0.11
Intraoperative CPB (vs ECMO), *n*	3.89	1.66-9.13	0.002
Operation time, minutes	1.01	1.00-1.01	0.009
Intraoperative total transfusion, ml	1.00	1.00-1.00	0.52

CI, confidence interval; CLAD, chronic lung allograft dysfunction; CPB, cardiopulmonary bypass; CT, computed tomography; ECMO, extracorporeal membrane oxygenation; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation.

Discussion

We investigated the influence of intraoperative CPB and ECMO support during LDLLT on the postoperative course. In this study, patient background data (e.g., age, sex, body weight, body mass index), FVC size matching, 3-dimensional CT volumetry size matching, and underlying diseases were not significantly different between the 2 groups. This implied that the features of these 2 extracorporeal support methods for LDLLT were not markedly affected by confounding factors, at least with regard to the short-term outcomes.

According to previous studies of lung transplantation from deceased donors,[2-7] CPB is linked to more bleeding, greater inflammatory response due to the passage of blood through the open circuit, and higher grade of PGD compared with ECMO. It has been reported that CPB induces complement activation, endotoxin release, leukocyte activation, and the release of numerous inflammatory mediators.[19] Notably, this is the first study to demonstrate that weight gain was more marked in the CPB group compared with the ECMO group, which could lead to systemic edema. In addition, transfusion-associated circulatory overload and transfusion-related acute lung injury might be partially linked to PGD, particularly in patients receiving relatively small grafts under CPB.[20] Although the likelihood of reoperation for bleeding and delayed chest closure was not statistically different between the 2 groups, a clear trend favored intraoperative ECMO. The overall lower incidence of PGD grade 3 was thought to be due to a shorter ischemic time and better quality of donor lung in living-donor lung transplantation than in CLT. In addition, in this study, 3 patients in the CPB group who developed PGD grade 3 had longer ICU stay and mechanical ventilation duration, whereas no significant difference of the duration of ICU stay and ventilation was noted between the CPB groups and the ECMO groups, possibly due to the small number of patients with PGD grade 3.

Two of the 3 PGD 3 cases in the CPB group were PAH. One case had ILD. There were 3 cases of PAH in the CPB group, 2 of which were PGD3. There were 2 cases of PAH in the ECMO group, and neither of them had PGD. When we excluded the 5 patients with PAH, the total amount of

blood transfused was similarly lower in the ECMO group (3,840 ml vs 7,415 ml, $p = 0.003$), and the 5-year survival rate was significantly better in the ECMO group (84.1% vs 68.9%, $p = 0.023$), and the number of CLAD cases was also lower in the ECMO group (9 cases in the CPB group, 8 cases in the ECMO group, $p = 0.014$). Although the occurrence of PGD may be related to PAH, a similar trend was observed even when patients with PAH were excluded.

The differences from CLT regarding intraoperative bleeding in LDLLT are as follows: (1) extracorporeal circulation is used in all cases; (2) patients with post-HSCT lung injury or lymphangioleiomyomatosis often undergo pleurodesis as a treatment for pneumothorax; (3) since many cases are in poor condition, it may be necessary to establish extracorporeal circulation early in the surgery and then perform pleural dissection. To reduce bleeding, we have replaced CPB with ECMO and lowered the amount of anticoagulant used.

Regarding long-term survival after lung transplantation, the superiority of intraoperative ECMO is currently controversial. Some studies[5,21] indicated that 1-year survival was better in the ECMO group vs the CPB group, whereas others[3,6] did not observe a significant difference between the 2 groups. Nevertheless, it has been confirmed that PGD is predominant in patients receiving CPB compared with those receiving ECMO, and PGD is related to 90-day and 1-year mortality after lung transplantation.[9,10] Moreover, PGD is an important risk factor of bronchiolitis obliterans syndrome in CLT.[22-24] Although the mechanisms by which PGD predisposes to the development and progression of bronchiolitis obliterans syndrome have been discussed in terms of systemic inflammation, autoimmunity, etc., they have yet to be elucidated.[22-24] Li et al[25] reported that PGD grade 3 was not associated with CLAD; however, in that study, PGD grade 3 was associated with baseline lung allograft dysfunction, which was defined as failure to achieve a forced expiratory volume in 1 second and FVC of at least 80% predicted after lung transplantation. In both hypotheses,[22-25] PGD appears to be related to lung allograft dysfunction in the chronic phase after lung transplantation. In the present study, 24 hours after surgery, there was no longer a significant difference in PGD 3. We confirmed that CLAD was more frequent, and CLAD-free survival was worse in the CPB group compared with the ECMO group in LDLLT. The direct relationship between PGD and the onset of CLAD was not observed. Although multivariate Cox proportional hazard analysis revealed that intraoperative CPB was the significant factor for CLAD-free survival independently of age and operation time, complex factors in the perioperative and postoperative periods may have led to CLAD.

Some limitations of the present study should be mentioned. Firstly, due to the retrospective nature of this investigation, disease severity or indications for lung transplantation were not controlled. In addition, the small sample size from a single center limited our ability to perform a multivariate analysis for the evaluation of confounding factors that may have affected the results. Secondly, there is a historical difference in the frequency of CPB and ECMO use (as shown in Figure 1). This might introduce some bias because patients in the ECMO group had more opportunities to receive advanced medical management. Since 2012, CPB has been used in specific cases, such as pediatric cases, pointing to the existence of a selection bias. Finally, the small number of patients who developed PGD grade 3 was insufficient to examine the relationship between PGD and the onset of CLAD. In addition, due to the small number of events, multivariate analysis was not performed.

In conclusion, intraoperative ECMO was associated with less primary graft dysfunction vs CPB, possibly due to the reduced requirement for intraoperative transfusion and less systemic edema manifested as intraoperative weight gain. The present study is the first to report this finding. The better short-term outcomes observed in the ECMO group may be related to the better long-term outcomes of patients undergoing LDLLT, such as the less frequent occurrence of CLAD.

CRediT authorship contribution statement

M.I. and A.A. had full access to the dataset analyzed in the study and take responsibility for the integrity of the data and the accuracy of the results. M.I., A.A., T.F.C.Y., and H.D. contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript. All authors contributed to the acquisition of data and drafting of the manuscript for important intellectual content.

Disclosure statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhlto.2024.100070.

References

1. Date H, Sato M, Aoyama A, et al. Living-donor lobar lung transplantation provides similar survival to cadaveric lung transplantation even for very ill patients. Eur J Cardiothorac Surg 2015;47:967-73.
2. Magouliotis DE, Tasiopoulou VS, Svokos AA, Svokos KA, Zacharoulis D. Extracorporeal membrane oxygenation versus cardiopulmonary bypass during lung transplantation: a meta-analysis. Gen Thorac Cardiovasc Surg 2018;66:38-47.
3. Biscotti M, Yang J, Sonett J, Bacchetta M. Comparison of extracorporeal membrane oxygenation versus cardiopulmonary bypass for lung transplantation. J Thorac Cardiovasc Surg 2014;148:2410-6.

4. Machuca TN, Collaud S, Mercier O, Cheung M, Cunningham V, Kim SJ. Outcomes of intraoperative extracorporeal membrane oxygenation versus cardiopulmonary bypass for lung transplantation. J Thorac Cardiovasc Surg 2015;149:1152-7.
5. Ius F, Kuehn C, Tudorache I, Sommer W, Avsar M, Boethig D. Lung transplantation on cardiopulmonary support: Venoarterial extracorporeal membrane oxygenation outperformed cardiopulmonary bypass. J Thorac Cardiovasc Surg 2012;144:1510-6.
6. Bermudez CA, Shiose A, Esper SA, Shigemura N, D'Cunha J, Bhama JK. Outcomes of intraoperative venoarterial extracorporeal membrane oxygenation versus cardiopulmonary bypass during lung transplantation. Ann Thorac Surg 2014;98:1936-43.
7. Ohsumi A, Date H. Perioperative circulatory support for lung transplantation. Gen Thorac Cardiovasc Surg 2021;69:631-7.
8. Hoechter DJ, Shen Y-M, Kammerer T, et al. Extracorporeal circulation during lung transplantation procedures: a meta-analysis. ASAIO J 2017;63:551-61.
9. Diamond JM, Lee JC, Kawut SM, et al. Clinical risk factors for pulmonary graft dysfunction after lung transplantation. Am J Respir Crit Care Med 2013;187:527-34.
10. Liu Y, Liu Y, Su L, et al. Recipient-related clinical risk factors for primary graft dysfunction after lung transplantation: a systematic review and meta-analysis. PLoS One 2014;9:e92773.
11. Date H, Aoe M, Nagahiro I, et al. Living-donor lobar lung transplantation for various lung diseases. J Thorac Cardiovasc Surg 2003;126:476-81.
12. Chen-Yoshikawa TF, Date H. Three-dimensional image in lung transplantation. Gen Thorac Cardiovasc Surg 2018;66:19-26.
13. Heid CA, Khoury MK, Maaraoui K, et al. Acute kidney injury in patients undergoing cardiopulmonary bypass for lung transplantation. J Surg Res 2020;255:332-8.
14. Christie JD, Carby M, Bag R, Corris P, Hertz M, Weill D. Report of the ISHLT Working Group on Primary Lung Graft Dysfunction part II: definition. A consensus statement of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2005;24:1454-9.
15. Verleden GM, Glanville AR, Lease ED, et al. Chronic lung allograft dysfunction: definition, diagnostic criteria, and approaches to treatment – a consensus report from the Pulmonary Council of the ISHLT. J Heart Lung Transplant 2019;38:493-503.
16. Date H. Living-donor lobar lung transplantation. Springer; 2019:103-25. https://doi.org/10.1007/978-3-540-73796-4_5.
17. Aoyama A, Chen-Yoshikawa TF, Minakata K, et al. Sparing native upper lobes in living-donor lobar lung transplantation: five cases from a single center. Am J Transplant 2015;15:3202-7.
18. Chen-Yoshikawa TF, Tanaka S, Yamada Y, et al. Intermediate outcomes of right-to-left inverted living-donor lobar lung transplantation. Eur J Cardiothorac Surg 2019;56:1046-53.
19. Wan S, LeClerc JL, Vincent JL. Inflammatory response to cardiopulmonary bypass. Chest 1997;112:676-92.
20. Semple JW, Rebetz J, Kapur R. Transfusion-associated circulatory overload and transfusion-related acute lung injury. Blood 2019;133:1840-53.
21. Bittner HB, Binner C, Lehmann S, Kuntze T, Rastan A, Mohr FW. Replacing cardiopulmonary bypass with extracorporeal membrane oxygenation in lung transplantation operations. Eur J Cardiothorac Surg 2007;31:462-7.
22. Daud SA, Yusen RD, Meyers BF, et al. Impact of immediate primary lung allograft dysfunction on bronchiolitis obliterans syndrome. Am J Respir Crit Care Med 2007;175:507-13.
23. Huang HJ, Yusen RD, Meyers BF, et al. Late primary graft dysfunction after lung transplantation and bronchiolitis obliterans syndrome. Am J Transplant 2008;8:2454-62.
24. Kreisel D, Krupnick AS, Puri V, et al. Short- and long-term outcomes of 1000 adult lung transplant recipients at a single center. J Thorac Cardiovasc Surg 2011;141:215-22.
25. Li D, Weinkauf J, Kapasi A, et al. Baseline lung allograft dysfunction in primary graft dysfunction survivors after lung transplantation. Resp Med 2021;188:106617.