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A multicenter analysis of lung transplantation outcomes comparing donation after circulatory death and donation after brain death

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BACKGROUND: Donor organ shortage is a barrier to lung transplantation. Donation after circulatory death (DCD) may offer a solution, although it is underutilized. The objective of this study was to compare survival and other postoperative outcomes between DCD and donation after brain death (DBD).

METHODS: We performed a multicenter analysis of Multi-Institutional Extracorporeal Life Support (ECLS) Registry data from 11 lung transplant centers in the United States and Europe. Demographics and clinical parameters were compared using chi-square test and Fisher's exact test. Survival was assessed by Kaplan-Meier curves and compared by log-rank test with propensity score matching.

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RESULTS: Of 1,585 patients included in the study, 135 (8.5%) received DCD lungs and 1,450 (91.5%) received DBD lungs. DCD recipients had higher rates of obstructive lung disease ($p = 0.042$), longer total ischemic time ($p < 0.0001$), and higher rates of primary graft dysfunction (PGD) at t0h ($p < 0.0001$) and t24h ($p = 0.0005$). PGD at t48h and t72h was not significantly different between DCD and DBD recipients. Ninety-day survival was lower among DCD recipients (91.2%) compared to DBD recipients (97.4%, $p = 0.038$). Survival was higher without ECLS ($p = 0.014$), whereas ex vivo lung perfusion (EVLP) ($p = 0.47$) did not affect survival.

CONCLUSIONS: Overall, our data showed excellent 90-day survival for DCD and DBD recipients, although DCD recipients had relatively lower survival. EVLP was not associated with survival, which may guide future strategies to optimize DCD utilization.

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Background

Irreversible end-stage lung disease is a fatal illness affecting millions of people worldwide annually. In most cases, the only hope of cure for patients with this disease is lung transplantation. However, donor organ shortage remains a critical challenge to obtaining a lung transplant (LT) in a timely fashion. In the United States alone, more than 4,500 patients a year require LTs.[1] With an average waitlist mortality between 15% and 20%, there is a major need for solutions to remedy the current donor shortage.[1]

LTs primarily come from donation after brain death (DBD), but donation after circulatory death (DCD) has emerged as another option over the last decade. Several studies have demonstrated similar outcomes between DCD and DBD, particularly regarding survival and persistent primary graft dysfunction (PGD).[2,3] However, they are mostly limited to retrospective single-center analyses and United Network for Organ Sharing (UNOS) database studies, with few multicenter studies.

There is a profound discrepancy between the availability of DCD lungs and their utilization. In the United States, the 2018 Organ Procurement and Transplantation Network reported 121 DCD LTs compared to 2,426 DBD LTs.[4] Globally, the 2016 International Society of Heart and Lung Transplantation reported 146 DCD LTs compared to 935 DBD LTs.[3] This discrepancy is the result of multiple factors in DCD, including concerns for graft ischemia, limited resources, and a lack of standardized protocols.[5,6] Thus, there continues to be a need to analyze the results of DCD LTs in comparison to DBD LTs using multicenter registries that capture granular contemporary practice patterns and outcomes.

The use of ex vivo lung perfusion (EVLP) is a promising modality for assessing and reconditioning DCD lungs outside of the body. This practice has been associated with excellent 1-year survival despite higher rates of high-grade PGD immediately after reperfusion compared to standard donor lungs.[7] The risk of high-grade PGD was recently shown to be associated with the use of intraoperative extracorporeal life supports (ECLS) during LT in a multicenter international registry of high-volume LT centers.[8] This registry, known as the Multi-Institutional ECLS Lung Transplant Registry, is among the largest multicenter LT registries and was developed to obtain granular data on the effects of intraoperative practices on LT outcomes. This study provides multicenter international data on DCD vs DBD outcomes from the ECLS Registry, representing a robust multicenter experience from leaders in the field of lung transplantation that we believe will benefit existing literature and expand the understanding of LT practices and strategy.

Objectives

Our primary objective in this study was to query the ECLS Lung Transplant Registry to compare survival outcomes between DCD and DBD LTs and to determine whether these outcomes were affected by the use of intraoperative ECLS or EVLP. Secondary objectives included the comparison of early survival, PGD, and related in-hospital events and complications.

Methods

Study design

This is a multicenter analysis of DCD and DBD LTs. Patients were initially stratified by donor type, either DCD or DBD, and then further stratified by use of EVLP for additional analyses (Figure 1). Data were obtained through the Multi-Institutional ECLS Lung Transplant Registry, as described in earlier publications by Loor et al[8] and Subramaniam et al.[9] The registry includes data from LTs performed at 11 high-volume centers in the United States and Europe: Baylor Medical Center, Duke University, Hannover Medical School, Massachusetts General Hospital, St. Joseph's Hospital, Temple University, University of

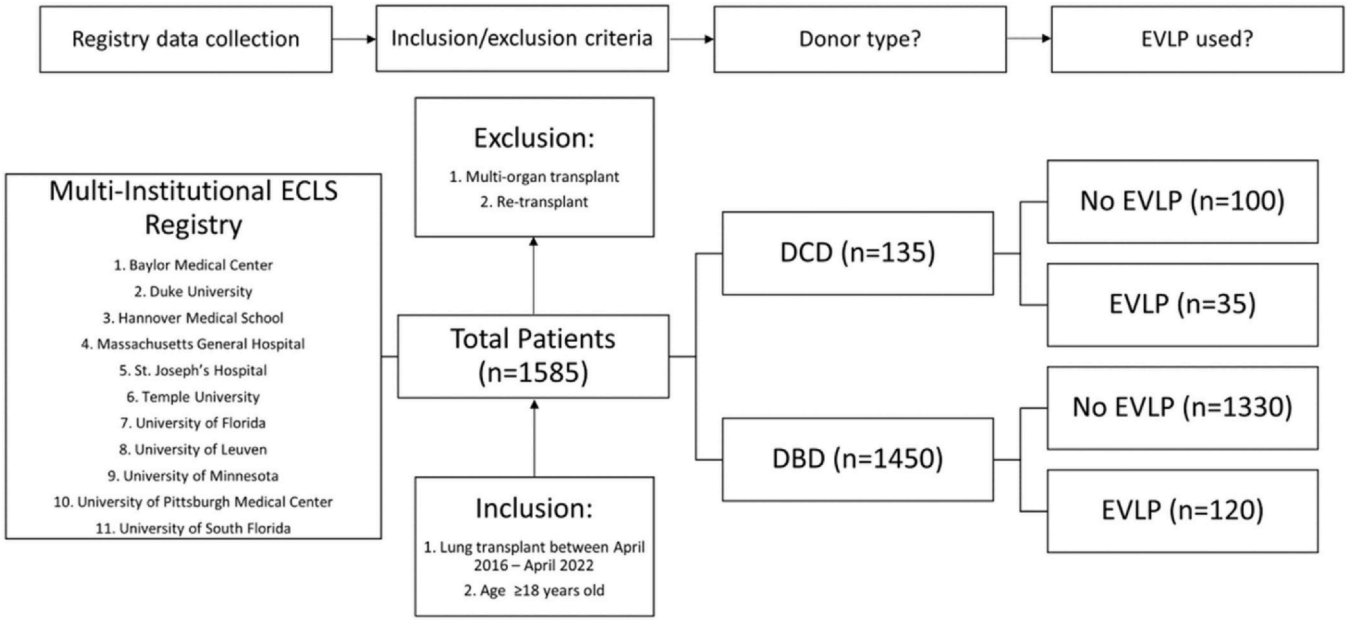

Figure 1 Multi-Institutional ECLS Registry study design. DBD, donation after brain death; DCD, donation after circulatory death; ECLS, extracorporeal life support; EVLP, ex vivo lung perfusion.

Florida, University of Leuven, University of Minnesota, University of Pittsburgh Medical Center, and University of South Florida. Institutional review board approval and waiver of consent were obtained at each center. Data use and transfer agreements were signed by all centers. Baylor College of Medicine was the central coordinating center. The Temple University Health System institutional review board approved this study (IRB#25314).

Setting

Totally 1,585 patients received LTs over a 6-year period (April 2016-April 2022) as obtained through the Multi-Institutional ECLS Lung Transplant Registry. Data were entered into an online Health Insurance Portability and Accountability Act-compliant database and deidentified for analysis. Data elements uploaded to the registry are regularly collected for patient care and available to download for interim results for research purposes. No changes to clinical practice were initiated as part of this study.

Participants

Eligibility criteria included patients ≥18 years old who planned to undergo lung transplantation. Patients who underwent heart-lung transplantation, other multiorgan transplantation, and retransplantation were excluded.

Variables

The ECLS Registry collects data prospectively and retrospectively on peri- and postoperative details that may be relevant to patient outcomes after LT. Prospective entries are gathered in real time throughout the transplant. Acknowledging that most centers do not have a real-time collection method or personnel who can achieve this, retrospective entries are permitted as close as possible to the time of transplant. Recipient baseline characteristics included age, gender, lung allocation score (LAS), primary diagnosis, and comorbidities. Primary diagnosis was grouped into cystic fibrosis, obstructive lung disease, pulmonary vascular disease, and restrictive lung disease. Donor characteristics included age, gender, smoking history, cytomegalovirus (CMV) status, extended criteria, PaO_2/FiO_2 (P/F) ratio, and cause of death. The cause of death was grouped into anoxia, cerebrovascular/stroke, head trauma, and central nervous system tumor. Postoperative variables included PGD, death at 90 days, major postoperative complications, and length of stay (LOS). PGD was graded according to the 2016 International Society of Heart and Lung Transplantation guidelines.[10] Postoperative pneumonia refers to treated pneumonia that was confirmed by chest X-ray. EVLP was used according to center-specific policies, for LTs with extended donor criteria or to improve lung quality. EVLP devices included the Organ Care System by TransMedics and XVIVO Perfusion System by XVIVO. Preoperative cardiopulmonary support included extracorporeal membrane oxygenation (ECMO), intra-aortic balloon pump (IABP), mechanical ventilation, and noninvasive positive pressure ventilation (NIPPV). Intraoperative ECLS included cardiopulmonary bypass (CPB), ECMO, and modified bypass.

Statistical methods

To account for heterogeneity between DCD and DBD groups and to minimize the likelihood of selection bias, propensity score-matched analysis was performed. The matching ratio was 1:2. The nearest neighbor 1:2 variable ratio, parallel, balanced propensity-matching method was

used after generating propensity scores from the variables age, gender, body mass index, ECMO, total ischemic time, and primary diagnosis. Variables included in the propensity score matching model are clinically relevant variables for transplantation or statistically significant potential confounding recipient demographics with baseline characteristics. The propensity score-matched analysis created 2 well-matched groups for comparative outcomes analysis (Table S1).

Demographics and clinical parameters were compared using chi-square test for categorical variables and Fisher's exact test for continuous variables. Continuous variables that were not normally distributed were evaluated using Wilcoxon nonparametric testing. Categorical variables were listed with counts and percentages, while means or medians and standard deviations were specified for continuous variables.

Survival was assessed by Kaplan-Meier curves and log-rank test. Patients were stratified by donor technique, ECLS, and EVLP. Survival was assessed in-hospital, at 30 days, and 90 days. p-Value < 0.05 was considered statistically significant. Analyses were performed using Stata v17 (StataCorp LLC., College Station, TX).

Results

Patient demographics

Of 1,585 total patients, 135 (8.5%) received DCD lungs and 1,450 (91.5%) received DBD lungs. The most common diagnoses were restrictive lung disease in 764 patients (48.2%), followed by obstructive lung disease in 553 (34.9%), cystic fibrosis in 201 (12.7%), and pulmonary vascular disease in 67 (4.2%). Table 1 shows the demographics and baseline characteristics of DCD vs DBD transplantation. DCD recipients were older (58.0 vs 54.1 years, $p = 0.0004$), had higher rates of obstructive lung disease (45.2% vs 33.9%, $p = 0.042$), and lower rates of preoperative NIPPV (2.2% vs 8.8%, $p = 0.022$) compared to DBD. DCD donors had higher rates of death due to anoxia (36.3% vs 29.0%) and lower rates of death due to head trauma (23.7% vs 30.8%) compared to DBD ($p < 0.0001$). DCD lungs also had higher rates of extended donor criteria (88.1% vs 48.9%, $p < 0.0001$) and longer total ischemic times (515.4 vs 432.5 minutes, $p < 0.0001$).

Table 2 shows the demographics and baseline characteristics of EVLP utilization. One hundred and fifty-five (9.8%) patients received lungs with EVLP. The OCS device was used for 149 of these cases (96.1%), the XPS device for 3 cases (1.9%), and 3 cases were unspecified (1.9%). Among EVLP patients, 35 (22.6%) were DCD and 120 (77.4%) were DBD. Within the DCD group, EVLP lungs had higher rates of extended donor criteria (94.3% vs 86.0%, $p < 0.0001$) and anoxia as donor cause of death (40.0% vs 35.0%, $p < 0.0001$). EVLP lungs had longer total ischemic time (614.3 vs 480.8 minutes, $p < 0.0001$) and higher rates of intraoperative ECMO (20.0% vs 3.0%, $p = 0.0036$). For the DBD group, EVLP lungs had higher LAS (50.2 vs 44.7, $p < 0.0001$), higher rates of extended donor criteria (81.7% vs 45.9%, $p < 0.0001$), and anoxia as donor cause of death (39.2% vs 28.1%, $p < 0.0001$). EVLP lungs had longer total ischemic time (584.7 vs 418.8 minutes, $p < 0.0001$) and higher rates of intraoperative CPB (38.3% vs 31.4%) and ECMO (6.7% vs 3.1%, $p < 0.0001$).

Patient clinical variables

Table 3 shows postoperative outcomes by DCD vs DBD transplantation. DCD recipients had higher rates of PGD grade 3 at t0h (41.5% vs 21.7%, $p < 0.0001$) and t24h (29.6% vs 17.4%, $p = 0.0005$). However, PGD grades at later time points, t48h ($p = 0.07$) and t72h ($p = 0.45$), were not significantly different between the groups. DCD recipients had higher rates of pneumonia (28.1% vs 15.8%, $p < 0.0001$) and renal failure/dialysis (14.1% vs 8.3%, $p = 0.036$) compared to DBD. DCD recipients also had longer hospital LOS (39.9 vs 33.3 days, $p = 0.021$) and intensive care unit (ICU) LOS (19.6 vs 13.7 days, $p = 0.0004$).

Table 4 shows postoperative outcomes by EVLP utilization. Within the DCD group, EVLP lungs had longer ICU LOS (23.5 vs 17.8 days, $p < 0.0001$). Within the DBD group, EVLP lungs had higher rates of grade 3 PGD at t0h (33.3% vs 20.7%, $p < 0.0001$) and t24h (22.5% vs 16.9%, $p = 0.001$), but there was no difference in PGD rates at later time points. EVLP lungs had higher rates of postoperative pneumonia (20.0% vs 15.4%, $p < 0.0001$) and longer ICU LOS (18.1 vs 13.2 days, $p < 0.0001$).

Survival for DCD vs DBD

For the full cohort, the in-hospital survival rate was 98.8%, 90-day was 97.0%, and 1-year was 94.7%. For DCD recipients, the in-hospital survival rate was 95.0%, 90-day was 91.2%, and 1-year was 86.0%. For DBD, the in-hospital survival rate was 99.1%, 90-day was 97.4%, and 1-year was 95.5%. Survival was lower among DCD recipients before ($p = 0.0066$) and after propensity matching ($p = 0.038$) (Figure 2).

Survival by ECLS and EVLP

Five hundred and eighty-two (36.7%) patients required intraoperative ECLS, including 511 (32.2%) patients on CPB, 59 (3.7%) patients on ECMO, and 1 (0.1%) patient on modified bypass. The 90-day survival among patients with intraoperative ECLS was 95.1% compared to 98.5% without ECLS. The 90-day survival among patients with EVLP was 95.5% compared to 97.1% without EVLP. Survival was lower among patients who received ECLS ($p = 0.014$); however, there was no significant difference in survival based on EVLP utilization ($p = 0.47$) (Figure 3).

Table 1 Recipient and Donor Demographics With Baseline Characteristics for DCD and DBD Transplantation

Demographic variable	Total ($n = 1585$)	DCD ($n = 135$)	DBD ($n = 1,450$)	p-value
Recipient demographics				
Recipient age	54.5 ± 13.6	58.0 ± 11.9	54.1 ± 13.6	0.0004[a]
Recipient gender				0.37
Female	696 (43.9%)	54 (40.0%)	642 (44.3%)	
Male	889 (56.1%)	81 (60.0%)	808 (55.7%)	
LAS	45.0 ± 16.8	43.6 ± 16.9	45.2 ± 16.8	0.065
Recipient primary diagnosis				0.042[a]
Cystic fibrosis	201 (12.7%)	12 (8.9%)	189 (13.0%)	
Obstructive lung disease	553 (34.9%)	61 (45.2%)	492 (33.9%)	
Pulmonary vascular disease	67 (4.2%)	3 (2.2%)	64 (4.4%)	
Restrictive lung disease	764 (48.2%)	59 (43.7%)	705 (48.6%)	
Recipient chronic steroid use	610 (38.5%)	56 (41.5%)	554 (38.2%)	0.76
Recipient diabetes	291 (18.4%)	25 (18.5%)	266 (18.3%)	0.91
Recipient renal failure/dialysis	24 (1.5%)	3 (2.2%)	21 (1.4%)	0.47
Recipient prior lung surgery	245 (15.5%)	19 (14.1%)	226 (15.6%)	0.80
Donor demographics				
Donor age	39.7 ± 15.2	41.1 ± 14.3	39.5 ± 15.3	0.23
Donor gender				0.069
Female	684 (43.2%)	48 (35.6%)	636 (43.9%)	
Male	901 (56.8%)	87 (64.4%)	814 (56.1%)	
Donor smoking history	618 (39.0%)	51 (37.8%)	567 (39.1%)	0.40
Donor CMV positive	844 (53.2%)	63 (46.7%)	781 (53.9%)	0.054
Donor extended criteria	828 (52.2%)	119 (88.1%)	709 (48.9%)	< 0.0001[a]
Donor last P/F before retrieval	415.3 ± 100.8	419.0 ± 92.5	414.9 ± 101.5	0.64
Donor cause of death				< 0.0001[a]
Anoxia	470 (29.7%)	49 (36.3%)	421 (29.0%)	
Cerebrovascular/stroke	540 (34.1%)	44 (32.6%)	496 (34.2%)	
Head trauma	478 (30.2%)	32 (23.7%)	446 (30.8%)	
Central nervous system tumor	4 (0.3%)	0 (0.0%)	4 (0.3%)	
Other/unspecified	93 (5.9%)	10 (7.4%)	83 (5.7%)	
Total ischemic time	439.6 ± 142.7	515.4 ± 164.4	432.5 ± 138.4	< 0.0001[a]
Warm ischemic time	58.6 ± 37.7	54.8 ± 19.2	59.2 ± 39.6	0.20
Preoperative cardiopulmonary support	246 (15.5%)	13 (9.6%)	233 (16.1%)	0.076
Preoperative cardiopulmonary support				0.022[a]
Type	106 (6.7%)	8 (5.9%)	98 (6.8%)	
ECMO	1 (0.1%)	0 (0.0%)	1 (0.1%)	
IABP	8 (0.5%)	2 (1.5%)	6 (0.4%)	
Ventilator	130 (8.2%)	3 (2.2%)	127 (8.8%)	
NIPPV	1 (0.1%)	0 (0.0%)	1 (0.1%)	
Other/unspecified				
Intraoperative ECLS	582 (36.7%)	58 (43.0%)	524 (36.1%)	0.15
Intraoperative ECLS type				0.23
CPB	511 (32.2%)	48 (35.6%)	463 (31.9%)	
ECMO	59 (3.7%)	10 (7.4%)	49 (3.4%)	
Modified bypass	1 (0.1%)	0 (0.0%)	1 (0.1%)	
Other/unspecified	11 (0.7%)	0 (0.0%)	11 (0.8%)	
Intraoperative ECLS time	250 ± 113.9	265.4 ± 117.9	248.3 ± 113.4	0.26

Abbreviations: CMV, cytomegalovirus; CPB, cardiopulmonary bypass; DCD, donation after circulatory death; DBD, donation after brain death; LAS, lung allocation score; ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; NIPPV, noninvasive positive pressure ventilation; P/F, PaO_2/FiO_2.

Data are displayed as mean ± standard deviation for continuous variables and number (percent of group total) for categorical variables. Age is displayed in years. Time is displayed in minutes. Warm ischemic time represents the average between right and left lungs.

[a]$p < 0.05$.

Table 2 Recipient and Donor Demographics and Baseline Characteristics for DCD and DBD Transplantation With EVLP Utilization

Demographic variable	Total (n = 1,585)	DCD without EVLP (n = 100)	DCD with EVLP (n = 35)	DBD without EVLP (n = 1,330)	DBD with EVLP (n = 120)	p-value
Recipient variables						
Recipient age	54.5 ± 13.6	58.1 ± 11.7	57.6 ± 12.9	54.2 ± 13.6	52.8 ± 14.6	0.004[a]
Recipient gender						0.58
Female	696 (43.9%)	39 (39.0%)	15 (42.9%)	584 (43.9%)	58 (48.3%)	
Male	889 (56.1%)	61 (61.0%)	20 (57.1%)	746 (56.1%)	62 (51.7%)	
LAS	45.0 ± 16.8	43.9 ± 18.1	42.8 ± 13.0	44.7 ± 16.6	50.2 ± 18.7	< 0.0001[a]
Recipient primary diagnosis						0.17
Cystic fibrosis	201 (12.7%)	9 (9.0%)	3 (8.6%)	172 (12.9%)	17 (14.2%)	
Obstructive	553 (34.9%)	46 (46.0%)	15 (42.9%)	459 (34.5%)	33 (27.5%)	
Pulmonary vascular	67 (4.2%)	1 (1.0%)	2 (5.7%)	60 (4.5%)	4 (3.3%)	
Restrictive	764 (48.2%)	44 (44.0%)	15 (42.9%)	639 (48.0%)	66 (55.0%)	
Recipient chronic steroid use	610 (38.5%)	38 (38.0%)	18 (51.4%)	506 (38.0%)	48 (40.0%)	0.56
Recipient diabetes	291 (18.4%)	19 (19.0%)	6 (17.1%)	243 (18.3%)	23 (19.2%)	0.99
Recipient renal failure/dialysis	24 (1.5%)	1 (1.0%)	2 (5.7%)	20 (1.5%)	1 (0.8%)	0.23
Recipient prior lung surgery	245 (15.5%)	16 (16.0%)	3 (8.6%)	200 (15.0%)	26 (21.7%)	0.24
Donor variables						
Donor age	39.7 ± 15.2	41.3 ± 14.7	40.4 ± 13.3	39.7 ± 15.4	37.4 ± 14.1	0.27
Donor gender						0.27
Female	684 (43.2%)	34 (34.0%)	14 (40.0%)	585 (44.0%)	51 (42.5%)	
Male	901 (56.8%)	66 (66.0%)	21 (60.0%)	745 (56.0%)	69 (57.5%)	
Donor smoking history	618 (39.0%)	35 (35.0%)	16 (45.7%)	513 (38.6%)	54 (45.0%)	0.42
Donor CMV status	844 (53.2%)	44 (44.0%)	19 (54.3%)	711 (53.5%)	70 (58.3%)	0.25
Donor extended criteria	828 (52.2%)	86 (86.0%)	33 (94.3%)	611 (45.9%)	98 (81.7%)	< 0.0001[a]
Donor last P/F before retrieval	415.3 ± 100.8	422.4 ± 84.8	409.8 ± 111.5	413.3 ± 101.5	431.3 ± 101.3	0.25
Donor cause of death						< 0.0001[a]
Anoxia	470 (29.7%)	35 (35.0%)	14 (40.0%)	374 (28.1%)	47 (39.2%)	
Cerebrovascular/stroke	540 (34.1%)	32 (32.0%)	12 (34.3%)	466 (35.0%)	30 (25.0%)	
Head trauma	478 (30.2%)	23 (23.0%)	9 (25.7%)	406 (30.5%)	40 (33.3%)	
Central nervous system tumor	4 (0.3%)	0 (0.0%)	0 (0.0%)	4 (0.3%)	0 (0.0%)	
Other/unspecified	93 (5.9%)	10 (10.0%)	0 (0.0%)	80 (6.0%)	3 (2.5%)	
Total ischemic time	439.6 ± 142.7	480.8 ± 130.8	614.3 ± 207.7	418.8 ± 125.2	584.7 ± 181.5	< 0.0001[a]
Warm ischemic time	58.6 ± 37.7	56.5 ± 20.1	50.4 ± 16.4	59.1 ± 39.6	59.3 ± 39.8	0.20
Preoperative cardiopulmonary support	246 (15.5%)	11 (11.0%)	2 (5.7%)	215 (16.2%)	18 (15.0%)	0.18
Preoperative cardiopulmonary	106 (6.7%)		1 (2.9%)	87 (6.5%)	11 (9.2%)	0.075
Support type	1 (0.1%)	7 (7.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	
ECMO	8 (0.5%)	0 (0.0%)	0 (0.0%)	5 (0.4%)	1 (0.8%)	
IABP	130 (8.2%)	2 (2.0%)	1 (2.9%)	121 (9.1%)	6 (5.0%)	
Ventilator	1 (0.1%)	2 (2.0%)	(0.0%)	1 (0.1%)	0 (0.0%)	
NIPPV		0 (0.0%)				
Other/unspecified						
Intraoperative ECLS	582 (36.7%)	38 (38.0%)	20 (57.1%)	466 (35.0%)	58 (48.3%)	0.053
Intraoperative ECLS type	511 (32.2%)	35 (35.0%)	13 (37.1%)	417 (31.4%)	46 (38.3%)	0.0036[a]
CPB	59 (3.7%)	3 (3.0%)	7 (20.0%)	41 (3.1%)	8 (6.7%)	
ECMO	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	
Modified bypass	11 (0.7%)	0 (0.0%)	0 (0.0%)	7 (0.5%)	4 (3.3%)	
Other/unspecified						
Intraoperative ECLS time	250.0 ± 113.9	277.8 ± 122.0	235.0 ± 103.4	250.1 ± 113.4	231.7 ± 113.1	0.24

Abbreviations: CMV, cytomegalovirus; CPB, cardiopulmonary bypass; DCD, donation after circulatory death; DBD, donation after brain death; LAS, lung allocation score; ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; NIPPV, noninvasive positive pressure ventilation; P/F, $PaO_{2/FiO2}$.

Data are displayed as mean ± standard deviation for continuous variables and number (percent of group total) for categorical variables. Age is displayed in years. Time is displayed in minutes. Warm ischemic time represents the average between right and left lungs.

[a] $p < 0.05$.

Table 3 Postoperative Outcomes for DCD and DBD Transplantation

Outcome variable	Total ($n = 1,585$)	DCD ($n = 135$)	DBD ($n = 1,450$)	p-value
PGD grade at t0h				< 0.0001[a]
0-2	1,150 (72.6%)	68 (50.4%)	1,082 (74.6%)	
3	371 (23.4%)	56 (41.5%)	315 (21.7%)	
Missing	64 (4.0%)	11 (8.1%)	53 (3.7%)	
PGD grade at t24h				0.0005[a]
0-2	1,234 (77.9%)	87 (64.4%)	1,147 (79.1%)	
3	292 (18.4%)	40 (29.6%)	252 (17.4%)	
Missing	59 (3.7%)	8 (5.9%)	51 (3.5%)	
PGD grade at t48h				0.070
0-2	1,248 (78.7%)	96 (71.1%)	1,152 (79.4%)	
3	276 (17.4%)	31 (23.0%)	245 (16.9%)	
Missing	61 (3.8%)	8 (5.9%)	53 (3.7%)	
PGD grade at t72h				0.45
0-2	1,265 (79.8%)	102 (75.6%)	1,163 (80.2%)	
3	243 (15.3%)	23 (17.0%)	220 (15.2%)	
Missing	77 (4.9%)	10 (7.4%)	67 (4.6%)	
Death at 90 days	48 (3.0%)	11 (8.1%)	37 (2.6%)	0.001[a]
Airway dehiscence	45 (2.8%)	7 (5.2%)	38 (2.6%)	0.11
Tracheostomy	65 (4.1%)	6 (4.4%)	59 (4.1%)	0.83
Take back for bleed	142 (9.0%)	19 (14.1%)	123 (8.5%)	0.062
Pneumonia	267 (16.8%)	38 (28.1%)	229 (15.8%)	< 0.0001[a]
Renal failure/dialysis	140 (8.8%)	19 (14.1%)	121 (8.3%)	0.036[a]
Stroke	45 (2.8%)	6 (4.4%)	39 (2.7%)	0.23
Hospital LOS	33.9 ± 36.3	39.9 ± 38.0	33.3 ± 36.1	0.021[a]
ICU LOS	14.1 ± 25.1	19.6 ± 31.1	13.7 ± 24.5	0.0004[a]

Abbreviations: DCD, donation after circulatory death; DBD, donation after brain death; ICU, intensive care unit; PGD, primary graft dysfunction; LOS, length of stay, displayed in days.

Data are displayed as mean ± standard deviation for continuous variables and number (percent of group total) for categorical variables.

[a] $p < 0.05$.

Survival for DCD vs DBD by ECLS

Among ECLS patients, 58 (43.0%) were DCD recipients and 524 (36.1%) were DBD recipients. DCD and DBD recipients had higher 90-day survival without intraoperative ECLS compared to with ECLS. The 90-day survival for DCD recipients with ECLS was 88.7% vs 94.8% without ECLS. The 90-day survival for DBD recipients with ECLS was 95.7% vs 98.8% without ECLS. Survival was higher without intraoperative ECLS before ($p = 0.0046$) and after propensity matching ($p = 0.039$) (Figure 4).

Survival for DCD vs DBD by EVLP

The 90-day survival for DCD recipients with EVLP was 88.6% vs 93.0% without EVLP. The 90-day survival for DBD recipients with EVLP was 96.6% vs 97.4% without EVLP. There was no significant difference in survival based on EVLP for DCD ($p = 0.5$) and DBD recipients ($p = 0.79$) (Figure 5).

Survival by PGD

We also compared 90-day survival for patients with PGD grade 3 vs PGD grades 0 to 2 at t0h before and after propensity matching to account for potential confounders. While survival was significantly lower for patients with PGD grade 3 before propensity matching ($p = 0.0084$), it was not significantly different after propensity matching ($p = 0.17$) (Figure 6).

Discussion

In this multicenter analysis of DCD and DBD LTs, we demonstrated an overall high 90-day survival rate of 97.0% for our cohort of 1,585 patients. We noted a lower 90-day survival of 91.2% among 135 DCD LTs compared to 97.4% among 1,450 DBD LTs before and after propensity matching. The use of DCD lungs is of increasing interest to expand the donor pool and address organ shortages. However, there is limited data on outcomes after DCD transplantation, mostly confined to single-center studies that are subject to greater variability and UNOS database studies that do not accurately capture the granularity of contemporary LT practices and outcomes.

An SRTR database study by Bobba et al in 2022 analyzed survival outcomes between 728 DCD LT recipients and 27,205 DBD LT recipients, which showed no difference in overall survival.[11] Another single-center study by

Table 4 Postoperative Outcomes for DCD and DBD Transplantation With EVLP Utilization

Outcome variable	Total $n = 1,585$)	DCD without EVLP ($n = 100$)	DCD with EVLP ($n = 35$)	DBD without EVLP ($n = 1,330$)	DBD with EVLP ($n = 120$)	p-value
PGD grade at t0h						
0-2	1,150 (72.6%)	53 (53.0%)	15 (42.9%)	1,006 (75.6%)	76 (63.3%)	< 0.0001[a]
3	371 (23.4%)	41 (41.0%)	15 (42.9%)	275 (20.7%)	40 (33.3%)	
Missing	64 (4.0%)	6 (6.0%)	5 (14.3%)	49 (3.7%)	4 (3.3%)	
PGD grade at t24h						
0-2	1,234 (77.9%)	65 (65.0%)	22 (62.9%)	1,058 (79.5%)	89 (74.2%)	0.001[a]
3	292 (18.4%)	29 (29.0%)	11 (31.4%)	225 (16.9%)	27 (22.5%)	
Missing	59 (3.7%)	6 (6.0%)	2 (5.7%)	47 (3.5%)	4 (3.3%)	
PGD grade at t48h						
0-2	1,248 (78.7%)	70 (70.0%)	26 (74.3%)	1,059 (79.6%)	93 (77.5%)	0.24
3	276 (17.4%)	24 (24.0%)	7 (20.0%)	223 (16.8%)	22 (18.3%)	
Missing	61 (3.8%)	6 (6.0%)	2 (5.7%)	48 (3.6%)	5 (4.2%)	
PGD grade at t72h						
0-2	1,265 (79.8%)	77 (77.0%)	25 (71.4%)	1,064 (80.0%)	99 (82.5%)	0.43
3	243 (15.3%)	15 (15.0%)	8 (22.9%)	206 (15.5%)	14 (11.7%)	
Missing	77 (4.9%)	8 (8.0%)	2 (5.7%)	60 (4.5%)	7 (5.8%)	
Death at 90 days	48 (3.0%)	7 (7.0%)	4 (11.4%)	34 (2.6%)	3 (2.5%)	0.002[a]
Airway dehiscence	45 (2.8%)	6 (6.0%)	1 (2.9%)	34 (2.6%)	4 (3.3%)	0.31
Tracheostomy	65 (4.1%)	4 (4.0%)	2 (5.7%)	52 (3.9%)	7 (5.8%)	0.81
Take back for bleed	142 (9.0%)	16 (16.0%)	3 (8.6%)	114 (8.6%)	9 (7.5%)	0.12
Pneumonia	267 (16.8%)	28 (28.0%)	10 (28.6%)	205 (15.4%)	24 (20.0%)	< 0.0001[a]
Renal failure/dialysis	140 (8.8%)	13 (13.0%)	6 (17.1%)	109 (8.2%)	12 (10.0%)	0.087
Stroke	45 (2.8%)	4 (4.0%)	2 (5.7%)	37 (2.8%)	2 (1.7%)	0.52
Hospital LOS	33.9 ± 36.3	38.4 ± 32.7	44.6 ± 50.9	33.2 ± 36.4	34.0 ± 33.2	0.13
ICU LOS	14.1 ± 25.1	17.8 ± 30.6	23.5 ± 32.3	13.2 ± 24.8	18.1 ± 21.2	< 0.0001[a]

Abbreviations: DBD, donation after brain death; DCD, donation after circulatory death; EVLP, ex vivo lung perfusion; ICU, intensive care unit; LOS, length of stay (displayed in days); PGD, primary graft dysfunction.

Data displayed as mean ± standard deviation for continuous variables and number (percent of group total) for categorical variables.

[a] $p < 0.05$.

Inci et al in 2018 compared 90-day survival between 21 transplants from DCD donors and 130 transplants from DBD donors.[12] They found no significant differences in survival between the groups and had no 90-day mortality in the DCD group, compared to our mortality of 8.8% among DCD recipients.[12] However, these were single-center studies and limited by a smaller sample size.

A multicenter study by van Suylen et al in 2017 also found no difference between survival outcomes for 130 DCD and 296 DBD recipients.[13] They demonstrated a 1-year survival rate of 87% for DCD recipients, which is similar to our survival rate of 86.0%.[13] However, their 1-year survival rate for DBD recipients was 82%, lower than ours at 95.5%. Compared to this multicenter study, our DCD and

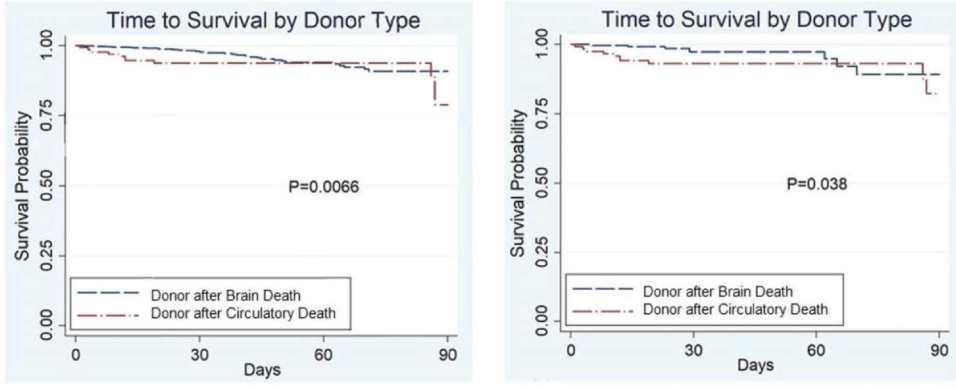

Figure 2 Kaplan-Meier 90-day survival curves for recipients of DCD and DBD lung transplantation before (A) and after propensity score matching (B). DCD recipients had significantly lower 90-day survival compared to DBD recipients before ($p = 0.0066$) and after propensity matching ($p = 0.038$). DBD, donation after brain death; DCD, donation after circulatory death.

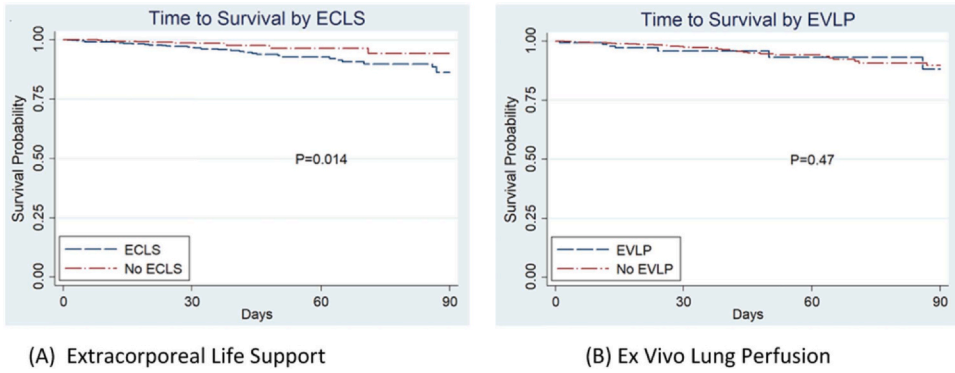

Figure 3 Kaplan-Meier 90-day survival curves for recipients of intraoperative ECLS (A) and EVLP (B). There was significantly lower 90-day survival with ECLS compared to without ECLS ($p = 0.014$). There was no significant difference in 90-day survival based on utilization of EVLP ($p = 0.47$). ECLS, extracorporeal life support; EVLP, ex vivo lung perfusion.

DBD groups had good survival outcomes. Our difference in survival rates between the groups may be due to the high survival of our DBD recipients rather than poor survival of our DCD recipients.

We found no difference in rates of grade 3 PGD at t48h and t72h. DCD lungs had a greater incidence of PGD at t0h and t24h but showed no significant difference compared to DBD lungs as time progressed. This is an important finding as PGD is a significant cause of morbidity, such as bronchiolitis obliterans syndrome and other forms of chronic lung allograft dysfunction, as well as both early and late mortality in LTs, regardless of the donor type. The risk of mortality is greatest among patients with persistent high-grade PGD at later time points, that is, t48h and t72h.[14] PGD occurs as a result of multiple insults during procurement, storage, and implantation of the donor lung, with ischemia-reperfusion injury believed to play a major role in its pathogenesis.[14] Concerns for PGD contribute to the underutilization of DCD in LT, which makes understanding the prevalence and treatment of PGD of great importance in working to increase the donor organ pool.[15] The treatment of PGD is generally supportive, including lung protective strategies, reperfusion strategies, use of inhaled nitric oxide, prostaglandins, prostacyclins, surfactant, and EVLP, although severe cases may require ECMO.[14]

It has been proposed that because DCD lungs do not experience the catecholamine surge and inflammatory cascade that follows brainstem death, they may have decreased rates of PGD.[15] Unlike in DBD, DCD organs undergo a period of warm ischemia during the withdrawal of life--sustaining therapy and between circulatory arrest and lung procurement.[15] However, the duration at which warm ischemia compromises survival in DCD LTs is not well-defined and may be longer than traditionally reported.[16]

In our cohort, rates of grade 3 PGD were 41.5% for DCD recipients compared to 21.7% for DBD at t0h and 29.6% for DCD compared to 17.4% for DBD at t24h. A UNOS database study by Villavicencio et al in 2018 demonstrated a similarly high PGD rate of 40% at t0h for 389 DCD recipients, which was not significantly different from PGD rates among the DBD group at t24h and subsequent time points.[2] Another study by Barbero et al demonstrated similar PGD rates of 26% and 17% between 23 DCD recipients and 163 DBD recipients at t24h.[17] This is favorable for the increased utilization of DCD lungs, as it suggests that despite initial deleterious effects from warm ischemia, lung recovery is achieved relatively quickly. Regarding other postoperative complications, DCD recipients had higher rates of postoperative pneumonia compared to DBD recipients, which is likely multifactorial. For example, DCD

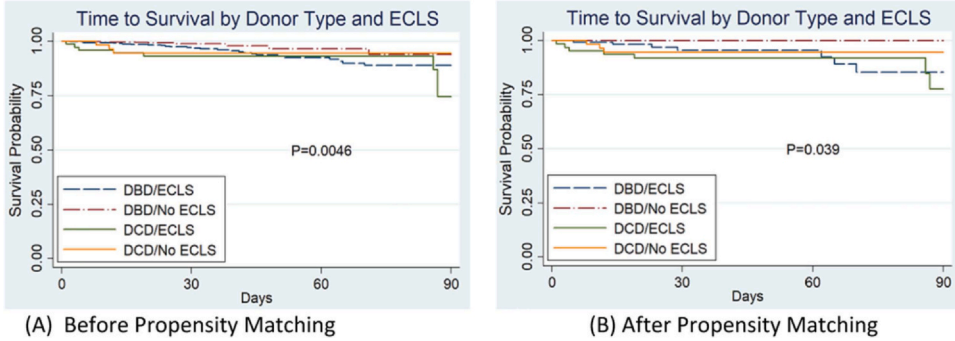

Figure 4 Kaplan-Meier 90-day survival curves for recipients of DCD and DBD lung transplantation with and without utilization of intraoperative ECLS before (A) and after propensity score matching (B). DCD and DBD recipients had significantly lower 90-day survival with ECLS compared to without ECLS before ($p = 0.0046$) and after propensity matching ($p = 0.039$). DBD, donation after brain death; DCD, donation after circulatory death; ECLS, extracorporeal life support.

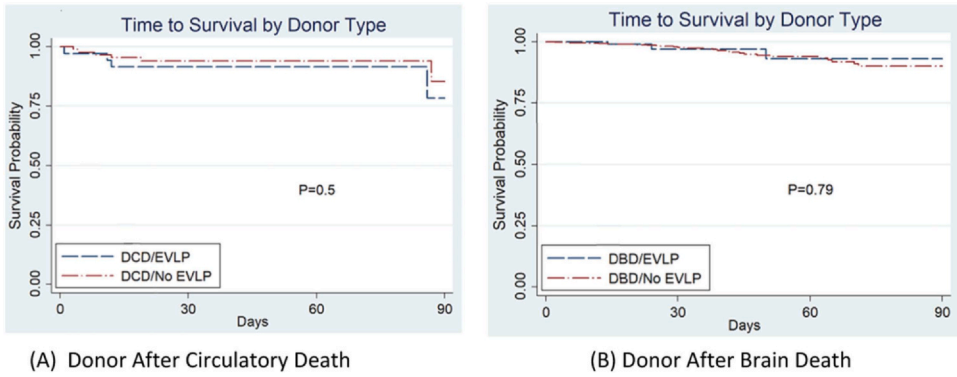

Figure 5 Kaplan-Meier 90-day survival curves for DCD (A) and DBD (B) transplantation with and without EVLP utilization. There was no significant difference in 90-day survival with EVLP compared to without EVLP for DCD ($p = 0.5$) and DBD recipients ($p = 0.79$). DBD, donation after brain death; DCD, donation after circulatory death; EVLP, ex vivo lung perfusion.

recipients had higher rates of ventilator use preoperatively and longer hospital and ICU LOS postoperatively, which could contribute to an increased risk of ventilator-associated pneumonia or hospital-acquired pneumonia.

We also stratified patients by ECLS and EVLP utilization. Intraoperative ECLS was not significantly different between DCD recipients at 43.0% compared to DBD at 36.1%. This is contrary to what others have shown. A single-center study by Sef et al in 2020 explored rates of perioperative ECMO and found that DCD (N = 25) compared to DBD recipients (N = 80) had higher rates of intraoperative ECMO (56.0% vs 36.2%).[18] Our study did not demonstrate these differences in ECLS between DCD and DBD recipients; however, survival was different between recipients who required ECLS vs those who did not.

Our study showed that DCD and DBD recipients had significantly lower 90-day survival with ECLS compared to without ECLS. Intraoperative ECLS allows for controlled perfusion and protective ventilation of the graft during LT, which may reduce rates of ischemia-reperfusion injury and the development of PGD.[19] Indications for intraoperative ECMO and other ECLS strategies in LT include hypercapnia, low arterial saturation less than 90%, low cardiac index less than 2 liter/min/m^2, and pulmonary arterial hypertension.[20] Beyond these indications, some authors have recently proposed the routine use of intraoperative ECLS in LT given its potential protective effect on the graft.[21] However, despite advances in ECLS technology, it is an invasive technique associated with specific complications, including major bleeding, thromboembolic events, systemic inflammatory responses, and infections, that contribute to postoperative morbidity and mortality. Similar to our study, a study by Ius et al in 2018 showed that intraoperative ECLS was associated with decreased survival in comparing 1,020 LT recipients based on ECMO utilization.[20] Our findings suggest that intraoperative ECLS is not without risks and requires careful consideration in selecting patients who require and are appropriate candidates for intraoperative ECLS, regardless of the donor technique.

Lastly, we investigated EVLP utilization and found no significant difference in survival outcomes with and without the use of EVLP. EVLP is of clinical importance in increasing the donor organ pool and improving long-term outcomes, as it preserves donor lungs in a normothermic, perfused, and ventilated environment to reduce tissue injury resulting from hypothermia and anaerobic metabolism.[22] EVLP also enables the evaluation of physiologic parameters in marginal donor lungs, such as pulmonary vascular pressures, P/F ratios, lung edema, and upregulation of inflammatory and cell death pathways, to assess the risks for

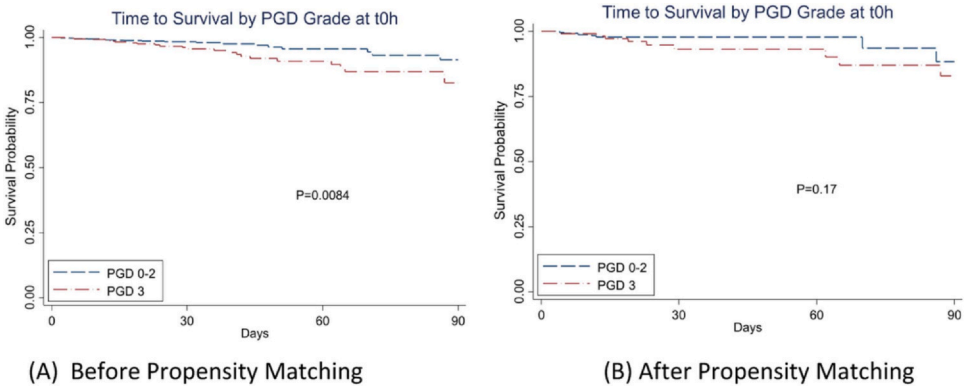

Figure 6 Kaplan-Meier 90-day survival curves for patients with PGD grade 3 and PGD grades 0 to 2 at t0h before (A) and after propensity score matching (B). PGD grade 3 was associated with significantly lower 90-day survival compared to PGD grades 0 to 2 before ($p = 0.0084$) but not after propensity matching ($p = 0.17$). PGD, primary graft dysfunction.

ischemia-reperfusion injury and high-grade PGD.[22] It allows surgeons to evaluate objective measures of organ function before transplantation, which may be particularly important for DCD LTs given the lack of standardized guidelines.[23] Additionally, EVLP offers future potential as a therapeutic platform for the delivery of localized, targeted, lung-specific therapies, including anti-inflammatory agents, immunosuppressive therapies, and antimicrobial treatments.[22] In our study, EVLP was utilized according to center-specific guidelines for the assessment and reconditioning of high-risk extended criteria donor lungs, including but not limited to P/F ratios < 300, presence of pulmonary edema, poor lung compliance, and high transfusion requirements.[24] Although EVLP lungs had longer total ischemic times and higher rates of intraoperative ECMO, survival was similar to non-EVLP lungs. These findings are in agreement with a 2019 study published by Divithotawela et al in 2019 that demonstrated no difference in survival between 95 DCD LTs with EVLP and 46 DCD LTs without EVLP.[25] A recent study by Furukawa et al in 2023 showed a 28% shorter survival time for 158 DCD LTs with EVLP compared to 469 DCD LTs without EVLP; however, the groups had similar survival at 3-year post-transplant.[26] Ultimately, further studies are needed to validate the routine use of EVLP, but our data suggest that it may be a useful strategy in the assessment of DCD organs.

Limitations

We noted a size discrepancy between the DCD and DBD groups, in concordance with published data suggesting that DCD is widely underutilized. This raises concern for selection bias, as we did not assess DCD lungs deemed unsuitable for transplantation, due to poorer quality or other reasons, which may have negatively skewed our results. Furthermore, the size discrepancy may affect our conclusions if the DCD group is not sufficiently large enough to capture the variability and true outcomes of this population, as our results are limited to patients within the ECLS Registry. However, propensity score matching was performed to create comparable groups for analysis and to account for possible confounders. As this is a multicenter study, there is variability in procedures and policies between different institutions that limit the generalizability of our findings. For example, protocols for DCD transplants are variable and not provided by all centers in our study, particularly among the European centers, which constituted 31% of our DCD transplants. Other variables, such as the use of intraoperative ECLS, are subject to surgical decision-making without standardized guidelines that exist across centers. Ultimately, having this information would be beneficial to understand the rationale for ECLS use and aid in the interpretation of our results. As our study contains recent data, we do not have extended survival outcomes beyond 1 year, although patient data will continue to be collected over a 5-year period for future study. Ultimately, further long-term follow-up is needed to validate optimal DCD utilization.

Conclusion

In this multicenter international study, we demonstrated excellent 90-day survival among DCD and DBD recipients, although survival was relatively lower among DCD recipients. Rates of survival were similar among patients with and without the use of EVLP. Our findings support the use of strategies, such as DCD and EVLP, to address the donor organ shortage and increase access to LT globally.

Author Contributions

M.A.K., G.L., D.V.R., and M.H. were responsible for the inception and planning of the study. M.A.K., G.L., D.V.R., and M.H. gathered and reviewed data to confirm accuracy and integrity. H.C., M.W., and H.Z. ran statistical analysis on data and interpreted results. All authors critically revised and approved the final manuscript for publication. All authors made significant contributions to the final manuscript and accepted accountability for the submitted work.

Disclosure statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Fabio Ius reports a relationship with Biotest AG that includes consulting or advisory and funding grants. Gabriel Loor reports a relationship with TransMedics Inc. that includes consulting or advisory and funding grants. Gabriel Loor reports a relationship with AbioMed Inc. that includes consulting or advisory and funding grants. Gabriel Loor reports a relationship with AtriCure Inc. that includes funding grants. Gabriel Loor reports a relationship with JLH foundation that includes funding grants. Gabriel Loor reports a relationship with the American Association for Thoracic Surgery that includes funding grants. Gabriel Loor reports a relationship with Baylor College of Medicine that includes funding grants. Matthew Hartwig reports a relationship with CSL Behring that includes consulting or advisory. Matthew Hartwig reports a relationship with Intuitive Surgical Inc. that includes consulting or advisory. Matthew Hartwig reports a relationship with Biomed Innovations that includes funding grants. Gabriel Loor reports a relationship with Noon Endowment that includes funding grants. Matthew Hartwig reports a relationship with Paragonix Technologies, Inc. that includes funding grants. Matthew Hartwig reports a relationship with TransMedics Inc. that includes funding grants. Matthew Hartwig reports a relationship with Lung Bioengineering that includes funding grants. Arne Neyrinck reports a relationship with XVIVO that includes speaking and lecture fees. Yoshiya Toyoda reports a relationship with TransMedics Inc. that includes funding grants. Yoshiya Toyoda reports a relationship with Cerus Corporation that includes funding grants. Yoshiya Toyoda reports a relationship with EvaHeart Inc. that includes

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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.2024.100132.

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