Effect of mode of intraoperative support on primary graft dysfunction after lung transplant

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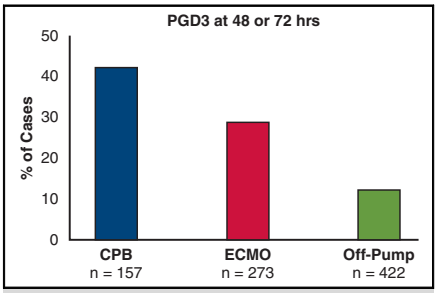
ABSTRACT

Objective: To clarify the relationship between the use of extracorporeal life support during lung transplantation and severe primary graft dysfunction (PGD), we developed and analyzed a novel multicenter international registry.

Methods: The Extracorporeal Life Support in Lung Transplantation Registry includes double-lung transplants performed at 8 high-volume centers (>40/year). Multiorgan transplants were excluded. We defined severe PGD as grade 3 PGD (PGD3) observed 48 or 72 hours after reperfusion. Modes of support were no extracorporeal life support (off-pump), extracorporeal membrane oxygenation (ECMO), and cardiopulmonary bypass (CPB). To assess the association between mode of support and PGD3, we adjusted for demographic and intraoperative factors with a stepwise, mixed selection, multivariable regression model, ending with 10 covariates in the final model.

Results: We analyzed 852 transplants performed between January 2016 and March 2020: 422 (50%) off-pump, 273 (32%) ECMO, and 157 (18%) CPB cases. PGD3 rates at time point 48-72 were 12.1% (51 out of 422) for off-pump, 28.9% for ECMO (79 out of 273), and 42.7% (67 out of 157) for CPB. The adjusted model resulted in the following risk profile for PGD3: CPB versus ECMO odds ratio, 1.89 (95% CI, 1.05-3.41; $P = .033$), CPB versus off-pump odds ratio, 4.24 (95% CI, 2.24-8.04; $P < .001$), and ECMO versus off-pump odds ratio, 2.24 (95% CI, 1.38-3.65; $P = .001$).

Conclusions: Venoarterial ECMO is increasingly used at high-volume centers to support complex transplant recipients during double-lung transplantation. This practice is associated with more risk of PGD3 than off-pump transplantation but less risk than CPB. When extracorporeal life support is required during lung transplantation, ECMO may be the preferable approach when feasible. (J Thorac Cardiovasc Surg 2022;■:1-11)



Univariate analysis of PGD rates by mode of intraoperative support.

CENTRAL MESSAGE

Off-pump LTx were associated with lower risk of PGD than ECLS-supported LTx in a multicenter registry analysis. When ECLS is required, ECMO may incur less risk of PGD than CPB does.

PERSPECTIVE

PGD remains the chief early threat to a successful lung transplant outcome. Among the few factors that clinicians can modify to reduce risk is the mode of intraoperative cardiopulmonary support. This study is the first effort by an international multicenter consortium of high-volume surgical practices to identify emerging patterns of intraoperative support and their effects on outcomes.

See Commentary on page XXX.

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Abbreviations and Acronyms

CPB = cardiopulmonary bypass
ECLS = extracorporeal life support
ECMO = extracorporeal membrane oxygenation
FEV1 = forced expiratory volume in 1 second
F_{IO_2} = fraction of inspired oxygen
LAS = lung allocation score
LTx = lung transplantation
PAP = pulmonary artery pressure
PGD = primary graft dysfunction

Scanning this QR code will take you to the table of contents to access supplementary information. To view the AATS Annual Meeting Webcast, see the URL next to the webcast thumbnail.

Primary graft dysfunction (PGD) is the most common source of morbidity after lung transplantation (LTx) and has been associated with the use of intraoperative extracorporeal life support (ECLS). However, this association has not been found consistently across single-center experiences.[1-4] ECLS practices vary across transplant centers and rely on individual surgeon preferences because only limited multicenter registry data are available to guide practice.

During LTx, the pneumonectomy and hilar exposure necessitate ventilatory or hemodynamic support strategies. The most common modes of support include no ECLS (off-pump) with single-lung ventilation and perfusion, and ECLS by either extracorporeal membrane oxygenation (ECMO) or cardiopulmonary bypass (CPB). CPB was associated with 15% greater absolute risk of PGD than off-pump in a Lung Transplant Outcomes Group analysis of risk factors for PGD.[5] Furthermore, PGD was associated with a 22% greater risk of 1-year mortality. Subsequent studies by single centers have provided further evidence that CPB is associated with elevated risk of PGD, bleeding, and mortality in lung transplant recipients.[4,6,7] Yet other studies have shown excellent outcomes with CPB, including favorable graft function and survival, even with higher-risk recipients and donors.[1,8-11]

ECMO has become a popular mode of intraoperative support because it can provide gas exchange and hemodynamic stability while reducing the amount of extracorporeal tubing and volume reservoir, which increase the risk of inflammation.[6,12] A study by Hoetzenecker and colleagues[3] showed remarkably low rates of PGD in LTx performed with routine use of venoarterial ECMO. Yet, a study by Ius and colleagues[13] showed a more complicated perioperative and early postoperative course in patients supported by intraoperative ECMO versus off-pump, with no difference in PGD rates. Other single-center experiences have demonstrated the benefits of ECMO over CPB in terms of postoperative lung function, bleeding, and survival, but several inconsistencies remain.[2,4,6,14]

To further investigate the effects of intraoperative mode of support on LTx outcomes, we established a multicenter international collaboration among 10 high-volume LTx centers to form the ECLS in LTx Registry. Data from this registry were analyzed to study the association between the mode of support and the incidence of grade 3 PGD (PGD3).

METHODS

Patient Population

The ECLS in LTx Registry was established to identify intraoperative factors associated with patient outcomes. The registry includes data from double-lung transplants performed at 10 high-volume centers (>40 LTx per year): 8 in the United States and 2 in Europe. Institutional review board approval was obtained at each contributing institution. Waiver of consent was granted for all retrospective case entries and some prospective entries. Consent was obtained for all other prospective case entries. The coordinating center (Baylor College of Medicine, Houston, Tex) institutional review board (No. H-41540, approved January 22, 2021) was shared with all sites as a template. Data were entered into an online Health Insurance Portability and Accountability Act-compliant database and analyzed at the coordinating center (Baylor College of Medicine). Data use and transfer agreements were signed by all participating centers.

The current analysis examined data from 8 of the 10 centers, which had already actively enrolled subjects for analysis (6 in the United States and 2 in Europe): Baylor College of Medicine, Duke University Health System (Durham, NC), Hannover Medical School (Hannover, Germany), Massachusetts General Hospital (Boston, Mass), University of Florida (Gainesville, Fla), University Hospitals Leuven (Leuven, Belgium), Temple University School of Medicine (Philadelphia, Pa), and University of Minnesota Medical School (Minneapolis, Minn).

Three forms of support were examined in a per-protocol fashion: off-pump, ECMO, and CPB. The ECMO group included both venovenous ECMO, which was used mostly for oxygenation or ventilatory support, and venoarterial ECMO used for oxygenation and ventilatory support, as well as hemodynamic support. The designation for the mode of support was based on the most invasive mode used in the case (CPB > ECMO > off-pump). For example, a case that started off-pump and converted to ECMO was designated as ECMO. A case that started on ECMO and converted to CPB was designated as CPB. Multiorgan and single-lung transplants were excluded. Recipient demographic characteristics and donor and intraoperative details were entered into the registry in a retrospective fashion. Data elements uploaded to the registry are regularly collected as part of patient care. No changes in clinical practice were initiated as a part of this study. Mode of support was chosen according to individual surgeon preference or program pathways. Through discussion at investigator meetings, we identified several tendencies related to support strategies before and throughout the conduct of the study. In general, programs that were accustomed to off-pump surgery used ECLS sparingly for hemodynamic or bleeding concerns. Programs accustomed to ECLS used CPB or ECMO more liberally to facilitate hemodynamic status, oxygenation, and exposure. Concerns about air, drainage, flows, exposure, or bleeding were general reasons for conversion from ECMO to CPB. In most cases performed through a sternotomy, CPB was used prophylactically. Some centers that preferentially used CPB gradually transitioned to ECMO over the course of the study. Pulmonary arterial hypertension was defined as mean

pulmonary artery pressure (PAP) by right heart catheterization >20 mm Hg, systolic PAP by echocardiography ≥40 mm Hg, or an established diagnosis of primary or secondary pulmonary hypertension.[15]

Outcomes

The primary outcome for this analysis was PGD, which was graded according to the 2016 International Society for Heart and Lung Transplantation guidelines. We defined severe PGD as PGD3 recorded at 48 or 72 hours after reperfusion. To maximize the consistency of PGD scoring, the coordinating center provided education on scoring in individual instructional sessions and by circulating examples of PGD grading. The data coordinating center reviewed all PGD grades and their data elements, including time of entry, Pao_2 values, oxygen saturations, and Pao_2 to inspired oxygen fraction (Fio_2) ratios. Select chest radiographs were interpreted by the coordinating center when needed in the event of incongruency in data entry or at the sites' request. Secondary outcomes included postoperative morbidity and mortality.

Statistics

Statistical software SAS version 9.4 (SAS Institute Inc) was used to analyze the ECLS registry data at the coordinating center. Descriptive analyses were applied for demographic variables and medical condition variables. Means and SDs were calculated for continuous variables; frequencies and percentages were calculated for categorical variables. Differences among types of support in demographic variables, medical variables, and outcomes were also tested. Continuous variables were tested with analysis of variance; categorical variables were tested with χ^2 tests or Fisher exact tests if at least 1 of the frequencies from the contingency table was <5.

We performed a multiple regression analysis to explore the effect of mode of support on PGD3, adjusting for demographic, medical, and intraoperative factors. For this analysis, we used the stepwise selection method, beginning with 21 covariates and ending with 10 covariates in the final model that were previously identified as donor or recipient risk factors for PGD: mode of support, recipient age, recipient body mass index, primary diagnosis, pulmonary hypertension, mean PAP, prior lung surgery (nontransplant), extended-criteria donor, donor ever smoked, and total ischemic time (Table E1).

Although multiple logistic regression was our prespecified primary analysis method for this study, we performed additional sensitivity analysis to test the results. To assess the effect of missing values in our data, modeling was conducted in both a case-complete fashion and by using multiple imputation by chained equations. Model coefficients were calculated and combined over 5 imputed datasets (Tables E2 and E3). Similar results were obtained from both methods. To account for multilevel clustering across centers, we also compared the postoperative outcomes associated with different modes of support groups by using a generalized estimating equation model (Table E4).

Finally, to provide an additional test to compare the effects of mode of support on PGD, we used propensity matching (Table E5). For this analysis, 1-to-1 matching without replacement by propensity score was performed by using the nearest neighbor method with a caliper of 0.012 SD of the logit to compare CPB with ECMO, and with a caliper of 0.025 SD of the logit to compare ECMO with off-pump. Matching was carried out with the psmatch2 package in STATA version 14 (STATA Corp, College Station, Tex). Balance in the baseline covariates of matched data was examined by using standardized mean differences. We compared the postoperative variables between groups using a generalized estimating equation model. The standardized mean differences were reported.

RESULTS

Patient Population

We analyzed 852 LTx operations performed between January 2016 and March 2020: 422 (50%) off-pump, 273 (32%) ECMO, and 157 (18%) CPB cases (Figure 1). There were several demographic differences among the groups (Table 1). Compared with the ECLS group, the off-pump group had a greater percentage of patients with obstructive lung disease, a lower percentage of patients with pulmonary hypertension, and fewer patients hospitalized at the time of transplant, as well as no patients with preoperative ECMO. The off-pump group also had a lower mean recipient body mass index, lower mean PAP, lower forced expiratory volume in 1 second (FEV1), and lower lung allocation score (LAS) than either of the ECLS groups.

The distribution of primary diagnoses in the CPB and ECMO groups was similar, with restrictive lung disease being the most common diagnosis. Because of the small number of pulmonary vascular disease cases, these were grouped together with restrictive lung disease to facilitate the analysis. The number of patients with pulmonary vascular disease as the primary diagnosis was 12 (7.6%), 16 (5.9%), and 4 (0.1%) for the CPB, ECMO, and off-pump groups, respectively. The number of patients with severe pulmonary hypertension, defined as mean PAP ≥40 mm Hg, was 42 (26.9%), 50 (20.2%), and 16 (4.5%) for the CPB, ECMO, and off-pump groups, respectively. A detailed breakdown of pulmonary hypertension cases is provided in Table E6.

Compared with the other groups (CPB and off-pump), the ECMO group had the highest mean LAS, the largest proportion of patients hospitalized, and the largest proportion of patients on life support and ECMO at the time of transplant. This suggests that on average, the recipients requiring ECMO were more critically ill than the other groups. The CPB group had a greater percentage of patients with pulmonary hypertension and a slightly greater mean PAP than the

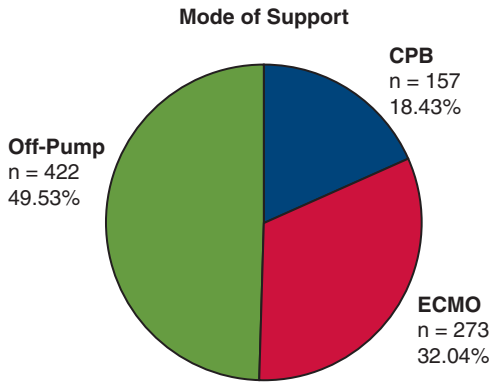


FIGURE 1. The study cohort comprises 852 patients who underwent lung transplant operations between January 2016 and March 2020 across 8 centers (6 in the United States and 2 in Europe). The figure shows the distribution of frequencies for each mode of support used during the operation. *Off-pump*, Single-lung ventilation and perfusion without extracorporeal life support; *CPB*, cardiopulmonary bypass; *ECMO*, extracorporeal membrane oxygenation.

TABLE 1. Recipient, donor, and operative characteristics associated with the mode of intraoperative support during lung transplantation

Variable	CPB (n = 157)	ECMO (n = 273)	Off-pump (n = 422)	*P* value
Recipient characteristics				
Primary diagnosis (n = 852)				<.001
Obstructive lung disease	32 (20.4)	58 (21.2)	201 (47.6)	
Cystic fibrosis	25 (15.9)	48 (17.6)	69 (16.4)	
Restrictive lung disease	100 (63.7)	167 (61.2)	152 (36.0)	
Sex (n = 852)				.312
Male	87 (55.4)	161 (59.0)	224 (53.1)	
Female	70 (44.6)	112 (41.0)	198 (46.9)	
Age (y) (n = 852)	53.9 ± 14.8	53.6 ± 14.5	54.9 ± 13.4	.449
BMI (n = 851)	25.3 ± 5.4	25.1 ± 4.6	23.7 ± 4.2	<.001
Condition at transplant, hospitalized (n = 851)	30 (19.1)	78 (28.6)	37 (8.8)	<.001
Pulmonary hypertension* (n = 850)	130 (82.8)	196 (72.1)	267 (63.4)	<.001
Mean PAP (mm Hg) (n = 759)	31.8 ± 13.3	30.9 ± 15.3	24.9 ± 8.3	<.001
Lung allocation score (n = 852)	47.8 ± 15.7	50.2 ± 18.6	39.4 ± 11.4	<.001
FEV1 (L) before transplant (n = 638)	1.3 ± 0.7	1.3 ± 0.7	1.0 ± 0.7	<.001
FEV1 % predicted before transplant (n = 637)	38.5 ± 20.2	41.5 ± 20.6	31.1 ± 18.0	<.001
Life support before transplant (n = 851)	15 (9.6)	44 (16.1)	35 (8.3)	.005
Preoperative ECMO	7 (4.5)	32 (11.7)	0 (0.0)	<.001
Prior cardiac surgery (n = 792)	7 (4.8)	9 (3.4)	14 (3.7)	.755
Prior lung surgery (nontransplant) (n = 794)	21 (14.5)	40 (15.0)	68 (17.8)	.533
Previous lung transplant (n = 851)	5 (3.2)	7 (2.6)	9 (2.1)	.765
Prior pleurodesis (n = 793)	9 (6.2)	10 (3.8)	11 (2.9)	.202
Chronic steroid use† (n = 743)	38 (38.8)	121 (46.0)	158 (41.4)	.355
Donor characteristics				
Donor age (y) (n = 852)	35.5 ± 13.1	38.5 ± 14.9	41.7 ± 15.6	<.001
Donor sex (n = 852)				.932
Male	91 (58.0)	158 (57.9)	239 (56.6)	
Female	66 (42.0)	115 (42.1)	183 (43.4)	
Extended-criteria donor‡ (n = 807)	90 (60.8)	166 (62.2)	233 (59.4)	.779
Donor ever smoked (n = 774)	71 (50.0)	114 (43.9)	147 (39.5)	.093
Donor type (n = 852)				.818
DBD	143 (91.1)	246 (90.1)	377 (89.3)	
DCD	14 (8.9)	27 (9.9)	45 (10.7)	
Last PF ratio (n = 764)	450.0 ± 85.2	423.8 ± 93.4	410.7 ± 94.7	<.001
EVLP (n = 852)	7 (4.5)	30 (11.0)	24 (5.7)	.010
Operative characteristics				
ECMO type (n = 271)				
VV		36 (13.3)		
VA/VVA		235 (86.7)		
Total ischemic time (min) (n = 849)	358.8 ± 126.1	450.2 ± 137.4	439.8 ± 117.8	<.001

Values are presented as n (%) or mean ± standard deviation. Under primary diagnosis, restrictive lung disease represents a composite of restrictive lung disease and pulmonary vascular disease. This was done to facilitate the analysis because of the small number of primary pulmonary hypertension cases (see Table E6). *CPB*, Cardiopulmonary bypass; *ECMO*, extracorporeal membrane oxygenation; *BMI*, body mass index; *PAP*, pulmonary artery pressure; *FEV1*, forced expiratory volume in 1 second; *DBD*, donor after brain death; *DCD*, donor after circulatory death; *PF*, final Pao_2 to inspired oxygen fraction ratio in the donor before procurement; *EVLP*, ex vivo lung perfusion; *VA*, venoarterial; *VV*, venovenous; *VVA*, venovenous-arterial. *Mean PAP by right heart catheterization >20 mm Hg, systolic PAP by echocardiography ≥40 mm Hg, or a diagnosis of pulmonary hypertension. †Steroids ≥5 mg for >2 weeks. ‡Extended-criteria donors had 1 or more of the following characteristics: age >55 y, anticipated ischemic time >6 hours, Pao_2 to inspired oxygen fraction ratio <300, >20 pack-years smoking, DCD, or abnormal chest radiograph.

ECMO group. Other recipient complexities such as prior cardiac surgery, lung surgery, pleurodesis, and chronic steroid use were evenly distributed between all 3 groups.

Donor and Operative Characteristics

Several differences in donor characteristics were noted among support strategies (Table 1). The off-pump group had a higher mean donor age and lower mean donor Pao_2:Fio_2 ratio than the CPB or ECMO groups. ECMO cases had a greater mean donor age and a lower mean donor Pao_2:Fio_2 ratio than CPB cases. There was no difference among the groups in the proportion of extended-criteria donors, probably because of variability in the interpretation of abnormal radiographic findings. LTx from donors after circulatory death was fairly evenly distributed across modes of support.

Table E7 shows the breakdown of modes of support by center. There was substantial variation in the use of support between centers, with a range of 0% to 67% for CPB, 19.7% to 73% for ECMO, and 0% to 78.6% for off-pump.

Right-to-left ECMO support with either venoarterial or venoveno-arterial configuration was used in the majority of ECMO cases. Venovenous ECMO was the only form of ECMO used intraoperatively in 13.2% of ECMO cases (36 out of 271). We noted variability among centers in the percentage of ECMO cases that used venovenous ECMO, with a range of 0% to 45.7% (Table E8).

Primary Outcome = PGD

PGD3 occurred at 48 to 72 hours in 12.1% of off-pump cases, 28.9% of ECMO cases, and 42.7% of CPB cases (Figure 2). When multiple regression analysis was used to adjust for covariates, the adjusted odds ratio (OR) of developing severe PGD depending on the mode of support was 4.24 for CPB versus off-pump (95% CI, 2.24-8.04; $P < .001$), 2.24 for ECMO versus off-pump (95% CI, 1.38-3.65; $P = .001$), and 1.89 for CPB versus ECMO (95% CI, 1.05-3.41; $P = .033$) (Table 2). Thus, ECMO was associated with a lower risk of severe PGD than CPB was, but the risk was greater with ECMO than with off-pump surgery.

To confirm these results, we performed additional sensitivity analyses using multiple imputation, multilevel clustering at the center level, and propensity matching (Tables E2-E5). Multiple imputation showed that the results were consistent after adjusting for missing data. The rates of PGD3 reported across sites ranged from 8% to 40% (Table E7). Multilevel cluster analysis produced similar findings with the exception of the loss of significance for CPB versus ECMO (OR, 1.8; 95% CI, 0.92-3.47; $P = .09$). We then compared 100 propensity-matched pairs of patients supported with CPB or ECMO. The odds ratio for developing PGD3 at 48 to 72 hours for CPB versus ECMO in this matched analysis was 1.58 (95% CI, 1.01-2.48; $P = .045$). We also compared 171 propensity-matched pairs of patients supported with ECMO or an off-pump strategy. The odds ratio for developing PGD3 at 48 to 72 hours for ECMO versus off-pump in this matched analysis was 1.81 (95% CI, 1.18-2.78; $P = .007$).

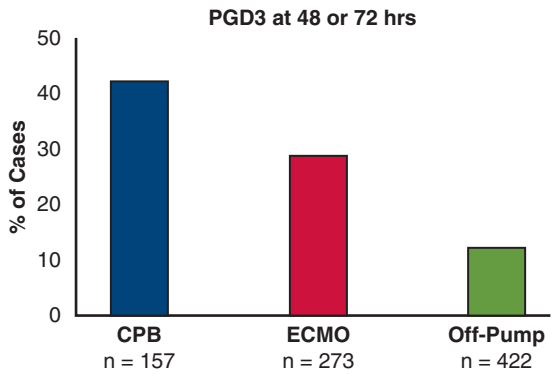


FIGURE 2. Univariate analysis comparing grade 3 primary graft dysfunction (*PGD3*) rates 48 to 72 hours after lung transplant reperfusion associated with the mode of support used during the operation. *CPB*, Cardiopulmonary bypass; *ECMO*, extracorporeal membrane oxygenation; *Off-pump*, single-lung ventilation without extracorporeal life support.

Secondary Outcomes

As a secondary unadjusted analysis, we assessed the occurrence of different clinical outcomes according to the mode of support used for the LTx procedure (Table 3). Patients who underwent off-pump LTx had the lowest morbidity rate, the shortest postoperative length of stay, and the best in-hospital and 1-year survival rates. Among the 594 patients for whom we had 1-year survival data, the 1-year survival rates were 91%, 84%, and 84% for the off-pump, ECMO, and CPB groups, respectively ($P = .037$). When compared with CPB patients, ECMO patients had less PGD3 within 72 hours, fewer reintubations and tracheostomies, slightly more postoperative ECMO, longer length of hospital stay, and similar survival. The frequency of PGD2 or PGD3 at 48 to 72 hours after reperfusion was 74.5% (114 out of 157), 49.5% (135 out of 273), and 32.7% (138 out of 422) for the CPB, ECMO, and off-pump groups, respectively.

DISCUSSION

Evidence suggests that PGD in LTx is associated with the use of CPB, but the relative effects of other modes of intraoperative support are unclear.[1-7] The current study provides the first large, international, multicenter analysis of the association of mode of intraoperative support with PGD. Our key findings were that use of any ECLS was associated with an elevated risk of PGD3 at 48 to 72 hours after LTx and that CPB was associated with greater risk than ECMO.

In this novel registry, the breakdown of cases suggests that ECLS plays a major role in the intraoperative support of patients undergoing LTx. As expected, the off-pump approach was used in lower-risk recipients with less pulmonary hypertension than ECLS was. Surprisingly, 63% of the off-pump patients had pulmonary hypertension related to their underlying parenchymal disease, which suggests that pulmonary hypertension alone does not necessitate ECLS. The decision to support such patients may depend on other factors, such as the degree of pulmonary hypertension and intraoperative right ventricular function. Also, the off-pump cases had the lowest mean FEV1 at baseline, suggesting the feasibility of this approach for adequate intraoperative gas exchange even in patients with advanced contralateral lung dysfunction. However, the lower FEV1 probably reflects obstructive lung disease, which is

TABLE 2. Adjusted logistic regression analysis of the association of mode of support used during lung transplantation on grade 3 pulmonary graft dysfunction at 48 to 72 hours

Mode of support	Odds ratio	95% CI	*P* value
CPB vs ECMO	1.89	1.05-3.41	.033
CPB vs off-pump	4.24	2.24-8.04	<.001
ECMO vs off-pump	2.24	1.38-3.65	.001
Recipient age	0.98	0.96-1.00	.065
BMI	1.07	1.01-1.13	.020
Primary diagnosis (cystic fibrosis vs restrictive)	0.75	0.42-1.36	.35
Primary diagnosis (obstructive vs restrictive)	0.91	0.61-1.38	.67
Pulmonary hypertension*	0.96	0.71-1.29	.79
Mean PAP	1.02	1.01-1.04	.01
Prior lung surgery	1.37	1.05-1.78	.02
ECD	1.16	0.93-1.46	.18
Ever smoked	1.18	0.95-1.46	.13
Total ischemic time	1.002	1.000-1.003	.063

Multivariate model adjusted for mode of support, recipient age, recipient body mass index (BMI), primary diagnosis, pulmonary hypertension*, mean pulmonary artery pressure (PAP), prior lung surgery (nontransplant), extended-criteria donor (ECD), donor ever smoked, and total ischemic time. The restrictive diagnosis group is a composite of restrictive lung disease and pulmonary vascular disease. *CPB*, Cardiopulmonary bypass; *ECMO*, extracorporeal membrane oxygenation. *Mean PAP by right heart catheterization >20 mm Hg, systolic PAP by echocardiography ≥40 mm Hg, or a diagnosis of pulmonary hypertension.

ADULT

traditionally associated with sufficient oxygenation during off-pump cases. Although we did not have complete data related to ventilation and perfusion distribution between native lungs, typically, off-pump LTx begins with ventilating and perfusing the lung with the best perfusion on ventilation/perfusion scan and follows with ventilating and perfusing the newly implanted donor lung. In this regard, it was also surprising that the average donor Pao_2:FIo_2 ratio was lowest in the off-pump group. Collectively, these findings suggest that off-pump lung transplant can be feasible in a variety of scenarios.

Notably, off-pump strategies were used in selected redo lung transplants and patients with prior pleurodesis, prior cardiac surgery, and prior lung surgery at a frequency similar to that seen in ECLS cases. Similarly, the off-pump group had a higher mean donor age than the ECLS group. Off-pump patients had a longer mean total ischemic time than CPB patients but not ECMO patients. These recipient and donor complexities are often used to justify the use of ECLS. Thus, the modes of support recorded in the ECLS in LTx Registry suggest that in some but not all cases, off-pump and ECLS would have been equally acceptable choices.

Analysis of recipient demographic characteristics and medical conditions showed what may have been a tendency to select CPB over ECMO for patients with pulmonary hypertension. The similar mean PAP between these 2 groups suggests that ECMO was perceived as a feasible option for patients with pulmonary hypertension. Most of the ECMO cases were venoarterial rather than venovenous, probably because of the additional hemodynamic support that venoarterial ECMO provides, concerns about pulmonary hypertension, and concern about right ventricular strain while the PA is clamped on the first side. Interestingly, the ECMO group had the sickest patients, as evidenced by the highest mean LAS score, greatest number of patients on preoperative ECMO, and greatest percentage of patients hospitalized and on life support before transplant. In addition, the ECMO group had higher-risk donor features than the CPB group, including greater donor age, lower donor final Pao_2:FIo_2 ratios, longer ischemic time, and twice as much use of ex vivo lung perfusion. These findings suggest that ECMO is playing an increasing role in the intraoperative management of complex patients undergoing LTx.

The most significant and novel finding in this study was that, after we controlled for multiple covariates, the OR for developing PGD3 within 48-72 hours was greater for ECMO versus off-pump (OR, 2.24; 95% CI, 1.38-3.65; $P = .001$), CPB versus off-pump (OR, 4.24; 95% CI, 2.24-8.04; $P < .001$), and CPB versus ECMO patients

TABLE 3. Outcomes associated with the mode of support used during lung transplantation

Outcome	CPB (n = 157)	ECMO (n = 273)	Off-pump (n = 422)	*P* value
PGD3 within 72 h* (n = 852)	101 (64.3)	127 (46.5)	95 (22.5)	<.001
Reintubated (n = 730)	32 (34.4)	51 (19.8)	51 (13.5)	<.001
Tracheostomy (n = 793)	40 (27.6)	54 (20.3)	37 (9.7)	<.001
Postoperative ECMO (n = 804)	34 (22.2)	65 (24.3)	16 (4.2)	<.001
Death in 90 d (n = 812)	13 (8.5)	23 (9.0)	16 (4.0)	.020
Death before discharge (n = 823)	13 (8.6)	23 (8.8)	13 (3.2)	.004
Death in 1 y (n = 594)	21 (16.4)	28 (15.7)	26 (9.0)	.037
Postoperative LOS (n = 848)	34.3 ± 33.3	38.2 ± 46.1	27.8 ± 23.7	<.001

Values are presented as n (%) or mean ± SD. *CPB*, Cardiopulmonary bypass; *ECMO*, extracorporeal membrane oxygenation; *PGD3*, grade 3 primary graft dysfunction; *LOS*, length of stay. *Time point 0 to 72 hours.

(OR, 1.89; 95% CI, 1.05-3.41; $P = .033$). This suggests a stepwise increase in the risk of PGD proportional to the degree of support, with ECMO being the middle ground between off-pump and CPB. The mechanism for this distribution of risk may be related to inflammatory activation caused by the ECLS circuits.[16] Theoretically, ECMO provokes less inflammatory activation than CPB—and thus less risk of PGD—because of the shorter tubing lengths, heparin-coated circuit, centrifugal pump, durable oxygenators, and lack of a volume reservoir.[12] Supporting this theory are several reports of greater adverse graft-related and systemic effects associated with CPB use during LTx compared with ECMO or off-pump surgery.[4-7,14] Another potential explanation for the increased PGD risk with mechanical support in general may come from the unpredictability of blood flow to the newly implanted lung. Most centers will attempt to maintain pulsatility to the new lung after implantation. But, depending on flows and drainage, there could conceivably be relative warm ischemia to the new lung while on CPB. This is less likely, albeit possible, with ECMO as well. On the other hand, a study by Hartwig and colleagues[17] failed to show an effect of time of ECLS on PGD3 at 48 to 72 hours. We would expect that if the newly implanted lung were subjected to warm ischemia during ECLS, then the duration of that support would influence the risk of PGD3, but that was not the case.

The group at the Medical University of Vienna routinely uses intraoperative ECMO for LTx[3,18] and argues that a standardized lung transplant approach and controlled reperfusion are beneficial. Indeed, our data appear to support the notion that even for higher-risk cases, ECMO is a safe and reasonable strategy for reducing PGD and improving postoperative outcomes. But our data do not support a uniform approach for the use of ECMO, which could increase ECLS-associated risks such as bleeding, neurologic complications, and vascular complications. Clarifying the risk associated with routine ECMO use would require a randomized controlled trial or a prospective study comparing ECMO with off-pump support strategies in well-matched, low-risk recipients. Moreover, there are clearly several scenarios in which CPB may be necessary, and there are many proponents of CPB who have been able to achieve good results with it after LTx.[1,2,8,19-21] But the current data suggest a heightened risk of postoperative graft dysfunction with CPB that should be weighed against the potential gains in each individual scenario.

An unexpected observation in the current multicenter analysis was that PGD rates were higher than those seen in prior reports on LTx. Whereas we observed an overall PGD3 rate of 23.1% at 48-72 hours, the Lung Transplant Outcomes Group report by Diamond and colleagues in 2012 showed a PGD3 rate of 16.8% at these time points.[5] There are several potential reasons for this difference, including our use of the updated 2016 International Society for Heart and Lung Transplantation scoring guidelines, which offer greater clarity around the grading of patients on noninvasive ventilation than the 2005 guidelines. A recent study by our group showed that the updated guidelines could increase detection of PGD by 42%.[22] In addition, intraoperative ECMO was not included in the LTOG analysis, and there could certainly be differences among patient populations. Substantial differences in PGD outcomes across studies are not uncommon and can be explained by differences in guidelines, the timing of blood gas collections, availability of oxygen saturation and blood gas data in extubated patients, differences in interpretation of chest radiograph results, and differences in ventilator-related parameters. For example, a study by Hoetzenecker and colleagues[3] showed a PGD3 rate of 1.3% at T72 hours, whereas a study by Divithotawela and coworkers[23] showed a PGD3 rate of 9.5% at T72 hours. Although PGD scoring may not enable a fair comparison of graft function across studies, it is an excellent tool for comparing PGD within groups in a single study.

Finally, we also observed a higher-than-expected rate of postoperative ECMO use that could not be entirely explained by preoperative ECMO use. The indications for postoperative ECMO use can vary substantially, from marginal oxygenation to prophylactic use, depending on center practices. The excellent 1-year survival outcomes would suggest that the postoperative practice patterns were appropriate, but specific indications for ECMO use and associated outcomes will require further study. The fact that CPB and ECMO cases had similar postoperative rates of ECMO use (22% and 24%) but different PGD3 rates at 48 to 72 hours was not entirely surprising. ECMO alone is not sufficient for a designation of PGD3 because it can be used prophylactically, in which case it is ungradable. Patients who are not on ECMO can have PGD3 even when extubated. And patients on postoperative ECMO can be decannulated before the 48- to 72-hour time frame. Thus, postoperative ECMO use alone is not necessarily indicative of graft function at 48 to 72 hours.

Limitations

A strength of the ECLS in LTx Registry is robust data entry from multiple high-volume centers, which has previously not been collectively evaluated for the purposes of understanding the effects of modes of support. On the other hand, there may be heterogeneity in practices that cannot be fully accounted for. Centers typically favor one intraoperative support strategy over the other. It is difficult to account for confounding variables that emerge from site-specific preferences in this regard. In addition, whereas elective versus urgent conversions to CPB have been suggested to be important for outcomes after lung transplant,[7] we were not able to stratify patients according to urgency of ECLS use in this study because data regarding planned versus

unplanned conversions were missing for many patients. In recent years, the use of intraoperative ECLS has evolved from a last resort to a more prophylactic approach, making it difficult to determine whether a conversion was planned or unplanned. Understanding the risk associated with the urgency of conversion would require a strict prospective study design with real-time data capture and clear definitions for planned and unplanned conversions.

Furthermore, this is a nonrandomized, observational outcomes registry study, and such studies are always subject to confounders that could bias the results, because surgeons must use their best judgment on a case-by-case basis to choose the best mode of support. For instance, we noted baseline differences between our patient groups, such as lower-risk recipient features in the off-pump group compared with the others. To account for such differences, we considered several options, including propensity score matching. Ultimately, we used a multivariate regression model in this first analysis of the ECLS in LTx registry to avoid discarding substantial amounts of potentially important observations.[24] Future studies that seek to explore differences in more evenly matched groups are being considered by the ECLS in LTx steering committee.

The results of sensitivity analysis—that is, the imputational model, center level cluster analysis, and propensity-matched analysis—generally support the findings of the multivariate logistic model. However, they also temper the conclusion that the risk of PGD with CPB is different than with ECMO, for 2 reasons. First, the analysis for clustering at the center level failed to show a statistical difference for PGD3 at 48 to 72 hours between CPB and ECMO. Also, the propensity-matched analysis showed only a marginal difference between CPB and ECMO in terms of PGD3 at 48 to 72 hours ($P = .045$). Of note, the current analysis was underpowered to detect a difference between matched pairs of CPB versus ECMO cases. A sample size of 371 CPB and 742 ECMO patients would be needed to provide 80% power to detect a statistically significant difference with a 2-sided $\alpha = 0.0167$ and a 1:2 enrollment ratio. Thus, we conclude that differences in the incidence of PGD3 between CPB and ECMO may be clinically important, although this retrospective analysis is underpowered to show statistical significance.

The current study is also limited to observations made in the first postoperative year and therefore provides no data regarding the effects of mode of support on long-term graft function. Also, the inclusion criteria of centers performing >40 LTx per year could limit the generalizability of our findings. Although we believe our findings could help centers improve results related to PGD, we recommend that centers continue to review their own results and protocols to decide on best practices. Finally, this study had PGD3 as the primary end point. Although contributors to the registry receive extensive education on PGD grading, interrater variability is still possible. The potential for inconsistencies in PGD scoring was further reduced by having the raw data used for PGD scoring sent to the coordinating center along with the

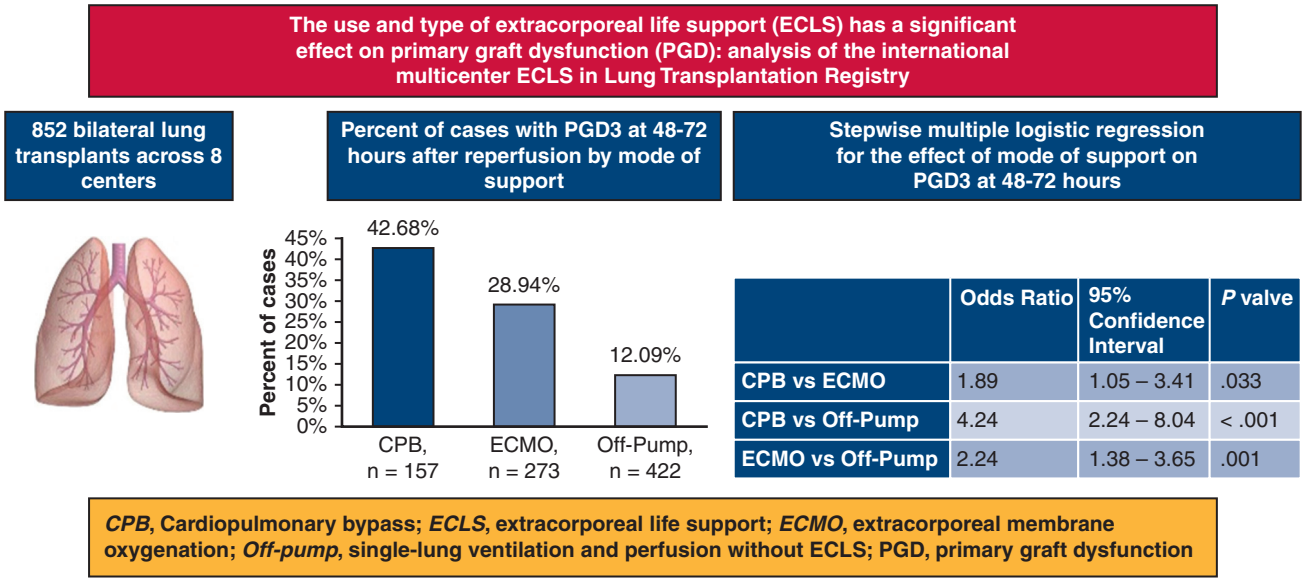
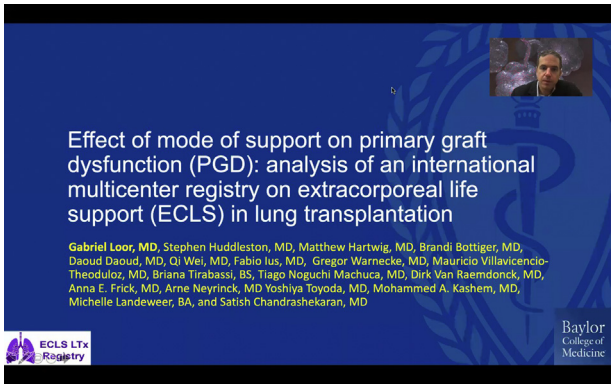


FIGURE 3. Summary of the general study design and results of this investigation. The cohort comprises 852 patients who underwent lung transplant operations between January 2016 and March 2020 across 8 centers (6 in the United States and 2 in Europe). A univariate analysis was performed to compare grade 3 primary graft dysfunction (*PGD3*) rates 48 to 72 hours after lung transplant reperfusion by the mode of support used during the operation. A stepwise multiple logistic regression adjusting for 10 covariates in the final model suggested that both cardiopulmonary bypass (*CPB*) and extracorporeal membrane oxygenation (*ECMO*) are associated with greater risk of PGD3 than using single-lung ventilation and perfusion without extracorporeal life support (*ECLS*) (off-pump) strategy, but the risk may be greater with CPB than with ECMO.



VIDEO 1. Dr Gabriel Loor, first author and surgical director of the lung transplant program at Baylor College of Medicine, describes the study design, results, and significance of the study analyzing the association between mode of intraoperative support during lung transplantation and primary graft dysfunction. Video available at: https://www.jtcvs.org/article/S0022-5223(22)00119-2/fulltext.

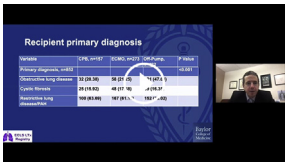
final score. Other outcomes are presented as observations without control for potentially confounding factors.

CONCLUSIONS

The results of this registry analysis suggest that ECMO plays an important role in the intraoperative support of complex patients undergoing double-LTx, with outcomes that are at least as good as, if not superior to, those of CPB (Figure 3 and Video 1). Cases performed off-pump were associated with the lowest risk of severe PGD and the least morbidity. Our findings suggest that for LTx procedures, an off-pump strategy should be the first choice when the surgeon believes it is safe and feasible. In cases in which ECLS use is preferable, the choice of ECMO over CPB when feasible may reduce the risk of severe PGD.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://aats.blob.core.windows.net/media/Publications/AM21_TH14%20-%20Lung%20Transplant.mp4-Webcast%20(presentation).mp4.



Conflict of Interest Statement

Dr Loor is on an advisory board for Impella and receives institutional grant support from Maquet, Transmedics, and Medtronic. All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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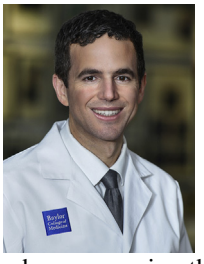
Key Words: cardiopulmonary bypass, extracorporeal life support, extracorporeal membrane oxygenation, lung transplantation, outcomes, primary graft dysfunction

Discussion

Presenter: Dr Gabriel Loor

Dr Stephanie Chang (*New York, NY*). Thank you very much, Dr Loor. That was a very nice registry analysis. I think overall it shows results that are consistent with data showing that bypass has more inflammation and higher rates of primary graft dysfunction (PGD) compared with extracorporeal membrane oxygenation (ECMO). However, some other data are contrary to some other papers. One study in 2020 evaluating lung transplants performed on ECMO showed only a 4% PGD rate. What do you think the difference is between the other study and your study, which showed a significantly higher rate of PGD?



Dr Gabriel Loor (*Houston, Tex*). That's a great question, Dr Chang. Thank you. The data I think you're citing is a single-center experience and that was kind of the impetus behind putting together all the centers for the current analysis. Honestly, I don't put 100% stock in the actual rate of PGD when comparing them across studies but rather, I see value in the use of PGD rates as a benchmark to assess interventions within your own individual analysis.

There is, especially when you get into extubated patients, some variability in how PGD is graded. And we certainly had strict guidelines here and all the centers went through virtual workshops on how we were going to grade PGD in this particular analysis and so those were the rates that we saw. I think in some ways it's consistent, though, with the data from prior single center analyses in that it did show that ECMO reduces the risk.

You saw that in this international registry there was a tendency to use ECMO for very complex scenarios, almost exclusively in many instances. The ECMO cohort had increased risk donors and recipients, and yet despite that the rate of PGD was actually lower than we would expect when we compared it with some of the other groups. So, I think it's consistent, although the final verdict remains to be determined.

Dr Chang. For these cases, were they all done through thoracotomy/clamshell versus sternotomy because that also can influence bypass use?

Dr Loor. Yes. The majority, but not all, of the cases that were done through sternotomy were cardiopulmonary bypass cases. Not all cardiopulmonary bypass cases necessarily used sternotomy. We do have the breakdown of that. It was fairly, evenly distributed with the notable exception that sternotomy cases were seen almost exclusively in cardiopulmonary bypass.

Dr Chang. Okay. So, it was roughly 50%. How many were done through sternotomy?

Dr Loor. I would say that the sternotomy was more like 30%. It was a slightly lower amount than the number of cases done through cardiopulmonary bypass.

Dr Chang. I don't know if you guys did a subset analysis, but if so, did you ever look at if you exclude ECMO bridge to transplant, and you have a standard idiopathic pulmonary fibrosis or pulmonary hypertension patient who comes from home for transplant, is it still the same risk of PGD for them? Those data will help influence the decision that surgeons will be making. If someone is ECMO bridge to transplant, they will stay on ECMO or be converted to bypass, with a higher rate of PGD. But what do you think that data regarding support for non-ECMO bridge lung transplant patients would or did show?

Dr Loor. I completely agree with you. You have a choice. You can take the effort to stay off, or just make it easier and stay on or go on venoarterial support and that choice depends on the answer to your question. We have not specifically looked at that just yet. That wasn't a part of this particular predetermined statistical methodology. But we do have centers that are asking that specific question right now. We may be able to get to that answer perhaps with propensity match populations looking specifically at idiopathic pulmonary fibrosis, controlling for their pulmonary hypertension. I don't know what the answer to that is going to be. But I suspect that it will perhaps be no better, may be no worse. It's hard to say.

Dr Chang. Okay. Last question and I'll let you go. In cardiopulmonary bypass, while there are pump suckers

for bleeding, patients are therapeutically anticoagulating on full heparinization so there is the risk of increased bleeding or needing more blood products. Was there a difference in amount of blood transfusion or fluid overload between the 3 groups, and could that contribute to the PGD rate?

Dr Loor. Yes. So, we do have an analysis ongoing on the risk of transfusion and PGD and that's interesting data that I can't completely speak to just yet. I will say for sure that the cardiopulmonary bypass group had more transfusions than the off-pump group and not astronomically more than the ECMO group per se.

And the nice thing about this registry is that it included a lot of sites and some of the sites actually use cardiopulmonary bypass prophylactically not just in emergency scenarios. They just use it for all cases. Thus, it's not like all cardiopulmonary bypass cases were done with massive transfusions. Not at all, in fact the massive transfusion cases were the outliers and the exception rather than the rule for either of the groups. But I do agree with you, certainly fluid and blood product use could contribute to any graft outcomes.

Dr Chang. Thank you very much. It was a wonderful study and I appreciate your time.

TABLE E1. Adjusted logistic regression analysis for effect of mode of support on severe primary graft dysfunction (PGD) (PGD3 at 48-72 hours after reperfusion). The model considered 20 initial variables in addition to mode of support. Logistic regression with stepwise selection yielded 10 covariates in the final model

Initial covariates	Final model
Mode of support (off-pump, CPB, ECMO)	Mode of support (off-pump, CPB, ECMO)
Recipient age	Recipient age
Recipient BMI	Recipient BMI
LAS at time of transplant	Primary diagnosis*
Mean PAP	Pulmonary hypertension†
Primary diagnosis*	Mean PAP
Medical condition at time of transplant	Prior lung surgery (non-transplant)
Prior lung surgery (non-transplant)	ECD§
Prior cardiac surgery	Donor ever smoked
Prior lung transplantation	Total ischemic time
Prior pleurodesis	
Pulmonary hypertension†	
Chronic steroid use‡	
Donor age	
Last donor PF ratio before procurement	
Total ischemic time	
Donor sex	
ECD§	
Donor type (DBD vs DCD)	
Donor ever smoked	
EVLP	

CPB, Cardiopulmonary bypass; *ECMO*, extracorporeal membrane oxygenation; *BMI*, body mass index; *LAS*, lung allocation score; *PAP*, pulmonary artery pressure; *PF*, Pao_2 to inspired oxygen fraction ratio in the donor before procurement; *ECD*, extended-criteria donor; *DBD*, donor after brain death; *DCD*, donor after circulatory death; *EVLP*, ex vivo lung perfusion. *Primary diagnosis includes obstructive lung disease, cystic fibrosis, and a composite of pulmonary vascular disease and restrictive lung disease. †Mean PAP by right heart catheterization >20 mm Hg, systolic PAP by echocardiography ≥40 mm Hg, or a diagnosis of pulmonary hypertension. ‡Steroids ≥5 mg for >2 weeks. §ECDs had 1 or more of the following risk factors: age >55 years, anticipated ischemic time >6 hours, Pao_2 to inspired oxygen fraction ratio <300, >20 pack-years smoking, DCD, and abnormal chest radiograph.

TABLE E2. Multiple imputation analysis

Variable	N	No missing	Missing rates (%)
Missing rate			
PGD3 in 48-72 h	853	0	0.0
Recipient age	853	0	0.0
BMI	851	2	0.2
PHTN*	851	2	0.2
Mean PAP	759	94	11.0
Total ischemic time	791	62	7.3
Mode of support	852	1	0.1
Primary diagnosis	853	0	0.0
Prior lung surgery	795	58	6.8
ECD	808	45	5.3
Ever smoked	775	78	9.1
After multiple imputation			
PGD3 in 48-72 h	853	0	0.0
Recipient age	853	0	0.0
BMI	853	0	0.0
PHTN*	853	0	0.0
Mean PAP	853	0	0.0
Total ischemic time	853	0	0.0
Mode of support	853	0	0.0
Primary diagnosis	853	0	0.0
Prior lung surgery	853	0	0.0
ECD	853	0	0.0
Ever smoked	853	0	0.0

PGD3, Grade 3 primary graft dysfunction; *BMI*, body mass index; *PHTN*, pulmonary hypertension; *PAP*, pulmonary artery pressure; *ECD*, extended-criteria donor. *Mean pulmonary artery pressure by right heart catheterization >20 mm Hg, systolic pulmonary artery pressure by echocardiography ≥40 mm Hg, or a diagnosis of pulmonary hypertension.

TABLE E3. Model results (after multiple imputation)

Parameter	Odds ratio	95% CI	*P* value
Mode (CPB vs ECMO)	1.960	1.241-3.096	.004
Mode (CPB vs off-pump)	4.015	2.466-6.535	<.0001
Mode (ECMO vs off-pump)	2.048	1.332-3.149	.001
Recipient age	0.987	0.970-1.004	.142
BMI	1.071	1.023-1.121	.004
Primary diagnosis (cystic fibrosis vs restrictive)	0.615	0.296-1.277	.192
Primary diagnosis (obstructive vs restrictive)	0.560	0.359-0.872	.010
PHTN*	0.909	0.566-1.459	.693
Mean PAP	1.022	1.006-1.039	.007
Prior lung surgery	1.622	1.019-2.583	.042
ECD	1.425	0.978-2.077	.065
Ever smoked	1.307	0.814-2.099	.255
Total ischemic time	1.001	0.999-1.002	.355

Multivariate model adjusted for mode of support, recipient age, recipient body mass index (BMI), primary diagnosis, pulmonary hypertension (PHTN)*, mean pulmonary artery pressure (PAP), prior lung surgery (nontransplant), extended-criteria donor (ECD), donor ever smoked, and total ischemic time. The restrictive diagnosis group is a composite of restrictive lung disease and pulmonary vascular disease. *CPB*, Cardiopulmonary bypass; *ECMO*, extracorporeal membrane oxygenation; *PGD*, primary graft dysfunction. *Mean PAP by right heart catheterization >20 mm Hg, systolic PAP by echocardiography ≥40 mm Hg, or a diagnosis of pulmonary hypertension.

TABLE E4. Adjusted analysis accounting for clustering at the center level

Parameter	Odds ratio	95% CI	*P* value
Mode of support (CPB vs ECMO)	1.786	0.920-3.468	.087
Mode of support (CPB vs off-pump)	4.107	2.789-6.049	<.0001
Mode support (ECMO vs off-pump)	2.300	1.216-4.348	.010
Patient age	0.976	0.967-0.986	<.0001
BMI	1.080	1.021-1.144	.008
Primary diagnosis (cystic fibrosis vs restrictive)	0.422	0.227-0.782	.006
Primary diagnosis (obstructive vs restrictive)	0.641	0.405-1.017	.059
PHTN*	0.883	0.554-1.407	.600
Mean PAP	1.023	1.009-1.038	.002
Prior lung surgery	1.992	1.177-3.373	.010
ECD	1.427	1.002-2.032	.049
Ever smoked	1.310	1.012-1.696	.040
Total ischemic time	1.001	1.000-1.002	.023

Multivariate model adjusted for mode of support, recipient age, recipient body mass index (BMI), primary diagnosis, pulmonary hypertension (PHTN)*, mean pulmonary artery pressure (PAP), prior lung surgery (nontransplant), extended-criteria donor (ECD), donor ever smoked, and total ischemic time. The restrictive diagnosis group is a composite of restrictive lung disease and pulmonary vascular disease. *CPB*, Cardiopulmonary bypass; *ECMO*, extracorporeal membrane oxygenation; *PGD*, primary graft dysfunction. *Mean PAP by right heart catheterization >20 mm Hg, systolic PAP by echocardiography ≥40 mm Hg, or a diagnosis of pulmonary hypertension.

TABLE E5. Propensity-matched analysis

	CPB (n = 100)	ECMO (n = 100)	SMD (%)
CPB vs ECMO			
Primary diagnosis			
Cystic fibrosis	15 (15.0)	18 (18.0)	8.3
Obstructive lung disease	23 (23.0)	23 (23.0)	0.0
Restrictive lung disease*	62 (62.0)	59 (59.0)	6.2
BMI	25.2 ± 5.1	25.2 ± 4.4	0.9
Mean PA	30.8 ± 13.8	30.9 ± 14.4	1.1
LAS at transplant	46.6 ± 15.4	47.4 ± 16.2	5.1
Donor age	35.8 ± 13.4	35.8 ± 12.6	0.4
Total ischemic time	352.9 ± 116.5	360.4 ± 126.9	6.0
Donor ever smoked	49 (49.0)	48 (48.0)	2.0
Extended criteria donor	63 (63.0)	61 (61.0)	4.1
	ECMO (n = 171)	**Off-pump (n = 171)**	
ECMO vs off-pump			
Primary diagnosis			
Cystic fibrosis	24 (14.0)	24 (14.0)	0.0
Obstructive lung disease	49 (28.7)	51 (29.8)	2.5
Restrictive lung disease	98 (57.3)	96 (56.1)	2.4
BMI	24.9 ± 4.3	24.9 ± 4.0	1.2
Mean PA	27.4 ± 12.4	26.2 ± 10.1	9.6
LAS at transplant	43.7 ± 12.9	43.6 ± 13.4	1.1
Donor age	38.5 ± 15.0	39.2 ± 15.2	4.6
Total ischemic time	401.8 ± 131.0	389.2 ± 134.8	9.6
Donor ever smoked	71 (41.5)	75 (43.9)	4.7
Extended criteria donor	106 (62.0)	110 (64.3)	4.8

Results are expressed as n (%) or mean ± standard deviation as appropriate. Risk of grade 3 primary graft dysfunction (PGD) at 48 to 72 hours for cardiopulmonary bypass (CPB) versus extracorporeal membrane oxygenation (ECMO) was odds ratio, 1.583; 95% CI, 1.010-2.482; $P = .045$. Risk of PGD at 48 to 72 hours for ECMO versus off-pump as odds ratio, 1.808; 95% CI, 1.175-2.781; $P = .007$. *SMD*, Standard mean difference; *BMI*, body mass index; *PA*, pulmonary artery; *LAS*, lung allocation score. *Restrictive lung disease is a composite of restrictive and pulmonary vascular disease.

TABLE E6. Breakdown of pulmonary hypertension cases and severity of pulmonary artery pressures (PAP) between modes of support

	CPB (n = 157)	ECMO (n = 273)	Off-pump (n = 422)
Pulmonary vascular disease* (n = 32)	12 (7.6)	16 (5.9)	4 (0.1)
Pulmonary hypertension†	130 (82.8)	196 (72.1)	267 (63.4)
Secondary pulmonary hypertension‡	118 (75.2)	180 (65.9)	263 (62.3)
	CPB (n = 156)	**ECMO (n = 247)**	**Off-pump (n = 356)**
Mean PAP (mm Hg), (n = 759)			
Mean PAP ≤20 mm Hg	26 (16.7)	61 (24.7)	94 (26.4)
Mean PAP >20-30 mm Hg	66 (42.3)	95 (38.5)	197 (55.3)
Mean PAP >30-<40 mm Hg	22 (14.1)	41 (16.6)	49 (13.8)
Mean PAP ≥40 mm Hg	42 (26.9)	50 (20.2)	16 (4.5)

Values are presented as n (%). Percent is calculated to the column variable. *CPB*, Cardiopulmonary bypass; *ECMO*, extracorporeal membrane oxygenation. *Pulmonary vascular disease as a primary diagnosis for listing (ie, primary pulmonary hypertension). †Pulmonary hypertension is a field on the Extracorporeal Life Support Registry that is defined by presence of any of the following: mean PAP by right heart catheterization >20 mm Hg, systolic PAP by echocardiography ≥40 mm Hg, or a diagnosis of pulmonary hypertension. ‡Secondary pulmonary hypertension is defined as a case satisfying criteria for pulmonary hypertension but whose primary diagnosis was not designated as pulmonary vascular disease.

TABLE E7. Breakdown of mode of support and rate of grade 3 pulmonary graft dysfunction (PGD3) reported by center

Center de-identified code	CPB (n = 157)	ECMO (n = 273)	Off-pump (n = 422)	PGD3 at 48 or 72 h
H	98 (66.7)	29 (19.7)	20 (13.6)	50 (34.0)
G	29 (16.2)	35 (19.6)	115 (64.2)	51 (28.5)
F	1 (0.8)	34 (27.4)	89 (71.8)	24 (19.4)
A	0 (0)	19 (21.4)	70 (78.6)	11 (12.4)
B	5 (3.7)	49 (36.6)	80 (59.7)	22 (16.4)
C	13 (26.0)	15 (30.0)	22 (44.0)	20 (40.0)
D	1 (1.0)	73 (73.0)	26 (26.0)	8 (8.0)
E	10 (34.5)	19 (65.5)	0 (0)	11 (37.9)

Results expressed as number of cases (%). Percent calculated to the absolute number of the row variable.

TABLE E8. Breakdown of venovenous extracorporeal membrane oxygenation (VV-ECMO) use reported by center

Center de-identified code	VV-ECMO (n = 36)	Proportion of center's cases (%)	Proportion of center's ECMO cases (%)
H	0 (0)	0	0
G	16 (44.4)	8.9	45.7
F	3 (8.3)	2.4	8.8
A	6 (16.7)	6.7	31.6
B	7 (19.5)	5.2	14.3
C	3 (8.3)	6.0	20
D	1 (2.8)	1	1.4
E	0 (0)	0	0

Values are presented as n (%) or %.