# Lung Transplantation After Ex Vivo Lung Perfusion

## *Early Outcomes From a US National Registry*

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**Objective:** The objective of this study was to examine early lung transplant outcomes following EVLP using a large national transplant registry.

**Summary of Background Data:** Lung transplantation in the United States continues to be constrained by a limited supply of donor organs. EVLP has the potential to significantly increase the available pool of donor lung allografts through the reconditioning of ''marginal'' organs.

**Methods:** The united network for organ sharing registry was queried for all adults (age ≥18) who underwent first-time lung transplantation between March 2018 (when united network for organ sharing began collecting confirmed donor EVLP status) and June 2019. Transplants were stratified by EVLP use. The primary outcome was short-term survival and secondary outcomes included acute rejection before discharge and need for extracorporeal membrane oxygenation support post-transplant.

**Results:** A total of 3334 recipients met inclusion criteria including 155 (5%) and 3179 (95%) who did and did not receive allografts that had undergone EVLP, respectively. On unadjusted descriptive analysis, EVLP and non-EVLP cohorts had similar 180-day survival (92% vs 92%, $P = 0.9$). EVLP use was associated with a similar rate of acute rejection (13% vs 9%, $P = 0.08$) but increased rate of early extracorporeal membrane oxygenation use (12% vs 7%, $P = 0.04$). After adjustment, EVLP use was not associated with significantly increased mortality (adjusted hazard ratio 0.99, 95% confidence interval 0.62–1.58) or acute rejection (adjusted odds ratio 0.89, 95% confidence interval 0.40–1.97) compared to non-EVLP use.

**Conclusions:** In the largest national series of EVLP lung transplant recipients, EVLP is associated with early recipient outcomes comparable to that of non-EVLP recipients with similar baseline characteristics. Longer term follow-up data is needed to further assess the impact of EVLP on post-lung transplant outcomes.

**Keywords:** EVLP, ex vivo lung perfusion, lung transplantation

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The demand for donor lung allografts continues to outpace its supply, a problem compounded by the small proportion of donors that are deemed suitable for lung transplantation.[1] Strategies implemented to increase the availability of donor lungs have involved extending donor selection criteria to include ''marginal'' donor allografts, donation after circulatory death (DCD) donors, and the use of ex vivo lung perfusion (EVLP).[2] EVLP, a technology that was first introduced in the early 1990s, provides a platform for donor lung allograft assessment and reconditioning before transplantation to promote the use of organs that would have otherwise been discarded.[3–6] Serial dynamic reassessment of the donor allograft in combination with treatment for reversible injuries associated with donor brain death and management in the intensive care unit promotes the transplantation of previously unacceptable allografts, thus expanding the donor pool. EVLP has also been used for standard criteria donors, although the benefit of this strategy is controversial.[7]

Multiple reports, largely from small single center case series, have demonstrated recipient outcomes of EVLP supported organs comparable to that of conventional lung transplantation.[8–15] Recently, investigators from the Toronto Lung Transplant Program published their experience with 230 lung transplants performed after static EVLP assessment and treatment, demonstrating similar rates of long-term survival and chronic lung allograft dysfunction compared with their standard lung transplant patients.[16] There is a lack of data in the published literature regarding the US national experience with EVLP, however. Therefore, we aimed to compare short-term recipient outcomes associated with EVLP and conventional lung transplantation using a large national transplant registry.

## METHODS

### Data Source

The United Network for Organ Sharing (UNOS) organ procurement and transplantation network provided standard transplant analysis and research files containing deidentified donor and recipient transplant data from October 1987 through June 2019 with follow-up information through September 2019. The database includes prospectively collected data for all organ transplants performed in the US during this period.

### Study Population

The UNOS registry was queried for all adults (age ≥18) undergoing first-time single or bilateral orthotopic lung transplantation between March 1, 2018 and June 30, 2019. This time period was selected as it coincides with when UNOS began collecting confirmed donor EVLP status. Recipients with a prior history of transplantation or those undergoing multi-organ transplantation were excluded (Fig. 1).

### Data Analysis

Descriptive analysis of baseline recipient and donor characteristics was performed, stratified by allograft EVLP usage. Data are

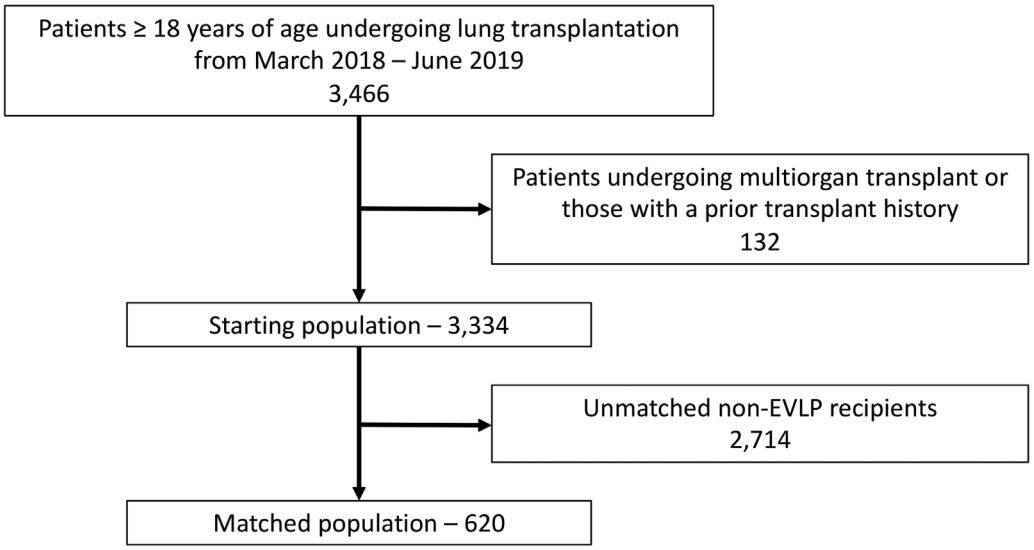


**FIGURE 1.** Study inclusion and exclusion criteria.

presented as median (interquartile range) for continuous variables and percent (count) for categorical variables, unless otherwise specified. Unadjusted comparisons between cohorts were performed using the Wilcoxon rank sum test for continuous variables and the Pearson $\chi^2$ test or Fisher exact test for categorical variables, as appropriate. Donor/recipient predicted total lung capacity ratios were calculated using previously published regression equations.[17,18] Grade 3 primary graft dysfunction (PGD) was defined using a modification of the definition from the 2016 consensus report of the International Society of Heart and Lung Transplantation's working group on PGD.[19] PGD grade 3 was defined as a $PaO_2/FiO_2$ (P/F) ratio at 72 hours post-transplant $<200$ or use of ECMO support. Patients not requiring invasive ventilation or ECMO at 72 hours post-transplant were classified as not having grade 3 PGD. Extended criteria donors were defined as those with a P/F ratio $<300$, DCD, age $>55$, $>20$ pack-year smoking history, or an abnormal chest radiograph; however, this designation was only used for unadjusted descriptive analyses whereas individual components were used for subsequent adjusted analyses. Unadjusted survival was analyzed using the Kaplan-Meier method, with differences between cohorts assessed using the log-rank test. Due to a high degree of missing PGD data, a subgroup analysis was performed examining unadjusted postoperative survival of recipients with missing 72-hour oxygenation data stratified by EVLP usage.

Adjusted post-transplant survival and risk of acute rejection before discharge were modeled using a multivariable Cox Proportional Hazards model and multivariable logistic regression model, respectively. Covariates in both models were selected a priori based upon clinically relevant factors available within the dataset and available degrees of freedom. In addition to allograft EVLP usage, covariates in the Cox model of overall survival consisted of donor age, DCD status, recipient age, lung allocation score (LAS), creatinine, single versus bilateral lung transplant, and annualized lung transplant center volume. Covariates in the logistic regression model for acute rejection included allograft EVLP usage and donor age, DCD status, history of traumatic brain injury, black race, ischemic time, and recipient antibody-based induction immunosuppression. Continuous variables were transformed using restricted cubic splines with 4 pre-specified knots based upon each variable's distribution. To account for correlations arising from hospital-level clustering, robust variance estimators were used for the multivariable Cox model and a random intercept was used for the multivariable logistic regression model. An adjusted subgroup analysis was performed restricted to only recipients of allografts from donation after brain death donors.

To further control for imbalances in baseline characteristics between the 2 study groups, a 1:3 propensity score matching sensitivity analysis was performed using a nearest neighbor algorithm and a standard caliper width of 0.1 of the standard deviation of the propensity score.[20] Patients were matched based on donor and recipient covariates including donor oxygenation (P/F ratio as continuous variable), age, sex, race, medical history, DCD status, extended versus standard criteria, and cause of death and recipient age, sex, race, medical history, medical condition, LAS, indication for transplant, pre-transplant ECMO requirement, type of lung transplant (single versus bilateral), and annualized lung transplant center volume. Comparisons between post-matching cohorts were performed by examining standardized mean differences. Recipient survival was analyzed using the Kaplan-Meier method and Cox proportional hazards regression and acute rejection before discharge was analyzed using logistic regression.

Two-sided $P$-values $\leq 0.05$ were considered statistically significant. Multivariable modeling was performed as complete case analyses. All statistical analyses were performed using R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). This analysis was deemed exempt by the Duke University Institutional Review Board.

## RESULTS

### Recipient and Donor Characteristics

In total, 3334 lung transplant recipients met inclusion criteria including 155 (4.6%) and 3179 (95.4%) that received allografts that were and were not supported with EVLP, respectively. Baseline recipient demographic and clinical characteristics stratified by allograft EVLP usage is presented in Table 1. Recipients in both cohorts had largely similar characteristics including comparable distributions of age, race/ethnicity, medical history, and diagnosis group ($P > 0.05$). Recipients in the EVLP cohort; however, had a significantly lower LAS at transplant and were less likely to undergo single organ lung transplantation.

**TABLE 1.** Recipient Baseline Characteristics Stratified by Lung Allograft EVLP Usage

| Variable | No EVLP (n = 3179) | EVLP (n = 155) | *P*-value |
|---|---|---|---|
| Male sex | 1,925 (60.6%) | 83 (53.5%) | 0.10 |
| Age (median [IQR]) | 61 (53–67) | 61 (55–65) | 0.64 |
| BMI (median [IQR]) | 25.8 (22.2–29.2) | 24.8 (22.3–28.2) | 0.31 |
| Race/ethnicity | | | |
| White | 2,487 (78.2%) | 121 (78.1%) | 0.53 |
| Black | 299 (9.4%) | 18 (11.6%) | |
| Hispanic | 299 (9.4%) | 14 (9.0%) | |
| Other | 94 (3.0%) | 2 (1.3%) | |
| Recipient history | | | |
| Diabetes | 655 (20.6%) | 37 (23.9%) | 0.38 |
| Malignancy | 311 (9.8%) | 12 (7.7%) | 0.48 |
| Diagnosis group | | | |
| A | 769 (24.2%) | 43 (27.7%) | 0.79 |
| B | 164 (5.2%) | 7 (4.5%) | |
| C | 319 (10.0%) | 15 (9.7%) | |
| D | 1,927 (60.6%) | 90 (58.1%) | |
| Recipient creatinine (mg/dL, median [IQR]) | 0.8 (0.7–1.0) | 0.8 (0.7–1.0) | 0.99 |
| Recipient bilirubin (mg/dL, median [IQR]) | 0.4 (0.3–0.6) | 0.4 (0.3–0.7) | 0.10 |
| Pre-transplant status | | | |
| Intensive care unit | 445 (14.0%) | 15 (9.7%) | 0.10 |
| Hospitalized (non-ICU) | 370 (11.7%) | 13 (8.4%) | |
| Not hospitalized | 2,355 (74.3%) | 127 (81.9%) | |
| Medical therapy | | | |
| IV antibiotics in 2 weeks before transplant | 358 (11.3%) | 9 (5.8%) | 0.05 |
| Ventilator support at transplant | 157 (4.9%) | 6 (3.9%) | 0.68 |
| ECMO support at transplant | 197 (6.2%) | 3 (1.9%) | 0.05 |
| Days on waitlist (median [IQR]) | 44 (14–132) | 45 (15–142) | 0.86 |
| Lung allocation score (LAS, median [IQR]) | 42.1 (35.6–58.0) | 38.4 (35.1–48.5) | 0.001 |
| Single organ lung transplant (SOLT) | 807 (25.4%) | 23 (14.8%) | 0.004 |
| Donor-recipient pTLC ratio (median [IQR]) | 1.0 (0.9–1.2) | 1.0 (0.9–1.2) | 0.24 |
| Antibody-based induction immunosuppression | 2,466 (77.6%) | 114 (73.5%) | 0.28 |
| Hospital annual lung transplant volume (median [IQR]) | 43 (32–89) | 42 (38–85) | 0.05 |

BMI indicates body mass index; ECMO, extracorporeal membrane oxygenation; EVLP, ex vivo lung perfusion; ICU, intensive care unit; IQR, interquartile range; pTLC, predicted total lung capacity.

Recipients of conventional and EVLP-perfused organs were transplanted at centers with similar annualized lung transplant volume (median 43 vs 42 transplants, $P \geq 0.05$). Compared with the 55 transplant centers that did not perform EVLP during the study period, the 16 EVLP centers performed a significantly greater number of lung transplants annually (median 42 vs 24 transplants, $P = 0.002$). Centers in UNOS region 4 (TX, OK) performed the greatest proportion of lung transplants using EVLP-perfused allografts (>9%) whereas centers in region 6 (Pacific Northwest, HI, AK) performed none (Fig. 2).

Donor characteristics stratified by EVLP usage are presented in Table 2. Compared with non-EVLP donors, EVLP donors were older, more likely DCD, and more likely extended criteria. Donor medical history and cause of death was similar between groups.

## Unadjusted Survival Analysis

Unadjusted Kaplan-Meier analysis of recipient survival stratified by allograft EVLP usage demonstrated similar survival between the 2 cohorts (Fig. 3A, logrank $P = 0.89$). Specifically, 90- and 180-day survival was estimated as 95.6% [95% confidence interval (CI) 92.1–99.1] and 92.1% (95% CI 87.5–97.0), respectively, among recipients of EVLP allografts compared with 94.8% (95% CI 93.9–95.6) and 92.4% (95% CI 91.4–93.4), respectively among recipients of non-EVLP allografts.

## Unadjusted Outcomes

On unadjusted descriptive analysis of recipient outcomes (Table 3), recipients of EVLP-perfused allografts had a longer length of hospital stay, more often required ECMO use in the 72-hours post-transplant, and more frequently experienced grade 3 PGD at 72-hours post-transplant. Rates of acute rejection before discharge were similar between the 2 cohorts. Missing recipient 72-hour oxygenation data resulted in the inability to analyze rates of grade 3 PGD in approximately 20% of recipients. In a subgroup analysis of recipients with missing 72-hour oxygenation data, EVLP usage did not impact survival (see Figure, Supplemental Digital Content 1, http://links.lww.com/SLA/C359, survival analysis of recipients with missing oxygenation data).

## Adjusted Outcomes

Cox proportional hazards regression was used to examine the association between EVLP use and overall recipient survival (Table 4). After adjustment, EVLP use was not independently associated with survival (adjusted hazard ratio 0.99, 95% CI 0.62–1.58). Similarly, in an adjusted logistic regression model for acute rejection before discharge (Table 4), EVLP use was not independently associated with acute rejection (adjusted hazard ratio 0.89, 95% CI 0.40–1.97). These findings remained unchanged in a subgroup analysis restricted to recipients of allografts from donation after brain death donors (Table 4).

A propensity score matching sensitivity analysis was performed to identify a subgroup of non-EVLP cohort recipients with similar baseline demographic and clinical characteristics as those in the EVLP cohort. 1:3 matching identified 465 recipients in the non-EVLP cohort with overall similar characteristics as the 155 EVLP cohort recipients (see Table, Supplemental Digital Content 2, http://links.lww.com/

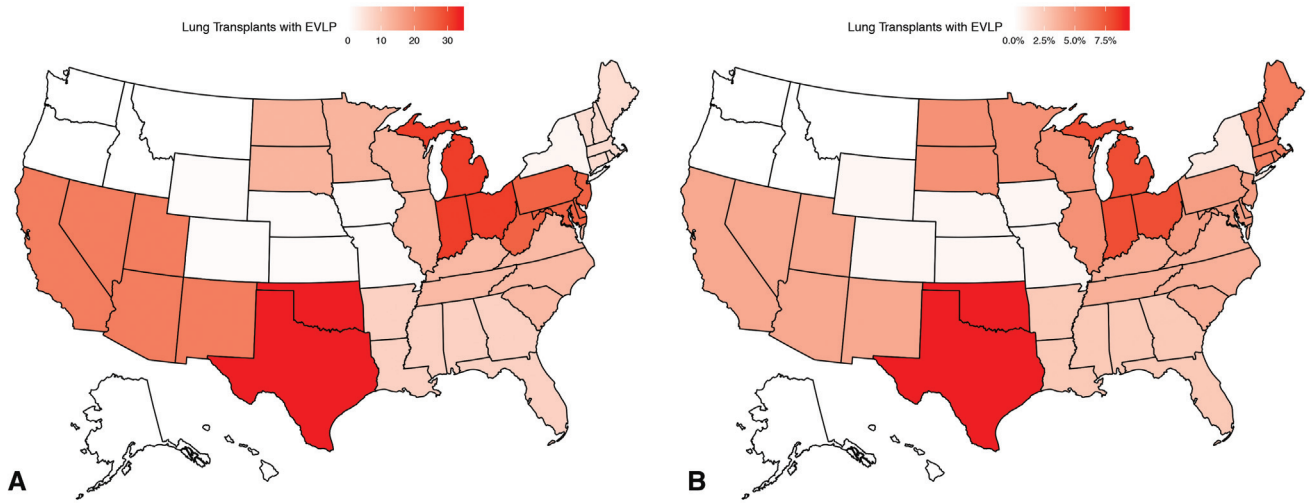


**FIGURE 2.** Total number (A) and proportion (B) of lung transplants performed with EVLP by UNOS region during the study period. EVLP indicates ex vivo lung perfusion; UNOS, United Network for Organ Sharing.

SLA/C360, recipient and donor characteristics of propensity matched cohort). Due to significant differences in the distribution of DCD donors between the 2 cohorts, donor DCD status remained relatively imbalanced after matching (standardized mean differences 0.26). Recipients of EVLP-perfused allografts had similar lengths of hospital stay and rates of acute rejection and PGD grade 3 compared with matched non-EVLP recipients (see Table, Supplemental Digital Content 3, http://links.lww.com/SLA/C361, recipient outcomes stratified

**TABLE 2.** Donor Baseline Characteristics Stratified by Lung Allograft EVLP Usage

| Variable | No EVLP (n = 3179) | EVLP (n = 155) | *P*-value |
|---|---|---|---|
| Donor male sex | 1,940 (61.0%) | 85 (54.8%) | 0.15 |
| Donor age (median [IQR]) | 34 (34–46) | 39 (27–50) | 0.003 |
| Donor BMI (median [IQR]) | 25.7 (22.7–29.4) | 26.6 (23.1–29.9) | 0.13 |
| Donor race/ethnicity | | | |
| White | 1,964 (61.8%) | 100 (64.5%) | 0.35 |
| Black | 549 (17.3%) | 19 (12.3%) | |
| Hispanic | 522 (16.4%) | 30 (19.4%) | |
| Other | 144 (4.5%) | 6 (3.9%) | |
| Donor history | | | |
| Cigarette use (>20 pack-yr) | 251 (7.9%) | 15 (9.7%) | 0.52 |
| Cocaine use | 679 (21.4%) | 29 (18.7%) | 0.49 |
| Diabetes | 268 (8.4%) | 16 (10.3%) | 0.50 |
| Hypertension | 774 (24.3%) | 45 (29.0%) | 0.22 |
| Cancer | 62 (2.0%) | 4 (2.6%) | 0.80 |
| Pulmonary infection | 2,290 (72.0%) | 103 (66.5%) | 0.16 |
| Donor P/F ratio (median [IQR]) | 438 (377–493) | 412 (355–474) | 0.002 |
| Donor creatinine (mg/dL, median [IQR]) | 1.0 (0.7–1.5) | 0.9 (0.7–1.4) | 0.07 |
| Donor bilirubin (mg/dL, median [IQR]) | 0.7 (0.4–1.1) | 0.6 (0.4–1.1) | 0.43 |
| Abnormal chest x-ray | 2,185 (68.7%) | 117 (75.5%) | 0.09 |
| DCD donor | 113 (3.6%) | 52 (33.5%) | <0.001 |
| Extended criteria* | 2,412 (75.9%) | 143 (92.3%) | <0.001 |
| Donor cause of death | | | |
| Anoxia | 1,024 (32.2%) | 49 (31.6%) | 0.85 |
| Cerebrovascular/stroke | 857 (27.0%) | 48 (31.0%) | |
| Head trauma | 1,214 (38.2%) | 54 (34.8%) | |
| CNS tumor | 19 (0.6%) | 1 (0.6%) | |
| Other | 65 (2.0%) | 3 (1.9%) | |
| ABO blood type | | | |
| A | 1,110 (34.9%) | 65 (41.9%) | 0.31 |
| B | 351 (11.0%) | 13 (8.4%) | |
| AB | 78 (2.5%) | 3 (1.9%) | |
| O | 1,640 (51.6%) | 74 (47.7%) | |

*Extended criteria defined as P/F ratio <300, DCD donor, age >55, >20 pack-yr smoking history, or abnormal chest x-ray.
BMI indicates body mass index; CNS, central nervous system; DCD, donation after circulatory death; EVLP, ex vivo lung perfusion; IQR, interquartile range; P/F, PaO2/FiO2.

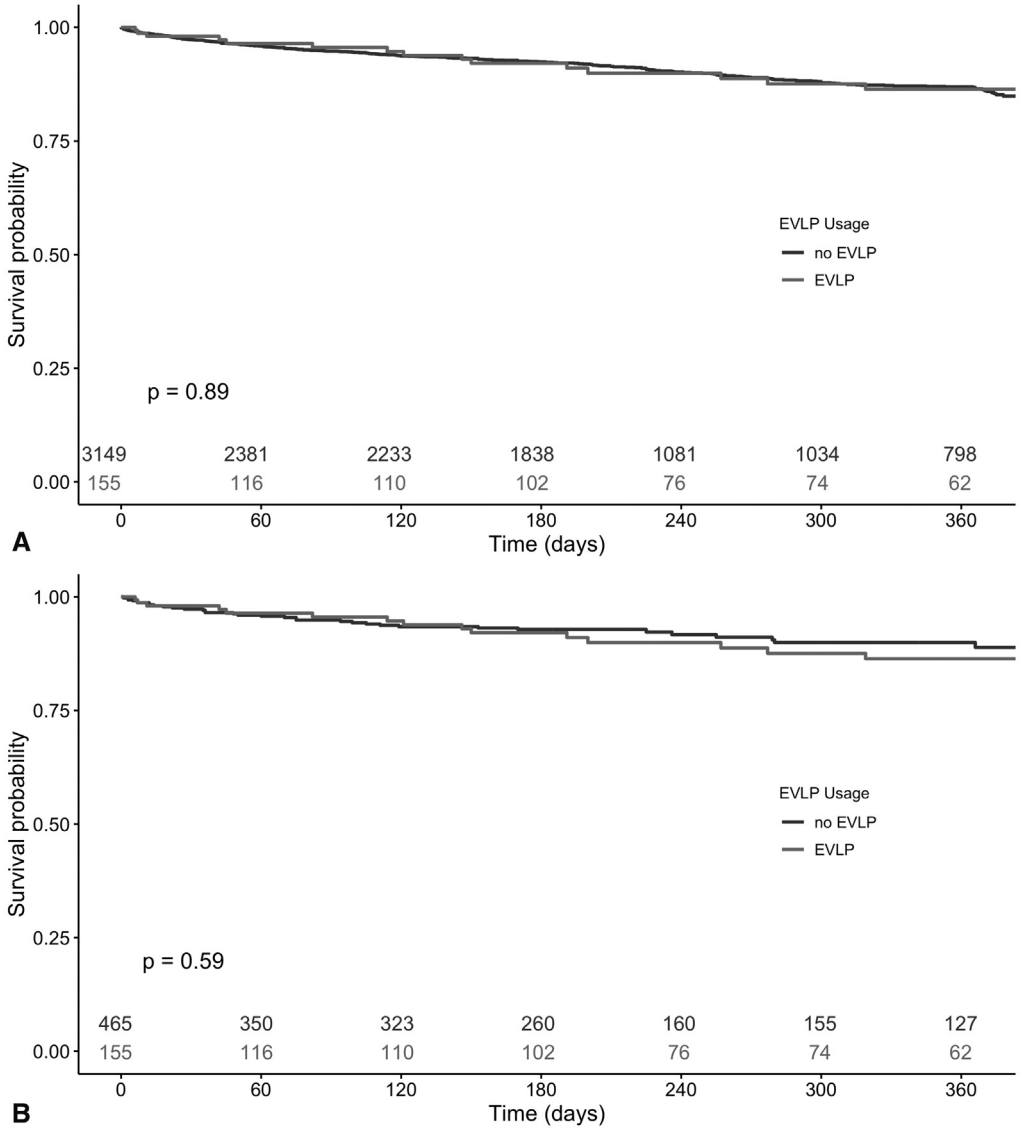


**FIGURE 3.** Kaplan-Meier recipient survival analysis of (A) overall study population and (B) propensity-matched cohort stratified by lung allograft EVLP usage. EVLP indicates ex vivo lung perfusion.

by EVLP usage in propensity matched cohort). EVLP usage, however, was associated with an increased usage of ECMO in the 72 hours post-transplant. Kaplan-Meier survival analysis again estimated similar survival between propensity score matched groups (Fig. 3B, logrank $P = 0.59$). On Cox proportional hazards survival analysis of the propensity matched cohort (see Table, Supplemental Digital Content 4, http://links.lww.com/SLA/C362, association between EVLP use and outcomes in propensity matched cohort), allograft EVLP usage was not associated with short-term recipient mortality (HR 1.18, 95% CI 0.64–2.16). The association between allograft EVLP usage and the risk of recipient acute rejection before discharge was examined using logistic regression (see Table, Supplemental Digital Content 4, http://links.lww.com/SLA/C362, association between EVLP use and outcomes in propensity matched cohort) and again demonstrated that EVLP usage was not associated with recipient acute rejection (OR 1.23, 95% CI 0.71–2.14).

## DISCUSSION

In this analysis of the UNOS lung transplant registry, we examined short-term outcomes of recipients of EVLP-supported lung allografts both in terms of rates of acute rejection and survival and compared these outcomes to those of conventional transplants. After controlling for differences in baseline donor and recipient characteristics with the use of multivariable regression and on a propensity score matched sensitivity analysis, we found no difference in short-term survival or rates of acute rejection between recipients of allografts that were and were not managed with EVLP.

The majority of donor lung allografts are discarded, often due to the deleterious effects of donor brain death and the associated inflammatory cascade on organ quality and function.[21] EVLP permits additional organ assessment time and has the potential to facilitate the reconditioning of ''marginal'' donor lung allografts

**TABLE 3.** Unadjusted Recipient Outcomes Stratified by Lung Allograft EVLP Usage

| Variable | No EVLP (n = 3179) | EVLP (n = 155) | *P*-value |
|---|---|---|---|
| Length of hospital stay (d, median [IQR]) | 18 (12–30) | 20 (13–37) | 0.04 |
| Acute rejection episode before discharge | 266 (8.5%) | 20 (12.9%) | 0.08 |
| ECMO use in 72 h post-transplant | 230 (7.4%) | 19 (12.3%) | 0.04 |
| PGD grade 3* | 554 (21.6%) | 34 (29.8%) | 0.05 |

*Missing data in 614 (19%) non-EVLP recipients and 41 (26%) EVLP recipients.
ECMO indicates extracorporeal membrane oxygenation; EVLP, ex vivo lung perfusion; IQR, interquartile range; PGD, primary graft dysfunction.

that would otherwise be discarded and facilitate the discernment between reversible and irreversible donor lung pathology, thus increasing the pool of available quality organs for transplant.[16] EVLP has also been successfully utilized in the context of standard criteria donor lungs, with improvement reported in subsequent rates of early PGD.[22] Although not analyzed here, prior studies have also demonstrated excellent functional outcomes and quality of life metrics following lung transplantation with EVLP-perfused allografts as well.[14] In one of the largest cohorts of EVLP-perfused donor lung allografts analyzed, we demonstrate no difference in short-term survival of these recipients compared with conventionally managed donor lungs. In the context of the published literature, these findings represent further evidence to support the safety of EVLP use in clinical lung transplantation.

However, concerns have evolved about the potential risks of EVLP allografts. In a 2016 single center analysis of 340 lung transplant recipients by Tikkanen and colleagues, the use of EVLP was associated with a significantly increased risk of developing post-transplant de novo donor-specific antibodies [adjusted hazard ratio 1.74 (95% CI 1.11–2.73)].[23] Although our understanding of the clinical significance of increased DSA in lung transplantation is still evolving, our data suggest that this does not translate to an increased rate of early acute cellular rejection among EVLP-perfused allografts, findings similar to the published literature.[16,24] As international experience with EVLP grows, it will be vital to examine the impact of this technology on longer term graft survival and the development of bronchiolitis obliterans syndrome and chronic lung allograft dysfunction.

Another concern about EVLP is the potentially heightened risk of PGD in recipients of these organs. The 2019 EXPAND single-arm trial of extended criteria donor lungs perfused with the portable organ care system (TransMedics Inc; Andover, MA) found an unexpectedly high rate of PGD grade 3 mostly seen in the DCD subgroup of donors and results of the follow-up randomized EXPAND II trial are pending.[25] Although we were unable to robustly analyze the association between EVLP use and rates of PGD due to a high degree of missing recipient 72-hour post-transplant oxygenation data, multiple published reports have suggested that EVLP use does not result in higher rates of PGD. Small single-center retrospective analyses by Cypel (2012), Sage (2014), Boffini (2014), Machuca (2015), and Wallinder (2016) all reported improved or comparable rates of PGD among EVLP allograft recipients compared with recipients of conventional transplants.[10,12,13,15,26] Furthermore, a larger 2019 retrospective series by Divithotawela and colleagues from Toronto reported lower rates of PGD grades 2 and 3 at 72-hours post-transplant among recipients of grafts supported with EVLP compared with the non-EVLP cohort.[16] The 2018 international INSPIRE trial examining the organ care system EVLP device for standard criteria donor organs similarly reported improved rates of PGD grade 3 during the first 72 hours compared with traditional cold storage as well.[22]

Although early results of EVLP use are indeed promising, the platform is still being utilized relatively infrequently, accounting for less than 5% of lung transplants performed in the US during the study period. Transplants with EVLP-perfused allografts are primarily being performed by high volume centers, accounting for less than a quarter of centers that perform lung transplantation nationally. Given the significant financial burden associated with EVLP, and the continued investigational nature of these devices with multiple ongoing clinical trials, the landscape of EVLP usage in the US is unlikely to change significantly in the near future without additional novel breakthroughs.[27,28] Should forthcoming clinical trials continue to produce positive results and payors continue to support the reimbursement of the technology, EVLP utilization has the potential to grow the pool of available donor allografts without sacrificing recipient outcomes. Further research is also necessary to characterize the financial barriers to wider implementation of EVLP.

As a retrospective review of registry data, this analysis has several important limitations. First, as UNOS only began collecting recipient-associated EVLP data in early 2018, we were unable to analyze longer-term recipient outcomes. Examination of long-term survival and the incidence of chronic rejection will be necessary to ensure that potential EVLP-associated donor pool expansion will not

**TABLE 4.** Association Between EVLP Use and Outcomes

| Outcome* | Unadjusted Hazard/Odds Ratio | 95% CI Lower | 95% CI Upper | *P*-value | Adjusted† Hazard/Odds Ratio | 95% CI Lower | 95% CI Upper | *P*-value |
|---|---|---|---|---|---|---|---|---|
| Overall cohort | | | | | | | | |
| Survival | 0.96 | 0.57 | 1.62 | 0.89 | 0.99 | 0.62 | 1.58 | 0.96 |
| Acute rejection before discharge | 1.60 | 0.98 | 2.60 | 0.06 | 0.89 | 0.40 | 1.97 | 0.77 |
| DBD donor‡ | | | | | | | | |
| Survival | 0.62 | 0.29 | 1.32 | 0.22 | 0.65 | 0.34 | 1.25 | 0.20 |
| Acute rejection before discharge | 1.58 | 0.87 | 2.87 | 0.13 | 1.16 | 0.46 | 2.88 | 0.76 |

*Overall survival modeled with cox proportional hazards regression, acute rejection modeled with logistic regression.
†Survival adjusted for EVLP, donor age, DCD donor, recipient age, recipient creatinine, recipient LAS, single versus bilateral organ lung transplant, and annual lung transplant center volume; rejection adjusted for EVLP, donor TBI, age, DCD donor, recipient age, black race, antibody-based induction immunosuppression, and ischemic time.
‡DBD donor subgroup analysis adjusted for above covariates except DCD donor (excluded).
CI indicates confidence interval; DBD, donation after brain death; EVLP, ex vivo lung perfusion.

negatively influence recipient outcomes. Second, we were unable to robustly analyze PGD given the high degree of missing 72-hour recipient oxygenation data in the database. Analysis of the non-missing data, however, demonstrated similar rates of PGD grade 3 between the EVLP and non-EVLP cohorts, in concordance with the majority of the published literature. Furthermore, similar survival between EVLP and non-EVLP cohorts was demonstrated in a subgroup analysis of patients with missing PGD data, suggesting that this missing data likely did not significantly bias our results. Third, the UNOS database does not contain the granularity required to differentiate between the various commercially available EVLP systems, which precluded a comparison of the platforms in this study. Detailed indications for EVLP usage are also not available for analysis. Fourth, as an analysis of recipient outcomes who underwent transplantation, we were unable to examine EVLP-perfused allograft discard rates, which is of great interest to the transplant community given the implications for resource utilization. Fifth, data granularity pertaining to the occurrence of an acute rejection episode before hospital discharge is lacking in the database, precluding a more detailed definition of this endpoint. Lastly, although this is the largest analysis of EVLP outcomes in the United States, the EVLP cohort was still relatively small, increasing the probability of type II error. We attempted to mitigate this risk by use of multiple endpoints, multivariable regression, and propensity score-matching.

## CONCLUSIONS

In conclusion, results from the first US national analysis examining EVLP usage suggest that EVLP-perfused lung allografts are associated with similar short-term outcomes as conventionally managed organs. Although currently accounting for only 5% of lung transplants performed nationally, growth in EVLP utilization seems to have the potential to significantly expand the donor pool without sacrificing early recipient outcomes.

## REFERENCES


1. Chambers DC, Cherikh WS, Goldfarb SB, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: thirty-fifth adult lung and heart-lung transplant report-2018; focus theme: multiorgan transplantation. *J Heart Lung Transplant*. 2018;37:1169–1183.
2. Courtwright A, Cantu E. Evaluation and management of the potential lung donor. *Clin Chest Med*. 2017;38:751–759.
3. Wierup P, Haraldsson A, Nilsson F, et al. Ex vivo evaluation of nonacceptable donor lungs. *Ann Thorac Surg*. 2006;81:460–466.
4. Steen S, Ingemansson R, Eriksson L, et al. First human transplantation of a nonacceptable donor lung after reconditioning ex vivo. *Ann Thorac Surg*. 2007;83:2191–2194.
5. Cypel M, Yeung JC, Hirayama S, et al. Technique for prolonged normothermic ex vivo lung perfusion. *J Heart Lung Transplant*. 2008;27:1319–1325.
6. Ingemansson R, Eyjolfsson A, Mared L, et al. Clinical transplantation of initially rejected donor lungs after reconditioning ex vivo. *Ann Thorac Surg*. 2009;87:255–260.
7. Cypel M, Neyrinck A, Machuca TN. Ex vivo perfusion techniques: state of the art and potential applications. *Intensive Care Med*. 2019;45:354–356.
8. Cypel M, Rubacha M, Yeung J, et al. Normothermic ex vivo perfusion prevents lung injury compared to extended cold preservation for transplantation. *Am J Transplant*. 2009;9:2262–2269.
9. Cypel M, Yeung JC, Liu M, et al. Normothermic ex vivo lung perfusion in clinical lung transplantation. *N Engl J Med*. 2011;364:1431–1440.
10. Cypel M, Yeung JC, Machuca T, et al. Experience with the first 50 ex vivo lung perfusions in clinical transplantation. *J Thorac Cardiovasc Surg*. 2012;144:1200–1206.
11. Wallinder A, Ricksten SE, Hansson C, et al. Transplantation of initially rejected donor lungs after ex vivo lung perfusion. *J Thorac Cardiovasc Surg*. 2012;144:1222–1228.
12. Sage E, Mussot S, Trebbia G, et al. Lung transplantation from initially rejected donors after ex vivo lung reconditioning: the French experience. *Eur J Cardiothorac Surg*. 2014;46:794–799.
13. Boffini M, Ricci D, Bonato R, et al. Incidence and severity of primary graft dysfunction after lung transplantation using rejected grafts reconditioned with ex vivo lung perfusion. *Eur J Cardiothorac Surg*. 2014;46:789–793.
14. Tikkanen JM, Cypel M, Machuca TN, et al. Functional outcomes and quality of life after normothermic ex vivo lung perfusion lung transplantation. *J Heart Lung Transplant*. 2015;34:547–556.
15. Wallinder A, Riise GC, Ricksten SE, et al. Transplantation after ex vivo lung perfusion: a midterm follow-up. *J Heart Lung Transplant*. 2016;35:1303–1310.
16. Divithotawela C, Cypel M, Martinu T, et al. Long-term outcomes of lung transplant with ex vivo lung perfusion. *JAMA Surg*. 2019;154:1143–1150.
17. Eberlein M, Reed RM, Maidaa M, et al. Donor-recipient size matching and survival after lung transplantation. A cohort study. *Ann Am Thorac Soc*. 2013;10:418–425.
18. Eberlein M, Reed RM. Donor to recipient sizing in thoracic organ transplantation. *World J Transplant*. 2016;6:155–164.
19. Snell GI, Yusen RD, Weill D, et al. Report of the ISHLT working group on primary lung graft dysfunction, part I: definition and grading-A 2016 consensus group statement of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant*. 2017;36:1097–1103.
20. Ho DE, Imai K, King G, et al. MatchIt: nonparametric preprocessing for parametric causal inference. *J Stat Softw*. 2011;42:1–28.
21. Snell GI, Griffiths A, Levvey BJ, et al. Availability of lungs for transplantation: exploring the real potential of the donor pool. *J Heart Lung Transplant*. 2008;27:662–667.
22. Warnecke G, Van Raemdonck D, Smith MA, et al. Normothermic ex-vivo preservation with the portable organ care system lung device for bilateral lung transplantation (INSPIRE): a randomised, open-label, non-inferiority, phase 3 study. *Lancet Respir Med*. 2018;6:357–367.
23. Tikkanen JM, Singer LG, Kim SJ, et al. De novo DQ donor-specific antibodies are associated with chronic lung allograft dysfunction after lung transplantation. *Am J Respir Crit Care Med*. 2016;194:596–606.
24. Fildes JE, Archer LD, Blaikley J, et al. Clinical outcome of patients transplanted with marginal donor lungs via ex vivo lung perfusion compared to standard lung transplantation. *Transplantation*. 2015;99:1078–1083.
25. Loor G, Warnecke G, Villavicencio MA, et al. Portable normothermic ex-vivo lung perfusion, ventilation, and functional assessment with the organ care system on donor lung use for transplantation from extended-criteria donors (EXPAND): a single-arm, pivotal trial. *Lancet Respir Med*. 2019;7:975–984.
26. Machuca TN, Mercier O, Collaud S, et al. Lung transplantation with donation after circulatory determination of death donors and the impact of ex vivo lung perfusion. *Am J Transplant*. 2015;15:993–1002.
27. Fisher A, Andreasson A, Chrysos A, et al. An observational study of donor ex vivo lung perfusion in UK lung transplantation: DEVELOP-UK. *Health Technol Assess*. 2016;20:1–276.
28. Loor G. EVLP: ready for prime time? *Semin Thorac Cardiovasc Surg*. 2019;31:1–6.