# Lung Retransplantation for Chronic Rejection: A Single-Center Experience

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*Background.* Chronic lung allograft dysfunction (CLAD) is nonreversible and remains the biggest obstacle to long-term survival after lung transplantation (LTx). Retransplantation is the sole definitive therapeutic option for CLAD. We analyzed our single-center experience with retransplantation as a treatment option for CLAD.

*Methods.* From March 1, 2010, to May 31, 2016, 419 consecutive patients underwent LTx at our institution; 29 of these procedures were retransplantations for CLAD. We analyzed demographic characteristics, lung allocation score, operation type, length of stay, and perioperative outcomes. Actuarial survival was estimated using Kaplan-Meier survival curves.

*Results.* In total, 29 of 419 patients (6.9%) underwent retransplantation for CLAD. Median time from primary LTx to retransplantation was 1,163 days (range: 304 to 3,971 days). Patients undergoing retransplantation were younger and had higher lung allocation scores than primary transplantation patients. Most LTx procedures were bilateral (93% of retransplantations, 95% of primary LTx). Rates of cardiopulmonary bypass, extracorporeal membrane oxygenation support for severe primary graft dysfunction, and re-exploration for bleeding were higher in retransplantation patients ($p = 0.010$, $p = 0.019$, and $p = 0.029$, respectively). One- and 5-year survival rates in the retransplantation group were similar to those of the primary LTx group (89.2% and 64.3% versus 89.7% and 58.2%, respectively; $p = 0.79$).

*Conclusions.* Lung retransplantation is a viable treatment option for CLAD after LTx. In this study, retransplantation patients were younger, had higher lung allocation scores, and were more likely to require cardiopulmonary bypass and postoperative extracorporeal membrane oxygenation support than primary LTx patients. Postoperative length of stay and short- and mid-term survival were comparable with those of primary LTx patients.

(Ann Thorac Surg 2017;■:■–■)


The use of lung transplantation (LTx) to manage patients with advanced lung disease has continued to expand over the past few decades [1]. However, the long-term survival after adult LTx lags behind survival rates reported for transplantation of other solid organs [1]. Chronic lung allograft dysfunction (CLAD) is the biggest obstacle to long-term survival after LTx.

Lung retransplantation has become increasingly common in the past decade [2]. Major indications for lung retransplantation include airway complications, acute graft failure due to primary graft dysfunction (PGD) or refractory acute rejection, and CLAD. Reported outcomes for lung retransplantation for airway complications, acute graft rejection, and graft failure within 90 days are inferior to those reported for lung retransplantation for CLAD [1, 3, 4]. Several studies have shown that long-term survival rates after lung retransplantation for CLAD approach the survival rates of primary LTx [3, 5].

From the published lung retransplantation data, we instituted a policy to offer lung retransplantation to select patients—only those with CLAD. To date, few reports have explored outcomes for lung retransplantations performed solely for CLAD. We present a single-center experience with lung retransplantation for the sole indication of CLAD and compared outcomes with those of patients who had undergone primary LTx.

## Patients and Methods

### Study Population

This study was approved by the Institutional Review Board at St. Joseph's Hospital and Medical Center. We reviewed the charts of patients who underwent LTx between March 1, 2010, and May 31, 2016, at Norton Thoracic Institute at St. Joseph's Hospital and Medical Center in Phoenix, Arizona. All 419 patients who received

Accepted for publication July 11, 2017.

Presented at the Fifty-third Annual Meeting of The Society of Thoracic Surgeons, Houston, TX, Jan 21–25, 2017.

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0003-4975/$36.00
http://dx.doi.org/10.1016/j.athoracsur.2017.07.025

**Abbreviations and Acronyms**

CLAD = chronic lung allograft dysfunction
CPB = cardiopulmonary bypass
ECMO = extracorporeal membrane oxygenation
HLA = human leukocyte antigen
LAS = lung allocation score
LOS = length of stay
LTx = lung transplantation
PGD = primary graft dysfunction

LTx during this time period were included in the study. Patients were separated into one of two groups: primary LTx or lung retransplantation. Patient selection for primary LTx and retransplantation was largely based on criteria set forth by the International Society for Heart and Lung Transplantation [6]. CLAD was defined as a persistent (ie, of at least 3 weeks' duration), irreversible decline in forced expiratory volume in 1 second or forced vital capacity to 80% or lower of best postoperative baseline values, not triggered by other causes of loss of function after transplantation [7, 8]. More specifically, candidates for lung retransplantation were patients with progressive CLAD that was functionally or physiologically limiting, were free of other major organ dysfunction, and all but 3 were ventilator-independent. The immunosuppression regime for both primary and retransplantation candidates was fairly uniform during the study period. Maintenance therapy constituted glucocorticoid, nucleotide synthesis inhibitor (mycophenolate mofetil), and calcineurin inhibitor (tacrolimus). In cases of documented nephrotoxicity from calcineurin inhibitor, patients were given a "drug holiday" and were switched to a mammalian target of rapamycin inhibitor (everolimus) to preserve renal function.

The two groups were compared for demographic characteristics and clinical characteristics before LTx, lung allocation score (LAS), type of operation (ie, unilateral versus bilateral LTx), intraoperative characteristics, and postoperative outcomes. The primary outcome measure was graft survival at 30 days, 90 days, 1 year, 3 years, and 5 years after LTx. Secondary outcome measures were rates of intraoperative cardiopulmonary bypass (CPB) use, rates of PGD at 48 to 72 hours after transplantation, need for extracorporeal membrane oxygenation (ECMO) rescue for severe PGD, duration of postoperative ventilator support, chest re-exploration for bleeding, and postoperative hospital length of stay (LOS).

### *Statistical Analysis*

Patients' demographic and clinical characteristics are reported using medians and interquartile ranges for continuous variables and frequencies; categorical variables are reported as proportions. The Wilcoxon rank sum test was used to compare continuous variables, and the Fisher exact test was used to compare categorical variables. Probabilities of graft survival were estimated using the Kaplan-Meier method. Graft survival was calculated from transplantation to death or from primary transplantation to retransplantation. Log-rank was conducted to compare survival probabilities between groups. Univariate and multivariable Cox regression was implemented to ascertain risk of death at 1 year after transplantation between primary LTx patients and retransplantation patients. Covariates with $p$ value less than 0.20 by univariate analysis were added to the final model for adjustment; therefore, age, sex, CPB use, LAS, human leukocyte antigen (HLA) class II antibody, serum creatinine at listing, LOS after transplantation, and PGD at 48 to 72 hours were added to the final model. A $p$ value of less than 0.05 was considered significant. All analyses were performed using Stata 2015 software, release 14 (StataCorp LP, College Station, TX).

## Results

### *Patient Characteristics*

In total, 419 patients underwent LTx during the study period. Of these, 390 patients (93.1%) underwent primary LTx; 29 patients (6.9%) underwent retransplantation (Table 1). The indication for all 29 retransplantations was CLAD. Median time to retransplantation after initial LTx was 1,163 days (range: 304 to 3971 days). Most LTx procedures were bilateral—27 of 29 in the retransplantation group (93.1%) and 374 of 390 in the primary LTx group (95.9%). Patients who underwent retransplantation were younger ($p < 0.001$) and had higher LAS ($p < 0.001$). A lower proportion of retransplantation recipients were men ($p = 0.01$). The most common primary end-stage lung diseases were cystic fibrosis (10/29, 34.5%) and fibrotic lung disease (9/29, 31.0%) in the retransplantation group, compared with fibrotic lung disease (186/390, 47.7%) and obstructive lung disease (169/390, 43.3%) in the primary LTx group. Waitlist time and rates of mechanical ventilation at listing were similar between groups. All retransplantations were performed across negative crossmatch, and no attempt was made to exclude prior mismatched HLA. Average class II panel reactive antibody levels were higher in patients undergoing retransplantation ($p = 0.008$).

The perioperative and postoperative outcomes of the two groups are shown in Table 2. Rates of CPB use during the transplantation procedure were higher in the retransplantation group ($p = 0.01$). Patients who underwent retransplantation had higher rates of ECMO support for PGD ($p = 0.019$) and chest re-exploration for bleeding ($p = 0.029$). Rates of reintubation and postoperative LOS were comparable between groups ($p = 0.71$ and $p = 0.25$, respectively). A comparable proportion of patients in both groups were discharged home ($p = 0.43$), with in-hospital mortality rates of 0.5% in the primary LTx group and 3.4% in the retransplantation group ($p = 0.19$).

Unadjusted probability of graft survival was comparable between groups (log-rank $p = 0.79$; Fig 1). In the retransplantation group, graft survival at 30 days, 90 days,