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A Comparative Analysis of Bronchial Stricture Following Lung Transplantation in Recipients With and Without Early Acute Rejection

Anthony W. Castleberry, MD, MMCI¹, Mathias Worni, MD, MHS^{1,2}, Maragatha Kuchibhatla, PhD³, Shu S. Lin, MD, PhD⁴, Laurie D. Snyder, MD⁵, Scott L. Shofer, MD, PhD⁵, Scott M. Palmer, MD, MHS⁵, Ricardo S. Pietrobon, MD, PhD, MBA¹, R. Duane Davis, MD, MBA⁴, and Matthew G. Hartwig, MD⁴

¹Duke University Medical Center - Division of General Surgery, Durham, NC, United States

²Inselspital, University of Berne - Department of Visceral Surgery and Medicine, Berne, Switzerland

³Duke University Medical Center - Division of Biostatistics, Durham, NC, United States

⁴Duke University Medical Center - Division of Thoracic Surgery, Durham, NC, United States

⁵Duke University Medical Center - Division of Pulmonary and Critical Care, Durham, NC, United States

Abstract

Background—Risk factors and outcomes of bronchial stricture following lung transplantation are not well defined. An association between acute rejection and development of stricture has been suggested in small case series. We evaluated this relationship using a large, national registry.

Methods—All lung transplants between 04/1994 and 12/2008 per the United Network for Organ Sharing database were analyzed. Generalized linear models were used to determine the association between early rejection and development of stricture after adjusting for potential confounders. The association of stricture with postoperative lung function and overall survival was also evaluated.

Results—9,335 patients were included for analysis. The incidence of stricture was 11.5% (=1,077/9,335) with no significant change in incidence during the study period ($p=0.13$). Early rejection was associated with a significantly greater incidence of stricture [adjusted odds ratio (AOR) 1.40, 95% confidence interval (CI) 1.22 - 1.61; $p<0.0001$]. Male gender, restrictive lung disease, and pre-transplant requirement for hospitalization were also associated with stricture. Those who developed stricture had and a lower postoperative peak percent predicted forced expiratory volume at one second (median 74% vs. 86% for bilateral transplants only, $p<0.0001$), shorter unadjusted survival (median 6.09 vs. 6.82 years, $p<0.001$) and increased risk of death after adjusting for potential confounders (adjusted hazard ratio 1.13, CI 1.03 - 1.23, $p=0.007$).

Corresponding author: Anthony W. Castleberry, MD, MMCI Department of Surgery Duke University Medical Center Box 3443 Medical Center Durham, NC 27710, USA anthony.castleberry@duke.edu.

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Conclusions—Early rejection is associated with an increased incidence of stricture. Recipients with stricture demonstrate worse postoperative lung function and survival. Prospective studies may be warranted to further assess causality and the potential for coordinated rejection and stricture surveillance strategies to improve postoperative outcomes.

Keywords

Transplantation; lung; Outcomes; Surgery; complications; Rejection (immunologic, lung)

Introduction

The number of lung transplants has continued to increase each year, with greater than 3,200 transplants performed worldwide in 2009.[1] Airway complications are an important limitation to successful lung transplantation, with bronchial stricture (referred to as “stricture”) as the most common manifestation in most series.[2-6] Despite the improvements in surgical technique and immunosuppression strategies, the incidence of stricture following lung transplantation in the modern era has been reported between 5 - 30%, with up to a 40% decrease in 5-year survival compared to patients without airway complications.[7-9]

The mechanism by which stricture may arise remains speculative.[2,10] Given its overall low prevalence, implications of developing this condition and the associated risk factors are not well defined.[2,3,8,10] Anecdotal reports from small series suggest a tendency of higher grades of acute rejection before and at the time of bronchial stenosis.[2,5,6] To date, there has not been a large, multicenter, longitudinal analysis to assess the association between early acute rejection and the development of post-transplant bronchial stricture. Our main objective was to evaluate this relationship using a cohort of all lung transplantations performed in the United States (US) and reported to the Organ Procurement and Transplantation Network (OPTN). We hypothesized that recipients with early acute rejection would manifest a higher incidence of stricture. As a secondary assessment, we investigated trends in the development of stricture, as well as the association of stricture with postoperative lung function and overall survival in this population-based analysis.

Patients and methods

The Institutional Review Board at Duke University Medical Center approved this study.

Data Source

The United Network for Organ Sharing (UNOS) Standard Transplant Analysis and Research files were used for this analysis, which contain data regarding every organ donation and transplant event occurring in the US since October 1, 1987.[11] Data are compiled from individual centers and entered by trained data entry personnel, with quality assurance controls in place including electronic data validation systems and on-site audits of participating institutions.[12] The dataset used for the current study comprises a prospectively collected open cohort of lung transplantations performed between 10/1987 and 12/2011 with follow-up through 03/2012.

Study Design

We performed a retrospective cohort analysis of all adult US lung transplantations as recorded in the UNOS/OPTN database. The study period ranged from 04/1994, when recording of stricture information began, through 12/2008 to allow a minimum of three years follow-up time to capture stricture incidence and resulting outcomes. To be included in the study, patients had to have a post-transplant follow-up visit documenting the presence or absence of stricture, which is a yes/no field on the “Adult Thoracic Transplant Recipient Follow-Up Worksheet” (Office of Management and Budget approved form number 0915-0157). This form is generated at six months post-transplant and on the transplant anniversary thereafter. Patients with unknown or missing stricture information were excluded. Additional exclusion criteria were patients undergoing multi-visceral transplant (other than heart-lung), recipients of a third lung transplant, pediatric recipients, and lobar or en-block double lung transplant recipients.

The primary predictor variable for our analysis was the presence or absence of an early acute rejection (defined as rejection requiring treatment within 1 year of transplantation), and as such patients were excluded if this information was missing or unknown. Covariates analyzed included age, gender, race (white, black, hispanic, asian, other/unknown), primary diagnosis [obstructive disease, restrictive disease, cystic fibrosis/bronchiectasis, pulmonary hypertension, graft failure (for retransplants) or other], type of transplant (bilateral sequential, single lung, combined heart/lung), transplant center volume (quantified as a continuous variable representing the total number of lung transplants performed by given center during the study period), year of transplant, chronic steroid use prior to transplantation, medical condition preceding transplantation (non-hospitalized, hospitalized, intensive care), requirement of life support at the time of transplant (ventilator, extracorporeal membrane oxygenation, intravenous inotropes, intra-aortic balloon pump, or inhaled nitric oxide), ventilator dependence at the time of transplant, days on the waitlist, allograft ischemic time (for bilateral transplants, this was the maximum ischemic time of either lung), and donor characteristics [age, history of diabetes, history of smoking, history of cocaine use, and arterial partial pressure of oxygen (PO₂) on inspired oxygen of 100%].

The primary outcome variable was the development of stricture post-transplantation. The trend in stricture incidence and proportion receiving endobronchial stenting therapy were also assessed. For those patients who developed stricture (regardless of predisposing risk factors) a secondary analysis was performed to evaluate postoperative peak forced expiratory volume at one second as a percent of the patient's predicted value (FEV₁), unadjusted and adjusted overall survival compared to recipients without stricture.

Sensitivity Analysis

Early infection (defined as any drug-treated infection prior to discharge) is only captured through January 2007 and therefore this data is missing for a substantial proportion of patients. As a sensitivity analysis of the primary model to assess for a potential confounding effect of early infection, we re-ran the multivariable logistic regression analysis to include early infection as an additional covariate for risk adjustment for the subset of patients where early postoperative infection data was available (n= 7,036 patients).

Statistical Analysis

Baseline characteristics were described for the overall sample. Medians and interquartile range (IQR) of 25th/75th percentiles were reported for continuous variables, and proportions (frequency, percentage) for discrete variables. Multivariable logistic regression was performed to assess the association between early acute rejection and the development of stricture, after adjusting for patient demographics, comorbidities, underlying diagnosis, technical aspects of the operative procedure, and donor characteristics. Covariates were determined a-priori based on variables previously established in the literature to represent potential confounders. These covariates were also evaluated for independent association with stricture development. Missing data for donor PO2 on 100% oxygen [n=2,222/9,335 (24%)] was imputed using multivariable regression based on the following donor variables: age, gender, body mass index (BMI), smoking status, presence of diabetes, terminal creatinine, evidence of pulmonary infection, use of inotropic support, left ventricular ejection fraction, and use of diuretics. In a similar manner, missing data for ischemic time [n=936/9,335 (10%)] was imputed based on the predictor variables of distance (in miles) from donor hospital to transplant center, procedure type (single, double, or heart/lung), and center volume. For the subset of patients where early postoperative infection data was available, multivariable logistic regression was performed in the manner described above with the addition of early drug-treated infection as a covariate for risk adjustment to assess the sensitivity of the model to this variable.

The trend over time in stricture development was assessed using the Cochran Armitage trend test.[13,14] This was analyzed for the study population as a whole, as well as separately analyzing the trend in incidence for high-volume vs. low volume centers using greater than 34 lung transplants per year to distinguish these groups based on previous strata for high-volume centers reported in the literature.[15] The trend in the proportion of bronchial strictures receiving endobronchial stent therapy was evaluated in the same manner. To assess survival of patients with and without stricture, Kaplan-Meier plots were constructed and compared using the log-rank test.[16] A separate sub-analysis was also constructed to assess survival for stricture treated with or without stenting in cases where stent information was available. Multivariable Cox proportional hazards regression modeling was used to assess the independent effect of stricture on time to death, adjusting for potential confounders as described above. The proportionality assumption was verified for covariates included in the Cox model. Patients undergoing combined heart/lung transplant were excluded from survival analyses. Multivariable linear regression was used to evaluate the association of stricture with peak postoperative FEV₁ (bilateral lung transplants only).

A probability value 0.05 was used to indicate statistical significance for all comparisons and analyses. Statistical analyses were performed using JMP Version 10.0 (SAS Institute Inc., Cary, NC) and R version 2.15.1 [R Core Team (2012). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL <http://www.R-project.org/>.]

Results

A total of 9,335 patients were included for analysis (median follow-up 4.6 years). Patients excluded from the final study population are summarized in Figure 1. The baseline recipient characteristics for the entire cohort are shown in Table 1 and the donor/transplant characteristics are shown in Table 2. The median age was 55 years (IQR 44 - 61 years) with 47.3% (n=4,417) female and 87.3% (n=8,152) white. Obstructive lung disease was the most common reason for transplant (42.8%, n=3,991). The proportion of patients receiving bilateral lung transplant was 50.9% (n=4,750) and combined heart/lung transplant 2.4% (n=223).

The incidence of stricture in our study population across all years was 11.5% (=1,077/9,335), which ranged from a high of 19.4% in 1995 to a low of 9.0% in 2000 and 2001 (Figure 2A). There was no statistically significant change in stricture incidence over the study period ($p=0.13$). When stratified by high-volume vs. low-volume centers, there was no significant change in stricture incidence over time for high volume centers ($p=0.63$). Low volume centers demonstrated a significant decrease in incidence of stricture ($p=0.01$) with peak incidence of 25.2% and 22.4% in 1995 and 1996, respectively, with the incidence more closely approximating high-volume centers in later years of the study (Figure 2B). The trend in endobronchial stent therapy also significantly declined over time from a peak of 84.6% in 1998 to a low of 58.1% in 2008 ($p=0.01$) (Figure 2C) [information on stenting was available for 1,059 of 1,077 (98.3%) of strictures]. Information on bronchial stricture formation is reported to UNOS at interval time periods, and as such the interval reporting date is known; however, the date of clinical diagnosis of stricture is not specified. Of the 1,077 bronchial strictures reported in the UNOS database, 631 (58.6%) were reported within the first postoperative year (defined as reporting date $\leq$ 395 days after transplant to allow for a 30-day reporting lag).

Patients who experienced early acute rejection were significantly more likely to also manifest bronchial stricture after adjusting for potential confounders [adjusted odds ratio (AOR) 1.40, 95% confidence interval (CI) 1.22 - 1.61; $p<0.0001$] (Table 3). The association between early acute rejection and bronchial stricture development retained equivalent statistical significance in the subset of cases where early infection data was available for inclusion as a covariate in the multivariable model ($p<0.0001$). Several additional covariates independently associated with stricture development were also identified: male gender (AOR 1.52, CI 1.33 - 1.75; $p<0.0001$), primary diagnosis other than obstructive lung disease ($p<0.05$ for all other diagnosis categories), hospitalization requirement prior to transplant (AOR 1.37, CI 1.05 - 1.79; $p=0.02$), and bilateral transplant compared to single lung (AOR 1.61, CI 1.36 - 1.92; $p<0.0001$). Higher center volume was associated with a significant reduction in stricture incidence (AOR per increase in center volume of 10 lung transplants per year 0.90, CI 0.87 - 0.92; $p<0.0001$) as was undergoing combined heart/lung transplant when compared to single lung transplant (AOR 0.33, CI 0.17 - 0.63; $p<0.001$). Increasing ischemic time was also associated with a decrease in stricture development (AOR per hour increase 0.87, CI 0.83 - 0.92; $p<0.0001$). Among single lung transplant recipients there was no significant difference in the incidence of stricture comparing single right to single left lung transplant (AOR 0.98, CI 0.80 - 1.19; $p=0.82$). History of diabetes in the donor was the

only donor characteristic associated with increased stricture (AOR 1.51, CI 1.10 - 2.07, $p=0.01$).

Patients who developed stricture had a significantly lower unadjusted overall survival compared to patients without stricture (6.1 vs. 6.8 years, respectively, $p<0.001$, Figure 3) [patients undergoing combined heart/lung transplant ($n=223$) were excluded from survival analyses]. The independent association of stricture with time to death based on multivariable Cox proportional hazard modeling retained statistical significance after adjusting for potential confounders [adjusted hazard ratio (AHR) 1.13, CI 1.03 - 1.23; $p=0.007$]. The development of stricture was also associated with worse postoperative lung function after adjusting for potential confounders, demonstrating a lower postoperative peak FEV₁ [median 74% (IQR 57 – 90%) versus median of 86% (IQR 69 – 102%); $p<0.0001$] (analysis of FEV₁ performed for bilateral lung transplants only).

Of the 1,077 patients in our study population who developed stricture, 703 (65.3%) received a stent, 345 (32.0%) were not stented, 18 (1.7%) had lack of information to determine the use of stenting as a treatment modality, and 11 (1.0%) were combined heart/lung recipients excluded from survival analyses [4 of 11 (36.4%) of which received stent]. For the 1,048 bilateral or single lung recipients where data on stent usage was available, the unadjusted survival was significantly lower in the cohort requiring stent placement ($p<0.0001$, Figure 4). This retained statistical significance based on multivariable adjusted Cox proportional hazard modeling for time to death adjusted for potential confounders (AHR 1.43, CI 1.19 - 1.73; $p=0.0001$).

Comment

Airway complications including bronchial stricture continue to afflict lung transplant recipients and impede successful lung transplantation. In the current study we provide further insight into this disease process by demonstrating an association between early acute rejection and bronchial stricture formation in the largest series of airway complications yet reported in the literature. The importance of further delineating the underlying mechanisms of this disease is evident by the association of stricture with worse postoperative outcomes represented in our study population, and further underscored by the lack of improvement in stricture incidence over the 15 years analyzed.

The proposed pathophysiology underlying bronchial stricture formation involves benign hyperplastic granulation tissue as well as intraluminal fibrosis causing airway obstruction. [17,18] It has been hypothesized that overstimulation of inflammatory mediators and the recruitment of macrophages to the bronchial endothelium contributes to this phenomenon, [4,18,19] which may in part explain the association between early rejection and stricture demonstrated by our study results. Additionally, early animal models evaluating histologic changes in recipient bronchi following lung transplantation demonstrated mononuclear cell infiltrates in the membranous and cartilaginous portion of the donor bronchial mucosa in cases of moderate or severe lung rejection.[20] Ruttmann et al. previously reported an increased risk of stricture formation in patients with early rejection, however their study population was limited to 10 patients with stricture.[21] Several studies have contradicted

these findings by demonstrating no relationship between acute rejection episodes and the occurrence of airway complications,[10,22,23] although relatively small sample sizes may have limited the ability to detect such a relationship. What also remains unknown is the relative importance of airway versus vascular rejection on the development of airway strictures.

While this proposed pathophysiology may imply a causal role of rejection in stricture formation, the retrospective nature of our review and the lack of specific diagnosis dates in the data source preclude determination of causality in the current study. Alternatively, the observed association between early rejection and stricture may relate to a common etiology to these processes, such as ischemia-reperfusion injury,[23] or to retained post-stricture secretions predisposing to inflammation or infection contributing to rejection.[4] Additionally, the presence of bronchial stricture, either symptomatic or asymptomatic, may lead to increased bronchoscopic surveillance with increased use of transbronchial biopsy resulting in an increase in detection of acute rejection.

Several additional variables which have previously been shown to negatively impact postoperative outcomes following lung transplantation were found to be independent predictors of stricture in our study. Patients with male gender had significantly higher incidence of stricture compared to female recipients, which is consistent with several large single center studies demonstrating inferior outcomes for male recipients;[24,25] however, conflicting reports on the impact of gender on lung transplant outcomes exist in the literature.[26,27] There was no significant interaction between gender and primary diagnosis in regards to stricture formation (data not shown), indicating that the impact of gender was independent of underlying disease. Bilateral lung transplant demonstrated higher risk of bronchial stricture compared to single lung, which is not unexpected given the increased number of airways at risk and multiple anastomoses; however, insufficient information is available to delineate the risk specific to the additional anastomoses given lack of specificity in our data source as to anastomotic vs. non-anastomotic stricture. The only donor characteristic significantly associated with increased stricture incidence was diabetes history, which has also been associated with postoperative mortality following lung transplantation.[28]

Patients with obstructive lung disease had decreased incidence of stricture complications relative to other diagnoses, which is also consistent with previous reports of better post-transplant outcomes in this diagnosis group.[29] Decreased stricture incidence with increasing center volume observed in our study population correlates with previous reports of improved lung transplant outcomes from high volume centers.[15] Lower incidence of stricture in combined heart/lung recipients may related to preserved bronchial blood supply during this operation.[17,30] Surprisingly, our results demonstrated a paradoxical relationship with increasing ischemic time associated with decreased incidence of stricture complications. While this could reflect willingness of transplant centers to travel further for high quality organs or reflect wider procurement distances for high volume centers, the association persisted despite adjusting for these potential confounders. Additionally, the level of statistical significance was maintained when records where the ischemic time was imputed [n=936/9,335 (10%)] were excluded from the analysis (data not shown). Though

counterintuitive, multiple reports in the literature demonstrate similar findings of a paradoxical impact of ischemic time on postoperative outcomes,[31-34] although reasons for this relationship have not been elucidated. The data source used for this analysis does not differentiate warm vs. cold ischemic time, which precludes further analysis of these components of the total ischemic time.

Previous attempts to delineate postoperative outcomes following stricture have been limited by the relative infrequency of this disease process.[8] Our results demonstrate significantly worse postoperative lung function for patients with stricture based on peak percent FEV₁, as well as shorter survival. Additionally, patients with bronchial stricture who underwent endobronchial stenting had significantly shorter survival than those without stenting, which retained significance after adjustment for potential confounders. In a single center series reported by Chhajed et al,[7] the survival of patients with airway complications needing intervention was lower than survival in patients who did not need intervention; however those who survived 30 days from intervention had a survival rate that was comparable to recipients without airway complications. Further interpretation of the observed shorter survival in endobronchial stent recipients in our study population would require additional detail including stricture severity, the location and length of the stricture, and duration of stent use, which is unavailable in our data source. Additionally, the potential for selection bias in determining stent recipients would require further evaluation.

These results should be interpreted in the context of the study design. Given the retrospective nature of this review, the potential for unmeasured confounders exists. Additionally, information on the location of the stricture (e.g. anastomotic vs. distal) or the degree of luminal narrowing was not available for analysis. The date of diagnosis of bronchial stricture and the date of endobronchial stenting were not available in our data source, and as such time-to-event analyses could not be performed for these occurrences. This lack of time-point precision also precluded the ability to determine the temporal relationship between early acute rejection and stricture formation. In cases of acute rejection, it is unknown whether the bronchoscopic and/or biopsy was done for surveillance or symptomatic reasons. Additionally, the ability to adjust for early postoperative infection is limited by the lack of detail in our data source to specify infectious process that were pulmonary in origin, which has previously been shown to have an association with bronchial stricture.[23,35]

Conclusions

Data from UNOS suggests that early rejection is associated with an increase in the incidence of bronchial stricture. Recipients with stricture demonstrate worse postoperative lung function and survival. Prospective studies may be warranted to further assess causality and the potential for coordinated rejection and stricture surveillance strategies to improve postoperative outcomes.

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Abbreviations (alphabetical)

AHR adjusted hazard ratio

AOR	adjusted odds ratio
BMI	body mass index
CI	confidence interval
FEV₁	forced expiratory volume at one second as a percent of the patient's predicted value
IQR	interquartile range
OPTN	Organ Procurement and Transplantation Network
PO₂	arterial partial pressure of oxygen
UNOS	United Network for Organ Sharing
US	United States

tx = transplant; UNOS = United Network of Organ Sharing.

Figure 1. Study inclusion algorithm

2A: Trend in incidence of bronchial stricture by year of transplant (entire study population). **2B: Trend in incidence of bronchial stricture by year of transplant (stratified by high-volume and low-volume transplant centers).** **2C: Trend in proportion of bronchial strictures receiving endobronchial stent therapy by year of transplant.**

NOTE: High volume versus low volume centers are distinguished by over/under 34 lung transplants per year.

Figure 2. Trends in bronchial stricture incidence and endobronchial therapy by year of transplant

* Indicates statistical significance.

Figure 3. Unadjusted Kaplan-Meier survival curves for patients with and without bronchial stricture (combined heart/lung excluded)

Number at Risk						
Stent	703	590	359	212	94	43
No stent	345	303	204	108	56	36

† Heart/lung transplant recipients excluded.

* Indicates statistical significance.

Figure 4. Unadjusted Kaplan-Meier survival curves for patients with bronchial stricture receiving stent vs. no stent. †

Table 1
Baseline recipient characteristics for entire cohort

Characteristic	n = 9,335
Age	55 (44, 61)
Age 60	2,770 (29.7%)
Female Gender	4,417 (47.3%)
Gender Mismatch	2,946 (31.6%)
Race	
White	8,152 (87.3%)
Black	676 (7.2%)
Hispanic	364 (3.9%)
Asian	86 (0.9%)
Other/Unknown	57 (0.6%)
Race Mismatch between donor and recipient	3,227 (34.6%)
Diagnosis	
Obstructive Disease	3,991 (42.8%)
Restrictive Disease	2,363 (25.3%)
CF/Bornchiectasis	1,448 (15.5%)
Pulmonary HTN/Eisenmenger/Valvular HD	484 (5.2%)
Graft Failure (re-transplants)	226 (2.4%)
Other	823 (8.8%)
Recipient Comorbidities	
Diabetes (n=9,052)	1,113 (12.3%)
Hypertension (n=6,791)	1,228 (18.1%)
Cerebrovascular Disease (n=6,768)	48 (0.7%)
Creatinine at Transplant	0.8 (0.7, 1.0)
BMI kg/m2 at Transplant (n=9,012)	24.0 (20.4, 27.5)
Chronic Steroid Use Pre-Transplant (n=8,932)	4,369 (48.9%)
Pre-Transplant Status	
Hospitalized	493 (5.3%)
Intensive Care Unit	357 (3.8%)
Requiring Life Support at Transplant [†]	521 (5.6%)
Requiring Ventilator at Transplant	243 (2.6%)
Pulmonary Function and Hemodynamics at TX	
Lung Allocation Score (n=3,952)	37.7 (33.7, 45.0)
Oxygen requirement (L) (n=6,291)	2.0 (2.0, 4.0)
FVC, % predicted (n=8,664)	48.0 (37.0, 61.0)
FEV/FVC (n=8,615)	0.61 (0.40, 1.02)
Mean PA Pressure (mm/Hg) (n=6,956)	25.0 (20.0, 31.0)
PVR (Wood units) (n=5,943)	2.7 (1.8, 3.8)
Cardiac Index (L/min/m2) (n=6,445)	2.8 (2.4, 3.3)

[†]Includes ventilator, extracorporeal membrane oxygenation, intravenous inotropes, intra-aortic balloon pump, or inhaled nitric oxide. Median (interquartile range) for non-parametric continuous variables. N (%) for categorical variables. The number of records with available data is displayed if different from the total study population due to missing data. Abbreviations: CF = cystic fibrosis; HTN = hypertension; HD = heart disease; BMI = body mass index; TX = transplant, FEV₁ = Forced expiratory volume at 1 second (%); FVC = forced vital capacity; PA = pulmonary artery; PVR = peripheral vascular resistance.

Table 2
Donor/transplant characteristics for entire cohort

Characteristic	n = 9,335
Donor/Graft Characteristics	
Days on Waitlist	193 (58, 527)
Type of Transplant	
Bilateral	4,750 (50.9%)
Combined Heart/Lung	223 (2.4%)
Donor Age	30 (20, 44)
Donor Diabetes	342 (3.7%)
Donor Cigarette Use	1,993 (21.5%)
Donor Cocaine Use (n=7,867)	809 (10.3%)
Terminal Creatinine	1.0 (0.8, 1.2)
Donor BMI	24.1 (21.5, 27.1)
HLA Mismatch Level (n=7,713)	
0	8 (0.1%)
1	27 (0.4%)
2	243 (3.2%)
3+	7,435 (96.4%)
CMV Mismatch (n=7,418)	1,684 (22.7%)
PO2 on 100% inspired oxygen	422.0 (375.0, 493.0)
Ischemic Time (hours)	4.7 (3.6, 5.8)

Median (interquartile range) for non-parametric continuous variables. N (%) for categorical variables. The number of records with available data is displayed if different from the total study population due to missing data. Abbreviations: BMI = body mass index; forced vital capacity; PA = pulmonary artery; PVR = peripheral vascular resistance; HLA = human leukocyte antigen; CMV = cytomegalovirus; PO2 = arterial partial pressure of oxygen.

Table 3
Multivariable logistic regression for development of bronchial stricture

Recipient, Donor, and Transplant Characteristics	Adjusted Odds Ratio	95% Confidence Interval		P-Value
		Lower	Upper	
Primary Predictor Variable				
Treated for acute rejection within 1 year	1.40	1.22	1.61	* <0.0001
Covariates				
Recipient/Transplant Characteristics				
Age (AOR per 5-year increase)	1.00	0.96	1.03	0.9099
Male Gender	1.52	1.33	1.75	* <0.0001
Race Mismatch between donor and recipient	1.01	0.88	1.16	0.8756
Primary Diagnosis (ref = obstructive disease)				
Restrictive Disease	1.73	1.46	2.05	* <0.0001
CF/Bronchiectasis	1.33	1.02	1.73	* 0.0352
Pulmonary HTN/Eisenmenger/Valvular HD	1.93	1.40	2.67	* <0.0001
Graft Failure (re-transplants)	1.60	1.04	2.44	* 0.0309
Other	1.64	1.28	2.11	* <0.0001
Type of Transplant (ref = single lung)				
Bilateral	1.61	1.36	1.92	* <0.0001
Combined Heart/Lung	0.33	0.17	0.63	* 0.0009
Center Volume (AOR per increase of 10 LTX/year)	0.90	0.87	0.92	* <0.0001
Year of Transplant (AOR per year increase)	0.98	0.96	1.01	0.2424
Chronic Steroid Use Prior to Transplant	1.03	0.90	1.18	0.6558
Medical Condition at Transplant (ref = not hospitalized)				
Hospitalized	1.37	1.05	1.79	* 0.0190
Intensive Care Unit	1.15	0.75	1.76	0.5179
Requiring Life Support at Transplant	0.93	0.63	1.39	0.7357
Ventilator Dependent at Transplant	1.29	0.71	2.35	0.3977
Days on the Waitlist (AOR per 90-day increase)	1.01	0.99	1.02	0.3599
Ischemic Time (AOR per hour increase)	0.87	0.83	0.92	* <0.0001
Donor Characteristics				

Recipient, Donor, and Transplant Characteristics	Adjusted Odds Ratio	95% Confidence Interval		P-Value
		Lower	Upper	
Age (AOR per 5-year increase)	1.02	0.99	1.04	0.1806
History of Diabetes	1.51	1.10	2.07	0.0110 *
History of Cigarette Use	0.97	0.82	1.15	0.7309
History of Cocaine	1.00	0.79	1.26	0.9717
PO2 (mm Hg) on 100% oxygen (AOR per 50-point increase)	1.01	0.98	1.04	0.4578

Abbreviations: OR = odds ratio; CF = cystic fibrosis; HTN = hypertension; HD = heart disease; LTX = lung transplant; PO2 = partial pressure of oxygen.