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

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Background. **Risk factors and outcomes of bronchial stricture after 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 transplantations between April 1994 and December 2008 per the United Network for Organ Sharing (UNOS) 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. **Nine thousand three hundred thirty-five 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 sex, restrictive lung disease, and pretransplantation requirement for hospitalization were also associated with stricture. Those who experienced stricture had a lower postoperative peak percent predicted forced expiratory volume at 1 second (FEV_1) (median 74% versus 86% for bilateral transplants only; $p < 0.0001$), shorter unadjusted survival (median 6.09 versus 6.82 years; $p < 0.001$) and increased risk of death after adjusting for potential confounders (adjusted hazard ratio 1.13; 95% CI, 1.03–1.23; $p = 0.007$).**

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.**

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The number of lung transplant procedures has continued to increase each year, with more 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 after lung transplantation in the modern era has been reported between 5% and 30%, with up to a 40% decrease in 5-year survival compared with patients without airway complications [7–9].

The mechanism by which stricture may arise remains speculative [2, 10]. Given its overall low prevalence, the implications of this condition developing 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 cellular 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 bronchial stricture after transplantation. Our main objective was to evaluate this relationship using a cohort of all lung transplantations performed in the United States 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

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Abbreviations and Acronyms

AOR = adjusted odds ratio
BMI = body mass index
95% CI = 95% confidence interval
FEV_1 = forced expiratory volume at 1 second (as a percent of the patient's predicted value)
IQR = interquartile range
OPTN = Organ Procurement and Transplantation Network
P_{O_2} = arterial partial pressure of oxygen
UNOS = United Network for Organ Sharing

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, which contain data regarding every organ donation and transplant event occurring in the United States since October 1, 1987, were used for this analysis [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 October 1987 and December 2011, with follow-up through March 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 April 1994, when recording of stricture information began, through December 2008 to allow a minimum of 3 years' follow-up time to capture stricture incidence and resulting outcomes. To be included in the study, patients had to have a follow-up visit after transplantation 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 No. 0915-0157). This form is generated 6 months after transplantation and on the anniversary of transplantation thereafter. Patients with unknown or missing stricture information were excluded. Additional exclusion criteria were patients undergoing multivisceral transplantation (other than heart-lung), recipients of a third lung transplant, pediatric recipients, and lobar or en bloc 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, sex, race (white, black, Hispanic, Asian, other/unknown), primary diagnosis (obstructive disease, restrictive disease, cystic fibrosis/bronchiectasis, pulmonary hypertension, graft failure [for repeated transplantation], 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 a given center during the study period), year of transplantation, chronic steroid use before transplantation, medical condition preceding transplantation (nonhospitalized, hospitalized, intensive care), requirement of life support at the time of transplantation (ventilator, extracorporeal membrane oxygenation, intravenous inotropic agents, intraaortic balloon pump, or inhaled nitric oxide), ventilator dependence at the time of transplantation, days on the waiting list, allograft ischemic time (for bilateral transplantation, 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 [P_{O_2}] on inspired oxygen of 100%).

The primary outcome variable was the development of stricture after transplantation. The trend in stricture incidence and proportion receiving endobronchial stenting therapy were also assessed. For patients in whom stricture developed (regardless of predisposing risk factors), a secondary analysis was performed to evaluate postoperative peak forced expiratory volume at 1 second (FEV_1) as a percent of the patient's predicted value, unadjusted and adjusted overall survival compared with recipients without stricture.

Sensitivity Analysis

Early infection (defined as any drug-treated infection before discharge) is captured only through January 2007, and therefore these data are 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 reran the multivariable logistic regression analysis to include early infection as an additional covariate for risk adjustment for the subset of patients in whom 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 and 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