Differential Outcomes With Early and Late Repeat Transplantation in the Era of the Lung Allocation Score

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Background. Rates of repeat lung transplantation have increased since implementation of the lung allocation score (LAS). The purpose of this study is to compare survival between repeat (ReTx) and primary (LTx) lung transplant recipients in the LAS era.

Methods. We extracted data from 9,270 LTx and 456 ReTx recipients since LAS implementation, from the United Network for Organ Sharing registry. Propensity scoring was used to match ReTx and LTx recipients. Kaplan-Meier analysis compared survival between LTx and ReTx groups, with and without stratification based on time between first and second transplant. Multivariable Cox models estimated predictors of survival in lung recipients.

Results. Comparing all ReTx to LTx demonstrates a survival advantage for LTx that is diminished with propensity score matching ($p = 0.174$). Considering LTx against ReTx greater than 90 days after the initial procedure, there are similar survival results ($p < 0.067$). In contrast, ReTx within 90 days was associated with a survival disadvantage that persisted despite matching ($p = 0.011$). In ReTx populations, factors conferring worse outcomes include intensive care unit admission, unilateral transplantation, poor functional status, and primary graft dysfunction as the indication for retransplantation ($p < 0.05$).

Conclusions. Late lung retransplantation appears to be as beneficial as primary transplantation in propensity-matched patients. However, survival is severely diminished in those retransplanted less than 90 days after primary transplantation. The utility of early retransplantation needs to be carefully weighed in light of risks.

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The incidence of repeat lung transplantation in the United States has increased over the last several years [1, 2] (Fig 1). This increase can be attributed to 2 factors that have greatly impacted the field of lung transplantation. First is the introduction of the lung allocation score (LAS) in May 2005 that prioritizes patients based on survival benefit and medical urgency [3]. The other driver is improvement in the practice of lung transplantation with accompanying increases in recipient survival. However, few studies have explored survival in recipients of lung retransplantation [1, 2, 4–9]. One of these, by Shuhaiber and colleagues [6] in the pre-LAS era, concluded that adjusting for confounders, purported differences in survival between repeat and primary lung transplantation, are nonsignificant.

The purpose of the current study was to review the national experience with lung retransplantation since LAS implementation. We evaluate survival for primary and repeat recipients with and without risk matching. We also analyze the importance of the duration between initial and repeat transplantation, hypothesizing that early retransplantation carries a greater mortality risk than late retransplantation. Lastly, we explore donor, recipient, and transplant factors in order to identify characteristics that promote longevity in lung retransplantation.

## Material and Methods

Study Population

The study protocol was approved by the Duke University Institutional Review Board; individual consent was not needed. The United Network for Organ Sharing national database was queried for adult transplantations recorded from May 2005 (after LAS implementation) to December 2011 [10]. Patients were excluded if they underwent multiorgan transplantation or were younger than 18 years of age. Analysis was limited to variables that were

Fig 1. Number and proportion of lung retransplantation performed in the United States by year. (LAS = lung allocation score.)
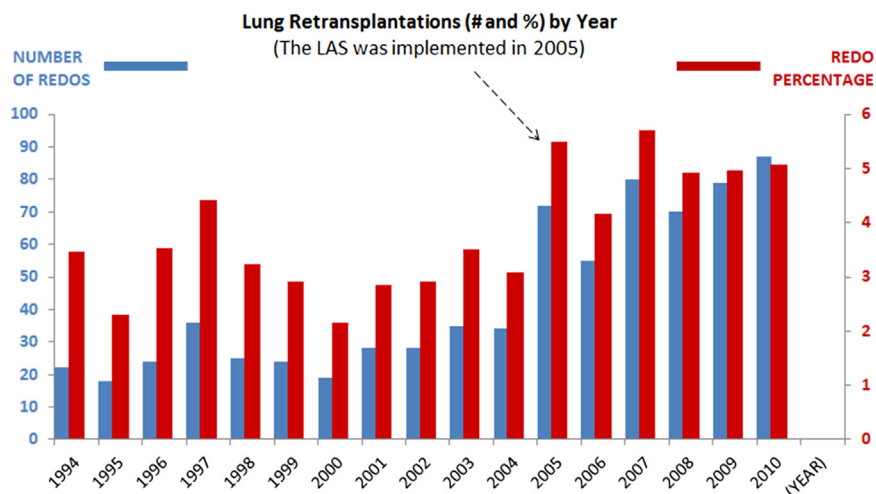
at least 80% populated, with most having available data for greater than 95% of patients.

Patients were categorized as primary (LTx) or repeat (ReTx) lung recipients. Additional cohorts were created for ReTx recipients receiving retransplantation greater (late-ReTx) or less than (early-ReTx) 90 days after initial lung transplantation [we defined early and late groups based on existing studies suggesting worse outcomes after retransplantation performed within 90 days [1, 11]. The primary study outcome was survival.

Propensity Matching

The ReTx recipients were matched 1:1 with LTx recipients based on the propensity score method as outlined by Austin [12], Rosenbaum and Rubin [13, 14], and D'Agostino and Rubin [15], and applied in lung transplantation by Shuhaiber and colleagues [6] and Castleberry and colleagues [16]. This method controls for differences in patient, donor, and transplant characteristics between cohorts. In this study, the propensity score itself estimates the probability of undergoing retransplantation. The score was calculated using a logistic regression model with covariate selection based on backward elimination. Variables included in the baseline model are noted in Table 1.

As previously established for dealing with missing data in propensity score analyses [6, 15, 16], an additional level was created for each categoric variable to indicate missing data. For continuous variables a value of 0 was imputed in empty fields, with creation of a new, binary variable indicating whether data were missing. Balance between matched cohorts was assessed using standardized differences with values below 0.2 indicating negligible differences in characteristics [17, 18].

Primary Analyses

Survival in matched and unmatched groups was compared using Kaplan-Meier, log-rank, and Cox regression methods. For matched samples, comparisons were performed using stratified analyses based on quartiles of the propensity score [19].

Risk matching and survival comparisons were repeated for retransplantations performed less than (early ReTx) or greater than 90 days (late ReTx) after the initial procedure. Further analyses compared ReTx recipients stratified into 3 groups based on time between initial and repeat transplantation: (1) < 90 days; (2) between 90 days and 2 years; and (3) greater than 2 years. Finally, we compared survival after lung retransplantation pre-LAS versus post-LAS implementation.

Secondary Analyses

Multivariable Cox regression models outlined predictors of survival after lung retransplantation. Models started out with the same variables from the propensity score analysis with final variable inclusion based on backward selection.

A final multivariable model identified predictors of survival in the overall cohort of lung recipients. This model included a 3-level variable designating patients as LTx, early ReTx, or late ReTx.

Results

Patient Characteristics

A total of 9,726 patients met study criteria, including 456 ReTx (4.7%) and 9,270 LTx (95.3%) patients (Table 1). For the ReTx cohort, diagnosis was obliterative bronchiolitis in 53% (n = 241) and primary graft dysfunction (PGD) in 17% (n = 77) of cases. Median number of days between initial and repeat transplantation was 1,056 (interquartile range [IQR] 473 to 2,176). Compared with LTx patients, ReTx recipients were younger (median age 51, IQR 34 to 61 vs 58, IQR 49 to 64), more often had cystic fibrosis or bronchiectasis as the underlying diagnosis (29%, n = 130 vs 14%, n = 1,295), and had higher LAS (median 47, IQR 40 to 70 vs 39, IQR 34 to 48). Number of wait-list days was lower for ReTx