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

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Abstract

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.

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

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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 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 categorical 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 recipients (median 43, IQR 12 to 125 vs 73, 22 to 229). Prior to matching, a considerable degree of imbalance was observed between ReTx and LTx cohorts with significant differences in 5 of 8 continuous and 11 of 17 categorical variables. No statistically significant differences existed after matching.

Primary Analysis

Unadjusted analysis comparing unmatched cohorts identified increased mortality for ReTx recipients compared with LTx recipients ($p < 0.001$; HR = 1.69, 95% CI 1.47 to 1.95; Fig 2A). Conversely, analysis in the 1:1 matched sample demonstrated no significant differences in survival between ReTx and LTx populations ($p = 0.174$; HR = 1.16, 95% CI 0.94 to 1.43; Fig 2B). Sixty-four ReTx recipients received repeat transplantation within 90 days of the initial procedure, while 392 patients received repeat transplantation greater than 90 days afterward. Unadjusted Kaplan-Meier analysis comparing unmatched groups demonstrated

decreased survival for both early-ReTx and late-ReTx compared with LTx recipients ($p < 0.001$, Fig 3A;B). After 1:1 matching, survival differences between LTx and ReTx persisted for early-ReTx ($p = 0.011$; HR = 2.02, 95% CI 1.09 to 3.71; Fig 3A), but did not reach statistical significance for late-ReTx ($p = 0.067$; HR = 1.23, 95% CI 0.97 to 1.55; Fig 3B).

Comparison after stratification into 3 groups for time between transplants demonstrated superior survival for patients receiving retransplant greater than 2 years after the first procedure (Fig 4). Compared with patients receiving retransplantation within 90 days, this difference achieved statistical significance ($p < 0.001$; HR = 0.42, 95% CI 0.28 to 0.62). Compared to patients receiving retransplantation between 90 days and 2 years after the initial procedure, there was a trend toward statistical significance, although it was not achieved ($p = 0.070$; HR = 0.75, 95% CI 0.55 to 1.03). Furthermore, analyses demonstrated improved survival for lung retransplantation performed in the LAS era compared with the pre-LAS era ($p = 0.002$; HR = 0.75, 95% CI 0.62 to 0.90; Fig 5).

Secondary Analysis

In the cohort of ReTx recipients, multivariable Cox-regression modeling identified preoperative intensive care unit (ICU) admission ($p < 0.001$; HR = 2.04, 95% CI 1.4 to 2.88), infection requiring intravenous antibiotics within the 2-week period before transplantation ($p = 0.003$; HR = 1.66, 95% CI 1.18 to 2.34) and unilateral retransplantation ($p = 0.048$; HR = 1.43, 95% CI 1.01 to 2.05) as factors that predict increased mortality. Additionally, indication for ReTx predicted outcomes, with worse survival for primary graft dysfunction compared with bronchiolitis obliterans syndrome ($p = 0.0127$; HR = 1.63, 95% CI 1.11 to 2.38).

Looking broadly at the overall cohort of lung recipients, analyses demonstrated worse survival for early-ReTx compared with first-time ($p < 0.001$, HR = 1.97, 95% CI 1.37 to 2.84) or late-ReTx ($p = 0.023$, HR = 1.58, 95% CI 1.06 to 2.34). Other factors associated with worse survival included elevated serum creatinine ($p < 0.001$, HR [per unit increase in creatinine] = 1.12, 95% CI 1.05 to 1.18), pretransplant ICU admission ($p < 0.001$; HR = 1.64, 95% CI 1.37 to 1.96), pretransplant hospital admission ($p = 0.025$, HR = 1.20, 95% CI 1.02 to 1.41), unilateral lung transplantation ($p < 0.001$, HR = 1.23, 95% CI 1.13 to 1.35), and limitations in performing activities of daily living (ADLs) ($p = 0.014$, HR = 1.12, 95% CI 1.02 to 1.23).

Comment

Repeat lung transplantation has become more common in recent years, making up increasingly larger proportions of the national experience with lung transplantation. In this study we report a survival disadvantage for repeat versus primary lung transplantation in the LAS era that is diminished after propensity-score matching to control for confounders. In other words, retransplantation may be as beneficial as primary lung transplantation in risk-matched patients. We show, however, that this post-matching equivalence in survival is not applicable across the entire population of retransplant recipients. Patients receiving organs shortly after primary transplantation are at increased risk for mortality, even after risk adjustment. Additionally, we identified other predictors of mortality in repeat

transplantation, including ICU admission, infection requiring intravenous antibiotics, procedure type, indication for surgery, and functional status. Altogether, these findings provide guidance for the selection of patients for repeat lung transplantation.

Study findings of comparable survival in risk-matched cohorts of repeat and primary lung recipients are consistent with existing literature. In an analysis of pre-LAS transplantations, Shuhaiber and colleagues [6] demonstrated that controlling for confounders, survival differences between primary and repeat transplant recipients are insignificant. Authors also observed that functional status and serum creatinine were predictors of survival in retransplantation. Other studies have identified predictors of mortality in lung retransplantation. Kilic and colleagues [5] demonstrated that mortality is highest in recipients with total functional need based on the Karnofsky scale. Aigner and colleagues [9] reported that the indication for retransplantation (PGD/bronchiolitis obliterans syndrome [BOS]) dictates patterns of survival. Others report increased mortality for early lung retransplantation, with the definition of “early” ranging from 90 days to 2 years, in various analyses [11, 20,21].

In the current study, providing the first evaluation of survival in patients receiving retransplantation in the LAS era, our data confirm that patients receiving lung retransplantation continue to experience reasonable survival compared with risk-matched first-time recipients. Given LAS era increases in the rate of lung retransplantation, this work provides an important update on the topic. Additionally, our work represents the first, risk-matched evaluation of survival in lung retransplantation based on the duration of time elapsed after the initial procedure. Our finding of a persistent survival disadvantage with early retransplantation despite matching provides confirmation of previously raised anecdotal concerns in the field about the viability of retransplantation performed shortly after the initial procedure. Results highlight the importance of careful recipient evaluation for prospects for long-term survival before proceeding with early retransplantation. At our center, retransplantation is considered on an individual case basis. Programmatically, we avoid redo lung transplantation in the elderly (over 60 to 65 years). Also, due to our center's experience, as well as findings from this current analysis, we avoid early retransplantation unless the patient demonstrates adequate function of other organs and the ability to perform active rehabilitation posttransplant.

Consistent with previous studies, preoperative functional status (hospitalization, ICU admission, or independence for ADLs) and indication for retransplantation (PGD/BOS) were identified as predictors of survival after lung retransplantation [5, 6, 20]. The finding of differential survival by indication for retransplantation is reinforced by our analysis with stratification into 3 groups by time between initial and repeat transplantation. These groups likely represent diagnosis categories for PGD (time < 90 days), early BOS (90 days < time < 2 years), and late BOS (time > 2 years). With such differing survival profiles, outcomes in these groups are likely determined based on varying predictive factors, an area of exploration for future work. It is important to note that in clinical practice, the specific indication for retransplantation is often unclear, justifying risk stratification based on time since initial transplantation, in addition to suspected reason for graft failure.

In contrast to previous studies, serum creatinine was not found to be a predictor of survival in retransplantation [2, 6]. It was, however, a predictor of survival in the entire cohort of lung recipients. One potential explanation for this is the exposure of retransplant recipients to calcineurin inhibitors after their initial operation. Having already suffered some degree of renal deterioration, the impact of these medications on creatinine may have already been accounted for prior to retransplantation. Therefore, the predictive capabilities of creatinine on survival in retransplant recipients will likely be blunted or nonexistent. Notwithstanding, the effect of creatinine on survival after lung retransplantation remains an area of priority for future investigations.

Implications of our findings to lung transplantation policy and practice are manifold. Results from the primary analysis confirm that lung retransplantation is a viable therapy for end-stage lung disease, conferring a comparable survival benefit to primary transplantation in appropriately selected patients. Temporal comparisons demonstrate improved survival after lung retransplantation since LAS implementation. This undoubtedly reflects improvements in the practice of lung transplantation, but it likely also reflects optimized candidate selection with the use of the lung allocation score. An important observation from our study, based on imbalance in patient characteristics, is that the average candidate for retransplantation is in worse medical condition than the average candidate for primary lung transplantation. However, we do not believe that this observation detracts from our findings. On the contrary, we believe that it strengthens the assertion that careful preparation is necessary prior to retransplantation in high-risk candidates.

Results from our secondary analysis provide further guidance for the practice of lung retransplantation. Analyses suggest that bilateral procedures should be performed, where possible, and that adequate attempts be made to completely treat systemic infections before surgery. Likewise, retransplantation from an ICU setting or in patients with exceptionally poor functional status carries excessive risk and should be avoided where possible.

Any analysis of lung retransplantation is incomplete without some consideration of the ethics of allocating a second lung to one individual, while others wait for the first one. Many studies have attempted to tackle this dilemma which measures the needs of the individual patient against the prospects of maximizing the distribution of available lungs [1, 6, 22–24]. While there is no consensus on the most ethically appropriate allocation algorithm for retransplantation, much work has gone into mitigating the problem by increasing organ availability and clarifying the characteristics of the ideal retransplant candidate. Our work falls in this latter category as we contribute to outlining the factors that improve outcomes in lung retransplantation. Based on our results the ideal candidate for retransplantation is at least 90 days out from the initial procedure and has enjoyed some postoperative functional recovery (ideally out of the ICU or hospital with some ability to perform ADLs).

An important limitation of our study is that we only consider patients who ultimately received organs. Transplant candidates who did not make it to listing provide a wealth of information that could contribute to our understanding of practice patterns in the field. Our inability to access this information limits the potential of our analyses. A second limitation exists in the retrospective design of our study which comes with the challenges associated

with non-prospective, nonrandomized analyses. Our statistical analysis with propensity-score matching and adjustment for potential confounders begins to address this limitation, albeit imperfectly given the possible existence of meaningful confounders that are not available to us. A final limitation is related to our use of the propensity score method which results in lower sample size. Time-based differences were robust despite identical modeling applied to both early and late retransplant cohorts, providing some validation of study findings.

In conclusion, when performed in appropriately selected patients, lung retransplantation in the LAS era continues to provide survival benefit that is comparable with that derived from primary lung transplantation. Candidates for retransplantation earlier than 90 days after initial lung transplantation are at increased risk for adverse outcomes, even after controlling for other confounders. These patients require special evaluation before undergoing the retransplant operation. Several other factors contribute to determining outcomes in retransplantation including functional status, transplant type, serious infection, and indication for retransplantation. Appropriate candidate selection for retransplantation can be achieved by optimizing these factors while balancing the need for retransplantation as a therapy for recurrent end-stage lung disease against the desire to distribute scarce lungs as “justly” as possible.

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Fig 1. Number and proportion of lung retransplantation performed in the United States by year (LAS = lung allocation score)

Fig 2. Kaplan-Meier survival curves comparing (A) unmatched and (B) matched groups of primary and repeat lung recipients

Fig 3. Kaplan-Meier survival curves comparing survival in (A) Early (< 90 days) and (B) late (90 days) retransplantation with survival in unmatched and matched groups of primary lung recipients

Fig 4. Survival by time between initial and repeat transplantation

	<i>Number at Risk</i>					
LAS	485	273	168	112	64	36
Pre-LAS	381	207	168	142	118	106

Fig 5. Comparative survival of lung retransplantation before and after the implementation of the lung allocation score (LAS)

Table 1
Baseline Characteristics for Matched and Unmatched Groups of Primary and Repeat Lung Recipients

Variables	Total Sample			1:1 Matched Sample		
	Primary (n = 9,270)	Repeat (n = 456)	p Value ^a	Primary (n = 429)	Repeat (n = 429)	Stand. Diff. ^b
Continuous covariates						
Donor age (years)	32 (21–46)	30 (21–45)	0.156	28 (20–46)	29 (21–45)	0.01
Donor BMI (kg/m ²)	25 (22–28)	25 (22–28)	0.700	25 (22–28)	25 (22–28)	–0.02
Recipient age (years)	58 (49–64)	51 (34–61)	<0.001 ^c	54 (31–62)	51 (36–61)	–0.01
Recipient BMI (kg/m ²)	25 (21–29)	22 (19–26)	<0.001 ^c	24 (19–28)	22 (19–26)	0.05
Wait list days	73 (22–229)	43 (12–125)	<0.001 ^c	52 (12–178)	45 (12–129)	0.01
Lung allocation score	39 (34–48)	47 (40–70)	<0.001 ^c	47 (37–85)	47 (40–67)	0.13
Ischemic time (hours)	4.8 (3.8–6.0)	4.8 (3.5–6.1)	0.873	4.9 (3.8–6.0)	4.8 (3.5–6.2)	0.03
Serum creatinine (mg/dL)	0.8 (0.7–1.0)	1.1 (0.8–1.3)	<0.001 ^c	0.8 (0.8–1.1)	1.0 (0.8–1.3)	–0.02
Days b/w transplants	NA	1,056 (473–2,176)	NA	NA	1056 (484–2171)	NA
Categorical covariates:						
Donor race (Caucasian)	5,771 (0.62)	268 (0.59)	0.267	261 (0.61)	252 (0.59)	0.04
Donor sex (female)	3,719 (0.40)	197 (0.43)	0.190	153 (0.36)	183 (0.43)	–0.14
Donor cause of death:			0.039 ^c			
CVA/stroke	3,356 (0.36)	158 (0.35)		137 (0.32)	148 (0.35)	–0.06
Head trauma	4,432 (0.47)	234 (0.51)		216 (0.50)	224 (0.52)	–0.04
Recipient race: (Caucasian)	7,801 (0.84)	398 (0.87)	0.131	373 (0.87)	374 (0.87)	0.00
Recipient sex (female)	3,822 (0.41)	203 (0.45)	0.164	171 (0.40)	190 (0.44)	–0.08
Underlying diagnosis:			<0.001 ^c			
Obstructive	2,997 (0.32)	120 (0.26)		101 (0.23)	114 (0.27)	–0.09
Restrictive	4,045 (0.44)	140 (0.31)		141 (0.32)	137 (0.32)	0.00
CF/bronchiectasis	1,295 (0.14)	130 (0.29)		120 (0.28)	118 (0.28)	0.00
PPH	398 (0.04)	26 (0.06)		22 (0.05)	25 (0.06)	–0.04
Other	535 (0.06)	40 (0.09)		45 (0.10)	35 (0.08)	0.07
Retransplant diagnosis:						

Variables	Total Sample			1:1 Matched Sample		
	Primary (n = 9,270)	Repeat (n = 456)	p Value ^a	Primary (n = 429)	Repeat (n = 429)	Stand. Diff. ^b
Obliterative bronchiolitis	NA	241 (0.53)	NA	NA	227 (0.53)	NA
PGD/acute rejection		77 (0.17)			72 (0.17)	
Other		138 (0.30)			130 (0.30)	
CMV (positive)	5,056 (0.55)	289 (0.63)	<0.001 ^c	267 (0.62)	270 (0.63)	-0.02
ABO match (level 1)	8,517 (0.91)	409 (0.90)	0.098	403 (0.94)	385 (0.90)	0.15
Medical condition:						
Ventilator	520 (0.06)	96 (0.21)	<0.001 ^c	101 (0.24)	83 (0.19)	0.12
ICU	690 (0.07)	118 (0.26)	<0.001 ^c	129 (0.30)	101 (0.24)	0.14
Hospitalized	1,407 (0.15)	182 (0.40)	<0.001 ^c	177 (0.41)	161 (0.38)	0.06
Procedure type (bilateral)	6,106 (0.66)	235 (0.52)	<0.001 ^c	245 (0.57)	226 (0.53)	0.08
Diabetes (yes)	1,628 (0.18)	221 (0.48)	<0.001 ^c	203 (0.47)	203 (0.47)	0.00
No limitation of ADLs	3,041 (0.33)	104 (0.23)	<0.001 ^c	94 (0.22)	103 (0.24)	-0.05
Employed (yes)	856 (0.09)	18 (0.04)	<0.001 ^c	22 (0.05)	17 (0.04)	0.05
IV drug treated infect. (Yes)	924 (0.10)	130 (0.29)	<0.001 ^c	128 (0.30)	119 (0.28)	0.04
Payer (Medicare/Medicaid)	4,001 (0.43)	208 (0.45)	0.110	194 (0.45)	196 (0.46)	-0.02

^a Student *t* test for continuous variables; χ^2 for categorical variables.

^b Standardized differences displayed below are estimated as the difference in the mean between the 2 groups being compared, divided by the square root of the pooled variance, with modification to reflection proportions for categorical variables. Values < 0.2 indicate negligible differences in values for the 2 groups.

^c Significant difference at the 5% level.

ADLs = activities of daily living; BMI = body mass index; CF = cystic fibrosis; CMV = cytomegalovirus; CVA = cerebrovascular accident; NA = not applicable; PGD = primary graft dysfunction; PPH = primary pulmonary hypertension.