ORIGINAL ARTICLE

Transplant size mismatch in restrictive lung disease

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SUMMARY

To maximize the benefit of lung transplantation, the effect of size mismatch on survival in lung transplant recipients with restrictive lung disease (RLD) was examined. All single and bilateral RLD lung transplants from 1987 to 2011 in the United Network for Organ Sharing (UNOS) Database were identified. Donor predicted total lung capacity (pTLC):Recipient pTLC ratio (pTLCr) quantified mismatch. pTLCr was segregated into five strata. A Cox proportional hazards model evaluated the association of pTLCr with mortality hazard. To identify a critical pTLCr, a Cox model using a restricted cubic spline for pTLCr was used. A total of 6656 transplants for RLD were identified. Median pTLCr for single orthotopic lung transplant (SOLT) and bilateral orthotopic lung transplant (BOLT) was 1.0 (0.69–1.47) and 0.98 (0.66–1.45). Examination of pTLCr as a categorical variable revealed that undersizing (pTLCr <0.8) for SOLT and moderate oversizing (pTLCr = 1.1–1.2) for SOLT and BOLT had a harmful survival effect [for SOLT pTLC <0.8: HR 1.711 (95% CI 1.146–2.557), $P = 0.01$ and for BOLT pTLC 1.1–1.2: HR 1.717 (95% CI 1.112–2.651), $P = 0.02$]. Spline analysis revealed significant changes in SOLT mortality by variation of pTLCr between 0.8–0.9 and 1.1–1.2. RLD patients undergoing SOLT are susceptible to detriments of an undersized lung. RLD patients undergoing BOLT have higher risk of mortality when pTLCr falls between 1.1 and 1.2.

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Key words
donor assessment, lung transplant, organ allocation, size mismatch

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Introduction

Lung transplantation is the most durable and efficacious treatment of end-stage lung disease, and the choice of donor organs has long been a subject of debate. Many donor characteristics including age, comorbidities, and smoking status have been examined with regard to their impact on outcomes following lung transplantation. More recently, some groups have examined the impact of donor and recipient lung size on survival following lung transplantation [1–4].

Due to limitations on ability to physically measure lung dimensions, predictors of lung size have been used instead. One example is predicted total lung capacity (pTLC), which estimates lung volumes using height as an independent variable [5]. This method has been validated and utilized to compare the relationship between donor and recipient lung size in previous studies [1–3,6–8].

However, previous efforts have not specifically focused on restrictive lung disease (RLD), instead including a heterogenous collection of patients. Lung

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transplant recipients with RLD represent a unique population as the pathophysiology of their disease makes choice of donor lungs important. In particular, patients with RLD often have chest wall contraction that affects pulmonary mechanics differently than other transplantation indications [9]. Moreover, it is common to have single orthotopic lung transplantation (SOLT) in restrictive disease, and there is currently minimal data regarding size matching in SOLT [9]. As such, the primary purpose of this study was to examine how the relationship of donor to recipient predicted lung capacity impacts long-term survival following both SOLT and bilateral orthotopic lung transplantation (BOLT) in patients with RLD.

Methods

Data source

The protocol for this retrospective analysis was approved by the Institutional Review Board at our institution. The United Network for Organ Sharing (UNOS) administers the Organ Procurement and Transplantation Network (OPTN) under contract with the U.S. Department of Health and Human Services (HHS). The UNOS Standard Transplant Analysis and Research file was queried to identify all lung transplants from 1987 to 2011. All patients with RLD as an indication for transplant were identified as defined by the primary diagnosis at the time of transplantation in the UNOS STAR file. Pediatric, multi-organ, and redo lung transplants were excluded.

Patient classification/outcome

The pTLC was calculated for all patients in the final cohort using the equation described by Stocks and Quanjer [5]; pTLC = 7.99 × Height − 7.08 or 6.60 × Height − 5.79 for males and females, respectively. For purposes of comparison, donor and recipients pTLC were compared as a ratio of the donor pTLC: recipient pTLC (pTLCr). Patients were then grouped based on the pTLCr with a pTLCr <0.9 being defined as undersized, pTLCr between, and including, 0.9 and 1.1 being similarly sized, and pTLCr >1.1 termed oversized. Given the differences in expected outcomes between single orthotopic lung transplantation (SOLT) and bilateral orthotopic lung transplantation (BOLT), patients were further stratified based on procedure. The primary outcome of the study was long-term survival. Secondary outcomes included postoperative need for dialysis, postoperative bronchial stricture, and length of stay.

Statistical methods

Following stratification as detailed above, comparisons amongst the three previously described groups were conducted using the analysis of variance (ANOVA) or the chi-square test for continuous and categorical variables, respectively. A Cochran–Armitage trend test was utilized to examine trends in sizing over time, by year. Given the concern that the initial stratification was too simple with regard to sizing the under and oversized, each category was broken into two groups. For undersized, they were pTLCr <0.8 and pTLCr between 0.8 and 0.9, while for oversized, it was pTLCr between 1.1 and 1.2 and pTLCr >1.2. Thus, a total of five groups were established for both SOLT and BOLT. As the primary endpoint was long-term survival, a Cox proportional hazard model for both SOLT and BOLT was employed to examine the independent effect of pTLCr on long-term survival. Variables included in the model were patient, donor, and procedural characteristics known to influence post-transplant survival. Additionally, Kaplan–Meier analysis was utilized to provide a visual representation of survival amongst the five groups.

While the initial Cox proportional hazard model identified the impact of pTLCr on survival, it did not indicate where changes in pTLCr had the greatest impact on survival. Thus, to address this limitation, we utilized a separate Cox proportional hazard model with a restricted cubic spline to determine where changes in pTLCr were greatest for both SOLT and BOLT. Relative mortality hazard was assessed in relation to a pTLC of 1.0 for both SOLT and BOLT.

In all cases, type I error was controlled at the level of comparison and a *P*-value of 0.05 was determined a priori to be the level of significance. All statistics were performed using R version 3.3.1, R Foundation for Statistical Computing, Vienna, Austria. Restricted cubic splines were developed using the package rms: Regression Modeling Strategies, R package version 4.5-0.

Results

From 1987 to 2011, 6656 lung transplants met inclusion criteria with $n = 3532$ (53.1%) undergoing SOLT and $n = 3124$ (46.9%) undergoing BOLT. Overall, in patients undergoing SOLT, 66.9% ($n = 2362$) were similarly sized, 19.7% ($n = 696$) were undersized, and 13.4% ($n = 474$) were considered oversized. For those

undergoing BOLT, 64.0% ($n = 1998$) were similarly sized, 24.1% ($n = 753$) were undersized, and 11.9% ($n = 373$) were oversized. In both cases, there was a trend toward the use of similarly sized and undersized lungs during the study time period (Fig. 1; $P < 0.01$ for both SOLT and BOLT).

Regarding donor characteristics, older donors were associated with under-sizing, while younger donors were associated with over-sizing in both SOLT and BOLT. With regard to recipients, under-sizing was associated with older recipients, while over-sizing was associated with younger patients for both SOLT and BOLT. In general, undersized SOLT and BOLT recipients were also associated with an increased incidence of diabetes, were more likely to be white race, and were more likely to be hospitalized or in the intensive care unit prior to transplant ($P < 0.01$ in all cases). In patients with available data, undersized patients had a statistically significant higher lung allocation score (LAS) (44.0 and 49.2 for SOLT and BOLT, respectively) than similarly sized (42.6 and 46.3 for SOLT and BOLT, respectively) and oversized recipients (41.7 and 46.3 for SOLT and BOLT, respectively), although this is unlikely to represent a clinically meaningful difference. Interestingly, in both SOLT and BOLT patients, being female was heavily associated with oversized pTLCr (92% and 96% female for SOLT and BOLT, respectively). Also, notable was the fact that patients who were undersized had a significantly shorter waitlist length (59 and 56 days for SOLT and BOLT, respectively), while patients who were oversized had a significantly longer waitlist time (155 and 97 days, respectively) ($P < 0.01$ for all comparisons) (Tables 1 and 2). Unadjusted analysis revealed no significant differences in postoperative dialysis requirement (for SOLT patients: 4.0%, 4.2%, and 3.9%; $P = 0.96$; for appropriately, under-, and over-sized, respectively; BOLT patients: 8.3%, 8.4%, and 6.6% for appropriately, under-, and over-sized, respectively; $P = 0.52$) and median length of stay (for SOLT patients: 12, 12, and 13 days; for appropriately, under-, and over-sized, respectively; $P = 0.24$; BOLT patients: 17, 17, and 17 days; $P = 0.24$ for appropriately, under-, and over-sized, respectively; $P = 0.37$). However, undersized patients had a statistically significant higher incidence of postoperative airway dehiscence (2.1% and 3.0% for SOLT and BOLT, respectively) compared to appropriately (0.8% and 1.4% for SOLT and BOLT, respectively) and over-sized recipients (1.1% and 1.7% for SOLT and BOLT, respectively) ($P = 0.03$).

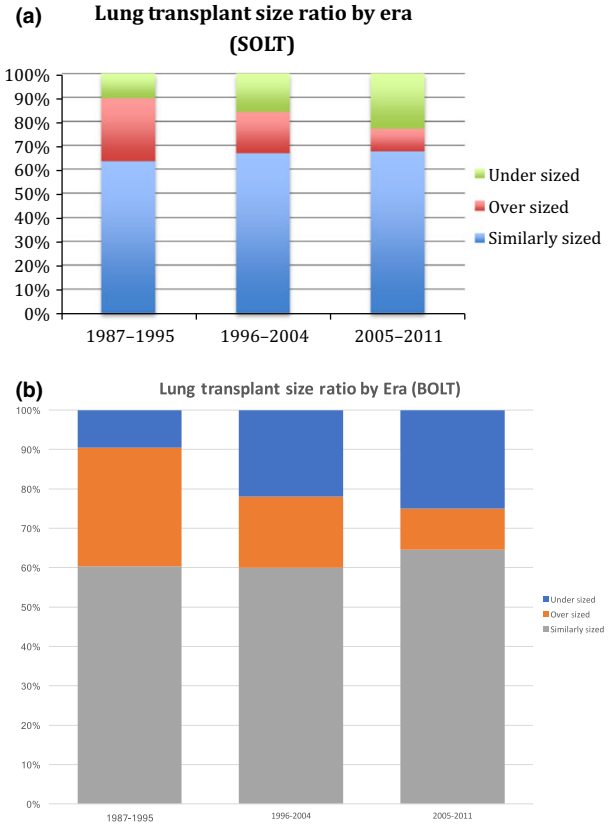

Figure 1 Sizing of transplant by era; (a) single orthotopic lung transplant and (b) bilateral orthotopic lung transplant For Cochran–Armitage trend, test sizing was analyzed by individual year, not era.

Following stratification into the five aforementioned groups, initial unadjusted survival analysis demonstrated that for both SOLT and BOLT patients, there was a significant difference amongst the groups with regard to long-term survival. For SOLT patients, a pTLCr of <0.8 or 1.1–1.2 portended the worst survival, while for patients undergoing a BOLT, a pTLCr of 1.1–1.2 was associated with the worst survival (Fig. 2). Following adjustment with a Cox proportional hazards model, the same pTLCr for both SOLT and BOLT was found to be independently associated with an increased risk of long-term mortality (Table 3). The following covariates were examined in the Cox model: donor age, BMI, history of cigarette use, and history of diabetes. Recipient factors examined included: gender (and gender mismatch), age, BMI, GFR, history of diabetes, functional status, medical condition, waitlist days, transplant era, center transplant volume, and CMV status.

Restricted cubic splines were then developed to ascertain the role of pTLCr in relative mortality hazard in both SOLT and BOLT (mortality relative to a pTLC of 1.0). For patients undergoing SOLT, decreasing pTLCr below 0.9 increased relative mortality. For patients undergoing BOLT, there was no particular degree of over- or under-sizing in which a change in pTLCr was

Table 1. Donor, recipient, and transplant characteristics for single orthotopic lung transplant patients ($N = 3532$).

Variable	Overall	Appropriately sized	Under sized	Over sized	*P*-value
Donor characteristics					
Age in years	31 (21, 45)	29 (20, 43)	41 (29, 51)	24.5 (18, 37)	<0.001
BMI (kg/m^2)	24.3 (21.7, 27.5)	24.4 (21.8, 27.4)	24.9 (21.9, 29.1)	23.7 (21.2, 26.4)	<0.001
Tobacco abuse	643 (19%)	419 (18.5%)	143 (21%)	81 (18.4%)	0.322
Drug use	1023 (29%)	751 (31.8%)	146 (21%)	126 (26.6%)	<0.001
Diabetes	158 (4.6%)	90 (3.9%)	45 (6.6%)	23 (5.2%)	0.013
Recipient characteristics					
Age in years	60 (54, 65)	60 (54, 65)	63 (58, 66)	57 (50, 63)	<0.001
BMI (kg/m^2)	27.2 (24.2, 29.8)	27.3 (24.2, 29.9)	27.1 (24.6, 29.5)	26.8 (23.1, 29.5)	0.087
GFR	88.6 (72.3, 97.8)	88.7 (73, 98.3)	89.3 (74.7, 97.1)	83.9 (68, 97.7)	0.063
Diabetes	493 (14.7%)	316 (14%)	130 (19.4%)	47 (11%)	<0.001
Ethnicity					
White	2943 (83.3%)	1988 (84.2%)	586 (84.2%)	369 (77.8%)	<0.001
Black	254 (7.2%)	166 (7%)	30 (4.3%)	58 (12.2%)	
Other	335 (9.5%)	208 (8.8%)	80 (11.5%)	47 (9.9%)	
Functional status					
ADL no assistance	1073 (33.3%)	749 (35%)	208 (31.7%)	116 (27.6%)	0.008
ADL with assistance	2147 (66.7%)	1393 (65%)	449 (68.3%)	305 (72.4%)	
Female gender	1152 (32.6%)	707 (29.9%)	9 (1.3%)	436 (92%)	<0.001
Lung Allocation Score	42.9 (38.2, 51.7)	42.6 (38, 50.2)	44 (38.7, 55.8)	41.7 (37.9, 52.4)	0.003
Operative characteristics					
Type of lung transplant (right or left)					
Single right	1515 (42.9%)	990 (41.9%)	338 (48.6%)	187 (39.5%)	0.002
Single Left	2017 (57.1%)	1372 (58.1%)	358 (51.4%)	287 (60.5%)	
Medical condition before transplant					
Not hospitalized	3185 (90.6%)	2136 (91%)	618 (89.2%)	431 (91.1%)	0.562
Hospitalized not in ICU	188 (5.4%)	119 (5.1%)	46 (6.6%)	23 (4.9%)	
In ICU	141 (4%)	93 (4%)	29 (4.2%)	19 (4%)	
Waitlist days	92 (27, 256)	93 (28, 253.8)	59 (18, 191.5)	155 (42.2, 353.5)	<0.001
Center Volume*	524 (312, 686)	520 (312, 661)	525 (312, 750)	423 (284, 617)	<0.001

All statistics displayed as median (interquartile range) or number (percent). ADL, activities of daily living; BMI, body mass index; GFR, glomerular filtration rate; ICU, intensive care unit; IQR, interquartile range.

*Center Volume defined as number of transplants during entire study period.

statistically associated with an increase or decrease in mortality (Fig. 3).

Discussion

The present study demonstrates that in patients with end-stage lung disease due to RLD requiring lung transplantation, the relationship between donor and recipient pTLC has a significant impact on survival, particularly in patients undergoing SOLT. While the effect on survival is relatively pronounced in patients undergoing SOLT, patients undergoing BOLT do not appear to be as affected by the relationship between donor and recipient lung size. Additionally, in recent years, it appears that transplant teams have been utilizing lungs that are more similarly sized between donor and recipient or undersizing the lungs, while shying away from oversizing transplants.

Given the limited number of available organs for lung transplantation, the importance of identifying the best possible match for a patient is essential. As we have described, the size matching of donor lungs to recipients has been discussed in the literature as a potential variable affecting outcomes following transplantation. However, a recent evidence-based review from Barnard and colleagues demonstrated that the evidence for size matching is somewhat lacking and guidelines are not well defined [9]. Most of the original studies examining this topic were very small case series with less than 100 patients, and although these studies provided recommendations on sizing, the number of patients examined limited them [10–14]. Mason *et al.* [4] published institutional data

Table 2. Donor, recipient, and transplant characteristics for bilateral orthotopic lung transplant patients (N = 3124).

Variable	Overall	Appropriately sized	Under sized	Over sized	*P*-value
Donor characteristics					
Age in years (IQR)	32 (21, 46)	30 (21, 45)	40 (26, 50)	22 (18, 35)	<0.001
BMI (IQR) (kg/m^2)	24.5 (21.9, 27.8)	24.5 (22.1, 27.6)	25.1 (22.1, 29.3)	23.9 (21, 26.6)	<0.001
Tobacco abuse	430 (13.9%)	273 (13.8%)	114 (15.3%)	43 (11.6%)	0.24
Drug use	969 (31%)	644 (32.2%)	191 (25.4%)	134 (35.9%)	<0.001
Diabetes	170 (5.5%)	111 (5.6%)	44 (5.9%)	15 (4.1%)	0.428
Recipient characteristics					
Age in years (IQR)	56 (48, 62)	56 (48, 61)	58 (50, 63)	53 (43, 59)	<0.001
BMI (IQR) (kg/m^2)	26.5 (23.4, 29.4)	26.6 (23.5, 29.5)	26.6 (24, 29.5)	25.5 (21.7, 28.6)	<0.001
GFR	93.8 (77.4, 104.5)	94.1 (77.9, 104.2)	92.9 (78.6, 103.5)	94.2 (75, 106.9)	0.855
Diabetes	466 (15.2%)	290 (14.7%)	136 (18.3%)	40 (11.1%)	0.005
Ethnicity					
White	2314 (74.1%)	1472 (73.7%)	588 (78.1%)	254 (68.1%)	<0.001
Black	441 (14.1%)	303 (15.2%)	64 (8.5%)	74 (19.8%)	
Other	369 (11.8%)	223 (11.2%)	101 (13.4%)	45 (12.1%)	
Functional status					
ADL no assistance	856 (28.9%)	552 (29.2%)	209 (28.7%)	95 (27.5%)	0.819
ADL with assistance	2110 (71.1%)	1340 (70.8%)	520 (71.3%)	250 (72.5%)	
Female gender	1125 (36%)	758 (37.9%)	9 (1.2%)	358 (96%)	<0.001
Lung allocation score	46.9 (40.2, 62.2)	46.3 (39.8, 60.9)	49.2 (41, 67.5)	46.3 (39.3, 59.1)	0.001
Operative characteristics					
Life support at transplantation	335 (10.8%)	206 (10.4%)	89 (11.9%)	40 (10.8%)	0.541
Medical condition before transplant					
Not hospitalized	2534 (81.8%)	1632 (82.5%)	598 (79.9%)	304 (82.2%)	0.237
Hospitalized not in ICU	241 (7.8%)	144 (7.3%)	62 (8.3%)	35 (9.5%)	
In ICU	321 (10.4%)	202 (10.2%)	88 (11.8%)	31 (8.4%)	
Waitlist days	68 (19, 216)	71 (19, 222)	56 (15, 170)	97 (26, 310)	<0.001
Center Volume*	525 (312, 1042)	525 (312, 1042)	570 (334, 1042)	511 (275, 695)	0.001

All statistics displayed as median (interquartile range) or number (percent). ADL, activities of daily living; BMI, body mass index; GFR, glomerular filtration rate; ICU, intensive care unit, IQR, interquartile range.

*Center Volume defined as number of transplants during entire study period.

from over 400 patients and found no correlation between lung size matching and patient outcomes.

Perhaps the largest data for this topic come from Eberlein and colleagues, and they have described their experience with heterogenous patient populations including all lung transplant patients in both institutional data sets and UNOS [1–3,7,8], as well as in patients with pulmonary hypertension [6]. With institutional data, they demonstrated that patients undergoing BOLT who had undersized lungs were more likely to have postoperative airway complications and primary graft dysfunction as well as higher hospital costs [1]. In a separate study, they also demonstrated that oversizing of BOLT with regard to pTLCr was associated with improved survival, increased expiratory airflow capacity, and a decreased incidence of bronchiolitis obliterans syndrome (BOS) [2,8]. Using a similar analysis in the UNOS dataset, they confirmed the conclusions from their institutional data and found that oversizing of the pulmonary allograft in BOLT was independently associated with improved survival, but there was no independent association seen in SOLT [3]. Similar benefits were found with oversizing in patients with pulmonary hypertension as well [6].

While these data are important for current guidelines, there are a few notable limitations to these studies. Perhaps most importantly these studies all examined a heterogeneous patient population, including multiple indications for transplantation such as obstructive lung disease, RLD, cystic fibrosis, and others. As noted earlier, the pulmonary mechanics and effects on chest physiology can be dramatically different in a patient with RLD as compared to someone with obstructive lung disease. Because of the heterogeneity of the patient population, the current guidelines for sizing of donor organs are relatively vague with no clear consensus in the most recent recommendations [9]. Another limitation of these studies centers on the definitions of over

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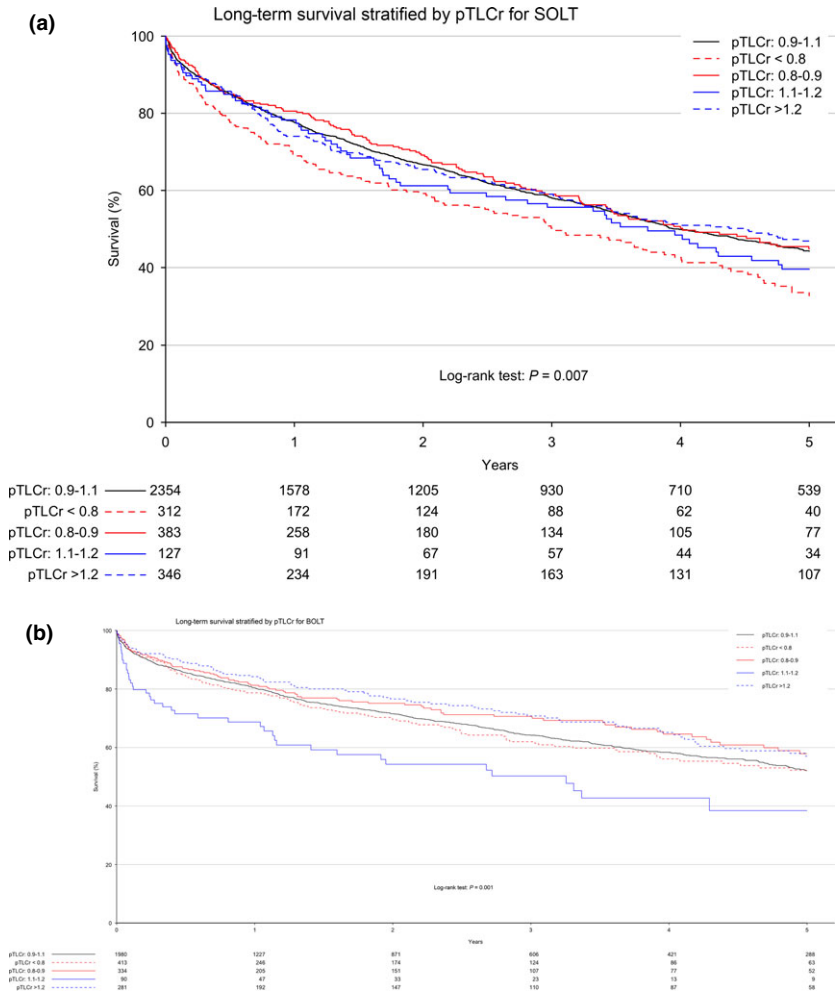

Figure 2 Kaplan–Meier analysis of survival stratified by predicted total lung capacity ratio (pTLCr) (a) single orthotopic lung transplant (SOLT) and (b) bilateral orthotopic lung transplant (BOLT).

and undersizing. In the institutional studies previously noted, oversized was defined as a pTLCr of >1 and undersizing was defined as a pTLCr <1. These strict criteria force one to almost identically match organs for appropriate sizing. It should be noted, however, that this manuscript utilizing UNOS data divided patients based on quartiles of pTLCr [3].

Our study, as previously emphasized, attempted to capture only the unique population of patients with RLD. Due to the unique pathophysiology of the disease —particularly on chest wall mechanics—it is important that these patients be examined separately from all patients undergoing lung transplantation. The results demonstrate that in patients who undergo SOLT for RLD with considerable undersizing (pTLCr <0.8) there was a significantly increased risk of mortality as well as incidence of airway dehiscence. Moreover, increasing pTLCr between 0.8 and 0.9 had a significant impact on improving of survival for patients undergoing SOLT. These results are important as the majority of prior research has focused on BOLT. However, our study demonstrates that patients with RLD are slightly more likely to receive a SOLT as compared to a BOLT. As patients receiving a SOLT are subsequently primarily reliant on only one allograft, undersizing the donor lung appears to have a detrimental effect as the transplanted lung may be insufficient for the recipient. Additionally, airway complications in undersized grafts may be the result of the technical difficulty of the bronchial anastomosis and/or increased risk for donor airway devascularization. Furthermore, these data suggest that transplant teams should strive to obtain a pTLCr as close to or greater than 0.9 as possible with small increases in pTLCr above 0.8 potentially have a significant impact on survival.

Having a pTLCr between 1.1 and 1.2 was also independently associated with increased mortality for BOLT; however, this association may have partly been a result of the relatively small number of patients with a pTLCr that fell in this range. However, in a restricted

Table 3. (A) Hazard ratio of effect of predicted total lung capacity ratio (pTLCr) on long-term mortality in single orthotopic lung transplant (SOLT) patients. (B) Hazard ratio of effect of pTLCr on long-term mortality in bilateral orthotopic lung transplant (BOLT) patients.

Variable	Hazard ratio	Lower 95% CI	Upper 95% CI	*P*-value
(A)				
pTLC ratio (Reference pTLC ratio 0.9–1.1)				
pTLC ratio <0.8	1.711	1.146	2.557	0.01
pTLC ratio 0.8–0.9	1.204	0.832	1.744	0.33
pTLC ratio 1.1–1.2	1.398	1.019	1.917	0.04
pTLC ratio >1.2	1.33	0.891	1.983	0.16
Donor BMI	0.986	0.975	0.997	0.009
Donor history of significant cigarette use	1.111	0.982	1.257	0.095
Donor history of diabetes	1.166	0.912	1.493	0.221
Gender mismatch	0.776	0.542	1.11	0.165
Recipient age (per 10 years)	1.202	1.118	1.292	<0.001
Recipient BMI	1.01	0.997	1.022	0.128
Recipient GFR at transplant	0.997	0.995	1	0.061
Recipient history of diabetes	0.989	0.852	1.148	0.883
Recipient functional status: ADL with assistance	1.36	1.219	1.517	<0.001
Recipient gender, female	0.897	0.784	1.027	0.116
Recipient medical condition: hospitalized, not in ICU	1.325	1.002	1.752	0.048
Recipient medical condition, in ICU	2.517	1.853	3.419	<0.001
Recipient on life support at time of transplant, yes	1.459	1.082	1.968	0.013
Waitlist years	0.95	0.889	1.015	0.129
Transplant Era, 1987–1995	1.104	0.837	1.457	0.484
Transplant Era, 1996–2004	1.238	1.087	1.41	0.001
Transplant center volume (per 100 transplants)	0.985	0.971	0.999	0.047
CMV mismatch, yes	1.035	0.922	1.163	0.56
(B)				
pTLC ratio (reference pTLC ratio 0.9–1.1)				
pTLC ratio <0.8	1.199	0.737	1.952	0.47
pTLC ratio 0.8–0.9	0.919	0.579	1.459	0.72
pTLC ratio 1.1–1.2	1.717	1.112	2.651	0.02
pTLC ratio >1.2	0.916	0.553	1.516	0.73
Donor age (per 10 years)	1.032	0.983	1.083	0.208
Donor BMI	0.996	0.983	1.01	0.605
Donor history of significant cigarette use	1.248	1.05	1.482	0.012
Donor history of diabetes	1.154	0.871	1.53	0.318
Gender mismatch	0.961	0.617	1.497	0.86
Recipient age (per 10 years)	1.121	1.043	1.205	0.002
Recipient BMI	0.992	0.977	1.008	0.337
Recipient GFR at transplant	0.996	0.993	0.999	0.007
Recipient history of diabetes	1.007	0.835	1.213	0.944
Recipient functional status: ADL with assistance	1.114	0.96	1.292	0.155
Recipient gender, female	0.999	0.845	1.181	0.993
Recipient medical condition: hospitalized, not in ICU	0.991	0.75	1.308	0.949
Recipient medical condition, in ICU	1.774	1.355	2.323	<0.001
Recipient on life support at time of transplant, yes	1.083	0.832	1.411	0.552
Waitlist years	0.978	0.914	1.047	0.523
Transplant Era, 1987–1995	2.02	1.227	3.324	0.006
Transplant Era, 1996–2004	1.198	0.998	1.437	0.052
Transplant center volume (per 100 transplants)	0.968	0.951	0.985	<0.001
CMV mismatch, yes	1.06	0.925	1.216	0.401

patient, an over-sized allograft placed in to an already restrictive chest cavity can potentially lead to diminished respiratory mechanics or even pulmonary tamponade. It is important to note, however, there was no obvious change in pTLCr for patients undergoing BOLT which appeared to have a significant impact on

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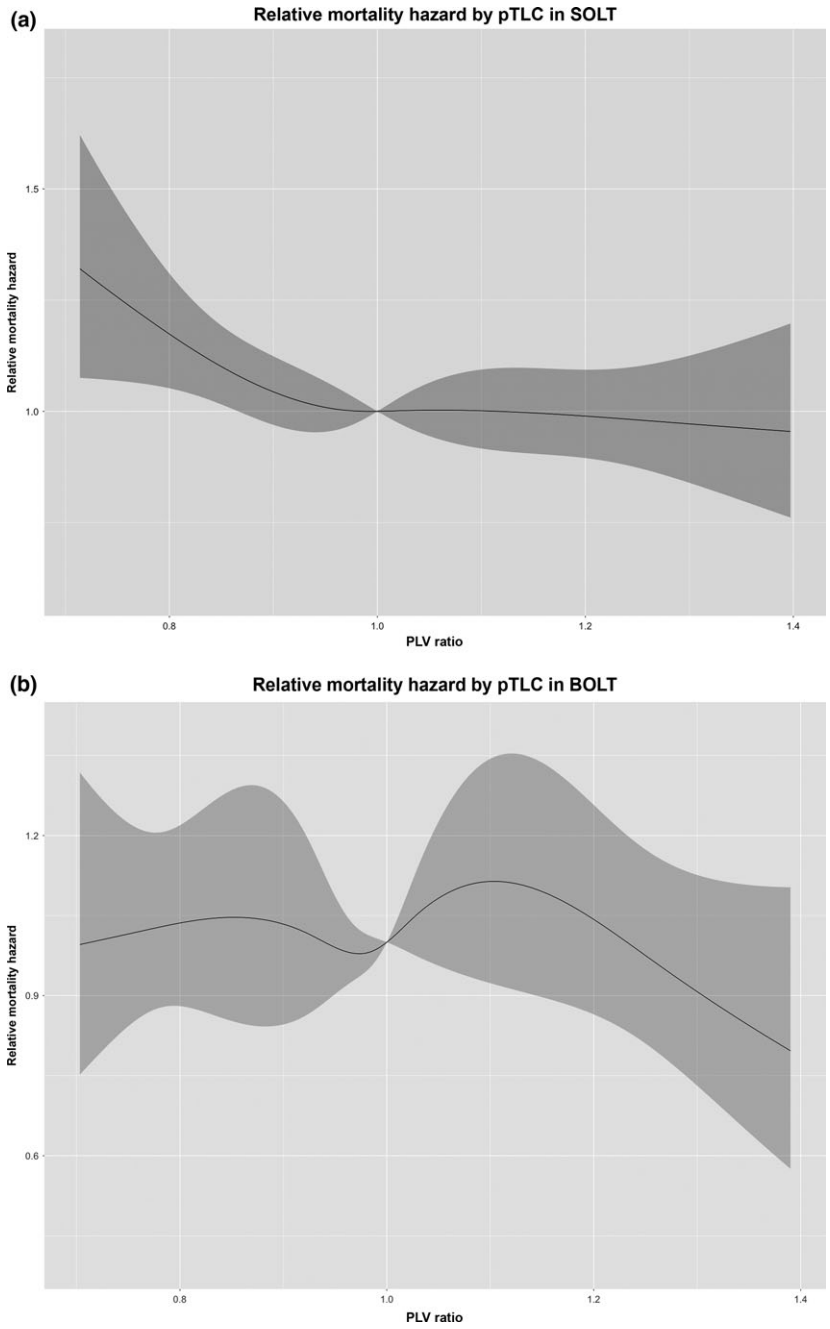

Figure 3 Restricted cubic spline of relative mortality hazard by predicted total lung capacity ratio (pTLCr) in (a) single orthotopic lung transplant (SOLT) and (b) bilateral orthotopic lung transplant (BOLT).

survival. This result is disparate from those derived from Eberlein and colleagues, and this may be a result of the heterogeneity of their study population. Notably, survival for patients undergoing BOLT was higher than for those with SOLT, and further comparisons about the benefit of BOLT versus SOLT with regard to size mismatch may be warranted. Based on our results, it appears that for patients undergoing BOLT, the fact the recipient receives two good lungs may be enough to provide appropriate survival within current norms of size matching. These data may further encourage the use of deceased donor lobar transplantation if necessary for appropriate sizing in the setting of a BOLT, but should lend some caution to this approach in patients undergoing SOLT. It should also be noted that pneumoreduction techniques are not captured in UNOS, so it is unclear if the over-sized allografts underwent downsizing prior to implantation.

Given the aforementioned results, it ultimately raises the question of how these data should impact current listing and organ allocation practices. The recent guidelines for sizing state that transplant teams should

consider lower and upper limits for pTLCr for patients being listed for transplant [9]. It does not appear that these size considerations are as important for patients undergoing BOLT for RLD, especially in regard to under-sizing of the allografts. However, for patients undergoing SOLT for RLD, it may be of benefit to establish what transplant teams feel is an appropriate organ based on size at the time of listing. There are also data suggesting that patients with RLD undergoing SOLT have somewhat disparate outcomes based on the laterality of the transplant. Furthermore, given our results, it may be reasonable to consider organ size as part of the organ allocation process for SOLT in RLD to help improve survival. If sizing was to be considered as part of the listing and/or organ allocation process, it would then be prudent to reach a consensus of how to estimate or measure the total lung capacity. One alternative to estimation of pTLC is actual TLC, which is derived from plethysmography. However, in RLD, previous data have demonstrated that actual TLC is not well correlated with donor pTLC and may underestimate the lung size that is acceptable for a recipient [15]. As such, pTLC appears to be the optimal means to estimate lung capacity, particularly as it is easy to use and does not require significant effort, which is important for donor lung capacity calculation. However, as technology continues to evolve, particularly with regard to imaging, other modalities may provide more accurate measurements. For example, CT scanning should be able to provide a volumetric approach to approximating chest cavity size and may provide for better size matching.

Limitations

It should be noted that our study has some notable limitations. Given the retrospective nature of the study and that the data were derived from a large national database, there is potential for bias associated with large retrospective cohort studies. Furthermore, the premise of calculating lung capacity is based on an estimate utilizing height alone. As this may not be the most accurate measurement, the data may be biased, however, as mentioned before pTLC appears to be more accurate for lung capacity measurements as compared to actual TLC in restrictive patients [15]. Furthermore, given our use of the UNOS dataset, we were unable to quantify the effect of size mismatch on various important outcomes including postoperative ventilator requirements, incidence of primary graft dysfunction, and incidence of BOS. Finally, our dataset includes patients from 1987 to 2011, and thus, there are many patients transplanted in the nonlung allocation score era and this may limit the applicability of the results to current transplant practices.

Conclusions

Given the limitation of available organs for lung transplantation, strategies to ensure appropriate allocation so as to maximize post-transplant survival are essential for the most efficient use of these organs. Size matching of the organs appears to be important for patients undergoing SOLT, but does not appear to have a significant effect on patients undergoing BOLT. Based on these data, transplant teams should aim to avoid undersizing potential organs for SOLT and continue to seek the best available organ regardless of size for patients listed for BOLT.

Authorship

AMG and MSM: data interpretation, authors BRE, PJS, BCG, BAY, and AAO: study design, statistical analysis, authors LRS, RDD, MGH: study genesis, study design, critical review, authors.

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Conflict of interest

The authors have declared no conflicts of interest.

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