

Single lung transplantation has equivalent long term outcomes to bilateral lung transplantation in patients with pulmonary hypertension associated with advanced lung disease

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Abstract

Whether bilateral lung transplantation (BLT) rather than single lung transplantation (SLT) should be preferentially performed for patients with World Health Association (WHO) Group 3 pulmonary hypertension (PH) associated with advanced lung disease has been controversial. We retrospectively examined the outcomes of 474 consecutive patients who underwent BLT or SLT at our center between 1999 and 2013. After exclusion of patients with cystic fibrosis or those undergoing retransplantation, 179 patients with PH were split into four groups based on their pulmonary artery pressure values (mild versus severe) and transplant type (BLT versus SLT). The incidence of grade 2-3 primary graft dysfunction and mechanical ventilation >48 hours was significantly higher for the BLT versus the SLT recipients. However, long-term survival via the Kaplan-Meier method and appropriate log rank tests did not differ significantly among the four cohorts. Because long-term outcomes for patients who undergo SLT for advanced lung disease associated with WHO Group 3 PH did not differ significantly from those for BLT recipients, even if PH was severe, we suggest that SLT can be performed safely in patients with Group 3 PH associated with ALD and potentially allows improved donor organ utilization.

Abbreviations: ALD: Advanced Lung Disease; BLT: Bilateral Lung Transplantation; CLAD: Chronic Lung Allograft Dysfunction; COPD: Chronic Obstructive Pulmonary Disease; CPB: Cardiopulmonary Bypass; FEV1: Forced Expiratory Volume in one second; FVC: Forced Vital Capacity; ICU: Intensive Care Unit; IPF: Idiopathic Pulmonary Fibrosis; LAS: Lung Allocation Score; LOS: Length of Stay; NO: Nitric Oxide; PA: Pulmonary Artery; PAP: Pulmonary Artery Pressure; PGD: Primary Graft Dysfunction; PH: Pulmonary Hypertension; SLT: Single Lung Transplantation; WHO: World Health Organization

Introduction

WHO (World Health Organization) Group 3 pulmonary hypertension (PH) is a relatively common complication of advanced lung disease (ALD), and its presence has been linked to worse survival for patients who undergo lung transplantation for ALD [1]. Due to concern that high pulmonary vascular resistance in the native lung increases the risk of significant reperfusion injury that can lead to high-grade primary graft dysfunction (PGD) and increased mortality, performing single lung transplantation (SLT) rather than bilateral lung transplantation (BLT) has been controversial in patients transplanted for ALD when Group 3 PH is present. Many centers preferentially list patients with significant Group 3 PH for BLT and avoid performing SLT for patients with ALD associated with a significant degree of PH [2-6].

Bilateral lung transplantation may not always be a viable option at centers with limited organ access, and the donor lung pool is effectively

halved if only BLT is performed in patients with ALD complicated by the presence of WHO Group 3 PH. Although a number of studies have examined outcomes for Group 3 PH and SLT [2-8], these studies have been limited by small sample sizes and relatively few patients with more severely increased pulmonary artery (PA) pressures. We reviewed our clinical outcomes in patients with mild versus more severe Group 3 PH while also comparing outcomes for patients who underwent SLT versus BLT to determine if significant differences in long-term survival could be detected.

Methods

This investigation was approved by the University of Wisconsin Human Subjects Committee (approval number M-2009-1308). Outcomes of 474 consecutive patients who underwent lung transplantation between 1999 and 2013 were retrospectively reviewed

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(Figure 1). Of these patients, 224 were found to have WHO Group 3 PH as documented by pre-operative cardiac catheterization. A total of 39 patients were then excluded for a diagnosis of cystic fibrosis, as they were not eligible to be listed for SLT, and another 6 patients were excluded due to retransplantation as their indication for transplant. The remaining 179 patients were divided into four groups according to their PA pressure values (mild versus severe) and whether they underwent SLT or BLT procedures. Our classification of PH severity was based upon criteria from the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension [9]. Mild PH was defined as having mean PA pressures of 26-40 mm Hg and severe PH as having systolic PA pressure >44 mm Hg or mean PA pressure >40 mm Hg. For patients that were transplanted prior to the implementation of the lung allocation score (LAS) system, LAS values were calculated retrospectively using historic data obtained prior to lung transplant.

All patients met widely accepted criteria based on their primary lung disease and were determined to be suitable candidates for lung transplantation [10]. Standard surgical techniques were used, and our protocol-driven postoperative care was given to all patients and included standard induction and maintenance immunosuppressive drugs, prophylactic and preemptive antibiotics, and follow-up at specific time intervals with thoracic imaging, pulmonary function testing, and surveillance bronchoscopy.

Chronic lung allograft dysfunction (CLAD) was defined as per the ISHLT/ATS/ERS international clinical practice guideline for the diagnosis of bronchiolitis obliterans syndrome (BOS) [11]. Patients were identified as having CLAD when they had a persistent decline in FEV1 to less than 80% of the best postoperative FEV1 that could not be

attributed to a reversible cause of allograft dysfunction. Graft survival was defined as either recipient death or loss of allograft function that required retransplantation.

Statistical analysis was performed using SPSS and GraphPad Prism software. Whether recipients developed CLAD and graft survival rates were compared between the four groups using Kaplan-Meier survival curves and associated log rank tests. For patient characteristics and perioperative outcomes, the chi-squared test was used to analyze categorical variables and ANOVA was used to analyze continuous variables.

Results

Baseline characteristics

No significant differences in selected pre-operative characteristics were observed for the four cohorts (gender, prevalence of diabetes, FEV1, FVC, pre-transplant oxygen requirements, or requirement for positive pressure ventilation) (Table 1). However, BLT recipients with severe PH were, on average, younger than the other groups (52 years, $p < 0.005$), both severe groups had higher LAS values (44.1 and 44.1, $p = 0.005$), and SLT severe recipients had higher baseline creatinine values (0.96 mg/dl, $p = 0.005$).

Recipient primary disease

There was a statistically significant difference in the indication for transplantation among the stratified groups (Table 2). Both the SLT and BLT groups with mild PH were more likely to have a diagnosis of chronic obstructive pulmonary disease (COPD) (BLT 45%, SLT 51%) versus the severe PH groups (BLT 33%, SLT 24%). Furthermore, SLT severe patients were more likely to have a diagnosis of idiopathic pulmonary fibrosis (IPF) (43%) compared to all other groups (BLT mild 20%, BLT severe 27%, SLT mild 26%, $p < 0.001$).

Intra-operative characteristics

Intra-operative characteristics included pre-incision pulmonary arterial pressure PA pressure measurements, organ ischemic time, and cardiopulmonary bypass (CPB) (Table 3). There were no statistical

Table 1. Pre-Transplant recipient characteristics. FEV1: Forced expiratory volume in one second; FVC: Forced vital capacity; PAP: Pulmonary artery pressure; PCWP: Pulmonary capillary wedge pressure.

Pre-operative Characteristics (mean values)	Pulmonary Hypertension Severity				p value
	BLT Mild (N=20)	BLT Severe (N=30)	SLT Mild (N=55)	SLT Severe (N=74)	
Male gender (%)	70	67	67	76	0.78
Mean age (years)	55	52	57	58	<0.005
Diabetes (%)	30	30	24	24	0.91
Race = Caucasian (%)	90	97	98	82	0.04
Body mass index (kg/m ²)	25.9	26.4	26.0	26.7	0.75
Mechanical ventilation (%)	10	20	11	11	0.57
Supplemental oxygen use (L/min)	3.5	4.6	3.6	4.1	0.29
FVC (% predicted)	49.8	46.5	46.1	46.7	0.84
FEV1 (% predicted)	28.4	33.0	31.3	38.6	0.075
Lung allocation score (LAS)	38.3	44.1	37.2	44.1	0.005
Serum creatinine (mg/dL)	0.81	0.88	0.92	0.96	0.005
PCWP (mm Hg)	19	39	54	70	0.166
Cardiac index (L/min/m ²)	2.77	3.09	2.94	2.73	0.073
Systolic PAP (mm Hg)	39.5	61.2	39.5	55.5	<0.001
Diastolic PAP (mm Hg)	23.7	31.0	21.4	25.9	<0.001
Mean PAP (mm Hg)	29.9	42.8	29.3	36.5	<0.001

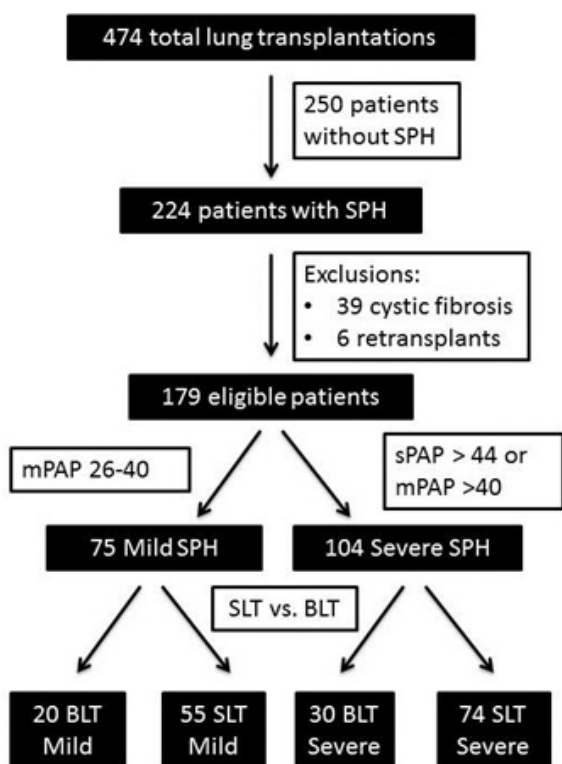


Figure 1. Flow chart depicting selection of recipients for inclusion in the study and pulmonary hypertension severity stratification.

Table 2. Transplant Indications (Primary Disease).AATD = alpha-1-antitrypsin deficiency; COPD = chronic obstructive pulmonary disease; IPF = idiopathic pulmonary fibrosis (*p* value derived by χ^2 analysis of all groups).

Primary Disease (transplant indication)	Pulmonary Hypertension Severity				<i>p</i> value
	BLT Mild (N=20)	BLT Severe (N=30)	SLT Mild (N=55)	SLT Severe (N=74)	
COPD/emphysema – N (%)	9 (45)	10 (33)	28 (51)	18 (24)	<0.0001
IPF – N (%)	4 (20)	8 (27)	14 (26)	32 (43)	
COPD with AATD – N (%)	4 (20)	3 (10)	8 (15)	2 (3)	
Sarcoidosis – N (%)	1 (5)	2 (7)	1 (2)	9 (12)	
Other (N/%)	2 (10)	6 (20)	4 (7)	13 (17)	

Table 3. Intra-operative characteristics. CPB:Cardiopulmonary bypass; mPAP: Mean pulmonary artery pressure; sPAP: Systolic pulmonary artery pressure.

Parameter (mean values)	Pulmonary Hypertension Severity				<i>p</i> value
	BLT Mild (N=20)	BLT Severe (N=30)	SLT Mild (N=55)	SLT Severe (N=74)	
CPB required (%)	80	80	14.5	39	<0.001
CPB duration (minutes)	194	227	170	164	<0.0005
Ischemic time (minutes)	266	351	343	302	0.066
sPAP (mm Hg)	40	61	39	56	<0.001
mPAP (mm Hg)	30	43	29	36	<0.0001

Table 4. Post-operative recipient characteristics. ECMO: Extracorporeal membrane oxygenation; ICU: Intensive care unit; PGD: Primary graft dysfunction.

Parameter (mean values)	Pulmonary Hypertension Severity				<i>p</i> value
	BLT Mild (N=20)	BLT Severe (N=30)	SLT Mild (N=55)	SLT Severe (N=74)	
ICU length of stay (days)	5.5	20.5	10.7	7.0	0.013
Prolonged ventilation >48 hrs (%)	45	67	20	24	<0.001
PGD Grade 0-1 (%)	55	33	80	76	<0.001
PGD Grade 2-3 (%)	45	67	20	24	
Nitric oxide use (%)	35	73	49	73	<0.001
Hospital length of stay (days)	24	41	23	23	0.026
Readmission within 30 days (%)	15	27	35	19	0.082
30-day mortality (%)	5	7	2	4	0.84

differences between the groups in regards to average organ ischemic time, although there was a trend toward longer times in the BLT severe and SLT mild groups (351 and 343 minutes) compared to the BLT mild and SLT severe groups (266 and 302 minutes, $p=0.066$). There was a significant difference in rates of CPB usage, with both BLT groups having higher rates of CPB (80% both groups) compared SLT patients (SLT mild 14.5%, SLT severe 39%, $p<0.001$). BLT severe recipients were found to have the longest duration of CPB (227 minutes, $p<0.005$).

Immediate postoperative outcomes

Postoperatively, BLT severe patients were found to have the longest intensive care unit (ICU) length of stay (20.5 days, $p=0.013$), highest incidence of prolonged ventilation (67%, $p<0.001$), and longest overall hospital stay (41 days, $p=0.026$) (Table 4). Rates of higher (grade 2 or 3) primary graft dysfunction (PGD) were significantly higher in both BLT groups (mild 45%, severe 67%) compared to both SLT groups (mild 20%, severe 24%, $p<0.001$). Nitric oxide (NO) use was significantly increased for both the SLT and BLT high PH groups (73% both), and NO use was also higher for SLT versus BLT with mild PH (BLT mild 35%, SLT mild 49%, $p<0.001$). There were no significant differences in rate of readmission within 30 days or 30-day mortality among all groups.

Long-term survival

There were no differences in long-term survival among the four groups (Figure 2). Unadjusted survival for BLT recipients with mild PH was 85.0%, 70.8%, and 56.7% at 1, 3, and 5 years respectively,

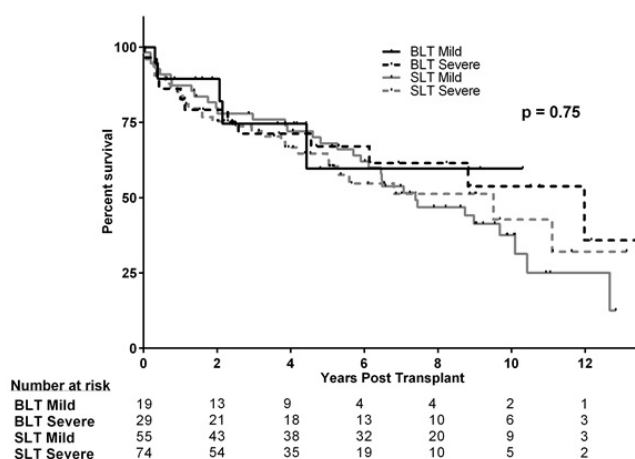


Figure 2. Long-term survival by Kaplan-Meier analysis.

compared to 83.3%, 68.9%, and 64.8% for the BLT group with severe PH. Unadjusted survival to the SLT cohort with mild PH was 87.3%, 77.9%, and 68.1% compared to 83.8%, 73.7%, and 62.5% in the SLT with mild PH cohort ($p=0.748$).

Freedom from chronic lung allograft dysfunction

Rates of CLAD were similar in all groups (Figure 3). Freedom from rejection for BLT patients with mild SPH was 93.3%, 60.6%, and 51.5% at 1, 3, and 5 years respectively compared to 92.4%, 76.9%, and 65.1% in the BLT severe group, 95.9%, 72.8%, and 48.2% in the SLT mild group, and 95.5%, 81.1%, and 68.6% in the SLT severe group ($p=0.415$).

Discussion

Our findings suggest that long-term outcomes for lung transplant recipients with ALD and significant Group 3 PH who undergo SLT are not significantly different from patients with PH who undergo BLT, nor did we identify significant differences among the recipient groups for mild versus severe PH. This was demonstrated by both equivalent long-term survival (Figure 2) and freedom from CLAD (Figure 3). Additionally, patients with PH who underwent SLT had lower rates of CPB usage and severe PGD (Tables 3 and 4), although this lower use of CPB may only reflect our program's tendency to use

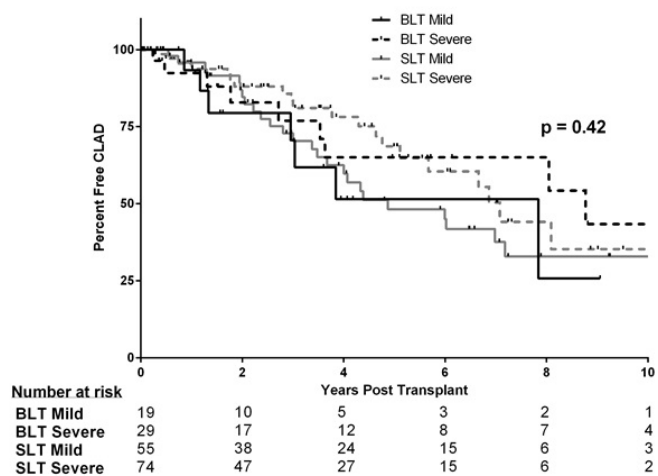


Figure 3. Freedom from chronic lung allograft dysfunction (CLAD) by Kaplan-Meier analysis.

CPB preventively for recipients perceived as being at increased risk for significant PGD following transplant. For recipients with severe PH, patients who underwent BLT had increased ICU length of stay (LOS), prolonged ventilation, and overall hospital LOS compared to those who underwent SLT.

Our results support previous studies that did not identify the presence of Group 3 PH as a risk factor for poorer survival after lung transplantation [2,7,8,12]. Additionally, our study supports our recently reported findings that the presence of Group 3 PH, even when severe, does not have a significant impact on outcomes for patients who receive SLT [13]. Our results suggest that SLT can be an appropriate consideration for patients with Group 3 PH in the setting of limited organ availability, and our study also has a much longer patient follow-up and larger patient population compared to prior studies of the effect of PH on lung transplant outcomes published by other transplant centers.

Reluctance to perform a SLT procedure in patients with significant Group 3 PH mostly stems from concern that the transplanted lung will be exposed to higher pulmonary pressures that will increase reperfusion injury and primary graft dysfunction. However, we found that our cohorts with mild or severe PH who underwent BLT had higher rates of severe PGD than SLT recipients (Table 4). This may be explained, at least in part, by the increased use of CPB for BLT recipients, who were more likely to be placed on CPB (80%) compared to SLT patients (14.5% mild, 39% severe). A recent meta-analysis examined recipient-related risk factors for PGD and found that CPB carried a significant risk of PGD, with an odds ratio of 2.29 [14], but this study did not find any correlation between SLT and increased risk for PGD. Taken together with our results, the theoretical risk of increased reperfusion injury does not appear to translate clinically to increased PGD risk when SLT is performed for patients with Group 3 PH.

Increasing the number of organs available for transplant has been a primary focus in the field of lung transplantation over the past decade, and a number of methods have been proposed or implemented to achieve this goal. A point-based system has been initiated in Israel that rewards potential donors by increasing the likelihood of receiving an organ themselves should they develop such need, and this policy has led to an increase in registered donors [15]. An “opt out” instead of the current “opt in” system (which theoretically will increase the

number of registered donors) has been under examination in the US [16], and other measures to increase the donor pool include utilizing living donors for lobar lung transplants, increased use of donation after cardiac death donors, using donors with a significant history of smoking, using donors older than 55 years, and rehabilitation of marginal lungs with *ex vivo* perfusion [17-22]. Our study suggests that using SLT for patients with ALD accompanied by PH (a population that historically has been treated with BLT) can increase organ availability without compromising outcomes. This approach would have the benefit of not only allowing organ block splitting from a double lung to two single lungs, but it would also allow centers to accept single lung offers that they may have historically declined. Indeed, in COPD, there is evidence to suggest that a policy of using SLT improves access to organs for other potential recipients without significantly increasing post-transplant mortality [23,24].

Our study has numerous limitations. This is a descriptive, retrospective analysis of non-randomized patients, and it is, therefore, subject to selection bias for patients chosen for SLT versus BLT procedures. Additionally, our recipients represent a heterogeneous population in terms of lung disease indication for transplantation, and relatively more patients received SLT versus BLT, which reflects our center’s policy of listing nearly all patients to receive either SLT or BLT to optimize organ utilization and decrease the risk of death on the waiting list if patients are listed for BLT only. Another limitation is the duration of the study period (approximately 14 years). Although this time period has allowed us to analyze outcomes for a large number of patients with a long period of follow-up, many changes in lung transplantation techniques and post-transplant management have occurred, and use of the LAS system was implemented in 2005, which has changed the primary indication for transplantation from COPD to idiopathic pulmonary fibrosis (IPF) at our institution. This trend of a change from COPD to IPF has been observed around the country in general after implementing the LAS [25]. Additionally, we have observed that following the implementation of the LAS at our institution, patients with the transplant indication of IPF were significantly older, had increased supplemental oxygen requirements, a lower cardiac index, and more comorbidities [26]. However, despite the increased disease severity and strong association of significant Group 3 PH with IPF, long-term recipient outcomes have not been significantly compromised for our patients with a pre-transplant diagnosis of pulmonary fibrosis [27].

We conclude that patients with WHO Group 3 PH associated with ALD, including those with more severely increased PA pressure values, can safely undergo a SLT procedure and have long-term survival that is not significantly different from candidates who receive a BLT procedure. Furthermore, our SLT recipients had lower rates of CPB use, lower incidence of PGD, and shorter post-transplant hospital LOS. We suggest that the presence of Group 3 PH should not be a contraindication to SLT, and the expanded use of SLT has the added benefit of functionally expanding a limited pool of donor lungs, especially for specific candidate populations, (e.g. older patients with IPF or COPD who have Group 3 PH). Future studies should target the validation of these results in a prospective fashion.

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Disclosures

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