AUDIT, RESEARCH AND GUIDELINE UPDATE

The presence or severity of pulmonary hypertension does not affect outcomes for single-lung transplantation

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ABSTRACT

Advanced lung disease (ALD) that requires lung transplantation (LTX) is frequently associated with pulmonary hypertension (PH). Whether the presence of PH significantly affects the outcomes following single-lung transplantation (SLT) remains controversial. Therefore, we retrospectively examined the outcomes of 279 consecutive SLT recipients transplanted at our centre, and the patients were split into four groups based on their mean pulmonary artery pressure values. Outcomes, including long-term survival and primary graft dysfunction, did not differ significantly for patients with versus without PH, even when PH was severe. We suggest that SLT can be performed safely in patients with ALD-associated PH.

INTRODUCTION

The presence of group 3 pulmonary hypertension (PH) in patients undergoing lung transplantation (LTX) for advanced lung disease (ALD) has been identified as a risk factor for complications such as primary graft dysfunction (PGD), which can significantly reduce 1-year survival rate.[1] Although it has been suggested that bilateral LTX (BLT) may be a better choice of procedure type for patients with ALD-associated PH and mean pulmonary artery pressure (mPAP) values >40 mm Hg,[2] other investigators have not reported a significant difference in survival for single-lung transplantation (SLT) versus BLT in patients with ALD-associated PH.[3] SLT offers the benefit of treating more patients with a scarce resource as well as making sure that single lung offers do not go to waste. At our own centre, we have not considered PH to be a contraindication to SLT, and when appropriate for other patient factors such as their primary disease process, we have used SLT in these patients. Therefore, we examined our immediate and long-term outcomes for SLT recipients with and without ALD-associated PH.

METHODS

This investigation was approved by the University of Wisconsin Human Subjects Committee (approval number M-2009-1308). Outcomes of 296 consecutive patients (none with a LTX indication of cystic fibrosis or primary PH) who underwent SLT between 1999 and 2013 were collected prospectively and analysed retrospectively. Eleven recipients were excluded due to retransplantation as their transplant indication, and six lacked PAP values. The remaining 279 patients were split into four groups based on right heart catheterisation (RHC) mPAP values (no PH (mPAP <26; N=150), mild PH (mPAP 26–40; N=55), moderate PH (systolic pulmonary artery pressure (sPAP) 45–59 or mPAP 41–55 mm Hg; N=54), and severe PH (sPAP >60 or mPAP >55 mm Hg; N=20)): grading of severity was based on criteria from the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension.[4] All subjects had at least one RHC, and when multiple RHCs were performed, the RHC value that was closest to the time of surgery was used. Mean time from preoperative RHC to LTX was 336 days. Lung allocation score (LAS) values were calculated for recipients transplanted prior to implementation of the LAS system in 2005.

Categorical data were summarised with frequency distributions and percentages. The mean ±SD values were calculated for variables that were normally distributed, and medians with interquartile ratios were presented for variables that were skewed. Continuous variables were compared using unpaired t test or non-parametric Mann–Whitney U test, whereas nominal variables were compared using χ^2 or the Fisher's exact test (as appropriate). The Kaplan–Meier method was used to assess lung graft survival and freedom from chronic lung allograft dysfunction (CLAD). Log-rank tests were used to assess statistical significance in survival and freedom from CLAD differences. Cox regression methods were used for multivariate analysis. A p value <0.05 (two-sided) was considered to be statistically significant. All analyses were performed using the SPSS statistical software program for Windows V.19.0 (SPSS, Chicago, Illinois, USA).

RESULTS

Baseline characteristics

Pretransplant characteristics of the study groups are given in the online supplementary table S1. A significantly higher LAS value (47.5) for the severe PH cohort correlated with decreased time on the waiting-list (81 days) compared with the other three groups. There was a statistically significant difference in the indication for LTX among the four groups (p<0.0001, online supplementary table S2). Patients without PH, mild PH or moderate PH were more likely to have a diagnosis of

COPD (34%, 51% and 32%, respectively) than the group with severe PH (5%).

Intraoperative characteristics and early postoperative outcomes

There was a significant difference in rates of cardiopulmonary bypass (CPB) usage (see online supplementary table S3), which was significantly higher for the severe PH cohort (65%) versus all other groups (15% (no PH), 15% (mild PH), 30% (moderate PH); $p<0.001$)), but the length of CPB was no different between groups. Postoperatively, patients with moderate and severe PH had a higher rate of nitric oxide (NO) use (70% and 80%; online supplementary table S4) compared with patients without PH or mild PH (40% and 49%; $p<0.001$). The use of extracorporeal membrane oxygenation (ECMO) was minimal in all groups, and although patients with severe PH were the highest, patients with moderate PH were the lowest. Despite these increases in NO and ECMO use, important clinical factors such as length of ventilation, prolonged ventilation and severe PGD were no different among the four groups. Furthermore, there were no differences in 30-day mortality, length of stay or readmission among the four groups.

Long-term survival and freedom from CLAD

There were no differences in long-term survival among the four groups (figure 1), and the incidence of CLAD was similar for all groups (see online supplementary figure S2). Furthermore, after controlling for age, time on the waiting-list, LAS values, serum creatinine, FEV_1 per cent predicted and pulmonary capillary wedge pressure, the presence of mild, moderate or severe PH was not found to be associated with increased risk of death (see online supplementary table S5). Additionally, when we analysed long-term survival for all subjects using a mPAP threshold of 35 mm Hg, there was no difference in Kaplan-Meier actuarial survival between the two groups (see online supplementary figure S3).

DISCUSSION

Our results corroborate the previous studies that reported no difference in survival after SLT in patients with ALD and coexisting PH (see online supplementary material discussion). However, our study is the first to examine the impact of different degrees of PH severity in patients undergoing SLT, has a longer time period of post-transplant follow-up and examined a larger number of recipients than previously published single-centre observational investigations.

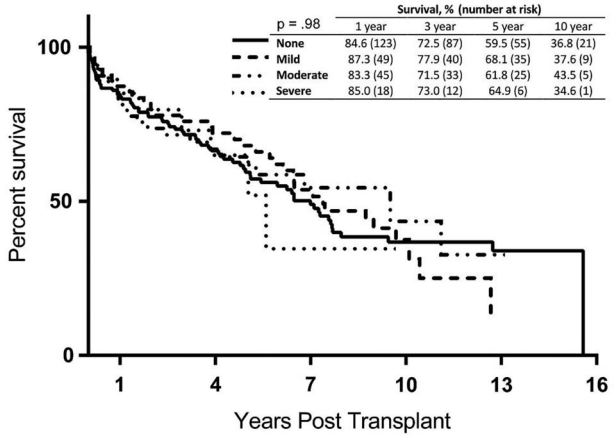

Figure 1 Long-term survival of single-lung transplant recipients with or without secondary pulmonary hypertension.

A major concern in performing SLT in patients with PH, especially when PH is severe, is the theory that the increased native lung haemodynamic pressures will promote hyperperfusion of the newly implanted lung and increase the risk of developing PGD.[4] Because of this concern, many centres preferentially perform BLT in all patients with PH. Although we observed a higher rate of NO usage in the severe PH cohort, we did not identify any significant differences in rates or severity of PGD, duration of assisted ventilation, intensive care unit (ICU) length of stay or overall hospital length of stay among our recipient cohorts. The increased rate of NO usage in this group is likely due to the fact that we aggressively use NO intraoperatively in most patients with PH, and NO is promptly discontinued postoperatively when the recipient has stabilised in the ICU. We have had a low threshold for using NO in SLT to maintain oxygenation and haemodynamics in patients with PH in preventive as opposed to salvage fashion, and most patients with elevated pulmonary pressures would have NO initiated prior to incision. Similarly, we routinely use CPB in all patients undergoing BLT, and it is frequently used for SLT recipients perceived to be at high risk of developing significant PGD. Cannulation is performed prior to implantation of the lung and CPB is initiated prior to reperfusion. The rate of ECMO usage in the severe group was also the highest; however, this may have been due to non-PH factors, as patients with moderate PH had the lowest rate of ECMO use and patients without PH were between the two groups. Most importantly, long-term survival was no worse in any of our PH groups compared with patients without PH; therefore, these minimal postoperative differences did not appear to have any clinical implications.

A relative lack of donor lungs is a continuing problem that significantly limits transplantation of candidates on the waiting-list, and new strategies to both increase the donor organ pool and optimally use donated lungs are much needed.[5] Our study suggests that SLT can be considered for patients with WHO group 3 PH rather than preferentially performing BLT, thereby increasing organ availability without compromising outcomes. Indeed, in COPD, there is evidence to suggest that a policy of using SLT improves access to organs for other potential recipients without a significant increase in post-transplant mortality.

Limitations of our study include its observational, retrospective design, the heterogeneity of recipients' lung disease diagnosis, the potential selection bias introduced for patients selected for SLT and the time span of 14 years. Implementation of the LAS, for one, has had the effect of changing the primary indication for transplantation from COPD to idiopathic pulmonary fibrosis (IPF) at our institution as well as worldwide. We and others have observed that patients with IPF listed for LTX following implementation of the LAS were generally older, had greater requirements for supplemental oxygen, had lower cardiac index values and had more comorbidities. This trend is likely to continue, especially with the recent candidate selection criteria update that suggests that candidates up to 75 years of age can be considered for transplant. Many of these elderly individuals are likely to have IPF, which is frequently accompanied by a moderate-to-severe degree of PH.

In conclusion, patients with PH, even when severe, who underwent SLT at our centre had no significant differences in immediate postoperative outcomes, incidence of CLAD or long-term survival when compared with patients without evidence of coexistent PH. We suggest that PH should not by itself be

considered to be a contraindication to SLT. This approach can help to expand a limited lung donor pool and allow lung blocks to be split such that two recipients can receive lungs from a single donor.

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Competing interests KCM has been an investigator in clinical trials sponsored by Abbott, Actelion, Altana, Amgen, Asthmatx, Bayer, Boehringer-Ingelheim, Bristol Meyers Squibb, Chiron, Discovery Labs, DuPont Merck, Fibrogen, Genentech, Gilead, GlaxoSmithKline, Inspire. InterMune, Johnson & Johnson, Novartis, Nycomed, Pfizer, Pharmaxis, PreAnalytiX, Roche, Ross, Vertex, and Wyeth. KCM has also served on a clinical advisory board for InterMune and serves on a clinical trial adjudication committee for Medimmune. All authors do not report any other relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was used in the production of this manuscript.

Ethics approval University of Wisconsin Human Subjects Committee.

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THE PRESENCE OR SEVERITY OF SECONDARY PULMONARY HYPERTENSION DOES NOT AFFECT OUTCOMES FOR SINGLE LUNG TRANSPLANTATION

ON-LINE SUPPLEMENT

Supplemental Methods:

The grading of severity used in the manuscript was based on criteria from the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension, [1] and all patients were diagnosed as having World Health Organization (WHO) Group 3 pulmonary hypertension (PH). All patients met criteria for lung transplantation (LTX), [2] and lung allocation score (LAS) values were calculated for recipients who received transplants prior to implementation of the LAS system in 2005 using the variables that were available close to the time of transplantation to allow analysis of the LAS as a variable for the entire study population. Chronic lung allograft dysfunction (CLAD) was defined according to the International Society for Heart and Lung Transplantation (ISHLT) clinical practice guideline, [3] and primary graft dysfunction (PGD) was defined by 2006 ISHLT guidelines.[4] Graft survival was defined as either recipient death or graft loss requiring re-transplantation. We also examined whether using a cut point of 35 mm Hg to differentiate recipients with mPAP values ≥35 mm Hg (more severe PH) versus those with no or less severe PH (<35 mm Hg mPAP values) revealed a significant difference in Kaplan-Meier survival estimates.

Since 2008 all emphysema patients (COPD, alpha-1-antitrypsin deficiency) have been listed for bilateral lung transplant. This has been a reaction to less than optimal outcomes with single lung transplantation (SLT) primarily due to native lung hyperinflation issues as well as to literature suggesting improved outcomes in these patients after bilateral lung transplantation (BLT). We have felt that all fibrotic/ILD patients are candidates for SLT as well as BLT, regardless of pulmonary pressures. Older patients (>65 years) are heavily considered for SLT listing only. Other indications for SLT include small chest space, especially as an oversized single lung will have a good outcome with sidedness directed by quantitative perfusion scan. When using single lungs, the contralateral lung was not utilized in all instances. However, if the quality of the lung was acceptable, then it was used by our or another institution. No lungs meeting implant criteria were discarded.

Results Given in This Supplement:

Recipient demographics and characteristics are given in Tables 1-5. Supplemental Figure 2 depicts freedom from CLAD, and supplemental Figure 3 depicts long-term survival when a cut point of 35 mm Hg was used to differentiate recipients with more severe PH (mPAP ≥35 mm Hg) versus those with milder or no PH (mPAP <35 mm Hg).

Supplemental Discussion:

Many patients with advanced lung disease (ALD) will develop Group 3 PH as their disease progresses, and the presence of PH has been identified as a predictor of worse survival for patients with COPD or interstitial lung disease (ILD).[1,5-7] Long-term supplemental oxygen therapy may provide some benefit for patients with COPD and PH, [8,9] and oxygen is often administered but of unproven benefit for hypoxemic patients with other forms of ALD complicated by PH.[9] However, effective therapies to prolong survival, such as vasodilators that have been shown to benefit patients with primary pulmonary hypertension, have yet to be

identified for patients PH, and vasodilator therapy for PH may impair gas exchange by blunting hypoxic pulmonary vasoconstriction.[10]

Lung transplantation may be the only therapeutic option that can improve quality of life and prolong survival for patients with ALD, but the presence of associated PH as well as performing SLT have been identified as risk factors for complications such as primary graft dysfunction (PGD), which was found to significantly reduce one-year survival.[11] Although it has been suggested BLT may be a better choice of procedure type for patients with PH and mean pulmonary artery pressures (mPAP) greater than 40 mm Hg,[12] this opinion was made on the basis of a limited number of recipients transplanted for WHO Group 3 PH without a statistically significant advantage for BLT. Other investigators have not reported a significant difference in survival for SLT versus BLT in patients with PH.[13-16] Neurohr et al.[17] suggested that BLT may be preferable to SLT for IPF patients with PH, but patients with significantly elevated mPAP due to PH were preferentially given BLT.

Significant controversy remains regarding SLT in patients with ALD-associated PH, and single center studies that have been reported to date have analyzed data for relatively few recipients and have not stratified recipients with Group 3 PH who received SLT according to severity of their PH. Because preferentially performing BLT procedures in patients with SPH puts significant restraint on the donor lung pool and SLT can allow lungs from a single donor to benefit two recipients, we reviewed our experience with SLT for patients without SPH and those with mild, moderate, or severe PH to determine whether outcomes are significantly affected by the presence and severity of PH when SLT procedures are performed. Our findings suggest that SLT is both safe and effective in patients with PH and that the presence of PH or the severity of PH does not have a significant adverse effect on long-term outcomes including long-term survival (Figure 1 in Main Document) and freedom from CLAD (On-line supplement; Figure 2). Furthermore, recipients with severe pre-transplant PH did not have worse outcomes than patients with normal PAP values. Additionally, when separating our patients into 2 cohorts defined as no or mild PH (mPAP <35 mm Hg) versus more severe PH (mPAP ≥35 mm Hg, long-term survival was not worse for the cohort with more severe PH (On-line supplement; Figure 3). Our results corroborate previous studies that reported no difference in survival after SLT in patients with coexisting PH.[12-15] However, our study is the first to examine the impact of different degrees of PH severity in patients undergoing SLT, has a longer time period of post-transplant follow-up, and examined a larger number of recipients than previously published single-center observational investigations, and our results suggest that SLT can be performed with reasonable safety in patients for whom SLT is an appropriate consideration even when candidates have relatively severe PH.

When survival rates in all of our cohorts are compared to United Network for Organ Sharing (UNOS) data, our survival outcome data match or exceed outcomes for SLT on a national level. The UNOS database reports an average survival of SLT patients of 84.2%, 60.7%, and 44.1% at one, three, and five years. We observed survival rates superior to the UNOS rates in all patient groups at three and five years. At one-year follow-up, post-transplant survival for our recipients (no PH = 84.6%; mild PH = 87.3%; moderate PH = 83.3%; severe PH = 85.0%) were at the level of the UNOS one-year survival data for SLT (84.2%), and there were no statistically significant differences in one-year survival among our PH severity cohorts at one year.

In addition to the lack of difference in short- and long-term survival for our SLT recipients without PH versus those with PH, our current study also failed to identify major differences in peri-operative events. A major concern in performing SLT in patients with PH, especially when severe PH is present, is the theory that the increased native lung hemodynamic pressures will promote hyper-perfusion of the newly implanted lung and increase the risk of developing PGD.[1] Because of this concern, many centers preferentially perform bilateral transplants in all patients with PH [13,17-19] Although we observed a higher rate of ECMO and NO utilization in the severe PH cohort, we did not identify any differences in rates or severity of PGD among our recipient cohorts, including those with the most severe SPH (Table 4). Additionally, we did not observe significant differences in duration of assisted ventilation, ICU length of stay, and overall hospital length of stay.

A relative lack of donor lungs is a continuing problem that significantly limits our ability to transplant waitlisted candidates, and new strategies to both increase the donor organ pool and optimally utilize donated lungs are much needed. Methods that seek to increase lung donations have been proposed. These include a point-based system in Israel that rewards potential donors by enhancing their likelihood of receiving a donated organ themselves should they eventually need one themselves; this policy has led to an increase in registered donors.[20] A policy of "opting out" instead of the current "opting in" system continues to be evaluated in the United States as one method of increasing the number of registered donors.[21] Other measures include utilizing living donors for lobar lung transplants, increased usage of donation after cardiac death donor organs, accepting donors with a significant smoking history, increased use of donors older than 55 years of age, and using *ex vivo* lung perfusion to reclaim and rehabilitate marginal donor lungs.[22-27] Our study suggests that SLT can be considered for patients with PH rather than preferentially performing BLT on these patients, thereby increasing organ availability without compromising outcomes. Indeed, in COPD, there is evidence to suggest that a policy of SLT improves access to organs for other potential recipients without significant increase in post-transplant mortality.[28,29]

Limitations of our study include its observational, retrospective analysis of non-randomized patients and the potential selection bias introduced for patients selected for SLT. Another concern is the prolonged period of 14 years. Although this has the advantage of accruing a considerable number of recipients for our analyses and a long follow-up period for many of our patients, many changes have occurred including implementation of the LAS, which has had the effect of changing the primary indication for transplantation from COPD to IPF at our institution as well as worldwide.[30] We and others have observed that patients with IPF listed for transplantation following implementation of the LAS were generally older, had greater requirement for supplemental oxygen, had lower cardiac index values, and had more comorbidities.[31] This trend is likely to continue, especially with the recent candidate selection criteria update that suggests that candidates up to 75 years of age can be considered for transplant.[32] Many of these individuals are likely to have IPF, which is frequently accompanied by a moderate to severe degree of PH.[6]

In conclusion, patients with ALD-associated WHO Group 3 PH, regardless of severity, who underwent SLT at our center had no significant differences in immediate postoperative outcomes, incidence of CLAD, or long-term survival when compared to patients without evidence of PH. We suggest that PH should not by itself be considered to be a contraindication to SLT, which has the added benefit of expanding a limited lung donor pool and allowing lung

blocks to be split such that two recipients can receive lungs from a single donor. Future studies will be aimed at validating these results in a prospective fashion, and analysis of a large database, such as that of the United Network for Organ Sharing, may help to identify whether SLT should or should not be performed in patients with WHO Group 3 PH.

Supplemental Table 1. Pre-Transplant Recipient Characteristics.

Pre-operative Characteristics (mean values)	Pulmonary Hypertension Severity				*p* value
	None	Mild	Moderate	Severe	
N	150	55	54	20	--
Male gender (%)	71	67	80	65	0.78
Mean age (years)	58	57	57	58	0.66
Diabetes (%)	27	24	22	30	0.57
History of smoking (%)	75	82	78	65	0.64
Coronary artery disease (%)	9	20	17	5	0.045
Congestive heart failure (%)	5	4	4	15	0.10
Systemic hypertension (%)	36	38	39	55	0.26
Race = Caucasian (%)	93	98	87	70	0.006
Body mass index (kg/m^2)	25.6	26.0	26.7	26.7	0.44
Mechanical ventilation (%)	13	11	11	10	0.97
Supplemental oxygen use (L/min)	3.6	3.6	4.3	3.7	0.38
FVC (% predicted)	51.4	46.1	47.9	43.6	0.083
FEV1 (% predicted)	40.1	31.3	36.5	44.4	0.024
Lung allocation score (LAS)	38.1	37.2	42.9	47.5	<0.001
Time on waitlist (days)	286	348	281	81	0.009
Serum creatinine (mg/dL)	0.91	0.92	1.00	0.96	0.033
PCWP (mm Hg)	10	16	16	15	<0.001
Cardiac index ($L/min/m^2$)	2.8	2.9	2.7	2.8	0.41
Systolic PAP (mm Hg)	31	39	50	72	<0.001
Diastolic PAP (mm Hg)	14	21	23	33	<0.001
Mean PAP (mm Hg)	21	29	44	46	<0.001

FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure

Supplemental Table 2. Transplant Indications (Primary Disease).

Primary Disease (transplant indication)	Pulmonary Hypertension Severity				*p* value
	None	Mild	Moderate	Severe	
All recipients (N)	150	55	54	20	--
COPD/emphysema – N (%)	51 (34)	28 (51)	17 (32)	1 (5)	NS
Idiopathic pulmonary fibrosis – N (%)	68 (45)	14 (26)	22 (41)	10 (50)	NS
COPD with AATD – N (%)	10 (7)	8 (15)	2 (4)	0	<0.0001
Sarcoidosis – N (%)	3 (2)	1 (2)	3 (6)	6 (30)	NS
Hypersensitivity pneumonitis (N/%)	4 (3)	0 (0)	2 (4)	2 (10)	NS
Other (N/%)	14 (9)	4 (6)	8 (13)	1 (5)	NS

AATD = alpha-1-antitrypsin deficiency; COPD = chronic obstructive pulmonary disease

Supplemental Table 3. Donor Age and Recipient Intra-operative Characteristics.

Primary Disease (transplant indication)	Pulmonary Hypertension Severity				*p* value
	None	Mild	Moderate	Severe	
Donor age (years)	32	30	32	40	0.103
CPB required (%)	15	15	30	65	<0.001
CPB duration (minutes)	116	170	186	142	0.109
Ischemic time (minutes)	313	343	307	289	0.276
sPAP (mm Hg)	41	41	51	67	<0.001
mPAP (mm Hg)	29	29	35	47	<0.001

CPB = cardiopulmonary bypass; sPAP = systolic pulmonary artery pressure; mPAP = mean pulmonary artery pressure

Supplemental Table 4. Post-operative Recipient Characteristics.

Pre-operative Characteristics (mean values)	Pulmonary Hypertension Severity				*p* value
	None	Mild	Moderate	Severe	
PGD Grade 0-1 (%)	82	80	78	70	0.325
PGD Grade 2-3 (%)	18	20	22	30	
ECMO (%)	4	7	0	10	0.045
Nitric oxide use (%)	40	49	70	80	<0.001
Length of ventilation (days)	3.0	4.5	2.8	2.4	0.652
Prolonged ventilation >48 hrs (%)	26	27	32	20	0.704
ICU length of stay (days)	6.3	10.7	8.0	4.3	0.163
Hospital length of stay (days)	22	23	25	16	0.390
Readmission within 30 days (%)	17	35	17	25	0.097
30-day mortality (%)	5	2	4	5	0.831

ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; PGD = primary graft dysfunction

Supplemental Table 5. Cox Multivariate Analysis of Risk Factors for Death.

Variable	HR (95% CI)	p-value
Age	1.045 (1.014-1.076)	0.004
Waiting list time	1.000 (0.999-1.001)	0.78
Lung allocation score	1.009 (0.988-1.031)	0.41
Serum creatinine	1.273 (0.547-2.962)	0.58
FEV1 (% predicted)	1.012 (1.003-1.021)	0.01
PCWP	1.011 (0.982-1.040)	0.48
Mild PH	1.062 (0.673-1.676)	0.80
Moderate PH	0.919 (0.7536-1.577)	0.76
Severe PH	1.137 (0.527-2.452)	0.74

FEV1 = forced expiratory volume in one second; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PH = hypertension

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Figure 2. Freedom from chronic lung allograft dysfunction (CLAD).

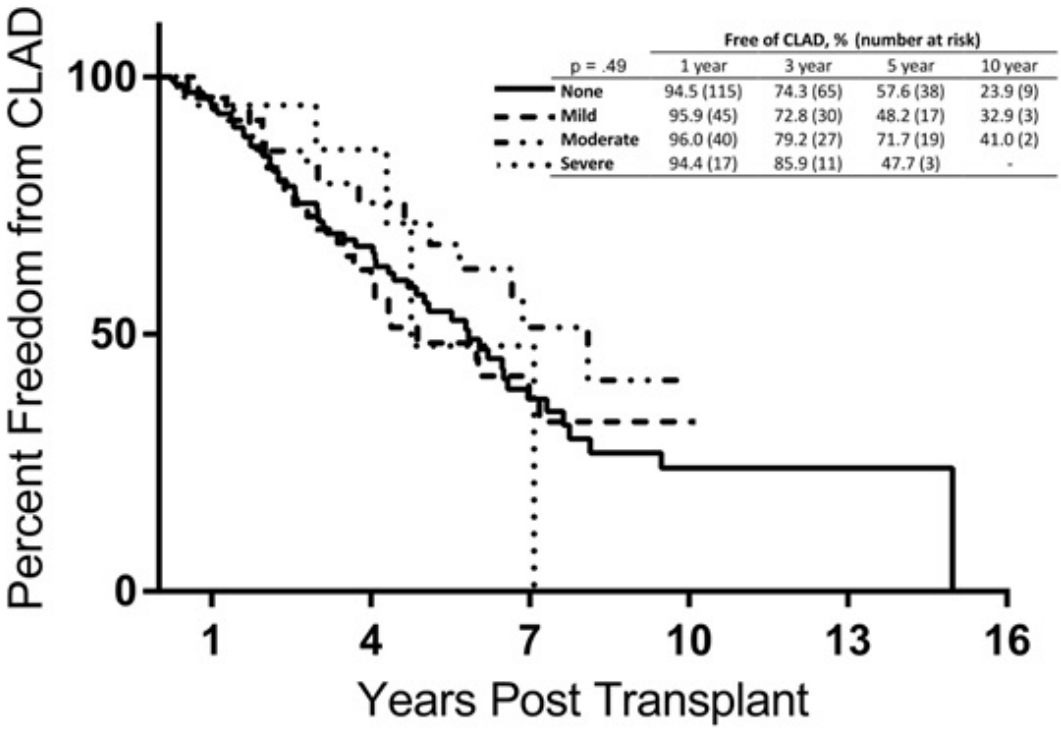

Figure 3. Recipient survival (Kaplan-Meier actuarial survival) using a threshold of 35 mm Hg for mPAP.