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ORIGINAL ARTICLE

Potential functional and survival benefit of double over single lung transplantation for selected patients with idiopathic pulmonary fibrosis

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Summary

Idiopathic pulmonary fibrosis (IPF) is a frequent indication for lung transplantation (LTX) with pulmonary hypertension (PH) negatively affecting outcome. The optimal procedure type remains a debated topic. The aim of this study was to evaluate the impact of pretransplant PH in IPF patients. Single LTX (SLTX, $n = 46$) was the standard procedure type. Double LTX (DLTX, $n = 30$) was only performed in cases of relevant PH or additional suppurative lung disease. There was no significant difference for pretransplant clinical parameters. Preoperative mean pulmonary arterial pressure was significantly higher in DLTX recipients (22.7 ± 0.8 mmHg vs. 35.9 ± 1.8 mmHg, $P < 0.001$). After transplantation, 6-min-walk distance and BEST-FEV_1 were significantly higher for DLTX patients (6-MWD: 410 ± 25 m vs. 498 ± 23 m, $P = 0.02$; BEST-FEV_1: 71.2 ± 3.0 (% pred) vs. 86.2 ± 4.2 (% pred), $P = 0.004$). Double LTX recipients demonstrated a significantly better 1-year-, overall- and Bronchiolitis obliterans Syndrome (BOS)-free survival ($P < 0.05$). Cox regression analysis confirmed SLTX to be a significant predictor for death and BOS. Single LTX offers acceptable survival rates for IPF patients. Double LTX provides a significant benefit in selected recipients. Our data warrant further trials of SLTX versus DLTX stratifying for potential confounders including PH.

Introduction

Idiopathic pulmonary fibrosis (IPF) is the most common form of the idiopathic interstitial pneumonias and the second most frequent lung pathology after chronic obstructive pulmonary disease leading to lung transplantation (LTX) [1]. None of the currently available medical therapies has a proven effect on survival, resulting in a mean life expectancy for newly diagnosed IPF cases of 2.9 to 5 years [2]. Retrospective studies have shown a survival benefit for lung transplantation over the best medical therapy for patients with progressive IPF [3]. Therefore, the current guidelines for the selection of lung transplant candidates promote the early referral of eligible IPF patients for transplantation [4]. For septic lung disease e.g. cystic fibrosis, double lung transplantation (DLTX) is the standard operative approach. However, in IPF patients, the optimal surgical procedure remains to be conclusively determined [5]. Traditionally, single lung transplant (SLTX) has been the treatment of choice for

IPF because restrictive pulmonary physiology would lead to selective ventilation and perfusion of the graft lung with favorable functional outcome. Moreover, less operative trauma, shorter procedure time and avoidance of longer ischemic time for the second lung with the risk of organ failure are arguments favoring SLTX [6]. By contrast, some studies have suggested that DLTX may reduce the damage to pulmonary function in case of early complications like reperfusion injury or acute graft rejection. Thus, DLTX may lead to better baseline functional parameters with superior pulmonary reserve and respiratory mechanics, eventually resulting in improved long-term survival rates [7]. Accordingly, the International Society for Heart and Lung Transplantation (ISHLT) registry data indicate a larger application of DLTX in recent years [1]. However, given the shortage of donor lungs and the dismal survival rates of IPF patients awaiting transplantation with the ethical implications of using two lungs for the same patient, the preferred surgical approach remains a debated topic [8].

Pulmonary hypertension (PH) is a common finding in IPF patients awaiting lung transplantation that significantly contributes to exercise limitation and has a negative impact on prognosis [9,25]. Some studies have identified preoperative PH in IPF patients receiving SLTX to be associated with an increased risk of early primary graft dysfunction, prolonged intensive care unit stay and higher 90-day-mortality [10–12]. However, as a result of the limitations of large database reviews, the heterogeneity of patient populations and the lack of controlled prospective trials, no superiority claim for a specific procedure type can be supported at this point [13,14]. To improve individual outcome and acknowledging the limited availability of donor organs, the Munich Lung Transplant Group has applied a simple decision-making process to guide the selection of SLTX or DLTX candidates as the implementation of our transplant program. We consider SLTX to be the appropriate surgical treatment option for IPF patients. Double LTX is only performed in cases of relevant preoperative PH or presence of suppurative lung disease. The aim of the present study was to assess the long-term impact of this approach on functional outcome and survival in IPF patients.

Methods

Patient population and standard care of lung transplant recipients

From January 1997 to December 2008, all 76 consecutive LTX patients with IPF were included in this study. The study was performed in accordance with recommendations of the local board on medical ethics at Ludwig Maximilians University of Munich. Informed written consent was obtained from each subject. The diagnosis of IPF was made according to the criteria of the American Thoracic Society and European Respiratory Society [15,16]. Follow-up data, including demographic data, bronchoscopy results, laboratory values, pulmonary function tests, immunosuppressive protocol, survival status and cause of death were obtained from prospectively maintained medical records and computerized databases through March 31, 2009. Patients received no induction therapy and were maintained on triple immunosuppression with corticosteroids, tacrolimus and mycophenolate mofetil as published previously [17,18]. In case of recurrent acute rejection (AR), toxicity, or Bronchiolitis obliterans Syndrome (BOS), patients were switched to an alternative immunosuppression regimen based on a case by case decision. Patients received a viral prophylaxis with acyclovir for 3 months. In addition, pre-emptive therapy with ganciclovir and/or immune globulin was initiated based on positive cytomegalovirus polymerase chain reaction.

Definitions

The diagnosis of BEST-FEV_1 and BOS was established using the International Society of Heart and Lung Transplantation (ISHLT) definition [19]. Acute rejection was diagnosed using standard histological criteria according to the Lung Rejection Study Group [20]. Any biopsy specimen with AR A $\geq$ 2 was considered positive and treated with methylprednisolone at a dose of 500 mg/day for three consecutive days. In case of AR A1, the decision to proceed with therapy was based on clinical status. Isolated lymphocytic bronchitis (LB, B grade) was not treated. Human leukocyte antigen (HLA) mismatches were determined in accordance with the European Federation of Immunogenetics [21]. Donor organ ischemic time for bilateral transplants was the mean of right and left lung ischemic time.

The lung allocation score

The lung allocation score (LAS) was retrospectively calculated using the online available LAS calculator provided by the United Network For Organ Sharing (UNOS) based on the data available at the most recent completed pulmonary function test before transplantation (http://www.unos.org/resources/fm_LAS_Calculator.asp).

Lung function testing

Pulmonary function tests included spirometry, body plethysmography, single breath diffusing capacity for carbon monoxide (DL_{CO}) and blood gas analysis in arterialized capillary blood from the ear lobe without

supplemental oxygen [22]. Parameters were calculated as percent of predicted [23]. The most recent complete pulmonary function test was used for pretransplant analysis. Post-transplant lung function parameters were calculated analogously to BEST-FEV_1 values.

Six-minute walk test

The distance covered in 6 min (6-MWD) was measured according to the American Thoracic Society statement [24]. For pretransplant analysis, the most recent completed test was included in the analysis. For post-transplant evaluation, the best available 6-MWD was considered in this study.

Right heart catheterization

A Swan-Ganz-catheter was inserted into the right femoral vein under local anesthesia. Hemodynamic parameters included heart rate (HR), pulmonary arterial pressure (PAP), right atrium pressure (RAP) and pulmonary capillary wedge pressure (PCWP). Cardiac output (CO) was obtained using the thermodilution method. Cardiac index (CI) and pulmonary vascular resistance (PVR) were calculated using standard formulas [25].

Determination of procedure type: single or double lung transplantation

Single LTX is the standard type of transplantation for IPF patients in our center. Double LTX was only performed in recipients with relevant PH determined by right heart catheterization or in cases complicated by suppurative lung disease with a clinically significant bronchiectatic component confirmed by high-resolution computed tomography scan. Relevant PH was defined as mean PAP ≥ 30 mmHg with normal PCWP. Right heart catheterization was performed in all IPF patients at the time of listing for lung transplantation. Follow-up right heart catheterization was performed in patients with suspected new onset PH based on serial cardiac echo-Doppler evaluation or in case of clinical worsening.

Statistical analysis

Statistics were calculated using SPSS statistics software version 17.0 for Windows (SPSS Inc., Chicago, IL, USA). The demographic data and outcomes between groups were compared using two-sided χ^2 test or two-sided Fisher's exact test (when expected cell size was <5) for categorical variables and two-sided Mann–Whitney *U*-test of independent samples for continuous variables. Data are presented as mean ± SEM (standard error of the mean) or as individual values and box and whisker plots displaying the median, the 25th and 75th percentiles and the smallest and largest value within 1.5 box lengths from the box. Survival and BOS-free survival were calculated using the Kaplan–Meier Method and groups were compared by means of log-rank testing. To evaluate for an association between potential risk factors and the development of BOS ≥ 1 initial univariate Cox regression analysis was used. Identified variables were included in subsequent multivariate Cox regression models with restriction to two co-variables as a result of the limited sample size. Results were considered statistically significant at $P < 0.05$.

Results

Patient cohorts

A total of 76 LTX recipients with IPF were included in this study. The mean duration of observation per patient was 3.15 ± 0.21 years (median 2.17, range 0.00–11.06) and the study included 240 patient-years of follow-up. Forty-six (60.5%) patients received SLTX and DLTX was performed in thirty (39.5%) recipients. The basic demographic and clinical information were statistically indistinguishable (Table 1). There was a weak trend towards younger recipients in the DLTX group without the difference reaching statistical significance ($P = 0.07$).

Pretransplant characteristics

Table 2 and Fig. 1 compare the details of preoperative lung function, hemodynamic and functional capacity parameters by procedure type. There was no statistically

Table 1. Basic characteristics of single lung transplantation and double lung transplantation recipients with idiopathic pulmonary fibrosis.

Group *n* (%)	SLTX 46 (60.5)	DLTX 30 (39.5)	*P*-value
Total follow-up post LTX (years ± SEM)	3.00 ± 0.44	3.40 ± 0.50	0.55
Female *n* (%)	21 (45.7)	12 (40.0)	0.40
Age (years ± SEM)	53.74 ± 1.15	50.38 ± 1.34	0.07
BMI (kg/m^2 ± SEM)	25.42 ± 0.91	24.16 ± 1.13	0.39
Ischemic time (min ± SEM)	320.7 ± 13.6	390.9 ± 18.6	0.03*
CMV mismatch *n* (%)	14 (29.5)	7 (22.0)	0.29
HLA mismatches, *n* (%)			
0–2	2 (4.3)	1 (3.3)	0.49
3–4	20 (43.5)	14 (46.7)	
5–6	24 (52.2)	15 (30.0)	

SLTX, single lung transplantation; DLTX, double lung transplantation; IPF, idiopathic pulmonary fibrosis; CMV, cytomegalovirus; CMV-mismatch, donor+/recipient−; HLA, human leukocyte antigen; BMI, body mass index; SEM, standard error of the mean.
*Significant.

Table 2. Pretransplant lung function, hemodynamic and functional capacity parameters.

Group *n* (%)	SLTX 46 (60.5)	DLTX 30 (39.5)	*P*-value
Hemodynamics			
Days pretransplant	281 ± 32	248 ± 37	0.39
PAPmean (mmHg)	22.7 ± 0.8	35.9 ± 1.8	<0.001*
PCWP (mmHg)	8.9 ± 0.7	8.6 ± 0.8	0.76
CI (l/min/m^2)	3.1 ± 0.1	2.8 ± 0.1	0.16
PVR (dyn × s × cm^{-5})	210 ± 17	473 ± 40	<0.001*
Lung function			
Days pretransplant	125 ± 15	148 ± 21	0.28
FVC (% pred)	35.6 ± 1.6	40.9 ± 2.5	0.069
DL_{CO} (% pred)	31.8 ± 2.4	20.3 ± 2.6	0.003*
pO_2 (mmHg)	44.3 ± 1.2	41.3 ± 1.5	0.11
6-MWD (m)	263 ± 19	241 ± 18	0.45
LAS	41.92 ± 1.17	41.11 ± 1.87	0.54

Data represent mean ± SEM.

SLTX, single lung transplantation; DLTX, double lung transplantation; PAPmean, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; CI, cardiac index; PVR, pulmonary vascular resistance; FVC, forced vital capacity; DL_{CO}, diffusing capacity for carbon monoxide (single breath method); pO_2, capillary pressure of oxygen; 6-MWD, 6-min-walk distance; LAS, lung allocation score; SEM, standard error of the mean.

*Significant.

significant difference in the length of the interval between date of last available pretransplant lung function test or right-heart catheterization and date of transplantation for the SLTX and the DLTX group, respectively. Moreover, pretransplant spirometry, functional capacity (6-MWD), capillary pressure of oxygen analysis and LAS demonstrated no significant difference. There was a trend for reduced pretransplant vital capacity in SLTX recipients without the difference reaching statistical significance ($P = 0.069$). However, DL_{CO} was significantly reduced in the DLTX group. Analysis of hemodynamic parameters demonstrated a significantly increased mean PAP and PVR for the entire DLTX cohort ($n = 30$). In 24 (80%) patients of the DLTX group, the procedure was performed in the presence of PH with a mean PAP of 39.0 ± 1.6 mmHg (median 37.2, range 31–57). Follow-up right-heart catheterization revealed previously undetected PH in nine (30%) DLTX patients (mean PAP 37.4 ± 2.7 mmHg) at a median of 194 days (range: 33–299) before transplantation resulting in a switch to DLTX. Six (20%) recipients (50.17 ± 1.96 years, 33% female, 6-MWD 273 ± 37 m, forced vital capacity (FVC) 38.2 ± 4.3% pred., pO_2 45.2 ± 2.7 mmHg, DL_{CO} 18.9 ± 2.3% pred.) received DLTX in the absence of rele-

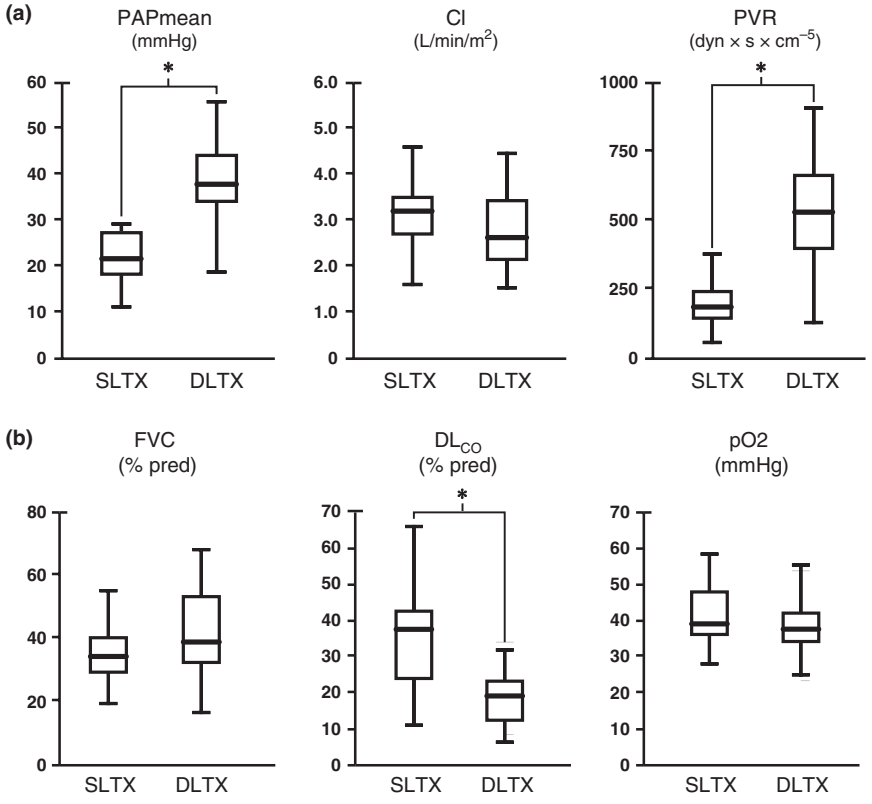

Figure 1 (a, b) Pretransplant hemodynamic and lung function parameters by procedure type. Box and whisker plots show the comparison of pretransplant mean pulmonary arterial pressure (PAPmean), cardiac index (CI), pulmonary vascular resistance (PVR), forced vital capacity (FVC), diffusing capacity for carbon monoxide (DL_{CO}) and capillary pressure of oxygen (pO_2) for single lung transplants (SLTX) and double lung transplants (DLTX). *$P < 0.05$. The horizontal line displays the median, the box edges show the 25th and 75th percentiles, and the whiskers show the smallest and largest value within 1.5 box lengths from the box.

Table 3. Post-transplant lung function and functional capacity parameters.

Group *n* (%)	SLTX 36 (52.1)	DLTX 26 (41.9)	*P*-value
Days post-transplant	210 ± 18	246 ± 23	0.20
BEST-FEV_1 (% pred)	71.2 ± 3.0	86.2 ± 4.2	0.004*
FVC (% pred)	70.7 ± 2.7	84.1 ± 4.0	0.007*
DL_{CO} (% pred)	50.2 ± 2.6	60.7 ± 2.8	0.009*
pO_2 (mmHg)	74.3 ± 0.9	77.1 ± 0.9	0.06
6-MWD (m)	410 ± 25	498 ± 23	0.02*

Data represent mean ± SEM.
SLTX, single lung transplantation; DLTX, double lung transplantation; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; DL_{CO}, diffusing capacity for carbon monoxide (single breath method); pO_2, capillary pressure of oxygen; 6-MWD, 6-min-walk distance; SEM, standard error of the mean.
*Significant.

vant PH (mean 22.5 ± 2.2 mmHg, median 21.8, range 19–29). Reasons for DLTX in these patients were clinically significant bronchiectasis with suppurative lung disease ($n = 5$) and pneumomediastinum in one case. Subgroup analysis revealed no statistically significant differences for basic clinical and lung function data between DLTX recipients with or without PH.

Functional outcome

A total of 62 (81.5%) transplant recipients were eligible for functional outcome analysis including BEST-FEV_1 classification. Thirty-six (78.2%) of SLTX recipients and 26 (86.6%) of DLTX recipients were able to perform complete pulmonary function tests and 6-MWD during follow-up ($P = 0.32$). Table 3 and Fig. 2 compare the details of post-transplantation lung function and functional capacity parameters by procedure type. There was no significant difference in the length of the interval between LTX and date of pulmonary function test defining BEST-FEV_1. However, functional capacity (6-MWD), DL_{CO}, FVC and BEST-FEV_1 were significantly higher in the DLTX group. There was a trend for reduced capillary pressure of oxygen in SLTX recipients without the difference reaching statistical significance ($P = 0.06$).

Survival and causes of death

The causes of death by procedure type are depicted in Table 4. There were a significantly higher number of deaths attributable to BOS in SLTX recipients. Moreover, the percentage of fatalities related to pulmonary infections was increased in the SLTX group without the difference reaching statistical significance. Interestingly, no fatal case during the first 90 days was attributable to pulmonary

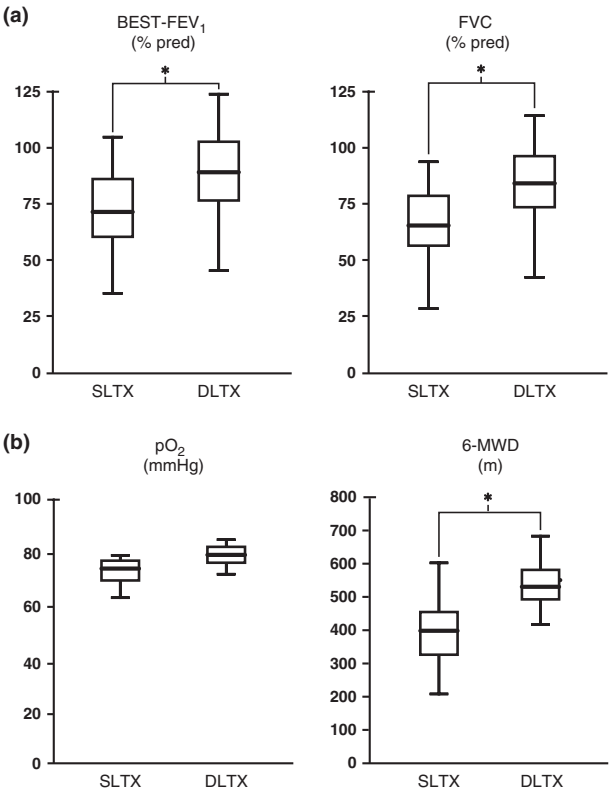

Figure 2 (a, b) Post-transplant lung function and 6-min walk distance by procedure type. Box and whisker plots show the comparison of post-transplant BEST-FEV_1 (forced expiratory volume in 1 s), forced vital capacity (FVC), capillary pressure of oxygen (pO_2) and 6-min walk distance (6-MWD) for single lung transplants (SLTX) and double lung transplants (DLTX). *$P < 0.05$. The horizontal line displays the median, the box edges show the 25th and 75th percentiles, and the whiskers show the smallest and the largest value within 1.5 box lengths from the box.

infection in the DLTX group whereas three SLTX recipients died as a result of bacterial ($n = 2$) or cytomegalovirus ($n = 1$) infection. Cases of death directly linked to AR episodes or malignancies have not been recorded during the study period. The overall survival rates for the entire cohort of patients ($n = 76$) were 86.8% at 3 months, 80.3% at 6 months, 73.5% at 1 year, 64.8% at 3 years, 53.1% at 5 years, and 40.1% at 7.5 years. Long-term survival calculated by means of Kaplan–Meier estimates revealed a significantly reduced survival in SLTX recipients (Fig. 3a). The overall survival rates for SLTX ($n = 46$) and DLTX ($n = 30$) recipients were 82.6% vs. 93.3%, 73.9% vs. 90.0%, 69.6% vs. 79.5%, 55.3% vs. 74.2% and 41.7% vs. 66.8% at 3 months, 6 months, 1, 3 and 5 years, respectively. There was a strong trend for increased 90-day mortality in SLTX recipients without the differences reaching statistical significance ($P = 0.06$).

Table 4. Causes of death after lung transplantation by procedure type.

	n = 33				
	SLTX *n* = 26 (78.8)		DLTX *n* = 7 (21.2)		
	Time after transplant				
Cause of death (%)	<90 days *n* = 10 (38.5)	>90 days *n* = 16 (61.5)	<90 days *n* = 2 (28.6)	>90 days *n* = 5 (71.4)	*P*-value
Tech. complications/others	2 (7.7)	0 (0)	0 (0)	1 (14.2)	0.31
Pulmonary infection					
Cytomegalovirus	1 (3.8)	0 (0)	0 (0)	0 (0)	0.08
Non-Cytomegalovirus	2 (7.7)	2 (7.7)	0 (0)	2 (28.6)	
BOS ≥ stage 1	0 (0)	12 (46.1)	0 (0)	2 (28.6)	0.039*
Graft failure	5 (19.3)	2 (7.7)	2 (28.6)	0 (0)	0.61

SLTX, single lung transplantation; DLTX, double lung transplantation; BOS, bronchiolitis obliterans syndrome; SEM, standard error of the mean.
*Significant.
Values given in parenthesis are percentages.

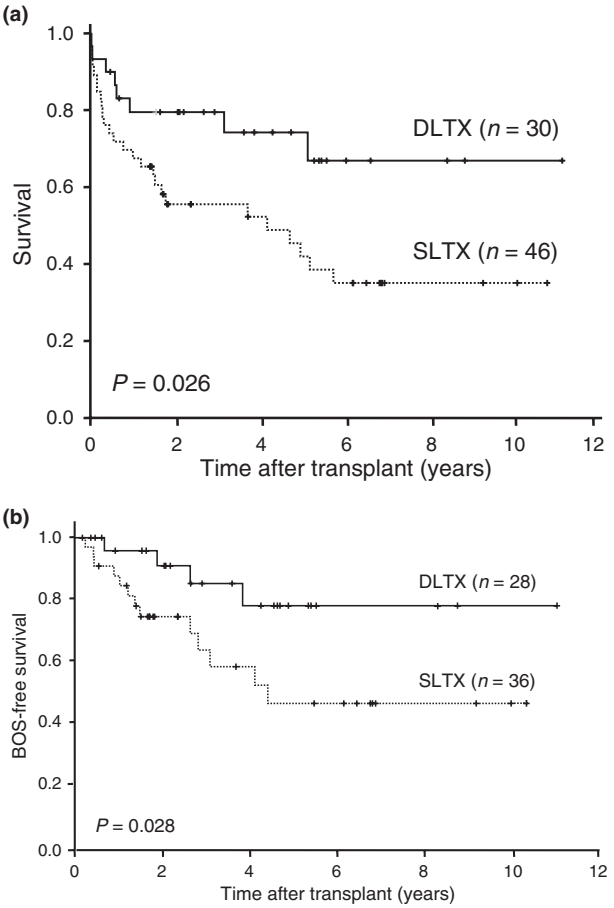

Figure 3 (a, b) Survival and bronchiolitis obliterans syndrome (BOS)-free survival by procedure type. Survival and BOS-free survival stratified by single lung transplantation (SLTX, dashed line) or double lung transplantation (DLTX, solid line).

However, 1-year mortality was significantly higher in the SLTX group when compared with DLTX patients ($P = 0.024$). The long-term survival benefit for DLTX recipients was sustained throughout the study period for patients alive at 3 months with survival rates of 76.7% vs. 83.2% at 1 year, 59.3% vs. 76.3% at 3 years and 43.8% vs. 73.2% at 5 years, respectively ($P = 0.038$). However, this significant survival benefit could no longer be demonstrated using a 6-months conditional survival cut-off (85.1% vs. 91.7%, 68.9% vs. 79.4%, 50.9% vs. 77.2% at 1, 3 and 5 years, $P = 0.092$). Subgroup analysis revealed no statistically significant difference for survival between DLTX recipients with or without PH ($P = 0.63$).

Acute rejection and bronchiolitis obliterans syndrome

An acute rejection episode AR ≥ 2 was detected in 33.3% ($n = 25$) and AR = 1 in 29.1% ($n = 22$) recipients, respectively. Acute rejection was associated with a significantly reduced survival and increased risk of BOS ≥ 1 (Table 5). However, there was no statistically significant difference for the percentage of detected AR ≥ 2 episodes with 15 (35.6%) in SLTX and 10 (29.6%) in DLTX patients ($P = 0.33$) or confirmed AR = 1 episodes with 14 (30.0%) in SLTX and seven (22.1%) in DLTX recipients ($P = 0.21$). Moreover, subgroup analysis demonstrated no significant difference for the number of detected ARs episodes per patient grade AR = 1 (SLTX: 0.46 ± 0.15 vs. DLTX: 0.39 ± 0.17, $P = 0.72$) and AR ≥ 2 (SLTX: 0.44 ± 0.12 vs. DLTX: 0.36 ± 0.21, $P = 0.33$) between the procedure types during the first year. Overall, BOS ≥ 1 was diagnosed in 17 (26.6%) of 64 eligible recipients during the study period. In this study, 14.3% ($n = 4$) of DLTX patients and 36.1% ($n = 13$) of SLTX patients

Table 5. Univariate Cox regression analysis of risk factors for bronchiolitis obliterans syndrome and death.

	Death		BOS stage ≥ 1	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (≥50 years)	1.21 (0.59–2.47)	0.59	1.09 (0.35–2.79)	0.86
Type of transplant				
DLTX	1.00	0.022*	1.00	0.015*
SLTX	3.69 (1.63–8.66)		2.58 (1.36–7.02)	
HLA mismatches				
3–4	1.00	0.79	1.00	0.56
5–6	1.13 (0.46–2.76)		1.56 (0.35–6.95)	
CMV mismatch (d^+/r^-)	1.27 (0.55–2.93)	0.52	1.33 (0.38–4.71)	0.66
Acute rejection ≥2	3.85 (1.74–7.80)	0.009*	2.74 (1.99–7.59)	0.013*

SLTX, single lung transplantation; DLTX, double lung transplantation; BOS, bronchiolitis obliterans syndrome; HR, hazard ratio; CI, confidence interval; CMV, cytomegalovirus; CMV-mismatch, donor+/recipient–; HLA, human leukocyte antigen; AR, acute rejection.
*Significant.

developed BOS during the study period ($P = 0.033$). Single LTX recipients demonstrated a significantly increased risk for BOS ≥ 1 and subsequently reduced BOS-free survival Table 5, Fig. 3b). Subgroup analysis revealed no statistically significant differences for BOS-free survival between DLTX recipients with or without PH ($P = 0.33$).

Risk factors for death and bronchiolitis obliterans syndrome

Cox regression analysis was performed to detect associations of potential predictor variables for death and BOS stage ≥1. Univariate analysis revealed that only SLTX and detection of AR episodes AR ≥ 2 were significantly associated with BOS stage ≥1 and death (Table 5). To determine if single lung transplantation is a risk for death and BOS separate from AR episodes, multivariate Cox regression analysis was used. It demonstrated that SLTX remained a significant predictor for BOS stage ≥1 and death (survival: hazard ratio (HR) 2.98, 95% confidence interval (CI) 1.61–8.85, $P = 0.036$; BOS: HR 1.86, 95% CI 1.40–7.87, $P = 0.023$).

Discussion

Lung transplantation for IPF has been shown to confer a survival benefit over the best medical therapy. However, choice of single versus double lung transplantation for IPF is far less clear. Despite the well known fact that many centers have a bias towards offering DLTX in IPF patients with PH, only few articles have focused attention on this topic. Although multi-institutional studies are benefiting from large numbers for statistical analysis, they include centers with varied experience and data are missing from a substantial number of patients making comparisons accounting for multiple transplant variables including PH difficult. Interestingly, published analysis of single-center experiences with LTX for IPF did either not specifically mention preoperative PH or failed to provide clear criteria for the application of either SLTX or DLTX in these patients [7,13]. This study defines short- and long-term outcome including functional results for LTX in IPF patients with procedure type selection guided mainly by the assessment of preoperative PH.

The previous data of the UNOS and ISHLT cohorts suggested an early (1-month and 90-day) and late (3-year) survival advantage for SLTX in IPF patients [6,12]. By contrast, recent ISHLT registry data indicated similar survival rates for SLTX and DLTX recipients during the first year and diverging survival curves throughout subsequent years indicating superior long-term outcome in DLTX patients [1]. We speculate that improved surgical and critical care management strategies in successive eras have overcome the former increased perioperative mortality for DLTX recipients, thereby explaining these discrepant results during the early phase after transplantation. Moreover, the mentioned large database reviews for IPF patients and the experience with non-IPF recipients suggest that the coexistence of elevated preoperative pulmonary artery pressure may define a subset of recipients who are at increased mortality risk after SLTX and are therefore likely to benefit from the continuing international trend in favor of DLTX [1,5].

Munich Lung Transplant Program patients undergoing transplantation for IPF had somewhat worse short- and long-term survival than patients undergoing transplantation for other indications [17]. Nevertheless, the overall survival rates for IPF patients in our institution compare favorably with international registry data [1]. Our findings are in line with those of other high-volume transplant institutions indicating that the recipients underlying disease, age and clinical condition at the time of trans-

plantation significantly influence the risk of death and BOS [7,14].

In a pretransplant setting, prevalence of PH assessed by right heart catheterization is reported in 28–46% of IPF patients and has been shown to be related to the decreased diffusing capacity independently of restrictive lung physiology [26]. In accordance with these findings, relevant PH with significantly increased PVR was detected in 24 (31.5%) of our cases prior to transplantation, demonstrating a significantly reduced DL_{CO} without differences in spirometry values in comparison with IPF patients without PH. Despite the effort, we made to adequately monitor pretransplant patients, we cannot rule out the possibility that we missed some cases of progressive PH during waiting time resulting in an underestimation of PH prevalence in our transplant population [27]. Interestingly, additional significant exercise limitation imposed by PH was not revealed using 6-MWD testing, most likely reflecting the overall miserable functional status of LTX candidates.

In accordance with the recent findings of Mason *et al.* and current ISHLT registry data, we found SLTX to be associated with a trend for an increased 90-day mortality risk and a significantly reduced long-term survival [7]. This finding was even sustained throughout the study period for patients alive at 3 months after transplantation. In theory, DLTX should additionally provide an enhanced functional reserve leading to improved functional outcome, which may increase survival during times of acute pulmonary stress (e.g. infection, AR). Thereby, DLTX may postpone the development of respiratory failure secondary to BOS. However, the data of Meyers *et al.* reporting on 45 patients with IPF demonstrated no functional or survival benefit for DLTX recipients [13]. By contrast, our own DLTX cohort revealed a significant better pulmonary function test performance and superior functional capacity in comparison with SLTX recipients consistent with subsequently longer BOS-free survival and decreased rate of BOS-related deaths. In fact, survival after DLTX in IPF patients closely approximated survival rates in non-IPF patients [17]. Given the trend for an increased rate of fatal infectious complications in SLTX patients and the strong association of BOS with recurrent viral, bacterial and fungal infections, the impact of the native lung and different pathogens (e.g. CMV, *Pseudomonas* spp., and *Aspergillus* spp.) remains to be elucidated using a larger sample size. In accordance with theses findings, Burton *et al.* reported significantly higher baseline FEV_1 values and longer duration of BOS-free survival in DLTX recipients when compared with SLTX patients for their overall transplant population. However, as a result of the way in which BOS is graded relative to maximal post-transplant lung function, the BOS criteria systematically discriminate against recipients with lower absolute baseline FEV_1 values. Therefore, there might be no real difference in the rates of BOS development according to the procedure type *per se* but a relative over-diagnosis of BOS in SLTX recipients because of lower lung volumes [28].

We clearly recognize the inherent limitations of our study with respect to our observational design, limited sample size and lack of adequate control group. The basic choice of single versus double transplantation in our program is guided by the presence or absence of PH. However, our interdisciplinary transplant committee takes additional subjective criteria into consideration. Therefore, a selection bias towards SLTX for older and sicker patients although not statistically significant may have an important impact on overall outcome. Weiss *et al.* demonstrated that SLTX in candidates with a high LAS presents a risk for reduced survival at 1 year not merely dependent on the existence of PH [29]. However, we did not detect a statistically significant difference for SLTX and DLTX recipients with the overall LAS suggesting an intermediate risk at the time of evaluation As a serial calculation of LAS levels might better reflect changes in disease severity, we can not rule out the possibility of relevant differences between the groups closer to the time of transplantation. Taken together, our data strongly contribute to the growing body of evidence that DLTX might be beneficial for carefully selected IPF patients. This highlights the need for a large multi-center randomized trial of single versus double LTX for IPF stratifying for potential confounders including age and PH. We speculate that in a subset of patients with PH, DLTX will allow potential survival and functional benefits to be realized over intermediate- and long-term follow-up without being negated by immediate perioperative mortality.

Authorship

NC: wrote the paper; HP, TD, LS, VWW, MT, LH, BR, ZG, HR, CS, FL, UP, BI: collected data; NC, HP: analyzed data; BJ: designed study.

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