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What is expected in lung function after lung transplantation due to end-stage pulmonary silicosis?

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Abstract

In this study, we aimed to determine the impact of lung transplantation (LTx) on pulmonary function tests (PFTs) and survival among patients with end-stage silicosis. We included patients with end-stage silicosis on the wait list for LTx, between January 1989 and July 2015 (N = 26). Sixteen of these patients received LTx; 10 were eligible, but did not undergo LTx (non-LTx) during the study period. Retrospective information on PFTs (spirometry [volumes and flows], 6-minute walking test [6MWT], and DLCO) was retrieved from patients' medical charts, including baseline information for all patients and follow-up information for the LTx. At baseline, most patients presented with spirometric and 6MWT values that were suggestive of severe disease (FEV_1/FVC 76.5 ± 29.7; 6MWT 267.4 ± 104.5 m). Significant increases in these values were observed at follow-up in the LTx (P = .036 and .151, respectively). The overall median survival of patients in the LTx and non-LTx was 3.35 years (95% CI: 0.16-14.38) and 0.78 years (95% confidence interval [CI]: 0.12-3.65) (P = 0.002), respectively. For patients with end-stage silicosis, LTx offers significant benefits regarding pulmonary function and survival when compared to non-LTx, and is a reliable tool to help this critical population of patients, whose only treatment option is LTx.

KEYWORDS
lung transplantation, pneumoconiosis, silicosis, survival

1 | INTRODUCTION

Silicosis is the most prevalent pneumoconiosis in Brazil. It is particularly associated with the industries of mining, non-metallic mineral transformation, and metallurgy. About 5.6% of the Brazilian population is exposed to silica, and this exposure can lead to silicosis, which is especially common in the male population. Silicosis can cause severe respiratory symptoms relatively early in life and is responsible for more disabilities than any other respiratory environmental disease, making it a major public health problem.[1-4] Silicosis slowly progresses to chronic lung disease with end-stage interstitial fibrosis, resulting in impaired pulmonary function. Currently there is no specific treatment for silicosis. Although stopping silica exposure can improve the prognosis, it does not prevent disease progression, which ultimately leads to death.[5-9]

According to data from the International Society for Heart and Lung Transplantation,[10] silicosis rarely indicates lung transplantation (LTx). However, end-stage silicosis can cause irreversible and severe lung damage, and in this case, LTx can be lifesaving and may represent the only option for these patients.[11] In this study, we aimed

to determine the impact of lung transplantation (LTx) on pulmonary function tests (PFTs) and survival among patients with end-stage silicosis.

2 | PATIENTS AND METHODS

This observational retrospective cohort study was carried out at Irmandade da Santa Casa de Misericordia de Porto Alegre (ISCMPA), Brazil, and was approved by the ethics committee of ISCMPA. Sixty percent of all LTxs in Brazil are performed at ISCMPA. Indeed, ISCMPA performs more LTxs than any other hospital in Latin America.[12] Patients referred to the ISCMPA outpatient evaluation center have generally received a prior diagnosis of silicosis from a medical professional, based on criteria established by the US National Institute for Occupational Safety and Health (including occupational history and imaging).[13] Once patients are registered at the ISCMPA, we confirm diagnoses of silicosis based on positive exposure history and on a profusion of 1/0 or greater for rounded opacities involving at least the upper lung zones according to standardized International Labor Office classifications (a criterion used to assess pulmonary and respiratory environmental diseases).[4,13] As there are currently no criteria to classify end-stage silicosis, which would call for LTx, we use the current International Society of Heart Lung Transplantation guidelines to define end-stage disease.[14,15] Patients who meet the above criteria are placed on the LTx wait list following a high-resolution chest computed tomography (CT) scan.[16-18] In this study, we included all patients on the wait list for LTx due to end-stage silicosis at the ISCMPA between January 1, 1989, and July 31, 2015 (N = 26). Sixteen of these patients received LTx (LTx group); 10 were eligible, but did not undergo LTx (non-LTx group) during the study period.

Donor organ procurement and transplantation has been described elsewhere in detail.[19] All patients in the LTx group received standard triple immunosuppressive regimen and antibiotic prophylaxis with piperacillin-tazobactam and vancomycin, which was eventually adjusted according to pre-operative cultures. After hospital discharge for LTx, patients undergo complete follow-up. In the first year, they are followed up 1 week after discharge (ie, about 1 month after LTx surgery), once per week for the first month, then once a month for the following 6 months, and finally every 3 months for the subsequent 6 months. In the second year, patients undergo 2 follow-up visits (one every 6 months), and thereafter annual visits are scheduled.

The following PFTs, spirometry (forced vital capacity [FVC], forced expiratory volume in first second [FEV_1], total lung capacity [TLC], and residual volume [RV]), the 6-minute walking test (6MWT), and carbon monoxide diffusion in the lung (DLCO), were performed on all patients at baseline (before LTx) and at all follow-up visits. PFTs were performed at ISCMPA and met the American Thoracic Society criteria for reproducibility and validity. Retrospective information on these PFAs was retrieved from patients' medical charts. Follow-up information for the LTx group consisted of two PFT values: the first examination, that is, the follow-up visit 1 month after LTx surgery; and the best examination, that is, the best recorded PFT values from the first year of follow-up. Spirometric values were used to categorize restrictive, obstructive, and mixed conditions.

Data were analyzed with Statistical Package for the Social Sciences (SPSS 18.0; SPSS Inc., Chicago, IL, USA). Categorical variables were expressed as absolute and relative frequencies. Continuous variables were presented as mean values ± standard deviations (SD) or as median and percentile values. Due to the small sample size, we used nonparametrical statistical tests. For two independent groups, we used the Mann-Whitney test. For categorical data, the chi-square (χ^2) test was used. When values under 5 were present, Fisher's exact test was used. The Friedman test was applied in the intragroup analysis during three different time intervals, and the Wilcoxon test was used for the nonparametric paired data on 6MWT and pulmonary systolic artery pressure. For survival analysis, time zero was defined as the day patients were added to the wait list. Cumulative survival probabilities were estimated using the Kaplan-Meier method; differences in survival were evaluated with the log-rank test. Cox proportional hazards regression was used to examine the association of selected variables with survival and was presented as hazard ratios with 95% confidence intervals (CIs). In all cases, P values < .05 were considered to be statistically significant.

3 | RESULTS

Of the 26 patients included in this study, none were lost to follow-up. All were middle-aged males with a history of exposure to chronic or subacute silica dust, 72% required oxygen at rest, 46.2% had a history of smoking, and 34.6% were positive for tuberculosis. Common symptoms reported by patients at baseline included dyspnea (n = 12; 75%) and dry cough associated with breathlessness (n = 4; 25%).

Spirometric results at baseline among all 26 patients showed that 65.4% had severe restrictive conditions; the mean TLC in these patients was 2.93 ± 1.49 L, the mean RV was 1.31 ± 0.79 L, and the mean DLCO was also demonstrative of severe conditions (36 ± 17%). Mixed conditions were observed in 34.62% (24.13 ± 5.67%) of the study sample. The remaining patients suffered from COPD, and of these patients, 33% had a history of smoking (9.44 pack-years). Among those with severe restrictive conditions, 82.35% had a FVC of less than 40% (27.07 ± 6.2%). Additionally, these patients showed impaired pulmonary function according to 6MWT (267.4 ± 104.5 m), which was associated with desaturation on exertion (10.7 ± 5.4%). Mean pulmonary artery pressure at baseline was 54.7 ± 24.3 mm Hg, and only one patient was not diagnosed with pulmonary hypertension (Table 1).

All 16 patients in the LTx group underwent unilateral LTx, equally distributed between the right and the left sides. Due to the scarcity of donors and the long waiting list at ISCMPA, it is our policy to perform unilateral LTx whenever possible. Normal spirometric values were observed in all patients from the LTx group within 1 month of LTx surgery, with improvement in TLC (3.45 ± 1.74 L) and stable RV (1.23 ± 0.60 L), as well as incremental improvement in FEV_1 and FVC that lasted until the end of the first year of follow-up (Table 2).

TABLE 1 Clinical characteristics of the listed patients to lung transplantation due to end-stage silicosis

Characteristics	Total (N=26)	Non-LTx (n=10)	LTx (n=16)	*P* value
Age, y	45.4 ± 11	42 ± 12.7	44.7 ± 10.1	.586
Height, m	1.68 ± 0.06	1.65 ± 0.04	1.66 ± 0.07	.060
Weight, kg	60.4 ± 11.6	51.5 ± 4.96	64.65 ± 12.78	.041
Time exposed, y	149 ± 114.7	135 ± 123.8.	149 ± 111	.586
Smoking history	4 (4-60)	0 (0-60)	12 (1-24)	.229
VEF_1 (L)	1.04 ± 0.51	0.80 ± 0.16	1.20 ± 0.50	.036
FEV_1% predicted	30.0 ± 17	21.03 ± 4.49	35.6 ± 17.9	.001
FVC (L)	1.56 ± 0.62	1.26 ± 0.40	1.74 ± 0.56	.009
FVC % predicted	37 ± 16	27.32 ± 8.97	42.29 ± 14.72	.002
FEV_1/FVC	76.5 ± 29.7	81.17 ± 25.91	73.59 ± 270	.737
DLCO, %	36 ± 17	35.4 ± 14.25	35.8 ± 16.4	.417
sPAP, mm Hg	54.7 ± 24.3	60.7 ± 25.10	50.87 ± 20.35	.310
Use of O_2, L/min	2.07 ± 1.6	2.15 ± 2.06	2.03 ± 1.22	.737
6MWT (distance), m	267.4 ± 104.5	223.3 ± 118.6	295.0 ± 87.54	.151
6MWT (ΔSpO_2%)	10.7 ± 5.4	9.7 ± 6.1	11.4 ± 5.00	.771

Data are presented as mean ± SD or mean (range).
Non-LTx, non-lung transplantation; LTx, lung transplantation; DLCO, diffusing capacity of the lung for carbon monoxide; sPAP, systolic pulmonary arterial pressure; 6MWT, 6-minute walking test; y, years; FEV_1, forced expiratory volume in first second; FVC, forced vital capacity.

TABLE 2 Comparison of respiratory functional status of patients undergone to lung transplantation

		Lung transplantation				
Variables	Waiting list	1st examination/test	Best examination/test	P^a	P^b	P^c
FEV_1 (L)	1.04 ± 0.51	1.85 ± 0.97	2.14 ± 1.13	.001	.039	.001
FEV_1% predicted	30.0 ± 17.0	54.56 ± 29.40	65.88 ± 34.47	.003	.010	.001
FVC (L)	1.56 ± 0.62	2.22 ± 1.16	3.08 ± 1.58	.017	.002	.001
FVC% predicted	37.0 ± 16.0	52.38 ± 27.72	68.41 ± 34.16	.044	.001	.001
FEV_1/FVC	76.5 ± 29.7	83.36 ± 9.220	71.20 ± 37.64	.179	.010	.001
6MWT, m	267.4 ± 104.5	502.63 ± 78.900	567.65 ± 58.000	.000		
6MWT, Δ SpO_2	10.7 ± 5.40	.00 ± 3.0	4.32 ± 3.17	.001		
sPAP (mm Hg)	54.7 ± 24.3	26.0 ± 14.0		.001		

Data are presented as mean ± SD.
FEV_1, forced expiratory volume in first second; FVC, forced vital capacity; 6MWT, 6-minute walking test; sPAP, systolic pulmonary artery pressure.
[a]Waiting list vs 1st examination/test (1st month).
[b]1st examination/test vs best examination (1st year).
[c]Evaluative comparison between the three different scenarios.

Median overall survival for all 26 patients in the study sample was 693.5 (46-5250) days, but it differed considerably between the non-LTx group and the LTx group (288.5 [46-1333] days vs 1226 [60-5250] days, respectively; *P* = .002). In the LTx group, median overall survival in the month after LTx was 85.7%, and survival rates 1, 3, and 5 years after LTx were 69%, 44%, and 25%, respectively (Figure 1).

Ten years after LTx, three (18.75%) patients were still alive, and two of them (12.5%) were still alive at the end of follow-up, 13 years after their LTx procedure. Eight patients died during follow-up: four due to pulmonary sepsis, one due to pulmonary embolism, one committed suicide, and two died from unknown causes.

4 | DISCUSSION

Pneumoconiosis is a group of lung diseases that develops due to continuous inhalation of mineral dust particles in the environment, and silicosis is the main subgroup of this condition. Despite efforts to reduce exposure through laws and regulation, Brazil still has a high prevalence of pneumoconiosis, particularly silicosis.[2,4,20]

LTx is a reasonable option to treat respiratory failure in patients with end-stage silicosis. However, due to the rarity of this condition, there are very little data available in the current literature. As silicosis mainly occurs in developing countries, we might expect a higher

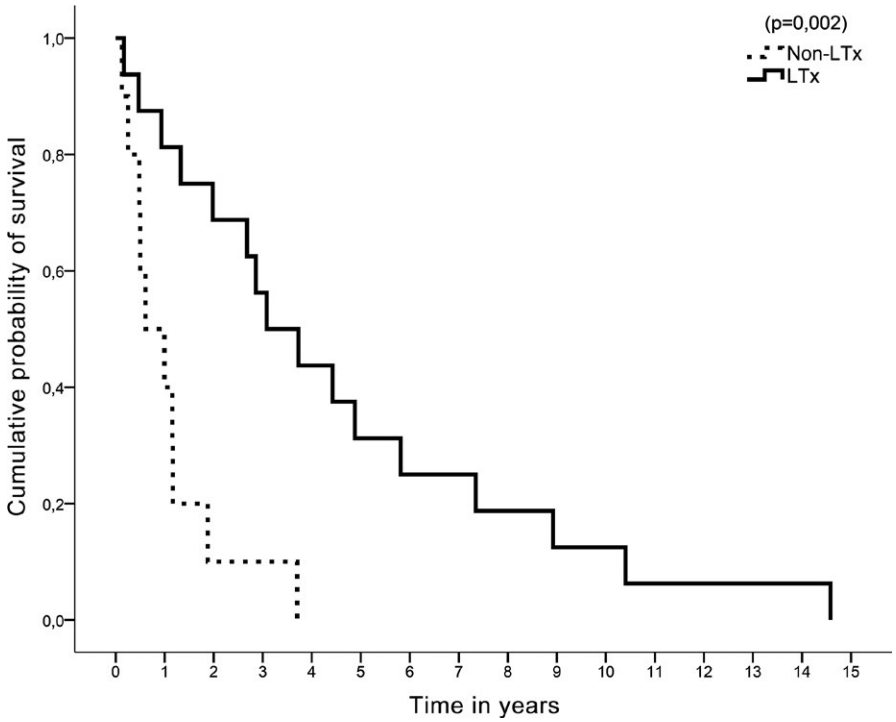

FIGURE 1 Population survival after entry on the waiting list for lung transplantation. Non-LTx, not submitted to lung transplantation; LTx, submitted to lung transplantation

prevalence of silicosis-induced LTx at ISCMPA compared to international data; however, we previously reported that silicosis accounted for only 3.51% of LTx procedures at ISCMPA.[12]

The parameters used to differentiate end-stage silicosis-induced LTx are not well established. Many existing studies used expanded indication criteria for COPD and idiopathic pulmonary fibrosis to assess the respiratory status of silicosis patients, but this does not seem to be the most accurate method. For instance, interstitial fibrosis observed in end-stage silicosis may produce high pulmonary artery pressure that may negatively influence LTx outcomes, and lung destruction and alveolar macrophage dysfunction commonly found in silicosis patients tend to favor tuberculosis infection.[13,15,21-23] Therefore, before LTx, all patients should be asked about their history of tuberculosis and undergo a tuberculosis skin test with purified protein derivative (PPD). In the present study, 37.5% patients had previous tuberculosis treatment, but PPD was positive (values over 10 mm) in only one, for whom standard treatment in the form of isoniazid for 6 months was recommended before LTx could be considered.[7,24,25]

We used PFTs to estimate the impact of silica in the lung parenchyma. PFTs are used to differentiate between restrictive and obstructive patterns, and can also predict the stage of the disease. FVC and FEV_1 values trend down as the disease progresses, accompanied by increased radiologic findings.[26] One study analyzed 526 spirometries of patients with various stages of silicosis and reported an obstructive pattern in 67.2%.[17] On the other hand, another study analyzed patients with advanced silicosis who were on the waiting list for LTx, and found PFTs compatible with severe restrictive conditions. The pattern of PFTs may change as the disease progresses.[27]

We observed PFTs indicative of restrictive conditions in 65.4% of our total study sample (FVC 37% ± 16%, FEV_1 30% ± 17%, DLCO 36% ± 17% of predicted values). A previous data report by our group reviewed the PFTs of 44 patients with idiopathic pulmonary fibrosis (IPF), a similar structural disease, before and after LTx. Pre-LTx values were FEV_1 1.48 ± 0.48 L (52% ± 17% of predicted values), FVC 1.78 ± 0.60 L (50% ± 18% of predicted values), and FEV_1/FVC 83±19, and all patients showed a marked improvement post-LTx.[28]

When baseline PFTs from our LTx group were compared to those from the non-LTx group, the non-LTx group showed a worse spirometric result (FVC 42.29 ± 14.72% and 27.32 ± 8.97%, $P = .002$; FEV_1 35.6% ± 17.9% and 21.03 ± 4.49, $P = .001$, respectively). Moreover, the non-LTx group had a lower mean weight (51.5 ± 4.96 kg vs 64.65 ± 12.78 kg, $P = .041$ in the LTx group), which may suggest malnutrition.

Improvement in pulmonary function after LTx in patients with silicosis was also reported in patients with a pre-LTx mean FEV_1/CVF of 63.47 ± 17.2, a FVC of 50.20% ± 10.8%, and a FEV_1 of 40.48% ± 7.9%. In these patients, post-LTx values were FEV_1/CVF 66.38 ± 11.7, FVC 60.80% ± 11.4%, and, especially, FEV_1 73.95% ± 16.4%. In addition, they demonstrated that elevated pre-LTx mean pulmonary artery pressure returned to normal value post-LTx.[21] We observed similar findings in our study, with PFT values 1 month after LTx surgery of FVC 2.22 ± 1.16 L (52.38% ± 27.72%), FEV_1 1.85 ± 0.97 L (54.56% ± 29.4%), TLC 3.43 ± 1.74 L, and RV 1.23 ± 0.6 L, and continuous improvement throughout the first year of follow-up: FVC 3.08 ± 1.58 L (65.88% ± 34.47%), FEV_1 2.14 ± 1.13 L (71.20% ± 37.64%), which is similar to findings among IPF patients after LTx.[28]

The 6MWT is widely used to analyze respiratory function. In our study, all patients had a mean 6MWT value of 267.4 ± 104.5 meters at baseline, presenting a decrease in the saturation levels of 10% ± 5.4%. At follow-up, patients in the LTx group were able

to walk 502.63 ± 78.9 m, with a smaller decrease in the saturation level (mean 0% ± 3%; P = .001). Previously, it was reported that patients who walk less than 315 m tend to have a worse prognosis,[29] so it is important to notice how sick our patients were before LTx. We believe that this improvement in 6 MWT, which coincided with normal PFT values, contributes to a better quality of life for patients who undergo LTx.

Our results support the recommendation proposed in 2011 by Mao et al.; in that study, LTx was indicated for silicosis patients with hypoxemia at rest or with a decrease in pulse oximetry in the 6MWT below 88%, FVC <60% of predicted, DLCO <39%, or FEV_1 <30% or showing a rapid declining in lung function. FEV_1 >30% with persistent hypercapnia or pulmonary hypertension and New York Heart Association class III or IV[11] were also criteria for LTx.

Singer and colleagues reviewed the US transplant registry database (US Organ Procurement and Transplantation Network Registry) and found that, among the 8129 LTx procedures performed between March 2005 and October 2010, 37 (0.5%) were due to pneumoconiosis, and within this group, only 19 LTx were due to silicosis. Survival for patients with silicosis at 6 months, and at 1 and 3 years post-LTx were 86%, 86%, and 76%, respectively.[30] In contrast, the survival rates we observed in our LTx group at 1, 3, and 5 years post-LTx were 69%, 44%, and 25%, respectively, similar to a recent report on IPF patients undergoing single LTx at ISCMPA (first-year survival, 70%).[28]

We speculated that the poor pre-operative status, as well as factors like the particularities of a developing country and the scarcity of resources like extracorporeal membrane oxygenation support, may have influenced our outcomes. We also recognize that our study has limitations as it is a single institution retrospective analysis, and although there was a significant number of patients with silicosis on the wait list for LTx, it remains a limited cohort.

In summary, although there are still no well-established parameters to indicate LTx due to end-stage silicosis, we concluded that LTx offers a significant benefit regarding survival and lung function when compared to the patients with silicosis who did not undergo LTx. Our report reinforces the role of LTx in the management of silicosis patients as a reliable tool to help this critical population of patients whose only treatment option is LTx.

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CONFLICT OF INTEREST

None.

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