



Long-term survival following unilateral lung transplantation for end-stage silicosis relative to idiopathic pulmonary fibrosis

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TO THE EDITOR,

Silicosis is an occupational disease caused by exposure to free crystalline silicon dioxide that evolves as a progressive granulomatous inflammation, eventually leading to pulmonary fibrosis. Although cessation of exposure to silica improves the prognosis, it does not prevent disease progression, which ultimately leads to death. Lung transplantation (LTx) is the only therapeutic alternative for patients with end-stage silicosis, with a significant survival benefit when compared to conservative management. The procedure usually has a complicated intraoperative course due to bleeding and hemodynamic instability; therefore, only a restricted number of patients with end-stage silicosis worldwide have undergone transplantation.^(1,2) Few studies have reported the intraoperative complications and long-term outcomes of LTx in these patients, and most of the data derives from studies in centers located in the United States.⁽²⁻⁹⁾ However, little is known regarding the survival outcomes of the procedure in Latin America.

We conducted a retrospective study in a single quaternary center to evaluate the intraoperative and postoperative outcomes of patients with end-stage silicosis who underwent unilateral LTx between 1989 and April 2017. The outcomes of the end-stage silicosis group were compared to those of a group of patients with idiopathic pulmonary fibrosis (IPF), for whom intraoperative and postoperative LTx outcomes are well known in the literature. The IPF pairs were selected from a group that underwent LTx from 2012 to 2016 in order to best match for sex, age, and pre-transplant pulmonary function capacity. The diagnosis of silicosis and IPF were confirmed by pathological analysis of the explanted lung. End-stage silicosis was defined according to the International Society of Heart and Lung Transplantation guidelines.⁽¹⁰⁾ Donor organ procurement and transplantation have been described elsewhere in detail.⁽⁴⁾ After transplantation, all patients received a standard triple immunosuppressive regimen (cyclosporine, azathioprine, and prednisone) and antibiotic prophylaxis. Non-parametric tests were used to compare the two groups. The Mann-Whitney test was used for continuous variables, whereas the chi-squared (χ^2) or Fisher's exact test were used for categorical variables. Cumulative survival probabilities after LTx were estimated using Kaplan-Meier curves, and differences in survival were tested with the log-rank test. A p-value lower than 0.05 was considered significant for all tests.

A total of 16 patients with end-stage silicosis and 16 IPF pairs were included in the study. The intraoperative complications and hospitalization course of both groups are shown in Table 1. The patients with silicosis were significantly younger than the IPF patients, a fact that is related to the natural history of each disease. Intraoperative bleeding, blood drainage from the chest tube, and the need for packed red blood cells were more than two times higher in the population with silicosis. None of the silicosis patients received any antiplatelet agent, and only one IPF patient was taking aspirin (100 mg daily) until the time of transplantation. Two IPF and seven silicosis patients received extracorporeal circulation intraoperatively, and none required extracorporeal membrane oxygenation (ECMO) at any time during hospital stay. However, the length of ICU and total hospital stay were not significantly different between groups.

The median time of follow-up was 4.1 years for the fibrosis group (IQR 1.9 – 5 years) and 4.7 years (IQR 2.1 – 5 years) for the silicosis group. One year following LTx, the survival rates were 81.3% for silicosis and 87.5% for fibrosis. The 3-year estimated survival rate was 68.3% for silicosis and 56.3% for fibrosis. The Kaplan-Meier curves for estimated survival revealed that silicosis was not associated with a significantly higher 5-year mortality rate when compared to fibrosis (50% for both groups, $p = 0.883$).

In this single-center study, we found that the long-term survival of patients with end-stage silicosis following unilateral LTx was not significantly different from that of the IPF patients. This observation is in accordance with more recent studies from other centers, particularly in the United States,^(2-4,6) and adds to the current body of evidence contrasting with the findings of Giuseppe et al.⁽⁹⁾ in which patients with silicosis following LTx had worse survival compared to IPF patients.

Intraoperative complications of LTx in silicosis are challenging not only due to the difficulty in dissecting the lungs, but also the significant amount of bleeding. The more complicated intraoperative course of silicosis could potentially worsen the outcomes of these patients, including increased length of stay (LOS) and decreased survival after LTx. In the present comparison, however, there was no significant difference in the LOS between patients with IPF and those with silicosis. More importantly, this study demonstrated that the 5-year survival rate

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Table 1. Clinical characteristics and intraoperative and postoperative parameters of end-stage silicosis and IPF patients submitted to LTx.

Parameter	Silicosis n = 16	IPF n = 16	p-value
Age, years	44 ± 10	61 ± 8	<0.001
Smoking history (pack-year)	7 (44)	13 (81)	0.066
Time of exposure to silica, years	9 [4-14]	-	-
FEV ₁ , % predicted	35 ± 17	50 ± 17	0.022
FVC, % predicted	42 ± 14	47 ± 13	0.341
sPAP, mmHg	50 ± 20	48 ± 12	0.491
Intraoperative bleeding*, mL	1709 [1322-2775]	300 [262-662]	<0.001
Blood drainage 1h to 24h (chest tube)**, mL	2022 [1572-2716]	510 [350-725]	<0.001
Total blood drainage (chest tube), mL	4757 [3917-6905]	1505 [991-2112]	0.001
Volume of intraoperative RBC, mL	1035 [431-1725]	500 [500-750]	0.014
Need for ECC, n (%)	7 (44)	2 (12)	0.113
Time of ECC, min	83 ± 22	143 ± 32	0.009
Ischemic duration, min	281 ± 67	247 ± 65	0.152
Length of chest tube stay, days	9 ± 3	4 ± 2	<0.001
Length of ICU stay, days	11 ± 6	7 ± 5	0.093
Length of hospitalization, days	25 ± 18	20 ± 7	0.289
Median time on waiting list, years	1.3 ± 0.4	1.5 ± 0.6	0.180

Note: Data was presented as No. (%), mean ± SD, or median [IQR]. IPF, idiopathic pulmonary fibrosis; FEV₁, forced expiratory volume in first second; FVC, forced vital capacity; sPAP, systolic pulmonary arterial pressure; RBC, red blood cell; ECC, extracorporeal circulation; ICU, intensive care unit. *The intraoperative blood loss was measured by the volume of blood aspirated from the surgical field, as well as by weighing the compresses moistened with blood from the surgical field. **Total content drained through the chest tube in the first 24 hours after surgery.

after LTx in silicosis did not differ from that of the IPF patients, despite the worse intraoperative course.

This study had several limitations, being a retrospective cohort performed at a single institution. Despite our attempt to best match the IPF patients with those with silicosis undergoing lung transplantation (especially for sex), the natural history of each disease limits such approach. Our control population may have been subjected to selection bias, as we attempted to match the characteristics to those of the silicosis group. Even though the silicosis population underwent transplantation at an earlier period (recruitment between 1989 and April 2017) than the fibrosis group (2012 to 2016), there were no significant differences between groups regarding survival. Lastly, we did

not include any case of bilateral LTx since there are limited bilateral procedures for IPF or none for silicosis at our service.

In conclusion, our cohort of patients with end-stage silicosis undergoing LTx at a single center in Brazil demonstrated that, despite the worse intraoperative course, such complications did not yield a lower long-term survival rate compared to IPF patients.

AUTHOR CONTRIBUTIONS

FAP, SA, DZN, and GW: Conceptualization, Methodology, Investigation, Data curation, Writing - original draft. GM, SMC, BH, LASF, and JJC: Investigation, Data curation, Writing - review & editing.

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