SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2020; 37 (3); e2020007 DOI: 10.36141/svdld.v37i3.9346

Lung transplantation for Interstitial Lung disease, the experience of an outpatient clinic

Maria Jacob[1], *Carla Damas*[1]
[1] Pulmonology department, Centro Hospitalar Universitário de São João, Porto, Portugal

To the Editor,

Interstitial lung diseases (ILD) comprise a heterogeneous group of disorders that can lead to diffuse remodelling and structural damage to the healthy lung tissue and progressive loss of its function (1). Several ILDs are progressive, and their prognosis is often poor. Particularly, idiopathic pulmonary fibrosis (IPF) has a very poor outcome, resulting in progression to respiratory failure and death on an average of four years after the diagnosis (2). Meanwhile, other ILDs, such as idiopathic nonspecific interstitial pneumonia (NSIP), connective tissue disease-associated ILD (CTD-ILD), and chronic hypersensitivity pneumonitis (CHP), can also have a progressive course; however, their prognosis is usually more favourable than that of IPF. Although medical therapies have led to improvement in the prognosis of ILDs over the past years, they are rarely effective, and disease progression is inevitable. Therefore, lung transplant (LTx) remains as a viable treatment option (3).

LTx is a therapeutic option for selected patients with progressive and refractory ILDs that can potentially improve both the quality of life and life expectancy(4-5). According to the latest data from the International Society for Heart and Lung Transplantation (ISHLT), the second most common LTx indication is ILD (30%) and, idiopathic interstitial pneumonia (IIP), together with chronic obstructive pulmonary disease without Alpha-1-antitrypsin deficiency and cystic fibrosis, contributed the most to the growth in the number of transplants (3). The ISHLT has published specific referral and listing guidelines for ILDs (6) which include close monitoring for clinical and functional deterioration. Patients with advanced ILDs are prone to a fast decline or acute exacerbations that may require high-flow oxygen or mechanical ventilation. Although the latter could be a bridge to lung transplant, it lacks benefit in the majority of ILD patients (7). Awake extracorporeal membrane oxygenation (ECMO) as a bridge to lung transplant is gaining popularity, as improvements in technology have made it more feasible with less risk (8). Proper selection of patients is critical when deciding to implement awake ECMO support, especially in this category of patients.

The LTx outpatient clinic, at the Centro Hospitalar Universitário São João (Porto, Portugal), is a tertiary, non-transplant referring hospital. It is useful in achieving a systematic approach on the initial evaluation of LTx candidates, monitoring patients on waiting lists and also in the post-LTx follow-up. In this study, the authors aimed to show the clinical and demographic characteristics, at baseline, of ILD patients submitted to LTx. Moreover, we wanted to display the complications after LTx and survival.

This retrospective study included ILD patients evaluated for LTx at our outpatient clinic. Cases were included between 2006 and 2019. Categorical variables are presented as frequencies and percentages and

Received: 27 February 2020
Accepted after revision: 17 June 2020
Correspondence: Maria Jacob
Pulmonology Department,
Centro Hospitalar Universitário de São João
Alameda Prof. Hernâni Monteiro, 4200-319 Porto– Portugal
Email: maria.gsgj@gmail.com

were compared with the use of Fisher's test or the Chi-square test, as appropriated. Continuous variables are presented as mean and standard deviation, or median and interquartile range and were compared with the use of t-test or the Mann-Whitney test, as appropriated. Kaplan-Meier curve and the log-rank test were used to assess survival. All statistical analysis was performed using SPSS v.25.0 (IBM Corp., USA).

Overall, from the 213 patients in the LTx outpatient clinic, 72 (33.8%) have been evaluated for ILD. From those, 47 patients (65.3%) were referred for LTx and, 29 (56.9%) were transplanted. The majority were female (n=16, 55.2%), with a mean age of 48.4±11 years. Eighteen (72%) were non-smokers. The main indications for LTx were chronic hypersensitivity pneumonitis (n =13, 44.8%) and IIP (n=9, 31%; that included 7 patients with IPF and 2 with NSIP); followed by sarcoidosis (n=3, 10.8%), CTD-ILD (n=2, 6.9%; secondary to rheumatoid disease and to Sjogren's syndrome) and lymphangioleiomyomatosis (n=2, 6.9%). Unilateral LTx was performed in 24 (85.7%) patients and bilateral LTx in 4 cases (14.3%). Six months was the median while in waiting list (1 and 54 months, minimum and maximum respectively). There were two patients in which awake ECMO was used as a bridge to lung transplant: a 48 years-old women with CHP, admitted with acute exacerbation and submitted to a successful bilateral LTx (18 months in active list) and, a 46 years-old man with CHP, included in active list in the admission for an acute exacerbation, that died, while waiting for lung transplant, with acute left ventricular failure. Five (17.2%) patients died during the surgical procedure or shortly after that, and it was observed an association with males (p=0.011) and past smoking history (p=0.015), Table 1. Acute allograft rejection was diagnosed in 15 patients (51.7%), and in eleven cases happened in the first year post-transplant. In terms of late complications, the most commonly seen was chronic lung allograft dysfunction (CLAD, n=11, 44%), with a median time to rejection of 62.9 months (IQR: 72.5 months). Three patients with CLAD had, previously, acute allograft rejection. Other complications were infection (aspergillosis was diagnosed in 5 patients, CMV infection in 2 and pneumocystosis in 1) and malignancy (2 patients had squamous skin cancer). Two patients received re-transplantation. Ten patients died later on during follow-up. Survival at 1 and 5 years is 75% and 56%,

Table 1. Baseline characteristics of patients who underwent LTx – data are presented as n (%) or mean (±standard deviation). BMI: Body Mass Index; mMRC: modified Medical Research Council; FVC: forced vital capacity; DLCO: diffusing lung capacity for carbon monoxide; 6MWD: six-minute walk distance

	Total (n=29)	**Successful LTx (n=24)**	**Early death after LTx (n=5)**	**p-value**
Age, years	48.4 (±11)	48.2 (±11.3)	49.2 (10.3)	0.858
Male sex	13 (44.8)	8 (33.3%)	5 (100%)	**0.011**
BMI, kg/m2	26.5±7.1	25.8±4.8	29.9±15.6	0.638
Non-smoker	18 (62.1%)	18 (81.8%)	0	**0.015**
mMRC ≤2	21 (75%)	18 (78.3%)	3 (60%)	0.574
Oxygen requirement at rest	23 (82.1%)	20 (87%)	3 (60%)	0.207
Corticosteroid use	22 (78.6%)	17 (73.9%)	5 (100%)	0.553
Immunosuppressant use	16 (57.1%)	13 (56.5%)	3 (60%)	0.887
UIP pattern	24 (85.7%)	20 (87%)	4 (80%)	0.687
%FVC (%)	40.7±18.2	53±20.6	50.5±5.9	0.201
%DLco (%)	27.5±9.8	25.3±9.2	38.7±0.9	0.253
6MWD (m)	224.7±149	320±150.9	317.5±201.5	0.349
Median waiting time, months (IQR)	6 (7)	6 (9)	6 (8)	0.343
Unilateral LTx	24 (85.7%)	21 (87.5%)	3 (75%)	0.481

respectively. Median overall survival, after LTx, was 6.6 years, with a tendency to lower median survival in IIP (1.2 years) and CHP (4.2 years), though no statistical difference was observed between different categories (*Log Rank test*: p=0.759). The presence of acute allograft rejection is associated with a significantly lower median overall survival. CLAD seems to have better survival in the first two years after LTx, still with a tendency to worsen over time. It was diagnosed in a median 5.2 years after LTx, with a median overall survival of 7.3 years (Figure 1).

Of the non-LTx group, 18 (25%) patients were refused by the transplant centre, 7 (9.7%) were discharged (either due to transplant refusal or absen-

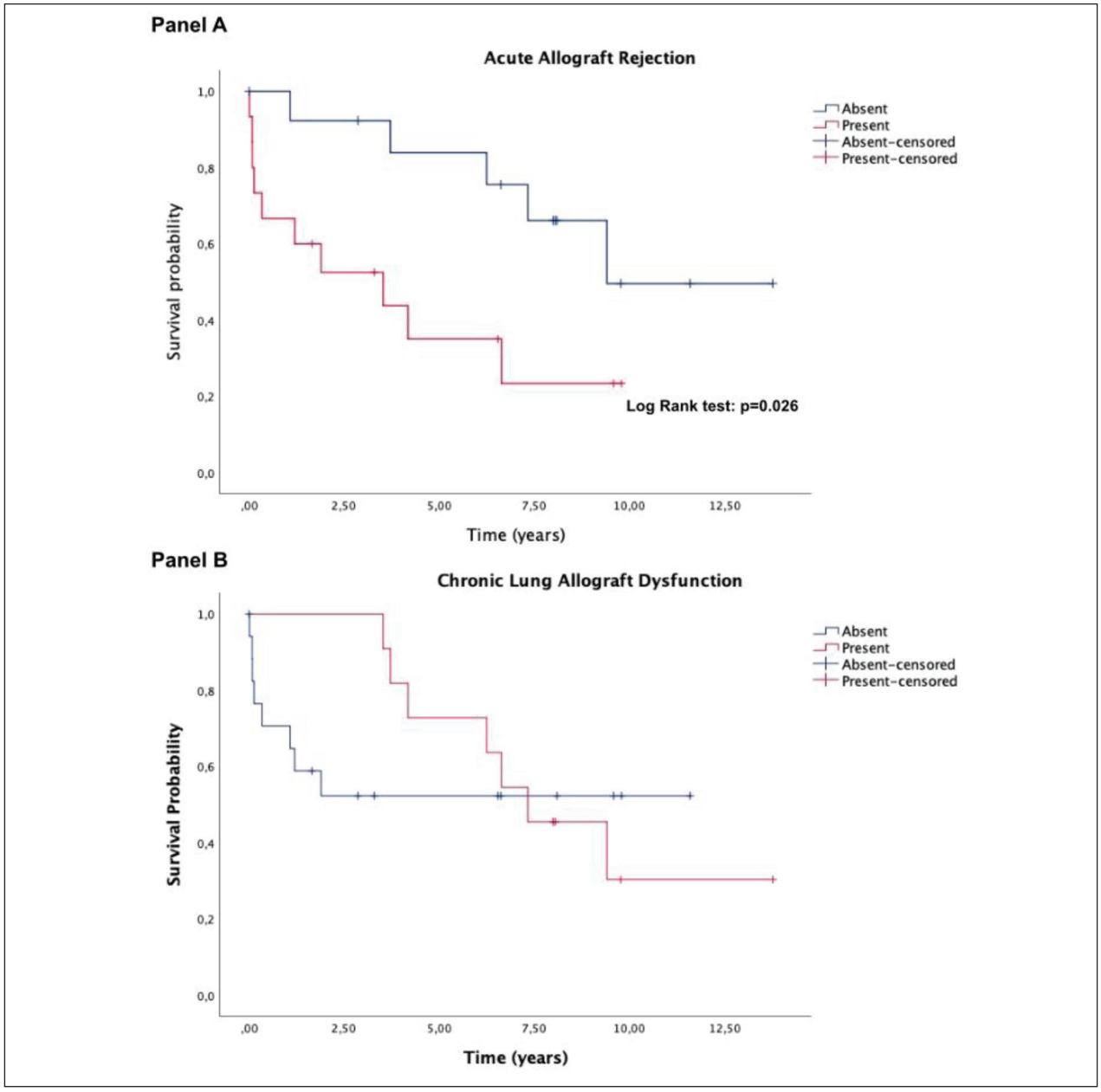

Fig. 1. Panel A - Acute allograft rejection is associated with a significantly lower median overall survival (3.5 vs. 9.4 years); Panel B - CLAD is associated with a median overall survival of 7.3 years (as in its absent, median overall survival was not reach yet). CLAD: chronic lung allograft dysfunction

teeism) and, 4 (5.6%) died while in active transplant list; the remaining are either actively on the LTx list (n=6), clinical surveillance (n=6) and in study (n=2).

Lung transplantation is challenging. The limited availability of lungs, the complexity of the medical intervention, that requires a dedicated recipient and medical team, represent just a few obstacles. Although lung transplantation in ILD has been steadily increasing in the past decades, the experience in the literature is still scarce. Our data demonstrate a higher LTx referral among patients with ILD than previously described in literature [to mention that the authors excluded patients with silicosis, previously described by Redondo, et al. (9)]. Also, the median overall survival shows a trend towards previous reports (4,6,10). More reports are needed about ILD disease and lung transplant, particularly to investigate which clinical, functional or disease specific characteristics are related with lung transplantation survival. These data support that lung transplantation remains an appropriate therapeutic option for selected ILD patients.

References

1. Travis WD, Costabel U, Hansell DM, King TE, Jr., Lynch DA, Nicholson AG, et al. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. American journal of respiratory and critical care medicine. 2013;188(6):733-48.10.1164/rccm.201308-1483ST
2. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. American journal of respiratory and critical care medicine. 2011;183(6):788-824.10.1164/rccm.2009-040GL
3. Yusen RD, Edwards LB, Dipchand AI, Goldfarb SB, Kucheryavaya AY, Levvey BJ, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-third Adult Lung and Heart-Lung Transplant Report-2016; Focus Theme: Primary Diagnostic Indications for Transplant. J Heart Lung Transplant. 2016;35(10):1170-84.10.1016/j.healun.2016.09.001
4. Thabut G, Mal H, Castier Y, Groussard O, Brugière O, Marrash-Chahla R, et al. Survival benefit of lung transplantation for patients with idiopathic pulmonary fibrosis. J Thorac Cardiovasc Surg. 2003;126(2):469-75.10.1016/s0022-5223(03)00600-7
5. Singer JP, Singer LG. Quality of life in lung transplantation. Semin Respir Crit Care Med. 2013;34(3):421-30.10.1055/s-0033-1348470
6. Weill D, Benden C, Corris PA, Dark JH, Davis RD, Keshavjee S, et al. A consensus document for the selection of lung transplant candidates: 2014--an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2015;34(1):1-15.10.1016/j.healun.2014.06.014
7. Faverio P, De Giacomi F, Sardella L, Fiorentino G, Carone M, Salerno F, et al. Management of acute respiratory failure in interstitial lung diseases: overview and clinical insights. BMC Pulm Med. 2018;18(1):70.10.1186/s12890-018-0643-3
8. Kearns SK, Hernandez OO. "Awake" Extracorporeal Membrane Oxygenation as a Bridge to Lung Transplant. AACN Adv Crit Care. 2016;27(3):293-300.10.4037/aacnacc2016792
9. Redondo MT, Vaz M, Damas C. End-stage silicosis and lung transplantation: A way forward. Rev Port Pneumol. 2014;20(6):341-.10.1016/j.rppneu.2014.09.004
10. De Oliveira NC, Osaki S, Maloney J, Cornwell RD, Meyer KC. Lung transplant for interstitial lung disease: outcomes for single versus bilateral lung transplantation. Interact Cardiovasc Thorac Surg. 2012;14(3):263-7.10.1093/icvts/ivr085