# Lung Transplantation in Pulmonary Arterial Hypertension: The Portuguese Experience

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## ABSTRACT

**Background.** In patients with pulmonary arterial hypertension (PAH), refractory to medical therapy, lung transplantation emerges as an option. This study describes the outcomes of 8 PAH patients who underwent lung transplantation.

**Methods.** A retrospective, single-center study was conducted among patients with PAH who underwent lung transplantation in our center.

**Results.** Patients had a median age of 46 years, with female sex predominance (75%). Causes of HAP were pulmonary veno-occlusive disease (n = 5, 62.5%), idiopathic PAH (n = 2, 25%), and heritable PAH (n = 1, 12.5%). Pre-transplant hemodynamics revealed a median mean pulmonary artery pressure of 58.5 mm Hg (48-86). All patients received bilateral lung transplants with extracorporeal membrane oxygenation support, displaying immediate post-transplant hemodynamic improvement. Primary graft dysfunction grade 3 (PGD 3) was observed in 75% of patients. Five patients (62.5%) died, with a 72.9% survival at 12 months and 29.2% at 24 months post-transplantation.

**Conclusion.** Our study reveals the complexity and challenges of lung transplants in patients with PAH. Despite notable immediate hemodynamic improvements, high rates of PGD 3 and the survival rate remain a concern. Further research to define optimal peri and post-transplant management to improve survival is required.

PULMONARY hypertension (PH) is a devastating disease characterized by the proliferation and remodeling of the pulmonary vasculature with an increase in pulmonary vascular resistance and pulmonary artery pressure that results in right heart failure and eventual death [1]. PH is defined by a mean pulmonary artery pressure (mPAP) > 20 mm Hg accessed by right heart catheterization. Depending on the etiology and hemodynamic profile of PH, the disease is classified into different groups; of these, pulmonary arterial hypertension (PAH) corresponds to group 1 [1,2].

PAH is an uncommon disease associated with a poor prognosis. It has an estimated incidence of 0.008 to 1.4 cases/100,000 person−years [3]. Meanwhile, when idiopathic (IPAH), it has an incidence of 1-2 per million [4]. Until 2009, the 1-year, 2-year, and 3-year mortality rates for patients with PAH were 10%, 19%, and 25%, respectively. Since then, medical treatment has been evolving with many pharmacologic classes of drugs suitable for patients with PAH now approved and management changes with drug combination strategies. These drugs improve hemodynamics, symptoms, exercise capacity, quality of life, and time to clinical worsening and reduce mortality [5,6]. Although mortality has decreased, it remains high with a 1-year, 2-year, and 3-year mortality of 7%, 17%, and 20% [7].

Some patients are refractory to medical therapy, and lung transplantation is the only viable option [2,6]. Therefore, referral to a Lung Transplant center should be considered early in the absence of a good response to an optimized medical

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treatment, when patients present with an intermediate−high or high risk of death and when the PAH cause is pulmonary capillary hemangiomatosis or pulmonary veno-occlusive disease (PVOD) [2]. PVOD has a poor prognosis and limited response to PAH therapy, making lung transplant the only curative option [8,9]. Patients with PH tend to have the highest mortality rate on lung transplant waiting lists (18%-41%) [10].

According to the International Society of Heart Lung Transplantation (ISHLT) registry, patients with idiopathic PAH comprise 2.9% and PAH non-IPAH 1.5% of all lung transplants, raising these percentages to 4.1% and 1.9%, respectively, if only double lung transplants are considered [11]. Most centers adopted bilateral lung transplants as the procedure of choice for PAH [8,9].

The aim of this study was to perform a descriptive analysis of patients with PAH who underwent lung transplants and their respective outcomes (duration of hospital admission, complications, and survival) in our center.

## MATERIALS AND METHODS

This is a retrospective study that included patients diagnosed with PAH who underwent lung transplants in Hospital de Santa Marta, Centro Hospitalar Universitário de Lisboa Central, from January 2019 until April 2023. This is the only lung transplant center in Portugal. The first lung transplant due to PAH was done in January 2019. Therefore, this single-center study represents all the Portuguese experience in lung transplants in this type of patient during this period.

Patients were referred from different Portuguese hospitals. Before the transplant, all of them were submitted to a thorough clinical and laboratory evaluation, as well as a thoracic CT scan, ventilation/perfusion scintigraphy, pulmonary function testing, and a Doppler echocardiogram. Patients already had a previous hemodynamic evaluation with a right catheterization. Pulmonary function tests included spirometry and plethysmography for the measurement of expiratory flow rates and lung volumes. The diffusion capacity for carbon monoxide was also estimated by the single-breath method.

All patients undergoing lung transplantation met the listing criteria for lung transplantation in accordance with the ISHLT [12].

Primary graft dysfunction (PGD) is defined, according to ISHLT, as infiltrates on chest X-ray in the first 72 hours after lung transplantation, indicating reperfusion edema. In patients on postoperative extracorporeal membrane oxygenation (ECMO), it was graded as PGD grade 3 following the consensus report by ISHLT.

A descriptive analysis of transplant patients with PAH was performed: demographic data, causes of pulmonary hypertension, pre-transplant clinical evaluation, hemodynamic by right catheterization, length of stay, complications related to lung transplantation, and mortality.

Statistical analysis: continuous variables, as they do not have a normal distribution, are presented as median and IQR. Categorical variables are presented in absolute and relative frequency. For survival analyses, the Kaplan−Meier statistics with log-rank testing using SPSS version 19 (IBM SPSS, Inc).

## RESULTS

In the study period, a total of 161 patients underwent lung transplantation for all causes. Of these, 8 underwent lung transplantation due to PAH and were included in the study.

### Demographic Characteristics

Most patients were women (n = 6/75%) with a median age of 46.0 (29.3-59.3) years. The most frequent diagnosis was PVOD (n = 5, 62.5%); 2 patients had IPAH, and 1 patient had heritable PAH (BMPR2 mutation). The majority were already on triple lung vasodilator therapy. The assessment done before lung transplant and previous therapy regimen is presented by patients in Table 1.

The median time on the waiting list was 4 months (3-16 months).

The median time from diagnosis to referral was 5 years (1-15 years). Regarding the PVOD group, it was 1.5 years (1-5 years).

## BASAL HEMODYNAMICS

The median mPAP was 58.5 mm Hg (48-86), and the median pulmonary vascular resistance was 13.8 Wu (11.2-16.8). Hemodynamic evaluation by right heart catheterization for each patient is presented in Table 2.

## LUNG TRANSPLANT

All patients were submitted to bilateral lung transplantation under central veno-arterial extracorporeal membrane oxygenation (Fig. 1), and no deaths were observed intraoperatively. ECMO as a bridge to transplantation was not necessary in any patient. In 3 patients, venoarterial (VA) ECMO was removed at the end of the procedure with no need for postoperative ECMO. Venovenous ECMO was necessary for 1 patient from postoperative day 7 to 11. Intra and postoperative VA ECMO was employed in 4 patients, being removed on the 2nd (1 patient), 4th (1 patient), and 6th postoperative day (2 patients) (Fig. 2).

All patients had immediate hemodynamic improvement after transplantation, as demonstrated by the median systolic pulmonary artery pressure (sPAP) evaluated by direct needle measurement intraoperatively (Supplementary Figure S1). The preoperative median sPAP recorded value of 73 mm Hg (44-80) lowered to a postoperative median recorded value of 35 mm Hg (30-35).

### Length of Stay and Complications

The median length of stay was 62.5 days (19-200).

The median mechanical ventilation time was 13 days (8-77). A percutaneous tracheostomy was performed in 2 patients due to the need for prolonged endotracheal intubation on postoperative days 12 and 17.

PGD grade 3 was observed in 6 (75%) patients.

**Table 1. Characterization of Patients With PAH**

| Patient | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| Cause | Idiopathic | Hereditary | PVOD | PVOD | Idiopathic | PVOD | PVOD | PVOD |
| NYHA | III | IV | III/IV | III | IV | III | III | III/IV |
| Hospital admissions in the previous year | 0 | 2 | 2 | 0 | 1 | 0 | 1 | 2 |
| Pulse rate (bpm) | 110 | 83 | 83 | 85 | 117 | 92 | 90 | 88 |
| Blood pressure (mmHg) | 81/48 | N/A | 112/62 | N/A | 132/64 | N/A | N/A | 110/60 |
| Nt-proBNP | 1090 | 2161 | 575 | 465 | 4730 | N/A | 549 | 1280 |
| Respiratory tests (%) | FEV1 91% DLCO 93% | FEV 1 63% DLCO N/A | FEV 1 93%; DLCO 27.6% | FEV1 41%, DLCO 53% | N/A | FEV1 94% DLCO 46% | FEV1 94% DLCO 35% | FEV1 94% DLCO 91% |
| Pericardic effusion | Mild | Mild | Absent | Mild | Moderate | Mild | Absent | Absent |
| 6MWD (m) | 400 | 181 | 345 | 320 | 560 | 430 | 180 | 506 |
| Renal failure | Absent | Absent | Absent | Absent | Absent | Absent | Absent | Absent |
| Lung vasodilator treatment | Triple | Triple | Double Bosentan | Triple | Triple | Triple | Triple | Triple |
| | Epoprostenol | Treprostinil | Sildenafil | Selexipag | Epoprostenol | Selexipag | Epoprostenol | Treprostinil |
| | Riociguat | Ambrisentan | | Bosentan | Riociguat | Macitentan | Riociguat | Ambrisentan |
| | Macitentano | Sildenafil | | Sildenafil | Macitentan | Sildenafil | Macitentano | Sildenafil |

DLCO, lung diffusion capacity for carbon monoxide; 6MWD, 6-minute walking distance; FEV1, forced expiratory volume in 1 second; N/A, not available; NYHA, New York Heart Association; PVOD, pulmonary veno-occlusive disease.

All 4 patients with solely intraoperative VA ECMO developed PGD. In the intra and postoperative ECMO group (n = 4), 2 patients developed PGD.

Cellular rejection was observed in 2 patients, 1 A2 rejection (1 year post-transplant) and 1 A1 rejection (4 months post-transplant); both remained alive at the time of the study.

No form of CLAD was observed.

### Mortality

A total of 5 patients died; of these, 2 patients had in-hospital death. We identified a 30-day and 3 months survival of 87.5%. At 12 months, survival was 72.9% (95% CI: 27.6-92.5), and at 24 months, 29.2% (95% CI: 4.2-61.9) (Supplementary Figure S2).

The median follow-up time was 15.03 months (0.63-40.73).

Among the recorded causes of death, regarding intra-hospital deaths, 1 was attributed to anoxic encephalopathy (after cardiac arrest), and the other to nosocomial pneumonia with no isolated agent. There was another in-hospital recorded death after the patient had previously been discharged due to *Pseudomonas aeruginosa* pneumonia. The other 2 deaths were attributed to tuberculosis and COVID-19 infection.

## DISCUSSION

This report describes a single-center experience with lung transplantation in PAH.

As previously reported [13−16], the hemodynamic improvement is remarkable. Namely, our results also display this trend (Supplementary Figure S1). We observed a rapid drop in pulmonary artery pressures and an improvement in right ventricular function in the operating room.

In previous ISHLT reports, it was described that patients with IPAH undergoing lung transplantation have worse overall survival when compared with lung transplantation due to pulmonary disease; however, when survival exceeds the 3-month mark, they have the best 20-year survival rate (excluding cystic fibrosis) among all groups [11,17].

Our results show 87.5% survival at 30 days and 3 months and a 75% survival at 1 year, comparable with ISHLT 2019 registry results [11]. Higher volume centers like the Vienna group showed better outcomes, with a 1-year survival of 93% [18].

Patients with PVOD, given the limited options, the rapid deterioration, and the severity of the disease as soon as the diagnosis is made, should be promptly referred for lung transplant [19]; otherwise, they can miss the optimal referral and transplantation window. In addition, they have a higher risk of dying on the waiting list compared with patients with other causes of PAH [10]. Our patients' median time to referral was 5 years after the diagnosis, 1.5 years specifically in the PVOD group. Although quicker in comparison, 18 months is probably a too-long period for PVOD to evolve, which can explain the worse survival observed in these patients.

We report 2 in-hospital deaths after lung transplant. The postoperative care of such complex patients is challenging, and pulmonary artery hypertension is an independent risk factor for

**Table 2. Hemodynamic Characterization of Patients With PAH**

| Patients | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | Mean |
|---|---|---|---|---|---|---|---|---|---|
| PAP (mm Hg) Systolic/diastolic/mean | 153/61/97 | N/A/N/A /57 | 86/47/60 | 95/33/57 | 136/52/89 | 73/36/48 | N/A/N/A/45 | 114/59/77 | 58.5 (48-86) |
| PWCP (mm Hg) | 13 | N/A | 17 | 7 | 12 | 14 | 15 | 13 | 13 (12-15) |
| PVR (Wu) | 17 | 14.6 | 16.26 | 12.8 | 13.05 | 10.65 | 8.5 | 21 | 13.8 (11.2-16.8) |
| Cardiac index (L/min/m$^2$) | 3.1 | 1.88 | 2.34 | 2.2 | 3.5 | 1.61 | 1.98 | 3.3 | 2.5 (1.9-3.3) |

PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; PWCP, pulmonary capillary wedge pressure.

PGD after lung transplant [20−22]. Left ventricle dysfunction may arise as a complication requiring pharmacologic and organ support measures. An increased pulmonary arterial pressure in the general population was previously associated with an increased risk of death for PGD for several reasons not fully understood, probably due to increased shear stress applied by a well-trained right ventricle resulting in subsequent pulmonary edema during reperfusion [6,15,23]. Others attributed respiratory failure during weaning from mechanical ventilation to an incapacity of the left ventricle to handle an increased preload in the postoperative period: elevated pulmonary vascular resistance results in reduced cardiac output, causing a long-standing underfilling of the left ventricle. Measures to optimize fluid overloads, such as forced diuresis, hemofiltration, pharmacologic inotropic support, and delayed extubation, may be insufficient [12]. By reducing preload, preemptive ECMO support can improve systemic circulation and help efficient gas exchange, allowing the heart to adapt and protect the lungs from a hyperdynamic right ventricle [24−26].

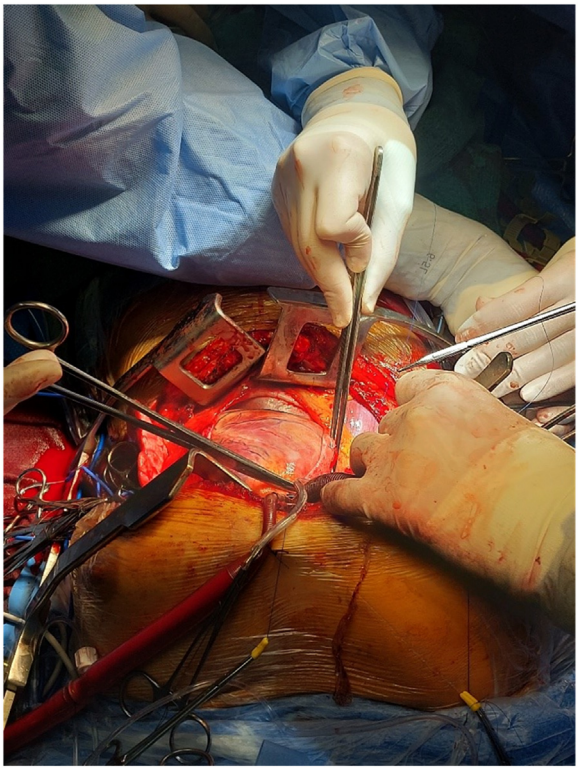

**Fig 1.** The patient undergoing a bilateral lung transplant with extracorporeal membrane oxygenation support.

Our findings revealed that 75% (n = 6) of patients experienced PGD. Among those solely supported by intraoperative ECMO (n = 4), 4 (100%) developed PGD, with 1 needing venovenous ECMO due to PGD. Additionally, 2 patients (50%) undergoing prolonged ECMO support (n = 4) exhibited PGD. These results contrast unfavorably with the Vienna group's findings of 54.8% and 18.9% incidence of PGD in these groups, respectively [18]. These findings are mostly related to a low number of patients transplanted due to PAH, bigger numbers might change these trends, related to experience and the odds.

The prophylactic extension of ECMO postoperatively offers the possibility for lung protective mechanical ventilation, and its routine use can improve outcomes [12]. The optimal strategy with ECMO is yet to be defined: some suggest weaning over 3 to 7 days, depending on the hemodynamic and ventilation status [20]. Others start gradually decreasing flow since day 1 post-transplant, regulating it according to patients' hemodynamic and respiratory needs; ECMO is explanted when a 1.5 L/min flow is tolerated without significant impairment [18]. The weaning time is strongly related to heart remodeling; echocardiography, NTproBNP, and serial chest X-ray translate this remodeling and can guide us on ECMO weaning. Further studies are required to define the patients who would benefit from postoperative ECMO [12].

At 3 years, a 30% survival was observed, which is not as favorable as other results in the literature (ISHLT registry ≈60% [11], Vienna group 88% [18]). All these post−1-year deaths were related to infectious diseases. We believe this may be correlated with our limited sample size.

Being this the initial experience of a center, many difficulties arrived, leading to an increasing understanding of the pathophysiology and proper care of this disease. We should enhance the need for an early referral to the transplantation center of this subset of patients, and we expect to improve these outcomes in the future with cumulative experience and more standardized care.

Our study has some limitations: it is a descriptive retrospective analysis with a small sample size. Another limitation is the duration of the study period, which does not allow us to have a long follow-up period. On the other hand, this approach ensures

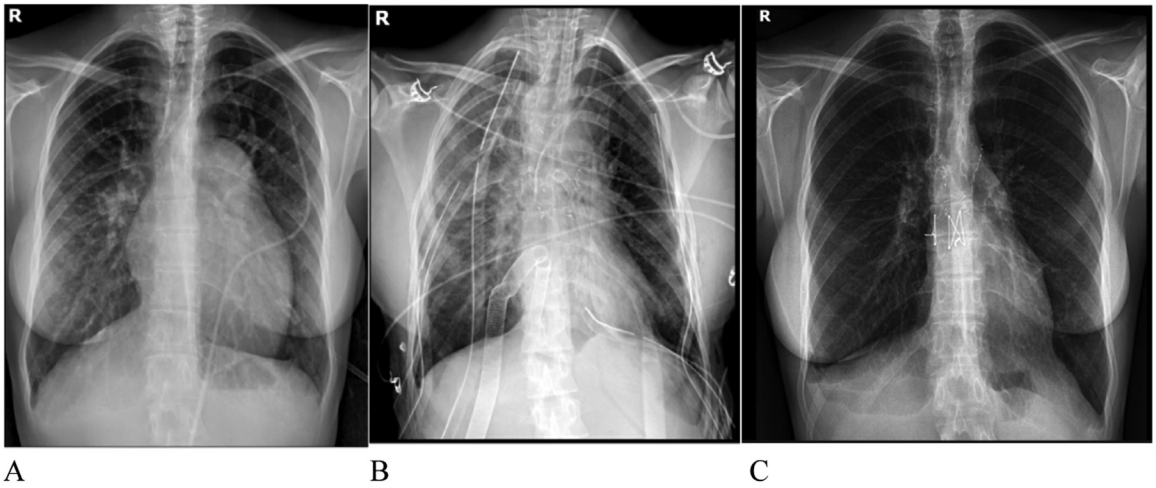


**Fig 2.** **(A)** Chest X-ray before lung transplant, **(B)** Chest X-ray 1 day after lung transplant (note extracorporeal membrane oxygenation cannulae), and **(C)** Chest X-ray 10 months after lung transplant.

greater consistency in transplant technique and post-transplant care between patients.

## CONCLUSIONS

Lung transplant is an effective and ultimate therapy in PAH. These findings, based on a limited sample size, are an auto-analysis regarding lung transplants in PAH in our center. We demonstrate substantial hemodynamic improvements immediately post-transplantation; however, we also realize the complexity and challenges of the perioperative and post-transplant management in patients with PAH. Our group believes that with the evolving knowledge, it will be possible to surpass the initial critical period after lung transplantation and achieve a longer survival for patients with PAH.

## DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

## SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.transproceed.2024.01.013.

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