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# A Contemporary Review of Adult Lung Transplantation and the Portuguese Lung Transplant Program Revised

Maria Inês dos Reis Rodrigues

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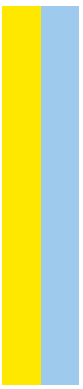

# A Contemporary Review of Adult Lung Transplantation and the Portuguese Lung Transplant Program revised

Maria Inês dos Reis Magalhães Rodrigues | inesreisrodrigues@gmail.com

Mestrado Integrado em Medicina

Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto

**Orientador:** Professor Doutor Humberto José da Silva Machado

Professor Associado Convidado do Instituto de Ciências Biomédicas Abel Salazar

Assistente Hospitalar Graduado Sénior de Anestesiologia do Centro Hospitalar do Porto

Diretor do Serviço de Anestesiologia do Centro Hospitalar do Porto

Adjunto da Direção Clínica do Centro Hospitalar do Porto

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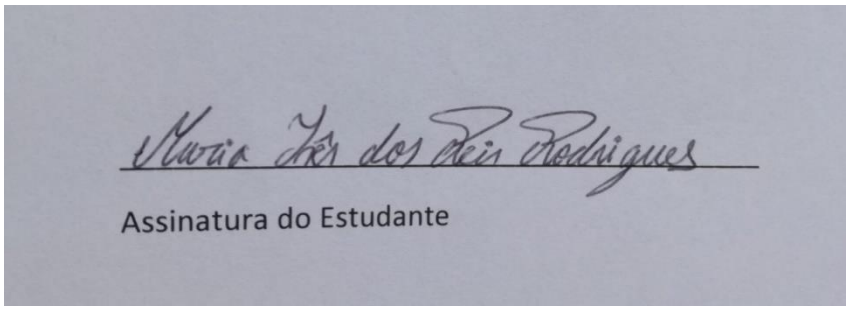
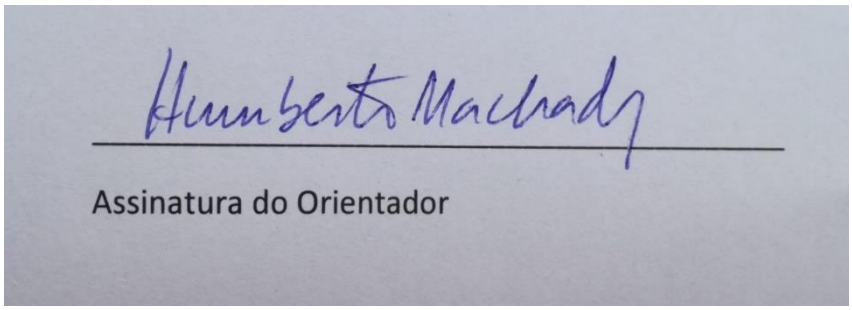


Assinatura do Estudante



Assinatura do Orientador

**24 de maio de 2019**

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Ao Professor Doutor Humberto Machado pela orientação, disponibilidade, interesse e apoio que sempre demonstrou, indispensáveis para a realização do presente trabalho.

Aos meus pais e irmã, pelos valores transmitidos e por toda a ajuda e companheirismo ao longo do meu percurso de vida.

**Resumo**

**Introdução:** O transplante pulmonar é atualmente uma opção terapêutica para doentes com doença pulmonar terminal. Nos últimos 30 anos verificou-se um constante crescimento na área da transplantação pulmonar e, com o desenvolvimento de novos fármacos imunossupressores e o aperfeiçoamento de técnicas cirúrgicas e de conservação de órgãos, houve um aumento da sobrevivência e da qualidade de vida dos doentes transplantados.

Em Portugal, o programa de transplantação pulmonar teve início em 2001 no Hospital Santa Marta, Centro Hospitalar de Lisboa Central. Apesar de ser o único centro de transplantação pulmonar do país, um número crescente de transplantes pulmonares tem vindo a ser realizado, passando de 8 transplantes realizados em 2009 para 34 transplantes realizados em 2017.

Contudo, e comparativamente com outros transplantes de órgãos sólidos, o transplante pulmonar apresenta os piores *outcomes* a longo prazo. A falta de dadores de órgãos e a elevada incidência de rejeição crónica são alguns dos principais obstáculos.

**Objetivo:** Este trabalho tem como objetivo apresentar uma visão abrangente da transplantação pulmonar no adulto a nível mundial, realçando o programa de transplantação pulmonar português. Destacam-se os avanços ocorridos nos últimos anos, o seu impacto clínico e os desafios que ainda persistem.

**Métodos:** A pesquisa foi baseada em artigos de língua inglesa, encontrados no Pubmed assim como nas diretrizes/consensos da International Society for Heart and Lung Transplantation.

**Resultados:** A doença pulmonar obstrutiva crónica, a pneumonia intersticial idiopática e a fibrose quística foram as principais indicações de transplante pulmonar nas últimas décadas, em particular com um aumento do número de transplantes realizados por pneumonia intersticial idiopática nos últimos anos. Verificou-se também um crescimento progressivo da realização de transplantes pulmonares bilaterais comparativamente a transplantes unilaterais.

A sobrevivência a 1 ano aumentou entre 1999 e 2015, contrariamente à sobrevivência aos 5 anos que não se alterou significativamente neste período.

Quer um aumento da função pulmonar pós-transplante quer um aumento da qualidade de vida foram também verificados nos doentes transplantados.

Observou-se um uso crescente de fármacos imunossupressores de indução e manutenção, especialmente o uso de antagonistas dos recetores da interleucina 2 (IL2RAs) como terapia de

indução. Uma elevada incidência de neoplasias nos doentes transplantados foi constatada, com 42% dos doentes com cancro aos 10 anos pós-transplante, sendo o cancro de pele o mais frequente.

**Conclusão:** Desde que James Hardy realizou o primeiro transplante pulmonar em 1963, mais de 50 000 transplantes foram realizados nos últimos 30 anos a nível mundial, sendo atualmente aceite como opção terapêutica para doenças pulmonares terminais. Apesar dos constantes avanços e progressos, a escassez de órgãos e a elevada rejeição crónica ainda precisam de ser superadas para que o transplante pulmonar possa atingir o seu máximo potencial terapêutico. A *Ex vivo Lung Perfusion* e o xenotransplante pulmonar podem contribuir na resolução de alguns destes problemas, levando assim a futuros desenvolvimentos no campo da transplantação pulmonar.

**Palavras-Chave :** Transplante Pulmonar, Adulto, Indicações, Outcomes, Portugal

**Abstract**

**Background**: Since James Hardy performed the first cadaveric human lung transplant in 1963, lung transplant has gained widespread acceptance as a therapeutic option for selected patients with end-stage lung diseases, leading to improved survival and improved quality of life.
With the development of immunosuppressive regimens and better surgical and organ preservation techniques, a constant growth within the last 30 years has been observed with more than 50.000 lung transplants performed to date worldwide.
In Portugal, lung transplant program started in 2001 at Hospital Santa Marta, Centro Hospitalar de Lisboa Central. Being the only lung transplant center in the country, it has improved its clinical activity over the years, from 8 cases of lung transplant in 2009 to 34 in 2017.
Nevertheless, the global picture of lung transplant still pale, having the worst long-term outcomes when compared with other solid organ transplants. The organ donor shortage and the high incidence of chronic lung allograft dysfunction represent some of the major obstacles.

**Objective**: This review aims to give a comprehensive overview of the current status of adult lung transplantation in the world and in Portugal, highlighting the many advances that have occurred, its clinical impact in multiple contexts and the challenges that still persist.

**Methods**: A literature review based on English-language articles and guidelines/ consensus documents of the International Society for Heart and Lung Transplantation.

**Results**: Recipients with chronic obstructive pulmonary disease, idiopathic interstitial pneumonia and cystic fibrosis, were the major contributors for the increasing numbers in lung transplants seen in the last decades. Recently, the percentage of recipients with chronic obstructive pulmonary disease without α-1-anti-trypsin deficiency has gradually decreased while the percentage of transplants for idiopathic interstitial pneumonia has increased. Furthermore, a progressive growth of bilateral lung transplants comparatively with single transplants has occurred.
The 1-year survival has significantly increased across time, contrarily to the 5-year survival that has not change significantly. Although pulmonary function and activity level after lung transplant are reasonably good, significant impairment in exercise capacity persists. Additionally, health-related quality of life in lung recipients is good, with the majority of lung transplant recipients reporting satisfaction with their decision to receive transplant.

Regarding immunosuppressive therapy, an increasing use of induction and maintenance immunosuppressive agents has been observed, especially the use of IL2RAs as induction therapy. Furthermore, malignancy rates have increased over time, with 42% of the recipients at 10 years post-transplantation having cancer. Skin cancer was the most frequently reported of all cancers.

**Conclusions**: A half-century has elapsed since the first lung transplant was performed, being now accepted as the treatment of choice for end-stage lung diseases.
Although the continuous advances and progress, the shortage of organs and the chronic rejection still need to be overcome so lung transplant can reach its full potential.
Ex vivo lung perfusion and lung xenotransplantation may help to resolve these problems, leading to future developments in the field of lung transplantation.

**Keywords:** Lung Transplantation, Adult, Indications, Outcomes, Portugal

**Abbreviations**

**AATD**: α-1-Anti-Trypsin Deficiency

**BLT:** Bilateral Lung Transplant

**BOS:** Bronchiolitis Obliterative Syndrome

**CF:** Cystic Fibrosis

**CLAD:** Chronic Lung Allograft Dysfunction

**COPD:** Chronic Obstructive Pulmonary Disease

**ECLS:** Extracorporeal Cardiac Life Support

**ECMO:** Extracorporeal Membrane Oxygenation

**EVLP:** Ex Vivo Lung Perfusion

**GNB:** Gram-Negative Bacteria

**HRQL:** Health-Related Quality of Life

**IL2RAs:** Interleukin 2 Receptor Antagonists

**ILD:** Interstitial Lung Disease

**IIP:** Idiopathic Interstitial Pneumonia

**IPAH:** Idiopathic Pulmonary Arterial Hypertension

**IPF:** Idiopathic Pulmonary Fibrosis

**ISHLT:** International Society for Heart and Lung Transplantation

**LAS:** Lung Allocation Score

**LDLLT:** Living Donor Lobar Transplantation

**PGD:** Primary Graft Dysfunction

**SLT:** Single Lung Transplant

**Index**

**Index of figures**

## Introduction

The first attempts in lung transplantation were made by Vladimir Demikhov, a soviet scientist who performed in 1946 a single-lung transplant in a dog that eventually failed from bronchial anastomotic dehiscence. In fact, technical problems such as the healing of the bronchial anastomosis, the high immunogenicity of the lungs and the high risk of pulmonary infections, have delayed the development and progression in lung transplantation. Indeed, it was only in 1963 that James Hardy and his team, performed the first cadaveric human single lung transplant.[1]

However, with the discovery of cyclosporine a significant resurgence of interest in lung transplantation was seen, and in 1986 the Toronto Lung Transplant Program performed the very first successful single-lung transplant. Later, the first successful bilateral-lung transplant, was performed by the same team, first using an *en bloc* technique with a tracheal anastomosis, then using the bilateral sequential transplantation technique, the most performed technique today all over the world.[1]

Up to the present day, over 50.000 lung transplants were performed worldwide, establishing itself as the standard therapy for end-stage lung diseases.[2]

## Indications

Currently, and according to the International Society for Heart and Lung Transplantation (ISHLT) the primary indications for lung transplant are chronic obstructive pulmonary disease (COPD) not associated with α-1-anti-trypsin deficiency (AATD) (31%), interstitial lung disease (ILD) (30%), composed mainly by idiopathic interstitial pneumonia (IIP) (24.8%), and bronchiectasis mostly caused by cystic fibrosis (CF) (16%). Idiopathic pulmonary arterial hypertension (IPAH) (2.9%), and non-IPAH (1.6%), also represent a small proportion.[2] Although controversial, the number of lung transplants in lung cancer has slowly increased, being effective in a few particular cases, such as advanced multifocal bronchioloalveolar carcinoma.[3]

## Mechanical bridges to transplant

Extracorporeal Cardiac Life Support (ECLS) has been recognized as a potential bridge to lung transplant for patients with respiratory failure. In fact, patients treated with venoarterial extracorporeal membrane oxygenation (ECMO) while remaining awake, not sedated, and not intubated (“awake ECMO”) seem to have better outcomes compared to conventional

mechanical ventilation. Indeed, Fuehner et al., retrospectively analyzed the outcomes of patients treated with conventional mechanical ventilation as bridge strategy with patients treated with “awake ECMO”, reporting a survival at 6 months of 80% in the “awake ECMO” group compared with a survival of 50% in the mechanical ventilation group.[4]

Additionally, Hoetzenecker et al., after analyzing data between 2006 and 2016 of adults who received ECLS as a bridge to transplant, concluded that using ECLS in the first lung transplant, would lead to good short-term and long-term outcomes in selected patients. On the other hand, ECLS as a bridge to retransplantation demonstrated a shorter survival compared to first lung transplant.[5]

According to the ISHLT, ECLS is recommended in young patients with a good potential for rehabilitation. On the other hand, ECLS is not indicated in cases of septic shock, multi-organ dysfunction, severe arterial occlusive disease, heparin-induced thrombocytopenia, prior prolonged mechanical ventilation, advanced age and obesity.[6]

**Acute Rejection**

Acute rejection cell-mediated, commonly occurs in the second postoperative week. At the moment, transbronchial biopsy is the standard procedure for diagnosing acute rejection, with perivascular and parenchymal lymphocytic infiltrates typically found on histologic examination. However, radiologic findings such as perihilar and lower-lobe opacities, interlobular septal thickening, and pleural effusions favor a diagnosis of acute rejection. Additionally, several episodes of acute rejection are a predisposing factor for chronic rejection.[7]

According to the ISHLT, acute rejection remains a significant post-transplant complication. In fact, 28% of recipients with follow-up between 2004 and 2016 experienced at least 1 episode of treated acute rejection in the first post-transplant year.[8]

A longitudinal study, from 1996 to 2007, tried to identify some risk factors for acute rejection after lung transplant. In fact, moderately sensitized recipients identified by class II panel-reactive antibody exceeding 10% and those with HLA mismatches at the B and DR *loci*, were found to be more prone to acute rejection. Nevertheless, such immunologic variations appear to be nowadays well managed with current donor selection and immunosuppression protocols and, in the modern era of transplantation it is a very uncommon cause of mortality.[9]

**Infection**

Bacterial infections are the most common cause of pneumonia after lung transplant, with gram-negative bacteria being responsible for the majority of the cases. Pneumonia is the most frequent manifestation, occurring at least in 75% of lung transplant recipients within three months after transplantation. In fact, the risk of bacterial infection is the highest within the first month after the surgery and *Pseudomonas aeruginosa* and *Klebsiella* species are some of the most commonly isolated bacteria.[7]

On the other hand, fungal infections develop in 15% to 35% of patients after LT, with more than 80% being caused by *Candida spp.* and *Aspergillus spp.*, with a mortality rate of nearly 60%.[10]

Regarding viral infections, *Cytomegalovirus* remains a significant problem after lung transplant. Indeed, despite advances in viral diagnosis, prophylaxis, and treatment strategies, CMV infection rate is still at least 50%. Additionally, the serostatus of the donor and recipient is a recognized risk factor since a seronegative recipient with a seropositive organ has the highest risk for primary infection after transplantation.[7]

**Chronic Lung Allograft Dysfunction**

According to the ISHLT, the 5-year survival for lung transplant is only 54%[2] with the major responsible for this rather low survival being the development of chronic rejection. Chronic Lung Allograft Dysfunction (CLAD) is the main cause of morbidity and mortality after the first year following lung transplant[11] and occurs at least in 50% of recipients 5 years after LT.[12]

Chronic rejection was first defined as pathological bronchiolitis obliterative syndrome (BOS), diagnosed on the basis of a persistent ≥20% decline from the best post-transplant forced expiratory volume in one second (FEV1), without other identifiable cause. Nevertheless, during the last years it has become clear that not every chronic decline in FEV1 was obstructive nor irreversible, which led to new insights into chronic rejection after lung transplant.[13] Consequently, the term CLAD was introduced to describe pathologies that can manifest as airflow restriction and/or obstruction mainly as a result of chronic rejection. Three distinct phenotypes of chronic rejection are now identified: bronchiolitis obliterans, neutrophilic reversible allograft dysfunction, and restrictive allograft syndrome. As each phenotype has unique pathology and histopathological findings, treatment regimens should be adapted to the underlying etiology.[14]

Alloimmune rejection (acute cellular rejection, antibody-mediated rejection, and lymphocytic bronchiolitis), gastroesophageal reflux, persistent bronchoalveolar lavage neutrophilia and

infections (viral, bacterial, and fungal), are some of the risk factors for the development of CLAD.[13]

In fact, in a recent study, Orfanos et al., investigated the connection between post-transplant recolonization with gram-negative bacteria (GNB) or de novo colonization with a new GNB species, reporting a correlation between de-novo colonization with a new species of GNB and the development of CLAD. On the other hand, the recolonization seems to be a protective factor against CLAD.[11] Additionally, Botha et al., also reported an association between de novo colonization of the lung allograft by *Pseudomonas* and the subsequent development of BOS.[15]

Concerning fungal infections, the occurrence of fungal pneumonia previously to BOS is an independent predictor of subsequent CLAD.[16] Air pollution is also considered to be a risk factor for the development of CLAD among lung transplant recipients.[17]

The median survival after the onset of BOS is approximately 2.5 years, although, early-onset BOS (within 2 years after transplantation) or BOS onset grade 2 or 3 (high-grade onset) has a worse survival[18], with restrictive CLAD having a worse prognosis than obstructive CLAD[13] Some randomized controlled trials suggest that azithromycin may have a role in preventing and/or attenuating CLAD[19,20] but evidence for other therapies remains relatively poor. Retransplantation in well-selected patients with BOS seems to be the only possible treatment to achieve long-term survival.[21]

**Recurrence of Primary Disease**

Recurrence of primary disease in the allograft may appear as early as two weeks or as late as two years after transplantation.[7] According to one multicenter retrospective study that reviewed 1,394 transplant recipients, the rate of recurrence was 1%. Sarcoidosis was the most common disease reported to recur, with a recurrence rate of approximately 35%.[22]

**Morbidity associated with surgery and drug therapy**

Much of the morbidity in long-term survivors of LT is related to drug side-effects. Calcineurin inhibitors are associated with nephrotoxicity and chronic kidney disease remains one of the most common complications in lung transplant patients at 5 years post-transplant: 14% have creatinine >2.5 mg/dL, 2.4% are on dialysis, and 0.9% require kidney transplant. Additionally, although corticosteroids continue to be a keystone of immunosuppressive therapy, being used as part of the maintenance immunosuppressive regimen in over 90 % of lung transplant recipients, they also carry multiple side effects such as hypertension, glucose intolerance and

osteoporosis.[23] The surgery is also associated with pain and discomfort, which is often more severe when a thoracotomy or clamshell incision have been performed, comparatively with a sternotomy. In addition, post-thoracotomy neuralgia can be associated with considerable and prolonged pain, often requiring specific therapy such as anti-convulsant and/or tricyclic antidepressant drugs for control.[24]

**Bronchial Anastomotic Complications**

In the early era of lung transplantation, disruption of the airway anastomosis was one of the main causes of death among patients. Depending on the reporting system, the incidence of airway complications can vary from 1.6% to 33%. Despite the fact that the donor organ is devascularized and systemic arterial blood supply is not normally connected, there are other factors that may favor anastomotic airway complications, such as the contamination of bronchial anastomoses fields, tension at the anastomosis site, and donor-recipient size mismatch.[25] Additionally, necrosis and dehiscence occur mostly in the early phase, while stenosis occur mainly in the late phase. Furthermore, the incidence of early complications has been decreasing, while the relative incidence of late complications has been increasing.[26]
Indeed, Moreno et al., analyzed the risk factors for airway complications, reporting that bilateral lung transplant, post-transplantation airway colonization, and post-transplant intubation longer than 72 hours were associated with airway complications such as stenoses, dehiscences, and malacias.[27]

**Donor-Recipient Size Mismatch**

Size matching is essential in lung transplant and has a significant influence on clinical outcomes, as it has been associated with prolonged stay in intensive care units, persistent atelectasis, pneumothorax, hyperinflation, decreased maximal exercise capacity, and earlier occurrence of bronchiolitis obliterans syndrome. Some of the criteria used for size matching consist of height comparisons between donor and recipient and pulmonary function test results. However, height is not a good predictor of lung volume as it is not a very accurate method. Recently, three-dimensional computed tomography (3D-CT) volumetry has been used to assess lung volume. In fact, it has been shown to be more reproducible than total lung capacity measurements, being a new promising technique for the assessment of lung volume.[28,29]

**Methods**

A comprehensive search of the medical literature was conducted by using the online platform **PubMed**. The principal search phrases used were: “Lung Transplantation/adverse effects AND Postoperative complications, acute rejection”; “Lung transplantation AND Anastomotic Airway Complications”; “Lung Transplantation/adverse effects AND bronchiolitis obliterans syndrome, bronchiolitis obliterans/microbiology”; “Lung transplantation AND pulmonary function and exercise performance”; “Lung transplantation AND Japan, living-donor lobar lung transplantation”; “Lung Transplantation/adverse effects AND bronchiolitis obliterans/etiology AND azithromycin/therapeutic use”; “Lung Transplantation/methods AND computed tomography, size matching, pulmonary transplantation”; “Lung Transplantation/methods AND Single versus Bilateral Lung Transplantation”; “Lung Transplantation/methods AND Pulmonary Fibrosis/surgery, Idiopathic Pulmonary Fibrosis/mortality”; “Lung Transplantation/mortality AND Cystic Fibrosis/surgery AND Cystic Fibrosis/mortality”; “Lung transplantation AND Portugal”; “Lung Transplantation/methods AND Hypertension, Pulmonary/surgery”; “Lung transplantation AND ATG, Acute rejection”; “Lung transplant AND survival benefit, end-stage lung disease” and “Lung Transplantation/adverse effects AND recent advances”. From 623 articles found, 53 were selected to this review.

**The Journal of Heart and Lung Transplantation** was also consulted, and the search phrases used (included in the title) were: “Lung transplantation AND induction therapy”; “Infections AND bronchiolitis obliterans syndrome”; “Lung Transplant AND Pulmonary fibrosis, survival”; “Lung Transplant AND survival benefit, cystic fibrosis” and “Normothermic Ex Vivo Lung Perfusion”. From 81 articles found, 5 were selected.

Furthermore, by consulting **The American Journal of Transplantation** and using the following search phrases (included in the title): “Posttransplant, chronic lung allograft dysfunction”; “Lung Transplantation AND Azithromycin”; “Bronchiolitis Obliterans Syndrome AND Induction, survival”, 5 articles were found and 3 were chosen.

**The American Journal of Respiratory and Critical Care Medicine** was also consulted and the following search phrases (included in the title) employed: “Lung Transplant AND Portugal”; “Lung Transplant AND cystic fibrosis, survival benefit”; “Lung Transplantation AND Health-related Quality-of-Life “; “Bronchiolitis Obliterans AND Bilateral Lung Transplant Recipients”; “Lung Transplantation AND Extracorporeal Membrane Oxygenation”. From 33 articles found, 5 were selected.

By consulting the medical journal **The Annals of Thoracic Surgery** and using the following search phrases (included in the title): “Lung Transplantation AND acute rejection”; “Single- Versus Double-Lung Transplantation AND pulmonary fibrosis”; “Single lung transplantation AND pneumonectomy”; “Lung transplantation AND pulmonary vascular disease”; “Lung transplantation AND pulmonary hypertension”; “Lung Transplantation AND pulmonary fibrosis, survival” and “Lung transplantation AND emphysema” 39 articles were found and 7 were chosen.

The article – “Portuguese lung transplant program revisited (Nave, Aguiar, Ramos and Fragata, 2016) was consulted in the **Journal of Cardiothoracic and Vascular Anestesia**, by using the following search phrase – “Lung Transplant Portugal “.

**The International Society for Heart and Lung Transplantation**´s website was also consulted for the following guidelines and consensus documents: “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.” ; “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. “; “The Registry of the International Society for Heart and Lung Transplantation: thirty-fourth Adult Lung And Heart-Lung Transplantation Report—2017; Focus Theme: Allograft ischemic time”; “An international ISHLT/ATS/ERS clinical practice guideline: diagnosis and management of bronchiolitis obliterans syndrome.” and “International guidelines for the selection of lung transplant candidates: 2006 update--a consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation”.

**Inclusion criteria**

In this review were eligible case reports, clinical trials, comparative studies, multicenter studies, randomized controlled trials, systematic reviews and reviews all written in English and that dated between 1998 and 2019, regarding adult lung transplant.

Guidelines and consensus documents from ISHLT that dated between 2006 and 2017 were also included.

**Exclusion criteria**

For this review were excluded articles regarding pediatric lung transplantation, heart-lung transplantation and lung retransplantation.

## Results

### Number of adult lung transplants and year of transplantation

According to the ISHLT, 53,890 adult lung transplants were performed between 1990 and 2014. Recipients with COPD without A1ATD, IIP and CF were the major contributors to these numbers. Nevertheless, from 1999 to 2014, the percentage of transplants for COPD without A1ATD have slowly decreased from 40% to <30%, while the percentage of transplants for IIP have increased from 16% to 33%. Concerning the age and sex of recipients, IIP had the greatest proportion of recipients >65 years old, and CF had the greatest proportion of recipients 18 to 34 years old, with IIP being the most frequent diagnosis in males and COPD the most frequent in females.[2] According to the 2016 annual data report of the Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients (OPTN/SRTR), the use of the ECMO, the Donation after Circulatory Death (DCD) and the Ex-Vivo Lung Perfusion (EVLP) may have contributed to the increased number of lung transplants. In fact, the use of the ECMO alone or with mechanical ventilation, have increased from 2.3% in 2011 to 5.8% in 2016. Furthermore, DCD donors have also increased from 1.0% to 4.0% from 2011 to 2016, which may be related with the improvement in EVLP technology.[30]

### Adult lung transplant centers

According to the ISHLT, 170 centers perform lung transplant procedures. From these, 48 (28%) perform 30 or more transplants annually, corresponding to 66% of the total procedures, 18 (11%) perform 50 or more transplants annually which correspond to 37% of total procedures, and 56 centers (33%) had fewer than 10 transplants per year and performed just 4% of the total procedures. Concerning the geographic location of transplant centers, North American centers have a small proportion of recipients transplanted for CF and a major proportion transplanted for IIP comparatively to European centers.[8]

### Single Lung Transplant vs. Bilateral Lung Transplant

The number of bilateral lung transplants has been increasing during the past 3 decades with a slightly decrease in recent years.[8] In the US, 1757 bilateral lung transplants were performed in 2016 in contrast to 588 single lung transplants, with bilateral lung transplants reaching 74.9% of all lung transplants in this year.[30]

Concerning the best type of surgical procedure (single vs bilateral transplant) for primary diagnostic indication, in certain lung diseases such as COPD and ILD, there is no general consensus on the best approach. One of the exceptions is in patients with septic lung disease such as cystic fibrosis, where bilateral transplant is the only acceptable transplant technique due to the potential risk of contamination of the new lung with the preexisting infection.[31]

**Survival by primary diagnostic indication for lung transplantation**

According to the ISHLT, the median survival of adults who received primary lung transplant from January 1990 to June 2015 was 6 years, with recipients surviving to 1 year after primary transplant having a conditional median survival of 8.1 years.[8]

In fact, 1-year survival has increased across time (72% for 1990–1998, 80% for 1999–2008, and 84% for 2009–2015). On the other hand, 5-year survival (46%, 55%, and 57%, respectively), has not change much between the more recent eras (1999-2008 and 2009-2015).[8]

Additionally, unadjusted survival rates favor bilateral lung transplant (BLT) with a median survival of 7.4 years compared to 4.6 years for single lung transplant (SLT). Nevertheless, post-transplant unadjusted survival is directly impacted by the indication for transplant. In fact, each disease has several factors that directly influence the short- and long-term survival outcomes. For instance, patients who receive transplants for cystic fibrosis have superior long-term survival compared with all other diagnoses.[8] Indeed, the median survival for cystic fibrosis patients is 8,9 years old, while for COPD with AATD is 6,7 years old, and for COPD without AATD is 5,6 years. Idiopathic interstitial pneumonia has a median survival of 4,8 years.[2]

These differences can be partially explained by patients' characteristics at the time of lung transplant. For instance, patients with COPD are generally older, more frequently tobacco smokers and have more comorbidities than patients with CF. Nevertheless, other prognostic factors include characteristics of the recipient (age, 6 min walking distance, use of mechanical ventilation, dialysis or hospitalized in ICU) and of the donor (diabetes, age, gas exchange at the time of harvest, cause of death). Furthermore, the donor/recipient interaction (number of HLA mismatches, CMV or gender mismatch), the surgical approach (single *vs.* bilateral) and the center volume can also interfere in the outcome.[12]

When analyzing the subgroups within primary diagnostic indications, in ILD category, the 6 ILD subtypes (connective tissue disease; hypersensitivity pneumonitis; idiopathic interstitial pneumonia; interstitial lung disease; eosinophilic granuloma; occupational) had a similar post-transplant survival, whereas in the PH category, PAH associated with congenital heart disease

(PAH-CHD) had lower post-transplant survival in comparison to IPAH and pulmonary arterial hypertension in connective tissue diseases (PAH-CTD). In the bronchiectasis group, those with CF had better unadjusted survival than those without CF.[2]

Regarding the COPD group, COPD without A1ATD had lower post-transplant survival in comparison to COPD with A1ATD. A survival benefit in patients with alpha 1-antitrypsin deficiency is probably related to the greater number of bilateral procedures and the younger age of the candidates.[2]

**Functional Outcomes**

Concerning the activity level and according to the ISHLT registry, >80% of survivors at 1, 3 and 5 years post-lung transplant declare no activity limitation, about 15% need some assistance, and a small percentage need total assistance with activities.[24]

In fact, Bartels et al., in a recent study that included 153 lung transplant recipients, reported that exercise capacity did not match the improvement in lung function. Additionally, BLT did not show better results in the improvement of exercise capacity comparatively with SLT. Severe chronic deconditioning, as well as drug effects, are probably some of the factors that may have contributed for these results.[32]

Additionally, the employment outcomes are not very optimistic, with only 20% of recipients working full-time at 1 year, and approximately 30% working full-time in 5 years. In addition, re-hospitalisation is close to 65% within the first year, and remains approximately 45% between 4 to 5 years post-transplant. Most of the hospitalisations are related with episodes of rejection or infection.[24]

The peak in pulmonary function is normally seen between 3 to 12 months after lung transplant, with a declining thereafter due to the development of CLAD. Almost normal FEV1 can be expected in patients with PAH, whereas idiopathic pulmonary fibrosis (IPF) patients have typically FEV1 between 60% and 80% of predicted value, and COPD patients achieve typically FEV1 in the 50–60% range.[12]

**Quality of life**

Improving recipient quality of life is certainly a crucial objective of lung transplant. It has even been proposed that for diseases such as COPD, improving health-related quality of life (HRQL) is the main goal in these patients.[33]

Overall, improvement of HRQL in lung recipients was good, as approximately 90% of LT recipients declared satisfaction with their decision to receive LT and, for many patients, the quality of life obtained outweighed a potential reduction in longevity. Nevertheless, the lack of accepted standard definitions and assessment tools, and the limited survival of LT recipients, make the analysis of HRQL still a challenge.[24]

**Immunosuppression therapy**

During the past thirty years, immunosuppressive therapy has had a great development with an increasing number of induction and maintenance immunosuppressive agents, allowing a more individualized immunosuppressive therapy.[23]

According to the ISHLT, from the adults who received lung transplant between January 2004 to June 2016, received post-transplant prednisone and survived to hospital discharge, 60% received induction therapy. In fact, the proportion receiving an interleukin-2 antagonist has increased over time, with more than 80% receiving an interleukin-2 antagonist in the last years. Conversely, the proportion of patients receiving polyclonal anti-lymphocyte globulin/anti-thymocyte globulin has decreased, while a small but static proportion of patients have received alemtuzumab. Concerning maintenance therapy, tacrolimus plus mycophenolate mofetil/mycophenolic acid, remain the most common regimen at 1 year after transplant. The use of cyclosporine and azathioprine has gradually decreased during the past decade.[8]

**Causes of Death and Comorbidities**

According to the ISHLT, after the first year, graft failure was the leading cause of death, accounting for more than 40% of the deaths. Those transplanted for CF had a higher frequency of diabetes and a lower frequency of hyperlipidemia post-transplant within 1 year and within 5 years. The frequency of systemic hypertension (around 80%) and renal dysfunction (around 50%) within the first 5 post-transplant years were similar among the diagnostic groups.[2]

Furthermore, malignancy rates have increased over time, with 42% of the recipients at 10 years post-transplantation having cancer. Skin cancer was the most frequently reported of all cancers. However, post-transplant lymphoproliferative diseases and other malignancies remain important morbid conditions.[2]

## Discussion

### Single Lung Transplant vs Bilateral Lung Transplant

Although the surgical techniques of single and bilateral lung transplant are well described, there is a lack of high-quality evidence comparing both surgeries , making practice patterns remaining mostly institution or individual-specific.[31]

A progressive growth of bilateral lung transplants has been observed during the past years in comparison to single lung transplants.[8] Although the earliest reports referred a higher peri-operative mortality in patients who received BLT, recent reports report no major differences in peri-operative mortality between single and bilateral surgeries.[31] While much speculation still exists about the reason bilateral lung transplant confers a long-term survival advantage, a retrospective study reported a decreased rate of BOS in patients who went through this type of procedure. In fact, procedure type was found to be an independent risk factor for BOS, with bilateral lung transplant group having a significantly lower incidence of BOS (31.7%) than the single lung transplant group (49.3%).[34]

Regardless the potential benefit of bilateral lung transplant there are also advantages in single lung transplant, such as helping more patients, the simpler surgical technique and the shorter total ischemic time.[31]

On the other hand, in Japan the living donor lobar transplantation (LDLLT) has been practically the only option for most Japanese patients until 2010, when the Japanese Organ Transplant Law was revised, allowing the family of the brain dead donors to decide on the organ donation. Since then, an increasing in the number of organ donations from brain dead donors has occurred. Nevertheless, Japanese transplant centers have a huge experience with living lobar transplantation. Some of the advantages of LDLLT compared to cadaveric lung transplantation include a shorter waiting list time and ischemic time, less primary graft failure and bronchial complications. However, in LDLLT, as only two lobes are implanted, proper size matching between the donor and recipient is crucial, being often inevitable the implantation of small grafts which may lead to high pulmonary artery pressure and lung edema.[35]

### Single Lung Transplant vs Bilateral Lung Transplant by primary diagnostic indication

### Chronic Pulmonary Obstructive Disease

Many studies have compared the outcomes of BLT versus SLT for emphysema. The majority have concluded that survival rates were better with bilateral lung transplant, reporting that with SLT, the hyperinflation of the native lung could lead to poorer results. However, in many of these studies the groups were not homogeneous and confounding factors might have influenced the final results. For instance, the selection bias, that occur when BLT is performed preferentially in younger or healthier recipients, may have led to better outcomes. [36,37]

In the largest survival analysis of COPD recipients since the establishment of the lung allocation score (LAS), it was compared the short-term (1 year) and long-term (5 year) survival in patients with COPD undergoing BLT versus SLT. Although survival at 1 year after transplant did not differ between SLT and BLT groups, the 5 years mortality was reduced in recipients who underwent BLT instead of SLT (51% versus 59%).[38]

Furthermore, Thabut et al. analyzed data from 9883 COPD patients who underwent lung transplant, reporting that BLT led to prolonged survival comparatively with SLT in patients with COPD, particularly those younger than 60 years.[39]

Additionally, in a retrospective study, Cassivi et al. analyzed the outcomes of lung transplants for emphysema in patients with genetically determined alpha-1 antitrypsin deficiency (AAD) and patients with COPD. Bilateral lung transplant for emphysema led to a better long-term survival, with a 5-year survival rates of 66.7% comparatively with 44.9% in single lung transplant.[36]

Nevertheless, in other study, the outcomes of single and bilateral-lung transplant recipients since the LAS was implemented were compared. Although BLT was associated with better graft survival than SLT in patients with IPF, in COPD patients there was no survival difference between both surgical approaches.[40]

In fact, Delgado et al. also analyzed data from all lung transplants (BLT and SLT) performed in emphysema patients at their center, by the same team and with similar subsequent follow-up conditions, reporting no differences in long-term mortality and morbidity between both groups. The results also supported the decision of performing SLT as the first line treatment in emphysema, as it is an approach that alleviate the donor organ shortage and decrease waiting list morbidity and mortality, with similar 5-year outcomes. Additionally, it can be complemented with lung volume reduction surgery in the native lung or subsequent transplantation of the contralateral lung if needed.[37]

**Interstitial Lung Disease**

In patients with interstitial pulmonary fibrosis, bilateral lung transplant has been pointed as having better long-term outcomes compared with single-lung transplant.[40]

Villavicencio et al., compared the risks and benefits of bilateral versus single lung transplant in pulmonary fibrosis. In patients who received bilateral lung transplant, 10-year survival was 55%, compared with 32% in patients who had only single lung transplant. Results also showed that patients of all ages, except those older than 70, had improved survival rates with BLT, with a mean survival among patients younger than 60 of 8.1 years in SLT patients versus 11.5 years in BLT patients. Therefore, it was suggested that BLT was the most adequate procedure in patients younger than 70 years of age. Furthermore, in patients with mean pulmonary artery pressure ≥30 mm Hg and an allocation score ≥45, SLT should not be performed.[41]

Nevertheless, in other study the survival by procedure type (BLT vs SLT) within three age groups (30 to 49 years, 50 to 59 years, and 60 to 69 years) of pulmonary fibrosis transplanted patients was compared. Contrarily to previous studies where BSLT was the preferential choice for younger patients with pulmonary fibrosis, it was reported that patients younger than 60 years of age, seemed to have better survival with SLT than with BSLT. In fact, early (1-month) and late (3-year) survival in recipients aged 30 to 49 years was remarkably better with SLT than BSLT (early, 90.9% versus 77.1%; late, 63.8% versus 46.2%, respectively). However, the reasons for these results are not clear and further studies are necessary.[42]

Indeed, in a recent study, Spratt et al., analyzed records of IPF lung transplant patients after the introduction of the Lung Allocation Score. The authors reported no difference in the survival between single and bilateral lung transplant. However, BLT was associated with prolonged postoperative ventilation and length of stay compared with SLT. Additionally, in older patients, patients without PH and patients with PH and advanced disease, SLT seem to be a better choice for IPF, instead of BLT.[43]

Meyers et al., also analyzed the outcomes of single and bilateral lung transplant for idiopathic pulmonary fibrosis, demonstrating that there were no benefit of bilateral over single lung transplant for patients with this diagnosis.[44] Recent analysis also support this idea, reporting no statistical difference in graft survival between recipients undergoing BLT vs SLT[45], suggesting that the increased use of SLT for IPF patients may increase the availability of organs to other candidates, without affecting outcomes.

**Cystic Fibrosis**

As a consequence of the nature of the suppurative lung disease, bilateral lung transplant is recognized as the standard technique in cystic fibrosis, and is normally performed via a bilateral single lung transplant or a heart-lung transplant.[46]

Liou et al. in a retrospective observational cohort study from 115 CF centers in the United States, divided CF patients into groups based on a 5-year survival prediction model (survival group 1: <30%; survival group 2: 30 to <50%; survival groups 3-5: 50 to <100%.). An increment in 5-year survival after bilateral lung transplant of CF patients in survival group 1 were reported. Conversely, survival group 2 had imprecise survival effects, and groups 3-5 had negative survival effects from transplantation. Therefore, it was suggested that selection of patients with CF for transplantation based on group 1 survival predictions, would maximize survival benefits to patients.[47]

Although bilateral lung transplant is the standard technique in CF patients, single lung transplant has been attempted in some particular situations. In a case report, the authors perform SLT with contralateral pneumonectomy (CP) in 3 CF patients, suggesting that SLT with CP can be a solution for certain patients with end-stage CF. Furthermore, the best results were achieved if CP was done before lung transplantation.[48]

**Pulmonary Arterial Hypertension**

Nowadays, most transplant centers prefer bilateral lung transplant to single lung transplant for PAH. In fact, single-lung transplant has been less performed due to the adverse postoperative outcomes, such as pulmonary edema, graft dysfunction, and need for prolonged mechanical circulatory support.[49]

Indeed, according to Conte et al., patients with primary (idiopathic) PAH who received a bilateral lung transplant had better survival than those who received a single lung transplant. In fact, in the group of patients with connective tissue disease-associated PAH and secondary PAH, there was also a survival benefit with bilateral lung transplant when the mean pulmonary artery pressure was greater than 40 mmHg.[50]

Nevertheless, a few years ago, SLT and BLT were equally performed in patients with primary pulmonary hypertension and it was not clear which procedure would be the most adequate.[50]

For instance, in a retrospective study, the outcomes in single versus bilateral lung transplant for IPAH were compared, with the survival being nearly the same, with 81% and 84% at 1-month for the single and bilateral-lung groups, and the same at 1-year (67%) and at 4-year (57%) for both

groups. Therefore, it was suggested that certain selected lung transplant recipients with pulmonary hypertension would have similar outcomes after single or bilateral-lung transplant.[51]

**Survival benefit**

The success of lung transplant may be assessed by several different outcome measures. Nevertheless, survival has classically been the main outcome against which lung transplant has been judged.[24] In fact, survival after lung transplant remains poor comparatively with other solid organ transplants, with a 1- and 5 -year survival rates of 84% and 57%, respectively.[8] Nonetheless, most of the evidence about post-transplant survival comes from large registries that aggregate the outcomes of transplants performed in the past in centers that may no longer exist, with those performed recently in high volume centers.[12]

Since Hosenpud et al., reported in 1998 that lung transplant would not confer any survival benefit for patients with end-stage emphysema[33] several studies have been questioning the survival benefit of lung transplant for other indications, such as cystic fibrosis and Eisenmenger syndrome. These findings, together with the high cost of this intervention, have led some U.S. health insurers to question and even deny lung transplant in cystic fibrosis patients7.[52]

Nevertheless, some of these studies have limitations, including the use of cohorts from an era before the implementation of the LAS (53). Additionally, as randomized controlled trials have never been conducted, assessment of the survival benefit of lung transplant relies on observational studies, which makes assessing survival benefit of lung transplant difficult. In fact, some studies estimate survival benefit by comparing the survival of patients who did and did not undergo transplantation which can be dubious, as patients on a waiting list for lung transplant are a highly selected subset of patients as they undergo a meticulous selection process, where patients with significant comorbidities are excluded, which can lead to an improvement of prognosis.[52]

Furthermore, the comparison of survival in a transplanted patient with the expected survival if the same patient did not receive a transplant, using a scoring system such as the BODE index[54] may also be arguable, as the population used to develop this scoring system would not qualify for lung transplant.[52]

According to Vock et al., the majority of U.S. lung transplant recipients since the implementation of the LAS, were estimated to have a survival benefit at 2 and 3 years of 73.8% and 81.9%, respectively. Nevertheless, the survival benefit seems to depend on the LAS at the time of transplant, with little survival benefit for patients who are transplanted at a LAS below 35.[53] In

fact, Vock et al., by using the LAS data of all wait-listed patients, analyzed the survival benefit of lung transplant, reporting that most of the adults undergoing transplantation experienced a survival benefit, with those with higher lung allocation scores, restrictive native lung disease or cystic fibrosis having the highest potential benefit.[53]

**Survival Benefit by primary diagnostic indication**

**Chronic Obstructive Pulmonary Disease**

COPD without α-1-anti-trypsin deficiency is considered the most common indication for lung transplant. The combined group of COPD, with (5%) and without (31%) α-1-anti-trypsin deficiency, accounts for more than 33% of all lung transplants.[8]

Although a clear impact on life expectancy after LT for selected patients with end-stage pulmonary diseases such as cystic fibrosis has been reported, for emphysematous patients data is not so clear.[33]

In fact, it is still being discussed how to weigh expected survival benefit with gains in quality of life. This idea is reinforced in a study, where patients with COPD had the poorest survival benefit comparatively with patients with cystic fibrosis or idiopathic pulmonary fibrosis, with quality of life being a more significant outcome for COPD patients.[52]

Singer et al., in a recently published study reported that COPD patients experienced similar quality-of-life benefits comparable to patients with cystic fibrosis or interstitial lung diseases, concluding that diagnosis by itself should not be used to discriminate between potential lung transplant recipients, if improvement in health-related quality-of-life is a desired goal of transplantation.[55] Lahzami et al., also analyzed the role of the BODE score and its survival effect in COPD patients who received lung transplant. By retrospectively reviewing 54 lung transplants performed for COPD, the authors concluded that most patients had an individual survival benefit from lung transplant regardless of their pre-transplant BODE score. However, it was observed a global survival benefit only in patients with a BODE score of ≥7, suggesting that this is the appropriate population to transplant. Although, patients with a BODE score of 5 to 6, are not expected to have a survival benefit, they experienced similar quality of life benefits from transplant as patients with a BODE score of 7 to 10 (54). Nevertheless, a recent study reported that the assumption of prognosis based on the BODE score could overestimate mortality risk in lung transplant candidates with COPD.[56]

**Interstitial Lung Disease**

ILD is the second most common indication for lung transplant[8] with IPF being the most frequent adult form of interstitial pneumonia of unknown origin.[57]

In fact, and although lung transplant rates for candidates with ILD have been increasing in recent years due to changes in allocation of donor lungs, including the LAS in the United States and Eurotransplant in Europe, the waiting list mortality remains high. In fact, retrospective cohort studies show a median survival of 2 to 3 years from diagnosis, and only 20% to 30% patients survive more than 5 years after diagnosis, making it extremely important to exist an early referral of patients with ILD. Some of the predictors of worse survival include older age, dyspnea, low or declining pulmonary function, pulmonary hypertension, concomitant emphysema, extensive radiographic involvement, low exercise capacity or exertional desaturation and usual interstitial pneumonitis on histopathology.[6]

IPF has the worst post-transplant survival comparatively to other common lung transplant indications, and according to ISHLT and OPTN data, the one-year survival ranged from 75% - 81% and five-year survival 47% - 53%. Additionally, OPTN data reported a higher wait list mortality for IPF patients versus other diagnoses.[57]

Indeed, Thabut et al. assessed the survival benefit provided by lung transplant in patients with a diagnosis of IPF according to American Thoracic Society criteria. After lung transplant, a survival of 79.4% at 1 year, 63.5% at 2 years, and 39% at 5 years was reported. Furthermore, the multivariable analysis showed that lung transplant lowers the risk of death by 75%, suggesting that lung transplant is successful in improving the survival of selected patients with idiopathic pulmonary fibrosis.[58]

**Cystic Fibrosis**

According to the ISHLT, bronchiectasis related to cystic fibrosis are the third most common indication for lung transplant, whereas non–cystic fibrosis bronchiectasis originate a much lower proportion of transplants.[8]

Thabut et al., analyzed data from the United Network for Organ Sharing Registry and identify adult patients with CF on a wait list for LT in the United States between 2005 and 2009. In fact, it was reported a 69% reduction in the immediate risk of death when lung transplant was performed. Additionally, it was also observed a direct relationship between LAS and LT: the higher the LAS, the greater the survival benefit of LT.[59]

Indeed, in a study conducted in 2009 in a medical center in Zurich, the authors compared 5-year post-transplant survival with a calculated 5-year survival without lung transplant, using a predictive 5-year survivorship model, drawing the conclusion that lung transplant offer a true survival benefit to patients with end-stage CF lung disease.[60]

Furthermore, in other study, cystic fibrosis demonstrated the greatest relative survival benefit comparatively with other transplant indications. Specifically, the relative survival benefit of transplantation was 54.4% greater for those with cystic fibrosis compared with those with obstructive lung disease, with the proportion of transplant recipients with a 2-year expected survival benefit differing between 39.2% for those with obstructive lung disease and 98.9% for those with cystic native diseases.[53]

Although Liou et al., had reported that only cystic fibrosis patients with a 5-year survival prediction model <30% would have improved survival after lung transplant[47], recent studies found that lung transplant confers survival benefit for the majority of patients with cystic native diseases, suggesting that should not be reservations about pursuing lung transplant for appropriately selected patients with cystic fibrosis. In fact, the study by Liou et al. included a historically older cohort and preceded the implementation of the LAS which may have induced worst outcomes.[53]

**Pulmonary Arterial Hypertension**

Lung transplant has been commonly performed for patients in diagnostic groups 1 (pulmonary arterial hypertension), 3 (PH owing to lung diseases or hypoxemia) and 5(PH with unclear multifactorial mechanisms)[61], with IPAH comprising 2,9% of all transplant recipients and 4.1% of bilateral lung transplant recipients according to the ISHLT.[8] Nevertheless, before therapy with pulmonary vasodilators was available for PAH, median survival was only 2.8 years from the time of diagnosis.[62]

The benefits of lung transplant in pulmonary hypertension are remarkable: according to a retrospective study, data of 100 patients transplanted for idiopathic pulmonary hypertension or pulmonary hypertension secondary to congenital heart disease were analyzed. In both single and bilateral lung transplant recipients, a reduction in mean pulmonary artery pressures (from 65.9±13.1 mmHg pre-transplant to 21.9±5.9 mmHg post-transplant) and pulmonary vascular resistance (18.8±8.0 Woods Units pre-transplant to 2.1±0.9 Woods Units post-transplant) were seen at 24 hours and sustained at 1 year later.[63]

Nevertheless, and according to the ISHLT, survival rates at 3 months (76%), and 1 year (71,1%) after lung transplant were the lowest for patients with IPAH, when compared to patients with IPF (85%, 74.1%), CF (90%, 82.6%), and COPD (91%, 82.4%) respectively. The low survival rate at 3 months in IPAH patients was mostly due to early complications such as primary graft dysfunction.

Indeed, a diagnosis of IPAH was the greatest categorical risk factor for one-year mortality. However, if lung transplant recipients with IPAH live for at least one year, there is a lower risk of 5-year mortality and significantly improved long-term survival (median survival 9.3 years) comparatively with patients with COPD (6.6 years) and IPF (6.7 years).[64]

**Immunosuppression therapy**

Although protocols may vary depending on the transplant center, conventional maintenance therapy generally consists of triple drug therapy with a antiproliferative agents (azathioprine, mycophenolate, sirolimus, everolimus), calcineurin inhibitor (cyclosporine or tacrolimus) and corticosteroids. Approximately 50% of lung transplant centers use induction therapy, such as polyclonal antibody preparations (equine or rabbit anti-thymocyte globulin (ATG)), interleukin 2 receptor antagonists (IL2RAs) (daclizumab or basiliximab), or alemtuzumab[65] and according to the ISHLT, from the centers that use induction therapy, the majority use an IL2RA.[8]

In fact, Furuya et al. analyzed the effect of alemtuzumab, basiliximab and no induction therapy, in adults who received bilateral lung transplants. A longer median survival was observed for recipients who had received induction therapy compared with those who have not received any. Furthermore, either alemtuzumab or basiliximab were independently associated with survival, with alemtuzumab treated recipients having a lower incidence of BOS at 5 years (22.7% versus 55.4 versus 55.9%).[66]

In other study, Hartwig et al., hypothesized that rATG induction would reduce BOS and improve long-term graft survival. Therefore, 44 lung recipients were prospectively randomized and the group who received conventional immunosuppression plus rATG induction had fewer early rejections compared with the control group (5% vs 41%) who only received conventional immunosuppression. Although there was a tendency toward a delay in BOS onset among rATG subjects comparatively with control subjects (2,376 days vs 1,108 days) there was no significant difference in graft survival between the groups at 8 years and the overall rejection incidence did not differ. Additionally, although the incidence of infections did not vary between groups, the

rATG group had a higher rate of malignancies making the anti-thymocyte globulin induction therapy not a very good option.[67]

However, randomized controlled trials comparing induction agents in lung transplant have never been made.[65] In fact, the only randomized trial conducted internationally in multiple centers about the use of rATG as induction therapy, reported no significant benefit with the use of this drug.[68]

Some reports have also been published regarding the use of aerosolized cyclosporine. A larger case-control study was performed, demonstrating a survival advantage in lung transplant recipients with biopsy-documented bronchiolitis obliterans who received aerosol cyclosporine, plus conventional immunosuppression over to conventional immunosuppression alone. Despite these results, future randomized studies should be performed for more definitive conclusions, such as the dose/response relationship can be drawn.[69]

**Lung Transplantation: The Portuguese Program Revised**

In Portugal, the lung transplant program started in 2001 at the Hospital Santa Marta, Centro Hospitalar de Lisboa Central, the single lung transplant center in the country.[70] Over the past decade, transplant numbers have increased substantially from 10 cases of lung transplant in 2010 to 19 cases in 2014 and 34 in 2017 (figure 1).

Indeed, the clinical files of 81 lung transplant patients treated between 2009 and 2015 were reviewed and demographic variables, type of transplant, pre-transplant diagnosis, duration of anesthetic procedure, type of circulatory support, hospital stay and 3-month mortality were analyzed, with the following results being reported:

-45 patients (55.6%) were male and 36 were female (44.4%) with a mean age of 46.1 ± 13.19 years;

-The most frequent indications for lung transplant, accounting for more than 80% of the cases, were pulmonary fibrosis (n = 14), extrinsic allergic alveolitis (n = 13), COPD (n= 13), cystic fibrosis (n=11), alpha-1 antitrypsin deficiency (n=9) and bronchiectasis (n=7);

-Single lung transplant was performed in 51 cases (63%);

-Average time for the anesthetic procedure was 719.33 ± 172.1 minutes for bilateral lung transplant and 515.98 ± 135.6 minutes for single lung transplant;

-No cardiopulmonary support was used in 62 patients (76.5%). Conventional cardiopulmonary bypass was used in 10 patients (12.3%) and ECMO in the remaining 9 patients (11.1%);

-Postoperatively, median time for mechanical ventilation, ICU stay and hospital length of stay was 4, 26 and 41 days, respectively;

- Overall survival rate at the 3 month was 91.4%.[71]

Although COPD plays an important role as primary indication for lung transplant in Portugal, ILD, more specifically, pulmonary fibrosis and extrinsic allergic alveolitis seem to be the major indications for transplant.[70,71]

Indeed, in a previous article, Fragata (2014) has already reported that the majority of transplants (53%) were performed due to parenchymal disorders, such as pulmonary fibrosis, with the other indications for lung transplant being COPD (22%), CF (16%) and non-CF bronchiectasis (9%). By that time, the 3-month survival was 83.5%, the 1 year survival was 71.3%, and 5 years survival was 48,5%.[70]

Santos et al., also analyzed the occurrence of airway complications in lung transplant patients from 2008 to 2013 at the Hospital Santa Marta. In fact, from the 68 lung transplants performed, 29 were BLT and 39 were SLT with a total of 97 airway anastomosis. Among the 97 anastomosis performed, airway complications occurred in 28 (28.8%), with 3 cases requiring endobronchial therapy. Additionally, excess granulation tissue occurred in 11, stenosis in 7, necrosis in 4, traqueobronchomalacia in 2 and anastomotic dehiscence in 1. Two patients died of airway complications, one with anastomotic dehiscence and the other with necrosis concomitant with Aspergillus infection, with the mortality directly related with airway complications being 2.9%. Although severe complications, such as those that require endobronchial therapy do not occur often, they still have a clinical impact on patients.[72]

In a recent study, Fragata et al., retrospectively analyzed the incidence of malignancies in lung transplant recipients in Portugal between June 2001 and December 2017. From the 182 lung transplants performed between 2001 and 2017, a total of 12 malignancies were identified. The most common malignancy was skin cancer, more specifically cutaneous squamous cell cancer (2,2%), followed by lymphomas (1,6%), lung cancers (1,6%) and gastric cancers (1,1%).[73]

Concerning the cost-effectiveness of lung transplant in Portugal, Mendonça et al. analyzed the costs and outcomes of lung transplant and its evolution since it was first performed in 2000. The authors collected data for all the patients waiting for transplant from 31 December 2000 until 31 December 2010 (n = 61), reporting a cost of lung transplant of 77,223€ per QALY and 121,276€ per life-year. Nevertheless, as survival improved considerably from 5.15 years over the 2001-2010 period to 6.94 years for the 2008-2010 period, in the 2008-2010 period, the cost-effectiveness ratio decreased to €79,016 per life-year gained and €69,241 per QALY.[74]

Even though lung transplant is above the accepted cost-effectiveness thresholds, the life-threatening indications for lung transplant, the lack of alternative treatments and the very favorable impacts on the quality of life of the patients, makes lung transplant an important therapeutic option despite its economic value.[74]

Due to the remarkable good outcomes, comparable with those published by the International Society of Heart and Lung Transplantation, the Portuguese lung transplant program has a great potential for growth in the future years.

**Ex vivo Lung Perfusion**

A big challenge in the lung transplant community is how to increase the number of usable donor lungs without compromising the success of the procedure. Usually, only 15% of lungs donors are used for transplantation. This low number may be partially explained as donor lungs are subjected to several injurious mechanisms, such as barotrauma and pulmonary edema.[75]

By increasing the number of lung transplant performed in individual transplant centers by 15–30%, EVLP has become a promising technique for evaluating and reconditioning donor lungs that would have been considered unusable in the past.[76]

In fact, the role of EVLP for reconditioning of lungs donors was investigated in multiple studies and currently ongoing trials. The results from the first prospective clinical trial were published in 2011. In this trial, a group of 23 high-risk donors met the inclusion criteria for EVLP and among these, 20 sets of lungs (87%) were considered suitable for transplantation. Afterwards, this group was compared to a group of 116 patients who went through transplantation according to the standard criteria. Indeed, it was not observe any significant differences in primary graft dysfunction (PGD), days on mechanical ventilation after transplant, ICU stay, hospital stay, and 30-day mortality between both groups.[75]

At the ISHLT meeting in 2013, the Toronto, Paris and Vienna groups presented their EVLP experience combined, with a total of 125 clinical EVLP performed. From these, 103 lungs treated with EVLP were later transplanted with excellent short and intermediate outcomes, with the occurrence of PGD at 72 hours being 5% and the 12-month mortality being 12%.[77]

Even though the expectations that EVLP will overcome some limitations of lung transplantation are high, there are still some unresolved questions such as the optimal time needed to keep the lungs on EVLP device, or the optimal time to start EVLP assessment. All these questions need further research so the best way in managing this new technology can be found.[78]

**Lung Xenotransplantation**

The shortage of organs and cells from deceased individual remains a critical problem worldwide. The use of pigs as sources of organs could potentially become a solution for this problem. For the time being, the main failure mechanism is the development of an inflammatory response causing a vascular injury, interstitial and tracheal edema. Nevertheless, and for the first time, drugs that target complement activation, coagulation, and inflammation have remarkably improved the survival of xenogeneic pig lungs, either during ex vivo human blood perfusion or

in life-supporting *in vivo* models. Overcoming delayed loss of vascular barrier function injury seems to be crucial to make lung xenografts a potential treatment option in the future.[79]

**Key Learning Points**

- Lung transplant is a recognized treatment for end-stage lung diseases and according to the ISHLT, the most common indications are COPD, ILD and bronchiectasis.[2]

- Infection is the leading cause of mortality during the first year and remains a major cause of morbidity and mortality over the long term after lung transplant. Bacterial infections are the most common cause of pneumonia after lung transplant.[7]

- Chronic Lung Allograft Dysfunction is the main cause of morbidity and mortality after the first year following lung transplant and occur at least in 50% of recipients 5 years after lung transplant.[11,12] CLAD has two well-described phenotypes: the bronchiolitis obliterans syndrome (BOS) and the more recently recognised restrictive allograft syndrome.[14] Azithromycin seems to be a potentially therapy in preventing and/or attenuating CLAD. However, evidence for other treatments remains relatively poor.[19,20]

- Size matching is crucial in lung transplant. Recently, three-dimensional computed tomography (3D-CT) volumetry has become a promising technique for the assessment of lung volume.[28,29]

- A progressive growth of bilateral lung transplants have been observed during the past years in comparison to single lung transplants.[8] In certain indications, such as COPD and ILD, there is no general consensus on the best approach. One of the exceptions, is in patients with septic lung disease such as cystic fibrosis, where bilateral transplant is the only acceptable transplant modality.[31]

- There is a lack of high-quality evidence comparing BLT and SLT, making practice patterns remaining largely institution or individual-specific.[31] One of the exceptions is in cystic fibrosis patients, where BLT is recognized as the standard technique.[46]

- Many studies have compared the outcomes of BLT versus SLT in DPOC patients. The majority have concluded that survival rates were better with bilateral lung transplant.[36]

[38,39] Nevertheless, other studies report no survival difference between both surgical approaches. [37,40]

- In patients with interstitial pulmonary fibrosis, BLT has been pointed as having better long-term outcomes compared with single-lung transplant.[41] However, some studies report SLT as a better choice for IPF, instead of BLT.[42-45]

- Survival after lung transplant remains poor comparatively with other solid organ transplants, with 1- and 5 -year survival rates of 84% and 57%, respectively.8 According to the ISHLT, the median survival for cystic fibrosis patients is 8,9 years old, whereas for COPD with AATD is 6,7 years old, and for COPD without AATD is 5,6 years. Idiopathic interstitial pneumonia has the worst median survival of 4,8 years.[2]

- Randomized controlled trials have never been conducted, making the assessment of the survival of lung transplant depending mainly on observational studies.[12]

- A diagnosis of IPAH was the greatest categorical risk factor for one-year mortality, with survival rates at 3 months (76%) and 1 year (71,1%) after lung transplantation being the lowest for patients with IPAH when compared to patients with IPF (85%, 74.1%), CF (90%, 82.6%), and COPD (91%, 82.4%) respectively.[65]

- The improvement of the quality of life should not be dismissed in lung transplantation. In fact, some studies reinforce this idea, with quality of life being a more important outcome than survival, particularly in COPD patients.[52,55]

- Approximately 60% of adults who underwent lung transplantation received induction therapy, with an increasing in the use of IL2RA by transplantation centers.[8] Although randomized controlled trials have not been conducted comparing induction agents in lung transplantation[65], Furuya et al. by reviewing the United Network for Organ Sharing database, reported a longer median survival for recipients who had received any induction agent compared with patients who did not receive any.[66]

- According to the ISHLT registry, >80% of survivors at 1, 3 and 5 years post-lung transplant report no activity limitations.[24] After 3 to 12 months following LT, the majority of PAH patients have a normal FEV1, whereas IPF patients have typically a FEV1 between 60% and 80% of predicted value, and COPD patients achieve typically FEV1 in the 50–60% range.[12] Nevertheless, exercise capacity did not match the improvement in lung function. Additionally, BLT did not improve exercise tolerance comparatively with SLT.[32]

- The Portuguese lung transplant program started in 2001. Over the past decade, transplant numbers have increased from 10 cases of lung transplant in 2010 to 34 in 2017, and it is expected to grow in the future years. In Portugal ILD and COPD seem to be the major indications for transplant. Additionally, SLT was more frequently performed compared to BLT.[70-72] The most common malignancy identified in lung transplant patients was skin cancer, more specifically cutaneous squamous cell cancer.[73]

- Ex vivo Lung Perfusion has shown good results in reconditioning donor lungs with optimistic short and intermediate outcomes.[75,77] Additionally, for the first time, drugs that target complement activation, coagulation, and inflammation have improved the survival of xenogeneic pig lungs, which may open doors to use lung xenografts as a treatment option in the future.[79]

**Conclusion**

The last 20 years have seen tremendous progress in lung transplant outcomes. Despite these advances, morbidity and mortality remain high when compared with other solid organ transplants. Additionally, there are several stumbling blocks, including donor shortage and chronic lung allograft dysfunction. The advances and developments surrounding these factors will have a significant impact on shaping the field within the coming years. New technology such as Ex Vivo lung perfusion and xenotransplantation may lead to future developments in the field of lung transplantation. The science that involves lung transplant, surgical technique, and postoperative management is in constant evolution and far from being established. Therefore, it is important that research in lung transplantation continues to be performed, so lung transplant can reach its full potential as an effective and enduring treatment option for patients with advanced lung disease in the near future.

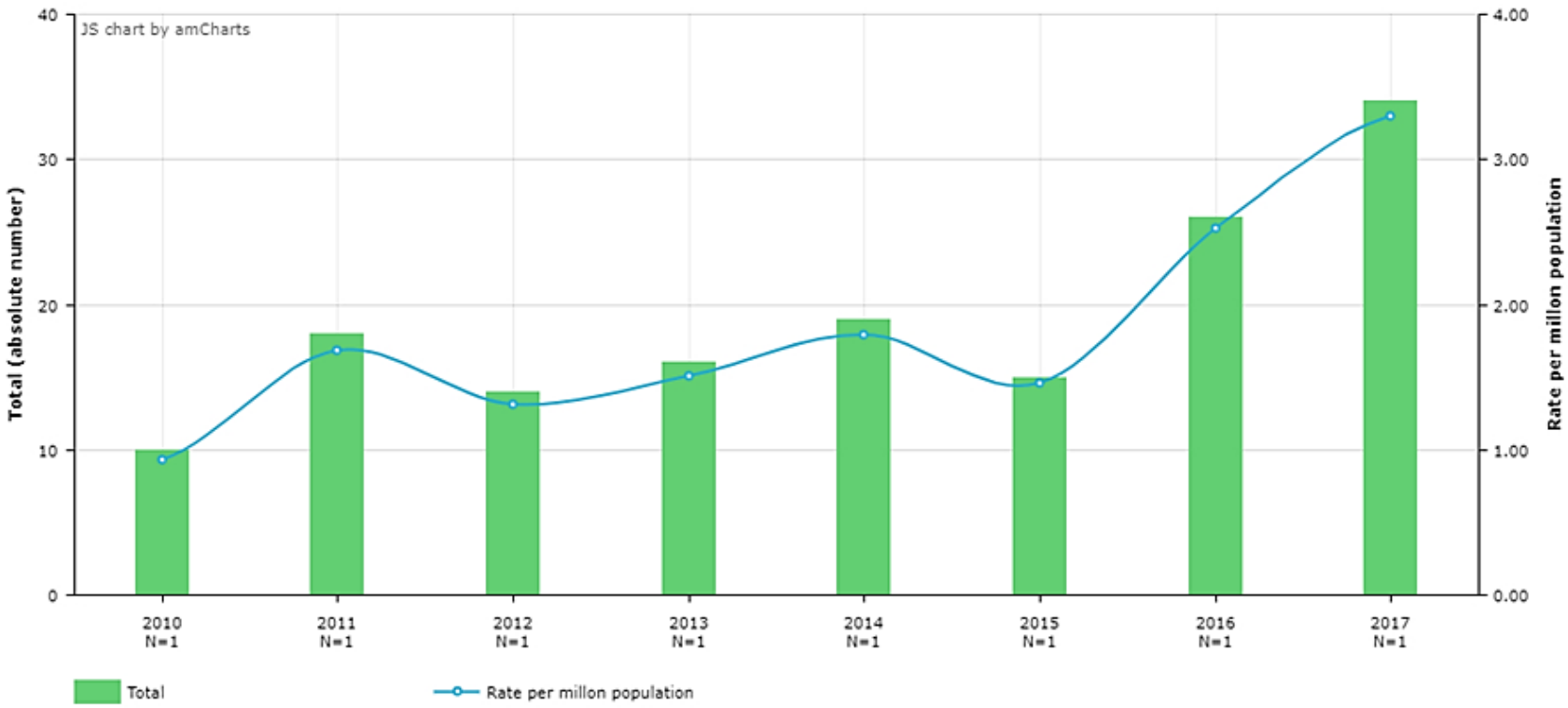


***Figura 1*** *-Total Lung Transplants Portugal (2010-2017).* *Source: GODT (http://www.transplant-observatory.org)*

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A Contemporary Review of Adult Lung Transplantation and the Portuguese Lung Transplant Program Revised

Maria Inês dos Reis Rodrigues



INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR