Review Article

# Lung Transplantation for Idiopathic Pulmonary Fibrosis: A Narrative Review

**Nazia Mehfooz[1], Farhana Siraj[2], Parvaiz A Koul[1,2]**

[1]Departments of Pulmonary Medicine and [2]General Medicine, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Jammu and Kashmir, India

## Abstract

Idiopathic pulmonary fibrosis (IPF) is a debilitating and progressive lung disease without an identifiable cause. It is the most common form of interstitial pneumonias. The prognosis is worst in this disease with median survival of just 2–3 years after diagnosis without a lung transplant. Currently, there are no proven medical therapies to cure IPF. Pharmacological agents such as nintedanib and pirfenidone retard the progression of the disease to an extent but without any survival benefit. The only therapeutic option for IPF is lung transplantation with proven survival benefit. The major concern with lung transplantation is waiting time mortality. Lung allocation score was introduced in 2005 to reduce this mortality. Both single- and double-lung transplantations are used worldwide for IPF. Bilateral lung transplantation has been seen to have better survival rates in some studies, but there are no randomized trials which favor this recent trend. The posttransplant survival is lower than seen in other indications for lung transplantation. Posttransplant follow-up should be vigilant to detect complications as early as possible and treat them accordingly.

**Keywords:** Idiopathic pulmonary fibrosis, lung allocation score, lung transplantation, survival

## Introduction

Idiopathic pulmonary fibrosis (IPF) is a particular type of chronic, progressive fibrosing interstitial pneumonia of unknown origin. It is characterized by a usual interstitial pneumonia pattern on histopathology and/or radiology. In adults, it is the most common form of interstitial pneumonia.[1] The disease as of now is not curable, but in recent years, an increase in the efforts in the development of treatment is seen with the aim of delaying the progression of the disease. An official ATS/ERS/JRS/ALAT statement guidelines (2011)[1] did not recommend specific medical therapies for IPS, but in the subsequent revision of the same guidelines in 2015,[2] nintedanib and pirfenidone were given conditional recommendation for the treatment of IPF. These two molecules decrease the progression of the disease and stabilize lung function, but unfortunately fail to halt or reverse the lung damage.[3]

Lung transplantation is the only option that is seen to have survival advantage in IPF.[4] The mean numbers of years patients live after the diagnosis of IPF is 3 years, and 5-year survival rate is around 30%–35%.[5] Lung transplantation for the treatment of IPF showed 74%, 45%, and 22% survival rates at 1, 5, and 10 years, respectively, as on 2009.[6] The 5-year posttransplant survival rate has increased to 50% as reported in 2017.[7] Taking into account these data about survival rates, it is evident that lung transplantation in such patients is not without survival benefits.

Lung transplantation in humans started with the efforts of a vascular surgeon named Hardy.[8] He is credited with the first-ever human lung transplant in 1963 in a patient with advanced lung cancer and a lung abscess. The second lung transplant was done by George Magovern and Adolph Yates at Presbyterian-University Hospital in Pittsburgh.[9] Both these lung transplant patients died within a month, giving an overall set back to initial attempts. The first "successful" lung transplant was done by Derom *et al.* in 1971 in Belgium in

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**Address for correspondence:** Dr. Nazia Mehfooz, Department of Pulmonary Medicine, Sher-i-Kashmir Institute of Medical Sciences, Soura, Srinagar, Jammu and Kashmir, India.
E-mail: nazia_skims_rm@yahoo.com



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a patient who had end-stage silicosis. This patient survived for 10.5 months.[10] Dr. Joel Cooper and Toronto group in 1983 performed the first successful single-lung transplant for pulmonary fibrosis. Three years later, the same group did transplant in two patients of pulmonary fibrosis with satisfactory results.[11]

The United Network for Organ Sharing (UNOS) in 2005 introduced the lung allocation score (LAS) for the waiting list prioritization for lung transplantation.[12] The LAS takes into consideration the risk of mortality when waiting and the survival benefit after transplantation. With the introduction of LAS, a significant increase has taken place in the United States in the percentage from 33.8% to 46% of patients included on the waiting list with pulmonary fibrosis.[13] Over the years, IPF has become a prominent indication for lung transplantation in patients with end-stage lung disease and is gradually surpassing the other indications for lung transplantation.[14]

Since the first double lung transplant by Patterson *et al.* in 1988, there has been an increase in double-lung transplant.[15] In IPF, there has been an increase of 30% from 1998 to 2007 in the number of bilateral lung transplants.[6] Lung transplantation will be reviewed in this article in terms of pretransplant considerations, single versus double transplant, posttransplant survival rates, and medical complications after transplant.

## Pretransplant considerations

There are two clinical decisions which are to be taken into consideration in the treatment of IPF. The first one is to decide when and which patient is to be referred to a transplant unit and the second one is when to enroll patients on the transplant waiting list. Lung transplantation is not an easy process for either the patient or his/her family. Patients have to be informed about the procedure and its results. It is important to ensure that patients actively participate in the treatment process spanning over a period of time.[16] Selection of candidate is based on assessment of individual cases in terms of survival expectancy with and without transplant taking into consideration significant comorbidities and complications that may worsen the predicted result.

As a general rule, lung transplantation should be offered to the patients with IPF only when there is an expected increase in the posttransplant life expectancy over life expectancy without the transplant.[17] There should not be delay in the referral of pulmonary fibrosis patients to lung transplantation units. The International Society for Heart and Lung Transplantation (ISHLT) guidelines of 2006[18] recommend transplantation for patients with IPF if any of the following conditions are met: 10% or greater decrease in forced vital capacity (FVC) during 6 months of follow-up, Diffusing capacity of the lungs for carbon monoxide (DLCO) of <39% predicted, high-resolution computed tomography showing honey combing (fibrosis score of >2), or a decrease in oxygen saturation <88% during a 6-min walk test.[18]

A 2014 update from Pulmonary Transplantation Council of the ISHLT recommends that the following class of patients are eligible for transplantation in IPF: patients who have a high risk of death (>50%) in the following 2 years without transplantation, >80% chance of survival at least 90 days after the intervention, and high probability of surviving 5 years after the transplant (>80%) from any other medical condition.[19]

Center-to-center variations exist with regard to exclusion of candidates, but then there are some absolute contraindications for lung transplantation. Absolute contraindications for lung transplantation in IPF include recent malignancy, another vital organ dysfunction, extreme obesity, uncorrected coronary disease, and clinical instability. The other less absolute contraindications are[18] bleeding disorders, chest wall deformities, infection with multidrug resistant microorganisms or tuberculosis, severely altered functional status with inability to rehabilitate, severe psychiatric disorders, poor family and social support, nonadherence to treatment, and drug abuse in the past 6 months.[18]

Relative contraindications include age >65 years, unstable clinical condition such as irreversible shock or ventilator dependence, poor functional status with poor tendency for rehabilitation, and obesity as defined by body mass index (BMI) >30 kg/m$^2$.[18] In view of variable progression of the disease, clinicians encounter difficulty in deciding when to include a patient on the waiting list. All prognostic factors, potential deterioration when waiting for transplantation, and the expected delay should be taken into consideration.

The ISHLT 2014 consensus criteria for timing of listing are desaturation to <88% on 6-min walk test, decline in DLCO ≥15% over 6 months, decline in FVC ≥10% over 6 months, distance <250 m on 6-min walk test, decline in distance >50 m over 6 months, history of respiratory hospitalization, and pulmonary hypertension.[19]

In the initial era of lung transplantation, before 2005, priority for lung transplantation was given to the patient according to the time period he/she has been on the waiting list. This system had its inherent defects and there was a need to revise this method of priority for lung transplantation. The UNOS in 2005 revised this system and introduced the concept of LASs to prioritize organ allocation based on the projected survival advantage of transplantation.

LAS involves assessing the expected risk of death when waiting for lung transplantation (urgency) and the projected life expectancy after transplant (benefit).[20] The LAS is aimed to identify the best-suited candidates for transplant and to decrease waiting list mortality. LAS scores range from 0 to 100 and patients with higher scores indicate greater predicted survival benefit and get priority.[13]

The elements of the LAS calculation are as follows: [21] factors used to predict waiting list survival; FVC (% predicted); pulmonary artery systolic pressure; $O_2$ required at rest; age at offer; BMI; New York Heart Association (NYHA) functional

status; diagnosis; 6-min walk distance; continuous mechanical ventilation; diabetes; factors used to predict posttransplant survival; FVC (% predicted); mean pulmonary capillary wedge pressure; continuous mechanical ventilation; age at transplant; $PaCO_2$; serum creatinine, NYHA functional status, and diagnosis.[21]

Implementation of the LAS has resulted in an increase in the number of IPF patients receiving a lung transplant and has led to an increase in the percentage of patients with IPF and other restrictive diseases undergoing lung transplantation on the wait list from 33.8% to 46.1%.[13] Before the introduction of LAS, patients with IPF had waiting list mortality of 28%–47%.[22,23] With the introduction and adoption of the LAS, IPF mortality on the waiting list reduced significantly to as low as 11%. [24] This mortality is still significant even though the use of LAS represents significant improvement. LAS correlates strongly with 90-day and 1-year survival in patients with IPF. Increase in the LAS by 1 point correlates to a 2% increase in mortality at 1 year.[25]

There is no single variable which accurately predicts the survival of IPF patients and so, multidimensional models which predict success and survival have been developed. Three multidimensional models of prediction are composite physiological index (CPI); gender, age, and physiology (GAP); and risk stratification score (RISE). These models predict mortality in patients with IPF, but actual role in patients undergoing lung transplantation needs further validation. The CPI takes into account physiological variables and the existence of emphysema. GAP assesses Sex, Age, and Physiological variables such as Medical Research Council Dyspnea Score (MRCDS) and 6MWT.[16] The parameters assessed individually such as FVC% and DLCO are not good predictors of mortality as compared to GAP and RISE scales.[26] These IPF scales can prove useful in deciding when to refer a patient to a transplantation unit and when to include patient on the waiting list.

The GAP calculator classifies patients into three mortality risk stages:[27]

- Stage I: GAP score 0–3; estimated risk of mortality in the 1st year is low; 5.2%, lower than the mortality associated with transplantation
- Stage II: GAP score 4–5; estimated risk of mortality is 16.9%, similar to transplantation. In this stage, the decision to include on the waiting list must be individualized, taking into account the preferences of the patient and the waiting time estimation
- Stage III: GAP score 6–8; estimated risk of mortality is high; 41.7%, leaving no doubts regarding the benefit of transplantation.

After the patient is listed for lung transplantation and a LAS has been assigned, functional state assessment monitoring is regularly done. Complications should be promptly detected and managed. Oxygen supplementation needs to be assured and participation in pulmonary rehabilitation is also important. One must watch for signs of clinical deterioration such as increase in oxygen demand and development of pulmonary hypertension, and LAS should be duly updated.[28]

Acute exacerbation of IPF is often a worrisome event. High requirement of oxygen and need for ventilator support would elevate LAS scores significantly.[28] Esophageal dysmotility and gastroesophageal reflux disease (GERD) assessment should be done in patients with IPF. GERD is seen in patients with IPF with a prevalence of 50%–85%. GERD is an important factor due to its potential negative impact on lung transplant outcomes. Gastroesophageal reflux surgery before transplantation can be a preventive measure against chronic rejection.[29,30]

Abnormalities of BMI in lung transplant patients is an independent risk factor for mortality with values below 17 $kg/m^2$ increasing the mortality while on the waiting list,[16] while more than 25 $kg/m^2$ increases the cardiovascular risk and perioperative complications. BMI >30 $kg/m^2$ is an independent risk factor for early mortality.[31,32] Prior thoracic surgery predicts increased intraoperative blood loss and longer intensive care unit stay, but does not increase mortality.[22]

Catheterization of heart is routinely performed for elderly patients with IPF to diagnose concurrent coronary artery disease and to determine pulmonary vascular pressures.[20] Pulmonary hypertension is a risk factor for primary graft dysfunction (PGD) and also elevates the LAS.[33] Osteoporosis, a common old age problem, is also seen with advanced lung disease. It may increase the risk of fractures postoperatively which in turn impairs the quality of life after transplantation.[16]

Significance of length of telomere and its association with survival of patients with IPF has come into literature in 2015. Shorter life expectancy in IPF is seen to be associated with short telomere length.[34] Sporadic IPF and family-related cases have telomere shortening with mutations on telomerase RNA component and telomerase reverse transcriptase in 25% and 37% of cases, respectively.[35] Telomere shortening has been observed with worse survival in transplant cases.[36] With the current literature and available results of research on significance of length of telomere on survival, its pretransplant implications in IPF at present seems inadequate and warrants further investigation.

Other considerations in IPF patients waiting for transplant are extracorporeal membrane oxygenation (ECMO) and preoperative physiotherapy. ECMO is sometimes utilized as a bridge to lung transplantation and its use depends on the preference of transplant centers, especially in young patients.[37] Preoperative physiotherapy is useful for patients with decreased exercise tolerance. It significantly improves symptoms and physical activity levels in IPF patients.[38]

There is no evidence-based justification for the use of corticosteroids in IPF. There are concerns that chronic, high-dose corticosteroid use leads to increased risks of poor airway anastomotic healing after lung transplant, but at the

same time, improved surgical techniques over the past years give hardly any scope of dehiscence in such patients.[28]

The use of steroids is currently recommended in two situations: acute exacerbation and troublesome symptoms such as refractory coughing.[16] The role of antifibrotic drugs in patients waiting for lung transplant is not well established in literature and is purely based on case series. On the one hand, these drugs have been shown to provide some stabilization in disease allowing for more time on the lung transplant waiting list and improved condition of the patient preoperatively. On the other hand, potential concern has been raised as these drugs are seen to impair anastomotic healing and pose increased risk of dehiscence.[39] The safety of continuing antifibrotic therapy in the pretransplant window is not clear. Two recent articles by Delanote *et al*.[39] in 2016 and Leuschner *et. al*.[40] in 2017 do not support an increased risk of posttransplant complications in IPF patients treated with antifibrotics. Patients requiring preoperative ventilatory support are at higher risk of death at 1 and 5 years after transplant.[22]

## Type of Transplant

The choice of transplant, whether bilateral or unilateral, is still a matter of debate. As of now, the evidence from studies that compare the results of unilateral versus bilateral transplant to recommend the use of either of this procedure is poor and primitive for providing a definitive choice. Proponents of single lung transplant believe that there is scarcity of donors for lung transplant and two donor lungs can be used in two patients of IPF. They also believe that shorter time on the waiting list, fewer preoperative complications, simplicity of procedure, less cardiac manipulation and shorter ischaemic time makes it procedure of choice.[25,28] Proponents of bilateral transplant argue that it could provide the recipient with better compliance, better increase in lung volumes, and complete avoidance of native lung pathologic manifestations after the procedure.[17] As long as there are no clear evidence based proofs, the choice of transplant type will depend on institutional preferences taking into consideration presence or absence of pulmonary hypertension, age of patient, perfusion differences between two lungs, and any comorbid conditions.[25]

Unilateral transplantation has since decades been considered as the elective type of transplant in patients with pulmonary fibrosis.[17] As per ISHLT database, a clear preference to perform bilateral transplant has been seen in recent years from 1997 to 2011. In 2011, 53.5% of lung transplants among IPF patients reported to the ISHLT database were BLT and 46.5% were SLT.[13] There are no randomized trials to address this debate. Unadjusted analyses of data from individual centers and experiences of different authors do favor bilateral lung transplant in view of better long-term survival, but after adjustment for patient characteristics, the differences tend to disappear keeping this debate alive.[41]

## Posttransplant Survival

The survival of posttransplant patients in IPF is lower than with other medical conditions requiring lung transplant. The possible reason for low survival is chronic rejection. Their mortality is higher within 1 year, more so within the first 3 months after transplant. Early graft dysfunction and non-*Cytomegalovirus* (CMV) infections are the main causes of death seen during the 1st year after transplantation.[16] After transplantation, there is survival benefit and quality of life improves.[28] ISHLT registry data based on the records of 11,609 IPF patients transplanted from 1990 to 2014 show that the median posttransplant survival was 4.8 years. One-year and 5-year posttransplant survival were 77.2% and 48.5%, respectively.[42] Organ Procurement and Transplantation Network (OPTN) data analysis revealed that 1-year, 3-year, and 5-year survival ranged from 68% to 80%, 50% to 61%, and 32% to 49%, respectively.[13]

Age is considered one of the main factors influencing the survival in such patients. A recent ISHLT report showed that younger lung transplant recipients have better survival than older ones. One study showed that the median survival in patients younger than 50 years from the time of the initial visit was 100 months and it decreased to 27 months in patients in the age group of 60–70 years.[43]

## Posttransplant Medical Complications

Lung transplantation in IPF is not without complications. Early complications arise due to posttransplant immunosuppression and drug toxicity. Infections and acute rejection are the most frequent complications encountered during the 1st year.[44] About 30%–40% of recipients have at least one episode of rejection in the 1st year after transplant.[45] Bacterial infections are most common within the first 2 months. The most common organism is *Pseudomonas aeruginosa* followed by *Staphylococcus aureus*. Viral infections can occur during the 1st month. CMV is especially seen in them. Fungal infections are sometimes seen in the immediate postoperative period, but usually occur after the 1st month. Other infections that can occur during intermediate period are *Pneumocystis jiroveci* and tuberculosis.[16] Sepsis occurs in 15.2% of patients with IPF accounting for 60% of 6-month mortality, thus making it the most common cause of death.[46] From the ISHLT registry, graft failure and infection were the most common causes of death in IPF patients in the first 30 days after transplant and accounted for approximately 40% of deaths during this period.

Acute and chronic rejection can occur. ISHLT registry data based on 14,516 lung transplants between 2004 and 2015 revealed that 28% of all recipients were treated for acute rejection between hospital discharge and 1-year posttransplant[42] PGD is also a complication seen in posttransplant patients of IPF seen in the range of 10%–25%. PGD is associated with significantly worse short-term mortality. The probable mechanism of injury is ischemia–reperfusion insult.[47,48]

Complications after the 1st year are neoplasia and chronic lung allograft dysfunction (CLAD).[44] CLAD or chronic rejection is a significant problem seen in 12% of the patients in the 1st year and more than 50% after 5 years.[16] CLAD can manifest as the more common entity, bronchiolitis obliterans syndrome (BOS) or restrictive allograft syndrome (RAS). BOS is characterized by progressive decreases in airflow on spirometry with fibrotic lesions occurring at the level of bronchioles. RAS is characterized by restrictive pattern on spirometry with fibrotic lesions that occur at the periphery of the lung.[49,50] BOS is seen after lung transplantation with an incidence of 28% by 2.5 years and 74% by 10.0 years.[6]

Other complications in the native lung after single-lung transplants are development of mycetomas, pneumothorax, and bronchopleural fistula.[28] Malignancy accounts for a substantial percentage of deaths in patients surviving for long term. Malignant neoplasm has an incidence of 13% at 5 years and 28% at 10 years.[6] In patients where the native disease is associated with telomere shortening, an increased risk of cytopenias after lung transplant is seen.[36]

IPF patients show an increased incidence of both CAD and other vascular diseases including pulmonary embolism (PE). PE occurs in as many as 27% of lung transplant recipients with IPF.[51] As per International Society for Heart and Lung transplantation (IHSLT) registry, cardiovascular causes and multiple organ failure were responsible for 12.8 and 14.4% of deaths, respectively, during this period in IPF patients.[42] Airway complications can occur in about 9% of cases and the most common ones are stenosis, excessive granulation tissue, bronchomalacia, or dehiscence.[46] Other complications are hemodynamic instability (39.2%), renal failure (19.6%), muscle weakness (13.2%), bleeding (13.3%), and chances of reoperation (6.6%).[52]

## Conclusions

Lung transplantation is the only treatment option with actuarial survival benefit in selected group of patients with pulmonary fibrosis. After the introduction of LAS in 2005, IPF has become the most common and important indication for lung transplantation. Even after the inception of LAS, waiting list mortality has decreased, but it remains a matter of concern. Early referral of candidate to a transplant unit is encouraged due to the variable progression of the disease. Lung transplantation is a complex surgery predisposing the candidate to many complications. Therefore, it requires a thorough pretransplant assessment of candidates. There are a few factors that need special consideration before transplant as these can negatively affect the posttransplant survival such as coronary artery disease, gastro-esophageal reflux disease (GERD) and pulmonary hypertension. A recent trend has been seen favoring bilateral lung transplantation over single-lung transplantation for IPF patients although there are no randomized controlled trials to favor either. The choice depends on patients' characteristics and institutional preferences with special consideration given to waiting list and mortality. The posttransplant follow-up should be regular to achieve precise level of immunosuppressive treatment and early detection of complications. Infections and acute rejection are the most frequent complications in the 1st year of transplantation.

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## Conflicts of interest

There are no conflicts of interest.

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