

Patient characteristics and outcome of end-stage lung diseases referred for lung transplantation in North India

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ABSTRACT

Objective: Most countries worldwide have transplant registries for patients with end-stage lung diseases (ESLD) requiring lung transplantation. There is no such lung transplant registry in India. Herein, we describe the demographic profile and clinical outcomes among patients referred for lung transplantation at a tertiary care center in North India. **Materials and Methods:** This was a prospective, observational study of consecutive patients with chronic respiratory diseases who were referred for lung transplantation between July 2013 and December 2016. Patients were evaluated using standard criteria for listing for lung transplantation. **Results:** Of the 176 patients assessed for lung transplantation, 167 were included in the study. The mean (standard deviation [SD]) age of the study population (52.1% females) was 53.2 (14.7) years. Interstitial lung disease (ILD, 46.7%), chronic obstructive pulmonary disease (COPD, 25.7%), and bronchiectasis (10.2%) were the most common diseases in this population. The median (interquartile range, IQR) survival was worst for patients with bronchiolitis (78.5 [9–208] days) and idiopathic pulmonary fibrosis (IPF, 93.5 [19–239] days) and best for patients with idiopathic pulmonary arterial hypertension (757 [340–876] days) and COPD (578 [184–763] days). Only 13% of the patients expressed willingness for lung transplantation. Patients willing for transplantation died earlier than those unwilling (median [IQR], 102 [36–224] days vs. 310 [41–713] days, $P < 0.001$). **Conclusion:** ILD was the most common cause of ESLD in patients referred for lung transplantation. The waitlist mortality was highest for patients with bronchiolitis and IPF. Despite having ESLD, very few patients were willing for lung transplantation. Patients willing for lung transplantation died earlier than those who were unwilling.

KEY WORDS: Chronic obstructive pulmonary disease, cor pulmonale, end-stage lung disease, interstitial lung disease, lung transplantation

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INTRODUCTION

Chronic respiratory diseases are the third leading cause of death both worldwide and in India.^[1,2] Lung transplantation remains the final frontier for end-stage lung diseases (ESLD) which are not adequately controlled despite best medical therapies.^[3] Most countries with active lung transplantation programs have their own lung transplant registries.^[4–7] However, India does not

have a centralized transplant registry for lung transplant despite having a significant burden of respiratory diseases. Although an Indian Transplant Registry was established in 2005 through the efforts of the Indian Society of Organ Transplantation, it is still in its first phase of development and currently captures only data related to kidney and liver transplants.^[8] Hence, the details of patients eligible

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for lung transplantation remains largely unknown in India. In this study, we describe the spectrum of patients with ESLD referred for lung transplantation and their outcomes.

MATERIALS AND METHODS

This was a prospective study conducted in the Department of Pulmonary Medicine at the Postgraduate Institute of Medical Education and Research, Chandigarh, India, between July 2013 and December 2016. Consecutive patients attending the chest clinic who were referred for lung transplantation were enrolled in the current study. The study protocol was approved by the Institute Ethics Committee and a written informed consent was obtained from all the study participants.

Inclusion and exclusion criteria

Consecutive patients with ESLD meeting the criteria for lung transplantation listing were included in the study. Patients were evaluated using the existing International Society for Heart and Lung Transplantation (ISHLT) criteria for listing for lung transplantation at the time of evaluation.^[9,9] However, during the analysis, to ensure uniformity, we applied the latest version of the ISHLT criteria (2014 update) to all the study subjects.^[9] In our practice, a large number of patients cannot perform spirometry or 6-min walk test (6MWT). In these patients, the ISHLT criteria cannot be applied; however, they were considered for listing if they had New York Heart Association (NYHA) Class III/IV symptoms despite maximal available therapy and/or pulmonary hypertension. Patients were excluded if they had pulmonary hypertension secondary to congenital or acquired cardiac defects, pregnancy, or if they failed to give consent.

Clinical assessment

The demographic and clinical details of all the patients were recorded. Functional status of the patients was assessed using the NYHA class.^[10] Resting arterial oxygen saturation was measured using pulse oximetry. Arterial blood gas analysis was done when clinically indicated. Pulmonary function tests were performed using a dry rolling seal spirometer (Spiroflow; PK Morgan Ltd.; Kent, UK) to determine the lung function measurements, as previously described.^[11] 6MWT was performed as per the standards set by the American Thoracic Society (ATS).^[12,13] A 12-lead electrocardiogram and echocardiography were performed in all the study participants. Pulmonary hypertension was considered to be present if consistent features were observed in electrocardiogram, echocardiogram, contrast-enhanced computed tomography (CT) thorax, and/or right heart catheterization.^[14]

Diagnosis of chronic lung disease

Diagnosis of diffuse parenchymal lung disease was made according to the ATS-European Respiratory Society (ERS) criteria by a multidisciplinary team comprising of pulmonologists, a radiologist, and a pathologist.^[15] The

diagnosis of chronic obstructive pulmonary disease (COPD) was made based on the presence of risk factors and demonstration of obstruction on spirometry.^[16] The diagnosis of posttuberculosis (TB) sequelae was made based on the presence of a prior history of TB and consistent radiological features (fibrosis, cavitation, and volume loss) after ruling out active TB and other differential diagnoses.^[17] The diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH) was made based on consistent radiological features on CT pulmonary angiography and evidence of pulmonary hypertension.^[18] A diagnosis of bronchiectasis was made based on the high-resolution CT findings.^[19]

Statistical analysis

Continuous variables were expressed as mean \pm standard deviation (SD) and categorical values were expressed as numbers and percentages. The time to death after listing for lung transplantation was analyzed using Kaplan–Meier survival analysis. Statistical analyses were performed using the commercial statistical package SPSS (IBM SPSS Statistics, version 22; IBM Corporation, Armonk, NY, USA). $P < 0.05$ was considered statistically significant.

RESULTS

Over a period of 42 months, a total of 176 patients were referred for lung transplantation. Of these patients, nine were excluded (alternative diagnoses [$n = 4$], not ESLD [$n = 4$], Eisenmenger's syndrome [$n = 1$]). The remaining 167 patients were considered to have ESLD and were included in the final analysis [Table 1]. The mean (SD) age of the study population (52.1% women) was 53.2 (14.7) years. Resting hypoxemia was observed in 57.5% of participants. Features of pulmonary hypertension

Table 1: Patient characteristics (n=167)

Characteristic	Value
Age in years, mean (SD)	53.2 (14.7)
Female gender	87 (52.1)
Resting hypoxemia	96 (57.5)
Pulmonary hypertension	92 (55.1)
Diagnosis	
ILD	78 (46.7)
NSIP	50 (29.9)
IPF	28 (16.7)
COPD	43 (25.7)
Bronchiectasis	17 (10.2)
Hypersensitivity pneumonitis	6 (3.6)
Sarcoidosis	7 (4.2)
Bronchiolitis	4 (2.4)
Idiopathic PAH	4 (2.4)
CTEPH	2 (1.2)
Others*	6 (3.6)

*Other lung diseases included the following: Bullous lung disease ($n=1$), lymphocytic interstitial pneumonia ($n=1$), remodeled asthma ($n=1$), posttuberculous destroyed lung ($n=3$). All values are represented as n (%) unless otherwise stated. COPD: Chronic obstructive pulmonary disease, CTEPH: Chronic thromboembolic pulmonary hypertension, ILD: Interstitial lung disease, IPF: Idiopathic pulmonary fibrosis, NSIP: Nonspecific interstitial pneumonia, PAH: Pulmonary arterial hypertension, SD: Standard deviation

were found in 55.1% of the participants. The most common disease categories were interstitial lung disease (ILD), COPD, and bronchiectasis. Among the patients with ILD, 35.9% had idiopathic pulmonary fibrosis (IPF) while a majority (64.1%) of subjects had a fibrotic form of idiopathic nonspecific interstitial pneumonia (NSIP).

Nearly one-third of the population (55 subjects, 32.9%), would not have been listed based on the ISHLT 2014 criteria [Table 2]. The reasons for this were inability to perform spirometry, inability to perform 6MWT, and lack of disease-specific criteria in the ISHLT guidelines. The following diseases lacked specific listing criteria: bronchiolitis, CTEPH, hypersensitivity pneumonitis, lymphocytic interstitial pneumonia, post-TB destroyed lung, remodeled asthma, and sarcoidosis.

The median overall survival (interquartile range [IQR]) was 231 (39–694) days [Table 3]. Amongst the individual diseases, bronchiolitis had the worst median (IQR) survival (78.5 [9.3–207.8] days) followed by IPF (93.5 [18.8–239] days) and bronchiectasis (117 [10–662] days), while idiopathic pulmonary arterial hypertension had the best survival (757 [339.5–875.3] days) followed by COPD (578 [184–763] days) and CTEPH (350 days).

Only 21 (12.6%) patients were willing to undergo transplantation. Of them, only three were alive at

the end of the study. The median (IQR) survival was significantly shorter for those who were willing to undergo transplantation compared to those who were unwilling (102 [35.5–224] days vs. 310 [40.8–712.8] days, $P < 0.001$).

Case studies

A 39-year-old female was diagnosed with ILD (NSIP) 8 years ago. Her disease initially responded partially to immunosuppressive therapy; however, it had progressed over the last few years. She was on supplemental oxygen for the last 1 year. She also developed cor pulmonale and features of congestive heart failure requiring diuretic therapy. She was then referred for lung transplantation. At referral, she was unable to perform spirometry due to the advanced nature of her disease. She was willing to undergo lung transplantation; however, it could not be performed in a timely manner, and she expired 10 months after the transplant referral.

A 58-year-old male was symptomatic for 3 years with dry cough and dyspnea following which he was diagnosed with IPF. He was started on oral pirfenidone. However, his disease continued to progress despite therapy, and he developed resting hypoxemia requiring long-term oxygen therapy (LTOT). Subsequently, he developed severe pulmonary artery hypertension. He was referred for lung transplantation. Although he was initially keen to undergo lung transplantation, his interest quickly waned. He felt that the outcomes for lung transplantation surgery were poor. Moreover, he was not convinced of the expertise of the institute as its lung transplant program was in its infancy. The patient expired 10 months after the transplant referral.

A 63-year-old male was suffering from COPD for the last 15 years. His symptoms had worsened over the last 2 years, and he had multiple exacerbations requiring hospitalization. For the past 1 year, he was using LTOT. Despite LTOT, he developed cor pulmonale. He was referred for lung transplantation. However, the patient considered the procedure to be “too risky.” Moreover, he

Table 2: Reasons for inability to list patients for lung transplantation using the International Society for Heart and Lung Transplantation criteria (n=55)*

Reason	n (%)
Inability to perform spirometry	29 (52.7)
Inability to perform 6MWT	29 (52.7)
Lack of disease-specific criteria	24 (43.6) [#]

*Numbers may not add up to total as one patient may have had multiple reasons; [#]These included sarcoidosis (n=7), hypersensitivity pneumonitis (n=6), bronchiolitis (n=4), posttuberculous destroyed lung (n=3), chronic thromboembolic pulmonary hypertension (n=2), lymphocytic interstitial pneumonia (n=1), and remodeled asthma (n=1). 6MWT: 6-min walk test

Table 3: Patient outcomes

	Total cases, n	Alive, n (%)	Deaths, n (%)	Lost to follow-up, n (%)	Survival in days, median (IQR)
ILD	78	19 (24.4)	49 (62.8)	10 (12.8)	130 (31.5–456.8)
NSIP	50	14 (28)	31 (62)	5 (10)	249 (40.3–700)
IPF	28	5 (17.9)	18 (64.3)	5 (17.9)	93.5 (18.8–239)
COPD	43	14 (32.6)	22 (51.2)	7 (16.2)	578 (184–763)
Bronchiectasis	17	8 (47.1)	6 (35.3)	3 (17.6)	117 (10–662)
Hypersensitivity pneumonitis	6	3 (50)	2 (33.3)	1 (16.7)	262.5 (21.5–733.8)
Sarcoidosis	7	2 (28.6)	2 (28.6)	3 (42.9)	327 (78–836)
Bronchiolitis	4	1 (25)	1 (25)	2 (50)	78.5 (9.3–207.8)
Idiopathic PAH	4	2 (50)	1 (25)	1 (25)	757 (339.5–875.3)
CTEPH	2	1 (50)	0 (0)	1 (50)	350
Others*	6	3 (50)	2 (33.3)	1 (16.7)	38 (0.8–383.5)
Total	167	53 (31.7)	85 (50.9)	29 (17.4)	231 (39–694)

*Other lung diseases included the following: Bullous lung disease (n=1), lymphocytic interstitial pneumonia (n=1), remodeled asthma (n=1), posttuberculous destroyed lung (n=3). COPD: Chronic obstructive pulmonary disease, CTEPH: Chronic thromboembolic pulmonary hypertension, ILD: Interstitial lung disease, IPF: Idiopathic pulmonary fibrosis, IQR: Interquartile range, NSIP: Nonspecific interstitial pneumonia, PAH: Pulmonary arterial hypertension

lacked health insurance and was unwilling to spend money as the outcome was “uncertain.” He expired 14 months after the transplant referral.

DISCUSSION

In the current study, ILD and COPD were the most common causes of ESLD. Most of the patients were referred late and had a median survival of only 231 days after transplant referral. Surprisingly, only 13% of these patients were willing to undergo lung transplantation.

In our study, the most common disease among the lung transplant eligible candidates was ILD, followed by COPD and bronchiectasis. COPD has been the most common indication for lung transplantation globally, followed by ILD.^[5,20] However, in the United States, this trend has recently changed, and ILD has now become the most common indication for lung transplantation.^[21] Although the prevalence of COPD in India is higher than ILD, the higher number of participants with ILD in our study could be due a referral bias.^[22] Another reason for this is that the mortality in advanced COPD is much less compared to ILD.^[23] A similar observation has been made in another study, where COPD constituted only 12% of the patients listed for transplantation.^[24]

Another interesting observation in our study was that NSIP was more common than IPF for transplant enlisting. This is in contrast to other centers where IPF is the most common type of ILD requiring lung transplantation.^[25] It is possible that NSIP patients with a relatively longer survival are referred for transplantation while IPF patients with a comparatively shorter survival die before or during the process of referral. This is supported by the fact that the median survival was < 100 days in our study participants with IPF. In comparison, other studies have shown survival in IPF ranging from 8 to 12 months while on waitlist.^[26,27] Thus, it is imperative to sensitize both the treating physicians and patients for lung transplantation so that a timely referral is made early during the illness.

Nearly one-third of our population could not be listed for lung transplantation using existing criteria for lung transplantation. Patients with advanced ILD may be unable to perform spirometry and hence may not be listed using these criteria. This was reflected in our study population who presented late in their course of the disease. In fact, more than half of our study population was oxygen-dependent and were symptomatic at rest. Hence, many of these patients had difficulty in performing physically demanding investigations such as spirometry and 6MWT. The ISHLT also does not have specific recommendations for many conditions including hypersensitivity pneumonitis, post-TB sequelae, sarcoidosis, bronchiolitis, and others. Sarcoidosis and post-TB sequelae are important causes for chronic lung diseases in India.^[28]

Only 13% of the patients screened showed willingness to undergo lung transplantation. As highlighted by the case studies, there could be several reasons for this. In a developing country like India, financial issues are crucial reasons for foregoing a lung transplant. This is further compounded by the expenses for prolonged immunosuppression and management of infections in the posttransplant period. The outcome of lung transplantation is not as good as other organ transplants such as heart, liver, or kidney. While these organs have a median survival of around 10 years after transplantation, the median survival after lung transplantation is only 5 years.^[29] Cultural differences and perceptions regarding life could have also influenced decisions of the patients and their family regarding lung transplantation.

Our study is not without limitations. Ours is a tertiary care center, and the burden of ESLD may not be a true representation of the burden of ESLD at other centers in India. We could perform only one lung transplantation after 4 years into the program due to the slow pace of infrastructure development. The patient died 2 weeks after surgery due to hospital-acquired pneumonia and sepsis.

CONCLUSION

ILD was the most common chronic pulmonary condition for which transplant referral was done. Patients with ESLD were referred for lung transplantation very late during their disease, causing marked difficulty in assessment for transplantation. Despite their poor condition, most of the participants in our study were unwilling to undergo lung transplantation.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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