Original Article

Challenges, experiences, and postoperative outcomes in setting up first successful lung transplant unit in India

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ABSTRACT

Background: Lung transplantation (LT) has emerged as a definitive cure for a plethora of end-stage lung diseases (ESLDs). With improvements in immune-suppression protocols, the posttransplantation survival rates have gone up. **Aim:** The study reported the initial experience of the India's single largest lung transplant program on clinicopathological profile, procedures, challenges encountered, and outcomes. **Settings and Design**: A retrospective analysis was done from data available at three centers of Institute of Heart and Lung Transplant, Gleneagles Global Hospitals across Chennai, Bengaluru, and Mumbai. **Materials and Methods:** A total of 132 patients underwent lung (single or bilateral) or combined heart and lung transplant between April 2017 and March 2020. All the participants had 30 days' follow-up. Postoperative complications, graft rejection, and 30-day mortality were reported. Kaplan–Meier survival analysis and logistic regression analysis were performed. **Statistical Analysis Used:** Kaplan–Meier survival and binary logistic regression was performed. **Results:** Interstitial lung diseases, 65.91%, were the most common diagnosis. Bilateral LT (81.3%) was the most common type of LT performed. Grade III primary graft dysfunction was observed in 16 (12.1%). Distal airway stenosis (21.97%) was the most common complication followed by anastomotic stenosis (14.30%). Gram-negative bacterial sepsis (52%) was the leading cause of death. Cumulative probability of survival at 1 month was 0.85 (95% confidence interval [CI] 0.80–0.92), and at 1 year, it was 0.78 (95% CI, 0.72–0.86). **Conclusion**: This study establishes the fact that despite multiple challenges, LT is a viable option for selected patients with ESLDs in India and should encourage early referrals to a transplant center.

KEY WORDS: Extracorporeal membrane oxygenation, heart transplantation, lung transplantation, mortality

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INTRODUCTION

Lung transplantation (LT) has emerged as a definitive treatment option for a plethora of end-stage lung diseases (ESLDs), including chronic obstructive pulmonary disease (COPD), interstitial lung diseases (ILDs), cystic fibrosis (CF), non-CF bronchiectasis, and pulmonary hypertension.[1] Since the first double LT by James D Hardy in the year 1963,[2] many other centers across the globe have reported successful single, double lung, and heart-LTs.[3,4]

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Rapid progress had been made from the initial period of uncertainties in technique, high allograft rejection rates, ischemic donor airway dysfunction, high opportunistic infection rates, and lower survival rates.[5,6] Although still evolving, standard operating procedures have been established for various technical aspects.[7] With improvements in immune-suppression protocols, the acute allograft rejection rates have come down, and the posttransplantation survival rates have gone up.[8,9]

A recent report by the International Society for Heart and LT (ISHLT), over 50,000 LTs were done from 1995 to June 2015. COPD with and without alpha1 antitrypsin deficiency accounted for 36.5%, ILD (including idiopathic pulmonary fibrosis) for 29.7%, CF for 15.8% cases.[10] In India, the first single LT (SLT) was performed at Global Hospital, Chennai, in 2012.[11] Since then, several centers across India have performed LT and are in the process of establishing a lung transplant program. Until date, no scientific study is available reporting the experience and outcomes of LT from India. The present research apart from reporting the profile of LT performed in our center, also shares experience, outcomes, and challenges encountered in setting up and successfully running a LT program in India.

MATERIALS AND METHODS

The current study is a retrospective analysis of patients who underwent lung transplant (single or bilateral) or combined heart and lung transplant at the Institute of Heart and Lung Transplant, Gleneagles Global Hospitals across Chennai, Bengaluru, and Mumbai between April 2017 and March 2020. All the study participants had completed 30 days of follow-up period by the time of reporting.

Recipient selection

Recipient selection was made as per lung transplant referral and listing criteria for various diseases enumerated in the ISHLT 2014 guideline.[12] Postreferral, each potential recipient underwent comprehensive transplant evaluation to assess the cardio-respiratory-metabolic parameters by the multidisciplinary transplant team and decision was made regarding the type of transplant (single lung, bilateral lung, or combined heart-lung).[13]

Lung procurement protocol

In accordance with the National Organ Transplant Act in India, for a thoracic organ transplant, only brain-dead patient's organs were accepted for transplantation.[14] Postretrieval, the lung was preserved in Perfadex solution (70 ml/kg body weight anterograde perfusion and 250 ml in each pulmonary vein for retrograde perfusion). The organ was packed in the same perfusate in a protective triple bag and appropriate temperature conditions a (4°C) were maintained until it reached the operating room.[15]

Surgical technique for implantation

SLT was done through anterolateral or posterolateral thoracotomy incision. Bilateral LT (BLT) was done sequentially through bilateral anterolateral thoracotomy or clamshell incision. The heart-lung transplants were done using routine median sternotomy. Before closing the chest, a bronchoscopic evaluation was done to check the anastomotic sites and look for any evidence of airway bleed, clots, or copious secretion suggesting primary graft dysfunction (PGD).[16]

Infectious prophylaxis

All recipients received broad-spectrum anti-infective prophylaxis to cover Gram-positive, Gram-negative bacteria, fungi, and virus. All recipients were initiated on lifetime prophylaxis for Pneumocystis carinii, and long-term for cytomegalovirus and fungal infections. Recipients with a history of TB, especially with positive interferon gamma release assay were given INH prophylaxis as well.[17]

Immunosuppression protocol

Standard induction protocol was followed with basiliximab before transplantation, and intraoperative methylprednisolone 250 mg was administered just before repercussion of each implanted lung. Mycophenolate sodium was added from 2nd postoperative day, followed by tacrolimus if the renal function was normal. Any clinical suspicion of rejection was treated in accordance with the ISHLT guidelines.[7]

Long-term follow-up

Postdischarge, each patient was monitored closely on a daily basis through a smart phone-based application which directly integrates to hospital EMR, and it routinely schedules visits to the transplant center.

Statistics

Data were expressed as mean ± standard deviation or median (range) for continuous variables and as numerical values and percentages for categorical variables. Kaplan–Meier survival analysis was performed for 30-day mortality. Binary logistic regression was performed to assess the association between various demographic, clinical, transplant-related variables, and mortality. The $P < 0.05$ was considered statistically significant. Statistical analysis was performed using Rstudio and coGuide Statistics software, Version 1.0, BDSS corporation. Bangaluru, India.[18]

RESULTS

The final analysis included data of 132 recipients.

The age range of participants was 16–71 years with a mean of 48.60 ± 13.45, with a male-female ratio of 1.24:1. ILD constituted the most common diagnosis among 87 (65.91%) people, followed by bronchiectasis in 13 (9.85%) and PPH in 9 (6.82%) people. Chronic hypersensitivity pneumonitis

and idiopathic pulmonary fibrosis were the common ILDs. Eight (6.06%) participants needed preoperative mechanical ventilation, 14 (10.61%) needed preoperative extracorporeal membrane oxygenation (ECMO) as a bridge to transplant [Table 1].

BLT was the most common type of LT performed in 102 (77.3%), among which 4 (3%) participants needed additional coronary artery bypass grafting (CABG). Intraoperative ECMO was utilized in 19 (14.4%), 57 (43.2%) utilized intraoperative CPB (On pump), rest were done off-pump. The mean days on ventilator was 7.13 ± 8.43 days, mean ICU stay was 15.76 ± 11.66 days, and the mean duration of hospital stay was 28.61 ± 22.35 days. Postoperative renal support was needed for 37 (28%) recipients [Table 2].

Grade III PGD was observed in 16 (12.1%) people. Airway complications were the most common complications, contributed primarily by distal airway stenosis (29, 21.97%) and anastomotic stenosis in 19 (14.30%). Bacteremia and fungal airway infection was seen in 14 (10.61%) and 10 (9.09%) recipients, respectively. Among rejection, the acute cellular rejection was the most common type of rejection seen in 34 (25.76%) people, 3 (2.27%) each had antibody-mediated and RAS (chronic rejection) each. Only one recipient had a hyperacute rejection [Table 3].

At 1 month, Sepsis was the most common cause of death in 12 (63.15%) people followed by severe PGD 3 (15.79%), AMR hyperacute rejection hyper ammonia, unrelated gastrointestinal (GI) bleed with 1 (5.26%) each, respectively. At 1 year, Gram-negative bacterial sepsis was the most common cause of death in 13 (52%) people and three participants each (12%) died due to severe PGD and GI bleed. Fungal sepsis, hyperacute rejection, stroke, AMR, intracranial bleed/hyper ammonia, TB, and hyper ammonia were seen in one 1 (4%) subject each [Table 4].

The odds of 30-day mortality was 3.846 times more in ECMO patients compared to off-pump (95% confidence interval [CI] 1.063–13.91, $P = 0.04$). Most of these patients were on preoperative ECMO as a bridge to transplant as presented in Table 5. Kaplan–Meier survival plotting showed cumulative probability of survival at 1 month was 0.856 (95% CI 0.80–0.92) and 1 year it was 0. 788 (95% CI, 0.72–0.86) [Figure 1].

DISCUSSION

This article represents the initial challenges and experience of patients who underwent thoracic transplantation during 3 years in India's single largest lung transplant program. The critical challenges in the current setting are the lack of standard donor management protocol and late referral of the patients, mainly at the verge of requiring mechanical ventilation or ECMO. In our study, we have used an aggressive donor management protocol to optimize donor to improve donor functions.

In the current study, the mean age of the participants was 48.60 ± 13.45, ranging between 16 and 71. Males were 73 (55.30%), and females were 59 (44.70%) among the study population. Our study was in accordance with many studies in literature where the age ranged between

Table 1: Summary of demographic and anthropometric parameters (*n*=132)

Demographic and anthropometric parameters	Summary
Age (mean±SD)	48.60±13.45 (range 16-71)
Gender, *n* (%)	
Male	73 (55.30)
Female	59 (44.70)
Height	162.48±9.14 (range 142-191)
Weight	62.04±12.56 (range 38-96)
BMI	23.49±4.36 (range 14.1-37)
Nationality, *n* (%)	
Indian	104 (78.79)
International	28 (21.21)
Presenting diagnosis, *n* (%)	
ILD	87 (65.91)
Bronchiectasis	13 (9.85)
PPH	9 (6.82)
CHD	6 (4.55)
COPD	7 (5.30)
Cystic fibrosis	3 (2.27)
Others	7 (5.30)
ILD (*n*=87), *n* (%)	
Chronic hypersensitivity pneumonitis	26 (29.88)
Idiopathic pulmonary fibrosis	21 (24.13)
Nonspecific interstitial pneumonia	17 (19.54)
Connective tissue disorder	15 (17.24)
Sarcoidosis	8 (9.19)
Preoperative mechanical ventilation	8 (6.06)
Preoperative extracorporeal membrane oxygenation (ECMO)	14 (10.61)
Preoperative duration of rehabilitation (months), mean±SD	4.5±4.27 (range 0.13-24.00)

BMI: Body mass index, ILD: Interstitial lung diseases, SD: Standard deviation, PPH: Primary pulmonary hypertension, CHD: Congenital heart disease, COPD: Chronic obstructive pulmonary disease

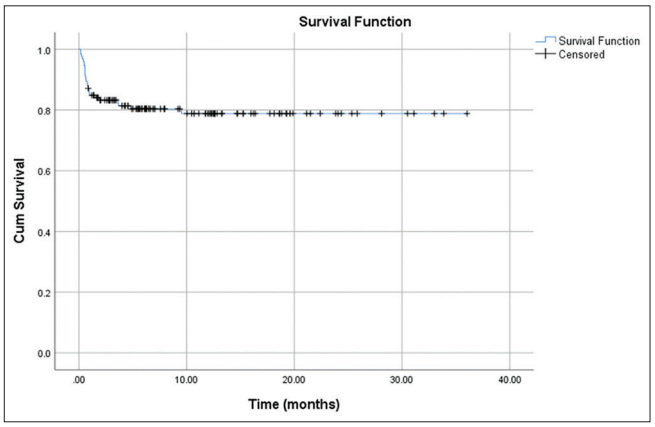

Figure 1: Kaplan-Meier survival analysis depicting cumulative survival

Table 2: Summary of the type of transplantation and intraoperative and postoperative findings (*n*=132)

Surgical data	Summary
Transplant type, *n* (%)	
Bilateral lung transplant	102 (77.3)
Bilateral lung transplant, CABG	4 (3)
Heart and lung transplant	19 (14.39)
Single lung transplant	7 (5.30)
Intraoperative ECMO	19 (14.4)
Intraoperative CPB (ON pump)	57 (43.2)
Intraoperative CPB time (h) (*n*=55)	4.17±1.36 (range 1.32-7.50)
Intraoperative ECMO time (h) (*n*=19)	4.5±0.96 (range 3.25-6.38)
Ischemia time (h) (*n*=117)	6.51±1.45 (range 2.45-11.63)
Off-pump, *n* (%)	56 (42.4)
Incision type, *n* (%)	
Clamshell	104 (78.8)
Median sternotomy	19 (14.4)
Anterolateral sternal sparing	9 (6.8)
Postoperative ECMO, *n* (%)	14 (10.61)
Tracheostomy, *n* (%)	34 (25.76)
Days on ventilator (mean±SD)	7.13±8.43 (range 1-46)
Days in ICU (mean±SD)	15.76±11.66 (rang 5-60)
Days in hospital (mean±SD)	28.61±22.35 (range 5-163)
Postoperative renal support, *n* (%)	37 (28.0)

CABG: Coronary artery bypass grafting, ECMO: Extracorporeal membrane oxygenation, ICU: Intensive care unit, SD: Standard deviation, CPB: Cardiopulmonary bypass

Table 3: Descriptive analysis of postoperative complications in the study population (*n*=132)

Postoperative complications	*n* (%)
PGD Grade 3	16 (12.1)
Hyper ammonia	3 (2.27)
Airway complications	
Distal airway stenosis	29 (21.97)
Anastomotic stenosis	19 (14.39)
Bronchomalacia	10 (7.58)
Dehiscence	7 (5.30)
Vanishing bronchus syndrome	3 (2.27)
Infective complications	
GNB	14 (10.61)
Fungal airway infection	12 (9.09)
Mycobacterium TB	6 (4.55)
Virus	4 (3.03)
Non-TB mycobacterium	3 (2.27)
Rejection	
Antibody-mediated rejection	3 (2.27)
RAS (chronic rejection)	3 (2.27)
Acute cellular rejection	34 (25.76)
A1	19 (55.88)
A2	10 (29.41)
A3	4 (11.76)
Hyper acute rejection	1 (2.94)

PGD: Primary graft dysfunction, GNB: Gram-negative bacteremia, TB: Tuberculosis, RAS: Restrictive allograft syndrome

minimum of 16 to maximum of 75 years. The reason for wide range of ages being nature of the disease. Transplants were indicated early in age for disease such as pulmonary arterial hypertension and bronchiectasis whereas diseases such as COPD, ILD are end-stage diseases effecting later in life.[19-21]

Our LT study highlights few unique differences from the data published in worldwide medical literature and the ISHLT registry. Globally, the most common indications for LT include COPD (>40%), pulmonary fibrosis (25%), and CF (16%).[8] Similarly, Meyer *et al*. reported COPD as the most frequent indication for LT.[16] However, LT s performed in India, ILD (65.91%) is the most common indication followed by bronchiectasis (9.85%), primary pulmonary hypertension (6.82%), and COPD (5.30%). The difference is due to younger population and effective treatment options available for COPD compared to ILD in India.

Majority (77.3%) of participants had BLT , 14.39% had heart and LT, and 5.30% had SLT , and 3% had double LT with CABG indicating CAD patients also benefit from LT. Similar results were reported by Balsara *et al*.[21] who observed 86.4% had double LT, 13.6% SLT in their study. In a systematic review done by Hu *et al*., BLT had better long-term survival rate (5 years), better postoperative lung function and less bronchiolitis obliterans syndrome compared to SLT. SLT is preferred for elderly patients >70 years with DPLD.[22]

Intraoperatively, the average time needed for the CBP was 4.17 ± 1.36 h and 4.5 ± 0.96 h was required ECMO, to support oxygenation or to stabilize hemodynamic, which was successfully removed at the end of surgery. The odds of 1-month mortality was 3.846 times in intraoperative ECMO patients compared to off pump (95% CI 1.063–13.91, P = 0.04) and was statistically significant. This includes 14 patients who were placed on ECMO preoperative as a bridge to transplant. Similarly, Toyoda *et al*. reported the cardiopulmonary bypass time was longer in the pretransplant ECMO group (277 ± 69 min vs. 225 ± 89 min, P =0.02), with no difference in ischemic time.[23] As a program, all our initial cases were done on CBP support, but later on moved on to off-pump method which is currently preferred as it provides a smoother postoperative course. It offers advantage of faster recovery due to less vasoplegia and reduces the incidence of postoperative multiorgan dysfunction and infections.

Complications reported in the current study were distal airway stenosis (21.97%), bacteremia 10.61%, antibody-mediated rejection (25.76%), PGD grade 3 (12.1%), and RAS chronic rejection (2.27%). Our high rate of airway complications reflect the quality of donors which are mostly extended criteria donors; many are hemodynamically unstable on multiple inotropes before transplant and are already colonized by Multi-Drug-Resistant (MDR) pathogens. In India, we also have high incidence of posttransplant infections, especially with Gram-negative organisms. MDR Acinetobacter, carbapenemase-producing Klebsiella, and MDR pseudomonas and fungal airway colonization with *Aspergillus* have also been a problem posttransplant. To counter this, we have used IV, nebulized antibiotics and antifungals during the postoperative phase. Our immunosuppressant dosages are also much less compared to the western subjects as the infection is a greater problem than a rejection for our patients. To tailor

immunosuppression, we performed protocol surveillance biopsies to look for rejection and did infection surveillance in BAL for viruses, bacterial infections, and aggressively treat them.[11]

Alvarez *et al*. in his study, reported airway stenoses are a continuing problem in lung transplant recipients and reported an incidence of perianastomotic stenosis up to 40% and non-anastomotic distal bronchial stenosis up to 4% in patients after LT.[24] Granton *et al*. suggested that PGD after LT, formerly referred to as reimplantation response, is widely perceived to be a consequence of ischemia-reperfusion injury.[25] Whitson *et al*. have identified donor age and donor smoking history, lung preservation solutions as a relative shortage of donor's lungs have led to the use of donation after cardiac death (DCD), as well as *ex vivo* perfusion and reconditioning of marginal lungs significant risk factors for the development of PGD.[26] PGD is a syndrome of acute lung injury that occurs within the first 72 h after LT. PGD is characterized by pulmonary edema with diffuse alveolar damage that clinically manifests itself as progressive hypoxemia and radiographic pulmonary infiltrates without other identifiable causes.

Table 4: Summary of mortality and its causes in the study population (*n*=132)

Mortality	Frequency, *n* (%)
Causes of mortality (30 days) (*n*=19)	
Sepsis	12 (63.15)
Severe PGD	3 (15.79)
AMR	1 (5.26)
Hyper acute rejection	1 (5.26)
Hyper ammonia	1 (5.26)
Unrelated GI bleed	1 (5.26)
Causes of mortality (1 year) (*n*=26)	
GNB sepsis	13 (52)
Severe PGD	3 (12)
GI bleed	3 (12)
Fungal sepsis	1 (4)
Tuberculosis	1 (4)
Hyperacute rejection	1 (4)
Stroke	1 (4)
AMR	1 (4)
Intracranial bleed/hyper ammonia	1 (4)
Hyper ammonia	1 (4)

AMR: Antibody-mediated rejection, GNB: Gram-negative bacteremia, PGD: Primary graft dysfunction, GI: Gastrointestinal

In India, donor management protocol varies from hospital to hospital. Liberal use of IV fluids resulted in fluid overload, lung congestion, fall in PF ratios combined with heavy infection burden ultimately made lungs nonusable for transplant. This can be countered by maintaining adequate intravascular volume guided by CVP and judiciously using the vasopressors, inotropes helps maintaining adequate mean arterial pressure ensuring maximum utilization of all organs including heart and lung.

To improve survival after LT, in-depth knowledge of the various factors such as pre-transplantation patient characteristics, surgical risk factors, and posttransplantation course are required.[27] In the current study, cumulative probability of survival at 1 month and 1 year were 0.85 and

Table 5: Factors affecting mortality (30 days) in the study population in logistic regression (*n*=132)

Factor	Mortality (30 days)		OR (95% CI)
	Mortality	Alive	
Age groups			
≤50 (*n*=66)	8 (12.12)	58 (87.88)	Baseline
>50 (*n*=66)	11 (16.67)	55 (83.33)	1.450 (0.543-3.873)
Gender			
Male (*n*=73)	9 (12.33)	64 (87.67)	Baseline
Female (*n*=59)	10 (16.95)	49 (83.05)	1.451 (0.548-3.845)
Presenting diagnosis (2 categories)			
Non-ILD (*n*=45)	7 (15.56)	38 (84.44)	Baseline
ILD (*n*=87)	12 (13.79)	75 (86.21)	0.869 (0.316-2.386)
Preoperative mechanical ventilation			
No (*n*=124)	16 (12.9)	108 (87.1)	Baseline
Yes (*n*=8)	3 (37.5)	5 (62.5)	4.050 (0.882-18.603)
Preoperative ECMO			
No (*n*=118)	15 (12.71)	103 (87.29)	Baseline
Yes (*n*=14)	4 (28.57)	10 (71.43)	2.747 (0.764-9.877)
Type of transplant			
Single lung transplant (*n*=7)	1 (14.29)	6 (85.71)	Baseline
Bilateral lung transplant (*n*=106)	14 (13.21)	92 (86.79)	0.913 (0.102-8.161)
Heart and lung transplant (*n*=19)	4 (21.05)	15 (78.95)	1.600 (0.147-17.411)
ECMO/CPB			
Off pump (*n*=56)	6 (10.71)	50 (89.29)	Baseline
On pump (*n*=57)	7 (12.28)	50 (87.72)	1.167 (0.366-3.717)
ECMO (*n*=19)	6 (31.58)	13 (68.42)	3.846 (1.063-13.911)
Postoperative ECMO			
No (*n*=118)	15 (12.71)	103 (87.29)	Baseline
Yes (*n*=14)	4 (28.57)	10 (71.43)	2.747 (0.764-9.877)

OR: Odds ratio, CI: Confidence interval, ILD: Interstitial lung diseases, ECMO: Extracorporeal membrane oxygenation, CPB: Cardiopulmonary bypass

0.78 this was similar to the ISHLT report of 2016 where the 1 year survival rate was 80%. The report analyzed the data of all lung transplants done between 1990 and 2014.[28] A cohort study was done by Yang *et al*. in Taiwan, to compare the cumulative early outcome of lung transplants between two cohorts of lung transplant patients. The Kaplan–Meier plotting by the researchers showed a 1 year survival of the cohorts were 40% and 85%, respectively. This difference was statistically significant and was attributed to the difference in the age and other baseline characters.[29] GNB sepsis (52%), severe graft dysfunction (12%), and GI bleed (12%) were the main reasons for mortality after 30 days' period. According to logistic regression analysis, taking non-ILD as a baseline, odds of 1-month mortality was 0.8 times more for ILD. Compared to single lung transplant, heart, and lung transplant had 1.6 times more odds of 1-month mortality. One-month mortality rate reported by Akram *et al*. and He *et al*. was 12.5% and 14%, respectively.[19,20] Suboptimal donor management combined with heavy donor infection burden, variability in ventilator management, and minimal time available to optimize donor have all contributed to mortality. Logistic issues like nonaffordability of charter flight for retrieval of organs minimizing the ischemic time like west have also been a major challenge.

CONCLUSION

Lung transplant is an option for patients with irreversible lung disease and chronic respiratory failure. Team approach like establishment of green corridor by traffic police department in transporting organ inter-city, postoperative judicious surveillance of immunosuppression helps in successful program. Careful evaluation, investigation and optimizing recipients with pulmonary rehab, nutritional consultation, and psychologist motivation are required. The need of the hour is to educate physicians andpulmonologists to actively discuss this option with the patients early during the disease course and refer them early to the transplant units. Our study proves that LT is a viable option in India despite several challenges and provides the patients with ESLD a better quality of life and a better survival.

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Conflicts of interest

There are no conflicts of interest.

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