Effectiveness of Lung Transplantation in Patients With Interstitial Lung Diseases

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ABSTRACT

Background. Interstitial lung diseases (ILDs) are a heterogeneous group of more than 200 diseases manifested by progressive exercise dyspnea, radiological lung changes, and ventilation restrictive disorders. ILDs are the second most common indication for lung transplantation (LTx). Our study group consisted of 139 patients who qualified for LTx at the Silesian Center for Heart Diseases between 2004 and 2018. Of the 139, 92 patients died while on the waiting list, and 47 patients underwent LTx. Medical records including laboratory test results, spirometry, and the 6-minute walk test (6MWT) were analyzed to determine eligibility for LTx. We also assessed quality of life post-LTx.

Results. Patients who qualified for LTx showed decreased values of parameters measured by spirometry (43.69 ± 19.05% of forced expiratory volume in the first second [FEV1] and 43.07 ± 20.55% of forced vital capacity [FVC] and severe desaturation during the 6MWT (SpO_2 = 88.78% before 6-minute walk test and 73.23% after the test). After LTx, longer distances were achieved in the 6MWT (235.47 ± 159.57 m during qualification vs 533.2 ± 34.15 m 12 months after LTx) and increased values of spirometry. On average, patients had stopped working 6 years prior to LTx.

Conclusion. There is no effective medical treatment for patients with end-stage ILDs. Therefore, lung transplantation is a lifesaving procedure for patients that also extends patients' lives and improves their quality of life.

INTERSTITIAL lung diseases (ILDs) include more than 200 diseases related to lung parenchyma. These disorders are categorized under a common name due to similar clinical and radiological features. Patients with ILDs have reduced forced vital capacity (FVC) and reduced exercise tolerance, both of which further decrease as the disease progresses. There exist many different causes of ILDs, including environmental exposure (asbestos, beryllium), medications (eg, bleomycin, amiodarone, nitrofurantoin), irradiation, and connective tissue and autoimmune disorders [1]. The American Thoracic Society and European Respiratory Society classify ILDs into 4 main groups: first, those resulting from a known cause or association (medication, occupational exposures, soft tissues diseases); second, idiopathic interstitial pneumonia; third, granulomatous ILDs (sarcoidosis, infections), and the fourth and final group consists of rare forms of ILDs (histiocytosis, neurofibromatosis) [2,3]. The most common disease in this

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classification is idiopathic pulmonary fibrosis (IPF), part of the idiopathic interstitial pneumonia group. A poor prognosis and limited therapeutic options for patients with IPF and other ILDs-end stages make lung transplantation (LTx) the only suitable option to improve quality of life and pulmonary function parameters [4]. Treatment choices and prognosis differ among the various types of ILDs; therefore, verifying the correct diagnosis is important. Nevertheless, patients with ILDs still have a poor prognosis because of the constant progression of fibrosis in the lungs [5,6]. The most common systemic complications are pulmonary hypertension and right ventricle heart failure [7]. Our aim in this study was twofold: first, to assess the pulmonary function of patients with ILDs from Silesian Centre for Heart Diseases at the time of qualification and at 3, 6, and 12 months after LTx; and second, to evaluate quality of life scores after lung transplantation.

MATERIALS AND METHODS

This retrospective study assessed 139 patients who qualified for LTx between 2004 and 2018 in the Lung Transplant Program of the Silesian Centre for Heart Diseases. The study group included 92 patients (66.19%) who died while on the waiting list and 47 patients who underwent LTx (33.81%). Patients included to the study suffered from hypersensitivity pneumonitis (N = 22; 5 after LTx), Langerhans cell histiocytosis (N = 5; 4 after LTx), pneumoconiosis (N = 12; 4 after LTx) idiopathic pulmonary fibrosis (N = 86; 26 after LTx), lymphangioleiomyomatosis (N = 4; 2 after LTx), and sarcoidosis (N = 10; 6 after LTx). Of the 47 transplanted patients, 15 patients underwent double lung transplantation, and 32 patients underwent single lung transplantation. During the qualification process, parameters of both groups of patients such as height (cm), weight (kg), body mass index (BMI; kg/cm^2), and time on the waiting list (days) in addition to laboratory tests measuring nutritional status (total protein [g/dL] and albumins [g/dL]), kidney function (serum creatinine [mg/dL]), glomerular filtration rate (GFR) (mL/min/1.73 m^2) and liver function (total bilirubin (mg/dL), aspartate transaminase (Ul/L), and alanine transaminase (UI/L) were analyzed. Additionally, this study paper reported data of pulmonary function tests such as the 6-minute walk test (6MWT; distance [m]), Borg's scale, desaturation after 6MWT, spirometry (forced expiratory volume in the first second [FEV1] and forced vital capacity [FVC]) during qualification to LTx. Laboratory and pulmonary function tests were also assessed 3, 6, and 12 months post-LTx. Survival in the transplanted group was estimated using the Kaplan-Meier curve. Quality of life responses were compared based on World Health Organization Quality of Life–Bref questionnaire (WHOQOL–Bref) in addition to an employment questionnaire created by the authors.

Table 1. Basic Characteristics of ILD Patients During Qualification to Lung Transplantation

	Deceased Patients (N = 92)	Transplanted Patients (N = 47)
Sex, men,%	55.43	74.47
Age at qualification, y	51.04 ± 9.52	46.8 ± 10.68
Time spending on waiting list, days	359 ± 356.46	321 ± 321.55
Age at lung transplantation, y		47.62 ± 10.66
SLT,%		68.08
DLT,%		31.92
Height, cm	166.01 ± 9.31	170.94 ± 7.73
Weight, kg	65.74 ± 15.28	68.93 ± 15.1
BMI, kg/m^2	23.67 ± 4.24	23.46 ± 4.32
ILDs diagnosis		
Hypersensitivity pneumonitis, %	18.48	10.64
Langerhans cell histiocytosis, %	1.09	8.51
Pneumoconiosis, %	8.69	8.51
Idiopathic pulmonary fibrosis, %	65.22	55.32
Lymphangioleiomyomatosis, %	2.17	4.26
Sarcoidosis, %	4.35	12.76
Total proteins, g/dL	7.23 ± 0.79	7.35 ± 1.03
Albumins, g/dL	4.08 ± 0.56	4.28 ± 0.42
Serum creatinine, mg/dL	0.76 ± 0.19	0.83 ± 0.23
GFR, mL/min/1.73 m^2	104.66 ± 36.45	100.33 ± 25.53
Serum bilirubin, mg/dL	0.72 ± 0.57	0.69 ± 0.47
Aspartate transaminase, Ul/L	23.51 ± 7.84	22.9 ± 7
Alanine transaminase, Ul/L	24.73 ± 20.23	22.98 ± 14.34
6MWT distance, m	189.3 ± 136.76	235.47 ± 122.6
Borg's scale	4.44 ± 1.78	3.33 ± 1.61
Desaturation after 6MWT	15.71 ± 9.26	15.55 ± 8.76
FEV1, %	44.97 ± 16.15	43.69 ± 17.9
FVC, %	42.52 ± 15.01	43.07 ± 19.5

Values are given as the mean ± standard deviation; the differences are not statistically significant.

Abbreviations: 6MWT, 6-minute walk test; BMI, body mass index; DLT, double lung transplantation; FEV1, forced expiratory volume in first second; FVC, forced vital capacity; GFR, glomerular filtration rate; ILDs, interstitial lung diseases; SLT, single lung transplantation.

Table 2. One-Year Follow-up Data of Transplanted Patients With ILDs

	Time After LTx		
	3 months	6 months	12 months
Total proteins, g/dL	6.85 ± 0.9	6.76 ± 0.62	7.03 ± 0.17
Albumins, g/dL	4.08 ± 0.46	4.11 ± 0.56	4.57 ± 0.2
Serum creatinine, mg/dL	1.59 ± 0.58	1.85 ± 0.75	1.89 ± 0.62
GFR, mL/min/1.73 m^2	53.45 ± 19.77	46.9 ± 18.48	41.6 ± 12.12
Serum bilirubin mg/dL	0.48 ± 0.34	0.41 ± 0.16	0.48 ± 0.20
Aspartate transaminase, UI/L	22.61 ± 13.82	19.88 ± 8.44	20.57 ± 4.93
Alanine transaminase, UI/L	31.02 ± 45.54	21.72 ± 27.4	18.86 ± 8.4
6MWT distance, m	481.47 ± 57.25	497.89 ± 36	533.2 ± 34.15
Borg's scale	2.31 ± 2.68	2.18 ± 2.41	2 ± 2.2
Desaturation after 6MWT	7 ± 6.16	5.64 ± 4.25	3.54 ± 3.03
FEV1, %	62.69 ± 23.31	62.38 ± 22.65	60.73 ± 23.78
FVC, %	60.8 ± 19.02	63.64 ± 16.84	65.32 ± 20.62

Values are given as the mean ± standard deviation.
Abbreviations: 6MWT, 6-minute walk test; FEV1, forced expiratory volume in first second; FVC, forced vital capacity; GFR, glomerular filtration rate.

Statistical Analysis

Descriptive statistics of analyzed data were expressed as mean ± standard deviation. A Kaplan-Meier curve was used for presentation survival time after lung transplantation. Statistica 10.0 statistical software (StatSoft Inc., Tulsa, Okla, United States) was used for statistical analysis.

RESULTS

Qualification Process

Between 2004 and 2018, 139 patients with ILDs were qualified for LTx in Silesian Centre for Heart Diseases. Basic characteristics, laboratory data, and pulmonary tests data of all qualified patients are presented in Table 1. There were 47 patients who underwent lung transplantation; the remaining 92 died while on the waiting list. Transplanted patients during qualification were higher and outweighed the deceased patients (170.94 ± 7.73 cm vs 166.01 ± 9.31 cm, 68.93 ± 15.1 kg vs 65.74 ± 15.28 kg, respectively). IPF and hypersensitivity pneumonia were most often qualified diagnoses (65.22% and 18.48%). Deceased patients reached 46.17 meters less during the 6MWT than transplanted patients (189.3 ± 136.76 m vs 235.47 ± 122.6 m) with similar desaturation during the test (15.71 ± 9.26 vs 15.55 ± 8.76, respectively). Spirometry revealed reduced values of FEV1 and FVC parameters in both groups.

Lung Transplantation

Among the 47 transplanted patients, most often diagnoses were IPF and sarcoidosis. Follow-up data were collected in Table 2. At the 1-year follow-up, the 6MWT results showed great progression as compared to results at the time of qualification and at 3, 6, and 12 months after transplantation. More than a 2-fold increase was observed in the distance between qualification time and 12 months after LTx (235.47 ± 159.57 vs 533.2 ± 34.15m; Fig 1A). Borg's scale changed from 3.33 ± 2.37 to 2 ± 2.2 after 1 year (Fig 1B). Oxygen saturation results before and after the 6MWT are presented in Fig 1C.

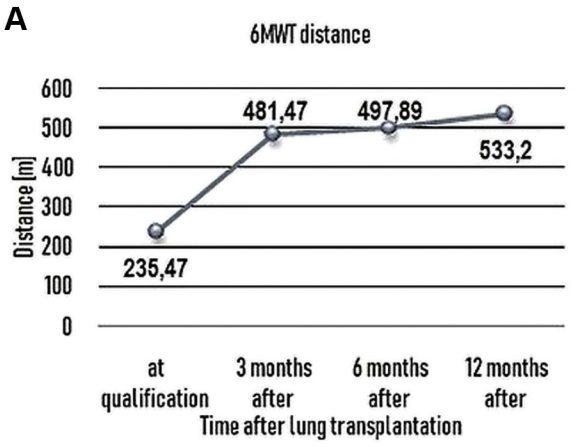
At the time of qualification, transplanted patients achieved 43.69 ± 19.05% of FEV1 and 43.07 ± 20.55% of FVC. During the 1-year surveillance period, the results of both FEV1 and FVC improved. After 3, 6, and 12 months, FVC increased as follows: 60.8 ± 19.02%, 63.64 ± 16.84% and 65.32 ± 20.62%. Values of FEV1 were also higher than at the time of qualification. After 12 months, it had increased to 65.32 ± 23.78% (Figs 1D and 1E).

Survival time after lung transplantation was assessed by Kaplan-Meier curve and is presented in Fig 2. Survival estimates after transplantation were 72%, 63%, and 60% at 1, 3, and 5 years.

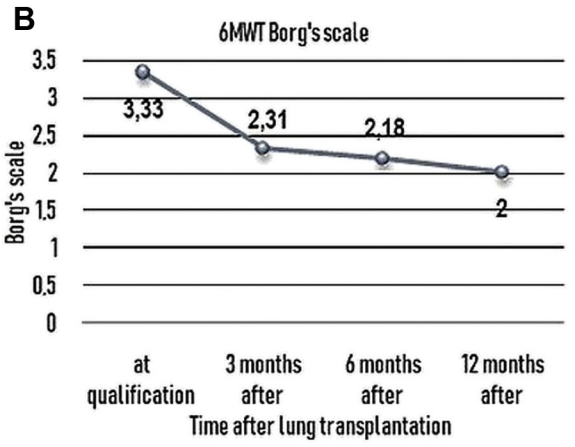
Quality of life among the 20 transplanted patients was assessed by the WHOQOL–Bref questionnaire. Patients obtained the following results: 26 ± 4.28, 22.9 ± 3.59, 11.3 ± 2.97, and 30.4 ± 4.19 points in the somatic, psychological, social, and environmental domain, respectively. On average, patients had stopped working 6 years prior to LTx. In total, 20% of the patients were able to return to work following LTx; the average time to return to work after LTx was 13.5 months.

DISCUSSION

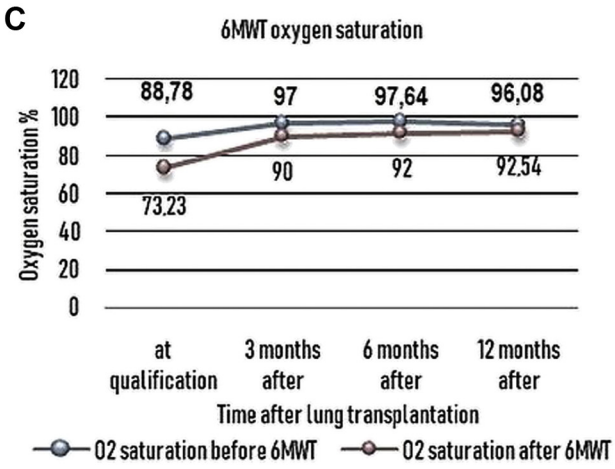
Lung transplantation is a viable method of treating patients with end-stage ILDs. According to the registry of the International Society of Heart and Lung Transplantation, the median survival rate after LTx is 5.2 years for idiopathic interstitial pneumonia (IIP) and 6.7 years for ILDs that are not idiopathic interstitial pneumonia [8]. Mason et al assessed that 1-, 3-, and 5-year survival rates among IPF patients after lung transplantation with were 73%, 56%, and 44%, respectively [9]. Kern et al evaluated the survival rate among hypersensitivity pneumonitis (96%, 89%, and 89%) vs idiopathic pulmonary fibrosis (86%, 67%, and 49%) after transplantation at the same intervals after transplantation [10]. A team from France published a study about the survival rate after LTx among Langerhans cell histiocytosis with the following results: 76.9%, 63.6%, and 57.2% at 1, 2,



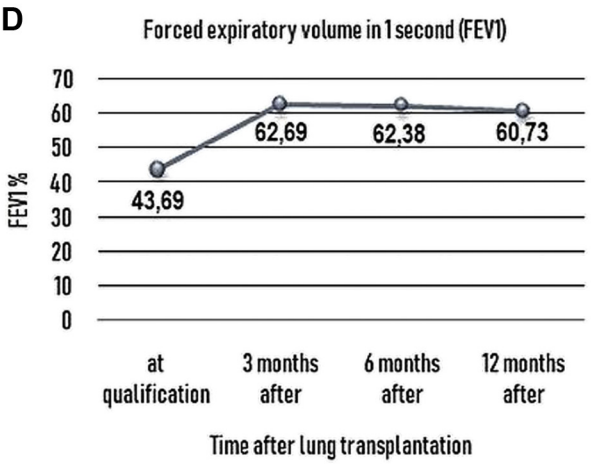
Improvement of distance obtained during 6-minute walk test 6MWT after lung transplantation of lung transplant recipients.



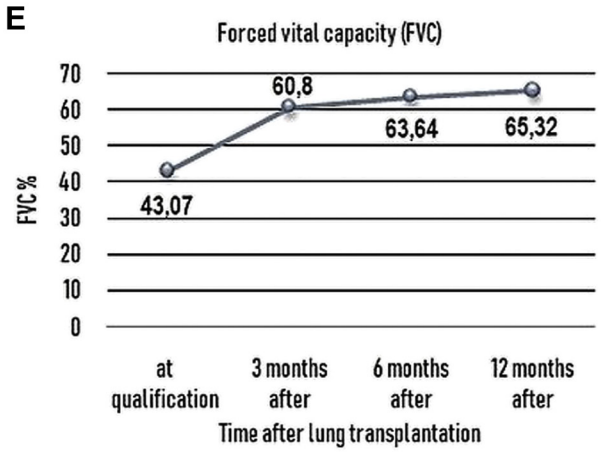
Improvement of Borg's scale obtained during 6-minute walk test 6MWT after lung transplantation of lung transplant recipients.



Improvement of oxygen saturation during 6-minute walk test 6MWT after lung transplantation of predicted transplant recipients.



Improvement of FEV1% after lung transplantation.



Improvement of FVC% after lung transplantation.

Fig 1. Results of the 6-minute walk test **(A, B, C)** and spirometry **(D and E)** before and 3, 6, and 12 months after transplantation. 6MWT, 6-minute walk test; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity.

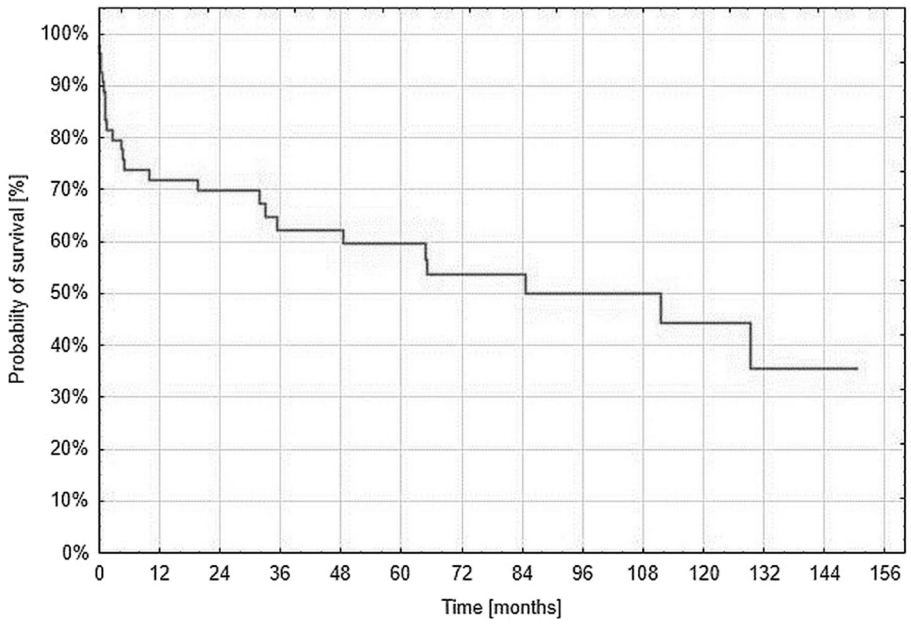


Fig 2. Survival after lung transplantation estimated by Kaplan-Meier curve.

and 5 years, respectively [11]. The results of our study are similar (72%, 63%, and 60% at 1, 3, and 5 years) to the results obtained by the cited studies. The difficulty in drawing conclusions is the heterogeneity of the study group, which includes patients with different interstitial lung diseases.

In our lung transplantation program, 139 patients with ILDs where qualified to LTx. Among these, only 47 (33.81%) underwent lung transplantation. The important, essential component of every LTx is donor-recipient matching. Patients with ILDs require downsizing of the donor lungs because of a reduction of thoracic volume. In Poland, the average height of men and women is 178.7 cm and 165.1 cm, respectively, thereby increasing the odds of taller patients to undergo a transplantation sooner [12]. The mean height of patients who underwent LTx was 170.94 cm; they were almost 5 cm taller than the deceased patients. The average height of donors who reported to our center was 171.38 cm.

Results of a pulmonary function test achieved by patients with end-stage lung diseases during qualification process is associated with the primary diagnosis.

In a single-center study, spirometry and 6MWT data were assessed among candidates with cystic fibrosis (CF) at qualification and during 12 months of follow-up after LTx [13]. Results of spirometry parameters in analyzed population increased: FEV1 from 21.13% at the time of qualification to 76.67% at 12 months after LTx and FVC from 34.18% at the time of qualification to 78.34% at 12 months after LTx. Distance in the 6MWT before LTx and after 12 months was extended by 175.55 m (from 377.65 m to 553.2 m) among CF patients. Comparing these results, patients with ILDs reached almost 298 m longer distance after the 1-year outcome (from 235.47 m to 533.2 m) but obtained lower improvement in spirometry: FEV1 from 43.69% at the time of qualification to 65.32% at 12 months after LTx and FVC from 65.32% at the time of qualification to 78.34% at 12 months after LTx. Despite the greater increase in distance in the 6MWT in patients with ILDs, the endpoint after 12 months of follow-up is like that of CF patients. The difference worth noting is the results of spirometry after 12 months of observation. Patients with CF always (with a few exceptions) receive a transplant of both lungs, which is not observed in patients with ILD. In addition, during donor-recipient matching, up-sizing should be done for CF patients, and downsizing should be done for patients with ILDs.

A subjective assessment of the quality of life by patients with ILDs indicates an improvement in their perceived quality of life following LTx. Results obtain in somatic (26.93 ± 4.68 points vs 15.79 ± 2.23 points), psychological (22.90 ± 3.59 vs 13.79 ± 2.51), and environmental (30.40 ± 4.19 vs 13.10 ± 2.43) domains were higher than in the healthy Polish population reported by Jaracz et al [14]. We found lower scores in the social domain among transplanted patients as compared to healthy responders (11.30 ± 2.97 points vs 14.87 ± 3.04 points). We speculate that this difference might be due to the long and multiple hospitalizations following surgery. Only 20% of transplanted patients were able to successfully return to work; this could also impact their assessment of their social life. The International Society of Heart and Lung Transplantation registry reports than an even lower number of patients were able to return to work 1 year post-LTx; their numbers indicate that only 13.6% of patients returned to work following LTx [8].

Lutogniewska et al [15] assessed dyspnea among patients with end-stage lung disease referred to lung transplantation center for qualification to LTx. Dyspnea evaluated in Borg's

scale (after 6MWT) was 5.6 ± 2.6 points among IPF patients and 6.6 ± 1.8 points among patients with idiopathic interstitial pneumonia. Comparing the results obtained in our study (2.31 ± 2.68 points, 2.18 ± 2.41 points and 2 ± 2.2 points after 3, 6, and 12 months post-LTx, respectively) to the study cited above, we can conclude that after a lung transplant, the subjective feeling of breathlessness (assessed after the 6MWT) is significantly reduced.

CONCLUSIONS

There is no effective medical treatment for ILDs. Therefore, lung transplantation is a lifesaving procedure for patients with ILD. LTx not only extends their lives but also improves their quality of life.

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