Lung Transplantation in Idiopathic Pulmonary Fibrosis: Risk Factors and Outcome

Moshe Shai Amor MD, Dror Rosengarten MD, Dorit Shitenberg MD, Barak Pertzov MD, Yael Shostak MD, Yory Peysakhovich MD, and Mordechai Reuven Kramer MD

Pulmonary Institute, Rabin Medical Center (Beilinson Campus), Petah Tikva, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

ABSTRACT **Background:** Idiopathic pulmonary fibrosis (IPF) has poor prognosis. Anti-fibrotic treatment has been shown to slow disease progression. Lung transplantation (LTx) offers a survival benefit. The 5-year survival after LTx in IPF is between 40 and 50%.

Objectives: To evaluate which IPF patients have better prognosis following LTx.

Methods: A retrospective study was conducted with all IPF patients who had undergone LTx in the Rabin Medical Center between 2010 and 2018. We collected data on pre-evaluation of pulmonary function tests, echocardiographic and right heart catherization, and anti-fibrotic treatments. The Kaplan-Meier method was used for survival analysis.

Results: Among 148 patients who underwent LTx, 58 were double LTx (DLT) and 90 single LTx (SLT). Mean age was 58.07 ± 9.78 years; 104 males and 44 females. DLT patients had significantly lower survival rates than SLT in the short and medium term after LTx. Patients with saturation above 80% after the 6-minute walk test (6MWT) had higher survival rates. Patients over 65 years of age had a lower survival rates. Those with pulmonary hypertension (PHT) above 30 mmHg had a poorer prognosis with lower survival rates.

Conclusions: IPF patients with higher mean PHT, older age (>65 years), and desaturation following 6MWT had lower survival rates following LTx. DLT may decrease survival rate compared to SLT just for the short and medium period of time after LTx. These results may lead to better selection of IPF patient candidates for LTx. Additional studies are warranted for choosing which patients will have better prognosis after LTx.

IMAJ 2020; 22: 741–746

KEY WORDS: idiopathic pulmonary fibrosis (IPF), lung transplantation (LTx), mortality, pulmonary hypertension (PHT), risk factor

Idiopathic pulmonary fibrosis (IPF) is defined in the American Thoracic Society consensus statement as a spontaneously occurring (idiopathic) specific form of chronic fibrosing interstitial pneumonia limited to the lung and associated with a pattern of usual interstitial pneumonia on high resolution computed tomography (CT) or histologic appearance on a lung biopsy [1].

The prevalence of IPF increases with advanced age with presentation commonly occurring in the sixth and seventh decades. IPF is rarely seen in patients younger than 50 years of age [1]. The prevalence is higher in men than women [2]. Overall, the incidence of IPF is increasing worldwide and conservative estimates range from 3 to 9 cases per 100,000 per year in Europe and North America [3].

The majority of patients have a history of cigarette smoking [1]. Patients commonly report a gradual onset of dyspnea on exertion and nonproductive cough over several months. Fatigue, fever, myalgias, and arthralgias are rarely reported.

Pulmonary function testing (PFT) in IPF typically demonstrate a restrictive pattern (e.g. reduced forced vital capacity [FVC], but normal ratio of forced expiratory volume in one second [FEV1]/FVC), a reduced diffusing capacity for carbon monoxide (DLCO), and with disease progression, a decrease in the 6-minute walk test (6MWT).

Untreated IPF progression, according to data from the placebo arm of clinical trials, suggests the rate of decline in FVC among untreated patients is 150–200 ml per year [4].

In recent years novel anti-fibrotic treatment for IPF has emerged, with drugs slowing the progression of lung fibrosis. Nintedanib, a receptor blocker for multiple tyrosine kinases, mediates elaboration of fibrogenic growth factors (e.g., platelet-derived growth factor, vascular endothelial growth factor, fibroblast growth factor) appears to slow the rate of disease progression in IPF [5,6].

In two subsequent trials (INPULSIS-1 and INPULSIS-2), a total of 1066 patients with IPF were randomly assigned to nintedanib 150 mg or placebo twice daily for 52 weeks [6]. In INPULSIS-1, the annual rate of decline in FVC was lower in the nintedanib group than the placebo group with a difference of 125.3 ml/year, 95% confidence interval (95%CI) 77.7–172.8). The results were similar in INPULSIS-2 where the difference in FVC decline was 93.7 ml/year (95%CI 44.8–142.7). In INPULSIS-2, an increase in the time to first exacerbation was noted (hazard ratio 0.38, 95%CI 0.19–0.77). In a 2-year extension of the TOMORROW trial, FVC decline was significantly less in patients taking nintedanib 150 mg twice a day compared with placebo or a lower dose of nintedanib (125.4 ml/year vs. 189.7 ml/year). The main benefits were reduction in the rate of decline in lung function and longer time to first exacerbation.

The second anti-fibrotic agent pirfenidone inhibits transforming growth factor beta (TGF-β)-stimulated collagen synthesis, decreases the extracellular matrix, and blocks fibroblast proliferation in vitro.

A pooled analysis of the combined patient populations of three global randomized phase 3 trials of pirfenidone vs. placebo and a meta-analyses of trials showed a reduction in treatment-emergent all-cause mortality, IPF-related mortality, and treatment-emergent IPF-related mortality for pirfenidone therapy compared with placebo [7].

Currently, with these drugs the only change in the course of the disease is a slower progression, thus IPF has become the most common interstitial lung disease among referrals for lung transplantation (LTx) and the second most frequent disease for which LTx is performed [8,9]. In the International Society for Heart and Lung Transplantation registry IPF is also the most frequent reason for LTx.

Moreover, patients with IPF have the highest death rate among the diagnostic groups on the transplant waiting list [10]. Thus, early referral for transplant evaluation should be considered, even before the response to initial medical therapy has been determined [11].

Under the current United Network for Organ Sharing (UNOS) system, priority for transplantation is determined by medical urgency and expected outcome using a lung allocation score (LAS). Scores are normalized to a continuous scale from 1 to 100, with higher scores representing higher urgency and greater potential transplant. In Israel, with the use of the LAS score, IPF patients get higher priority for LTx than patients with chronic obstructive pulmonary disease (COPD) or pulmonary hypertension (PHT).

Among 1256 patients transplanted in France between May 2005 and December 2007, the 1-year survival rate was 74% among those with scores in the highest lung allocation quartile (LAS 52.0–94.1) and 84% among those in the lowest lung allocation score quartile (LAS 31.1– 37.8) [12].

Unfortunately, the 5-year survival rate for LTx in IPF is 40–50%, compared with a 5-year survival rate of 53% for all LTx recipients [13-15].

Studies that compare single lung transplantation (SLT) to double lung transplant (DLT) suggest that DLT may have better long-term survival [11,13,16]. Following SLT, the low lung compliance and high vascular resistance of the remaining native lung preferentially direct both ventilation and perfusion to the transplanted lung. Cysts, bullae, and bronchiectasis that occasionally develop in the later stages of IPF can act as a nidus for infectious complications after SLT.

Mild-to-moderate secondary PHT preoperatively increased the risk of reperfusion injury in one study but did not appear to affect survival in two retrospective studies [17,18].

To evaluate which of the patients with IPF who undergo LTx have higher risk for mortality, we collected data on all IPF patients who underwent LTx at Rabin Medical Center (Beilinson Campus) in Petah Tikva, Israel, between 2010 and 2018. The data included demographic characteristics, single or double lung transplantation, mortality, parameters of the right heart catheterization (RHC), functional pulmonary test (FPT), echocardiography (ECHO) with evaluation of the right, and left ventricles function and estimation of the pulmonary arterial pressure; and after 2016 if the patient received anti-fibrotic agent prior to LTx.

PATIENTS AND METHODS

STUDY DESIGN

This retrospective study was conducted at the Rabin Medical Center, a 900-bed tertiary care university hospital. The facility is the only transplantation center in Israel that performs lung transplantation, conducting 50–60 procedures per year, for a total of more than 810 LTx. The study was approved by the hospital's ethics committee.

STUDY POPULATION

Eligible participants were all patients who underwent LTx with diagnosis of IPF in the years 2010–2017 at the Rabin Medical Center. Mortality data was collected until March 2018.

DATA COLLECTION

Data from the patient electronic medical records included:

- Demographic characteristics
- Diagnosis of IPF in the lung transplantation list
- Date of the transplantation
- Pre-transplantation evaluation of PFT including FVC, FEV1, FEV1/FVC, MEF 25, MEF 74, TLC, DLCO
- Pre-transplantation six-minute walk test (6MWT)
- Pre-transplantation saturation at rest and after 6MWT
- Echocardiographic pre-transplantation characteristics, including left ventricular ejection fraction (LVEF
- Estimation of the PHT
- Right ventricle (RV) dilatation
- Dysfunction
- Right heart catheterization (most of patients undergo evaluation with the FICK system, some patients undergo the evaluation in the thermodilution system)
- PHT systolic diastolic and mean
- Mean wedge pressure (PCW mean)
- Cardiac index (CI)
- Cardiac output (CO)
- Pulmonary vascular resistance (PVR)

We also collected data on anti-fibrotic treatment before transplantation.

STATISTICAL ANALYSIS

Statistical analyses were performed using SAS 9.2 software (SAS

Institute Inc., Cary, NC, USA). Continuous data were expressed as mean ± standard deviation or as median and interquantile range (25–75 percentiles) as appropriate, and compared by using the *t*-test and chi-square. $P < 0.05$ was considered significant. We generated survival curves for IPF LTx patients using standard Kaplan–Meier techniques and comparing between the data collection and the defined group. Hazard ratios (HR) and 95% confidence intervals (95%CI) were estimated for each comparison.

RESULTS

During the study period, 148 patients had undergone LTx. The mean age was 58.07 ± 9.78 years; 104 males and 44 females. In our cohort, 58 patients underwent DLT and 90 patients SLT [Table 1]. DLT had higher mortality rate compared to SLT ($P = 0.0159$) [Figure 1A].

When dividing the patients according to the distance reached on the 6MWT beyond and below 150 meters, there were no significant differences in mortality estimates between the groups [Figure 1B].

Table 1. Lung transplant receipts and their pre-transplantationevaluation

		Value
	Age	58.07 ± 9.78
	Gender	86 men 62 women
LTx	Lung transplantation DLT SLT	148 58 90
LFT	FEV1 FEV1/FVC TLC DLCO 6MWT	48.34 ± 17.38 0.84 ± 0.12 54.91 ± 7.15 28.9 ± 10.79 242.5 ± 133.31
RHC	PHT mean CO PVR (Woods units) Wedge pressure	26.85 ± 10.8 4.54 ± 1.56 4.01 ± 2.92 10.69 ± 6.21
Anti-fibrotic drugs	Overall Nintedanaib Pirfenidone	14 9 5
Echocardiographic	EF RV dysfunction RV dilatation	62.0 ± 14.5 22.2% 30.0%

6MWT = 6-minute walk test, DLCO = diffusing capacity for carbon monoxide, DLT = double LTx, EF = ejection fraction, FEV1 = forced expiratory volume in one second, FVC = forced vital capacity, LTx = lung transplantation, PHT = pulmonary hypertension, RV = right ventricle, SLT = single LTx

We evaluated the saturation after the 6MWT when dividing the two groups into those above and below 80%. We found that patients with saturation levels below 80% had a higher mortality rate [Figure 1C].

We evaluated mortality according to age (younger than 50 years, between 50 to 65 years, and older than 65 years). We found higher mortality rate at ages above 65 with *P* value 0.028 [Figure 1D].

We used the data collection from the right heart catheterization pre-transplantation and divided the patients into two groups: the group with higher pulmonary pressure had higher mortality rates as compared to the groups with lower PHT [Figure 2].

The use of anti-fibrotic treatment in IPF started in 2016. We evaluated the survival rate of patients who were treated with anti-fibrotic treatment prior to LTx. We found a higher mortality rate in the anti-fibrotic treatment groups compared to the non-treatment group ($P = 0.0104$ in the group taking pirfenidone, $P = 0.0319$ in the group taking nintedanib group) [Figure 3].

We found that each additional year of age increased mortality HR by 4.6% (95%CI 1.005–1.089). We also found that every increase by 1 mmHg in the mean pulmonary pressure increased mortality HR by 2.6%, 95%CI 1.000–1.053.

ECHOCARDIOGRAPHY ASSESSMENT OF THE LEFT VENTRICLAR EJECTION FRACTION

LVEF reduced the mortality HR by 8.5% for each percentage (95%CI 0.855–0.979). We found no significant differences in mortality HR in any of the pulmonary function test variables beside of the 6MWT, including the DLCO measurement.

DISCUSSION

IPF disease has a poor prognosis, thus LTx offers a survival benefit; nonetheless, among patients who undergo LTx, IPF patients have the least favorable survival rate. Our study was designed to assess the parameters that may play a role in the survival rate of IPF patients post LTx.

In our cohort, DLT patients had a significantly worse survival rate compared to SLT patients. In contrast, previous studies showed no difference between these two groups and some even showed better prognosis with DLT [11,13,16]. Some of those studies showed that DLT patients had better prognosis in the long-term but not in the short- or medium-terms. The time frames also assumed that those finding also shown in our cohort .Another explanation for the differences in our findings may be related to selection of patients, as patients chosen for DLT had higher pulmonary pressure, which possibly lead to a higher mortality rate.

When evaluating the patient 6MWT, we found no differences in the distance the patient achieved, although we found a significantly higher survival rate in the group of patients with saturation above 80% after 6MWT. du Bois et al. [19] showed similar results requiring oxygen after 6MWT predicted worse survival following transplantation.

Patients over 65 years of age had a lower survival rate as shown in Figure 1D. Indeed Singer et al. [20] recommended that recipients over 65 years of age should be identified to maximize the net benefits of the transplant. While Singer et al. [21] showed that LTx conferred large health-related quality-of-life benefits, which do not differ substantially in older recipients. Patients with

Figure 1. Lung transplantation survival rates. **[A]** Single lung transplantation (SLT)/double lung transplantation (DLT) survival, **[B]** 6-minute walk test (6MWT), **[C]** Saturation (6MWT), **[D]** Age survival

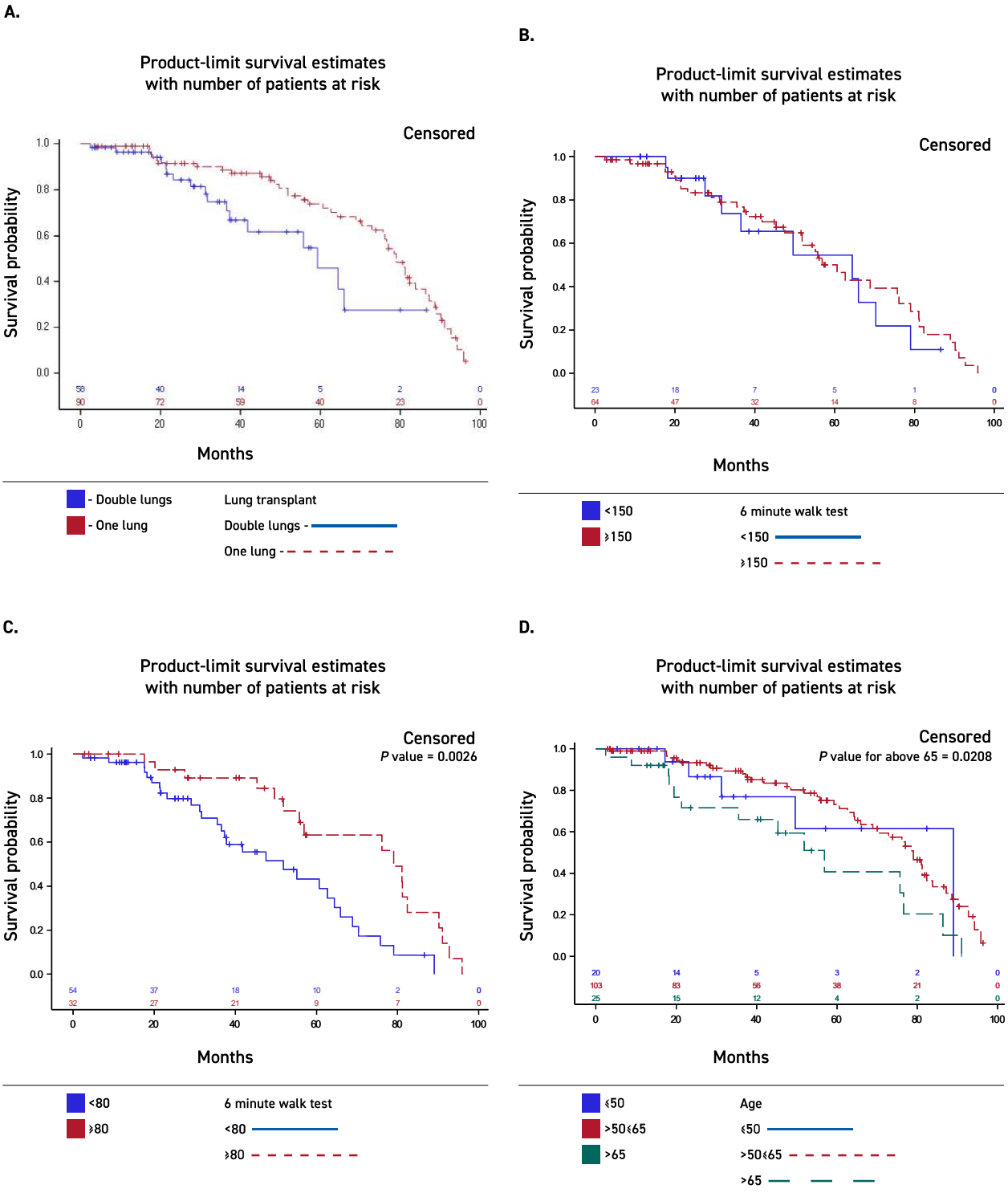


Figure 2. Pulmonary hypertension: right heart catheterization (RHC)

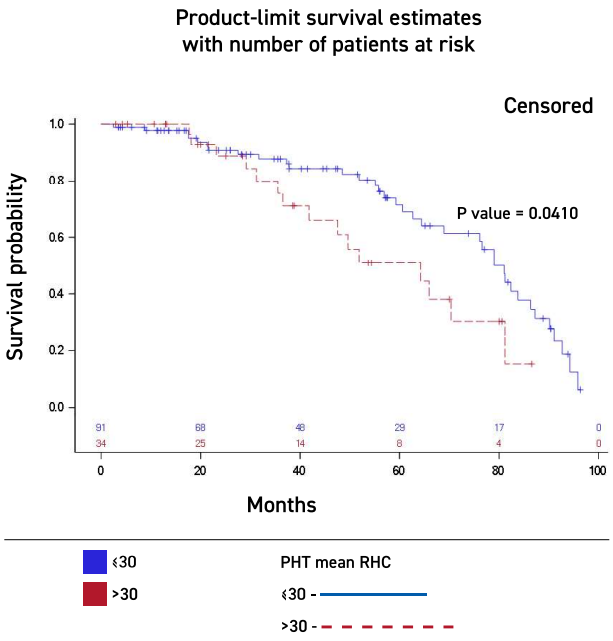
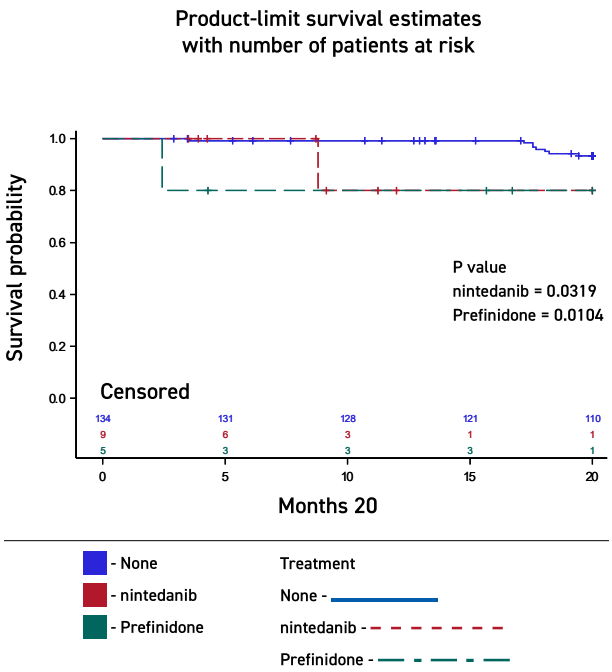


Figure 3. Anti-fibrotic treatment



mean PHT > 30 mmHg had a higher mortality rate; however, PVR values were found to have no significant difference. Indeed PH is a serious complication for IPF patients that negatively impacts survival [22]. However, following LTx there is resolution of PH. Consequently the PVR value had no effect on the mortality rate. Similarly, the estimated RV dysfunction as seen on the echocardiogram showed no significant HR difference following LTx, we assume that the RV dysfunction results after LTx, those why we don't have any difference between the groups.

Anti-fibrotic drugs may interfere with wound-healing after major surgery theoretically prevent sufficient bronchial anastomosis formation after LTx. Leuschner et al. [23] showed that previous use of anti-fibrotic therapy does not increase surgical complications or postoperative mortality after LTx. Conversely, in our study we found a significantly higher mortality rate with anti-fibrotic treatment regardless of which medication the patient received. However, only 14 patients received anti-fibrotic treatment (9 nintedanib and 5 pirfenidone) thus, further studies with enough participants to provide a statistically sample size are warranted to make definite conclusions.

EF represents the systolic contraction of the left ventricle. We found a significantly lower mortality HR in patients with higher EF rates. Those with better EF percentage who undergo LTx have better heart function and with better prognosis.

We evaluated the data on the cardiac output from the right heart catheterization. This trend was not evident, most probably because the majority of patients had higher EF rates and no difference in cardiac output

There were no significant differences in any of the pulmonary function test variables. Mackay et al. [24] concluded that IPF disease progression is a more sensitive indicator for transplantation referral than any single physiological measure of disease severity.

STUDY LIMITATIONS

We used data from a single hospital and single center experience, with data collected from the patient files. All tests (e.g., PFT ECHO and RHC) were performed at the same place but not always by the same operator. Due to missing data in some patients we only evaluated variables that had been recorded for most of the patients and used a statistical evaluation and correction to evaluate the results.

CONCLUSIONS

IPF patients with higher mean PHT, age above 65 years, and desaturation after the 6MWT have a higher mortality rate after LTx. Patients with greater EF have lower mortality rates. DLT may decrease survival rate compared to SLT for the short-term and also possibly due to selection bias. These results may lead to better selection of IPF patient candidates for LTx but more studies are needed to determine which patients will have better prognosis after LTx.

Correspondence
Dr. M.R. Kramer
Pulmonary Institute, Rabin Medical Center (Beilinson Campus), Petah Tikva 49100, Israel
Phone: (972-3) 972-7221, (972-3) 937-7224
email: kramerm@clalit.org.il

References

1. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011; 183: 788.
2. Kaunisto J, Salomaa ER, Hodgson U, et al. Idiopathic pulmonary fibrosis--a systematic review on methodology for the collection of epidemiological data. *BMC Pulm Med* 2013; 13: 53.
3. Bennett D, Mazzei MA, Squitieri NC, et al. Familial pulmonary fibrosis: clinical and radiological characteristics and progression analysis in different high resolution-CT patterns. *Respir Med* 2017; 126: 75.
4. Lama VN, Flaherty KR, Toews GB, et al. Prognostic value of desaturation during a 6-minute walk test in idiopathic interstitial pneumonia. *Am J Respir Crit Care Med* 2003; 168: 1084.
5. Wollin L, Wex E, Pautsch A, et al. Mode of action of nintedanib in the treatment of idiopathic pulmonary fibrosis. *Eur Respir J* 2015; 45: 1434.
6. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med* 2014; 370: 2071.
7. Nathan SD, Albera C, Bradford WZ, et al. Effect of pirfenidone on mortality: pooled analyses and meta-analyses of clinical trials in idiopathic pulmonary fibrosis. *Lancet Respir Med* 2017; 5: 33.
8. Alalawi R, Whelan T, Bajwa RS, Hodges TN. Lung transplantation and interstitial lung disease. *Curr Opin Pulm Med* 2005; 11: 461.
9. Yusen RD, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-second Official Adult Lung and Heart-Lung Transplantation Report--2015; Focus Theme: Early Graft Failure. *J Heart Lung Transplant* 2015; 34: 1264.
10. Thabut G, Mal H, Castier Y, et al. Survival benefit of lung transplantation for patients with idiopathic pulmonary fibrosis. *J Thorac Cardiovasc Surg* 2003; 126: 469.
11. Steinman TI, Becker BN, Frost AE, et al. Guidelines for the referral and management of patients eligible for solid organ transplantation. *Transplantation* 2001; 71: 1189.
12. Weiss ES, Allen JG, Merlo CA, et al. Lung allocation score predicts survival in lung transplantation patients with pulmonary fibrosis. *Ann Thorac Surg* 2009; 88: 1757.
13. Mason DP, Brizzio ME, Alster JM, et al. Lung transplantation for idiopathic pulmonary fibrosis. *Ann Thorac Surg* 2007; 84: 1121.
14. George TJ, Arnaoutakis GJ, Shah AS. Lung transplant in idiopathic pulmonary fibrosis. *Arch Surg* 2011; 146: 1204.
15. International Society for Heart and Lung Transplantation. Adult Lung Transplantation Statistics, 2014. [Available from https://www.ishlt.org/registries/slides.asp?slides=heartLungRegistry&year=2014 [Accessed 07 November 2014].
16. Grossman RF, Frost A, Zamel N, et al. Results of single-lung transplantation for bilateral pulmonary fibrosis. The Toronto Lung Transplant Group. *N Engl J Med* 1990; 322: 727.
17. Fitton TP, Kosowski TR, Barreiro CJ, et al. Impact of secondary pulmonary hypertension on lung transplant outcome. *J Heart Lung Transplant* 2005; 24: 1254.
18. Nathan SD, Shlobin OA, Ahmad S, et al. Serial development of pulmonary hypertension in patients with idiopathic pulmonary fibrosis. *Respiration* 2008; 76: 288.
19. du Bois RM, Albera C, Bradford WZ, et al. 6-Minute walk distance is an independent predictor of mortality in patients with idiopathic pulmonary fibrosis. *Eur Respir J* 2014; 43 (5): 1421-29.
20. Singer JP, Katz PP, Soong A, et al. Effect of lung transplantation on health-related quality of life in the era of the lung allocation score: a U.S. prospective cohort study. *Am J Transplant.* 2017; 17: 1334-45.
21. Singer LG, Chowdhury NA, Faughnan ME, et al. Effects of recipient age and diagnosis on health-related quality-of-life benefit of lung transplantation. *Am J Respir Crit Care Med* 2015 15; 192: 965-73.
22. Castria D, Refini RM, Bargagli E, et al. Pulmonary hypertension in idiopathic pulmonary fibrosis: prevalence and clinical progress. *Int J Immunopathol Pharmacol* 2012; 25: 681-89.
23. Leuschner G, Stocker F, Veit T, et al. Outcome of lung transplantation in idiopathic pulmonary fibrosis with previous anti-fibrotic therapy. *J Heart Lung Transplant* 2018; 37: 268-74.
24. Mackay LS, Anderson RL, Parry G, et al. Pulmonary fibrosis: rate of disease progression as a trigger for referral for lung transplantation. *Thorax* 2007; 62: 1069-73.

Capsule

Broad and strong memory CD4+ and CD8+ T cells induced by SARS-CoV-2 in UK convalescent individuals following COVID-19

The development of vaccines and therapeutics for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) will depend on understanding viral immunity. **Peng** et al. studied T cell memory in 42 patients following recovery from coronavirus disease-2019 (COVID-19) (28 with mild disease and 14 with severe disease) and 16 unexposed donors, using interferon-γ-based assays with peptides spanning SARS-CoV-2, except ORF1. The breadth and magnitude of T cell responses were significantly higher in severe compared to mild cases. Total and spike-specific T cell responses correlated with spike-specific antibody responses. The authors identified 41 peptides containing $CD4^+$ and/or $CD8^+$ epitopes, including six immunodominant regions. Six optimized $CD8^+$ epitopes were defined, with peptide-MHC pentamer-positive cells displaying the central and effector memory phenotype. In mild cases, higher proportions of SARS-CoV-2-specific $CD8^+$ T cells were observed. The identification of T cell responses associated with milder disease will support an understanding of protective immunity and highlights the potential of including non-spike proteins within future COVID-19 vaccine design.

Nature Immunol 2020; 21: 1336

Eitan Israeli