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Prognostic significance of antifibrotic agents in idiopathic pulmonary fibrosis after initiation of long-term oxygen therapy

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Abstract. *Background and aim:* Idiopathic pulmonary fibrosis (IPF) is a fatal and progressive interstitial lung disease with varying degrees of hypoxemia. Long-term oxygen therapy (LTOT) is frequently used to treat hypoxemia, however the prognostic factors for better survival in IPF patients after initiation of LTOT remain unknown. *Methods:* We retrospectively investigated favorable factors of survival in consecutive 55 IPF patients with chronic respiratory failure who were introduced LTOT. *Results:* The 6-, 12-, 18-, and 24-month survival rates in IPF patients after introduction of LTOT were 70.9%, 49.0%, 45.2%, and 32.3%, respectively. Univariate analysis demonstrated that low Glasgow Prognostic Score (GPS) (hazard ratio [HR] 0.482, p=0.043) and treatment with antifibrotic agents (HR 0.401, p=0.013) were associated with favorable survival, while multivariate analysis revealed that treatment with antifibrotic agents was the independent predictor (HR 0.449, p=0.032). Moreover, IPF patients treated with antifibrotic agents with LTOT had significantly longer survival than those without antifibrotic agents (p = 0.0106). *Conclusion:* In IPF patients who were introduced LTOT, treatment with antifibrotic agents was the independent factor for favorable survival. Treatment with antifibrotic agents may improve prognosis of IPF even after initiation of LTOT.

Key words: idiopathic pulmonary fibrosis (IPF), long-term oxygen therapy (LTOT), antifibrotic agents

Introduction

Idiopathic pulmonary fibrosis (IPF), the most common of idiopathic interstitial pneumonias, is a chronic, progressive and usually fatal lung parenchymal disease. The median survival of IPF patients from the time of diagnosis is estimated as 3 to 5 years (1, 2). Chronic hypoxemia is a common feature in patients with advanced IPF and oxygen supplementation is regarded as the standard treatment in order to reduce dyspnea and improve gas exchange (2-4). The 2011 ATS/ERS/JRS/ALAT international evidence-based guideline strongly recommended to treatment long term oxygen therapy (LTOT) for IPF patients with hypoxemia (5). However, there is little study regarding which clinical factors in IPF patients after initiation of LTOT are associated with better prognosis (3, 6). The aim of the present study was to investigate prognostic factors of IPF patients after initiation of LTOT in a real-life practice.

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Materials and methods

Methods

We retrospectively reviewed a total of 55 consecutive patients with idiopathic pulmonary fibrosis (IPF) who were introduced to LTOT between January 2014 and December 2020 at the Tokyo

Medical University Hospital. The subjects were followed up until death or June 2022. This study was approved by the ethical committee of Tokyo Medical University Hospital (approval No. T2021-0250). Informed consent was waived, as the study involved a retrospective chart review with minimal risk to the patients. All data were anonymized prior to analysis.

Data collection

Demographic variables including patients' characteristics (age, gender, smoking history, BMI), clinical data, and the use of medications (antifibrotic agents, immunosuppressive agents) were collected at the time of LTOT initiation from the electronic medical records. Baseline hematology data were collected, including the white blood cell count (WBC), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), hemoglobin level, C-reactive protein (CRP) level, lactate dehydrogenase (LDH) level, albumin level, sialylated carbohydrate antigen KL-6 (KL-6), pulmonary Surfactant Protein-D (SP-D). Systemic inflammatory indexes were calculated as according to the following formulas: NLR=ANC/ALC, ALI (advanced lung cancer inflammatory index) =BMI x albumin/NLR. GPS (Glasgow Prognostic Score) was classified into three groups according to blood CRP and albumin levels as reported previously (7, 8). We collected the pulmonary function test results, including the vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in one second (FEV1.0) and diffusing capacity of the lung for carbon monoxide (DLco). The severity of IPF within 6 months before initiation of LTOT was evaluated by the modified Gender-Age-Physiology (GAP) and modified GAP system. The modified GAP model was reported to be more accurate in predicting the prognosis of Asian IPF patients (9).

IPF was diagnosed according to the criteria by the ATS/ERS/JRS/ALT international guidelines (5, 10) and identified with a pattern of usual interstitial pneumonia on the basis of radiological finding by high-resolution computed tomography (HRCT) as described previously (11). All HRCT analyses were independently re-evaluated by trained pulmonologists (MI and SA) blinded to the patients' information. Patient selection, initial dose, dose reduction (escalation) or discontinuation of antifibrotic or immunosuppressive agents was decided by the attending physicians, considering the patients' condition. LTOT was introduced to IPF patients with chronic hypoxic condition determined by a partial oxygen pressure (PaO_2) < 60 Torr or IPF patients who desaturate with exercise (oxygen saturation < 90%).

Statistical analysis

Data were described as numbers (percentages) or median (interquartile range). Survival rates were calculated using the Kaplan-Meier method, and differences in survival rates between the groups were compared using the log-rank test. Favorable factors of survival after the introduction of LTOT were identified by both univariate and multivariate analysis using the Cox proportional hazard model. A comparison of the groups was performed by using the Mann-Whitney Test for continuous variables and Fisher exact test for categorial variables. A probability value of less than 0.05 was considered statistically significant. All statistical analyses were performed using EZR (version 1.54) (12).

Results

In total, 55 patients were included in this study. The clinical characteristics of the patients are shown in Table 1. The median age at which oxygen therapy was introduced with a diagnosis of IPF was 73 years (interquartile range (IQR): 68-80; minimum: 47 years, maximum: 89 years) and 45 patients (81.8%) were male. Forty-nine patients (89.1%) were ex-smoker. The median BMI was 21.1 (IQR:18.4-24.1). The mean time to LTOT from IPF diagnosis was 23.5 months (IQR:4.7-35.6). Thirty-four patients (64.2%, n=53) required less 2L/min oxygen flow at rest and 36 patients (67.9%, n=53) required more than 3L/min flow on exertion at the initiation of LTOT. The mean %FVC and %DLco were 68.7% (IQR:56.4-81.1, n=48) and 38.6% (IQR:34.1-52.4%), respectively. The mean modified GAP index was 8 points (IQR:5-9, n=38). Thirty-four (61.8%) patients refused antifibrotic treatment because of fear of side effects or high out-of-pocket spending. Twenty-one patients (38.2%) were treated with antifibrotic agents (nintedanib 15, pirfenidone 6). Of the 15 patients treated with nintedanib, 12 patients received and continued reduced-dose (200mg/day) of nintedanib due

Table 1. Clinical characteristics at the initiation of LTOT (n=55).

Variable	Value median (IQR)
Demographic variables	
Age, y	73 (68-80)
Sex	
Female	10 (18.2%)
Male	45 (81.8%)
Smoking	
ex -smoker	49 (89.1%)
never -smoker	6 (10.1%)
Time to LTOT from IPF diagnosis (months)	23.5 (4.7-35.6)
BMI, kg/m²	21.1 (18.4-24.1)
Laboratory variables	
Hemoglobin, g/dL	13.4 (11.5-14.4)
NLR	3.1 (2.1-6.5)
CRP, mg/dL	0.39 (0.15-1.20)
Albumin, g/dL	3.5 (3.1-3.8)
ALI	21.8 (11.3-40.2)
serum LDH, IU/L	221 (198-274)
serum KL - 6.U/ml	1123 (684-1527)
serum SP - D, ng/mL	197 (148-306)
GPS (0/1/2)	21 (38.1%)/24 (43.6%)/10 (18.2%)
Oxygen flow	
O□ at rest (<2/2-4L /min) (n =53)	34 (64.2%)/19 (35.8%)
O□ on exertion (<2/3/4-6L /min) (n =53)	17 (32.1%)/24 (45.3%)/12 (22.6%)
Pulmonary function test	
VC, percent predicted (n =48)	69.9 (57.4-83.1) %
FVC, percent predicted (n =48)	68.7 (56.4-81.1) %
FEV1.0, percent predicted (n =48)	79.4 (68.0-94.5)
DLco, percent predicted (n =38)	38.6 (34.1-52.4) %
GAP index (points) (n =38)	5 (4-5)
modified GAP index (points) (n =38)	8 (5-9)
modified GAP index (I /II /III) (n =38)	3 (9%)/14 (42.4%)/15 (45.6%)
Treatment during the study period	
antifibrotic agents	21 (38.2%)
nintedanib	15 (27.2%)
pirfenidone	6 (10.9%)
immnosuppressive agents	19 (34.5%)

Data are presented as median (interquartile range) or number (%). Abbreviations: LTOT:long-term oxygen therapy; IPF: idiopathic pulmonary fibrosis; BMI:body mass index; NLR:neutrophil lymphocyte ratio; ALI: advanced lung cancer inflammatory index; VC: vital capacity; FVC: forced vital capacity; DLco: diffusing capacity of the lung for carbon monoxide; GPS: Glasgow Prognostic Score; GAP: Gender-Age-Physiology score.

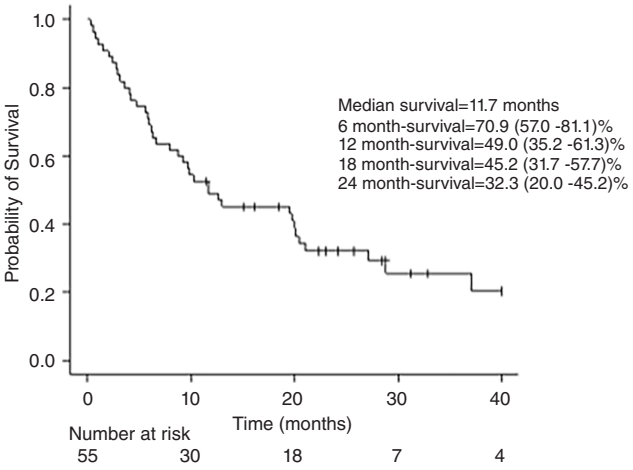

Figure 1. Kaplan-Meier survival curve of 55 consecutive IPF patients who were introduced LTOL.

to adverse event, such as diarrhea, nausea, anorexia and liver dysfunction. Of 6 patients treated with pirfenidone, all subjects received and continued low dose (600-1200mg/day) of pirfenidone during the study period. The mean length of follow-up was 466 days (range 10-1505 days). Fifteen subjects (27.2%) survived during the observation period.

The Kaplan-Meier survival curve for all patients is shown in Figure 1. The median survival times of the all subjects was 11.7 months (IQR:6.7-20.0). The 6-, 12-, 18-, and 24-month survival rates after the initiation of LTOT were 70.9%, 49.0%, 45.2% and 32.3%, respectively.

The results of the univariable and multivariable analysis are shown in Table 2. GPS 0 (hazard ratio [HR] = 0.482, 95% confidence interval [CI]: 0.237-0.976, p=0.043), treatment with antifibrotic agents (HR = 0.401, 95% CI: 0.194-0.827, p=0.013) were favorable factors. Multivariable analysis identified the treatment with antifibrotic agents as the independent factor for better survival (HR = 0.449, 95% CI: 0.216-0.932, p=0.032).

The comparison of the group stratified by the treatment with or without antifibrotic agents showed significant difference in inflammation markers both NLR and ALI at the initiation of LTOT (Table 3). The median duration of treatment with antifibrotic agents was 30.9 months (IQR:17.9-42.6, n=21). Fourteen of 21 patients started antifibrotic agents before the initiation of LTOT and continued during the study period. Seven patients started antifibrotic agents at the initiation of LTOT and continued during the study period. There was no significant difference in the survival time of subjects whose antifibrotic agents started before or at the initiation of LTOT (p=0.224). The survival curves of the groups treated with and without antifibrotic agents in IPF patients after the initiation of LTOT are shown in Figure 2. The median survival of IPF patients treated with antifibrotic agents who were introduced LTOT was significantly longer than that of without antifibrotic agents (27.1 vs 8.8 months, p = 0.0106).

Discussion

The present study demonstrated that treatment with antifibrotic agents was independent factor for better survivals in IPF patients who were introduced LTOT in a real-life study. To our best knowledge, this is the first study evaluating the significance of antifibrotic treatment on the prognosis of IPF patients with LTOT.

The prognosis of IPF is poor and the mean survival time from diagnosis is 3-5 years (1, 2). Several parameters to predict mortality of patients with IPF have been reported. Age, gender, smoking status, percent predicted VC, percent predicted FVC and percent predicted DLco, which were also components of modified GAP scores, have been generally accepted as prognostic factors in IPF (9, 13). In addition, BMI and systemic inflammatory indices such as NLR, ALI, GPS were reported to be prognostic markers in chronic lung diseases including IPF (7, 8, 14-16). We investigated those possible factors for survival of IPF after initiation of LTOT, however, only low GPS and treatment with antifibrotic agents were favorable factors in univariate analysis using the Cox proportional hazard model. GPS is a score based on systemic inflammation that combines serum albumin and CRP levels (7, 8). Recent report demonstrates that IPF patients with hypoalbuminemia have poorer outcome (17). GPS may be a useful predictor of IPF patients after introduction of LTOT. Baseline GAP or modified GAP stages have been reported to be significant prognostic determinants for mortality (9, 18). In the present study, GAP and modified GAP scores were not prognostic factors of survival in IPF patients after introduction of LTOT. Initiation of oxygen therapy has reported to be a marker of poorer prognosis with a median survival less than 18 months in a European IPF cohort (18), indicating the question of usefulness of GAP or modified

Table 2. Favorable factors of survival in IPF patients after induction of LTOT.

Variables	Hazard ratio	95% CI	P value		Hazard ratio	95% CI	P value
Univariate Cox analysis				**Multivariate Cox analysis**			
Younger age (<73 years)	0.596	0.313-1.135	0.116		0.557	0.285-1.087	0.086
Sex (female)	2.099	0.743-5.934	0.162		1.695	0.553-5.195	0.356
Smoking (never smoker)	0.337	0.081-1.401	0.135		0.307	0.067-1.416	0.131
Time from IPF diagnosis to LTOT (<23.5 months)	1.191	0.632-2.243	0.591				
BMI (>21.2)	0.675	0.356-1.281	0.229				
NLR (<3.1)	1.023	0.543-1.927	0.943				
ALI (<21.8)	1.387	0.737-2.610	0.312				
serum LDH (<221 IU/L)	1.558	0.826-2.937	0.171				
serum SP-D (<197 pg/ml)	0.613	0.320-1.172	0.139				
serum KL-6 (<1123 U/ml)	0.956	0.508-1.797	0.888				
GAP score (<5) (n=38)	0.716	0.335-1.528	0.387				
modified GAP score (<8) (n=38)	0.601	0.279-1.288	0.191				
GPS(=0)	0.482	0.237-0.976	0.043		0.501	0.243-1.033	0.061
%VC (>69.8%)	0.662	0.332-1.319	0.241				
%FVC (>66.6%)	0.929	0.467-1.840	0.832				
%DLco (>38.6%)	1.206	0.568-2.559	0.626				
O2 at rest (<2 L/min)	1.549	0.815-2.942	0.181				
O2 on exertion (<3 L/min)	1.612	0.777-3.342	0.199				
Treatment with antifibrotic agents	0.401	0.194-0.827	0.013		0.449	0.216-0.932	0.032
Treatment with immunosurppressive agents	1.041	0.539-2.001	0.904				

Abbreviations: LTOT:long-term oxygen therapy; IPF: idiopathic pulmonary fibrosis; BMI:body mass index; NLR:neutrophil lymphocyte ratio; ALI: advanced lung cancer inflammatory index; VC: vital capacity; FVC: forced vital capacity; DLco: diffusing capacity of the lung for carbon monoxide; GPS: Glasgow Prognostic Score; GAP: Gender-Age-Physiology score.

GAP on survival in IPF with LTOT will be further investigated.

Chronic hypoxemia is a common feature during clinical course of IPF and supplemental oxygen is strongly recommended for patients with advanced IPF in order to reduce breathlessness and improve exercise tolerance (2, 4, 5, 19). Even though its frequent use of LTOT, there is little information regarding the effectiveness of oxygen therapy and prognosis after the initiation of LTOT in interstitial lung disease (ILD) including IPF. A systematic review showed that the use of LTOT in ILD was at high risk of bias and impossible to estimate impacts on survival (3).

Higashiguchi et al. reported the 2-year survival rate of 49 idiopathic interstitial pneumonia (IIP) patients was 36.0%. Male gender and lower BMI were independent predictive prognostic factor of IIP patients with LTOT (20). Ahmadi et al. showed that the survival from initiation of LTOT was median 8.4 months in 285 ILD patients (21). Rantala et al. recently reported that the median survival of ILD patients with LTOT was 10.8 months, and the 1-yr survival was 47% in 138 ILD subjects (22). In this study limited to the IPF patients, the median survival of all subjects from initiation of LTOT is 11.7 months similar to previous studies. However,

Table 3. Comparison of clinical characteristics between the subgroup treated with and without antifibrotic agents.

Variable	With antifibrotic agents (n=21)	Without antifibrotic agents (n=34)	P value
Age (years)	73 (68-78)	77 (68-83)	0.105
Sex male	16 (76.2)	29 (85.3)	0.480
Smoking (ex-smoker)	18 (85.7)	31 (91.2)	0.664
Time to LTOT from IPF diagnosis (months)	28.4 (18.5-42.7)	21.8 (3.3-31.5)	0.056
BMI, kg/m2	21.4 (19.0-25.5)	21.0 (18.0-22.3)	0.234
NLR	2.75 (1.70-4.73)	3.51 (2.38-7.78)	0.048
ALI	31.5 (21.9-49.9)	15.8 (10.1-31.6)	0.013
serum LDH, IU/ml	221 (201-281)	220 (197-259)	0.735
serum KL-6, U/ml	1206 (565-1482)	1112 (800-1618)	0.654
serum SP-D, ng/ml	176 (146-211)	228 (159-395)	0.069
GAP score	4 (3-5)	5 (4-5)	0.098
Modified GAP score	7 (5-8)	8 (7-9)	0.202
GPS (0/1/2)	10/9/2 (47.6/42.9/9.5)	11/15/8 (32.4/44.1/23.5)	0.358
O2 at rest < 2L/min	16 (80%) (n=20)	18 (54.5%) (n=33)	0.080
O2 on exertion > 3L/min	12 (60%) (n=20)	24 (72.7%) (n=33)	0.375
%FVC	68.7 (56.4-83.8)	68.7 (56.8-78.2)	0.826
%DLco	39.2 (35.1-55.5)	38.4 (32.1-46.7)	0.304
Treatment with immnosuppretants	7 (33.3%)	12 (35.3%)	1.000
Antifibrotic agents			
Duration of treatment (months)	30.9 (17.9-42.6)		
Started before LTOT, duration of treatment (months)	14 (66.6%), 40.8 (21.5-44.9)		
Started at initiation of LTOT, duration of treatment (months)	7 (33.3%), 22.3 (13.1-27.4)		
Survival of subjects whose treatment started before LTOT (months)	18.3 (9.0-23.2)	p=0.224	
Survival of subjects whose treatment strated at initiation of LTOT (months)	24.5 (14.4-30.3)		

Data are presented as median (interquartile range) or number (%). Abbreviations: LTOT: long-term oxygen therapy; IPF: idiopathic pulmonary fibrosis; BMI:body mass index; NLR: neutrophil lymphocyte ratio; ALI: advanced lung cancer inflammatory index; VC: vital capacity; FVC: forced vital capacity; DLco: diffusing capacity of the lung for carbon monoxide; GPS: Glasgow Prognostic Score; GAP: Gender-Age-Physiology score.

the median survival of IPF patients treated with antifibrotic agents was significantly longer than that of patients without antifibrotics (27.1 vs. 8.8 months, p=0.0106). The comparison of the patient groups stratified by the use of antifibrotic agents showed significant differences in NLR and ALI. NLR and ALI have been reported to be systemic inflammatory and prognostic markers in various disease including patients with chronic respiratory failures (15, 16), however, the significance of these markers in advanced IPF patients with LTOT has not been established. The results from multivariable analysis and survival curve comparing subjects with or without antifibrotic agents suggest that treatment with antifibrotic agents may be beneficial in advanced IPF patients who are introduced to LTOT. The present study showed no significant difference in the mean survival time of subjects whose antifibrotic agents started before or at the initiation of LTOT (18.3 vs 24.5 months, p=0.244).

Australian and European IPF registry studies showed that patients receiving antifibrotic

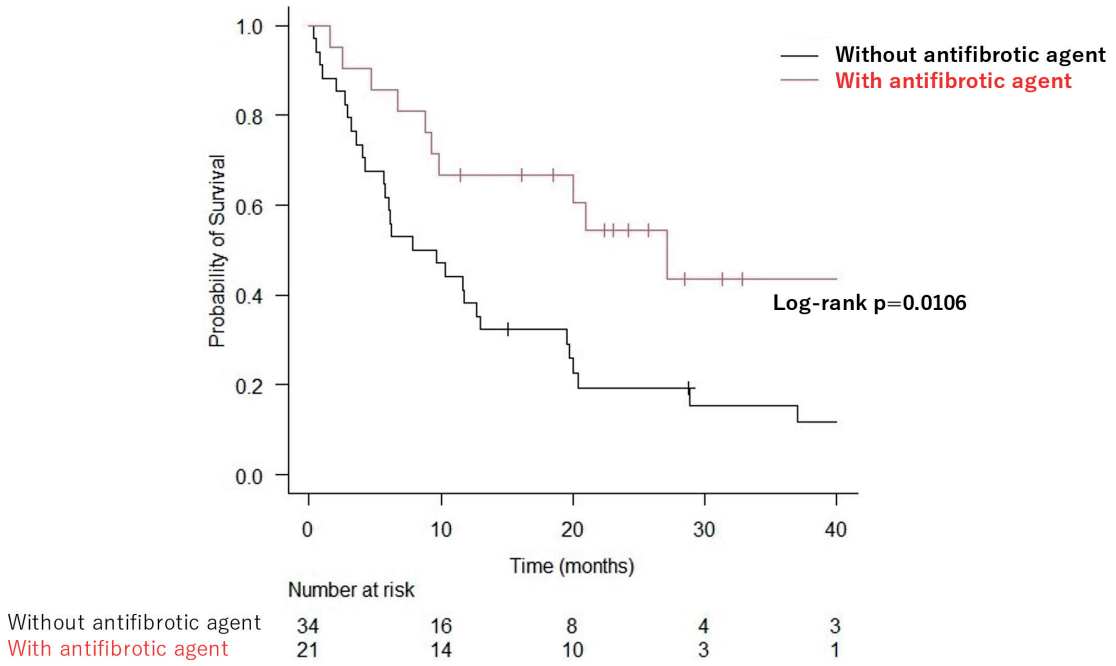

Figure 2. Kaplan-Meier survival curve comparing subjects with or without treated with antifbrotic agents. Median survival of subjects treated with antifibrotic agents and without antifibrotic agents were 27.1 months (IQR:9.3-NA, n=21) and 8.8 months (IQR:4.3-13.0, n=34, p=0.0106), respectively.

medications had better survival than those without antifibrotic medications (23, 24). The favorable effect of antifibrotic agents on better survival has been reported not only in clinical trial but also in real-world setting. In addition, preliminary data suggested the efficacy of both antifibrotic agents in severe IPF with lung function impairment (FVC < 50%). (25). In the present study, most of IPF patients were treated with doses of both nintedanib (200 mg/day) and pirfenidone (600-1200 mg/day) due to tolerability issues. Recent retrospective study demonstrated beneficial effects of low-dose pirfenidone (600-1200 mg/day) on survival and pulmonary function decline in IPF patients (26). The choice, initiation timing and dose reduction of antifibrotic agents could be associated with physicians' experience, patients' severity and possible adverse events in a real-world setting. Prognostic efficacy of antifibrotic medication on survival in IPF with LTOT will be further investigated, using large number of subjects.

Several limitations of the present study should be considered. First, this was a single-center retrospective study with a small sample size. The small number of the subjects limited the power of multivariable analysis to evaluate favorable factors for survival after LTOT. Second, the choice of initiating antifibrotic agents were decided by attending doctors, which could be a selection bias. The criteria of dose-reduction or discontinuation of antifibrotic agents were not yet standardized. However, as described, there was no significant difference in the treatment duration and survival time of subjects whose antifibrotic agents started before or at the initiation of LTOT. Third, due to progressive dyspnea and insufficient forced lung volume of the subject, GAP or modified GAP scores were not obtained from all IPF patients.

In conclusion, from a real-world clinical setting, low GPS and treatment with antifibrotic agents were both clinical predictors for IPF patients after initiation of LTOT. On multivariable analysis, treatment with antifibrotic agents was the independent factor of favorable survival of IPF patients with LTOT. This finding could provide better prognosis in IPF patients even after the initiation of LTOT.

Conflict of Interest: Each author declares that he or she has no commercial associations that might pose a conflict of interest in connection with the submitted article.

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