Scientific Research Publishing

Open Journal of Respiratory Diseases, 2024, 14, 111-121
https://www.scirp.org/journal/ojrd
ISSN Online: 2163-9418
ISSN Print: 2163-940X

Prognosis of Connective Tissue Disease Related Interstitial Lung Disease after Initiation of Long-Term Oxygen Therapy: Comparison with Idiopathic Pulmonary Fibrosis

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How to cite this paper: Ishiwari M., Kono, Y., Togashi, Y., Kobayashi, K., Kikuchi, R., Kogami, M. and Abe, S. (2024) Prognosis of Connective Tissue Disease Related Interstitial Lung Disease after Initiation of Long-Term Oxygen Therapy: Comparison with Idiopathic Pulmonary Fibrosis. *Open Journal of Respiratory Diseases*, **14**, 111-121.
https://doi.org/10.4236/ojrd.2024.144011

Received: October 25, 2024
Accepted: November 24, 2024
Published: November 27, 2024

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Abstract

Objective: The studies of long-term oxygen therapy (LTOT) for patents with connective tissue disease-related interstitial lung disease (CTD-ILD) are limited. This study aimed to evaluate the prognosis of CTD-ILD patients following the initiation of LTOT, compared to those with idiopathic pulmonary fibrosis (IPF). **Methods:** We conducted a retrospective analysis of patients with CTD-ILD and IPF who were introduced to LTOT between January 2014 and December 2020. **Results:** The study included 24 patients with CTD-ILD and 55 patients with IPF. At the initiation of LTOT, female gender, never-smoking history, higher body mass index (BMI), higher lactate dehydrogenase (LDH) level, lower pulmonary Surfactant Protein-D (SP-D) level and lower Gender-Age-Physiology (GAP) scores were more common in the CTD-ILD group (all < 0.05). The time from ILD diagnosis to LTOT initiation in CTD-ILD patients was significantly longer than IPF patients (36.0 vs 23.5 months, $p = 0.028$). Log-rank tests showed that CTD-ILD patients had significantly longer survival compared to IPF patients after the diagnosis of ILD ($p < 0.001$). However, no significant difference in survival after the initiation of LTOT was noted between patients with CTD-ILD and IPF ($p = 0.276$). **Conclusion:** Although patients with CTD-ILD had longer overall survival than those with IPF, there was no significant difference in prognosis after the initiation of LTOT between the two groups. Early intervention including treatment and management will be needed in CTD-ILD as in IPF.

Keywords

CTD-ILD, Idiopathic Pulmonary Fibrosis, IPF, Long-Term Oxygen Therapy,

LTOT

1. Introduction

Interstitial lung disease (ILD) consists of pulmonary disorders characterized by inflammation and/or fibrosis of the lung parenchyma associated with progressive dyspnea that frequently results in irreversible respiratory failure. The most prevalent forms of ILD include idiopathic pulmonary fibrosis (IPF), which accounts for approximately one-third of all ILD cases, connective tissue disease (CTD), which constitutes 25% of ILD cases, and hypersensitivity pneumonia, responsible for 15% of ILD cases [1]. Using high-resolution computed tomography (HRCT) to detect ILD in CTD patients, the prevalence varies among the definite CTDs: approximately 10% - 30% in rheumatoid arthritis (RA); 3% - 9% in systemic lupus erythematosus (SLE); 30% - 80% in idiopathic inflammatory myositis or polymositis (PM)/dematomyositis (DM); 20% - 50% in mixed CTD (MCTD); and 50-60% in diffuse systemic sclerosis (SSc), respectively [2]-[7]. The clinical course of connective tissue disease related interstitial lung disease (CTD-ILD) is believed to be heterogeneous with some patients having stable situations for long periods without medication and others experience rapid progression [6]. Although clinical, radiologic and pathological features are similar to that of other idiopathic interstitial pneumonias (IIPs), better prognosis in patients with CTD-ILD has been reported [8] [9]. The 2011 ATS/ERS/JRS/ALAT international evidence-based guidelines strongly recommended long-term oxygen therapy (LTOT) for IPF patients with hypoxemia [10]. LTOT is also considered for CTD-ILD patients in the presence of chronic respiratory failure [11].

However, there are few clinical studies on the prognosis of CTD-ILD after the initiation of LTOT. This study retrospectively examined the prognosis of CTD-ILD patients after the initiation of LTOT, with the hypothesis that the prognosis of CTD-ILD patients after LTOT is similar to that of IPF patients.

2. Methods

2.1. Study Subjects

We retrospectively reviewed a total of 24 consecutive patients with CTD-ILD 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. We also analyzed the IPF patients who were introduced to LTOT in order to compare them with CTD-ILD patients, as described previously [12]. This study received approval from Tokyo Medical University, Institutional Review Board (approval No: T2021-0250), and was performed according to the Declaration of Helsinki. Informed consent was waived, as the study involved a retrospective chart review with minimal risk to the patients. All data were anonymized before analysis.

2.2. Data Collection

Clinical materials of CTD-ILD or IPF patients, were collected from the electronic medical records, including demographic characteristics, clinical characteristics, laboratory examinations, pulmonary function tests and chest high-resolution (HR) CT findings. Glasgow Prognostic Score (GPS) was calculated as described previously [13] [14]. A pattern of usual interstitial pneumonia (UIP) was identified according to the criteria by the ATS/ERS/JRS/ALT international guidelines [15]. Initial drug selection and dosage, dose reduction (escalation) or discontinuation of treatment with corticosteroid or immunosuppressive and antifibrotic agents was decided by the attending physicians, considering the patients' condition. LTOT was introduced by the attending physicians in cases of chronic respiratory failure for CTD-ILD and IPF, i.e., resting partial pressure of arterial oxygen (PaO_2) < 60 Torr or pulse oximetric saturation (SpO_2) < 90% with exertion for more than one month. In our hospital, patients requiring LTOT are routinely hospitalized for educational training on oxygen therapy. The initiation of LTOT is defined as the date when patients are discharged with LTOT.

2.3. Statistical Analysis

Data were described as numbers (percentages) or median (interquartile range). A comparison of the groups was performed by using the Mann-Whitney Test for continuous variables and the Fisher exact test for categorical variables. Survival rates were calculated using the Kaplan-Meier method, and differences in survival rates between the groups were compared using the log-rank test. A probability value of less than 0.05 was considered statistically significant. All statistical analyses were performed using EZR (version 1.54) [16].

3. Results

3.1. Clinical Characteristics

Between January 2014 and December 2020, 647 patients started receiving LTOT at our hospital. Among these patients, we focused on cases in which LTOT was introduced due to chronic respiratory failure caused by CTD-ILD and IPF. In total, 24 patients with CTD-ILD and 55 with IPF who received LTOT were included in this study (**Figure 1**).

The baseline clinical features of patients with CTD-ILD (n = 24) and IPF (n = 55) were summarized in **Table 1.** Among 24 cases of CTD-ILD, 9 (37.5%) cases were RA, 4 (16.6%) cases were SSc, 2 (8.3%) cases were PM/DM, 5 (20.8%) cases were microscopic polyangiitis (MPA), 2 (8.3%) cases were Sjögren's syndrome (SS) and interstitial pneumonia with autoimmune features (IPAF, unclassifiable disease). The average ages were similar between the two groups. Female gender and a history of never smoking were more common in the CTD-ILD group ($p < 0.001$, $p = 0.0018$, respectively). The time from ILD diagnosis to LTOT initiation was significantly longer for CTD-ILD patients compared to those with IPF (36.0 vs 23.5 months, $p = 0.028$). BMI values at initiation of LTOT were significantly

lower in IPF patients than in those with CTD-ILD ($p = 0.027$). Serum LDH, SP-D and GAP index also differed between the two groups ($p = 0.049$, $p = 0.0029$ and $p < 0.001$, respectively). There was no significant difference in pulmonary function tests, including predicted forced vital capacity (%FVC) and predicted diffusing capacity of the lung for carbon monoxide (%DLco). Eighteen (75%) cases of CTD-ILD exhibited UIP pattern on HRCT. CTD-ILD patients were treated with corticosteroid and immunosuppressive agents more frequently than IPF patients ($p < 0.001$), however, antifibrotic agents were more commonly used in patients with IPF than in those with CTD-ILD ($p < 0.001$).

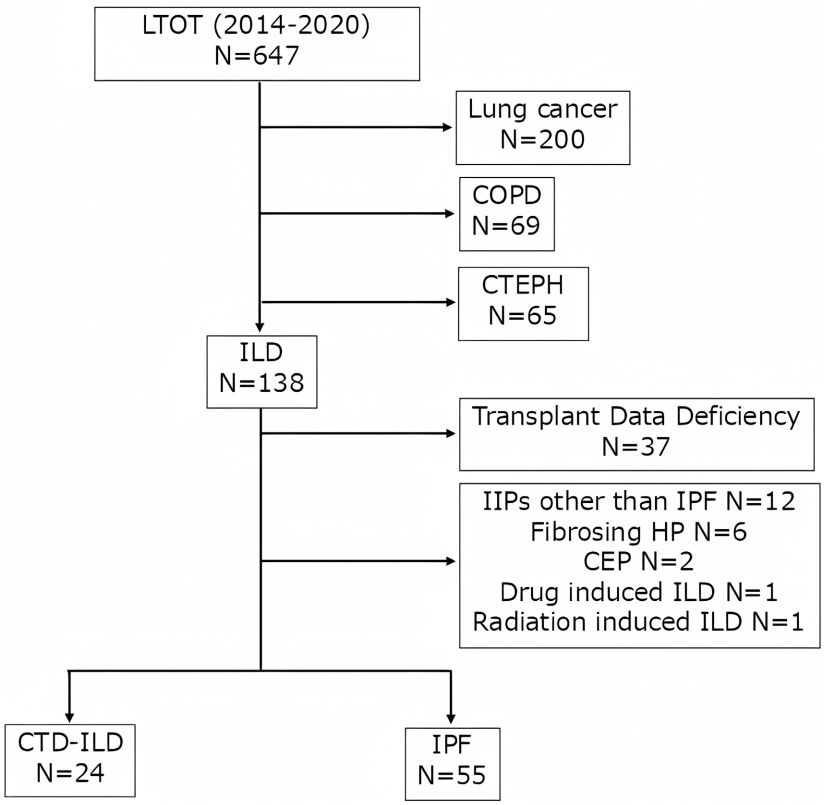

Figure 1. The chart flow of the study population. Out of 647 patients who started LTOT at our hospital, those with non-ILD causes were excluded, including lung cancer, COPD, and CTEPH. Patients who underwent transplants or had insufficient data were also excluded. The final study population comprised 24 patients with CTD-ILD and 55 with IPF who received LTOT.

Table 1. Clinical characteristics at the initiation of LTOT between patients with CTD-ILD and IPF.

	CTD-ILD (n = 24)	**IPF (n = 55)**	*p*-value
Variable	Value median (IQR)		
CTD			
RA	9 (37.5%)		
SSc	4 (16.6%)		
PM/DM	2 (8.3%)		
MPA	5 (20.8%)		

Continued

SS	2 (8.3%)		
IPAF (unclassifiable)	2 (8.3%)		
Demographic variables			
Age, years	69 (63 - 75)	73 (68 - 80)	0.105
Sex, male	9 (37.5%)	45 (81.8%)	< 0.001
Smoking			
Ex-smoker	13 (54.2%)	49 (89.1%)	0.002
Never-smoker	11 (45.8%)	6 (10.1%)	
Time to LTOT from ILD diagnosis (months)	36.0 (12.0 - 66.0)	23.5 (4.7 - 35.5)	0.028
BMI, kg/m^2	24.3 (21.0 - 26.5)	21.1 (18.4 - 24.1)	0.027
Laboratory variables			
Hemoglobin, g/dL	11.9 (10.9 - 13.7)	13.4 (11.5 - 14.4)	0.14
CRP, mg/dL	0.93 (0.15 - 2.35)	0.39 (0.15 - 1.20)	0.236
Albumin, g/dL	3.3 (3.2 - 3.6)	3.5 (3.1 - 3.8)	0.546
Serum LDH, IU/L	263 (218.5 - 292.7)	221 (198 - 273.5)	0.049
Serum KL-6, U/ml	1319 (790 - 2046)	1123 (684 - 1527)	0.18
Serum SP-D, ng/mL	114 (73 - 195.5)	197 (147 - 306)	0.003
GPS (0/1/2)	8 (33.3%)/6 (25.0%)/10 (41.7%)	21 (38.1%)/24 (43.6%)/10 (18.2%)	0.076
Oxygen flow			
O_2 at rest (< 2/2 - 4 L/min)	22(91.4%)/2(8.3%)	34 (64.2%)/19 (35.8%) (n = 53)	0.172
O_2 on exertion (< 2/3/4 - 6 L/min)	11 (45.9%)/8 (33.3%)/5 (20.8%)	17 (32.1%)/24 (45.3%)/12 (22.6%) (n = 53)	0.078
Pulmonary function test			
FVC (L)	2.07 (1.50 - 2.94) (n = 15)	2.12 (1.72 - 2.46) (n = 48)	0.443
FVC, percent predicted	84.8 (63.2 - 92.5)% (n = 15)	68.7 (56.6 - 81.0)% (n = 48)	0.211
DLco, percent predicted	42.6 (38.8 - 50.0)% (n = 15)	38.6 (34.0 - 52.4)% (n = 38)	0.695
GAP index (points)	1(1 - 2) (n = 15)	5 (4 - 5) (n = 38)	< 0.001
GAP index (I/II/III/IV)	9 (60.0%)/4 (26.6%)/1 (6.7%)/1 (6.7%) (n = 15)	0 (0%)/6 (15.7%)/24 (63.2%)/8 (21.1%) (n = 38)	
HRCT finding			
UIP pattern	18 (75%)	55 (100%)	< 0.001
Treatment during the study period			
Corticosteroids	23 (95.8%)	19 (34.5%)	< 0.001
Immunosuppressive agents	24 (100%)	0 (0%)	< 0.001
Antifibrotic agents	3 (12.5%)	21 (38.2%)	< 0.001
Nintedanib	3 (12.5%)	15 (27.2%)	
Pirfenidone	0 (0%)	7 (12.7%)	

Data are presented as median (interquartile range) or number (%).

3.2. Survival

The mean survival time from ILD diagnosis was 112.0 months (95% CI: 52 - 168)

for CTD-ILD patients and 46.2 months (95% CI: 35.7 - 52.9) for IPF patients. Kaplan-Meier method analysis revealed that CTD-ILD patients had significantly better overall survival than IPF patients (log-rank test, $p < 0.001$) (Figure 2).

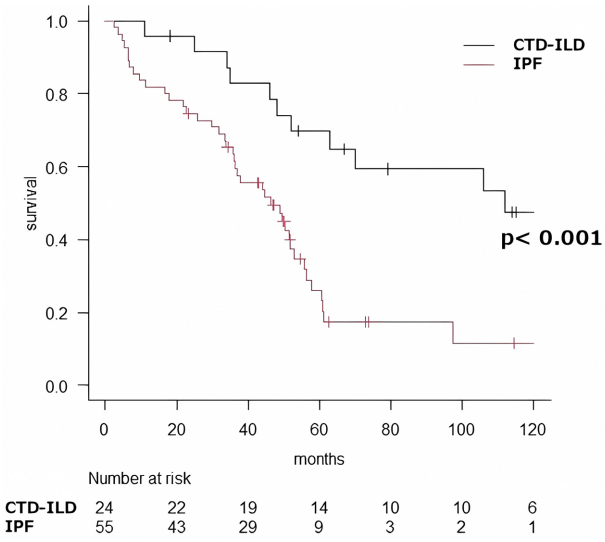

Figure 2. Kaplan-Meier survival curve of patients with CTD-ILD (n = 24) and IPF (n = 55) after the diagnosis of ILD. Median survival of patients with CTD-ILD and IPF after diagnosis of ILD was 112.0 (n = 24, 95% CI: 52 - 168) and 46.2 (n = 55, 95% CI: 35.7 - 52.9) months (log-rank test, $p < 0.001$), respectively.

However, the mean survival time after LTOT initiation was 628 days (95% CI: 170 - 1551) for CTD-ILD patients and 356 days (95% CI: 203 - 610) for IPF patients. Kaplan-Meier analysis showed no significant difference in survival between the two groups after LTOT initiation (log-rank test, $p = 0.276$) (Figure 3).

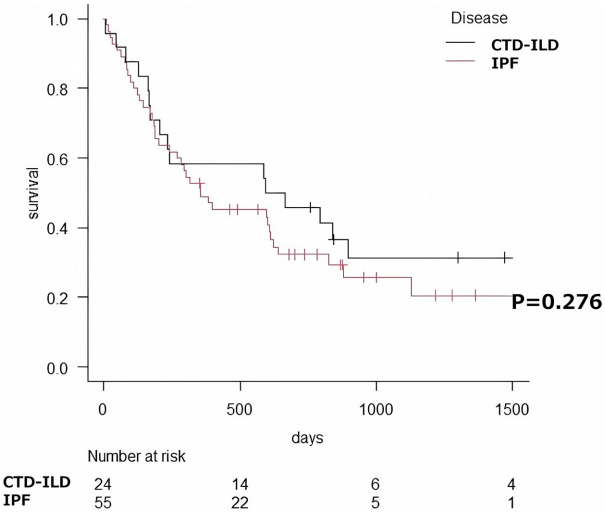

Figure 3. Kaplan-Meier survival curve of patients with CTD-ILD (n = 24) and IPF (n = 55) after the initiation of LTOT. Median survival of patients with CTD-ILD and IPF after diagnosis of ILD were 628 (95% CI: 170 - 1551) and 356 (95% CI: 203 - 610) days (log-rank test, $p = 0.276$), respectively.

4. Discussion

This retrospective study compared the clinical data and survival outcomes between 24 CTD-ILD patients and 55 IPF patients who were introduced to LTOT. Patients with CTD-ILD demonstrated better overall survival; however, there was no significant difference in prognosis after LTOT initiation between the two groups.

Recently, the definition and diagnostic criteria for progressive fibrosis-interstitial lung disease (PF-ILD) or progressive pulmonary fibrosis (PPF) have been proposed [17].

Various definitions of PF-ILD/PPF have been reported, based on expert opinions, clinical trial definitions, and the recently published international guidelines [18] [19]. PF-ILD/PPF has been reported in many CTDs, however, the prevalence and progression of PF-ILD/PPF have varied among CTDs [20] [21]. A recent prospective registry study reported that 45% (402/902) of CTD-ILD patients met the PF-ILD criteria, and the time to progression of ILD in patients with CTD-ILD was longer compared to IPF [22]. In our study, the time from ILD diagnosis to LTOT initiation was significantly longer for patients with CTD-ILD than for those with IPF (36.0 vs 23.5 months, $p = 0.028$). Additionally, patients with CTD-ILD had better overall survival than those with IPF (112.0 vs 46.2 months, $p < 0.001$), consistent with previous studies [8] [9].

On the other hand, there have been limited studies examining the prognosis of patients with CTD-ILD after the initiation of LTOT. As far as we know, there has been only one study regarding the prognosis of CTD-ILD patients with LTOT. Higashiguchi et al. reported that patients with interstitial pneumonia associated with collagen vascular disease (CVD-IP, $n = 27$) had significantly longer survival times from the initiation of LTOT compared to those with IIP ($n = 49$) (median survival, 51.7 months in CTD-ILD vs 18.8 months in IIP, $p < 0.001$) [23]. They also demonstrated that HRCT pattern was not associated with prognosis in either the IIP or CVD-IP groups. In the present study, we found no significant difference in mean survival time between CTD-ILD and IPF patients after the initiation of LTOT (628 vs 356 days, log-rank test, $p = 0.276$). The reasons for the differences in prognosis after the initiation of LTOT between the study by Higashiguchi *et al.* and the present study are uncertain; however, the proportion of UIP pattern on HRCT of CTD-ILD patients in the present study was higher (18/24 cases, 75%) compared to their study (8/27 cases, 29.6% with UIP/Possible UIP pattern). Additionally, the underlying CTDs differed between the two studies: the proportion of RA patients in our study (9/24 cases, 37.5%) was higher than in their study (5/27 cases, 18.5%). The UIP pattern on HRCT has been reported as an independent mortality risk in CTD-ILD, particularly in RA [24]-[26]. The high proportion of UIP patterns in HRCT and patients with RA may account for the different results between the two studies. CTD-ILD is usually treated individually and comprehensively based on the underlying diseases and patients' conditions. Pharmacological treatments including corticosteroids, immunosuppressive agents or biological products, and non-pharmacological management such as prevention of

infection decided by the attending physicians could also affect our results.

Recent clinical trials (SENSCIS and INBUILD studies) demonstrated that nintedanib, an antifibrotic agent, inhibited the annual decline of FVC in systemic sclerosis-interstitial lung disease (SSc-ILD) and PF-ILD/PPF [27] [28]. In this retrospective study between 2014 and 2020, patients with CTD-ILD were collected and analyzed before the proposal of the PF-ILD/PPF definition. Nintedanib was used in only 3 cases of CTD-ILD, all of which exhibited UIP patterns on HRCT. Two of three patients (each one case of RA and SSc) who were treated with nintedanib survived during the study period. We have recently reported the prognostic significance of antifibrotic agents in IPF patients undergoing LTOT [12]. IPF patients treated with antifibrotic agents in combination with LTOT had significantly longer survival compared to those not receiving antifibrotic agents. Moreover, in IPF patients who were introduced LTOT, treatment with antifibrotic agents was the independent factor for favorable survival. From the results of our study, the prognosis of CTD-ILD patients with UIP pattern may be similar to that of IPF patients after the initiation of LTOT. Early intervention of antifibrotic agents could contribute to better survival in patients with progressive CTD-ILD. Further studies are needed to establish the efficacy of antifibrotic agents in CTD-ILD patients undergoing LTOT.

This study has several limitations. First, as the data were collected from a single center, we could not entirely avoid selection bias associated with patients and the timing of LTOT introduction. Second, we could not completely exclude the possibility of opportunistic infection in CTD-ILD that might affect the prognosis. However, most patients died from progressive respiratory failure. The third and most significant limitation was the small number of patients with CTD-ILD undergoing LTOT, which did not allow for comprehensive multivariable analysis. Despite these limitations, this is the first report on the prognosis of CTD-ILD after the initiation of LTOT compared with IPF, and the results were significant and meaningful for clinical practice.

5. Conclusion

The overall survival of patients with CTD-ILD was significantly longer than that of patients with IPF. However, the results of our study revealed no difference in the prognosis of patients between the CTD-ILD and IPF groups after the initiation of LTOT. Therefore, in CTD-ILD, it is important to start early treatment and management, including the introduction of antifibrotic drugs, to prevent progression.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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