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Prognostic Prediction in Patients with Interstitial Lung Disease Following Long-Term Oxygen Therapy Initiation Using C-Reactive Protein

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Abstract

Introduction: Interstitial lung disease (ILD) is a progressive pulmonary disease, and many patients with ILD eventually require long-term oxygen therapy (LTOT) despite intensive treatment. Patients with ILD undergoing LTOT are usually in an advanced stage. It is clinically important to predict the prognosis of patients whose prognosis is potentially poor. However, the prognosis of patients with ILD undergoing LTOT remains unclear. Recently, serum C-reactive protein (CRP) has been reported to be associated with mortality in patients with ILD. The aim of this study was to evaluate the utility of CRP in predicting the prognosis of patients with ILD undergoing LTOT. **Methods:** We enrolled 101 patients with ILD undergoing LTOT at our hospital between January 2014 and December 2020. We categorized the patients based on their CRP levels and compared their median overall survival (OS). A Cox regression analysis was employed to determine the relationship between CRP levels and prognosis. **Results:** The number of patients categorized into Group A (CRP < 5 mg/L) and Group B (CRP ≥ 5 mg/L) was 42 and 59, respectively. The median OS of Group B was significantly shorter than that of Group A (7.66 months [95% CI: 4.24 - 13.0] vs. 20.4 months [95% CI: 9.63 - 28.8]; HR: 1.98; 95% CI: 1.24 - 3.19; $p < 0.01$). Multivariate Cox proportional hazards analysis demonstrated an independent association between CRP levels and OS (HR: 1.43; 95% CI: 1.12 - 1.83; $p < 0.01$). **Conclusion:** CRP is a promising tool for predicting the prognosis of patients with ILD undergoing LTOT.

Keywords

Interstitial Lung Disease, Long-Term Oxygen Therapy, CRP, Prognosis

1. Introduction

The prognosis of patients with interstitial lung disease (ILD) is poor [1] [2]. Oxygenation worsens as the disease progresses, and some patients with chronic respiratory failure are treated with long-term oxygen therapy (LTOT). In general, LTOT reduces the cardiac workload by alleviating hypoxic pulmonary vasoconstriction and preventing hypoxia. Chronic obstructive pulmonary disease (COPD) is a typical disease requiring LTOT, and it has been reported that LTOT improves the prognosis of COPD patients with chronic respiratory failure [3] [4]. However, little is known about the prognosis of ILD patients undergoing LTOT [5] [6]. Patients with ILD undergoing LTOT are generally in the advanced stages of the disease, and it is clinically important to predict the prognosis of patients whose prognosis is potentially poor. Therefore, identifying prognostic factors in ILD patients with chronic respiratory failure undergoing LTOT is crucial.

Several studies have shown that C-reactive protein (CRP) is associated with poor prognosis in patients with idiopathic pulmonary fibrosis (IPF) and collagen vascular disease-associated interstitial lung disease (CVD-ILD) [7] [8]. Recently, CRP has been reported to correlate with mortality in patients with various forms of ILD, including IPF, fibrotic hypersensitivity pneumonitis (Fibrotic-HP), rheumatoid arthritis-associated ILD, and systemic sclerosis-associated ILD [9]. CRP has been reported to affect the lungs by stimulating immune cells to release inflammatory factors, which are thought to contribute to ILD progression by promoting inflammation and activating fibroblasts [10] [11].

Building upon this knowledge, we aimed to investigate whether CRP could serve as a prognostic marker for patients with ILD undergoing LTOT.

2. Materials and Methods

2.1. Patients and Study Design

This study enrolled patients with ILD who initiated LTOT at Tokyo Medical University Hospital between January 2014 and December 2020. Patients who initiated LTOT for diseases other than ILD and received transplants and patients whose date of death or serum CRP levels were not identified were excluded. The clinical data of each patient were obtained from the medical records. The enrolled patients were divided into two groups based on their serum CRP levels, and clinical variables, including overall survival (OS), were retrospectively compared between the two groups. Patient survival was monitored until August 2021. Furthermore, we investigated the correlations between CRP levels and other parameters. The ethical committee of Tokyo Medical University approved this retrospective study protocol (approval number: T2021-0250) and waived the requirement for informed

consent. However, we provided the opportunity to refuse participation in this study using the opt-out method. All methods were performed in accordance with relevant guidelines and regulations.

2.2. Data Collection

The groups divided by serum CRP levels were determined on the day LTOT was initiated. Patients were categorized into Group A (CRP < 5 mg/L) and Group B (CRP ≥ 5 mg/L) based on their serum CRP levels. CRP levels were classified at 5 mg/L, as previously reported, as a marker for the presence of inflammation [9] [12] [13]. We also investigated the following: gender, age, body mass index (BMI), albumin (Alb), haemoglobin (Hb), lactate dehydrogenase (LD), surfactant protein D (SP-D), Krebs von den Lungen-6 (KL-6), % forced vital capacity (%FVC), % diffusing capacity of the lung for carbon monoxide (%DL_{CO}), six-minute walk test (6MWT) while inhaling supplemental oxygen [14], Gender-Age-Physiology (GAP) score [15], and oxygen flow at rest and on exertion. If blood tests were not performed on the day LTOT was initiated, the data obtained on the closest day within 3 months from the commencement of LTOT were recorded. If the pulmonary function test or 6MWT was not performed at the initiation of LTOT, the data obtained on the closest day within 6 months from its commencement were recorded. In addition, the use of antifibrotic agents (pirfenidone or nintedanib) and immunosuppressive agents (steroids, tacrolimus, or ciclosporin) were also recorded. The presence of current and previous cancer was also recorded. Current cancer was defined as cancer treated or followed up at the time of LTOT initiation, while a previous cancer was defined as a cured cancer. We divided ILD, based on medical records, into the following: idiopathic interstitial pneumonias (IIPs), CVD-ILD, fibrotic-HP, chronic eosinophilic pneumonia, drug-induced lung injury, and radiation-induced lung injury.

2.3. Diagnosis

Two respiratory physicians analysed the high-resolution computed tomography (CT) images. The diagnosis of IIPs was based on the exclusion of secondary ILD. Chest CT_patterns of patients with IIPs were classified into usual interstitial pneumonia (UIP), probable UIP, indeterminate for UIP, and alternative diagnosis based on international IPF guidelines; the latter three patterns were collectively defined as non-UIP patterns [16]. CVD-ILD was diagnosed based on the exclusion of other causes of lung injury and either on the presence of underlying collagen vascular disease or positive blood test results for autoimmune antibodies [17] [18]. The diagnosis of other types of ILD was based on the decision of the attending physician.

2.4. Statistical Analysis

All values are expressed as medians and interquartile ranges. Fisher's exact test and Mann-Whitney U test were used to compare baseline patient characteristics. Moreover, correlations were analysed using Spearman's correlation test. OS was assessed using the Kaplan-Meier curve. OS differences between groups were com-

pared using the log-rank test and univariate analysis with a Cox proportional hazards model. To evaluate the independent relationship between OS and parameters, a Cox proportional hazards model was employed. A p-value of less than 0.05 was set as the threshold for statistical significance. Statistical analyses were performed using EZR version 1.54 (Saitama Medical Center, Jichi Medical University, Saitama, Japan). Serum CRP levels below the lower detection limit set half the detection limit [19].

3. Results

3.1. Patient Characteristics

Between 2014 and 2020, 647 patients initiated LTOT in our hospital. Patients for whom LTOT was initiated for reasons other than ILD were excluded from the study. Other reasons for initiating LTOT included lung cancer, COPD, and chronic thromboembolic pulmonary hypertension. Additionally, patients who received transplants and those with insufficient data were excluded from the study. Ultimately, 101 patients were enrolled in this study (**Figure 1**). The median age of the patients was 73 (47 - 97) years, and 68.3% were men. The number of patients categorized into Group A and Group B was 42 and 59, respectively. Alb, Hb, CRP, and the number of patients with current cancer were significantly different between the two groups (**Table 1**). Next, we investigated the correlations between CRP levels and other parameters, including age, BMI, Alb, Hb, LD, SP-D, KL-6, %FVC, $\%DL_{CO}$, 6MWT, GAP score, oxygen flow at rest, and oxygen flow during exertion (**Table 2**). Alb and Hb demonstrated a weak negative correlation with CRP levels. We also examined the median CRP levels for each parameter: current cancer, previous cancer, use of antifibrotic agents, use of immunosuppressive agents, gender, and IIPs (**Table 3**). There was a significant difference in median CRP levels between patients with and without current cancer.

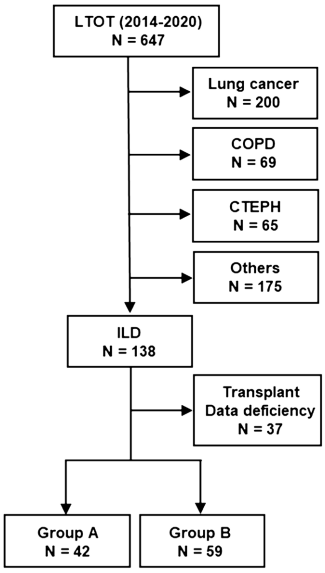

Figure 1. Flow chart of the study population.

Table 1. Characteristics of ILD patients and clinical parameters according to CRP levels.

	Group A (CRP < 5 mg/L)	Group B (CRP ≥ 5 mg/L)	p-value
No. of patients	42	59	
Male, n (%)	30 (71.4)	40 (67.8)	1.00
Age (years)	73.5 (47 - 88)	73 (59 - 97)	0.57
BMI (kg/m^2)	22.7 (13.8 - 30.7)	22.0 (16.1 - 39.4)	0.35
Alb (g/L)	35.5 (26 - 43)	32.0 (20 - 49)	**<0.01**
Hb (g/L)	13.5 (9.9 - 17.1)	12.2 (8.6 - 18.0)	**<0.01**
LD (U/L)	242 (155 - 595)	240 (150 - 609)	0.63
CRP (mg/L)	2.3 (3.0 - 4.5)	16 (5.0 - 105)	**<0.01**
SP-D (ng/mL)	196.5 (22.9 - 593) (N = 32)	198 (38.4 - 568) (N = 46)	0.68
KL-6 (U/mL)	1336.5 (242 - 9474) (N = 40)	1051 (263 - 4457) (N = 55)	0.37
%FVC (%)	73.4 (28.9 - 130.2) (N = 29)	72.6 (35.6 - 121.8) (N = 29)	0.94
%DL_{CO} (%)	40.7 (21.3 - 88.2) (N = 21)	42.6 (19.3 - 86.9) (N = 18)	0.97
6MWT (M)	235 (120 - 400) (N = 14)	260 (170 - 380) (N = 13)	0.98
GAP score	4 (0 - 6) (N = 21)	4 (0 - 6) (N = 18)	0.28
Oxygen flow at rest (L/min)	1 (0 - 3) (N = 41)	1 (0 - 4) (N = 56)	0.098
Oxygen flow on exertion (L/min)	3 (1 - 5) (N = 41)	3 (1 - 6) (N = 56)	0.54
Current cancer, n (%)	5 (11.9)	21 (35.6)	**<0.05**
Previous cancer, n (%)	7 (16.7)	7 (11.9)	0.57
Use of antifibrotic agents, n (%)	10 (23.8)	7 (11.9)	0.18
Use of immunosuppressive agents, n	33 (78.6)	35 (59.3)	0.054
IIPs			
UIP pattern, n (%)	16 (38.1)	21 (35.6)	0.84
Non-UIP pattern, n (%)	11 (26.2)	19 (32.2)	0.66
CVD-ILD, n (%)	9 (21.4)	16 (27.1)	0.64
Fibrotic HP, n (%)	4 (9.5)	1 (1.7)	0.31
CEP, n (%)	1 (2.4)	0 (0)	0.42
Drug-induced lung injury, n (%)	1 (2.4)	1 (1.7)	1.00
Radiation-induced lung injury, n (%)	0 (0)	1 (1.7)	1.00

Patients were categorized into Group A (CRP < 5 mg/L) and Group B (CRP ≥ 5 mg/L) based on their CRP levels. The median values and interquartile ranges are presented as appropriate. ILD: interstitial lung disease; CRP: C-reactive protein; No.: number; BMI: body mass index; Alb: albumin; Hb: hemoglobin; LD: lactate dehydrogenase; SP-D: surfactant protein D; KL-6: krebs von den Lungen-6; %FVC: %forced vital capacity; %DL_{CO}: %diffusing capacity of the lung for carbon monoxide; 6MWT: six-minute walk test; GAP: gender, age, and physiology; IIPs: idiopathic interstitial pneumonias; UIP: usual interstitial pneumonia; CVD-ILD: collagen vascular disease-interstitial lung disease; Fibrotic HP: Fibrotic hypersensitivity pneumonitis; CEP: chronic eosinophilic pneumonia.

Table 2. Correlations between CRP levels and other factors.

Factor	Correlation Coefficient	p-value
Age (years)	−0.01	0.95
BMI (kg/m^2)	−0.03	0.87
Alb (g/L)	−0.37	**<0.01**
Hb (g/L)	−0.32	**<0.01**
LD (U/L)	−0.08	0.46
SP-D (ng/mL)	−0.04	0.73
KL-6 (U/mL)	0.03	0.81
%FVC (%)	0.14	0.29
%DL_{CO} (%)	0.19	0.25
6MWT (M)	−0.22	0.45

Continued

GAP score	0.16	0.34
Oxygen flow at rest (L/min)	0.23	0.14
Oxygen flow on exertion (L/min)	0.23	0.17

CRP: C-reactive protein; BMI: body mass index; Alb: albumin; Hb: hemoglobin; LD: lactate dehydrogenase; SP-D: surfactant protein D; KL-6: krebs von den lungen-6; %FVC: %forced vital capacity; $\%DL_{CO}$: %diffusing capacity of the lung carbon monoxide; 6MWT: six-minute walk test; GAP: gender, age, and physiology.

Table 3. Comparison of median CRP levels across different clinical factors.

Factor	Median CRP	p-value
Current cancer (No vs. Yes)	4.75 vs. 12.0	**<0.05**
Previous cancer (No vs. Yes)	6.00 vs. 7.65	0.79
Use of antifibrotic agents (No vs. Yes)	7.80 vs. 2.40	0.07
Use of immunosuppressive agents (No vs. Yes)	8.65 vs. 5.00	0.18
Gender (Male vs. Female)	5.85 vs. 6.55	0.89
IIPs (UIP vs. non-UIP)	5.55 vs. 8.00	0.24

CRP: C-reactive protein; IIPs: idiopathic interstitial pneumonias; UIP: usual interstitial pneumonia.

3.2. Survival Analysis

The Kaplan-Meier survival curves for the patients are presented in **Figure 2**. During the observation period, 76 patients died, with a median OS of 11.8 months. In Group A, 28 patients died, whereas in Group B, 48 patients died. The median OS for patients in Group A and Group B was 20.4 months (95% confidence interval [CI]: 9.63 - 28.8) and 7.66 months (95% CI: 4.24 - 13.0), respectively (hazard ratio [HR]: 1.98; 95% CI: 1.24 - 3.19; $p < 0.01$). The one-year survival rates for Group A and Group B were 61.8% (95% CI: 45.4 - 74.6) and 38.9% (95% CI: 26.3 - 51.4), respectively ($p < 0.01$). The three-year survival rates were 29.2% (95% CI: 14.6 - 45.5) and 11.9% (95% CI: 4.1 - 24.2), respectively ($p < 0.01$). The five-year survival rates were 17.5% (95% CI: 5.4 - 35.5) and 7.9% (95% CI: 1.8 - 20.4), respectively ($p < 0.01$). The results suggest that high CRP levels are associated with a significantly shorter survival time.

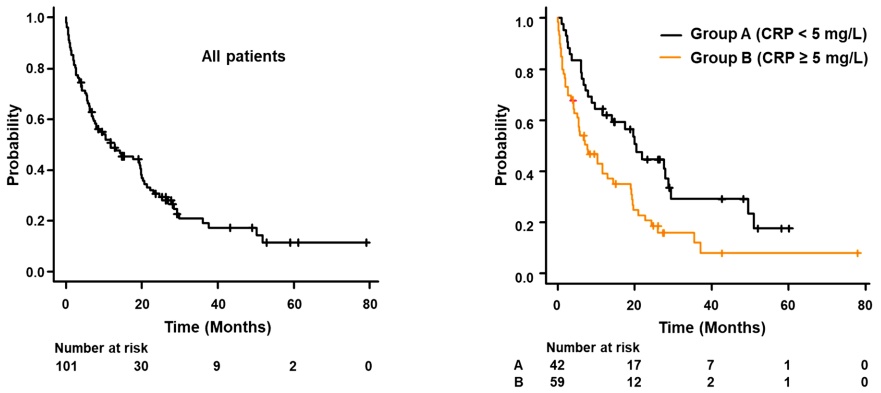

Figure 2. Kaplan-Meier survival curves for overall survival of patients with ILD after initiation of LTOT.

3.3. Multivariate Analysis of the Survival

Univariate Cox proportional hazards analysis for OS was performed using CRP levels, revealing a significant association between OS and CRP levels (HR: 1.15; 95% CI: 1.05 - 1.26; $p < 0.01$). Multivariate Cox proportional hazards analysis, which evaluated the independent association between OS and relevant parameters (Alb, Hb, CRP, BMI, %FVC, use of antifibrotic agents, and current cancer), found an independent association between OS and CRP levels (HR: 1.43; 95% CI: 1.12 - 1.83; $p < 0.01$) (Table 4). These findings suggest that elevated CRP levels are independently and positively associated with an increased risk of mortality.

Table 4. Multivariate Cox proportional hazards analysis for overall survival.

Factor	HR (95% CI)	p-value
Alb (g/dL)	0.50 (0.21 - 1.17)	0.11
Hb (g/L)	1.19 (0.98 - 1.45)	0.08
CRP (mg/L)	1.43 (1.12 - 1.83)	**<0.01**
BMI (kg/m^2)	0.92 (0.84 - 1.00)	0.05
%FVC (%)	0.98 (0.96 - 1.00)	0.06
Use of antifibrotic agents	0.83 (0.34 - 2.07)	0.70
Current cancer	0.52 (0.23 - 1.18)	0.12

HR: hazard ratio; CI: confidence interval; vs.: versus; Alb: albumin; Hb: hemoglobin; CRP: C-reactive protein; BMI: body mass index; %FVC: % forced vital capacity.

4. Discussion

This study demonstrated that CRP is associated with the mortality of patients with ILD undergoing LTOT. Several prognostic predictors of patients with ILD have been reported. Among the prognostic predictors, elevated CRP levels have been reported to be associated with earlier mortality in various types of ILD [7]-[9]. While the accuracy of prognostic predictors may vary with the degree of disease progression, the significance of CRP in predicting prognosis was demonstrated even in patients with ILD undergoing LTOT, who are typically in advanced stages.

CRP is an acute-phase inflammatory protein secreted by hepatocytes, with its levels increasing in response to inflammatory cytokines. Although the precise mechanism by which circulating CRP levels increase is not fully understood, several potential reasons for this increase can be considered. Secondary ILDs, such as CVD-ILD and Fibrotic-HP, are often associated with inflammatory diseases and are triggered by inflammatory stimuli. Thus, it is understandable that CRP levels increase in these types of ILD and correlate with prognosis. In contrast, IPF is thought to be less directly related to inflammation. However, elevated CRP levels have recently been reported as a risk factor for the development of IPF [20]. Therefore, CRP may play a role in the pathogenesis of IPF. Indeed, CRP can induce the secretion of interleukin-1 and tumor necrosis factor-α from alveolar macrophages [10]. These cytokines are believed to contribute to the pathogenesis of ILD by amplifying inflammation and activating fibroblasts [11]. Furthermore, CRP may have a direct pathogenic effect on the severity of lung tissue damage and

aberrant wound healing by amplifying pre-existing inflammation and tissue injury [21]. Another potential explanation for elevated CRP levels is infection, a significant cause of inflammation. Patients with ILD are reported to be particularly susceptible to chronic pulmonary infections, primarily caused by *Mycobacterium* and *Aspergillus* [22]. Additionally, many patients with ILD are treated with immunosuppressive agents, which increase their susceptibility to various types of infection. Furthermore, patients with ILD are prone to developing lung cancer [23], a condition that can also lead to elevated CRP levels.

The Kaplan-Meier analysis revealed that deaths were more prevalent at CRP levels exceeding 5 mg/dL, irrespective of the observation point. One explanation for the association between CRP levels and mortality in ILD is acute exacerbation, a highly lethal condition and the leading cause of mortality in these patients [23]. As previously mentioned, CRP can induce the secretion of inflammatory cytokines from alveolar macrophages. Thus, the lungs of ILD patients with elevated CRP levels may be in a highly inflammatory state, making them more susceptible to acute exacerbation. Previous studies have demonstrated that ILD patients with high CRP levels are prone to acute exacerbation [24] [25]. Additionally, we have reported that the Glasgow Prognostic Score, which includes CRP and Alb, predicts chemotherapy-triggered acute exacerbation in ILD patients with lung cancer [26] [27]. Another factor to consider is the association with systemic inflammation. In COPD, systemic inflammation, as assessed by CRP levels, has been reported to be associated with high resting energy expenditure, low exercise capacity, and impaired respiratory function [28]. Moreover, COPD patients with persistent systemic inflammation have been shown to exhibit increased all-cause mortality [29]. Circulating inflammatory cytokines, such as IL-1β and TNF-α, are elevated in ILD as well as COPD. This suggests that inflammatory cytokines originating from the lungs may translocate into the systemic circulation, contributing to systemic inflammation in both diseases [30]. The metabolic and functional impairments caused by systemic inflammation may also affect the prognosis of ILD. Mortality in ILD patients is also associated with infection and cancer, which are major causes of death in this population [23]. These factors are thought to contribute to the observed association between CRP levels and prognosis in ILD patients.

FVC is a key measure in assessing lung function, particularly in patients with ILD. In the context of ILD, a decline in FVC over time is often considered a significant indicator of disease progression and prognosis [31] [32]. However, in contrast to these reports, our multivariate analysis did not demonstrate an independent association between %FVC and prognosis. Since this study included only patients with advanced-stage ILD, inflammation may have a more pronounced impact on prognosis than lung function in the advanced stages of the disease.

The GAP score is reportedly a prognostic factor for IPF [33] [34]. Recently, it has also been applied to the prognosis of patients with anti-MDA5 antibody-positive [35]. When we divided the patients into two groups, the GAP score 0 - 3 and 4 - 6 groups, the median OS of the GAP score 4 - 6 group was significantly shorter

than that of the GAP score 0 - 3 group (data not shown). Therefore, the GAP score may be useful in predicting the prognosis of patients with ILD undergoing LTOT. However, the GAP score requires a pulmonary function test, making the scoring process difficult. In terms of availability, CRP is considered to be superior to the GAP score.

This study has several limitations. First, it was a single-center, non-randomized, retrospective study. As a result, we were unable to examine all possible prognostic factors or account for selective patient bias, such as the use of antifibrotic agents and underlying diseases. Second, approximately half of the patients in this study did not undergo pulmonary function tests due to severe dyspnea. Third, due to the retrospective design, we were unable to assess the cause of death, smoking history, and comorbidities in all enrolled ILD patients.

5. Conclusion

CRP is considered an important factor in the prognosis of patients with ILD undergoing LTOT. This study is clinically significant because prognostic predictors for patients with ILD undergoing LTOT have been poorly understood. Predicting prognosis using CRP is both simple and cost-effective. A large-scale, prospective multicenter study with a validation cohort is needed to confirm the validity of our results.

Conflicts of Interest

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

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