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

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# Abstract

**Background:**

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 52 IPF patients who were introduced LTOT.

**Results:**

The 6-, 12-, and 24-month survival rates in IPF patients after introduction of LTOT were 72.8%, 48.3%, and 28.9%, respectively. Univariate analysis demonstrated that gender female (hazard ratio [HR] 7.394, p=0.049) and treatment with antifibrotic agents (HR 2.285, p=0.022) were associated with favorable survival, while multivariate analysis revealed that treatment with antifibrotic agents was the independent predictor (HR 2.121, p=0.037). Moreover, IPF patients treated with antifibrotic agents with LTOT had significantly longer survival than those without antifibrotic agents (p = 0.0165).

**Conclusion:**

In IPF patients who were introduced LTOT, treatment with antifibrotic agents was the independent factor for favorable survival. Continuous treatment with antifibrotic agents may improve prognosis of IPF even after initiation of LTOT.


# 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 5years (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.

# Materials And Methods

**Methods**

We retrospectively reviewed medical records from consecutive 52 idiopathic pulmonary fibrosis (IPF) patients who were introduced to long-term oxygen therapy between 2014 and 2020 at the Tokyo Medical University Hospital. This study was approved by the Ethics Committee of Tokyo Medical University Hospital (approval No. T2021-0250). The requirement for informed consent was waived by the Ethics Committee of Tokyo Medical University because of the retrospective nature of the study. All data were anonymized prior to analysis. All methods were carried out in accordance with relevant guidelines and regulations.

## Data collection

Demographic variables including patients' characteristics (age, gender, smoking history, BMI), clinical data, and the use of medications (antifibrotic agents, immunosuppretants) were collected at the time of LTOT initiation. Baseline hematology data were collected, including the white blood cell count (WBC), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), hemoglobin level, 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 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 with 6 months before initiation of LTOT was evaluated by the modified Gender-Age-Physiology (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 agents was decided by the attending physicians, considering the patients' condition.

## 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, 52 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 43 patients (83%) were male. Forty-seven patients (90.3%) were ex-smoker. The median BMI was 21.1. Twenty-one patients (40.4%) were treated with antifibrotic agents (nintedanib 14, pirfenidone 7). Of the 14 patients treated with nintedanib, 12 received and continued reduced-dose (200mg/day) of nintedanib due to adverse event, such as diarrhea, nausea, anorexia and liver dysfunction. Of 7 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 415 days (range 8-1505 days). Fifteen subjects (28.8%) survived during the observation period.

The Kaplan-Meier survival curve for all patients is shown in Fig. 1. The mean survival times of this group was 11.7 months. The 6-, 12-, 24-month survival rates after the initiation of LTOT were 72.8%, 38.3% and 28.9%, respectively.

The results of the univariable and confidence interval multivariable analysis are shown in **Table 2**. Female gender (hazard ratio [HR] = 7.394, 95% [CI]: 1.01-54, p = 0.049), treatment with antifibrotic agents (HR = 2.285; 95% CI: 1.12–4.63, p = 0.022) were favorable factors. Multivariable analysis identified the treatment with antifibrotic agents as the independent factor for better survival (HR = 2.121, 95% CI: 1.045–4.304, p = 0.037). The comparison of the group stratified by the treatment with antifibrotic agents showed no significant difference in the characteristics and disease activity, such as age, BMI, modified GAP score and GPS (**Table 3**).

The survival curves of the groups with and without antifibrotic agents are shown in Fig. 2.

IPF patients treated with antifibrotic agents who were introduced LTOT had significantly longer survival than those without antifibrotic agents (p = 0.0165).

# 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 knowledge, this is the first study evaluating the significance of antifibrotic medication 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, percent predicted VC, percent predicted FVC and percent predicted DLco, which were also component 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 gender female and treatment with antifibrotic agents were favorable factors.

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, 17). Even though its frequent use of LTOT, there is little information regarding the effectiveness of oxygen therapy and prognosis after 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 (18). Ahmadi et al. showed that the survival from initiation of LTOT was median 8.4 months in 285 ILD patients (19). 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 (20). 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, the median survival of IPF patients treated with antifibrotic agents was significantly longer than that of patients without antifibrotics (20.4 vs. 7.9 months, $p = 0.0165$). The comparison of the patient groups stratified by the use of antifibrotic agents showed no significant difference in the characteristics and disease severity such as age, BMI, modified GAP score and GPS. The results from multivariable analysis and comparison of survival curve suggest that treatment with antifibrotic agents may be beneficial in IPF patients even after initiation of LTOT.

Australian and European IPF registry studies showed that patients receiving antifibrotic medications had better survival those not on antifibrotic medications (21, 22). 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%). (23). In the present study, most of IPF patients were treated with doses of both nintedanib (200mg/day) and pirfenidone (600-1200mg/day) due to tolerability issues. Recent retrospective study demonstrated beneficial effects of low-dose pirfenidone (600-1200mg/day) on survival and pulmonary function decline in IPF patients (24). 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. Continuation of antifibrotic agents with low-dose may be beneficial for IPF patients even after initiation of LTOT. Prognostic efficacy of antifibrotic medication on survival in IPF with LTOT will be further investigated in the future, using large number of subjects.

The limitations of the study are its retrospective nature and potential selection bias. First, we were not able to study all the possible factors that influenced the survival of IPF patients with LTOT. Due to progressive dyspnea and insufficient forced lung volume of the subject, modified GAP scores were not obtained from all IPF patients. Second, as described, the criteria of dose- reduction or discontinuation of antifibrotic agents were not yet standardized and, thus, decided by the attending doctors.

In conclusion, from a real-world clinical setting, gender female 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.

# Abbreviations

ALC: Absolute lymphocyte count; ALI: Advanced lung cancer inflammatory index; ANC: Absolute neutrophil count; CI: Confidence interval; DLco: Diffusing capacity of the lung for carbon monoxide; FEV1.0: Forced expiratory volume in one second; FVC: Forced vital capacity; GAP: Gender-Age-Physiology; GPS: Glasgow Prognostic Score; HR: Hazard ratio; HRCT: High-resolution computed tomography; IIP: Idiopathic interstitial pneumonia; ILD: Interstitial lung disease; IPF: Idiopathic pulmonary fibrosis; IQR: interquartile range; KL-6: Sialylated carbohydrate antigen KL-6; LDH: Lactate dehydrogenase; LTOT: Long-term oxygen therapy; SP-D: Pulmonary Surfactant Protein-D; WBC: white blood cell count

# Declarations

### Ethics approval and consent to participate

This retrospective study was reviewed and approved by the Institutional Review Board and Ethics Committee of Tokyo Medical University Hospital (approval No. T2021-0250). The members of the Ethics Committee of Tokyo Medical University Hospital were Yoshihiko Kanno, Akihiko Goto, Takafumi Hamaoka, Kazutoshi Harada, Souichiro Shimizu, Shigeki Nakamura, Mana Yoshimura, Takashi Oda, Hidenobu Kamohara, Akira Honda, Shuko Abe, Makoto Kurata, Hiroe Ito, Yukiko Yano, Teruo Miyazaki, Satoru Makita, Tutomu Hoshino, Hiroki Takeda. Consent to participate statement: The requirement for informed consent was waived by the Ethics Committee of Tokyo Medical University because of the retrospective nature of the study. No written informed consent was obtained from participants.

### Consent for publication

Not applicable

### Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available because of participants' privacy and confidentiality, but are available from the corresponding author on reasonable request.

### Competing interests

The authors declare that they have no competing interests.

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Not applicable

### Contributions

MI, YK, YT, HT, RK, KT and SA made substantial contributions to conception, design, data analysis and manuscript preparation. TO, NS and RM were involved in acquisition of data. MI□SA were responsible for the assessment of HRCT. All authors have read and approved the manuscript. All authors read and approved the final manuscript and have given their consent to publish.

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# Tables

Table 1. Clinical characteristics of the study subject (n=52)

| Variable | Value median (IQR) |
|---|---|
| Demographic variables | |
| Age, y | 73(68-80) |
| Sex | |
| Female | 9 (17%) |
| Male | 43 (83%) |
| Smoking | |
| ex-smoker | 47 (90.3%) |
| never-smoker | 5 (9.6%) |
| BMI, $kg/m^2$ | 21.1 (18.3-24.4) |
| Laboratory variables | |
| Hemoglobin, g/dL | 13.4 (11.5-14.4) |
| NLR | 3.1 (2.2-6.5) |
| CRP, mg/dL | 0.35(0.15-1.35) |
| Albumin, g/dL | 3.5 (3.1-3.8) |
| ALI | 21.7 (11.6-39.7) |
| serum LDH, IU/L | 216 (195-261) |
| serum SP-D, ng/mL | 197 (148-301) |
| serum KL-6, U/mL | 1124 (696-1513) |
| GPS (0/1/2) | 21 (40.4%)/21 (40.4%)/10 (19.2%) |
| Pulmonary function | |
| FVC, percent predicted (n=42) | 66.6 (55.9-75.3) |
| FEV1.0, percent predicted (n=42) | 77.4 (67.9-93.5) |
| DLco, percent predicted (n=32)) | 39.3 (35.0-52.8) |
| modified GAP index (points) (n=32) | 7 (5-8) |
| modified GAP index (I/II/III) | 2 (6.2%)/15 (46.9%)/15 (46.9%) |
| Treatment | |
| antifibrotic | 21 (40.4%) |
| nintedanib | 14 (26.9%) |

| | |
|---|---|
| pirfenidone | 7 (10.2%) |
| immnosupprentants | 19 (36.5%) |

NLR: neutrophil-to-lymphocyte ratio, ALI: advanced lung cancer inflammation index, GPS: glasgow prognostic score, FVC: forced vital capacity, FEV1.0%: forced expiratory volume  in one second, DLco: diffusing capacity for carbon monoxide

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) | 0.994 | 0.515-1.918 | 0.985 | | 1.092 | 0.566-2.108 | 0.793 |
| Sex (female) | 7.394 | 1.013-54 | 0.049 | | 6.819 | 0.927-50.150 | 0.059 |
| Smoking (never smoker) | 0.241 | 0.033-1.771 | 0.162 | | | | |
| BMI (>21.2) | 0.543 | 0.280-1.055 | 0.072 | | | | |
| NLR (<3.1) | 1.113 | 0.583-2.125 | 0.745 | | | | |
| ALI (<21.7) | 0.63 | 0.326-1.216 | 0.169 | | | | |
| serum LDH (<216 IU/L) | 1.072 | 0.561-2.045 | 0.834 | | | | |
| serum SP-D (<197 pg/ml) | 1.678 | 0.844-3.337 | 0.139 | | | | |
| serum KL-6 (<1124 U/ml) | 0.738 | 0.383-1.423 | 0.364 | | | | |
| GAP score (<7) | 1.427 | 0.613-3.322 | 0.409 | | | | |
| GPS(=0) | 0.549 | 0.274-1.098 | 0.089 | | | | |
| %FVC (>66.6%) | 0.965 | 0.466-1.998 | 0.924 | | | | |
| Treatment with antifibrotic agents | 2.285 | 1.126-4.634 | 0.022 | | 2.121 | 1.045-4.304 | 0.037 |
| Treatment with immunosurppretants | 1.244 | 0.638-2.423 | 0.521 | | | | |

Table3. Comparison of clinical characteristics between the subgroup treated with and without antifibrotic agents

| Variable | with antifibrotic agents (n=21) | without antifibrotic agents (n=31) | P value |
|---|---|---|---|
| Age (years) | 73 (68-78) | 76 (67.5-83) | 0.170 |
| Sex male | 17 (80.9) | 27 (87.1) | 0.833 |
| Smoking (ex-smoker) | 19 (90.5) | 28 (90.3) | 1.000 |
| BMI | 21.4 (20.5-24.2) | 20.8 (18.1-24.0) | 0.410 |
| serum LDH | 251 (202-277) | 215 (189-245) | 0.233 |
| serum KL-6 | 1280 (613-1733) | 1108 (804-1424) | 0.889 |
| serum SP-D | 186 (146-253) | 217 (160-342) | 0.211 |
| Modified GAP score | 7 (5-8) | 8 (7-9) | 0.067 |
| GPS (0/1/2) | 10/9/2 (47.6/42.9/9.5) | 11/12/8 (35.5/38.7/25.8) | 0.327 |
| %FVC | 67.6 (55.5-75.7) | 62.4 (56.7-75.3) | 0.930 |
| %DLco | 39.3 (37.8-56.9) | 36.9 (32.1-46.7) | 0.165 |
| Treatment with immnosuppretants | 6 (28.6%) | 11 (35.5%) | 0.765 |

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

# Figures

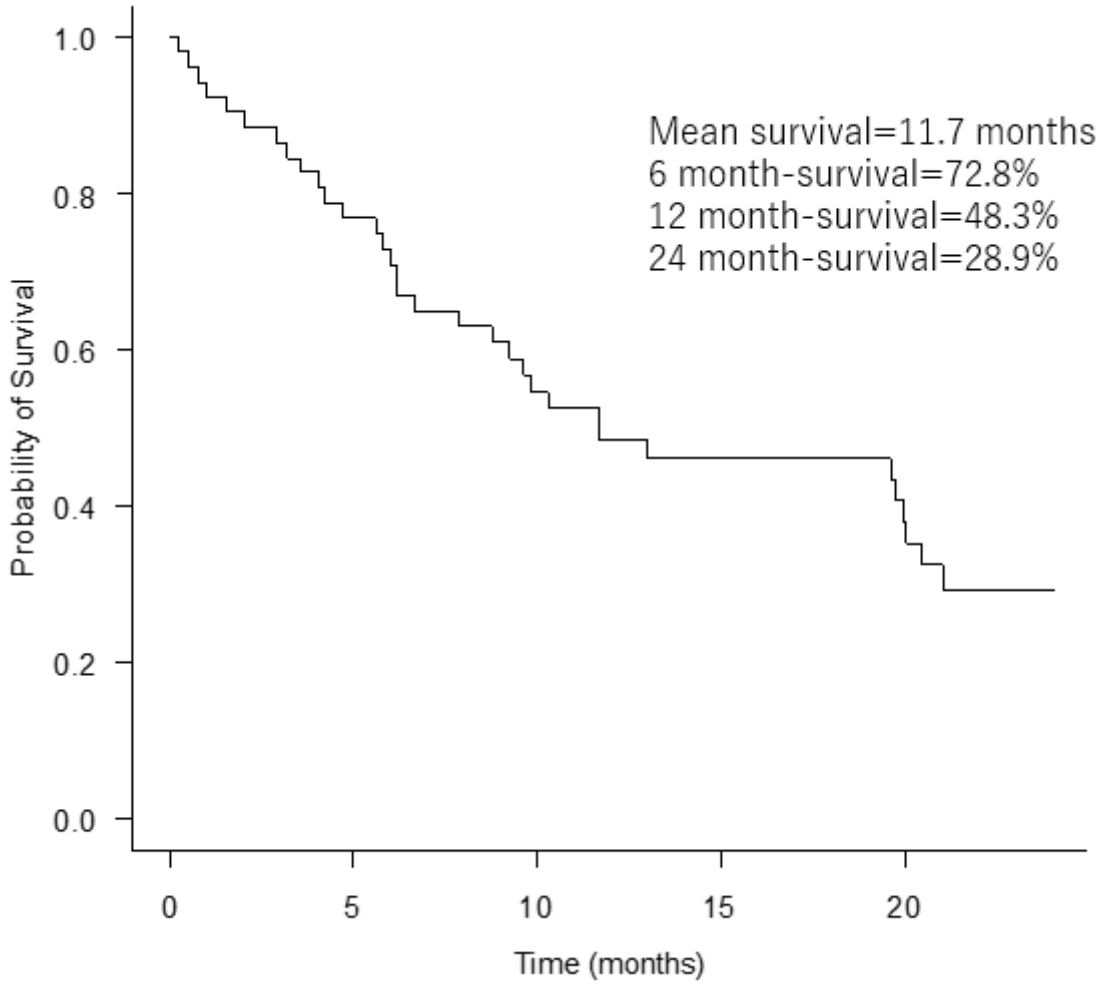
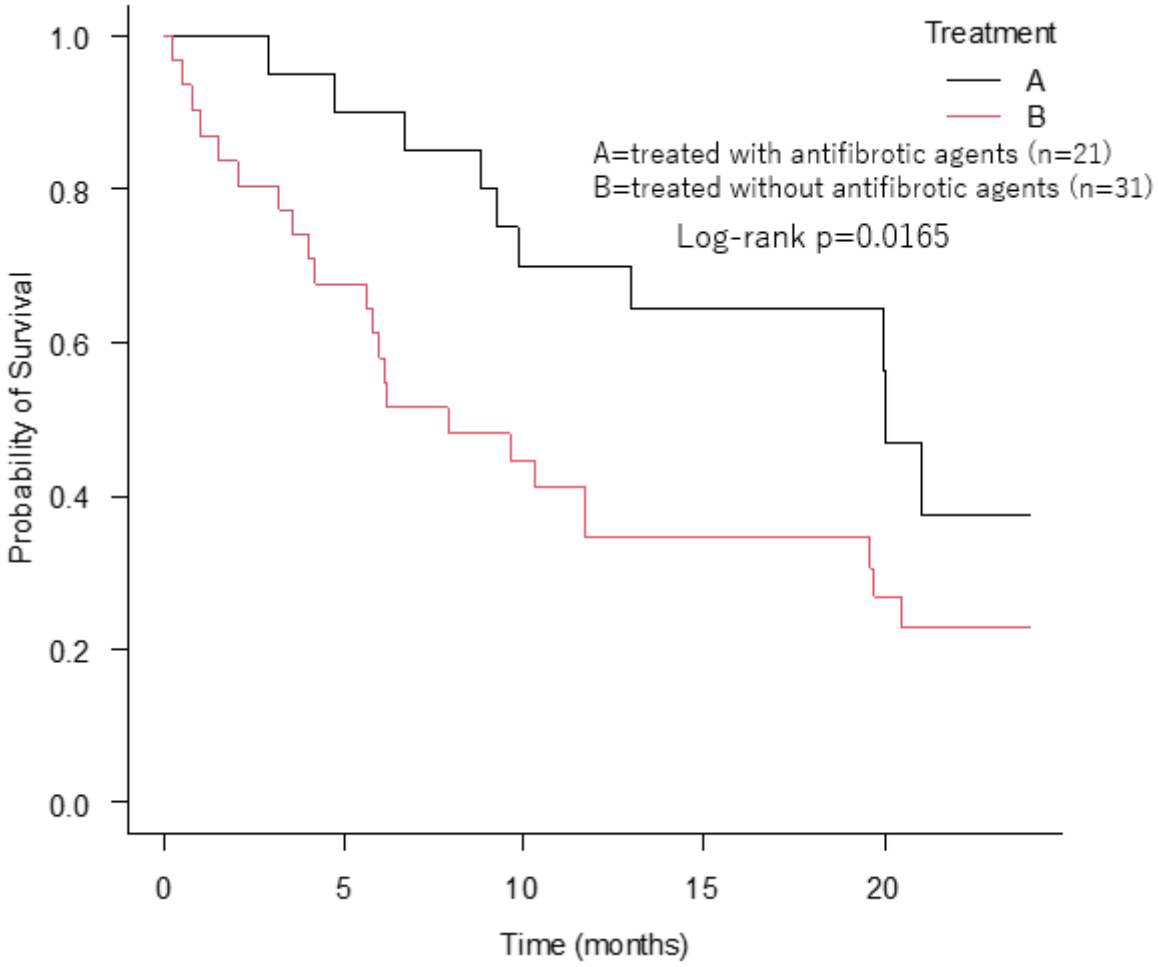



**Figure 1**

Kaplan-Meier survival curve for all patients




## Figure 2

Kaplan-Meier survival curves of the groups with and without antifibrotic agents