Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Is earlier always better? Timing of antifibrotic therapy and overall survival in idiopathic pulmonary fibrosis: a multicenter retrospective study

Junichi Aoyama

a-junichi@nms.ac.jp

Nippon Medical School Musashikosugi Hospital

Namiko Taniuchi

Nippon Medical School Musashikosugi Hospital

Sho Saito

Nippon Medical School Musashikosugi Hospital

Shunichi Nishima

Nippon Medical School Musashikosugi Hospital

Ken Okamura

Graduate School of Medicine, Nippon Medical School

Toru Tanaka

Graduate School of Medicine, Nippon Medical School

Yosuke Tanaka

Graduate School of Medicine, Nippon Medical School

Koichiro Kamio

Graduate School of Medicine, Nippon Medical School

Kenichiro Atsumi

Nippon Medical School Tama Nagayama Hospital

Takashi Hirose

Nippon Medical School Tama Nagayama Hospital

Yasuhiro Kato

Nippon Medical School Chiba Hokusoh Hospital

Tetsuya Okano

Nippon Medical School Chiba Hokusoh Hospital

Masahiro Seike

Graduate School of Medicine, Nippon Medical School

Yoshinobu Saito

Nippon Medical School Musashikosugi Hospital

Research Article

Keywords: Idiopathic pulmonary fibrosis, Antifibrotic therapy, Treatment initiation, Overall survival, Physician-judged deferred initiation, Real-world study, Referral delay, Prognosis

Posted Date: April 26th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9355521/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background

Antifibrotic therapies slow functional decline and improve survival in patients with idiopathic pulmonary fibrosis (IPF). Although early initiation is generally recommended, the optimal timing of treatment in real-world clinical practice remains uncertain. In particular, the relationship between the interval from diagnosis to treatment initiation and overall survival (OS), as well as the clinical implications of physician-judged deferred initiation, have not been fully clarified.

Methods

This multicenter retrospective cohort study included 150 patients diagnosed with IPF between April 2021 and March 2023 who received antifibrotic therapy. Treatment timing was evaluated using two definitions: 1) objectively defined intervals from diagnosis of IPF to treatment initiation (0–180, 181–364, and ≥ 365 days); and 2) physician-judged deferred initiation documented in medical records, defined as a clinician-guided postponement based on clinical, patient-related, or contextual considerations. The primary endpoint was OS. Landmark analyses were performed at 180 and 365 days to reduce immortal time bias. Survival outcomes were analyzed using the Kaplan–Meier method and Cox proportional hazards regression models. Multivariable analyses were used to adjust for relevant clinical covariates. In addition, reasons for delayed treatment initiation were examined.

Results

Among the 150 patients, longer diagnosis-to-treatment intervals were associated with longer OS in the landmark analyses. In contrast, patients with physician-judged deferred initiation showed no significant difference in OS (log-rank p = 0.164), although physician-judged deferred initiation was independently associated with OS in the multivariable analysis. In the multivariable analysis, older age, lower percent predicted forced vital capacity (%forced vital capacity), and a longer interval from referral to IPF diagnosis were also independently associated with OS. The most common reasons for delayed initiation included minimal or stable symptoms, concerns regarding adverse effects, and diagnostic uncertainty.

Conclusions

Physician-judged deferred initiation was independently associated with OS, likely reflecting underlying disease activity and clinical risk stratification rather than a direct causal effect of postponing therapy. These findings underscore the limitations of evaluating treatment timing solely by elapsed time and emphasize the importance of early diagnosis, timely referral to specialized centers, and individualized clinical decision-making in the management of IPF.

Clinical trial registration

Not applicable.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive interstitial lung disease characterized by irreversible fibrosis and remains associated with a poor prognosis. Antifibrotic agents, including nintedanib and pirfenidone, reduce the decline in forced vital capacity (FVC), suppress disease progression, and minimize acute exacerbations [1–4]. Therefore, these agents are currently considered the cornerstone of pharmacological therapy for IPF [5].

Based on these findings, international clinical practice guidelines recommend antifibrotic therapy for IPF. Since this is a progressive and irreversible disease, the importance of early diagnosis and treatment has been emphasized[6, 7]. However, whether initiating treatment as early as possible after diagnosis uniformly translates into improved survival for all patients with IPF has not been fully validated in real-world clinical practice. In particular, for patients with minimal symptoms or slowly progressive disease, physicians may opt for careful observation while considering potential adverse effects and impacts on quality of life [8].

Several studies have examined the relationship between the time from IPF diagnosis to initiation of antifibrotic therapy and prognosis [9–11]. However, these findings should be interpreted with caution. Patients with longer intervals before treatment initiation may inherently have lower disease activity and longer survival, making such analyses vulnerable to survival bias and immortal time bias. In real-world practice, physician-judged deferred initiation is based on disease severity, progression rate, and patient characteristics rather than mere passage of time[12]. To our knowledge, no previous study has simultaneously evaluated the effects of delay in antifibrotic therapy using both objective time-based measures and physician-judged deferred initiation.

Multiple factors, such as patient preferences, diagnostic uncertainty, and concerns regarding adverse effects, may contribute to delayed initiation of antifibrotic therapy. Nevertheless, real-world data systematically addressing these reasons for delay remain limited. Clarifying the background factors that underlie delayed initiation is essential for optimizing treatment strategies.

Therefore, the aim of this multicenter retrospective cohort study was to investigate the association between the timing of antifibrotic therapy initiation and overall survival (OS) in patients with IPF. The investigation involved the following approaches: 1) objective analysis based on the interval from diagnosis to treatment initiation; 2) analysis according to physician-judged deferred initiation; and 3) evaluation of the reasons for delayed initiation. Through these analyses, we sought to address the clinically relevant question of whether earlier initiation of antifibrotic therapy is always associated with better outcomes in the real-world management of IPF.

Methods

Study design and patients

This multicenter retrospective cohort study included patients diagnosed with IPF between April 1, 2021 and March 31, 2023 at four affiliated hospitals of Nippon Medical School (Tokyo, Japan), who ultimately received antifibrotic therapy (nintedanib or pirfenidone). Patients were diagnosed according to the 2018 American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association updated clinical practice guideline for the diagnosis of IPF[13]. Patients aged < 18 years, those with insufficient data in the medical records, and those who did not receive antifibrotic therapy were excluded from this investigation.

Definitions of timing and delay of antifibrotic therapy

Objective timing based on time from diagnosis

The objective timing of antifibrotic therapy initiation was defined based on the interval between IPF diagnosis and treatment initiation. Patients were categorized into three groups according to the interval from diagnosis to antifibrotic therapy initiation (0–180 days, 181–364 days, and ≥ 365 days). The diagnosis date was defined as the date of confirmed IPF diagnosis documented in the medical records.

Physician-judged deferred initiation

Physician-judged deferred initiation was recorded when the physicians explicitly documented in the medical records an intention to initiate antifibrotic therapy, but deferred initiation due to clinical considerations, including mild or stable disease, diagnostic uncertainty, patient preference, concerns regarding adverse effects, comorbidities, or socioeconomic factors. In other words, physician-judged deferred initiation was conceptualized as a composite, real-world construct that reflects a combination of disease-related, patient-related, and contextual factors, rather than a pure indicator of disease activity. Cases in which antifibrotic therapy was not considered or discussed were not classified as physician-judged deferred initiation.

Data extraction was performed by investigators at each participating center using a standardized data collection form. When ambiguity existed regarding the presence of physician-judged deferred initiation, the case was classified as “no deferred initiation” to minimize misclassification. This definition was analyzed independently of the objective diagnosis-to-treatment interval.

Data collection

Patient characteristics collected from medical records included age, sex, smoking history, body mass index (BMI), pulmonary function parameters (%FVC and percent predicted diffusing capacity for carbon monoxide [%DLco]), time from symptom onset to referral to a specialized center, and time from referral to diagnosis of IPF. In addition, the Gender–Age–Physiology (GAP) index (a validated severity assessment tool for IPF) was calculated. Relevant dates were extracted from clinical documentation.

Outcomes

The primary outcome was OS, defined as the time from the diagnosis of IPF to death due to any cause. Patients who were alive at the end of follow-up were censored at the date of last visit or study end.

Statistical analysis

Continuous variables are presented as medians with interquartile ranges and were compared using the Mann–Whitney *U* test. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate.

OS was estimated using the Kaplan–Meier method, and group comparisons were performed using the log-rank test. Landmark analyses at 180 and 365 days were conducted to minimize survival bias and immortal time bias in analyses based on diagnosis-to-treatment intervals. These analyses included only patients who were alive at each landmark time point.

Factors associated with OS were evaluated using Cox proportional hazards regression models. Multivariable models included variables with p-values < 0.10 in the univariable analyses, established prognostic factors (age and %FVC)[14], and clinically relevant variables (physician-judged deferred initiation and time from referral to diagnosis), using forced-entry methods. Hazard ratios and 95% confidence intervals were calculated. Patients with missing data were excluded from the relevant analyses using a complete-case approach. All statistical tests were two-sided, and p-values < 0.05 denoted statistically significant differences. All statistical analyses were conducted using SPSS software (version 27.0; IBM Corp., Armonk, NY, USA). Kaplan–Meier curves with numbers at risk were generated using EZR (Saitama Medical Center, Jichi Medical University), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

Ethical considerations

This study was approved by the Central Ethics Committee of Nippon Medical School, Tokyo, Japan (approval number: M-2023-175). Due to the retrospective nature of the study, the requirement for informed consent was waived[15].

Results

Patient characteristics

Table 1 summarizes the baseline characteristics of the entire study population (N = 150). The median age was 72 years, and the majority of patients were male. Most patients had a history of smoking, and approximately one-third had experienced an acute exacerbation prior to enrollment. Pulmonary function tests showed moderate impairment, with median values of FVC and %DLco consistent with typical IPF severity. According to the GAP index, patients were distributed across all levels of severity. Biomarkers such as Krebs von den Lungen-6 (KL-6) and alveolar-arterial oxygen difference ($AaDO_2$) also demonstrated wide variability. The median interval from IPF diagnosis to initiation of antifibrotic therapy was 317 days, indicating considerable variation in treatment timing.

Table 1
Baseline characteristics of patients with IPF (N = 150)

Characteristic	Value
Age (years)	72 (36–89)
Sex (male/female)	112/38
Smoking history (present/absent/unknown)	103/43/4
Acute exacerbation (yes/no)	53/97
Body mass index	23.5 (14.6–34.2)
FEV_1 (L)	1.90 (0.81–3.19)
FVC (L)	2.31 (0.21–3.80)
%FVC	76.8 (43.9–115.4)
%DLco	58.6 (13.8–139.3)
GAP index I/II/III/unknown	82/53/12/3
Albumin (g/dL)	4.0 (2.1–5)
KL-6 (U/mL)	1019 (276–7420)
$AaDO_2$ (Torr)	20.1 (– 28.3–81)
Duration from symptom onset to initial hospital visit (days)	6 (1–1825)
Interval between referral to a specialized center and diagnosis (days)	14 (1–3246)
Interval between IPF diagnosis and initiation of antifibrotic treatment (days)	317 (0–5205)

Continuous and categorical variables are presented as median (interquartile range) and number (%), respectively. Comparisons were performed using the Mann–Whitney U test for continuous variables and the chi-square or Fisher's exact test for categorical variables, as appropriate.

Abbreviations: AaDO2, alveolar-arterial oxygen difference; %DLco, percent predicted diffusing capacity of the lung for carbon monoxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; %FVC, percent predicted forced vital capacity; GAP, Gender–Age–Physiology; IPF, idiopathic pulmonary fibrosis; KL-6, Krebs von den Lungen-6.

Baseline characteristics of patients in each group are presented in Table 2. The baseline demographic, clinical, and physiological characteristics were generally comparable among the three groups stratified by time from IPF diagnosis to initiation of antifibrotic therapy. There were no significant differences in age, sex, smoking history, BMI, lung function parameters (FVC, %FVC, %DLco), GAP index, serum albumin, KL-6 levels, or $AaDO_2$ among the groups (all $p > 0.05$). Landmark analyses at 180 and 365 days included only patients who were alive at each respective time point. Kaplan–Meier analyses demonstrated significantly longer OS in patients with longer diagnosis-to-treatment intervals (Fig. 1a). In

the 180-day landmark analysis, the median OS was 3,983 days in patients with a longer interval from diagnosis to treatment initiation, compared with 1,674 days in those with a shorter interval (log-rank $p < 0.001$) (Fig. 1b). Similar results were observed in the 365-day landmark analysis, with median OS of 3,870 days and 1,753 days, respectively (log-rank $p < 0.001$) (Fig. 1c).

Table 2
Baseline characteristics according to the interval from IPF diagnosis to antifibrotic therapy initiation

Time from IPF diagnosis to initiation of antifibrotic therapy	**Group 0–180 days (N = 58)**	**Group 181–364 days (N = 17)**	**Group ≥ 365 days (N = 75)**	**p-value**
Age (years)	75 (57–89)	74 (64–87)	69 (36–86)	0.347
Sex (male/female)	46/12	14/3	52/23	0.313
Smoking history (present/absent/unknown)	40/14/4	11/6/0	52/23/0	0.127
Body mass index	22.8 (15.6–32.9)	23.3 (17.0–34.2)	24.1 (14.6–32.8)	0.301
FVC (L)	2.41 (0.90–3.73)	2.48 (1.32–3.62)	2.26 (0.21–3.80)	0.342
%FVC	74.6 (43.9–106.6)	91.1 (48–115.4)	78.7 (44.7–112.1)	0.209
%DLco	58.1 (13.8–101.5)	48.6 (22.9–121.5)	59.3 (27.8–139.3)	0.511
GAP index I/II/III/unknown	28/22/5/3	8/7/2/0	46/24/5/0	0.322
Albumin (g/dL)	4.0 (2.1–4.7)	4.0 (2.9–4.5)	4.0 (2.1–5.0)	0.967
KL-6 (U/mL)	1,088 (314–4,549)	895 (339–1,883)	968 (276–7,420)	0.277
$AaDO_2$ (Torr)	13.6 (− 28.3–70)	26.0 (16.1–43.5)	22.2 (− 13–81)	0.274
Overall survival measured from the time of IPF diagnosis (days)	1,854 (29–3,469)	2,118 (502–2,118)	4,163 (608–6,787)	<0.001

Continuous and categorical variables are presented as median (interquartile range) and number (%), respectively. Comparisons were performed using the Mann–Whitney *U* test for continuous variables and the chi-square or Fisher's exact test for categorical variables, as appropriate.

Abbreviations: $AaDO_2$, alveolar-arterial oxygen difference; %DLco, percent predicted diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; %FVC, percent predicted forced vital capacity; GAP, Gender–Age–Physiology; IPF, idiopathic pulmonary fibrosis; KL-6, Krebs von den Lungen-6.

OS was compared between patients with and without physician-judged deferred initiation. Baseline characteristics for these groups are shown in Table 3. When patients were stratified by the presence or absence of delay in the initiation of antifibrotic therapy, several baseline characteristics differed between groups. Patients without treatment delay were older, more likely to be male, and more likely to have a smoking history than those with delayed treatment (all $p < 0.05$). Lung function parameters showed mixed results; specifically, forced expiratory volume in 1 s (FEV_1) and FVC were significantly higher in the delayed-treatment group, whereas %FVC and %DLco did not differ significantly between the groups. No significant differences were observed in the frequency of acute exacerbation, BMI, GAP index, serum albumin, KL-6 levels, or $AaDO_2$. The duration from symptom onset to the initial hospital visit was significantly longer in the delayed-treatment group, while the interval between referral to a specialized center showed no significant difference between the groups.

Table 3
Background of patients based on the presence/absence of physician-judged deferred initiation

Characteristic	Patients with IPF (N=150)	Introduction of antifibrotic drugs		p-value
		No delay (N = 89)	Delay (N = 61)	
Age (years)	72 (36–89)	74 (36–89)	70 (45–82)	0.002
Sex (male/female)	112/38	60/29	52/9	0.014
Smoking history (present/absent/unknown)	103/43/4	55/30/4	48/13/0	0.045
Acute exacerbation (yes/no)	53/97	32/57	21/40	0.705
Receipt of public financial assistance for intractable diseases (yes/no)	110/40	64/25	46/15	0.634
Body mass index	23.5 (14.6–34.2)	23.1 (14.6–34.2)	23.8 (16.1–32.8)	0.149
FEV_1 (L)	1.90 (0.81–3.19)	1.79 (0.81–3.13)	1.96 (1.24–3.19)	0.004
FVC (L)	2.31 (0.21–3.80)	2.14 (0.90–3.73)	2.44 (0.21–3.80)	0.012
%FVC	76.8 (43.9–115.4)	75.4 (43.9–115.4)	82.3 (45.4–112.1)	0.243
%DLco	58.6 (13.8–139.3)	57.5 (13.8–139.3)	58.9 (22.9–132.3)	0.696
GAP index I/II/III/unknown	82/53/12/3	49/31/7/2	33/22/5/1	0.993
Albumin (g/dL)	4.0 (2.1–5)	4.0 (2.7–4.7)	4.0 (2.1–5.0)	0.420
KL-6 (U/mL)	1019 (276–7420)	974 (314–7420)	1044 (276–3766)	0.995
$AaDO_2$ (Torr)	20.1(− 28.3–81)	19.1 (− 4.5–81)	22.6 (− 28.3–73)	0.829
Duration from symptom onset to initial hospital visit (days)	6 (1–1825)	30 (1–1825)	60 (2–1825)	0.034

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

Multivariable models included variables with $p < 0.10$ in univariable analyses, established prognostic factors (age and %FVC), and clinically relevant variables.

Abbreviations: $AaDO_2$, alveolar-arterial oxygen difference; %DLco, percent predicted diffusing capacity for carbon monoxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; GAP, Gender–Age–Physiology; IPF, idiopathic pulmonary fibrosis; KL-6, Krebs von den Lungen-6.

Characteristic	Patients with IPF (N=150)	Introduction of antifibrotic drugs		p-value
		No delay (N = 89)	Delay (N = 61)	
Interval between referral to a specialized center and diagnosis (days)	14 (1–3246)	10 (1–2557)	14 (4–3246)	0.068
Interval between IPF diagnosis and initiation of antifibrotic treatment (days)	317 (0–5205)	317 (0 – 5205)	755 (0 – 4302)	0.010
Data are presented as median (interquartile range) or number (%).				
Multivariable models included variables with p < 0.10 in univariable analyses, established prognostic factors (age and %FVC), and clinically relevant variables.				
Abbreviations: $AaDO_2$, alveolar-arterial oxygen difference; %DLco, percent predicted diffusing capacity for carbon monoxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; GAP, Gender–Age–Physiology; IPF, idiopathic pulmonary fibrosis; KL-6, Krebs von den Lungen-6.				

The Kaplan–Meier analysis showed a trend toward shorter OS in patients with physician-judged deferred initiation; however, the difference was not statistically significant (log-rank p = 0.164) (Fig. 2).

The results of the univariable Cox proportional hazards regression analysis are shown in Table 4. Age, sex, BMI, and time from referral to diagnosis were associated with OS. Older age was associated with increased risk of mortality, whereas female sex and higher BMI were associated with reduced risk. Physician-judged deferred initiation and the interval between IPF diagnosis and treatment initiation were not significantly associated with OS in the univariable analysis.

Table 4
Univariable Cox proportional hazards regression analysis for overall survival

Variable	HR	95% CI	p-value
Age (years)	1.078	1.036–1.122	< 0.01
Sex (male/female)	0.386	0.172–0.867	0.017
Body mass index	1.004	1.000–1.007	0.048
FVC (L)	0.958	0.945–1.003	0.089
%FVC	0.985	0.968–1.002	0.074
%DLco	0.997	0.984–1.010	0.652
Albumin (g/dL)	0.671	0.349–1.291	0.233
KL-6 (U/mL)	1.000	1.000–1.000	0.694
SP-D	1.001	1.000–1.003	0.184
FEV_1	1.000	0.999–1.001	0.961
$\%FEV_1$	0.994	0.979–1.009	0.398
$AaDO_2$ (Torr)	0.991	0.977–1.005	0.212
Physician-judged deferred initiation	0.780	0.568–1.071	0.121
Duration from symptom onset to initial hospital visit (days)	1.001	1.000–1.002	0.074
Interval between referral to a specialized center and diagnosis (days)	1.000	1.000–1.001	0.024
Interval between IPF diagnosis and initiation of antifibrotic treatment (days)	1.000	1.000–1.000	0.143
HRs and 95% CIs were derived from univariable Cox proportional hazards regression models.			
Abbreviations: $AaDO_2$, alveolar-arterial oxygen difference; CI, confidence interval; %DLco, percent predicted diffusing capacity for carbon monoxide; GAP, Gender–Age–Physiology; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; HR, hazard ratio; IPF, idiopathic pulmonary fibrosis; KL-6, Krebs von den Lungen-6; SP-D, surfactant protein D.			

In the multivariable analyses, physician-judged deferred initiation, older age, lower %FVC, and a longer time from referral to diagnosis were associated with OS (Table 5). Among 61 patients with physician-judged deferred initiation, the most common reasons were the presence of minimal or stable symptoms, concerns regarding adverse effects, diagnostic uncertainty, slow progression of disease, and financial considerations (Fig. 3).

Table 5
Multivariable Cox proportional hazards regression analysis for overall survival

Variable	HR (95%CI)	p-value
Physician-judged deferred initiation	0.658 (0.473–0.992)	0.045
Age	1.083 (1.037–1.131)	< 0.001
Body mass index	1.002 (0.998–1.006)	0.405
%FVC (%)	0.977 (0.958–0.997)	0.022
Interval between referral to a specialized center and diagnosis (days)	1.001 (1.000–1.001)	0.029

Abbreviations: CI, confidence interval; FVC, forced vital capacity; HR, hazard ratio.

Discussion

In this multicenter retrospective cohort study, we used objective time-based indicators and physician-judged deferred initiation to investigate the association between the timing of antifibrotic therapy initiation and OS in patients with IPF. The findings provide important real-world insights into the decision-making process with regard to the initiation of antifibrotic therapy in clinical practice and the impact of these decisions on long-term outcomes.

As shown in Figs. 1a-c, the observation that patients with a longer interval between IPF diagnosis and initiation of antifibrotic therapy tended to have longer OS should not be interpreted as a recommendation to delay treatment. The results suggest that careful observation of disease behavior over a certain period, rather than immediate initiation of antifibrotic therapy after diagnosis, may be clinically reasonable for a subset of patients. These findings reaffirm the importance of individualized decision-making that takes into account the disease progression rate and clinical stability versus a uniform treatment strategy applied to all patients.

The management of IPF in real-world clinical settings is inherently heterogeneous. No significant differences were observed in measured baseline characteristics among the groups according to the interval from diagnosis to antifibrotic therapy initiation.

The longest OS was recorded in the ≥ 365-day group. This finding suggests that physicians determine the timing of antifibrotic therapy initiation by integrating clinical factors that cannot be fully captured through physiological measurements alone, including symptom burden, functional impairment, perceived disease progression rate, comorbidities, patient preferences, and socioeconomic considerations.

In the comparison based on physician-judged deferred initiation of antifibrotic therapy (Fig. 2), patients classified as having delayed initiation were not necessarily those for whom treatment was intentionally postponed. As noted above, in routine clinical practice, physicians may propose early treatment even when physiological parameters appear relatively preserved if disease progression is suspected based on symptoms or overall clinical assessment. However, treatment initiation may occasionally be delayed due to patient refusal, tolerability concerns, or other clinical factors.

The Kaplan–Meier analysis demonstrated no significant difference in OS according to the presence or absence of physician-judged deferred initiation, whereas a significant association was observed in the multivariable Cox proportional hazards regression model. This discrepancy is likely attributable to the unadjusted nature of the Kaplan–Meier analysis, in contrast to the multivariable analysis that accounts for established prognostic factors. Physician-judged deferred initiation may encompass clinically meaningful information that is not adequately reflected by baseline physiological indices alone; therefore, its impact may become apparent only after adjustment. These findings suggest that clinical judgment based on physician experience plays an important role in the management of IPF.

Importantly, physician-judged deferred initiation in this study should not be interpreted simply as inappropriate postponement of therapy. Rather, it represents a real-world decision-making construct that often incorporates clinical impressions of disease activity and prognostic risk, together with patient preferences, tolerability concerns, and socioeconomic or contextual factors. Therefore, the observed association between physician-judged deferred initiation and OS in the multivariable analysis is likely to be influenced by indication and other unmeasured confounders, rather than reflecting a direct causal effect of postponing therapy. Hence, physician-judged deferred initiation may partly capture underlying prognostic heterogeneity among patients with IPF, although it remains a heterogeneous measure that integrates both disease-related and non–disease-related considerations. Our findings do not imply that delaying therapy is beneficial or harmful per se, but rather highlight the complexity of real-world decision-making.

Additionally, the present results demonstrated that a longer interval from referral to a specialized center to IPF diagnosis was associated with worse OS. This finding is consistent with those of previous studies [16]. This evidence underscores the importance of early referral and timely diagnostic confirmation. Delayed diagnosis may limit opportunities for appropriate risk stratification, treatment planning, and longitudinal assessment of disease behavior, regardless of the timing of antifibrotic therapy initiation.

Our data do not contradict existing evidence demonstrating the efficacy of antifibrotic therapy or the benefit of early treatment in numerous patients with IPF[17]. They suggest that uniform immediate initiation of antifibrotic therapy following diagnosis is not required for all patients. Moreover, optimal timing should be determined through individualized assessment incorporating disease progression, patient characteristics, and shared decision-making.

Several limitations of this investigation should be acknowledged. Firstly, owing to the retrospective observational design of this study, causal inference cannot be established, and residual confounding

may persist despite multivariable adjustment. Secondly, detailed assessments of disease activity prior to antifibrotic therapy initiation, such as longitudinal decline in pulmonary function or radiological progression, were not uniformly available. Consequently, we were unable to fully adjust for the pre-treatment disease trajectory, which may have influenced both decisions regarding treatment timing and survival outcomes. Thirdly, variability in clinical judgment among physicians and institutions could not be fully eliminated. Physician-judged deferred initiation was defined based on documentation in medical records; thus, it is subject to potential information bias. Finally, patients who never received antifibrotic therapy were excluded from the analysis, which may limit the generalizability of our findings. Nevertheless, this study provides valuable real-world data that complement evidence from clinical trials and highlight the complexity of treatment initiation decisions in the management of IPF.

Conclusion

This study demonstrated that the optimal timing of antifibrotic therapy initiation in patients with IPF should be guided by individualized clinical judgment that considers the disease progression rate and clinical stability. Although longer intervals between diagnosis and treatment initiation were associated with favorable long-term outcomes, this finding should not be interpreted as evidence that treatment delay is beneficial. The evidence indicates that, in selected patients, a strategy of careful observation for a defined period may be compatible with a favorable prognosis.

These findings support the important role of physician judgment in prognostic risk stratification and treatment prioritization in patients with IPF and provide clinically meaningful insights to inform the optimization of treatment strategies in real-world practice.

Abbreviations

$AaDO_2$
Alveolar–arterial oxygen difference
BMI
Body mass index
CI
Confidence interval
DLco
Diffusing capacity for carbon monoxide
%DLco
Percent predicted diffusing capacity for carbon monoxide
FEV_1
Forced expiratory volume in 1 s
FVC
Forced vital capacity
%FVC

Percent predicted forced vital capacity
GAP
Gender–Age–Physiology
IPF
Idiopathic pulmonary fibrosis
KL-6
Krebs von den Lungen-6
OS
Overall survival

Declarations

Ethics approval and consent to participate

Compliance with Ethical Standards: This study was approved by the Central Ethics Committee of Nippon Medical School(Tokyo, Japan) (approval number: M-2023-175). Due to the retrospective nature of the study, the requirement for individual informed consent was waived, and an opt-out procedure was implemented. All procedures were performed in accordance with the Declaration of Helsinki of 1964 and its later amendments.

Consent for publication

Not applicable

Competing interests

JA, YM, TH, and MS received lecture honoraria from Nippon Boehringer Ingelheim.

Authors' information

Not applicable

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author Contribution

JA, NT, and YS contributed to the conceptualization and methodology of the study. JA, NT, and YT performed formal analysis. JA, NT, SN, SS, KO, TT, KA, and YK conducted the investigation and data curation. JA wrote the original draft. YS, YT, and MS reviewed and edited the manuscript. YS supervised the study. All authors read and approved the final version of the manuscript.

Acknowledgements

Not applicable

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

References

1. Azuma A, Nukiwa T, Tsuboi E, Suga M, Abe S, Nakata K, Taguchi Y, Nagai S, Itoh H, Ohi M, et al. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2005;171(9):1040–7.
2. Taniguchi H, Ebina M, Kondoh Y, Ogura T, Azuma A, Suga M, Taguchi Y, Takahashi H, Nakata K, Sato A, et al. Pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J. 2010;35(4):821–9.
3. King TE, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, Gorina E, Hopkins PM, Kardatzke D, Lancaster L, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2083–92.
4. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, Cottin V, Flaherty KR, Hansell DM, Inoue Y, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2071–82.
5. Raghu G, Rochwerg B, Zhang Y, Garcia CA, Azuma A, Behr J, Brozek JL, Collard HR, Cunningham W, Homma S, et al. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis. An Update of the 2011 Clinical Practice Guideline. Am J Respir Crit Care Med. 2015;192(2):e3–19.
6. Aiello M, Bertorelli G, Bocchino M, Chetta A, Fiore-Donati A, Fois A, Marinari S, Oggionni T, Polla B, Rosi E, et al. The earlier, the better: Impact of early diagnosis on clinical outcome in idiopathic pulmonary fibrosis. Pulm Pharmacol Ther. 2017;44:7–15.
7. Maher TM, Strek ME. Antifibrotic therapy for idiopathic pulmonary fibrosis: time to treat. Respir Res. 2019;20(1):205.
8. Maher TM, Molina-Molina M, Russell AM, Bonella F, Jouneau S, Ripamonti E, Axmann J, Vancheri C. Unmet needs in the treatment of idiopathic pulmonary fibrosis-insights from patient chart review in

five European countries. BMC Pulm Med. 2017;17(1):124.
9. Homma S, Sugino K, Sakamoto S. Usefulness of a disease severity staging classification system for IPF in Japan: 20 years of experience from empirical evidence to randomized control trial enrollment. Respir Investig. 2015;53(1):7–12.
10. Sugino K, Ono H, Watanabe N, Ando M, Tsuboi E, Homma S, Kishi K. Efficacy of early antifibrotic treatment for idiopathic pulmonary fibrosis. BMC Pulm Med. 2021;21(1):218.
11. Herberts MB, Teague TT, Thao V, Sangaralingham LR, Henk HJ, Hovde KT, Dempsey TM, Limper AH. Idiopathic pulmonary fibrosis in the United States: time to diagnosis and treatment. BMC Pulm Med. 2023;23(1):281.
12. Tyrer F, Bhaskaran K, Rutherford MJ. Immortal time bias for life-long conditions in retrospective observational studies using electronic health records. BMC Med Res Methodol. 2022;22(1):86.
13. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, Behr J, Cottin V, Danoff SK, Morell F, et al. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 2018;198(5):e44–68.
14. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, Colby TV, Cordier JF, Flaherty KR, Lasky JA, 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(6):788–824.
15. Otsuka T, Matsuyama K. Nippon Medical School's Ethical Review Processes for Studies Involving Human Subjects. J Nippon Med Sch. 2024;91(2):136–9.
16. Lamas DJ, Kawut SM, Bagiella E, Philip N, Arcasoy SM, Lederer DJ. Delayed access and survival in idiopathic pulmonary fibrosis: a cohort study. Am J Respir Crit Care Med. 2011;184(7):842–7.
17. Hoyer N, Prior TS, Bendstrup E, Shaker SB. Diagnostic delay in IPF impacts progression-free survival, quality of life and hospitalisation rates. BMJ Open Respir Res 2022, 9(1).

Figures

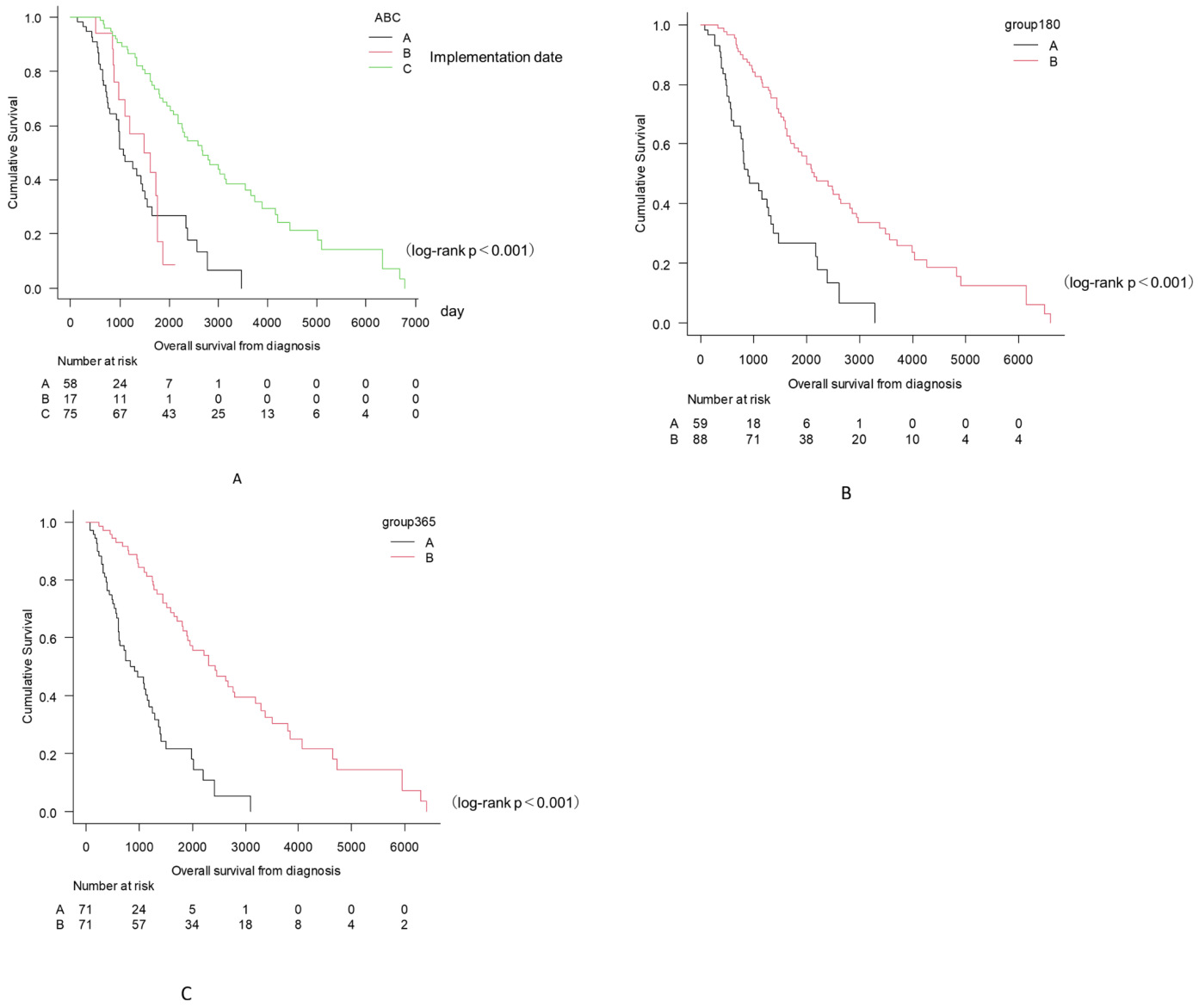


Figure 1

Overall survival according to the interval from idiopathic pulmonary fibrosis (IPF) diagnosis to initiation of antifibrotic therapy. (a) Kaplan–Meier curves stratified by the interval from diagnosis to treatment initiation: 0–180 days (Line A), 181–364 days (Line B), and ≥365 days (Line C). Overall survival was compared using the log-rank test ($p < 0.001$). (b) Landmark analysis at 180 days including only patients who survived beyond 180 days (N = 147). Lines A and B represent patients who initiated antifibrotic therapy within 180 days (≤180 days) and after 181days (≥181 days), respectively.

(c) Landmark analysis at 365 days including only patients who survived beyond 365 days (N = 142). Lines A and B represent patients who initiated antifibrotic therapy within 365 days (≤365 days) and after 365 days (≥366 days), respectively.

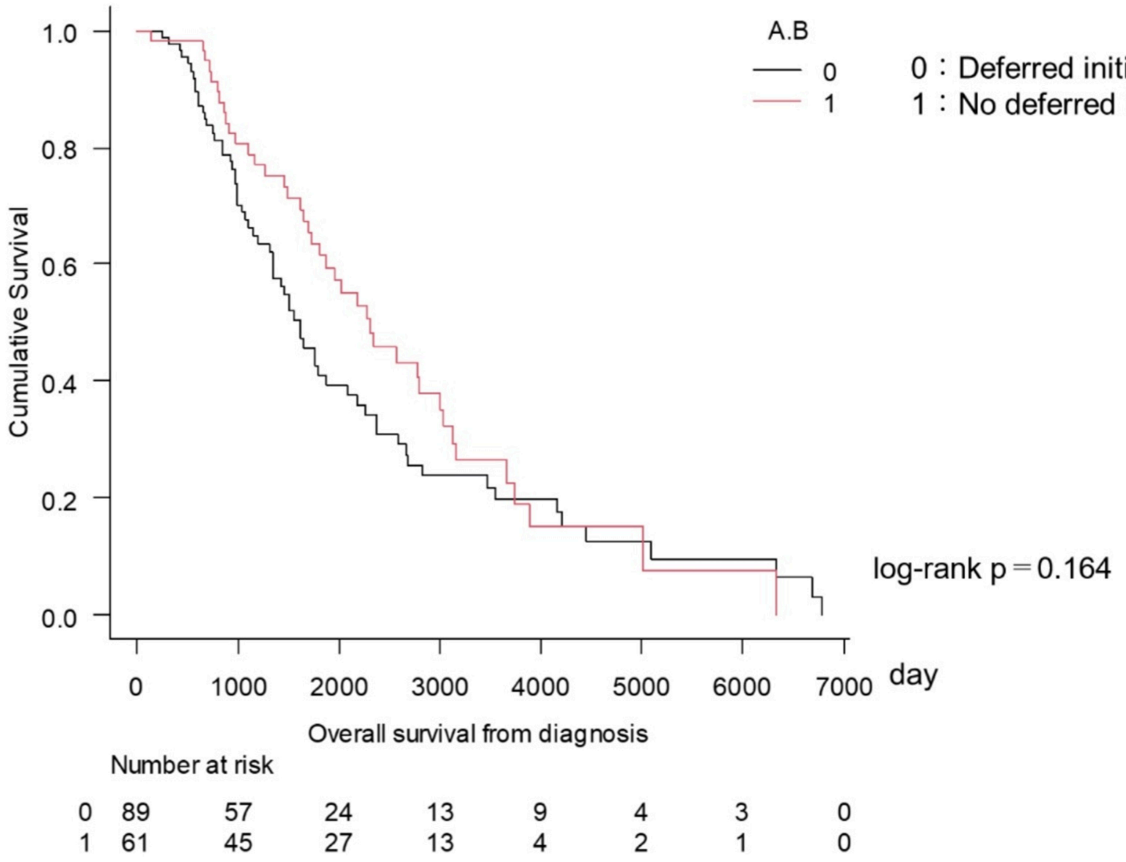


Figure 2

Overall survival according to physician-judged deferred initiation of antifibrotic therapy. Kaplan–Meier curves comparing overall survival between patients with and without physician-judged deferred initiation, as documented in medical records. Differences between groups were assessed using the log-rank test (p = 0.164). Landmark analysis was not performed because the definition of deferred initiation was independent of elapsed time.

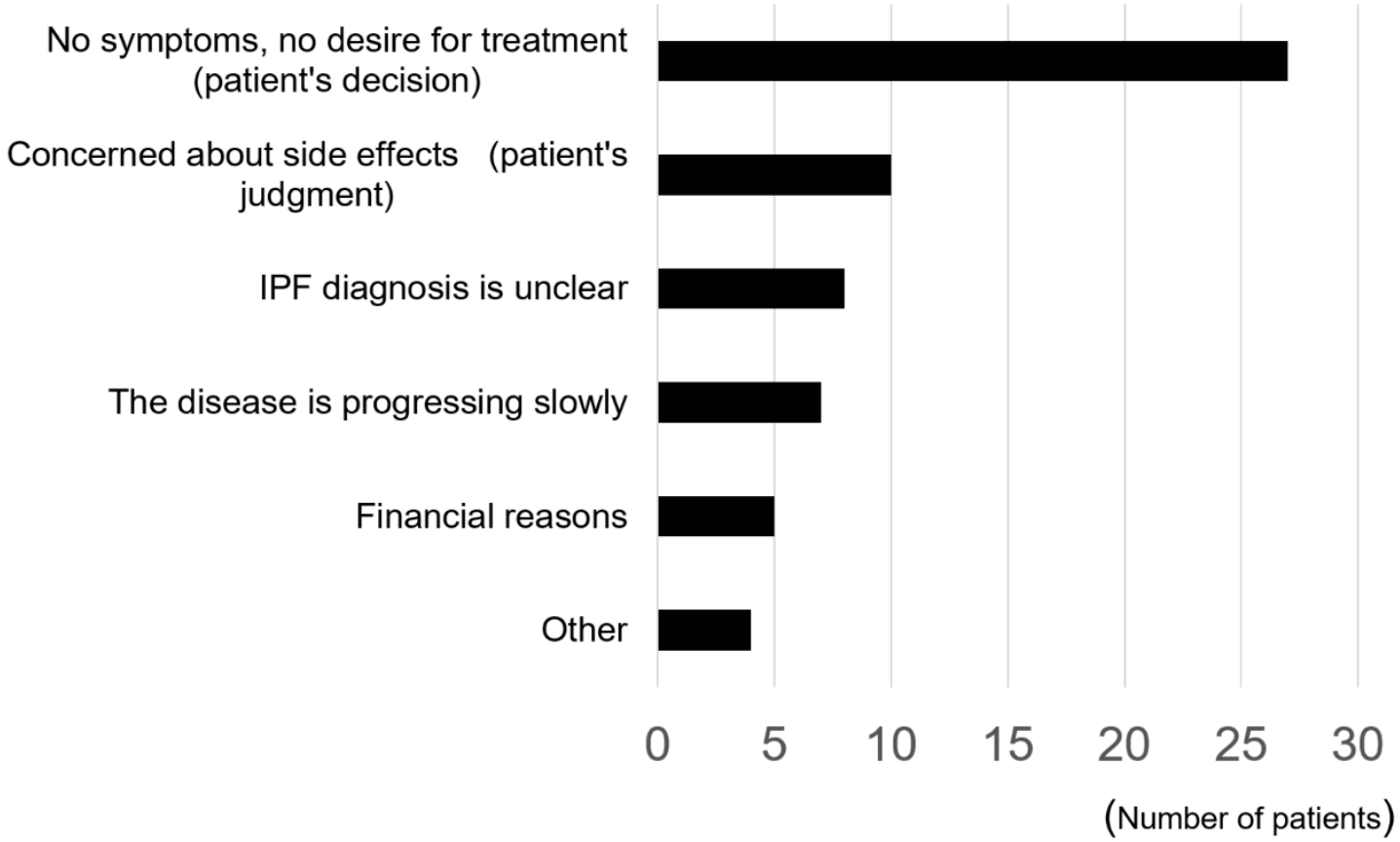


Figure 3

Reasons for physician-judged deferred initiation of antifibrotic therapy.
Distribution of documented reasons for deferred initiation among patients classified as having delayed treatment initiation. IPF, idiopathic pulmonary fibrosis.