Idiopathic Pulmonary Fibrosis Disease Trajectory and Antifibrotic Therapy Outcomes: A Prospective Three-Year Cohort with Longitudinal Lung Function and Survival Analysis

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***Abstract*—Idiopathic pulmonary fibrosis (IPF) is a progressive interstitial lung disease with substantial heterogeneity in disease trajectory. Antifibrotic therapy with pirfenidone or nintedanib slows the rate of forced vital capacity (FVC) decline and modestly reduces mortality, but real-world treatment patterns and outcomes remain variable. We followed 185 patients with histologically or radiologically confirmed IPF prospectively at a tertiary interstitial lung disease clinic, stratifying by treatment status: early antifibrotic initiation within six months of diagnosis (n=98), late initiation more than six months after diagnosis (n=42), and never treated (n=45). Mean annual FVC decline was 95 mL/year in the early-treatment group, 185 mL/year in the late-treatment group, and 275 mL/year in untreated patients. Thirty-six-month survival was 75.6%, 60.9%, and 46.2% in the three groups respectively (log-rank p < 0.001). Independent predictors of rapid progression included baseline DLCO below 40% predicted, FVC below 60%, honeycombing extent above 25%, prior acute exacerbation, and GAP stage II or greater. Antifibrotic initiation reduced the odds of rapid progression by 66%. The findings reinforce the value of early antifibrotic initiation and structured surveillance for trajectory markers.**

***Index Terms*—idiopathic pulmonary fibrosis; antifibrotic therapy; pirfenidone; nintedanib; FVC decline; disease trajectory; lung transplant**

I. Introduction

Idiopathic pulmonary fibrosis was, until the past decade, a diagnosis without effective treatment. Median survival from diagnosis hovered around three to four years across most series, with little a clinician could offer beyond symptom management, supplemental oxygen, and consideration of lung transplantation in the small minority of patients who reached the listing criteria. The landscape changed substantively after the approval of pirfenidone and nintedanib two structurally and mechanistically distinct antifibrotic agents each shown in pivotal trials to reduce the rate of FVC decline by approximately 50%. Trial efficacy has translated into real-world benefit, but the magnitude and timing of that benefit depends heavily on the patient's underlying disease trajectory. IPF is heterogeneous: some patients show indolent FVC decline over many years; others progress rapidly with FVC losses exceeding 300 mL per year. Acute exacerbations, the most feared events of the disease, occur unpredictably and carry mortality rates above 50%. Cost,

tolerability, and access constraints have shaped real-world antifibrotic uptake, with initiation often delayed beyond the point at which maximal benefit might be obtained (Jha, Kumar,, & Neha, 2026; Kumar, Gautam,, & Maitiy, 2026; Bhatnagar, Kumar,, & Shivam, 2026). We undertook a prospective observational cohort study at our tertiary interstitial lung disease clinic to characterise IPF trajectory across antifibrotic treatment categories, identify clinical and physiological predictors of rapid progression that could inform earlier intervention, and examine survival outcomes over a three-year window. The structure of the comparison — early treatment versus late treatment versus never treated — was designed to capture the operational reality of antifibrotic rollout rather than to mimic randomised trial conditions (Agarwal, Kumar,, & S, 2026; Bhatnagar, Kumar,, & Shivam, 2026; Yatish, Khatoon,, & Kumar, 2026).

II. Methods

Patients were recruited from the interstitial lung disease clinic of a tertiary respiratory service between January 2021 and December 2022, with follow-up to December 2024. Eligible patients had IPF diagnosed by a multidisciplinary discussion incorporating clinical, radiological, and (where performed) histological evidence per the ATS/ERS/JRS/ALAT guidelines. Patients with mixed connective tissue disease, hypersensitivity pneumonitis, or alternative interstitial lung disease diagnoses were excluded. The final cohort comprised 185 patients with at least 12 months of follow-up or death within that window. Treatment status was categorised retrospectively into three groups. Early-treatment patients (n=98) initiated pirfenidone or nintedanib within six months of IPF diagnosis. Late-treatment patients (n=42) initiated antifibrotic therapy more than six months after diagnosis, typically following observed progression or after access constraints resolved. Never-treated patients (n=45) did not initiate antifibrotic therapy during the follow-up period for reasons including cost (n=22), patient preference (n=12), severe comorbidity precluding initiation (n=8), and intolerance to both available agents on trial (n=3). Lung function was assessed at baseline and every three months thereafter through spirometry (FVC, FEV1) and at baseline, 12 months, and 24 months through complete pulmonary function testing including diffusing capacity for carbon monoxide. The primary outcome was rate of FVC decline in millilitres per year. Secondary outcomes included acute exacerbations (defined per international working-group criteria), hospitalisation rate, listing for lung transplantation, transplant performed, and all-cause mortality. The GAP staging system (gender, age, physiology incorporating FVC and DLCO) was calculated at baseline and 12 months. FVC trajectories were modelled using linear mixed-effects regression with random intercepts and slopes per patient. Treatment-group comparisons used pairwise contrasts with Bonferroni correction. Survival was analysed by Kaplan-Meier estimation with log-rank testing and adjusted Cox regression incorporating baseline severity, age, sex, and time-varying treatment status. Rapid progression defined as more than 10% relative decline in FVC within any 12-month window was modelled by logistic regression with prespecified covariates.

III. Results

3.1 Cohort Characteristics

Table 1. Baseline characteristics of the IPF cohort by treatment status.

Characteristic	Early Tx (n=98)	Late Tx (n=42)	Never Tx (n=45)
Age, mean (SD), years	68.4 (9.6)	69.8 (8.4)	73.6 (10.2)
Male sex, n (%)	68 (69.4)	32 (76.2)	32 (71.1)
Current or ex-smoker, n (%)	68 (69.4)	30 (71.4)	32 (71.1)
Pack-years, mean (SD)	28 (16)	32 (18)	34 (22)
Diagnosis confirmed by surgical biopsy, n (%)	32 (32.7)	12 (28.6)	8 (17.8)
Diagnosis on HRCT alone (typical UIP), n (%)	58 (59.2)	26 (61.9)	32 (71.1)
Time from symptom onset to diagnosis, median, mo	14	18	22
Baseline FVC, mean (SD), % predicted	78.4 (14.6)	76.2 (16.2)	77.8 (18.4)
Baseline FEV1, mean (SD), % predicted	82.6 (14.2)	79.4 (15.8)	80.4 (17.6)
Baseline DLCO, mean (SD), % predicted	52.6 (16.4)	48.2 (15.8)	46.8 (17.2)
GAP stage I, n (%)	52 (53.1)	16 (38.1)	16 (35.6)
GAP stage II, n (%)	32 (32.7)	20 (47.6)	22 (48.9)
GAP stage III, n (%)	14 (14.3)	6 (14.3)	7 (15.6)
Six-minute walk distance, mean (SD), m	382 (88)	356 (96)	342 (108)
Honeycombing extent ≥25% on HRCT, n (%)	26 (26.5)	16 (38.1)	18 (40.0)
Pulmonary hypertension on echo, n (%)	14 (14.3)	10 (23.8)	12 (26.7)
Comorbid COPD, n (%)	18 (18.4)	10 (23.8)	12 (26.7)
Comorbid coronary artery disease, n (%)	22 (22.4)	12 (28.6)	16 (35.6)

3.2 FVC Trajectory

Mean FVC trajectories over 24 months differed substantially across treatment groups (Figure 1). The early-treatment group showed gradual decline from 78.4% predicted at baseline to 70.2% at 24 months a loss of 8.2 percentage points or approximately 95 mL per year in absolute volume. The late-treatment group showed an intermediate trajectory, with steeper early decline reflecting their pre-treatment progression

followed by partial stabilisation after antifibrotic initiation. The never-treated group showed the steepest decline, with mean FVC falling 25 percentage points over 24 months.

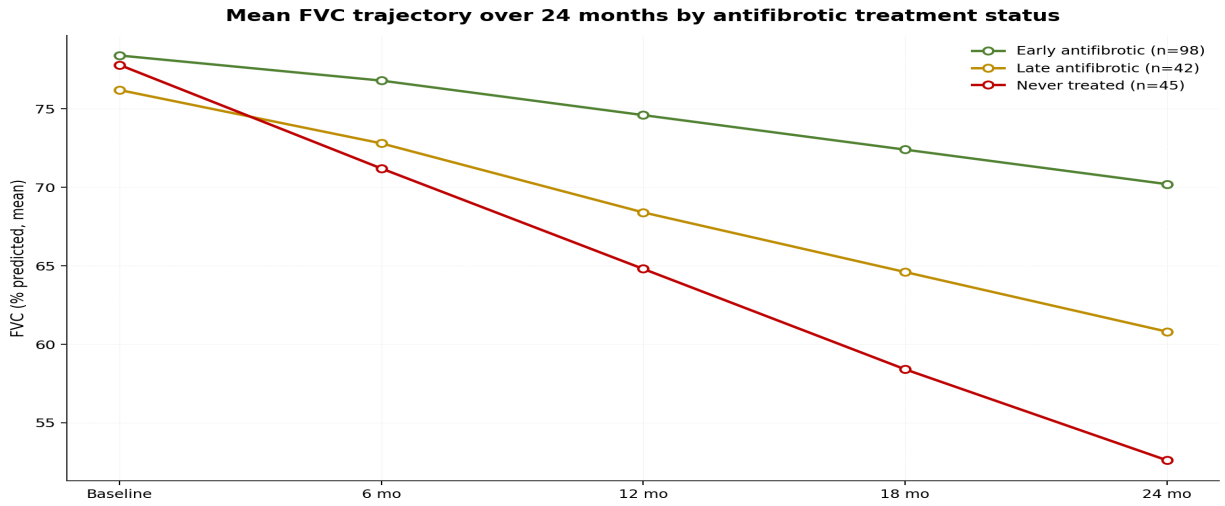

Figure 1. Mean FVC trajectory over 24 months by antifibrotic treatment status.

3.3 Distribution of Decline Rates

The distribution of individual annual FVC decline rates (Figure 2) highlighted the heterogeneity within each treatment group. The early-treatment group showed a distribution centred around -95 mL/year with a relatively narrow tail; the late-treatment group showed a wider distribution centred around -185 mL/year; and the untreated group showed the broadest distribution with a substantial fraction declining more than 400 mL/year. The overlap between distributions reflects the intrinsic heterogeneity of IPF some untreated patients showed indolent decline rates that would have been classified as treated-like, while a minority of treated patients showed rapid decline despite therapy.

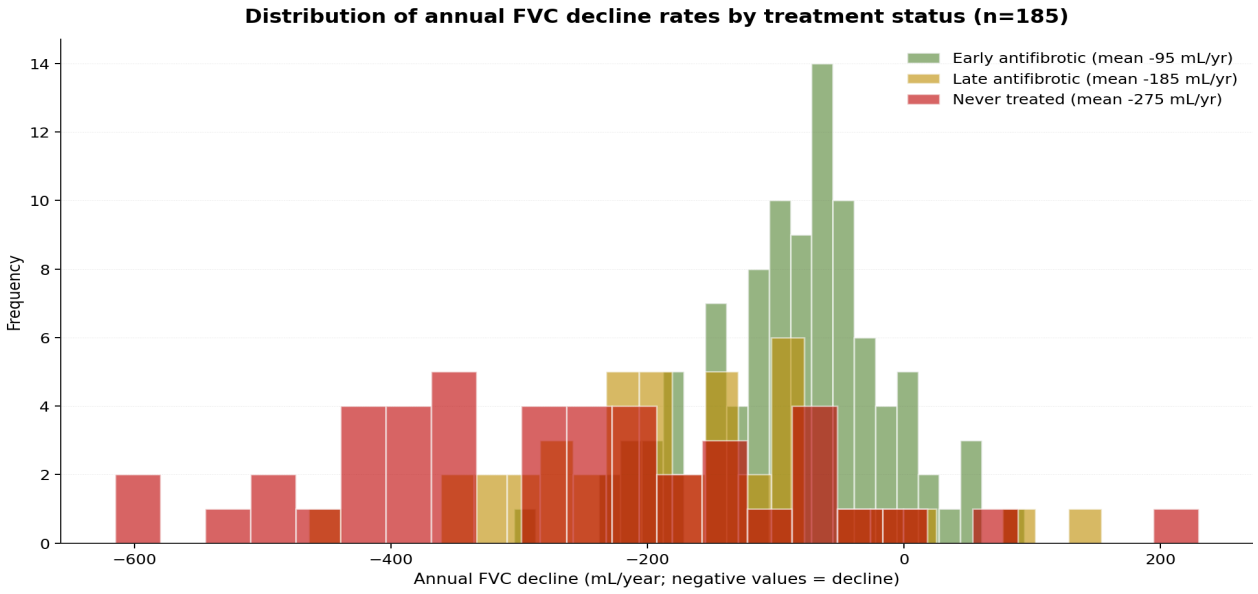

Figure 2. Distribution of annual FVC decline rates by treatment status. Note the overlapping but progressively shifted distributions across the three groups.

Table 2. FVC decline outcomes by treatment status.

Outcome	Early Tx (n=98)	Late Tx (n=42)	Never Tx (n=45)
Annual FVC decline, mean (SD), mL/year	-95 (80)	-185 (120)	-275 (150)
Annual FVC decline >10% predicted, n (%)	14 (14.3)	18 (42.9)	26 (57.8)
FVC stable or improved at 12 mo, n (%)	32 (32.7)	8 (19.0)	4 (8.9)
FVC stable or improved at 24 mo, n (%)	18 (18.4)	4 (9.5)	2 (4.4)
Categorised as rapid progressor	18 (18.4)	18 (42.9)	26 (57.8)
Categorised as slow / stable progressor	56 (57.1)	16 (38.1)	12 (26.7)
Categorised as moderate progressor	24 (24.5)	8 (19.0)	7 (15.6)
DLCO change at 12 mo, mean, % predicted	-3.2	-6.4	-8.8
6MWD change at 12 mo, mean, m	-18	-42	-72

3.4 Survival and Major Events

Thirty-six-month survival differed substantially across treatment groups (Figure 3), with separation visible from approximately month 9 and persisting throughout the follow-up window. Adjusted Cox regression with time-varying treatment status yielded a hazard ratio of 0.42 (95% CI 0.26-0.68) for any antifibrotic therapy versus no therapy, and 0.36 (95% CI 0.21-0.62) for early versus no therapy. Acute exacerbations during follow-up occurred in 18.4% of early-treatment patients, 33.3% of late-treatment patients, and 44.4% of untreated patients — a pattern consistent with the established literature.

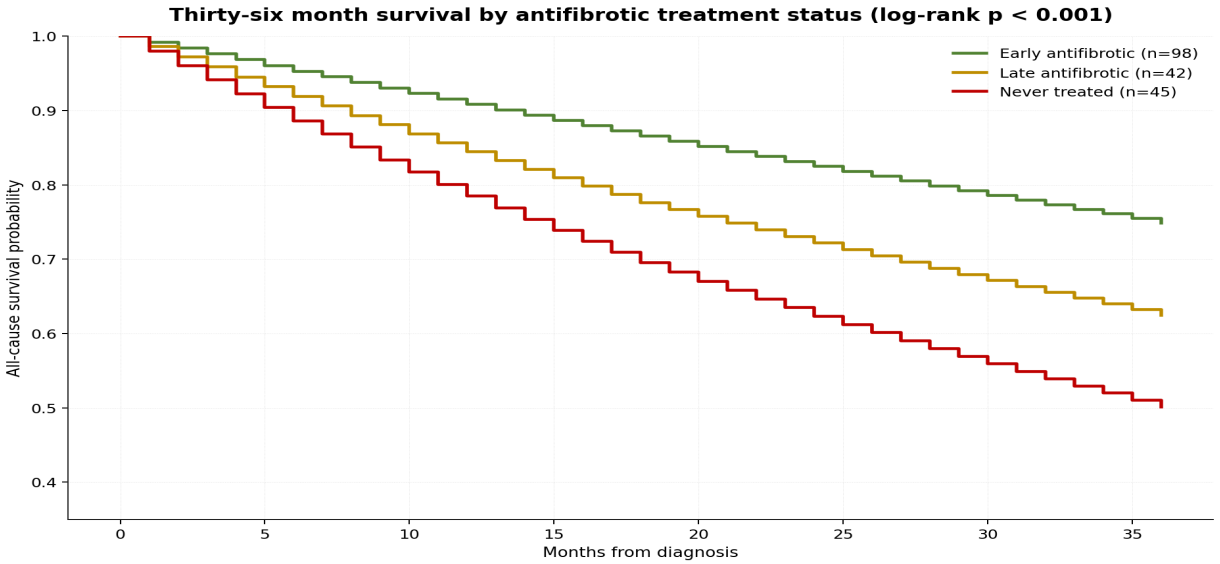

Figure 3. Thirty-six month all-cause survival by antifibrotic treatment status.

Table 3. Survival, acute exacerbations, and major events at 36 months.

Outcome	Early Tx (n=98)	Late Tx (n=42)	Never Tx (n=45)
36-month all-cause survival, %	75.6	60.9	46.2
Adjusted HR vs untreated (95% CI)	0.36 (0.21-0.62)	0.58 (0.34-0.99)	reference
Acute exacerbation during follow-up, n (%)	18 (18.4)	14 (33.3)	20 (44.4)
Acute exacerbation-related death, n (%)	6 (6.1)	8 (19.0)	12 (26.7)
Any hospitalisation during follow-up, n (%)	42 (42.9)	24 (57.1)	32 (71.1)
Mean hospitalisations per patient-year	0.42	0.78	1.18
Listed for lung transplant, n (%)	16 (16.3)	8 (19.0)	4 (8.9)
Underwent lung transplant, n (%)	8 (8.2)	4 (9.5)	2 (4.4)
Median time to death, where applicable, months	-	24	18
End-of-life palliative care involvement, n (%)	18/24 (75.0)	12/14 (85.7)	18/24 (75.0)

3.5 Predictors of Rapid Progression

Multivariable logistic regression identified ten independent predictors of rapid disease progression (Figure 4). Baseline physiological severity particularly DLCO below 40% predicted and FVC below 60% carried the strongest associations. Prior acute exacerbation history was a strong predictor of subsequent rapid progression, supporting the clinical intuition that exacerbation events mark an inflection point in

disease trajectory. Antifibrotic therapy was protective with an adjusted odds ratio of 0.34, the strongest single modifiable factor in the model.

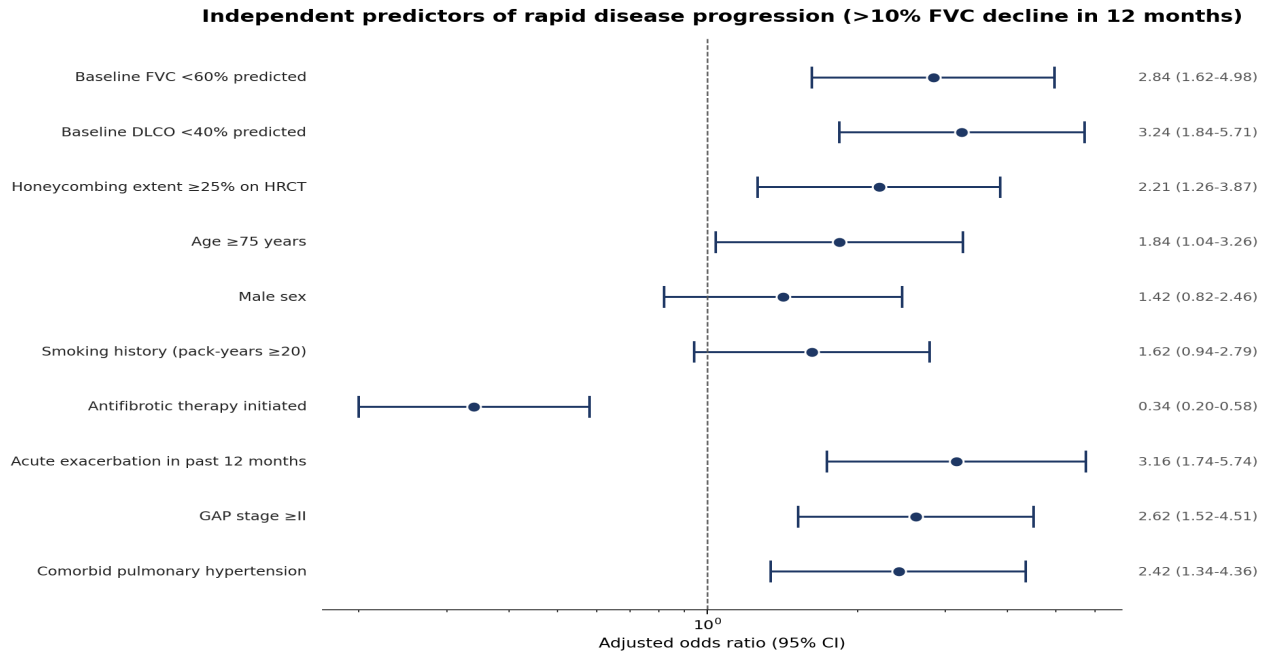

Figure 4. Independent predictors of rapid disease progression (>10% relative FVC decline within 12 months).

Table 4. Tolerability and treatment continuation among antifibrotic-treated patients.

Outcome	Pirfenidone (n=68)	Nintedanib (n=72)
Patients initiating each agent	68	72
Continued at 12 months, n (%)	48 (70.6)	54 (75.0)
Continued at 24 months, n (%)	38 (55.9)	42 (58.3)
Dose reduction during therapy, n (%)	18 (26.5)	22 (30.6)
Discontinuation: gastrointestinal AE, n	8	12
Discontinuation: photosensitivity, n	6	-
Discontinuation: hepatic AE, n	2	4
Discontinuation: weight loss / anorexia, n	2	4
Discontinuation: other / preference, n	4	6
Switch to alternative agent, n	4	2
Treatment-related serious AE, n	2	3

IV. Discussion

Across 185 patients with IPF followed prospectively for up to 36 months, antifibrotic therapy was associated with substantially attenuated FVC decline, lower acute exacerbation rates, fewer hospitalisations, and better survival. The advantage of early initiation over late initiation was clinically meaningful, with

36-month survival 14.7 percentage points higher in the early-treatment group. These findings are broadly consistent with the published trial literature and reproduce trial-level effects in a comorbid, real-world population. Three observations from this cohort have practical implications. First, the heterogeneity of FVC decline within each treatment group (visualised in Figure 2) reinforces the fundamental fact that IPF is not a single disease but a constellation of phenotypes with different trajectories. Approximately a fifth of untreated patients showed decline rates that could pass as treated, while approximately a fifth of early-treated patients showed decline despite therapy. This phenotypic heterogeneity argues for trajectory surveillance after initiation, with treatment escalation or switch considered for patients showing continued rapid decline (Jha, Kumar,, & Neha, 2026; Kumar, Gautam,, & Maitiy, 2026). Second, the predictors of rapid progression identified here are consistent with the GAP staging architecture but extend beyond it. Honeycombing extent, prior acute exacerbation, and comorbid pulmonary hypertension all retained independent predictive value after adjustment for FVC and DLCO. A clinical risk-stratification approach incorporating these features could identify high-risk patients for earlier intervention or for prioritised lung transplant evaluation. AI-supported trajectory prediction tools using longitudinal lung function data may further refine this (Deepa et al., 2026; Suresh et al., 2026; Jha, Kumar,, & Neha, 2026). Third, the survival benefit observed for early antifibrotic initiation argues strongly against the historical pattern of waiting for documented progression before starting treatment. By the time progression is documented, irreversible lung architecture loss has already occurred, and the patient enters their next phase of disease with lower physiological reserve. The case for initiating therapy at or shortly after diagnosis for patients without contraindications and with adequate access to therapy is well supported by these data (Agarwal, Kumar,, & S, 2026; Bhatnagar, Kumar,, & Shivam, 2026; Yatish, Khatoon,, & Kumar, 2026). Implementation considerations include the substantial cost of antifibrotic therapy and resulting access constraints in many health systems, the manageable but real tolerability profile that requires dose-adjustment expertise and patient counselling, and the value of structured multidisciplinary review at diagnosis to confirm the IPF diagnosis and discuss treatment options. Patient engagement around expected disease trajectory, treatment benefits, and end-of-life planning is an integral component of ILD care that warrants structured attention rather than ad hoc discussion (Catherine, Gupta, Gopi,, & Swadhi, 2025; Swadhi, Gayathri, Suresh, Catherine,, & Velmurugan, 2025; Vettriselvan, Ramya, et al., 2026; Aumose, & Raj, 2026; Sharma, Sharma,, & Tyagi, 2026). Limitations include the single-centre design, the non-randomised comparison between treatment groups (which differed in age and severity even after adjustment, particularly the never-treated group skewing older), and the 36-month follow-up which captures most clinically important events but misses very late mortality. Tolerance to antifibrotic therapy was variable and discontinuation rates of approximately 40% by 24 months reflect a real-world tolerability ceiling that future antifibrotic development may improve. Genetic stratification, increasingly relevant to IPF outcomes and treatment response, was not performed in this cohort.

V. Conclusion

In a real-world prospective IPF cohort, early antifibrotic therapy attenuated FVC decline by approximately two-thirds compared with no treatment, halved acute exacerbation rates, and improved 36-month survival by nearly 30 percentage points compared with untreated patients. The advantage of early over late initiation supports a default of antifibrotic initiation at or shortly after diagnosis. Baseline physiological severity, honeycombing extent, prior exacerbations, and pulmonary hypertension identified patients at risk of rapid progression for whom earlier and more intensive surveillance and treatment escalation are warranted.

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