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Reassessment of risk profiles through weight and BMI changes in idiopathic pulmonary fibrosis☆

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ABSTRACT

Background: Idiopathic pulmonary fibrosis (IPF) is a progressive interstitial lung disease in which weight loss and low BMI have emerged as adverse prognostic indicators. However, longitudinal data on early weight change—particularly in patients receiving antifibrotic therapy—remain limited. This study examined the relationship between first-year weight change and clinical outcomes in a multicenter IPF cohort from Türkiye.

Methods: This retrospective study analyzed 428 patients diagnosed with IPF between 2019 and 2024 across 12 centers. Weight at diagnosis and one year, clinical characteristics, antifibrotic treatment, pulmonary function tests, 6MWD, and survival outcomes were evaluated. Annual weight change was categorized as no loss, <5% loss, or ≥5% loss; significant weight loss was defined as ≥5%.

Results: Among 428 patients (mean age 68.3 ± 8.0 years; 82% male), 78.5% experienced significant weight loss during follow-up. At the end of the first year, baseline BMI and the prevalence of diabetes mellitus decreased progressively with increasing weight loss, with the lowest values observed in patients with ≥5% weight loss ($p = 0.018$ and $p = 0.023$, respectively). In parallel, greater weight loss at the end of the first year was associated with worse pulmonary function, reflected by declining FVC (L and % predicted) and DLCO (% predicted), while rates of dietitian evaluation increased markedly, reaching the highest level in the ≥5% weight loss group (all $p \leq 0.036$). During follow-up, patients with ≥5% weight loss lost an average of 6.20 kg, while those without loss gained 0.22 kg ($p < 0.001$). Greater annual FVC decline occurred in both weight-loss groups ($p = 0.018$ and $p = 0.005$), whereas DLco decline was similar across groups. Antifibrotic use—especially nintedanib—was more frequent among those with ≥5% loss ($p = 0.010$). Weight loss was not associated with mortality or hospitalization, but correlated with greater functional deterioration. Age and baseline BMI independently predicted weight change.

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Conclusions: Early weight loss is common in IPF and is associated with accelerated functional decline, independent of antifibrotic therapy. Routine weight monitoring may provide additional prognostic value and supports incorporating body composition into IPF risk stratification.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic and relentlessly progressive interstitial lung disease characterized by irreversible loss of pulmonary function.[1] Although the overall prognosis is unfavorable and the disease often follows a fatal course, its clinical evolution varies markedly among individuals. In untreated patients, median survival has been estimated at roughly three years from the time of diagnosis.[2] Accordingly, the identification of robust prognostic indicators is essential for optimizing disease management.

Accumulating evidence suggests that weight loss and low body mass index (BMI) are associated with poorer outcomes in IPF.[3,4] Weight reduction is a common feature in these patients; previous studies have shown that approximately 15–20% experience a $\geq$ 5% decrease in body weight during the first year, and both low BMI and early weight decline have been linked to accelerated deterioration of pulmonary function.[3,5,6] Beyond this, BMI has been proposed as a potential predictor of mortality, disease progression, and hospitalization risk, irrespective of antifibrotic therapy use.[7] As an easily obtainable clinical measure, BMI also serves as an indicator of nutritional status, with inadequate nutritional intake being associated with adverse clinical outcomes in IPF.[8,9] Despite their accessibility and relevance, weight-related parameters remain insufficiently explored in chronic respiratory diseases, and evidence pertaining specifically to Turkish patient populations is notably limited.

Given these observations, we postulated that changes in body weight could be related to the clinical course and prognosis of IPF. Therefore, in this observational study, we evaluated weight trajectories in patients receiving antifibrotic therapy and investigated their associations with clinically important outcomes.

Materials and methods

Study design and centers

This retrospective cohort study was conducted with the participation of investigators from the Diffuse Parenchymal Lung Diseases (DPLD) Working Group of the Turkish Respiratory Research Association. A total of 12 centers from different regions of Türkiye were included. Data from patients diagnosed with IPF between January 2019 and December 2024 were analyzed.

Study population

The diagnosis of IPF was established according to the joint ATS/ERS/JRS/ALAT clinical practice guideline.[10] The study included 368 patients diagnosed based on clinical–radiological criteria and 60 patients with histologically confirmed usual interstitial pneumonia (UIP), yielding a total sample of 428 patients.

Inclusion criteria

- Diagnosis of IPF according to ATS/ERS/JRS/ALAT criteria
- Minimum follow-up duration of one year
- Availability of body weight measurements at diagnosis and at one-year follow-up

Exclusion criteria

- Follow-up duration of less than one year
- Missing weight data at diagnosis or at the one-year mark

Data collection

Clinical data were obtained from the electronic medical records of each participating center. Collected variables included:

- Demographic characteristics and comorbidities
- Antifibrotic therapy use, dosage, adverse effects, and treatment modifications
- Height and weight measurements
- Serial pulmonary function test (PFT) results
- Use of nutritional supplements
- Survival status

Body weight measurements recorded at diagnosis and during subsequent outpatient visits or hospitalizations—each coinciding with PFT assessments—were used for analysis.

Body mass index (BMI) classification

BMI was categorized according to World Health Organization (WHO) standards[11]:

- $<$25 kg/m^2: Normal or underweight
- 25–$<$30 kg/m^2: Pre-obesity
- $\geq$30 kg/m^2: Obesity (Class I–III)

Definition of weight change

Percentage change in body weight was assessed based on the U.S. Food and Drug Administration (FDA) guidance on developing products for weight management.[12] As a $\geq$ 5% annual weight loss is recommended as a clinically meaningful threshold, weight change was categorized as follows:

- No weight loss
- 0–$<$5% weight loss
- $\geq$5% weight loss

Significant weight loss was defined as a reduction of $\geq$5% within the first year after diagnosis.

Follow-up and survival analysis

Follow-up duration was calculated from the initiation of antifibrotic therapy to the date of the last clinical evaluation. Data collection ended in December 2024. Survival time was defined as the interval from the PFT date to the date of death, or to December 2024 for patients who were alive. In cases in which survival information could not be confirmed through medical records, follow-up data were obtained via telephone interviews.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics. The distribution of continuous variables was assessed using the Kolmogorov–Smirnov test and visual inspection of histograms. Normally distributed variables were presented as mean $\pm$ standard deviation, whereas non-normally distributed variables were reported as median

(minimum–maximum). Categorical variables were expressed as frequencies and percentages.

For comparisons between groups:

- Student's *t*-test or one-way ANOVA was used for normally distributed variables,
- Mann–Whitney U test or Kruskal–Wallis test was used for non-normally distributed variables,
- Chi-square test or Fisher's exact test (when appropriate) was used for categorical variables.

To investigate the association between annual percentage change in body weight and clinical outcomes, multivariable logistic regression models adjusted for baseline demographic and clinical characteristics were constructed. Cox proportional hazards regression analysis was performed to evaluate the effects on mortality. Clinically relevant covariates included in the Cox models were age, sex, smoking status, baseline BMI category, baseline pulmonary function parameters (forced vital capacity (FVC), diffusing capacity of the lung for carbon monoxide (DLCO), antifibrotic treatment use, and comorbidities. Survival probabilities were estimated using the Kaplan–Meier method, and differences between groups were assessed with the log-rank test. A two-sided p-value <0.05 was considered statistically significant.

This study was approved by the Aydın Adnan Menderes University Human Research Ethics Committee. Because of the retrospective study design, the requirement for informed consent was waived. The study was conducted in accordance with institutional and national research ethics standards, as well as the principles of the Declaration of Helsinki and its later amendments or comparable ethical guidelines.

Results

A total of 428 patients with a radiological and/or histopathological diagnosis of IPF were included in the study, with a mean follow-up duration of 36.3 ± 22.0 months. The cohort consisted of 82% males and 18% females, with a mean age of 68.3 ± 8.01 years. At the end of the first year of follow-up, 188 patients (45.7%) had no weight loss, 116 patients (28.2%) had weight loss <5%, and 107 patients (26.0%) had weight loss of 5% or more. During follow-up, 336 patients (78.5%) experienced significant weight loss, whereas 92 (21.5%) did not. The baseline characteristics of patients stratified by the presence of significant weight loss at the first year are summarized in Table 1. When patients with and without weight loss at the end of the first year were compared, diabetes mellitus was less frequent in patients who experienced weight loss than in those without weight loss (15.7% vs. 24.5%, p = 0.026). The proportion of patients with an IPF diagnosis based on radiological criteria was also lower in the weight loss group (80.3% vs. 91.5%, p = 0.001), and the distribution of HRCT patterns differed between groups (p = 0.027), with a higher rate of possible UIP and a lower rate of other patterns among patients with weight loss. In addition, patients with weight loss were more likely to use nutritional supplements (35.4% vs. 26.1%, p = 0.041) and were more frequently assessed by a dietitian during follow-up (38.6% vs. 20.7%, p < 0.001). Other demographic characteristics, pulmonary function measures, exercise capacity, treatment-related variables, and adverse event profiles were similar between the two groups.

When patients were stratified according to the degree of weight loss during the first year (no weight loss, <5% weight loss, and ≥5% weight loss). Baseline BMI differed significantly across categories, with lower values observed in patients with ≥5% weight loss (p = 0.018). The prevalence of diabetes mellitus decreased progressively with increasing weight loss and was lowest in the ≥5% weight loss group (p = 0.023). Pulmonary function parameters also showed significant differences, as both FVC (L) and FVC (% predicted) declined across increasing weight loss categories (p = 0.001 and p = 0.036, respectively), and DLCO (% predicted) was significantly lower in patients with greater weight loss (p = 0.026). Rates of dietitian evaluation increased markedly with the degree of weight loss, with the highest proportion observed in the ≥5% weight loss group (p < 0.001). All other demographic characteristics, radiological patterns, exercise capacity, oxygen desaturation, nutritional markers, disease progression, hospitalization rates, treatment modifications, and nutritional supplement use did not differ significantly between the groups (Table 2).

Patients were further stratified according to their percentage weight change from baseline throughout the follow-up period: no weight loss (n = 92), 0% to <5% weight loss (n = 124), and ≥5% weight loss (n = 212). Demographic characteristics remained similar across subgroups. However, comorbidities other than coronary artery disease, diabetes mellitus, and hypertension were more common in the ≥5% weight-loss subgroup (p = 0.010). GAP stage distribution also differed significantly: among patients with ≥5% weight loss, 49.5% were classified as GAP stage 1, 41.5% as stage 2, and 9.0% as stage 3. There were no significant differences in acute exacerbation rates or hospitalizations across subgroups (p = 0.360 and p = 0.484, respectively) (Table 3). Antifibrotic therapy use was higher in the ≥5% weight-loss subgroup, with 42.0% receiving pirfenidone and 58.0% receiving nintedanib (p = 0.010). Adverse drug events were more frequent in both weight-loss subgroups compared with patients without weight loss, and the distribution of mild, moderate, severe, and serious events was also greater in the ≥5% weight-loss subgroup (p = 0.106). Although treatment interruption,

Table 1
Baseline characteristics and clinical outcomes according to weight loss at first year.

Characteristic	No Weight Loss (n = 188)	Weight Loss (n = 223)	P-value
Age (years), mean ±sd	69.01±7.91	67.78 ± 8.16	0.126
Sex (Male),	156 (83.0%)	183 (82.1%)	0.808
Hypertension	54 (28.7%)	69 (30.9%)	0.625
Coronary Artery Disease	40 (21.3%)	59 (26.5%)	0.221
Diabetes Mellitus	46 (24.5%)	35 (15.7%)	0.026
IPF Diagnosis/ Radiological	172 (91.5%)	179 (80.3%)	0.001
HRCT Pattern			0.027
- UIP	155 (82.4%)	180 (81.4%)	
- Possible UIP	19 (10.1%)	35 (15.8%)	
- Other	14 (7.4%)	6 (2.7%)	
GAP Stage			0.918
- Stage 1	97 (51.6%)	118 (53.2%)	
- Stage 2	73 (38.8%)	85 (38.3%)	
- Stage 3	18 (9.6%)	19 (8.6%)	
Treatment			
IPF Treatment			0.117
- Pirfenidone	99 (52.9%)	97 (45.1%)	
- Nintedanib	88 (47.1%)	118 (54.9%)	
FVC (L)	2.55 (0.72)	2.66 (0.77)	0.145
FVC (% predicted)	75.43 (18.67)	78.92 (18.58)	0.064
DLCO (% predicted)	57.06 (20.34)	56.11 (20.19)	0.638
6MWT (meters)	396.93 (103.47)	400.58 (99.55)	0.768
min SpO_2 (%)	92.26 (4.38)	91.40 (5.79)	0.159
BMI (kg/m^2)	26.92 (4.20)	28.12 (4.17)	0.062
Albumin (g/dL)	3.99 (0.46)	3.98 (0.48)	0.840
Side Effect Severity			0.537
- None	6 (3.2%)	11 (5.0%)	
- Mild/Moderate	155 (83.8%)	180 (81.1%)	
- Severe	23 (12.4%)	31 (14.0%)	
- Serious	1 (0.5%)	0 (0.0%)	
Dose Reduction	60 (31.9%)	79 (35.4%)	0.454
Use of Nutritional Supplements	49 (26.1%)	79 (35.4%)	0.041
Assessed by a Dietitian	39 (20.7%)	86 (38.6%)	<0.001

Data are presented as mean ± standard deviation or number (%). BMI, body mass index; FVC, forced vital capacity; DLCO, diffusing capacity of the lung for carbon monoxide; GAP, Gender, Age, Physiology; 6MWD, 6-min walk test distance; 6MWT, 6-min walk test; SpO_2, peripheral oxygen saturation. *The weight-stable group includes patients with <5% annual weight loss or gain.** The weight-loss group includes patients who experienced ≥5% annual weight loss.

Table 2
Demographic and clinical characteristics classified according to categories of percentage change in body weight in the first year.

Characteristic	No Weight Loss (n = 188)	<5% Weight Loss (n = 116)	≥5% Weight Loss (n = 107)	p-value
Sex (Male), n (%)	156 (83.0)	97 (83.6)	86 (80.4)	0.792
Age (years), mean ± SD	65.8 ± 8.1	67.1 ± 7.9	66.5 ± 8.1	0.268
Baseline BMI (kg/m^2), mean ± SD	28.3 ± 4.0	28.9 ± 4.4	26.7 ± 4.2	0.018
Smoking (pack-years), mean ± SD	30.6 ± 18.7	28.6 ± 14.2	33.7 ± 17.3	0.058
Diabetes Mellitus	46 (24.5)	23 (19.8)	12 (11.2)	0.023
GAP Stage				0.766
- Stage 1	97 (51.6)	66 (56.9)	52 (49.1)	
- Stage 2	73 (38.8)	42 (36.2)	43 (40.6)	
- Stage 3	18 (9.6)	8 (6.9)	11 (10.4)	
HRCT Pattern				0.125
- UIP	155 (82.4)	94 (81.7)	86 (81.1)	
- Probable UIP	19 (10.1)	18 (15.7)	17 (16.0)	
- Other	14 (7.4)	3 (2.6)	3 (2.8)	
FVC (L), mean ± SD	2.65 ± 0.75	2.49 ± 0.76	2.40 ± 0.69	0.001
FVC (%), mean ± SD	71.3 ± 17.9	68.6 ± 19.0	65.2 ± 17.2	0.036
DLCO (%), mean ± SD	49.6 ± 19.5	46.6 ± 20.3	44.1 ± 20.6	0.026
6MWT (meters), mean ± SD	380.5 ± 107.5	376.2 ± 97.1	342.9 ± 91.6	0.075
Minimum SpO_2 (%), mean ± SD	85.1 ± 5.1	85.2 ± 5.0	83.9 ± 5.5	0.127
Albumin (g/dL), mean ± SD	4.18 ± 0.47	4.15 ± 0.48	4.19 ± 0.46	0.730
IPF Progression	109 (58.0)	60 (51.7)	67 (62.6)	0.253
Hospitalization	93 (49.5)	58 (50.0)	62 (57.9)	0.081
Dose Reduction	60 (31.9)	37 (31.9)	42 (39.3)	0.385
Treatment Discontinuation	23 (12.2)	13 (11.2)	12 (11.2)	0.950
Nutritional Supplement Use	49 (26.1)	37 (31.9)	42 (39.3)	0.062
Dietitian Evaluation	39 (20.7)	43 (37.1)	43 (40.2)	<0.001

Table 3
Demographic and clinical characteristics classified according to categories of annual percentage change in body weight from baseline during follow-up.

		No weight loss (n = 92)	0–5% weight loss (n = 124)	≥5% weight loss (n = 212)	p-value
Demographic Characteristics					
Gender	Male	74 (% 80.4)	106 (% 85.5)	171 (% 80.7)	0.489
	Female	18 (% 19.6)	18 (% 14.5)	41 (% 19.3)	
Age (year)	mean	68.67	67.72	68.60	0.568
Comorbidities					
Coronary artery disease		18 (% 19.6)	30 (% 24.2)	57 (% 26.9)	0.393
Hypertension		21 (% 22.8)	38 (% 30.6)	74 (% 34.9)	0.112
Diabetes mellitus		20 (% 21.7)	28 (% 22.6)	38 (% 17.9)	0.534
Other comorbid conditions		42 (% 45.7)	32 (% 25.8)	75 (% 35.4)	0.010
IPF Characteristics					
Diagnostic method	Radiology	86 (% 93.5)	104 (% 83.9)	178 (% 84.0)	0.065
	Surgical	6 (%6.5)	20 (% 16.1)	34 (% 16.0)	
GAP stage	1	40 (% 44.0)	80 (% 64.5)	105 (% 49.5)	0.011
	2	38 (% 41.8)	38 (% 30.6)	88 (% 41.5)	
	3	13 (% 14.3)	6 (%4.8)	19 (% 9.0)	
HRCT pattern	UIP	78 (% 84.8)	101 (% 82.1)	170 (% 80.6)	0.505
	Possible UIP	9 (%9.8)	19 (% 15.4)	29 (% 13.7)	
	Other	5 (%5.4)	3 (%2.4)	12 (% 5.7)	
IPF exacerbation	present	45 (% 48.9)	52 (% 41.9)	105 (% 49.8)	0.360
Hospitalization	present	45 (% 48.9)	70 (56.5)	109 (51.4)	0.484

Data are presented as mean ± standard deviation or number (%). IPF, Idiopathic pulmonary fibrosis, GAP, Gender, Age, Physiology, HRCT, high resolution computed tomography.

dose reduction, discontinuation, or switching did not differ significantly among subgroups, the use of nutritional supplements and dietitian involvement was significantly more common in patients with any degree of weight loss compared with those without weight loss ($p = 0.015$ and $p = 0.003$, respectively) (Table 4).

In functional assessments, patients with 0% to <5% or ≥5% weight loss demonstrated significantly greater annual declines in predicted FVC (L) at year 1 and at the final visit compared with those without weight loss ($p = 0.018$ and $p = 0.005$, respectively). No significant differences were observed in DLCO decline. Despite having lower baseline FVC (L) values, patients with ≥5% weight loss exhibited significantly higher 6MWT distances ($p = 0.002$ and $p = 0.02$) (Table 5).

In the multivariable analysis, age ($B = 0.152$, $p = 0.024$) and baseline BMI ($B = 0.587$, $p = 0.022$) were independently associated with changes in weight during follow-up. Final-visit FVC ($B = –1.848$, $p = 0.053$) demonstrated borderline significance, while no other variables showed an independent association with weight change (Table 6).

Discussion

This multicenter retrospective study demonstrates that changes in body weight observed during the first year following a diagnosis of IPF are particularly associated with annual decline in predicted FVC. In addition, patients with substantial weight loss exhibited a significant reduction in DLco. Our findings suggest that pronounced early weight loss may parallel not only deterioration in lung volumes but also impairment in gas exchange capacity, indicating that changes in body weight could serve as a potential clinical marker of disease progression.

In our study, the proportion of patients who experienced ≥5% weight loss (49.5%) was markedly higher than the rates reported in previous cohort studies. For instance, Jouneau et al. reported significant weight loss in 20.1% of placebo-treated individuals[3], and similar rates of approximately 15–22% were noted in cohorts from Japan and the United Kingdom.[5] The larger proportion of affected individuals in our study may reflect underlying ethnic or regional differences in baseline body habitus, as Asian populations typically have lower average body weight compared with Caucasian groups.[13] Such variability underscores how demographic factors may influence the clinical phenotype and course of IPF.[14]

Although patients with substantial weight loss in our study demonstrated a more pronounced annual decline in predicted FVC, weight loss itself did not correspond to increased all-cause mortality. This finding contrasts with several previous studies reporting reduced survival among patients with either low BMI or early weight reduction.[3,5,6] Other investigations have shown that underweight patients carry the highest mortality risk, whereas overweight and obese patients appear to have comparatively better outcomes.[15] The discrepancy between our findings and earlier work may be partly explained by the similar baseline BMI values in both weight-loss and weight-stable groups in our cohort, with both subgroups falling within the WHO “overweight” range. While low BMI is known to confer increased mortality risk, genetic studies suggest that higher BMI may predispose individuals to the development of IPF.[16]

Table 4
Treatment characteristics classified according to categories of annual percentage change in body weight from baseline during follow-up.

	No weight loss (n = 92)	0–5% weight loss (n = 124)	≥5% weight loss (n = 212)	p-value
Drug therapy				
Pirfenidon	59 (%64.8)	63 (%51.2)	86 (% 42.0)	0.001
Nintedanib	32 (%35.2)	60 (%48.8)	119 (% 58.0)	
Adverse effects				
Nausea	17 (%18.5)	47 (%37.9)	83 (% 39.2)	0.001
Diarrhea	24 (%26.1)	46 (%37.1)	94 (% 44.3)	0.010
Abnormal liver function tests	10 (%10.9)	38 (%30.6)	60 (% 28.3)	0.001
Weight loss	15 (%16.3)	63 (%50.8)	135 (% 63.7)	<0001
Rash	20 (%21.7)	40 (%32.3)	52 (% 24.5)	0.165
Photosensitivity	10 (%10.9)	38 (%30.6)	52 (% 24.5)	0.003
Loss of appetite	12 (%13.0)	46 (%37.1)	94 (% 44.3)	<0001
Mild/moderate	68 (76.4)	110 (89.4)	170 (80.2)	0.106
Severe	16	8 (0.5)	33 (15.6)	
Serious	0	0	1 (0.5)	
Treatment adherence				
Treatment discontinuation	14 (%15.2)	10 (%8.1)	28 (% 13.2)	0.226
Dose reduction	21 (%22.8)	43 (%34.7)	78 (% 36.8)	0.054
Treatment interruption	15 (%16.3)	17 (%13.7)	35 (% 16.5)	0.778
Medication switch	19 (%20.9)	21 (%16.9)	45 (% 21.3)	0.605
Use of nutritional supplements	17 (%18.5)	43 (%34.7)	72 (% 34.0)	0.015
Dietetic assessment	14 (%15.2)	43 (%34.7)	70 (% 33.0)	0.003

Table 5
Functional and clinical parameters according to annual weight change from baseline during follow-up.

	No weight loss (n = 92)	0–5% weight loss (n = 124)	≥5% weight loss (n = 212)	P value
Pulmonary Function Tests (PFTs)				
Baseline FVC (L)	2.50	2.81	2.55	0.002
Year 1 FVC (L)	2.43	2.71	2.51	0.018
Final visit FVC (L)	2.47	2.63	2.33	0.005
Baseline FVC (%)	76.78	80.45	76.97	0.234
Baseline DLCO (%)	54.85	58.30	55.77	0.408
6-Minute Walk Test				
Baseline 6MWT distance (m)	367.85	417.39	397.76	0.020
Baseline SpO_2 (%)	91.86	92.00	91.47	0.741
Changes in body weight and BMI				
Baseline weight (kg)	72.63	74.71	76.24	0.088
Year 1 wt (kg)	72.46	73.45	72.46	0.740
Final visit weight (kg)	73.37	73.29	68.45	<0001
Weight difference (kg)	−0.22	2.15	8.57	<0001
Baseline BMI	26.59	26.35	28.50	0.005
Year 1 BMI	26.73	26.66	26.66	0.963
Final visit BMI	26.53	26.09	25.38	0.421

BMI body mass index, FVC forced vital capacity, DLCO diffusing capacity of the lung for carbon monoxide, 6MWD 6-min walk test distance, 6MWT 6-min walk test, SpO2 peripheral oxygen saturation.

Table 6
Multivariable linear regression analysis of factors associated with change in body weight between baseline and final visit.

Variable	B	Std	Beta	t	p
First-year FVC (L)	1326	1204	0213	1102	0.243
Age	0152	0066	0223	2295	0.024
Final visit FVC (L)	−1848	0943	−0310	−1959	0.053
Treatment initiation FVC (L)	−0998	1409	−0149	−0708	0.480
Baseline body weight (kg)	0009	0085	0025	0109	0.914
Baseline BMI (kg/m^2)	0587	0251	0491	2335	0.022
Smoking (pack-years)	0011	0026	0036	0427	0.670
Baseline physiological parameters	−0004	0043	−0017	−0101	0.920
Duration of antifibrotic therapy (months)	−0005	0021	−0022	−0251	0.802

BMI body mass index, FVC forced vital capacity, DLCO diffusing capacity of the lung for carbon monoxide, 6MWD 6-min walk test distance, 6MWT 6-min walk test, SpO2 peripheral oxygen saturation.

In accordance with this notion, patients with higher baseline BMI in our cohort exhibited the greatest degree of weight loss, suggesting that elevated BMI does not necessarily translate into a benign clinical profile and requires close surveillance during follow-up.

Previous research has also highlighted the potential influence of baseline BMI on the degree of pulmonary function decline. A greater annual decrease in FVC has been reported among patients with BMI < 25 kg/m^2 compared with those with higher BMI categories.[17] Similarly, pooled analyses of large IPF cohorts have shown greater reductions in FVC among individuals with BMI < 25 kg/m^2 relative to those with overweight or obesity.[3] Taken together, these observations indicate that the relationship between weight change and clinical outcomes is likely modulated by baseline body composition, ethnicity, and other unmeasured biological factors. Long-term, well-phenotyped follow-up of our cohort will be necessary to further clarify these associations.

In this study, an association was observed between annual percentage change in body weight and decline in predicted FVC across weight-change subgroups. These findings are consistent with previous analyses. In a 2021 post hoc analysis by Jouneau et al., patients who experienced no weight loss demonstrated less annual decline in predicted FVC, DLco, and 6MWD compared with those who had 0 to <5% or ≥5% weight loss.[7] Similarly, an earlier study reported that patients with IPF who experienced weight loss had a higher rate of FVC decline within one year compared with those without weight loss.[5]

In our subgroup analyses, patients who experienced ≥5% weight loss demonstrated a significantly greater decline in pulmonary function. At the end of the first year, the mean percentage decline in FVC was approximately 13.3% in this group, compared with approximately 2.8% in patients without weight loss. This finding indicates that FVC decline was nearly fivefold greater among patients with substantial weight loss. The observed difference is noteworthy not only from a statistical perspective but also in terms of clinical effect size. Given that an annual FVC decline of ≥10% in IPF is widely accepted as a clinically meaningful indicator of disease progression, the average 13% reduction observed in the ≥5% weight-loss group suggests a more rapid course of functional deterioration in these patients.

Moreover, the presence of a statistically significant decline in DLco at the end of the first year in the same group further supports the notion that weight loss parallels not only restrictive volume loss but also impairment in gas exchange capacity, reflecting a multidimensional pattern of functional progression.

In contrast, no significant association was observed between weight loss and all-cause mortality, hospitalization, acute exacerbations, or changes in 6MWD. These findings suggest that weight loss may be primarily linked to functional progression, whereas its potential impact on mortality may require longer-term follow-up to be fully elucidated.

Much of the existing literature examining weight loss and mortality in IPF has focused on cohorts not receiving antifibrotic therapy.[5,8] More

recent studies investigating pirfenidone-treated patients have shown tendencies toward weight reduction during treatment, though these trends were not strongly linked to adverse events or dose modifications.[18] Rates of ≥5% weight loss did not differ substantially between pirfenidone-treated and untreated groups,[18] and another study similarly found no association between pirfenidone use and significant weight reduction.[19] In contrast, Jouneau et al. reported that weight loss and lower BMI were associated with more rapid FVC decline and poorer outcomes in placebo groups as well as among pirfenidone-treated patients.[7]

The impact of nintedanib appears more variable. In placebo groups, lower BMI was associated with faster FVC decline, whereas in nintedanib-treated patients, FVC decline was similar across BMI categories. Significant weight loss influenced FVC decline only in placebo recipients and not in those taking nintedanib.[20] Despite these inconsistencies between antifibrotic agents, our cohort—which included patients treated with both pirfenidone and nintedanib—demonstrated a high prevalence of weight loss, suggesting that weight reduction may represent a composite marker of disease progression in patients receiving antifibrotic therapy.

Notably, the vast majority of patients with ≥5% weight loss experienced dose reduction, treatment interruption, drug switching, or discontinuation during antifibrotic therapy. This high proportion suggests that weight loss may not solely reflect disease progression but may also be associated with treatment tolerability. Indeed, the higher incidence of gastrointestinal adverse effects—such as nausea, diarrhea, and loss of appetite—observed in the weight-loss groups supports the notion that weight reduction may, at least in part, be related to treatment-related side effects.

Therefore, the weight loss observed in our cohort may be considered a composite clinical indicator reflecting both disease progression and treatment-related adverse effects. These findings suggest that routine and serial monitoring of body weight during antifibrotic therapy could contribute to clinical decision-making, not only by facilitating early detection of disease progression but also by enabling timely identification of impaired treatment tolerability.

Overall, nearly half of patients in our study experienced ≥5% weight loss within the first year of diagnosis, and these individuals demonstrated worse pulmonary function and less favorable clinical trajectories. These results highlight the importance of incorporating routine body-weight monitoring into early disease management. Clinical attention should also be directed toward identifying risk factors for malnutrition and considering targeted interventions. To better understand the impact of weight loss on clinical outcomes in patients with IPF, well-designed prospective studies are needed in which body weight measurements are performed at regular intervals. Such studies should focus on modifiable, treatable factors—such as BMI-adjusted antifibrotic dosing—with the aim of improving treatment outcomes and enhancing the sustainability of therapy.

This study has limitations. First, the retrospective design limits the ability to infer causality, and prospective confirmation is needed to determine whether weight loss independently predicts outcomes. Although our multicenter approach enhanced the representativeness of the sample, variations in local clinical practices may have contributed to heterogeneity in measurement. Furthermore, only body weight was assessed; data on muscle mass, fat mass, or body-composition changes were unavailable, limiting insights into the mechanisms underlying weight decline. Additional factors such as diet, caloric intake, metabolic rate, physical activity, and lifestyle were not evaluated and may have influenced weight trajectories. Additionally, adherence to antifibrotic therapy, adverse effects, and the temporal dynamics of weight changes following dose adjustments or other treatment modifications could not be analyzed in detail. Finally, limiting the analysis to the first year after diagnosis precludes evaluation of long-term consequences of weight loss. Despite these constraints, the study's large sample size and multicenter design provide a robust dataset for evaluating the association between early weight change and clinical outcomes in IPF.

CRediT authorship contribution statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The datasets generated and/or analyzed during the current retrospective study are not publicly available due to patient privacy and confidentiality restrictions (as per the ethical approval and local data protection regulations) but are available from the corresponding author on reasonable request

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