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Prognostic significance of body mass index and weight loss in patients with idiopathic pleuroparenchymal fibroelastosis

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Abstract. *Background and aim*: Idiopathic pleuroparenchymal fibroelastosis (IPPFE) is a rare form of idiopathic interstitial pneumonias; its physical characteristics include a slender build with platythorax and progressive weight loss. However, the clinical significance of body mass index (BMI) and weight loss remains unclear in patients with IPPFE. Therefore, we aimed to clarify the association between baseline BMI, weight loss after diagnosis, and the prognosis of patients with IPPFE. *Methods*: This retrospective study included 71 patients diagnosed with IPPFE at our institution between 2005–2021. BMI at diagnosis was classified into three: underweight (<18.5 kg/m^2), normal weight (≥18.5 to <25.0 kg/m^2), or overweight (≥25.0 kg/m^2). An annual rate of weight change after the diagnosis was evaluated, and ≥5% per year decrease was defined as a significant weight loss. We investigated clinical features and prognosis based on baseline BMI and weight loss. *Results*: Of the 71 patients, 48 (67.6%) and 23 (32.4%) were classified as underweight and normal weight, respectively, and none were overweight. Significant weight loss occurred in 24 (33.8%) patients, and they tended to have more cases of dyspnea and had significantly older age, lower BMI, higher rates of co-existence of lower-lobe interstitial lung disease, lower pulmonary function test results and higher incidence of pneumothorax after the diagnosis than those without weight loss. Patients with BMI <18.5 kg/m^2 and those with weight loss had a significantly worse prognosis than those with BMI ≥18.5 kg/m^2 or those without weight loss, respectively (p=0.005, p<0.001). Multivariate analysis revealed that low BMI and weight loss were independent poor prognostic factors. *Conclusions*: Low BMI and weight loss are associated with poor prognosis in patients with IPPFE.

Key words: body mass index, weight loss, idiopathic pleuroparenchymal fibroelastosis, prognosis

Introduction

Idiopathic pleuroparenchymal fibroelastosis (IPPFE) is a rare form of idiopathic interstitial pneumonias, characterized by predominantly upper lobe pleural and subpleural lung parenchymal fibrosis (1-6). The clinical course of IPPFE is heterogeneous, with some patients having a prognosis similar to or worse than that of idiopathic pulmonary fibrosis (IPF) (7). Although decrease in forced vital capacity (FVC) over time is an acceptable parameter for assessing disease progression and estimating the risk of further mortality in fibrotic interstitial lung disease (ILD) (8), patients with IPPFE may undergo inadequate follow-up pulmonary function tests, owing to the high frequency of pneumothorax complications (9). Identifying potential predictors of disease progression or prognosis in patients with IPPFE is an important challenge.

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Body mass index (BMI) is considered an indicator of nutritional status, and some studies have suggested an association between low BMI and poor outcomes in patients with fibrotic ILD (10-13). Additionally, studies have shown that weight loss is a commonly phenomenon in ILD, and that weight loss over time is associated with a decline in FVC and increased mortality in patients with fibrotic ILD (11,12,14-18). Although most of these studies included patients with IPF, a recent large cohort study demonstrated that low BMI and weight loss were independently associated with one-year mortality in patients with fibrotic ILD, including non-IPF patients (12).

The physical characteristics of patients with IPPFE include slender build with platythorax and progressive weight loss (2-6,19). Recently, a study showed that weight loss reflects disease progression in patients with pleuroparenchymal fibroelastosis (PPFE), including secondary PPFE (18). However, the clinical significance of BMI and weight loss in patients with IPPFE remains unclear. Therefore, in this retrospective study, we aimed to clarify the association between baseline BMI, weight loss after diagnosis, and the prognosis of patients with IPPFE.

Materials and Methods

Study population and diagnostic criteria for IPPFE

We retrospectively reviewed 83 consecutive patients diagnosed with idiopathic pulmonary upper lobe fibrosis or IPPFE at the Seirei Hamamatsu General Hospital between 2005 and 2021. Diagnosis of IPPFE was made via multidisciplinary discussion in our institution based on the following criteria (19): (1) a radiologic PPFE pattern on chest computed tomography (CT), characterized by bilateral subpleural dense consolidation with or without pleural thickening in the upper lobes and less marked or no involvement of the lower lobes; (2) radiologic confirmation of disease progression, characterized by an increase in upper lobe consolidation with or without pleural thickening and/or a decrease in upper lobe volume on serial radiologic assessment; and (3) exclusion of other lung diseases with identifiable etiologies, such as connective tissue disease (CTD), chronic hypersensitivity pneumonitis, pulmonary sarcoidosis, pneumoconiosis, and active pulmonary infection. Based on these criteria, nine patients were excluded, eight had underlying diseases with CTD, and one had no radiological confirmation of disease progression. Additionally, three patients without follow-up weight assessments were excluded from this study. Therefore, 71 patients with IPPFE were enrolled in this study. All high-resolution CT (HRCT) was reviewed by radiologists in our institution.

The ethics committee of Seirei Hamamatsu General Hospital approved the study protocol (approval number: 3852). The requirements for patient approval and informed consent were waived because the study was designed as a retrospective review.

Baseline BMI and weight loss after the diagnosis

Baseline BMI was calculated using height and weight at the time of diagnosis and classified into three categories: underweight (<18.5 kg/m^2), normal weight (≥18.5 to <25.0 kg/m^2), or overweight (≥25.0 kg/m^2). The annual rate of weight change was calculated by the following formula using weight change within two years after the diagnosis: the annual weight change = (latest weight − weight at baseline) / weight at baseline ÷ weight measurement interval (months) / 12 × 100. The annual weight loss was classified as follows: <2.5% per year decrease (including weight gain), ≥2.5 to <5% per year decrease, or ≥5% per year decrease, and ≥5% per year decrease was defined as a significant weight loss.

Data collection

Clinical data, including age, sex, smoking status, BMI, symptoms and physical findings at diagnosis, treatment for IPPFE, pneumothorax as a pulmonary complication after diagnosis, and outcomes, were obtained from the patients' medical records. The coexistence of lower-lobe ILD on HRCT was assessed and classified into usual interstitial pneumonia (UIP) and non-UIP patterns, according to the criteria described in a previous study (20). Laboratory data, including albumin, C-reactive protein (CRP), lactate dehydrogenase (LDH), Krebs von den Lungen-6 (KL-6), surfactant protein-D (SP-D), arterial oxygen partial pressure (PaO_2), and pulmonary function tests, including FVC, forced expiratory volume in 1 s (FEV_1)/ FVC, diffusing capacity for carbon monoxide (DLco), residual volume (RV), total lung capacity (TLC), and RV/TLC at diagnosis, were also obtained.

Statistical methods

The chi-square test or Mann-Whitney U-test was used to compare the two groups. The Kaplan-Meier method was used to estimate cumulative survival, and a log-rank test was performed. Cox proportional hazard analysis was used to identify significant variables that could predict the survival status. Statistical analyses were performed using JMP® 13 software (SAS Institute Inc., Cary, NC, USA). Statistical significance was set at $p<0.05$.

Results

Patient characteristics

Patient characteristics are summarized in Table 1. The median age was 69 years, and male sex (59.2%) and never-smokers (64.8%) were predominant. Most of the patients had a slender build and median BMI was 16.9 kg/m^2. Only four (5.6%) patients had confirmed PPFE histologically. Cough and dyspnea on exertion occurred in 33.8% and 46.5% of the patients, respectively, and 22.5% had fine crackles on chest auscultation. In the HRCT findings, 38 (53.5%) patients had a co-existence of lower-lobe ILD, of which 10 (28.2%) had a UIP pattern. Laboratory findings showed high serum KL-6 and/or SP-D levels in most of the patients. The pulmonary function tests showed restrictive ventilatory impairment with decreased FVC and an increased RV/TLC ratio.

During the observation period (median, 32 months), 88.7% of the patients had no pharmacological treatment for IPPFE, and long-term oxygen therapy (LTOT) was administered to 20 (28.2%) patients. After the diagnosis, complications of pneumothorax occurred in approximately half of the patients (47.5%). Thirty (42.3%) patients died,

Table 1. Patient characteristics.

	IPPFE (n=71)
Age, years	69 [61–76]
Gender Male, n (%)	42 (59.2)
Smoker, n (%)	25 (35.2)
BMI, kg/m^2	16.9 [15.3–19.2]
Pathological diagnosis, n (%)	4 (5.6)
Observation period, mo	32 [17–60]
Symptoms and physical findings	
Cough, n (%)	24 (33.8)
Dyspnea, n (%)	33 (46.5)
Fine crackle, n (%)	16 (22.5)
HRCT findings	
Lower-lobe ILD, n (%)	38 (53.5)
Lower-lobe UIP, n (%)	20 (28.2)
Laboratory findings	
Albumin, mg/dL	3.9 ± 0.5
CRP, mg/dL	0.7 ± 1.8
LDH, U/L	198 ± 40
KL-6, U/mL	561 ± 642
SP-D, ng/mL	187 ± 107
PaO_2, Torr	82.0 ± 9.8
Baseline pulmonary function tests	
FVC, L	2.03 ± 0.91
%FVC, %	67.8 ± 22.2
FEV_1/FVC, %	92.5 ± 9.6
%DLco, %	103.9 ± 28.9
RV, %	121.1 ± 36.9
TLC, %	88.8 ± 18.9
RV/TLC, %	46.7 ± 9.2
Treatment for IPPFE	
PSL and/or ISA*, n (%)	7 (9.9)
Pirfenidone, n (%)	2 (2.8)
LTOT, n (%)	20 (28.2)
Pulmonary complication	
Pneumothorax, n (%)	26 (36.6)
Outcome	
All-cause death**, n (%)	30 (42.3)
Respiratory-related death n, %	28 (39.4)

Data are presented as n (%), mean ± standard deviation, or median [interquartile range].
*PSL alone (n=5), PSL+cyclosporin A+pirfenidone (n=1), PSL+cyclophosphamide (n=1)
**Respiratory failure (n=22), Bacterial pneumonia (n=4), Pneumothorax (n=2), Sudden death (n=1), Chronic heart failure (n=1). Abbreviations: BMI, body mass index; CRP, C-reactive protein; DLco, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HRCT, high-resolution computed tomography; ILD, Interstitial lung disease; IPPFE, idiopathic pleuroparenchymal fibroelastosis; ISA, immune suppressive agents; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; LTOT, long-term oxygen therapy; mo, months; PaO_2, arterial oxygen partial pressure; PSL, prednisolone; RV, residual volume; SP-D, surfactant protein-D; TLC, total lung capacity; UIP, usual interstitial pneumonia.

with most commonly due to chronic respiratory failure (n=22).

Proportion of patients based on baseline BMI and weight loss

The proportion of patients with IPPFE based on baseline BMI and weight loss is shown in Figure 1. Of the 71 patients, 48 (67.6%) were classified as underweight (<18.5 kg/m^2), 23 (32.4%) as normal weight (≥18.5 to <25.0 kg/m^2), and none as overweight (≥25.0 kg/m^2) (Figure 1A). The annual weight change was determined at the mean period of 18.7 ± 6.5 months, and a significant weight loss of ≥5% per year occurred in 24 (33.8%) patients (Figure 1B). Additionally, weight loss of <2.5% per year and ≥2.5 to <5% per year occurred in 33 (46.7%) and 14 (19.7%) patients, respectively (Figure 1B).

Comparison of patient characteristics by baseline BMI

We compared clinical characteristics between patients with BMI <18.5 kg/m^2 (n=48) and those with BMI ≥18.5 kg/m^2 (n=23), as shown in Table 2. Patients with BMI <18.5 kg/m^2 had significantly lower serum albumin levels and FVC and higher FEV_1/FVC and RV/TLC than those with BMI ≥18.5 kg/m^2. There were no significant differences in the baseline characteristics, including age, sex, smoking habits, symptoms, physical findings, or co-existence of lower-lobe ILD on HRCT between the two groups.

Additionally, there was no significant difference in pharmacological treatment and the complication of pneumothorax after the diagnosis between the two groups; however, patients with BMI <18.5 kg/m^2 required significantly more LTOT and showed significantly poorer survival than those with BMI ≥18.5 kg/m^2 (log-rank test: p=0.005; Figure 2A).

Comparison of patient characteristics by weight loss

We compared the clinical characteristics between patients with weight loss (≥5% per year decrease; n=24) and those without weight loss (<5% per year decrease; n=47), as shown in Table 3. Patients with weight loss had significantly older age, lower baseline BMI, and higher incidence of fine crackles on auscultation and the co-existence of lower-lobe ILD on HRCT, and they tended to have more cases of dyspnea than those without weight loss. Additionally, patients with weight loss showed significantly lower serum albumin levels and higher CRP, KL-6, and SP-D levels, with significantly lower FVC, DLco and TLC, and higher FEV_1/FVC and RV/TLC in pulmonary function tests than those without weight loss.

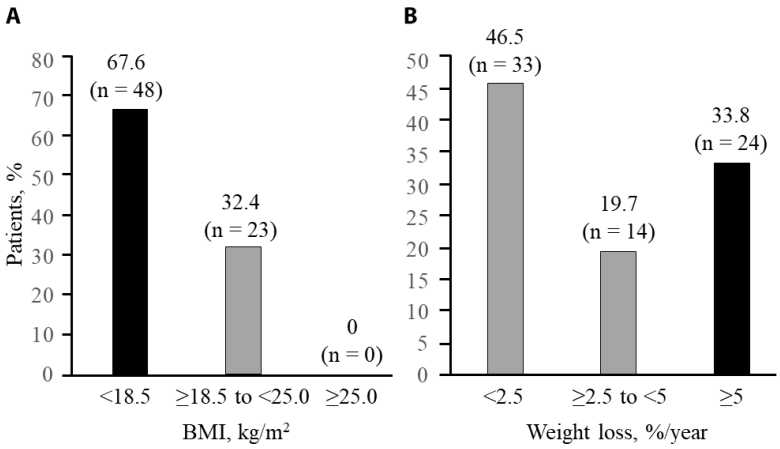

Figure 1. Proportion of patients based on baseline BMI and weight loss. Baseline BMI was classified into underweight (≥18.5 kg/m^2) and normal weight (≥18.5 to <25.0 kg/m^2) in 48 (67.6%) and 23 (32.4%) patients, respectively, and none was overweight (≥25 kg/m^2) (A). An annual weight loss of <2.5% per year, ≥2.5 to <5% per year, and ≥5% per year (defined as a significant weight loss) were observed in 33 (46.7%), 14 (19.7%), and 24 (33.8%) patients, respectively (B). Abbreviations: BMI, body mass index; IPPFE, idiopathic pleuroparenchymal fibroelastosis.

Table 2. Comparison of patient characteristics by baseline BMI.

	BMI <18.5 (n=48)	BMI ≥18.5 (n=23)	P-value
Age, years	70 [64–80]	67 [58–72]	0.06
Gender Male, n (%)	26 (54.2)	16 (69.6)	0.21
Smoker, n (%)	17 (35.4)	8 (34.8)	0.96
BMI, kg/m^2	16.0 [14.4–17.1]	20.4 [19.2–21.4]	<0.001
Pathological diagnosis, n (%)	2 (4.2)	2 (8.7)	0.45
Observation period, mo	28.5 [15.3–53.5]	46 [27–76]	0.04
Symptoms and physical findings			
Cough, n (%)	14 (29.2)	10 (43.5)	0.23
Dyspnea, n (%)	25 (52.1)	8 (34.8)	0.17
Fine crackle, n (%)	12 (25.0)	4 (17.4)	0.47
HRCT findings			
Lower-lobe ILD, n (%)	28 (58.3)	10 (43.5)	0.24
Lower-lobe UIP, n (%)	15 (31.2)	5 (21.7)	0.40
Laboratory findings			
Albumin, mg/dL	3.9 ± 0.5	4.2 ± 0.4	0.04
CRP, mg/dL	0.6 ± 1.0	0.9 ± 2.9	0.06
LDH, U/L	196 ± 35	201 ± 50	0.93
KL-6, U/mL	455 ± 224	778 ± 1057	0.67
SP-D, ng/mL	173 ± 93	217 ± 129	0.23
PaO_2, Torr	80.1 ± 9.8	86.3 ± 8.5	0.08
Baseline pulmonary function tests			
FVC, L	1.79 ± 0.88	2.47 ± 0.79	<0.01
%FVC, %	61.5 ± 22.0	80.0 ± 17.5	<0.01
FEV_1/FVC, %	94.8 ± 7.0	88.0 ± 12.2	<0.01
%DLco, %	103.6 ± 28.4	104.5 ± 30.9	0.98
RV, %	119.5 ± 40.5	124.1 ± 29.8	0.57
TLC, %	86.5 ± 19.0	93.0 ± 18.5	0.21
RV/TLC, %	49.3 ± 9.7	41.5 ± 4.9	<0.01
Treatment for IPPFE			
PSL and/or ISA, n (%)	4 (8.3)	3 (13.0)	0.54
Pirfenidone, n (%)	1 (2.1)	1 (4.4)	0.61
LTOT, n (%)	17 (35.4)	3 (13.0)	0.04
Pulmonary complication			
Pneumothorax, n (%)	20 (41.7)	6 (26.1)	0.20
Outcome			
All-cause death, n (%)	25 (52.1)	5 (21.7)	0.01
Respiratory-related death n, %	23 (47.9)	5 (21.7)	0.03

Data are presented as n (%), mean ± standard deviation, or median [interquartile range]. Abbreviations: BMI, body mass index; CRP, C-reactive protein; DLco, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HRCT, high-resolution computed tomography; ILD, Interstitial lung disease; IPPFE, idiopathic pleuroparenchymal fibroelastosis; ISA, immune suppressive agents; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; LTOT, long-term oxygen therapy; mo, months; PaO_2, arterial oxygen partial pressure; PSL, prednisolone; RV, residual volume; SP-D, surfactant protein-D; TLC, total lung capacity; UIP, usual interstitial pneumonia.

Table 3. Comparison of patient characteristics by weight loss.

	Weight loss (+) (n=24)	Weight loss (-) (n=47)	P-value
Age, years	72 [68–80]	67 [58–74]	<0.01
Gender Male, n (%)	16 (66.7)	26 (55.3)	0.35
Smoker, n (%)	8 (33.3)	17 (36.1)	0.81
BMI, kg/m^2	15.9 [14.6–17.5]	17.5 [16.0–19.7]	0.03
Pathological diagnosis, n (%)	3 (12.5)	1 (2.1)	0.08
Observation period, mo	25 [13–34]	46 [18–76]	<0.01
Symptoms and physical findings			
Cough, n (%)	10 (41.7)	14 (29.8)	0.32
Dyspnea, n (%)	15 (62.5)	18 (38.3)	0.05
Fine crackle, n (%)	9 (37.5)	7 (14.9)	0.03
HRCT findings			
Lower-lobe ILD, n (%)	19 (79.2)	19 (40.4)	<0.01
Lower-lobe UIP, n (%)	13 (54.1)	7 (14.9)	<0.001
Laboratory findings			
Albumin, mg/dL	3.8 ± 0.6	4.1 ± 0.4	0.04
CRP, mg/dL	0.9 ± 1.4	0.6 ± 2.0	<0.01
LDH, U/L	204 ± 46	195 ± 36	0.74
KL-6, U/mL	731 ± 927	473 ± 412	0.04
SP-D, ng/mL	224 ± 106	168 ± 104	0.03
PaO_2, Torr	83.3 ± 10.8	80.8 ± 8.7	0.30
Baseline pulmonary function tests			
FVC, L	1.70 ± 0.67	2.19 ± 0.97	0.04
%FVC, %	59.4 ± 18.2	72.2 ± 23.0	0.01
FEV_1/FVC, %	97.5 ± 3.8	89.8 ± 10.6	<0.01
%DLco, %	89.5 ± 26.4	111.7 ± 27.6	0.04
RV, %	106.9 ± 33.0	129.3 ± 37.1	0.10
TLC, %	76.2 ± 19.7	95.6 ± 14.7	<0.01
RV/TLC, %	50.4 ± 8.1	44.5 ± 9.1	0.03
Treatment for IPPFE			
PSL and/or ISA, n (%)	3 (12.5)	4 (8.5)	0.60
Pirfenidone, n (%)	1 (4.2)	1 (2.2)	0.64
LTOT, n (%)	10 (41.7)	10 (21.3)	0.07
Pulmonary complication			
Pneumothorax, n (%)	17 (70.8)	9 (19.2)	<0.001
Outcome			
All-cause death, n (%)	18 (75.0)	12 (25.5)	<0.0001
Respiratory-related death n, %	17 (70.8)	11 (23.4)	0.0001

Data are presented as n (%), mean ± standard deviation, or median [interquartile range]. Abbreviations: BMI, body mass index; CRP, C-reactive protein; DLco, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HRCT, high-resolution computed tomography; ILD, Interstitial lung disease; IPPFE, idiopathic pleuroparenchymal fibroelastosis; ISA, immune suppressive agents; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; LTOT, long-term oxygen therapy; mo, months; PaO_2, arterial oxygen partial pressure; PSL, prednisolone; RV, residual volume; SP-D, surfactant protein-D; TLC, total lung capacity; UIP, usual interstitial pneumonia.

There was no significant difference in the treatment of IPPFE between the two groups; however, patients with weight loss had a significantly higher incidence of pneumothorax after the diagnosis, and a significantly worse prognosis than those without weight loss (log-rank test: p<0.001; Figure 2B).

Univariate and multivariate analysis for mortality

Finally, we investigated the prognostic factors using univariate and multivariate Cox proportional hazards analysis in all the patients (Table 4). The univariate analysis showed that older age, male sex, lower baseline BMI, the co-existence of lower-lobe UIP pattern on HRCT, lower serum albumin level, lower %FVC, higher RV/TLC, and weight loss (≥5% per year decrease) were significantly associated with mortality. Multivariate analysis adjusted for age, sex, and %FVC revealed that low baseline BMI (hazard ratio 0.844 [0.704–0.991], p=0.04) and weight loss (hazard ratio 6.561 [2.391–20.404], p<0.001) were independent poor prognostic factors.

Discussion

In the present Asian study, we demonstrated that at diagnosis, approximately 2/3 of the patients were classified as underweight (BMI <18.5 kg/m^2), and 1/3 had a significant weight loss of ≥5% per year after the diagnosis. Weight loss was more common in advanced stage patients, and those with BMI <18.5 kg/m^2 and weight loss had a significantly worse prognosis than those with BMI ≥18.5 kg/m^2 or those without weight loss, respectively. Additionally, the multivariate analysis revealed that low BMI and weight loss were independent prognostic factors. These results suggested that weight change may be a clinically useful prognostic indicator in patients with IPPFE.

Body mass index is a widely used indicator of nutritional status that predicts the prognosis of several pulmonary diseases, including chronic obstructive pulmonary disease (21,22) and ILD (10-13). Studies have been shown that low BMI is associated with a decline in FVC and increased hospitalization and mortality in patients with fibrotic ILD (10-13). Additionally, unintentional weight loss is a frequent problem in patients with ILD, and several studies have reported a relationship between weight loss and poor prognosis (11,12,14-18). Pugashetti et al. first demonstrated that weight loss is common among patients with ILD, and is associated with an increased risk of mortality in patients with IPF and unclassifiable ILD (14). This finding was replicated in several IPF cohorts (15,16). Moreover, Jouneau et al. performed a post-hoc analysis from five randomized controlled trials of IPF patients; they showed that those with a baseline BMI <25 kg/m^2 or annualized weight loss had worse outcomes over 1 year than

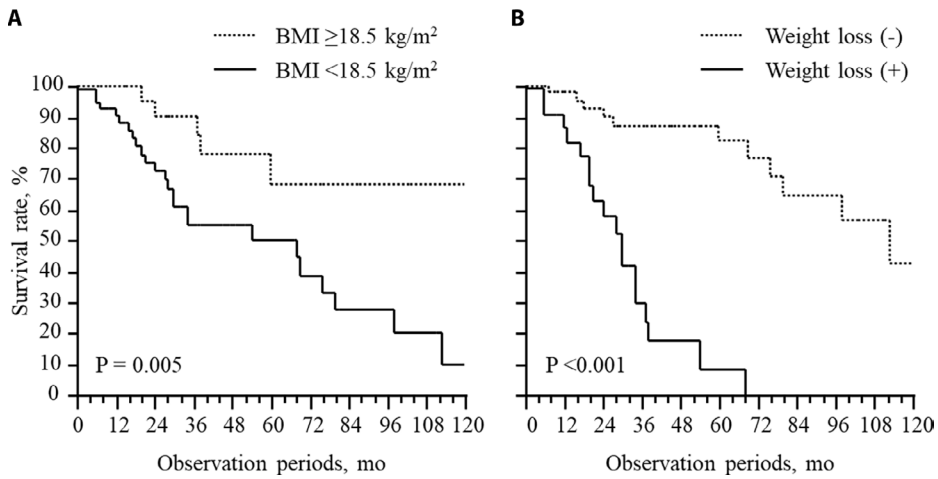

Figure 2. Survival curves in patients with IPPFE by baseline BMI and weight loss

Survival was significantly poorer in IPPFE patients with baseline BMI of <18.5 kg/m^2 (n=48) than in those with baseline BMI of ≥18.5 kg/m^2 (n=23) (log-rank test; p=0.0005) (A). Patients with IPPFE and significant weight loss (≥5% per year decrease; n=24) had a lower survival rate than those without a significant weight loss (<5% per year decrease; n=47) (log-rank test; p<0.0001) (B). Abbreviations: BMI, body mass index; IPPFE, idiopathic pleuroparenchymal fibroelastosis.

Table 4. Univariate and multivariate analysis for mortality.

	HR	95%CI	P-value
Univariate analysis			
Age, years	1.065	1.023–1.121	0.001
Male sex, n	2.457	1.121–5.954	0.02
Smoker, n	1.672	0.789–3.480	0.18
BMI, kg/m_2	0.837	0.730–0.951	0.006
Lower-lobe UIP, n	6.036	2.760–13.291	<0.001
Albumin, mg/dL	0.283	0.111–0.720	0.008
LDH, U/L	1.003	0.992–1.012	0.60
KL-6, U/mL	1.000	0.999–1.001	0.22
PaO_2, Torr	0. 991	0.951–1.033	0.67
%FVC, %	0.978	0.963–0.993	0.007
%DLco, %	0.987	0.964–1.007	0.20
RV/TLC, %	1.140	1.072–1.218	<0.001
PSL and/or ISA, n	2.814	0.814–7.521	0.09
Pneumothorax, n	3.059	1.484–6.532	0.002
Weight loss, n	10.796	4.333–31.007	<0.001
Multivariate analysis			
Age, years	1.059	1.009–1.115	0.02
Male sex, n	21.531	5.919–96.549	<0.001
%FVC, %	0.948	0.922–0.974	<0.001
BMI, kg/m^2	0.844	0.704–0.991	0.04
Weight loss, n	6.561	2.391–20.404	<0.001

Abbreviations: BMI, body mass index; CI, confidence interval; DLco, diffusing capacity for carbon monoxide; FVC, forced vital capacity; HR, hazard ratio; ISA, immune suppressive agents; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; PaO_2, arterial oxygen partial pressure; PSL, prednisolone; RV, residual volume; TLC, total lung capacity; UIP, usual interstitial pneumonia.

those with a baseline BMI ≥25 kg/m^2 or no weight loss (11). Furthermore, comes et al. recently showed that lower baseline BMI and weight loss were associated with one-year mortality in two large cohorts of over 1,700 patients with fibrotic ILD, including non-IPF patients (12). These findings suggest a robust and generalizable association between BMI, weight loss, and mortality in patients with fibrotic ILD.

The physical characteristics of IPPFE patients include slender build with platythorax and a majority of them develop severe weight loss similar to cachexia (2-6, 19). Only a few studies have shown an association between BMI or weight loss and prognosis in patients with IPPFE. Hayashi et al. showed that a lower BMI was significantly associated with poorer outcomes in 20 patients with IPPFE (23). Additionally, Kinoshita et al. reported that 15 (27.8%) of 54 patients with PPFE experienced significant weight loss, which was defined as an annual change in body weight ≥5%, and those with significant weight loss had a poorer survival outcome than those without such loss (18). Similar to their results, in our cohort, a significant weight loss was observed in 33.8% of the IPPFE patients; furthermore, low BMI and weight loss were independent poor prognostic factors. Based on previous evidence (10-18) and our findings, weight measurements over time may predict disease progression and prognosis in patients with fibrotic ILD, including those with IPPFE.

It has been reported that weight loss among patients with IPF may occur due to physical inactivity, which leads to loss of muscle mass and function or to loss of appetite (11,13,16). A previous study showed that patients with IPPFE have a lower BMI and a more pronounced loss of skeletal muscle than patients with IPF (24), suggesting an association between muscle weakness and weight loss. Additionally, it has been shown that low BMI in PPFE is associated with flat thorax progression (25), and that weight loss is significantly correlated with lower %FVC in patients with IPPFE (18,26). Based on these findings, it was speculated that the energy consumption for respiration is increased due to the flattened thoracic cage, in addition to the contraction of the lungs, which limits lung expansion in patients with IPPFE, thereby leading to progressive weight loss.

Currently, there is no established treatment for IPPFE. Nintedanib, an antifibrotic agent, may slow disease progression in patients with IPPFE; however, its efficacy remains controversial (27,28). Nutritional support and rehabilitation are important in these patients. In a retrospective study of 25 patients with IPPFE, Mori et al. reported that respiratory rehabilitation had beneficial effects on exercise capacity, dyspnea, anxiety, depression, and health-related quality of life, although pneumothorax and pneumomediastinum were major barriers to implementing pulmonary rehabilitation (29). Further studies are warranted to determine whether interventions including nutritional augmentation and rehabilitation, for patients with IPPFE experiencing ongoing weight loss can modulate the disease course and improve prognosis.

This study has several limitations. First, this was a retrospective study conducted at a single center.

Second, only a small number of the patients were included due to the rarity of the disease. Third, the clinical diagnostic criteria for IPPFE have not been validated, and only a few patients had a definitive histological diagnosis. Fourth, the intervals between the weight measurements varied in each case, which may have affected the results. Fifth, this study did not systematically confirm whether weight loss was unintentional, although patients with comorbidities that clearly affected weight change, such as advanced malignancy or uncontrolled fluid overload, were not observed during the weight follow-up. Finally, the results of the multivariate analysis of the prognostic factors for IPPFE should be carefully interpreted because of the small sample size and outcome incidence. Therefore, a large-scale prospective study is required to confirm our results.

In conclusion, weight loss is a common finding among patients with IPPFE, and low BMI and weight loss appear to be useful prognostic markers. Longitudinal weight assessment is important in the management of IPPFE.

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References

1. Travis WD, Costabel U, Hansell DM, et al. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 2013; 188: 733–48.
2. Watanabe K. Pleuroparenchymal fibroelastosis: its clinical characteristics. Curr Respir Med Rev 2013; 9: 229–37.
3. Bonifazi M, Montero MA, Renzoni EA. Idiopathic pleuroparenchymal fibroelastosis. Curr Pulmonol Rep 2017; 6: 9–15.
4. Chua F, Desai SR, Nicholson AG, et al. Pleuroparenchymal fibroelastosis. A review of clinical, radiological, and pathological characteristics. Ann Am Thorac Soc 2019; 16: 1351–9.
5. Kinoshita Y, Ishii H, Nabeshima K, Watanabe K. The pathogenesis and pathology of idiopathic pleuroparenchymal fibroelastosis. Histol Histopathol 2021; 36: 291–303.
6. Cottin V, Si-Mohamed S, Diesler R, Bonniaud P, Valenzuela C. Pleuroparenchymal fibroelastosis. Curr Opin Pulm Med 2022; 28: 432–40.
7. Fujisawa T, Mori K, Mikamo M, et al. Nationwide cloud-based integrated database of idiopathic interstitial pneumonias for multidisciplinary discussion. Eur Respir J 2019; 53: 1802243.
8. Cottin V, Wollin L, Fischer A, Quaresma M, Stowasser S, Harari S. Fibrosing interstitial lung diseases: knowns and unknowns. Eur Respir Rev 2019; 28: 180100.
9. Kono M, Nakamura Y, Enomoto Y, et al. Pneumothorax in patients with idiopathic pleuroparenchymal fibroelastosis: incidence, clinical features, and risk factors. Respiration 2021; 100: 19–26.
10. Alakhras M, Decker PA, Nadrous HF, Collazo-Clavell M, Ryu JH. Body mass index and mortality in patients with idiopathic pulmonary fibrosis. Chest 2007; 131: 1448–53.
11. Jouneau S, Crestani B, Thibault R, et al. Post hoc analysis of clinical outcomes in placebo- and pirfenidone-treated patients with IPF stratified by BMI and weight Loss. Respiration 2022; 101: 142–54.
12. Comes A, Wong AW, Fisher JH, et al. Association of BMI and change in weight with mortality in patients with fibrotic interstitial lung disease Chest 2022; 161: 1320–9.
13. Jouneau S, Rousseau C, Lederlin M, et al. Malnutrition and decreased food intake at diagnosis are associated with hospitalization and mortality of idiopathic pulmonary fibrosis patients. Clin Nutr 2022; 41: 1335–42.
14. Pugashetti J, Graham J, Boctor N, et al. Weight loss as a predictor of mortality in patients with interstitial lung disease. Eur Respir J 2018; 52: 1801289.
15. Nakatsuka Y, Handa T, Kokosi M, et al. The clinical significance of body weight loss in idiopathic pulmonary fibrosis patients. Respiration 2018; 96: 338–47.
16. Kulkarni T, Yuan K, Tran-Nguyen TK, et al. Decrements of body mass index are associated with poor outcomes of idiopathic pulmonary fibrosis patients. PLoS One 2019; 14: e0221905.
17. Jouneau S, Crestani B, Thibault R, et al. Analysis of body mass index, weight loss and progression of idiopathic pulmonary fibrosis. Respir Res 2020; 21: 312.
18. Kinoshita Y, Utsunomiya T, Koide Y, et al. Changes in body weight reflect disease progression in pleuroparenchymal fibroelastosis. Respir Med Res 2022; 83: 100980.
19. Enomoto Y, Nakamura Y, Satake Y, et al. Clinical diagnosis of idiopathic pleuroparenchymal fibroelastosis: A retrospective multicenter study. Respir Med 2017; 133: 1–5.
20. Lynch DA, Sverzellati N, Travis WD, et al. Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper. Lancet Respir Med 2018; 6: 138–53.
21. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 2004; 350: 1005–12.
22. Cao C, Wang R, Wang J, Bunjhoo H, Xu Y, Xiong W. Body mass index and mortality in chronic obstructive pulmonary disease: a meta-analysis. PLoS ONE 2012; 7: e43892.
23. Hayashi H, Nei T, Abe S, et al. Body mass index and arterial blood oxygenation as prognostic factors in patients with idiopathic pleuroparenchymal fibroelastosis. Sarcoidosis Vasc Diffuse Lung Dis 2017; 34: 35–40.
24. Suzuki Y, Yoshimura K, Enomoto Y, et al. Distinct profile and prognostic impact of body composition changes in idiopathic pulmonary fibrosis and idiopathic pleuroparenchymal fibroelastosis. Sci Rep 2018; 8: 14074.
25. Ishii H, Watanabe K, Kushima H, Baba T, Watanabe S, Yamada Y. Pleuroparenchymal fibroelastosis diagnosed by multidisciplinary discussions in Japan. Respir Med 2018; 141: 190–7.
26. Kono M, Tsunoda T, Ikeda S, et al. Clinical features of idiopathic pleuroparenchymal fibroelastosis with progressive phenotype showing a decline in forced vital capacity. Respir Investig 2023; 61: 210–9.
27. Nasser M, Si-Mohamed S, Turquier S, et al. Nintedanib in idiopathic and secondary pleuroparenchymal fibroelastosis. Orphanet J Rare Dis 2021; 16: 419.
28. Kinoshita Y, Miyamura T, Ikeda T, et al. Limited efficacy of nintedanib for idiopathic pleuroparenchymal fibroelastosis. Respir Investig 2022; 60: 562–9.
29. Mori Y, Yamano Y, Kataoka K, et al. Pulmonary rehabilitation for idiopathic pleuroparenchymal fibroelastosis: A retrospective study on its efficacy, feasibility, and safety. Respir Investig 2021; 59: 849–58.