Title: The clinical significance of body weight loss in idiopathic pulmonary fibrosis patients

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Abstract

Background

The significance of the nutritional status in idiopathic pulmonary fibrosis (IPF) is largely unknown. Temporal body weight (BW) change, a dynamic index of nutrition status, can detect the malnutrition more accurately than the conventional single-point body mass index evaluation.

Objective

To investigate how the temporal BW change influences the clinical courses of IPF.

Methods

This multicentre study enrolled IPF patients from four referral hospitals of interstitial lung diseases in Japan (the Japanese cohort, the derivation cohort) and the Royal Brompton Hospital (the UK cohort, the validation cohort). The annual rate of BW change from the initial presentation was evaluated. A >5% decrease of BW was defined as a significant BW loss.

Results

Twenty-seven out of 124 patients in the Japanese cohort and 13 out of 86 patients in the UK cohort showed significant BW loss. Patients with BW loss showed significantly worse survival in both cohorts. Multivariate analyses revealed that BW loss was an independent factor for decreased survival (Japanese cohort: $p = 0.047$, UK cohort: $p = 0.013$). A 6.1% loss of BW was chosen as the optimal cutoff value to predict the two-year mortality from the initial presentation. The stratified analysis revealed that a 6.1% or greater BW loss could predict worse survival specifically in cases without a greater than 10% decline in FVC.

Conclusions

BW loss is independently associated with the survival of IPF patients, particularly when a decline in the FVC was not observed. Further studies are needed to understand the mechanisms underlying BW loss in IPF.

Introduction

The clinical course of idiopathic pulmonary fibrosis (IPF) is characterized by a gradual decline in pulmonary function, which eventually results in mortality[1]. Although the prognosis of IPF is generally poor, patterns of progression do vary[2]. While some patients exhibit a rapid worsening just after diagnosis, some maintain a stable condition for years, whilst others experience a rapid decline after a period of stability[1, 3]. The need for a tool to predict the clinical course had led to the intensive investigation of prognostic factors in IPF[4-6]

Nutritional status has been shown to be a predictor of outcomes for some pulmonary diseases such as chronic obstructive pulmonary disease (COPD)[7] or tuberculosis[8]. For these diseases, an unbalanced nutritional status is associated with a poorer outcome. Conversely, the clinical significance of nutritional status or energy consumption has not been investigated for IPF patients[2], even though the body mass index (BMI) has been proposed as a prognostic factor[5, 9].

Although a single-point BMI is said to be an indicator of nutritional status, it is still unclear which cutoff value for BMI is appropriate in identifying malnutrition[10]. In addition, baseline BMI differs in association with factors including ethnicity, gender and social status[11]. To identify a malnutrition status such as cachexia, the use of temporal body weight (BW) change is, therefore, preferred[10], and previous studies have reported that temporal BW change has a stronger correlation with the outcomes of several diseases[12, 13]. A recent study showed that temporal BMI change could be a prognostic indicator of IPF, but the number of study subjects were relatively small [14]. Based on these considerations, we hypothesized that temporal BW loss could have a relationship with the clinical indices and the prognosis of IPF.

In the present study, we assessed BW change in IPF patients one year after presentation and investigated the clinical

characteristics of patients who exhibited significant BW loss. We then analyzed the associations between temporal BW loss and changes in pulmonary function or survival.

Materials and methods

Subjects and data collection

This multicentre cohort study enrolled IPF patients diagnosed at four regional referral hospitals for interstitial lung disease in Japan (Japanese cohort, derivation cohort) and Royal Brompton Hospital, United Kingdom (UK cohort, validation cohort). We enrolled patients who were diagnosed at Kyoto University Hospital from April 2007 to March 2013, Tenri Hospital from April 2004 to March 2012, Kobe City Medical Centre West Hospital from November 2006 to December 2012, Kyoto Central Clinic from January 2004 to May 2009, and the Royal Brompton Hospital from January 2008 to December 2010. The IPF diagnosis was made in accordance with the current criteria through the re-evaluation at each institute[15]. This study was approved by the review board of each institute.

Patients were included in this study if their BW change within one year after the initial visit could be evaluated. Patients with histories of malignancy within three years prior to, and one year after the first pulmonary function test (PFT) were excluded. Cases with a comorbid a chronic infectious disease or autoimmune disease were also excluded. In addition, patients were excluded from analyses if conditions involving excess body fluid (including renal failure, liver cirrhosis and exacerbation of congestive heart failure) were present during the first and follow-up PFT. We planned to exclude patients if intentional BW loss was apparent from their clinical records; however, no such case was identified.

Clinical data were collected from the patients' clinical records. The data of patients' BW and height were obtained from the

PFT record. The rate of BW change was calculated using the following formula: {%BW change = 100 × (BW at follow-up PFT − BW at initial PFT)/BW at initial PFT}. In reference to the criteria of cachexia, we defined a 5% or greater decrease in BW as a significant BW loss[10]. In accordance with a previous study, we considered the PFT performed between 270 days and 450 days after the initial study as the 'follow-up study one year after the initial study[16]. Respiratory hospitalisation[17], gastroesophageal reflux[18], use of antacids[19], diuretics and pirfenidone were also assessed as potential factors associated with prognosis or BW loss in patients with IPF.

Analysis of the association between BW loss and clinical indices

Factors associated with BW loss were investigated in both cohorts. We then compared the differences in survival from the initial PFT (Supplementary Fig. 1) between patients with or without significant BW loss. We also assessed the two-year survival rate, i.e. rate of survival at a time point of 730 days after the initial visit.

Statistical analysis

Statistical analyses were performed using EZR (Saitama Medical Centre, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria)[20]. A Fisher's exact test was used for the analysis of categorical variables. Continuous data were presented as means ± standard deviations, and a Student's t-test was used for the descriptive analysis comparisons. The logistic regression model was used for the analysis of factors associated with BW loss, and multivariate analysis was performed with stepwise selection of variables based on the Akaike information criterion (AIC). We

included factors which showed p value < 0.2 in univariate analysis for the Japanese cohort in the multivariate analyses. The log–rank test was used to evaluate the Kaplan-Meier curves for survival. In the analysis of survival, the cases were censored at the time of lung transplantation. The Cox proportional hazards test was used for univariate and multivariate analysis of survival, with the validity of the proportional hazards evaluated using Shoenfeld residuals. Stratified multivariate analysis was performed for the factors that violated the assumptions of proportional hazards. Multivariate analysis included previously reported prognostic factors of IPF, and was performed with a stepwise selection of variables based on the AIC. The optimal cutoff value in BW change to distinguish patients with a higher risk of two-year survival was calculated based on the receiver operating characteristic curve. A p value of < 0.05 was considered statistically significant.

Results

Patients' characteristics

In total, 124 patients in the Japanese cohort and 86 patients in the UK cohort were enrolled in this study (Table 1). In each cohort, lung transplantation was performed for only one patient. The median follow-up period (interquartile range) was 1360.8 (845.3–1691.3) days in the Japanese cohort and 1363.0 (911.5–1909.5) days in the UK cohort, respectively. The baseline BMI was substantially lower in the Japanese cohort compared with the UK cohort.

In both cohorts, patients with BW loss showed a significantly higher rate of FVC decline within one year. In the Japanese cohort, patients with a BW loss showed a significantly lower baseline %FVC compared with patients without a BW loss, whereas such a tendency was not observed in the UK cohort. Otherwise, in both cohorts, patients with or without BW loss showed comparable

characteristics.

Factors associated with significant BW loss

In the Japanese cohort, the following factors were associated with BW loss with a p value < 0.2: male gender, never smoked, diabetes mellitus, hypertension, initial %FVC, annual rate of FVC change, total protein and albumin. Multivariate analysis showed that annual rate of FVC change, diabetes mellitus, total protein, and never smoked showed significant associations with BW loss. We performed the same analysis for the UK cohort, and multivariate analysis revealed that only the rate of FVC change reproduced the significant association with BW loss. There was no association between BW loss and gastroesophageal reflux, use of antacids, use of diuretics, the introduction of pirfenidone or corticosteroid therapy (Table 2).

Survival

In the Japanese cohort, patients with a BW loss showed significantly worse survival (median: 1095 days, 95% confidence interval [CI]: 868 days–NA) than patients without BW loss (median: 2245 days, 95% CI: 1687–2704 days) ($p < 0.001$) (Fig. 1A). This tendency was reproducible in the UK cohort (patients with BW loss, median: 928 days, 95% CI: 583–1392 days, patients without BW loss, median: 1512 days, 95% CI: 1299–1780 days, $p = 0.029$) (Fig. 1B).

We also analyzed the causes of deaths, and we found that chronic disease progression was the major cause of death for the patients with BW loss. In contrast, the deaths due to malignancy were relatively infrequent (Supplementary Table 1).

Furthermore, we performed a Cox proportional hazards test for survival. Univariate analysis in the Japanese cohort showed a

significant association between survival and BW loss >5% (Hazard ratio [HR] 2.83, 95% CI: 1.61–5.30, $p = 0.001$); male gender (HR 2.83, 95% CI: 1.01–7.89, $p = 0.048$); %predicted FVC at baseline PFT (HR 0.96, 95% CI: 0.95–0.98, $p < 0.001$); %predicted DLco at baseline PFT (HR 0.94, 95% CI: 0.92–0.97, $p < 0.001$); or decline in the FVC >10% within one year (HR 4.88, 95% CI: 2.63–9.05, $p < 0.001$). In contrast, age at the baseline PFT (HR 1.02, 95% CI: 0.98–1.07, $p = 0.325$); smoking habits (never smoked) (HR 1.55, 95% CI: 0.77–3.11, $p = 0.223$); one-year respiratory hospitalisation (HR1.62, 95% CI: 0.87−3.00, $p = 0.126$) and BMI at the initial PFT (HR 0.99, 95% CI: 0.90–1.12, $p = 0.996$) did not show any association. These associations were reproduced in the UK cohort, except for the association with male gender.

We next included all the variables above in a model and performed multivariate analysis with a stepwise selection of variables based on the AIC. As a final model, the following factors remained as variables with a significant association: BW loss >5% (HR 2.51, 95% CI: 1.01–6.23, $p = 0.047$), male gender (HR 17.88, 95% CI: 4.00–80.01, $p < 0.001$), baseline %DLco (HR 0.94, 95% CI: 0.91–0.96, $p < 0.001$), and smoking habits (HR 6.76, 95% CI: 2.35–19.42, $p < 0.001$). In the UK cohort, BW loss >5% (HR 2.30, 95% CI: 1.20–4.43, $p = 0.013$), baseline %DLco (HR 0.95, 95% CI: 0.93–0.97, $p < 0.001$), FVC decline >10% (HR: 2.11, 95% CI: 1.29–3.46, $p = 0.003$) showed reproducible association. On the other hand, the association with male gender or never smoked was not reproducible in the UK cohort, whereas the initial BMI showed an independent association (HR: 1.06, 95% CI: 1.01–1.12, $p = 0.026$) (Table 3).

Evaluation of the Schoenfeld residuals in the UK cohort showed violation of the assumptions of proportional hazards analysis with regard to age at baseline, smoking status, and FVC decline (Supplementary Table 2). Accordingly, we added the stratified

analysis to the data by these factors, and found that body weight loss > 5% remained an independent prognostic factor[6].

Optimal cutoff value of BW loss to predict two-year mortality

The two-year mortality rate for the patients with BW loss in the Japanese cohort was 22.2%, which was significantly higher than that for the patients without BW loss (6.2%, $p = 0.023$). Also in the UK cohort, the rate tended to be higher (12.3% for the patients with BW loss, 30.8% for those without, respectively), even though it did not reach statistical significance ($p = 0.103$) (Table 1).

To determine an optimal cutoff value to predict the two-year mortality, we performed a receiver operating characteristic curve analysis based on the data of the Japanese cohort. As a result, a cutoff value of 0.705% (specificity: 52.7%, sensitivity: 83.3%) and 6.138% (specificity: 84.8%, sensitivity: 50.0%) were identified (area under the curve: 0.670) (Supplementary Fig. 2A), and we found that, 6.1% was the best cutoff value to distinguish patients according to survival (Supplementary Figs. 2B-E).

Stratified analysis based on the decline of the FVC

Among the temporal factors in IPF, the decline of FVC is the most established predictor of survival. We examined whether BW loss could provide additional information to the FVC decline in the prediction of survival. We performed a stratified analysis of survival in patients with or without a significant FVC decline (>10%). Among patients without significant FVC decline, the existence of a BW loss >6.1% was associated with a significantly worse chance of survival, both in the Japanese cohort ($p = 0.042$) and the UK cohort ($p = 0.041$) (Fig. 2).

Discussion

In the present study, we showed that the presence of BW loss in one year was associated with poorer survival. In particular, BW loss could identify patients with worse chance of survival among those who did not show a FVC decline. These results were reproducible for two independent cohorts in Japan and the UK.

BW loss has been recognized as a common complication of IPF[21]. In the present study, 21% of patients in the Japanese cohort and 15% of patients in the UK cohort showed more than 5% BW loss within one year. The present study revealed that there was no significant difference in the initial BMI between those with and without BW loss. This result may indicate that the occurrence of BW loss was not affected by the initial BMI, suggesting that a single-point measurement of BW is not enough to evaluate the status of IPF patients.

In addition, single-point BMI could be influenced by a patient's background such as ethnic characteristics. In this study, the Japanese cohort showed a substantially lower BMI compared to the UK cohort. This difference between Asian and Caucasian patient groups has been observed in previous studies[5, 9, 22-24]. Notably, one report from Korea indicated that the prognostic value of single-point BMI was not significant[23], in agreement with our Japanese cohort. On the basis of these data, we consider that it is difficult to set a uniform standard to evaluate single-point BMI as a prognostic factor in different populations.

The present study also showed that temporal BW loss is an independent prognostic factor for IPF patients even in the multivariate analysis including FVC decline as one of the variables. The majority of the patients with BW loss died from chronic disease progression, not from malignancy. Whereas the decline of the FVC is one of the most established parameters among the temporal prognostic factors in IPF[25, 26], the stratified analysis showed that BW loss could predict survival even for those who did

not show a significant decline in FVC. These results may suggest that, for a subset of patients, BW loss may reflect other aspects of disease progression that a FVC change cannot detect. Previous studies suggest that BW loss is caused by various conditions such as chronic inflammation, oxidative stress, reduced food intake due to loss of appetite or loss of muscle mass due to inactivity [27], which can be associated with the progression or the complications of IPF [28, 29]. Therefore, in daily practice, BW loss could be an easily measurable alert to notify the necessity of detailed evaluation for the disease activity or complications..

The significance of BW loss in IPF patients has been previously discussed in reference to COPD[9], one of the diseases in which the significance of nutrition status has been well studied. However, the present study indicated that nutritional status influences IPF and COPD differently. In COPD, the BMI is strongly associated with prognosis[30, 31], and is included as a factor in the integrated index for the prediction of prognosis[32]. In contrast, the present study suggested that the association between a single-point BMI and survival is weak. We speculate that the difference in the role of BMI in predicting survival from these two diseases is due to the manner of progression after the onset. In general, the progression of COPD is relatively modest than IPF, indicating that undiagnosed period after the disease onset is longer as for COPD patients. Considering that COPD is a systemic inflammatory disease[33], which induces BW loss in its early stages[12, 34], BW loss can be established at the time of diagnosis, In contrast, as for IPF patients, relatively rapid progression of disease may result in the diagnosis before the complication of overt BW loss. This characteristic may result in the highlighting of the significance of temporal factors in IPF compared to those in COPD.

The association between BW loss and mortality presents an opportunity to potentially benefit these IPF patients by supporting them nutritionally, although there is no previous report proving its efficacy. A recent study suggested that pulmonary rehabilitation had a positive impact on functional status and quality of life for interstitial lung disease patients including those with IPF[35, 36]. In

addition, it was proposed that the combination of nutritional support and rehabilitation was beneficial for improving exercise capacity and the quality of life in COPD[37]. Considering this, studies evaluating the efficacy of rehabilitation integrated with nutritional support are expected in the future.

This study includes several limitations. First, we included patients who received a follow-up PFT, which means patients who were unable to receive a follow-up PFT due to death or rapid worsening of the disease were excluded. Therefore, we might have focused on patients with comparatively better disease conditions. In addition, excluding patients who missed their follow-up PFT may have limited the study cohort. Second, we could not obtain the information needed for a detailed evaluation of nutrition status, such as intensity of daily activity[38] or the existence of appetite loss. In addition, we could not include other potential predictors for mortality in our analysis because of the retrospective design. These included hypoxia, exercise capacity and its temporal changes, pulmonary hypertension and the degree/severity of dyspnoea [1] [5]. Third, although we carefully excluded cases with apparent episodes of fluid excess, we could not obtain sufficient data to evaluate cardiac function (such as an echocardiogram or a right heart catheter), indicating that congestive heart failure may have had a potential effect on BW. Despite these limitations, the present study showed, for the first time, an association between BW change and survival. In addition, the results were confirmed by two independent and international cohorts, which further strengthen the reliability of the study. Results of this study may increase our understanding of the significance of energy imbalance and the efficacy of nutritional support in patients with IPF, as these aspects were previously underestimated.

In conclusion, BW change was independently associated with survival in IPF. In daily practice, BW change could be an easily measurable indicator of the prognosis for IPF patients. The nutritional status of patients with IPF has not been a focus of previous

studies; therefore, further studies are required to understand the mechanisms underlying BW loss in IPF.

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Financial Disclosure and Conflicts of Interest

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None of the authors have any conflicts of interest to declare regarding the publication of this manuscript.

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Table 1.Patients' characteristics

	Japanese cohort			UK cohort		
	BW loss (-)	BW loss (+)	*p* value	BW loss (-)	BW loss (+)	*p* value
	n=97	n=27		n= 73	n= 13	
Age at initial PFT, years	68.21 ±7.39	69.78 ±8.74	0.350	65.55 (9.84)	65.23 (12.38)	0.918
Male gender, n (%)	85 (87.6)	20 (74.1)	0.127	58 (79.5)	11 (84.6)	>0.99
Histological diagnosis, n (%)	27 (27.8)	10 (37.0)	0.353	16 (21.9)	2 (15.4)	0.727
Never smoked, n (%)	11 (11.3)	6 (22.2)	0.202	26 (35.6)	4 (30.8)	0.855
Comorbid diseases, n (%)						
Diabetes mellitus	27 (29.3)	3 (11.1)	0.120	17 (23.3)	2 (15.4)	0.801
Hyperlipidemia	20 (21.7)	5 (18.5)	>0.99	33 (45.2)	5 (38.5)	0.584
Ischemic heart disease	12 (12.3)	1 (3.7)	0.451	19 (26.0)	4 (30.8)	0.642
Hypertension	25 (27.2)	11 (40.7)	0.142	40 (54.8)	5 (38.5)	0.364
Congestive heart failure	3 (3.3)	1 (3.7)	>0.99	3 (4.1)	0 (0.0)	0.638
Gastroesophageal reflux	8 (8.2)	2 (7.4)	>0.99	36 (49.3)	7 (53.8)	>0.99
Pulmonary function test						
Initial %FVC, %	84.18 ±18.89	75.01 ±23.58	0.037	75.94 ± 17.70	73.52 ± 14.28	0.643
Initial %DLco, % [#]	46.78 ±15.19	42.64 ±12.95	0.236	41.38 ± 13.57	43.58 ± 9.67	0.579
Initial CPI[#]	40.04 ± 21.98	49.20 ± 19.74	0.073	50.46 ± 10.78	49.45 ± 9.53	0.752
Annual rate of FVC change, %	0.03 ± 9.66	-8.33 ± 13.91	<0.001	-4.72 ± 11.38	-13.99 ± 24.44	0.031
Initial BMI	23.82 ±2.66	23.76 ± 3.66	0.924	28.44 ± 4.90	27.46 ± 5.05	0.508
Laboratory Test						
KL-6 (U/ ml)	1119.06 ± 980.80	1320.09 ± 1021.80	0.387	NA	NA	
Total protein (g/ dl)	7.48 ± 0.52	7.64 ± 0.55	0.178	7.25 ± 0.60	7.15 ± 0.54	0.598
Albumin (g/ dl)	4.22 ± 0.32	4.09 ± 0.46	0.152	3.93 ±0.35	3.93 ± 0.35	0.984
Treatment, n (%)						
Pirfenidone	27 (27.8)	8 (29.6)	>0.99	17 (23.3)	3 (23.1)	>0.99
Corticosteroid	37 (38.1)	12 (44.4)	0.502	67 (91.8)	11 (84.6)	0.347
Proton pump inhibitor/H2 blocker	39 (40.2)	7 (25.9)	0.351	44 (60.3)	7 (53.8)	0.762
Diuretics	8 (8.2)	1 (3.7)	0.686	12 (16.4)	1 (7.7)	0.681
Acute exacerbation, n (%)	29 (29.9)	8 (29.6)	>0.99	6 (8.2)	0 (0.0)	0.647
Death, n (%)	38 (39.2)	17 (63.0)	0.186	57 (78.1)	13 (100.0)	0.115
Transplantation, n (%)	0 (0)	1 (3.7)	0.224	1 (1.4)	0 (0.0)	>0.99
One-year respiratory hospitalization (%)	15 (15.4)	10 (37.0)	0.027	8 (11.0)	1 (7.7)	>0.99
Two year mortality, n (%)	6 (6.2)	6 (22.2)	0.023	9 (12.3)	4 (30.8)	0.103

Data are presented as n or mean±SD, PFT: pulmonary function test, FVC: forced vital capacity, DLco: diffusing capacity of the lung for carbon monoxide, CPI: composite physiologic index. [#] Data were missing for 17 patients in Japanese cohort.

Table 2. Factors associated with BW loss

	Japanese cohort		UK cohort	
	Odds ratio (lower, higher 95% CI)	*p* value	Odds ratio (lower, higher 95% CI)	*p* value
Univariate analysis				
Age at initial PFT (years)	1.03 (0.97, 1.09)	0.348	0.99 (0.94, 1.06)	0.917
Male gender	0.40 (0.14, 1.15)	0.091	0.70 (0.14, 3.52)	0.668
Never smoked	2.23 (0.74, 6.73)	0.153	0.80 (0.23, 2.87)	0.736
Diabetes mellitus complicated	0.33 (0.09, 1.19)	0.090	0.58 (0.12, 2.87)	0.502
Hyperlipidemia complicated	0.90 (0.30, 2.70)	0.851	0.80 (0.23, 2.77)	0.726
Ischemic heart disease complicated	0.32 (0.04, 2.66)	0.294	1.34 (0.36, 4.98)	0.660
Hypertension complicated	2.11 (0.85, 5.25)	0.110	0.54 (0.16, 1.85)	0.324
Congestive heart failure complicated	1.24 (0.12, 12.40)	0.857	NA	0.991
Gastroesophageal reflux complicated	1.01 (0.20, 5.12)	0.989	1.20, (0.37, 3.91)	0.764
Initial %FVC (%)	0.98 (0.95, 0.99)	0.040	0.99 (0.96, 1.03)	0.639
Initial %DLco (%)	0.98 (0.95, 1.01)	0.235	1.01 (0.97, 1.06)	0.575
Annual rate of FVC change (%)	0.93 (0.89, 0.98)	0.002	0.96 (0.92, 0.99)	0.039
Initial BMI	0.99 (0.86, 1.15)	0.923	0.96 (0.84, 1.09)	0.503
Total protein (g/dl)	1.82 (0.76, 4.33)	0.178	0.97 (0.88, 1.08)	0.594
Albumin (g/dl)	0.37 (0.09, 1.47)	0.157	0.98 (0.18, 5.33)	0.984
Pirfenidone usage	1.10 (0.42, 2.85)	0.848	0.99 (0.24, 4.01)	0.987
Corticosteroid usage	1.37 (0.56, 3.34)	0.485	0.49 (0.09, 2.76)	0.420
Proton pump inhibitor/H2 blocker usage	0.61 (0.23, 1.61)	0.316	0.77 (0.24, 2.52)	0.664
Diuretics usage	0.48, (0.06, 4.07)	0.503	0.42, (0.05, 3.57)	0.430
Multivariate analysis (Stepwise)				
Annual rate of FVC change (%)	0.92 (0.86, 0.97)	0.003	0.96 (0.92, 0.99)	0.039
Diabetes mellitus complicated	0.16 (0.03, 0.96)	0.045		
Total protein (g/dl)	5.79 (1.61, 20.90)	0.007		
Never smoked	4.98 (1.19, 20.90)	0.028		

FVC: forced vital capacity, DLco: diffusing capacity of the lung for carbon monoxide, BMI: body mass index.

Table 3. Univariate and multivariate analysis for mortality

Japanese cohort			UK cohort		
	Hazard ratio (95% CI)	*p* value		Hazard ratio (95% CI)	*p* value
Univariate analysis					
Body weight loss > 5%	2.83 (1.61-5.30)	0.001		1.99 (1.06-3.74)	0.033
Age at initial PFT (years)	1.02 (0.98-1.07)	0.325		1.01 (0.98-1.03)	0.584
Male gender	2.83 (1.01-7.89)	0.048		1.29 (0.72- 2.33)	0.390
Never smoked	1.55 (0.77-3.11)	0.223		0.75 (0.45-1.25)	0.271
Initial %FVC (%)	0.96 (0.95-0.98)	<0.001		0.99 (0.97-0.99)	0.040
Initial %DLco (%)	0.94 (0.92-0.97)	<0.001		0.96 (0.94-0.98)	<0.001
FVC decline >10%	4.88 (2.63-9.05)	<0.001		2.08 (1.28-3.37)	0.003
Initial BMI	0.99 (0.90-1.12)	0.996		1.01 (0.97-1.06)	0.656
One-year respiratory hospitalization	1.62 (0.87-3.00)	0.126		2.07 (0.98-4.36)	0.055
Multivariate analysis (Stepwise)					
Body weight loss > 5%	2.51 (1.01-6.23)	0.047	Body weight loss > 5%	2.26 (1.17-4.35)	0.015
Male gender	17.88 (4.00-80.01)	<0.001	Initial %DLco (%)	0.95 (0.93-0.97)	<0.001
Initial %DLco (%)	0.94 (0.91-0.96)	<0.001	FVC decline > 10%	2.34 (1.41-3.87)	0.001
FVC decline > 10%	1.95 (0.82-4.66)	0.13	Initial BMI	1.06 (1.01-1.12)	0.012
Never smoked	6.76 (2.35-19.42)	<0.001			

FVC: forced vital capacity, DLco: diffusing capacity of the lung for carbon monoxide, BMI: body mass index.

Fig. 1. The survival rate based upon the existence of body weight (BW) loss.

The survival rate based upon the existence of body weight (BW) loss in the Japanese cohort (A) or the UK cohort (B) (Log–rank test). Patients with BW loss showed significantly worse survival in both cohorts [Japanese cohort, median: 1095 days, 95% confidence interval [CI]: 868 days–NA, UK cohort, median: 928 days, 95% CI: 583–1392 days] compared to patients without BW loss [Japanese cohort, median: 2245 days, 95% CI: 1687–2704 days, UK cohort, 1512 days, 95% CI: 1299–1780 days] (Japanese cohort: $p < 0.001$, UK cohort: $p = 0.029$). FVC, forced vital capacity.

Fig. 2. Stratified analysis of the survival rate.

Stratified analysis of the survival rate based upon the existence of body weight(BW) loss and the FVC decline (Log–rank test). In both cohorts, patients with a BW loss ≧ 6.1% showed a significantly worse survival in the subgroup of patients without a FVC decline (Japanese cohort: $p = 0.042$, UK cohort: $p = 0.041$). FVC, forced vital capacity.