Real-World Clinical Outcomes Based on Body Mass Index and Annualized Weight Change in Patients with Idiopathic Pulmonary Fibrosis

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ABSTRACT

Introduction: Identification of clinical characteristics associated with prognosis for idiopathic pulmonary fibrosis (IPF) may help to guide management decisions. This analysis utilized data from the Pulmonary Fibrosis Foundation Patient Registry to examine the relationships between clinical outcomes and both body mass index (BMI) at study enrollment (hereafter referred to as baseline BMI) and annualized percent change in body weight in patients with IPF in a real-world setting.

Methods: The following outcomes over 24 months were stratified by baseline BMI and annualized percent change in body weight: all-cause mortality; annualized change in percent predicted forced vital capacity (%FVC), percent predicted diffusing capacity for carbon monoxide, and 6-min walk distance; all-cause and

respiratory-related hospitalizations; and acute exacerbations.

Results: Overall, 600 patients with IPF were included (baseline BMI: < 25 kg/m^2, $n = 120$; 25 to < 30 kg/m^2, $n = 242$; ≥ 30 kg/m^2, $n = 238$; annualized percent change in body weight: no loss, $n = 95$; $> 0\%$ to $< 5\%$ loss, $n = 425$; $\geq 5\%$ loss, $n = 80$). Enrollment demographics and characteristics were generally similar across subgroups. There was no association between mortality and BMI. All-cause mortality was lower among patients who experienced no annualized weight loss versus those with $\geq 5\%$ (OR [95% CI] 3.28 [1.15, 10.95]) or > 0 to $< 5\%$ weight loss (OR [95% CI] 2.83 [1.14, 8.62]) over 24 months. Patients with baseline BMI < 25 kg/m^2 had a significantly greater estimated annualized decline in %FVC versus patients with baseline BMI ≥ 30 kg/m^2 (difference [95% CI] 1.47 [0.01, 2.93]). No relationship was observed between %FVC and weight loss. Other clinical outcomes were generally similar across subgroups.

Conclusions: Some clinical outcomes may be worse in patients with IPF who have a low BMI (< 25 kg/m^2) or who experience weight loss over 24 months, but the causation for these relationships is unknown. These results may help to inform management decisions for patients with IPF.

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Key Summary Points

Why carry out this study?

In patients with idiopathic pulmonary fibrosis (IPF), certain clinical characteristics, such as body mass index (BMI) and change in body weight, may be associated with prognosis.

Although the relationships between these characteristics and clinical outcomes in patients with IPF have recently been studied, there is a need for more research in large, well-characterized, real-world populations to help inform clinicians on management decisions for individual patients.

This analysis utilized data from an observational registry to examine the relationships between clinical outcomes and both BMI and annualized percent change in body weight in patients with IPF in a real-world setting.

What was learned from the study?

In this real-world population of patients with IPF, no association was found between mortality and BMI. However, an association was observed between weight loss and mortality over 24 months, whereby patients who experienced no annualized weight loss had lower all-cause mortality versus those who experienced more weight loss.

A lower BMI (< 25 kg/m^2) was associated with a greater decline in lung function, as measured by forced vital capacity (FVC), versus a higher BMI (≥ 30 kg/m^2), but no association was observed between percent predicted FVC and annualized weight loss.

Some clinical outcomes may be worse in patients with IPF who have a low BMI (< 25 kg/m^2) or who experience weight loss over 24 months. The causation of these relationships is unknown.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a progressive, fibrotic, interstitial lung disease (ILD) with unknown etiology [1]. Predicting prognosis and making management decisions is a challenge for clinicians because of the variable clinical course of IPF [1, 2]. As such, it may be helpful to identify specific clinical characteristics of patients with IPF that could be associated with prognosis in order to guide treatment and management decisions for individual patients [3–5].

Recently, the relationships between clinical outcomes and body mass index (BMI) and those between clinical outcomes and weight loss in patients with IPF have been studied. Two separate post hoc analyses using data from the pivotal nintedanib and pirfenidone clinical trials in patients with IPF both found that placebo-treated patients with baseline BMI < 25 kg/m^2 or higher annualized weight loss had worse outcomes over 1 year, such as a higher rate of forced vital capacity (FVC) decline, compared with patients with baseline BMI ≥ 25 kg/m^2 or less weight loss [6, 7]. Similarly, a series of real-world studies have suggested an association between lower BMI, greater decrements in BMI, or greater weight loss and the risk of mortality [8–10]. However, these studies were limited by their post hoc design within a clinical trial population and/or small patient numbers. As such, there is a need for more research in large, well-characterized, real-world populations.

The Pulmonary Fibrosis Foundation Patient Registry^{TM} (PFF-PR; NCT02758808) is an observational registry enrolling patients with a diagnosis of IPF or other ILDs. Since the registry was established in March 2016, approximately 2000

patients have been enrolled (ca. 60% with IPF) at 42 ILD care center sites in the USA. The purpose of the PFF-PR is to collect comprehensive data on diagnosis, symptoms, medication use, and outcomes in patients with IPF and other ILDs [11, 12]. To build on previous findings and further explore the relationships between clinical outcomes and both BMI (recorded at or prior to enrollment; hereafter referred to as baseline BMI) and annualized percent change in body weight in a real-world setting, we present an analysis that utilized data from a well-characterized patient population with IPF from the PFF-PR. We hypothesized that baseline BMI and annualized percent change in body weight would be associated with clinically significant outcomes, including decline in lung function and mortality.

METHODS

Study Design and Patient Population

The design and methods of the PFF-PR have been previously described [11]. This analysis included patients with IPF enrolled in the PFF-PR. Enrollment into the registry started in March 2016 and completed in August 2018. Eligible patients were ≥ 40 years of age and were required to have a diagnosis of IPF as determined in accordance with guideline criteria at the site of enrollment (since patients were enrolled in the registry prior to the publication of the ATS/ERS/JRS/ALAT 2018 diagnostic guidelines, the diagnosis of IPF was based on the ATS/ERS/JRS/ALAT 2011 guidelines [13]), weight and height data at enrollment, and ≥ 1 post-enrollment weight measurement. Patients were excluded from most analyses if they had undergone a lung transplant or if participation in the registry was terminated (withdrawal of consent, patient withdrawn by physician, patient no longer being seen at the research site, lost to follow-up, and other) during the 2-year study window, or if they had less than 2 years of data available. Regarding the exclusion of patients who had undergone a lung

transplant, this was due to the potential for these patients to have been adhering to weight management recommendations in order to qualify for lung transplantation surgery. However, transplant and other termination patients were not excluded from the time-to-event analysis. A 2-year study window was chosen to ensure sufficient long-term follow-up and to maximize the data available in the PFF-PR.

Enrollment in the PFF-PR was conducted with informed written consent from participating patients and the registry was approved by institutional review boards at each participating center. This post hoc analysis used de-identified patient data and was considered exempt from review by an institutional review board.

Independent Variables of Interest

All analyses were stratified by baseline BMI and annualized percent change in body weight during the 2-year study window. BMI was categorized on the basis of the World Health Organization (WHO) standards: $< 25 \text{ kg/m}^2$ (WHO normal or underweight), 25 to $< 30 \text{ kg/m}^2$ (WHO pre obesity), and $\geq 30 \text{ kg/m}^2$ (WHO obesity, class I–III) [14]. Categorization of annualized percent change in body weight was adapted from the US Food and Drug Administration Guidance for Developing Products for Weight Management: no weight loss, > 0 to $< 5\%$ weight loss, and $\geq 5\%$ weight loss [15].

Since BMI and annualized percent change in body weight were handled as categorical variables, their associations with outcomes were not assumed to be linear. A sensitivity analysis was performed in which all models were fit using continuous values of baseline BMI and annualized weight change values instead of categorized values. For ease of interpretation, and since the continuous variable models generally yielded results consistent with the categorical models, we present only the results from the categorical models in the main text; however, the results of the continuous variable models are provided in Tables S1 and S2 in the supplementary material. For comparison between

subgroups, baseline BMI < 25 kg/m² was chosen as the reference level for the BMI analysis, and no weight loss was the reference used for the analysis by annualized percent change in body weight.

Outcomes

Relationships between baseline BMI or annualized percent change in body weight were assessed for each of the following outcomes: all-cause mortality at 24 months (primary outcome); annualized changes from enrollment in percent predicted FVC, percent predicted diffusing capacity for carbon monoxide (DLco), and 6-min walk distance (6MWD) over 24 months (secondary outcomes); and all-cause hospitalization, respiratory-related hospitalization, acute exacerbations, and time-to-death over 24 months (exploratory outcomes).

Statistical Analysis

Demographics and clinical characteristics at enrollment were reported descriptively, stratified by BMI and by annualized percent change in body weight categories. Annualized change in body weight was estimated using a linear mixed model with a random intercept and slope for each patient and no additional predictors.

In all analyses, adjustments were made for enrollment values of sex, age, percent predicted FVC, percent predicted DLco, smoking history, supplemental oxygen use during exertion, medication use (pirfenidone, nintedanib, and corticosteroids), and pulmonary arterial hypertension. Patients with missing predictor values were excluded from all analyses under a missing completely at random assumption. The dominant source of missingness was enrollment percent predicted DLco ($n = 80$; 13.3% of patients).

Logistic regression was used to model binary outcomes (all-cause mortality, all-cause hospitalization, respiratory-related hospitalization, and acute exacerbations). Comparisons between factorial BMI or weight change levels were assessed through odds ratios (OR; with 95% profile likelihood confidence intervals [CIs]). Continuous outcomes (percent predicted FVC, percent predicted DLco, and 6MWD) were modeled with linear mixed models. A sensitivity analysis was conducted to determine whether 6MWD results differed when the model was restricted to include patients with > 1 measurement compared with patients with ≥ 1 measurement. Findings from both models were similar; therefore, results from the latter model are reported in the main text since they allow for a larger sample size and results from the former model are included in Tables S3A and S3B in the supplementary material.

Time-to-event analyses for mortality were modeled using competing-risk proportional hazards regression models. Lung transplants were handled as a competing risk and other causes of study termination were handled as missing at random. Comparisons between factorial BMI or weight change levels were assessed through hazard ratios (HR; with 95% t-type CIs). Time-to-event analyses were also performed for first all-cause hospitalizations and acute exacerbations, the results for which are presented in the supplementary material.

RESULTS

Patients

Overall, 600 patients enrolled in the PFF-PR who had not undergone a lung transplant or non-death early termination during the 2-year study window were eligible for inclusion in this analysis (baseline BMI: < 25 kg/m², $n = 120$; 25 to < 30 kg/m², $n = 242$; ≥ 30 kg/m², $n = 238$). A total of 65 patients were excluded since they did not have two full years of data available. Demographics and clinical characteristics at enrollment were generally similar across BMI subgroups. However, patients with lower baseline BMI generally had a different racial composition, were older, and had lower enrollment percent predicted DLco compared with patients with higher baseline BMI, and there was a smaller proportion of men with baseline BMI < 25 kg/m² compared with the higher baseline BMI subgroups (Table 1).

At 24 months, the annualized percent change in body weight subgroups consisted of

Table 1 Demographic and enrollment characteristics, stratified by baseline BMI and annualized percent change in body weight categories

Variable	Baseline BMI			Annualized percent change in body weight		
	< 25 kg/m^2 (*n* = 120)	25 to < 30 kg/m^2 (*n* = 242)	≥ 30 kg/m^2 (*n* = 238)	No weight loss (*n* = 95)	> 0 to < 5% weight loss (*n* = 425)	≥ 5% weight loss (*n* = 80)
Age, mean (SD)	73.6 (7.7)	71.5 (7.7)	69.2 (7.7)	69.3 (9.0)	71.3 (7.8)	71.3 (6.9)
Male sex, *n* (%)	77 (64.2)	200 (82.6)	168 (70.6)	63 (66.3)	324 (76.2)	58 (72.5)
Race, *n* (%)						
White	111 (92.5)	221 (91.3)	228 (95.8)	90 (94.7)	396 (93.2)	74 (92.5)
Black	0 (0.0)	5 (2.1)	4 (1.7)	1 (1.1)	6 (1.4)	2 (2.5)
Asian	7 (5.8)	8 (3.3)	0 (0.0)	1 (1.1)	11 (2.6)	3 (3.8)
Unknown	2 (1.7)	8 (3.3)	6 (2.5)	3 (3.2)	12 (2.8)	1 (1.2)
Smoking history, *n* (%)	72 (60.0)	152 (62.8)	156 (65.5)	64 (67.4)	259 (60.9)	57 (71.2)
Nintedanib treatment, *n* (%)						
Yes	42 (35.0)	79 (32.6)	70 (29.4)	23 (24.2)	131 (30.8)	37 (46.2)
No	77 (64.2)	163 (67.4)	167 (70.2)	72 (75.8)	292 (68.7)	43 (53.8)
Unknown	1 (0.8)	0 (0.0)	1 (0.4)	0 (0.0)	2 (0.5)	0 (0.0)
Pirfenidone treatment, *n* (%)						
Yes	37 (30.8)	87 (36.0)	92 (38.7)	26 (27.4)	163 (38.4)	27 (33.8)
No	82 (68.3)	155 (64.0)	145 (60.9)	69 (72.6)	260 (61.2)	53 (66.2)
Unknown	1 (0.8)	0 (0.0)	1 (0.4)	0 (0.0)	2 (0.5)	0 (0.0)
Corticosteroid treatment, *n* (%)						
Yes	19 (15.8)	41 (16.9)	52 (21.8)	18 (18.9)	73 (17.2)	21 (26.2)
No	100 (83.3)	201 (83.1)	185 (77.7)	77 (81.1)	350 (82.4)	59 (73.8)
Unknown	1 (0.8)	0 (0.0)	1 (0.4)	0 (0.0)	2 (0.5)	0 (0.0)
Supplemental oxygen with exertion, *n* (%)	78 (65.0)	137 (56.6)	157 (66.0)	61 (64.2)	250 (58.8)	61 (76.2)
Pulmonary arterial hypertension, *n* (%)	8 (6.7)	18 (7.4)	11 (4.6)	1 (1.1)	34 (8.0)	2 (2.5)
Uncorrected % DLco, mean (SD)	37.0 (14.5)	42.6 (16.6)	45.6 (14.9)	45.8 (14.8)	42.8 (15.9)	38.7 (15.8)
% FVC, mean (SD)	68.2 (18.2)	71.6 (15.9)	70.0 (16.6)	74.2 (16.3)	70.5 (16.8)	64.4 (14.6)

BMI body mass index, *DLco* diffusing capacity for carbon monoxide, *FVC* forced vital capacity, *SD* standard deviation

Table 2 Clinical outcomes at 24 months, stratified by baseline BMI category

Outcome	Baseline BMI (categorical)		
	< 25 kg/m² (n = 120)	25 to < 30 kg/m² (n = 242)	≥ 30 kg/m² (n = 238)
Primary outcome: all-cause mortality			
Total observations, N^a	98	210	212
Times response occurred, n	26	34	27
Estimate (95% CI)[b]	0.17 (0.11, 0.27)	0.12 (0.08, 0.17)	0.11 (0.07, 0.16)
Odds ratio (95% CI)[c]		0.65 (0.34, 1.25)	0.59 (0.30, 1.19)
Secondary outcome: annualized change in percent predicted FVC, %			
Number of patients, n^a	98	210	212
Enrollment FVC (95% CI)[d]	70.59 (68.88, 72.30)	71.10 (69.96, 72.24)	70.48 (69.33, 71.64)
Change (95% CI)[e]	− 3.53 (− 4.75, − 2.30)	− 2.78 (− 3.54, − 2.01)	− 2.06 (− 2.83, − 1.30)
Difference (95% CI)[f]		0.75 (− 0.70, 2.20)	1.47 (0.01, 2.93)
Secondary outcome: annualized change from enrollment in percent predicted DLco, %			
Number of patients, n^a	98	210	212
Enrollment DLco (95% CI)[d]	41.39 (40.35, 42.43)	42.25 (41.58, 42.91)	43.22 (42.54, 43.90)
Change (95% CI)[e]	− 3.73 (− 5.13, − 2.33)	− 4.04 (− 4.90, − 3.18)	− 3.04 (− 3.89, − 2.19)
Difference (95% CI)[f]		− 0.32 (− 1.96, 1.33)	0.69 (− 0.97, 2.35)
Secondary outcome: annualized change from enrollment in 6MWD, m			
Number of patients, n^g	76	150	136
Enrollment 6MWD (95% CI)[d]	411.39 (385.31, 437.48)	382.25 (363.86, 400.64)	332.12 (312.79, 351.45)
Change (95% CI)[e]	− 18.50 (− 34.53, − 2.46)	− 18.41 (− 29.80, − 7.02)	− 9.80 (− 21.26, 1.67)
Difference (95% CI)[f]		0.09 (− 19.71, 19.88)	8.70 (− 11.56, 28.96)
Exploratory outcome: all-cause hospitalizations			
Total observations, N^h	72	176	185
Times response occurred, n	18	44	40
Estimate (95% CI)[b]	0.24 (0.15, 0.35)	0.23 (0.17, 0.30)	0.22 (0.16, 0.28)
Odds ratio (95% CI)[c]		0.98 (0.51, 1.93)	0.89 (0.46, 1.78)
Exploratory outcome: respiratory-related hospitalizations			
Total observations, N^h	72	176	185
Times response occurred, n	5	20	20
Estimate (95% CI)[b]	0.04 (0.02, 0.11)	0.07 (0.04, 0.12)	0.08 (0.05, 0.13)
Odds ratio (95% CI)[c]		1.80 (0.64, 5.96)	2.00 (0.69, 6.77)

Table 2 continued

Outcome	Baseline BMI (categorical)		
	< 25 kg/m^2 (n = 120)	25 to < 30 kg/m^2 (n = 242)	≥ 30 kg/m^2 (n = 238)
Exploratory outcome: acute exacerbations			
Total observations, N^h	72	176	185
Times response occurred, n	3	11	12
Estimate (95% CI)[b]	0.02 (0.01, 0.09)	0.03 (0.02, 0.07)	0.04 (0.02, 0.08)
Odds ratio (95% CI)[c]		1.41 (0.38, 6.81)	1.69 (0.45, 8.39)

6MWD 6-min walk distance, *BMI* body mass index, *CI* confidence interval, *DLco* diffusing capacity for carbon monoxide, *FVC* forced vital capacity, *OR* odds ratio

[a]The total number of patients for whom a complete set of predictor variables (including enrollment DLco) was obtained was N = 520

[b]Probability of event occurrence for an average patient in the specified category

[c]Estimated OR for the specified category relative to reference (blank) category

[d]Estimated response for an average patient at enrollment

[e]Estimated change in the response variable per year

[f]Difference in estimated annualized change compared with the reference (blank) category

[g]The total number of patients with a complete set of predictor variables (including enrollment DLco) and non-missing 6MWD measurements was N = 362

[h]The total number of patients for whom a complete set of predictor variables (including enrollment DLco) was obtained, excluding 87 patients who died during the 2-year study window, was N = 433

95 patients with no weight loss, 425 patients with > 0 to < 5% weight loss, and 80 patients with ≥ 5% weight loss. In general, demographics and clinical characteristics at enrollment were similar across weight loss subgroups (Table 1). However, mean enrollment percent predicted FVC and percent predicted DLco values were lower in patients experiencing more weight loss compared with those experiencing less weight loss. Additionally, rates of nintedanib usage were higher in patients experiencing more weight loss versus those experiencing less weight loss.

Clinical Outcomes up to 24 Months Stratified by Baseline BMI

At 24 months, there was no difference observed in all-cause mortality across BMI subgroups (OR [95% CI] versus BMI < 25 kg/m^2: 0.65 [0.34, 1.25] for 25 to < 30 kg/m^2 and 0.59 [0.30, 1.19] for ≥ 30 kg/m^2) (Table 2). In the time-to-event analysis, which comprised 645 patients

(includes patients regardless of if they had undergone a lung transplant or non-death early termination or not), baseline BMI was not associated with the risk of mortality when comparing patients with either BMI of 25 to < 30 kg/m^2 (HR [95% CI] 0.72 [0.44, 1.19]; P = 0.203) or BMI of ≥ 30 kg/m^2 (HR [95% CI] 0.67 [0.39, 1.17]; P = 0.156) with the BMI < 25 kg/m^2 subgroup. Patients with baseline BMI < 25 kg/m^2 had a significantly greater estimated annualized decline in percent predicted FVC compared with patients with baseline BMI ≥ 30 kg/m^2, and a numerically greater (but non-significant) estimated annualized decline in percent predicted FVC compared with patients with baseline BMI 25 to < 30 kg/m^2 (Table 2). Relative to the reference category (< 25 kg/m^2), the differences in the estimated changes for percent predicted DLco and 6MWD, and the estimated ORs for all-cause hospitalization, respiratory-related hospitalization, and acute exacerbations were not statistically significant for the baseline BMI 25 to < 30 kg/m^2 and ≥ 30 kg/m^2 subgroups (Table 2).

Table 3 Clinical outcomes at 24 months, stratified by annualized percent change in body weight category

Outcome	Annualized percent change in body weight (categorical)		
	No weight loss (*n* = 95)	> 0 to < 5% weight loss (*n* = 425)	≥ 5% weight loss (*n* = 80)
Primary outcome: all-cause mortality			
Total observations, N^a	84	365	71
Times response occurred, *n*	5	65	17
Estimate (95% CI)[b]	0.05 (0.02, 0.13)	0.14 (0.10, 0.18)	0.15 (0.09, 0.25)
Odds ratio (95% CI)[c]		2.83 (1.14, 8.62)	3.28 (1.15, 10.95)
Secondary outcome: annualized change in percent predicted FVC, %			
Number of patients, n^a	84	365	71
Enrollment FVC (95% CI)[d]	71.23 (69.40, 73.05)	70.90 (70.03, 71.77)	69.38 (67.40, 71.37)
Change (95% CI)[e]	− 3.07 (− 4.24, − 1.91)	− 2.28 (− 2.88, − 1.68)	− 3.52 (− 4.85, − 2.20)
Difference (95% CI)[f]		0.79 (− 0.53, 2.11)	− 0.45 (− 2.22, 1.32)
Secondary outcome: annualized change from enrollment in percent predicted DLco, %			
Number of patients, n^a	84	365	71
Enrollment DLco (95% CI)[d]	42.75 (41.67, 43.83)	42.38 (41.87, 42.89)	42.78 (41.59, 43.96)
Change (95% CI)[e]	− 3.79 (− 5.10, − 2.47)	− 3.19 (− 3.86, − 2.52)	− 5.33 (− 6.89, − 3.78)
Difference (95% CI)[f]		0.60 (− 0.89, 2.08)	− 1.54 (− 3.58, 0.49)
Secondary outcome: annualized change from enrollment in 6MWD, m			
Number of patients, n^g	54	259	49
Enrollment 6MWD (95% CI)[d]	387.58 (355.50, 419.67)	370.20 (355.94, 384.45)	346.86 (314.64, 379.08)
Change (95% CI)[e]	− 29.39 (− 46.56, − 12.22)	− 14.94 (− 23.45, − 6.43)	0.46 (− 17.54, 18.45)
Difference (95% CI)[f]		14.45 (− 4.78, 33.68)	29.85 (5.31, 54.38)
Exploratory outcome: all-cause hospitalizations			
Total observations, N^h	79	300	54
Times response occurred, *n*	16	67	19
Estimate (95% CI)[b]	0.20 (0.12, 0.31)	0.22 (0.17, 0.27)	0.31 (0.20, 0.45)
Odds ratio (95% CI)[c]		1.10 (0.59, 2.15)	1.80 (0.80, 4.07)
Exploratory outcome: respiratory-related hospitalizations			
Total observations, N^h	79	300	54
Times response occurred, *n*	7	25	13
Estimate (95% CI)[b]	0.07 (0.03, 0.16)	0.06 (0.04, 0.09)	0.14 (0.07, 0.25)
Odds ratio (95% CI)[c]		0.76 (0.31, 2.08)	2.06 (0.73, 6.16)

Table 3 continued

Outcome	Annualized percent change in body weight (categorical)		
	No weight loss ($n = 95$)	> 0 to < 5% weight loss ($n = 425$)	≥ 5% weight loss ($n = 80$)
Exploratory outcome: acute exacerbations			
Total observations, N^h	79	300	54
Times response occurred, n	6	15	5
Estimate (95% CI)[b]	0.06 (0.02, 0.14)	0.03 (0.01, 0.06)	0.04 (0.02, 0.12)
Odds ratio (95% CI)[c]		0.45 (0.15, 1.42)	0.73 (0.19, 2.75)

6MWD 6-min walk distance, *CI* confidence interval, *DLco* diffusing capacity for carbon monoxide, *FVC* forced vital capacity, *OR* odds ratio

[a]The total number of patients for whom a complete set of predictor variables (including enrollment DLco) was obtained was $N = 520$

[b]Probability of event occurrence for an average patient in the specified category

[c]Estimated OR for the specified category relative to reference (blank) category

[d]Estimated response for an average patient at enrollment

[e]Estimated change in the response variable per year

[f]Difference in estimated annualized change compared with the reference (blank) category

[g]The total number of patients with a complete set of predictor variables (including enrollment DLco) and non-missing 6MWD measurements was $N = 362$

[h]The total number of patients for whom a complete set of predictor variables (including enrollment DLco) was obtained, excluding 87 patients who died during the 2-year study window, was $N = 433$

Clinical Outcomes up to 24 Months Stratified by Annualized Percent Change in Body Weight

All-cause mortality over 24 months was lower among patients who experienced no annualized weight loss versus both those with ≥ 5% weight loss (OR [95% CI] 3.28 [1.15, 10.95]) and those with > 0 to < 5% weight loss (OR [95% CI] 2.83 [1.14, 8.62]) (Table 3). In the time-to-event analysis ($n = 645$), risk of mortality was significantly higher among patients with either ≥ 5% weight loss (HR [95% CI] 2.84 [1.11, 7.26]; $P = 0.030$) or > 0 to < 5% weight loss (HR [95% CI] 2.52 [1.05, 6.04]; $P = 0.039$) versus those with no weight loss. Relative to the reference category (no weight loss), there was no significant difference in annualized change in percent predicted FVC or DLco in either the > 0 to < 5% weight loss subgroup or the > 5% weight loss subgroup. The no weight loss subgroup exhibited a significant annualized decline in 6MWD compared with the ≥ 5% weight loss group (Table 3), but the result was not significant when modeled with weight loss as a continuous variable. There was no significant difference in all-cause hospitalization, respiratory-related hospitalization, and acute exacerbations for the ≥ 5% weight loss and > 0 to < 5% weight loss subgroups relative to the reference category (no weight loss) (Table 3).

DISCUSSION

This analysis aimed to identify whether BMI and/or change in body weight are correlated with clinical outcomes in patients with IPF by using a large, real-world population from the PFF-PR. The results of this analysis suggest that some clinical outcomes may be associated with

baseline BMI and annualized percent change in body weight over 24 months, although the causation of the relationship is unknown. No association between mortality and baseline BMI was observed after adjusting for pulmonary function and other factors. However, an association was observed between weight loss and mortality, with patients at a higher risk of mortality being those who experienced more weight loss. This relationship is perhaps unsurprising since it may be expected that patients lose more weight when they are at risk of mortality due to a variety of underlying factors.

These results are consistent with other analyses that have investigated the relationship between mortality and BMI or weight loss. For example, in a real-world cohort study of 210 patients with IPF from hospitals in the UK and Japan, loss of body weight was an independent risk factor for decreased survival, with a weight loss of $\geq 6.1\%$ identified as a predictor of worse 2-year survival [16]. Furthermore, the Jouneau et al. 2021 post hoc analysis of pooled data from five randomized controlled trials of 1604 patients with IPF found that mortality was numerically higher in patients with weight loss versus those without weight loss. Mortality rates were similar across the groups stratified by baseline BMI [7]. In addition, a retrospective cohort study of patients with ILD in America found that less weight loss was associated with a lower risk of mortality in patients with IPF, with weight loss being identified as a potential longitudinal marker of ILD disease progression. Again, baseline BMI was not associated with mortality in this study [10]. In an observational, retrospective, multicenter study in patients with fibrotic ILD ($n = 1786$ from the Canadian Registry for Pulmonary Fibrosis; $n = 1779$ from the ILD registry at the University of California, San Francisco), a relationship between weight loss and 1-year mortality was also observed, whereby the risk of 1-year mortality was greater with increasing weight loss thresholds on unadjusted and adjusted analyses [17].

It should be noted that the lack of association found between baseline BMI and all-cause mortality in this study has not always been reflected in other studies. In a cohort study of 197 patients with IPF, higher BMI was associated

with better survival [18]. Similarly, a real-world Japanese study of 33 patients with IPF found that lower BMI independently contributed towards mortality [8]. The observational, retrospective, multicenter study in patients with fibrotic ILD also reported a relationship between BMI and mortality, whereby the highest risk of mortality was observed in patients who were underweight (BMI < 18.5 kg/m^2) and lowest in those who were overweight (BMI 25–29.9 kg/m^2) or obese (BMI > 30 kg/m^2) compared with a reference group (BMI 18.5–24.9 kg/m^2) [17]. The reason for this misalignment may be due to differing study designs, sample sizes, patient populations, BMI category definitions, the statistical analyses used, and/or standards of care, which may limit direct comparisons between these studies.

In the current study, an association was observed between baseline BMI and annualized decline in percent predicted FVC, with patients in the baseline BMI < 25 kg/m^2 subgroup demonstrating a significantly greater decline in percent predicted FVC than patients with baseline BMI ≥ 30 kg/m^2. Similarly, in the pooled post hoc analysis of 1604 patients with IPF, a greater annualized decline in percent predicted FVC was also observed in patients with BMI < 25 kg/m^2 versus those with BMI ≥ 30 kg/m^2 and 25–30 kg/m^2 [7]. In addition, post hoc analyses of the INPULSIS trials of nintedanib in patients with IPF showed numerically similar findings in placebo-treated patients [6]. In the current analysis, no relationship was found between BMI and percent predicted DLco or 6MWD. Whereas, in the Jouneau et al. 2021 post hoc analysis, patients with BMI < 25 kg/m^2 had a greater estimated annualized worsening of percent predicted DLco compared with patients with BMI ≥ 30 kg/m^2, and a numerically greater estimated annualized decline in 6MWD compared with patients with BMI 25 to < 30 kg/m^2 and ≥ 30 kg/m^2 [7].

There was no association between weight loss and annualized decline in percent predicted FVC or DLco reported in the current analysis. On the other hand, patients with no weight loss showed a decline in 6MWD whereas those with $\geq 5\%$ weight loss did not show a decline; however, it should be noted that patients in the no

weight loss subgroup had a longer 6MWD at enrollment and still ended the 24-month period with the longest 6MWD as compared with the other weight loss groups. In contrast, in the Jouneau et al. 2021 post hoc analysis, patients who had no weight loss were shown to have reduced estimated annualized worsening of percent predicted FVC, DLco, and 6MWD compared with patients with > 0 to $< 5\%$ or $\geq 5\%$ weight loss [7]. Similarly, it has previously been found that patients with IPF with body weight loss have a significantly higher rate of FVC decline within 1 year compared with patients with no body weight loss [16].

In the general population, there is consistent evidence showing that lung function is negatively impacted by obesity and weight gain [19–21]. However, our results showed the opposite effect, whereby lung function (as measured by FVC) showed a greater decline in patients with IPF with a low BMI compared with a high BMI. The hypothesis that a higher BMI may be protective against negative outcomes, including mortality, has been explored in other therapy areas such as chronic obstructive pulmonary disease [22, 23], cancer [24–26], and acute heart failure [27]. Results from these studies indicate the presence of a potential "weight paradox" whereby, although obesity is typically associated with negative outcomes due to factors such as cardiovascular disease [28, 29], weight loss can also be an indication of declining health [10, 30]. Therefore, a potential link between weight loss and poor outcomes may be less relevant in a patient who has dieted intentionally versus a patient who has lost weight due to appetite loss. As such, when evaluating a patient who has experienced weight loss, it is important to assess whether the weight loss was intentional or not to ensure the outcomes are being interpreted appropriately.

This analysis has a number of limitations to consider. Firstly, its retrospective, observational nature means that there were potential confounders that were not collected or identified from patients' medical records. Furthermore, the stratification of patients by baseline BMI and weight loss resulted in small patient numbers, and thus low occurrence of events, in some subgroups. In addition, the exclusion of those without DLco data at enrollment, and those who were lost to follow-up or who did not have a complete 2 years of data recorded in the PFF-PR led to a loss of information. Causation could not be considered in these analyses due to the observational nature of the data and the synchronicity between the weight change predictor and the study outcomes. The reason for any weight loss or gain was also not provided, so it cannot be determined whether weight changes were intentional or not. Furthermore, hospitalizations and weight loss occurred concurrently during the 24-month data collection period in the PFF-PR; therefore, it is possible that hospitalization may have impacted weight loss or vice versa.

CONCLUSIONS

The results of this retrospective analysis suggest that some clinical outcomes may be worse in patients with IPF who have a low BMI (< 25 kg/m^2) or who lose weight over 24 months compared with a higher BMI (< 25 kg/m^2) or those who do not lose weight. While the causation of these relationships is unknown, these data may help to inform management decisions for patients with IPF; however, future studies are required to investigate how weight management impacts outcomes.

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Compliance with Ethics Guidelines. Enrollment in the PFF-PR was conducted with informed written consent from participating patients and the registry was approved by institutional review boards at each participating center. This post hoc analysis used de-identified patient data and was considered exempt from review by an institutional review board.

Prior Presentation. Preliminary findings from the analyses included in this letter were presented as a poster at the virtual CHEST Annual Meeting 2020.

Data Availability. The PFF Patient Registry dataset is not available publicly, but it can be made available with a reasonable and direct request to the Pulmonary Fibrosis Foundation (PFF), a 501(c)(3) nonprofit organization. Investigators who are affiliated with either a participating PFF Care Center or current industry sponsors can access data at no cost by submitting a study proposal that undergoes a peer-review process to ensure that the research question is feasible, significant, and impactful. Others can access the dataset for a fee by submitting a completed ancillary study proposal for consideration. Qualified researchers may request access to individual patient-level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). For further details on Roche's Global Policy on the Sharing of Clinical Study Information and how to request access to related clinical study documents, see here: https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

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