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Fat-Free Mass Index Controlled for Age and Sex and Malnutrition Are Predictors of Survival in Interstitial Lung Disease

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Keywords
Body fat mass index · Fat-free mass index · Interstitial lung disease · Subjective global assessment · Survival

Abstract
Background: Literature focusing on nutritional variables and survival in interstitial lung disease (ILD) is limited by its focus on weight and BMI and has not considered body composition. ***Objectives:*** The primary objective of this study was to examine whether body composition measures, specifically fat-free mass index z-score (z-FFMI) and body fat mass index z-score (z-BFMI), were predictors of survival in fibrotic ILD patients. The second objective was to examine if nutrition status was a predictor of survival. ***Method:*** Seventy-eight outpatients diagnosed with fibrotic ILD were recruited in this cross-sectional study. Body composition data using dual frequency bioelectrical impedance analysis (BodyStat 1500MD; UK) and nutrition status using the subjective global assessment (SGA) were determined. To control for age and sex, z-FFMI and z-BFMI were calculated using population means. Participant charts were reviewed for diagnosis, age, disease severity, and exercise capacity. ***Results:*** Age (HR 1.08, 95% CI [1.03–1.13], $p < 0.01$), BMI (HR 0.90, 95% CI [0.84–0.97], $p < 0.01$]), z-FFMI (HR 0.70, 95% CI [0.56–0.87], $p = 0.02$), z-BFMI (HR 0.74, 95% CI [0.57–0.96], $p < 0.01$), 6-min walk distance (6MWD) (HR 0.99, 95% CI [0.99–1.00], $p < 0.01$), percent predicted diffusing capacity for carbon monoxide (%DLco) (HR 0.93, 95% CI [0.89–0.97], $p < 0.01$), and severe malnutrition (SGA-C) (HR 6.98, 95% CI [2.00–24.27], $p < 0.01$) were significant predictors of survival. When controlled for

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exercise capacity and disease severity, z-FFMI and severe malnutrition were significant predictors of survival independent of %DLco. ***Conclusion:*** z-FFMI and severe malnutrition were significant predictors of survival in fibrotic ILD patients independent of disease severity.

Introduction

Interstitial lung disease (ILD) is a group of disorders that involve disruption of the distal lung parenchyma, with various degrees of inflammation and/or fibrosis. A common form of ILD is idiopathic pulmonary fibrosis (IPF) and is characterized by progressive scaring of the lung parenchyma, with minimal inflammation. IPF is relentlessly progressive, with a dismal prognosis of 2–5 years, in the absence of treatment [1]. Clinical markers such as lung function, 6-min walk distance (6MWD), dyspnea scores, and BMI are reliable predictors of survival in ILD [2–4]. To date, research examining the relationship between nutritional factors and survival in ILD is limited by its focus on weight and BMI and has not fully addressed the influence of body composition and overall nutrition status on survival.

Low fat-free mass index (FFMI), fat-free mass (FFM) standardized for height, has been shown to be a predictor of mortality in various disease states [5, 6]. In IPF, Nishiyama et al. [7] found that FFMI, but not BMI, was a significant predictor of survival. Age, sex, and height are core biological factors affecting FFM, but it may also be affected by environmental factors such as physical activity and protein intake. Therefore, the calculation of an FFMI z-score (z-FFMI) aims to account for some of these confounding factors by generating a value indicating how far away an individual's measure is from the mean of healthy population reference values. Similarly, this can be used to calculate body fat mass index z-scores (z-BFMI).

In other chronic lung diseases, a significant portion of patients have been identified as malnourished [8, 9]. In ILD, the prevalence of malnutrition is not well established. The gold standard of nutrition assessment is the subjective global assessment (SGA), which has been validated in a variety of disease states [10, 11]. SGA considers diet, weight history, functional status, gastrointestinal issues, and disease history, combined with a physical examination, to identify signs of muscle wasting, subcutaneous fat loss, and edema, taken together to determine nutritional status.

The primary objective of this study was to examine whether measures of body composition, specifically z-FFMI and z-BFMI, are independent predictors of survival in ILD patients. The second objective was to determine the prevalence of malnutrition using SGA and examine if nutrition status is a predictor of survival.

Materials and Methods

Study Population

In this cross-sectional study, 78 patients diagnosed with ILD were recruited from an outpatient ILD clinic between November 20, 2013, and January 3, 2018. Survival status was determined as of January 03, 2020. Inclusion criteria included ambulatory patients over 18 years of age with diagnosis of a fibrotic ILD. Patients were excluded according to the following criteria: inability to provide consent due to communication issues (cognitive and motor), presence of cardiac implantable electrical devices, nonstable ILD patients defined as those with infections and/or fever, admitted to hospital in the previous month, or presence of an unstable comorbid illness. The study protocol was approved by the Western University Research Ethics Board (Protocol No. 104028 and 103186).

Diagnosis, Lung Function, and 6-Min Walk Test

The presence of fibrotic ILD was defined based on high-resolution chest computerized tomography (CT) scan and compatible pulmonary function tests (PFTs). After excluding all known causes of ILD, IPF was diagnosed based on clinical and radiographic criteria, and when necessary, on surgical lung biopsies, followed by multidisciplinary discussion [12, 13]. The diagnosis of fibrotic ILD other than IPF was based on clinical presentation; laboratoristic, bronchoscopic, and radiographic investigations; and, when indicated (e.g., nonspecific interstitial pneumonia cases), surgical lung biopsies. Patients with combined pulmonary fibrosis and emphysema were also excluded from the study, and coexisting emphysema was always minimal (≤5% of total lung volume). Patient charts were also reviewed for current medications. Time from diagnosis was calculated from the date ILD was diagnosed to the study recruitment date. PFTs and 6-min walk test (6MWT) were performed according to the American Thoracic Society guidelines [14, 15].

Body Composition Assessment

Body composition data were obtained using dual frequency bioelectrical impedance analysis (BIA) (BodyStat 1500MD; UK). BIA is an easy and convenient bedside tool that is validated in a variety of clinical settings [16–18]. Participants were asked to rest supine on a bed in the clinic while breathing normally. Resistance and reactance were measured via passing a 50-kHz electrical current through the body via 2 electrodes placed on the surfaces of the right hand and foot while measuring the impedance at fixed frequencies [19]. FFMI and BFMI were calculated using estimates of FFM and BFM obtained using BIA according to the following equations: FFMI = FFM (kg)/(height [m])^2 and BFMI = BFM (kg)/(height [m])^2, respectively. z-FFMI and z-BFMI were then calculated using population means by age and sex groups [20] according to the following equation: z-score = $(x - x_{\text{population mean}})$/standard

deviation$_{population}$ (standard deviation [SD]). FFMI and BFMI cutoffs suggested by Kyle et al. [20] were used to classify patients into the following categories: normal (normal FFMI and BFMI), sarcopenia (low FFMI and normal BFMI), obesity (normal FFMI and high BFMI), and sarcopenic obesity (low FFMI and high BFMI) [21].

Nutrition Assessment

SGA was completed according to the method outlined by Detsky et al. [10] and was completed by trained registered dietitians (S.R. and J.M.). SGA is considered the gold standard method to identify malnutrition combining dietary, weight, functional, gastrointestinal, and disease history with a physical examination to arrive at a categorical ranking. Categories A, B, and C represent well nourished, moderate malnutrition or suspected of being malnourished, and severe malnutrition, respectively.

Outcome

The primary outcome measure was 2-year lung transplant-free survival. The survival of patients was assessed starting from the time of their BIA assessment up to 2 years following this date.

Statistical Analysis

Descriptive statistics were evaluated; continuous variables are expressed as mean ± SD, and categorical variables are displayed as frequencies. Then, an independent samples *t* test was used to compare differences in means between sexes. Cox proportional hazard regression models were performed to identify significant predictors of survival. z-FFMI, z-BFMI, %DLco, and 6MWD were included in Cox regression models as continuous variables, while SGA categories (A, B, and C) were included as categorical variables. Receiver operator characteristic (ROC) analyses were used to determine the best cut point of a variable towards the endpoint, by examining accuracy of predicting endpoints (sum of sensitivity and specificity). Lung transplant-free survival was evaluated using Kaplan-Meier curves and the log-rank test. p values <0.05 were regarded as significant. Statistical analysis was performed with IBM® SPSS® Statistics Version 26 software package.

Results

Patient characteristics including diagnosis, clinical characteristics, body composition, and nutrition status are shown in Table 1. Mean age was 68.4 ± 10.0 years. 51.3% of participants were female. Mean BMI was 30.8 ± 7.3 kg/m^2. As expected, FFMI was significantly greater in males versus females ($p < 0.001$), and BFMI was significantly lower in males versus females ($p < 0.001$). Mean z-FFMI and z-BFMI, standardized for age and sex population norms [20], were 0.39 ± 1.98 SD and 2.27 ± 2.15 SD, respectively. The majority of patients were diagnosed with moderate malnutrition (48.7%). 60.3% of participants were classified as obese, while 11.5% had a normal body composition, 20.5% had sarcopenia, and 7.7% had sarcopenic obesity. Mean observation time was 19.4 ± 7.3

Table 1. Patient demographics ($N = 78$)

Clinical characteristics	Mean ± SD
Age, years	68.4±10.0
Anthropometry and nutritional indices	
BMI, kg/m^2	30.8±7.3
FFMI, kg/m^2	18.2±3.6*
Male	20.0±3.6
Female	16.4±2.7
BFMI, kg/m^2	12.6±5.5*
Male	9.9±3.8
Female	15.2±5.7
FFMI z-score (SD)	0.39±1.98
BFMI z-score (SD)	2.27±2.15
Pulmonary function and exercise capacity	
FEV_1 (% predicted)	75.1±18.9
FVC (% predicted)	71.1±19.5
DLco (% predicted)	40.6±17.1
6MWD, m	335.6±109.8
6MWD (% predicted)	74.4±22.9
Clinical characteristics	**Frequency (%)**
Scleroderma-related ILD	3 (3.8)
Vasculitis-related ILD	2 (2.6)
Sarcoidosis (stages III-IV)	2 (2.6)
ILD medications	
Proton pump inhibitors	43 (55.1)
Oxygen supplementation	24 (30.8)
Pirfenidone	16 (20.5)
N-acetylcysteine	12 (15.4)
Nintedanib	2 (2.6)
Body composition	
Normal	9 (11.5)
Sarcopenia	16 (20.5)
Obesity	47 (60.3)
Sarcopenic obesity	6 (7.7)
Nutrition status	
SGA-A (well nourished)	34 (43.6)
SGA-B (moderate malnutrition)	38 (48.7)
SGA-C (severe malnutrition)	6 (7.7)
Clinical characteristics	**Median (range)**
Years from diagnosis	1 (0–13)

Continuous, parametric variables are expressed as mean ± standard deviation. Continuous, nonparametric variables are expressed as median (range). BFMI, body fat mass index; FFMI, fat-free mass index; ILD, interstitial lung disease; SD, standard deviation; SGA, subjective global assessment; 6MWD, 6-min walk distance; %DLco, percent predicted diffusing capacity for carbon monoxide; %FEV, percent predicted forced expiratory volume; %FVC, percent predicted forced vital capacity. * Independent samples *t* test indicated significant difference ($p < 0.001$) between sexes.

Table 2. Univariate Cox proportional analysis

Variable	HR	95% CI	*p* value
Sex	1.76	(0.72–4.32)	0.22
Age	1.08	(1.03–1.13)	**<0.01**
Time from diagnosis	1.00	(0.85–1.17)	0.96
Prednisone	0.75	(0.29–1.95)	0.56
Pirfenidone	1.91	(0.73–4.98)	0.19
N-acetylcysteine	3.17	(1.21–8.28)	**0.02**
Supplemental oxygen	1.76	(0.72–4.31)	0.22
MMF	0.04	(0.00–10.03)	0.25
$\%FEV_1$	0.99	(0.97–1.02)	0.51
%FVC	0.99	(0.97–1.01)	0.36
%DLco	0.93	(0.89–0.97)	**<0.01**
BMI	0.90	(0.84–0.97)	**<0.01**
z-FFMI	0.70	(0.56–0.87)	**<0.01**
z-BFMI	0.74	(0.57–0.96)	**0.02**
6MWD	0.99	(0.99–1.00)	**<0.01**
SGA-A (well nourished)	1	–	–
SGA-B (moderate malnutrition)	2.04	(0.70–5.96)	0.20
SGA-C (severe malnutrition)	6.98	(2.00–24.27)	**<0.01**
Normal	1	–	–
Sarcopenia	5.49	(0.69–43.97)	0.11
Obesity	1.66	(0.21–13.28)	0.63
Sarcopenic obesity	5.61	(0.58–54.06)	0.14
Obesity	1	–	–
Sarcopenic obesity	3.23	(0.85–12.21)	0.08

CI, confidence interval; HR, hazard ratio; SGA, subjective global assessment; z-BFMI, body fat mass index z-score; z-FFMI, fat-free mass index z-score; 6MWD, 6-min walk distance; %DLco, percent predicted diffusing capacity for carbon monoxide; %FEV, percent predicted forced expiratory volume; %FVC, percent predicted forced vital capacity.

Table 3. Cox regression analyses to identify independent predictors of lung transplant-free survival

Variables	HR	95% CI	*p* value
Model 1			
z-FFMI (SD)	0.72	(0.53–0.98)	**0.03**
z-BFMI (SD)	0.78	(0.69–1.32)	0.78
Model 2			
z-FFMI (SD)	0.67	(0.51–0.86)	**<0.01**
DLco (% pred)	0.92	(0.88–0.97)	**<0.01**
Model 3			
z-FFMI (SD)	0.82	(0.65–1.03)	0.09
6MWD, m	0.99	(0.99–1.00)	**<0.01**
Model 4			
SGA-A (well nourished)	1	–	–
SGA-B (moderate malnutrition)	2.06	(0.56–7.63)	0.28
SGA-C (severe malnutrition)	7.24	(1.68–31.15)	**<0.01**
DLco (% pred)	0.93	(0.89–0.97)	**<0.01**
Model 5			
SGA-A (well nourished)	1	–	–
SGA-B (moderate malnutrition)	1.42	(0.47–4.26)	0.54
SGA-C (severe malnutrition)	3.13	(0.75–13.01)	0.12
6MWD, m	0.99	(0.99–1.00)	**<0.01**

CI, confidence interval; HR, hazard ratio; SD, standard deviation; SGA, subjective global assessment; z-FFMI, fat-free mass index z-score; z-BFMI, body fat mass index z-score; 6MWD, 6-min walk distance; %DLco, percent predicted diffusing capacity for carbon monoxide.

months. At the end of the 2-year observation period, 26% (n = 20) of participants had passed and 10% (n = 8) received a lung transplant.

The results of the univariate Cox proportional hazard model are summarized in Table 2. Age was not included in the models as z-FFMI, z-BFMI, and %DLco values control for differences in age. z-FFMI and SGA were not included in the same model as a component of SGA includes assessment of loss of lean body mass. The results of the multiple Cox proportional hazard models are shown in Table 3. z-FFMI was a significant predictor of survival independent of z-BFMI and %DLco but not 6MWD (models 1–3, Table 3). SGA-C (severe malnutrition) as compared to SGA-A (well nourished) was a significant predictor of survival independent of %DLco but not 6MWD (models 4–5, Table 3).

Results of ROC analysis for z-FFMI are displayed in Table 4. The ideal z-FFMI cutoff was <0.37 SD with 62.1% sensitivity and 80.0% specificity. Kaplan-Meier survival curves using the ideal cutoffs determined using ROC analysis for z-FFMI are shown in Figure 1.

Discussion/Conclusion

This study examined the influence of body composition parameters, z-FFMI and z-BFMI, and nutrition status on survival in a group of fibrotic ILD patients. z-FFMI, z-BFMI, and severe malnutrition (SGA-C) were shown to be significant predictors of survival in ILD. However, when controlled for disease severity, only z-FFMI and severe malnutrition were independent predictors of survival in ILD patients.

In our univariate analysis, BMI was found to be a significant predictor of survival in ILD patients. Research focusing on BMI and survival in IPF patients has demonstrated a paradoxical effect of obesity on survival, in that, an increased BMI acts as a protective factor on mortality.

Table 4. Results of ROC analysis

	AUC (95% CI)	*p* value	Cutoff (SD)	Sensitivity, %	Specificity, %
z-FFMI	0.74 (0.62–0.87)	<0.01	0.37	62.1	80.0

ROC, receiver operator characteristic; AUC, area under the curve; CI, confidence interval; SD, standard deviation; z-FFMI, fat-free mass index z-score.

In a study by Alakhras et al. [4], individuals with BMIs in the obese category (>30 kg/m^2) were shown to have significantly greater survival times than those with BMIs in the overweight category (25–30 kg/m^2) and the normal category (<25 kg/m^2) [4]. Similarly, Mura et al. [22] reported that for every 1-unit increase in BMI, there was a 11% lower risk of death at 3-year follow-up in IPF patients (HR 0.89, 95% CI [0.80–0.98], $p = 0.0165$). Adding to these results, progressive weight loss >5% of total body weight in 1 year has also been found to be an independent predictor of decreased survival in IPF [23]. Limited studies exist showing the relationship between increased BMI and decreased mortality in ILDs other than IPF. One recent study, which included a diverse group of ILDs including ILD secondary to connective tissue disease, hypersensitivity pneumonitis, and unclassifiable subtypes found that a loss in BMI >5% in 1 year was associated with significantly shorter survival times, and there was a 2-fold higher risk of death compared to those with a ≤5% loss in BMI in 1 year [24]. These results suggest that excess weight may act as a nutritional reserve in times of poor intake secondary to harsh side effects of medications, or during acute exacerbations of the disease. Interestingly, we found that only use of N-acetylcholine, an ILD medication used for its antioxidant effect [25], was associated with worsened mortality, but corticosteroids and other antifibrotic and anti-inflammatory medications were not related to survival.

A strong relationship exists between decreased FFMI and poor prognosis in other chronic respiratory diseases such as chronic obstructive pulmonary disease [5, 26, 27]; however, fewer studies exist in ILD. We demonstrated a 30% reduction in risk of death for every 1 SD increase in z-FFMI in our sample of 78 fibrotic ILD patients. Two recent studies exist examining FFMI and survival in IPF patients. The first study by Nishiyama et al. [7] found a 36% lower risk of death with every 1-unit increase in FFMI (HR 0.64, 95% CI [0.43–0.94], $p = 0.02$) in a group of Japanese IPF patients. Conversely, a study of IPF patients by Patel et al. [28] found no significant association

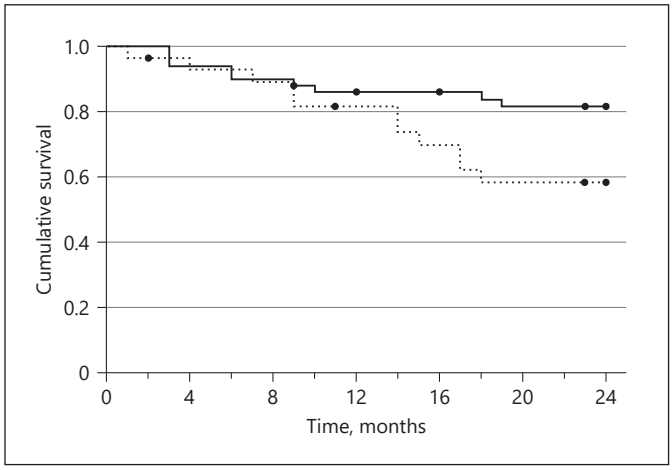

Fig. 1. Kaplan-Meier survival curve using ideal cutoff for z-FFMI ($p = 0.001$). The solid line represents z-FFMI ≥0.37 SD, and the dotted line represents z-FFMI <0.37 SD. Survival curves were compared using log-rank statistics (• represents censored cases). z-FFMI, fat-free mass index z-score.

between FFMI and all-cause mortality at 1-year. Although conflicting results, neither study controlled for age or sex when analyzing FFMI. Notably, despite not controlling for confounding factors, Nishiyama et al. [7] did demonstrate FFMI to be a significant predictor of survival in their study. This could be due to a nonsignificant difference in FFMI in males versus females in this sample. Different body composition norms in Japanese versus Caucasian cohorts such as lower BMI and FFMI have been demonstrated in previous studies [29]. However, between-sex statistics were not reported. Patel et al. [28] did not adjust for sex differences in their univariate analysis using FFMI as a continuous variable; however, when FFMI was used as a categorical variable, sex specific cutoffs were applied (FFMI ≥15 kg/m^2 for females and ≥17 kg/m^2 for males). A reference source for these cutoffs was not indicated; however, it is assumed that these cutoffs are based on the European Society for Parenteral and Enteral Nutrition diagnostic criteria for malnutrition [30]. Al-

though an important contributor to survival, cutoffs derived for identification of malnutrition may not be sensitive or specific to predicting survival outcomes, thus influencing these nonsignificant findings. Our study intended to control for patient characteristics such as age and sex which influence FFMI. Using z-FFMI, we were able to include both males and females together in our analyses, and we were able to control for factors such as age-related FFM loss which can skew results.

We also addressed the impact of body fat on survival. Interestingly, we found that z-BFMI was a significant predictor of survival. Although it has been demonstrated that excess weight can increase the workload of breathing and decrease physical performance [31], our results seem to suggest that greater amounts of body fat may be protective on survival. It is very likely that the protective effect of excess body fat on survival observed in this study is related to the relationship between FFM and body fat, in that, as body fat mass increases, greater amounts of FFM may be required to support this excess weight. Therefore, FFMI may be maintained through a weight-bearing effect. This is further supported by results of our analysis, in which z-BFMI was no longer a significant predictor of survival when controlled for z-FFMI. These results appear to suggest a component of sarcopenic obesity affecting the significance of z-BFMI as a predictor of survival in the presence of worsened disease status and poor exercise capacity. Specifically, research has shown that excess body fat, especially in the presence of low muscle mass, can have direct detrimental effects on physical performance [32], systemic inflammation [32], quality of life [32, 33], and prognosis [34]. We attempted to determine the influence of body composition on survival; however, we found no significant difference in odds of death in those with sarcopenia, obesity, nor sarcopenic obesity versus those with a normal body composition. Additionally, we assessed the specific difference between the obese and sarcopenic obese groups; however, there was not a significant difference ($p = 0.085$) in chance of death in sarcopenic obesity versus obesity. However, with only 6 patients identified as sarcopenic obese, our statistical power was limited.

Prevalence of malnutrition in ILD patients has been understudied, and clinical practice guidelines for the treatment and management of ILD offer limited guidance related to nutrition [1, 13]. Of the existing research, malnutrition prevalence varies greatly and is often identified by a single measure. Jouneau et al. [35] found that 28% of patients were malnourished using FFM, 4% were malnourished using BMI, and 5% were malnourished using midarm circumference. A conference abstract by Autore et al. [36] reported that 26% of patients were at risk of malnutrition using the Mini Nutritional Assessment Short Form, a validated screening tool designed for populations >65 years. In our study, the majority of patients were diagnosed with malnutrition, and those with severe malnutrition had a 7-fold increased risk of death compared to well-nourished patients. To the best of our knowledge, this study is the first to use a comprehensive nutrition assessment tool validated to diagnose malnutrition.

The modest sample size was a limiting factor of this study. First, we were limited to including no more than 2 predictor variables in the multiple Cox regression models keeping in line with the general recommendation that for each predictor variable, $n = 10$ outcomes, in this case deaths/tranplantations, are required to reduce the risk of overfitting the model [37]. Therefore, we were not able to control for both disease severity and exercise capacity with body composition parameters and nutrition status in the same model which may have produced different results. Second, with only 6 participants identified as sarcopenic obese, we were not able to fully address the question of whether increased body fat is protective in all cases. Similarly, limited numbers in our severe malnutrition group limited statistical power in our analyses. Diet history is included in the overall SGA score. We did not assess the influence of specific nutrients in the diet, such as protein, on survival, as it was not the aim of this study. We acknowledge, however, the potential that nutrition intake has on body composition. Our cross-sectional study only assessed body composition, lung function, and exercise capacity at 1 time point; however, monitoring changes over time, such as change in body composition or change in %FVC, can provide additional insights into their influences on survival. Additionally, we did not use a cohort of healthy individuals for comparison with our sample. However, the nature of calculating z-scores of body composition parameters innately compares our sample to healthy population norms of FFMI and BFMI. Lastly, it would be remiss to not acknowledge that BIA provides estimations of body composition using prediction equations. Our results are limited due to the use of estimates of FFM and BFM rather than actual measurements; therefore, to be able to truly determine an association between body composition and survival, these results would need to be confirmed using gold standard methods, for example, CT scans which have been used in other lung diseases [38].

These results are sufficiently encouraging to warrant further research into the nutritional status of ILD patients. Future research should focus on the influence of sarcopenic obesity on survival and how nutrition interventions targeted at maintaining or increasing muscle mass over time can affect survival in ILD patients. Furthermore, assessment of fat-free mass should be considered alongside or in place of BMI as a nutritional variable when analyzing survival risk of ILD patients as it can better identify those at risk of death. Additionally, chest CT scans are completed as part of diagnosis and clinical monitoring of ILD and should be leveraged to measure body composition parameters using a gold standard method. In conclusion, in our sample of 78 fibrotic ILD patients, z-FFMI and severe malnutrition independent of disease severity were significant predictors of survival in ILD patients.

Statement of Ethics

The study protocol was approved by the Western University Research Ethics Board (Protocol No. 104028 and 103186). Informed consent was obtained from all individual participants included in the study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Sylvia Rinaldi was primarily responsible for drafting, revising, and finalizing the manuscript and contributed to acquisition, analysis, and interpretation of the data; drafted the manuscript; and critically revised the manuscript. Jason Gilliland critically revised the manuscript. Colleen O'Connor critically revised the manuscript. Jamie Seabrook critically revised the statistical analyses used in the manuscript. Marco Mura contributed to acquisition, analysis, and interpretation of the data and critically revised the manuscript. Janet Madill contributed to acquisition, analysis, and interpretation of the data and critically revised the manuscript. All authors read and approved the final manuscript.

References

1 Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183(6):788–824.

2 Manali ED, Stathopoulos GT, Kollintza A, Kalomenidis I, Emili JM, Sotiropoulou C, et al. The medical research council chronic dyspnea score predicts the survival of patients with idiopathic pulmonary fibrosis. Respir Med. 2008;102(4):586–92.

3 Collard HR, King TE, Bartelson BB, Vourlekis JS, Schwarz MI, Brown KK. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2003;168(5):538–42.

4 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(5):1448–53.

5 Schols AM, Broekhuizen R, Weling-Scheepers CA, Wouters EF. Body composition and mortality in chronic obstructive pulmonary disease. Am J Clin Nutr. 2005;82(1):53–9.

6 Chang K-V, Chen J-D, Wu W-T, Huang K-C, Han D-S. Association of loss of muscle mass with mortality in liver cirrhosis without or before liver transplantation. Medicine. 2019;98(9):e14373.

7 Nishiyama O, Yamazaki R, Sano H, Iwanaga T, Higashimoto Y, Kume H, et al. Fat-free mass index predicts survival in patients with idiopathic pulmonary fibrosis. Respirology. 2017;22(3):480.

8 Günay E, Kaymaz D, Selçuk NT, Ergün P, Sengül F, Demir N. Effect of nutritional status in individuals with chronic obstructive pulmonary disease undergoing pulmonary rehabilitation. Respirology. 2013;18(8):1217–22.

9 Gupta B, Kant S, Mishra R. Subjective global assessment of nutritional status of chronic obstructive pulmonary disease patients on admission. Int J Tuberc Lung Dis. 2010;14(4):500–5.

10 Detsky AS, McLaughlin JR, Baker JP, Johnston N, Whittaker S, Mendelson RA, et al. What is subjective global assessment of nutritional status? JPEN J Parenter Enteral Nutr. 1987 Jan–Feb;11(1):8–13.

11 Baccaro F, Moreno JB, Borlenghi C, Aquino L, Armesto G, Plaza G, et al. Subjective global assessment in the clinical setting. JPEN J Parenter Enteral Nutr. 2007;31(5):406–9.

12 Flaherty KR, King TE, Raghu G, Lynch JP, Colby TV, Travis WD, et al. Idiopathic interstitial pneumonia: What is the effect of a multidisciplinary approach to diagnosis? Am J Respir Crit Care Med. 2004;170(8):904–10.

13 Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med. 2018;198(5):e44–68.

14 American Thoracic Society (ATS). ATS statement : guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166:111–7.

15 Standardization of Spirometry, 1994 Update. Standardization of spirometry, 1994 update. American Thoracic Society. Am J Respir Crit Care Med. 1995;152(3):1107–36.

16 Fuller NJ, Sawyer MB, Elia M. Comparative evaluation of body composition methods and predictions, and calculation of density and hydration fraction of fat-free mass, in obese women. Int J Obes Relat Metab Disord. 1994;18(7):503–12.

17 Ghosh S, Meister D, Cowen S, Hannan WJ, Ferguson A. Body composition at the bedside. Eur J Gastroenterol Hepatol. 1997;9(8):783–8.

18 Steiner MC, Barton RL, Singh SJ, Morgan MD. Bedside methods versus dual energy X-ray absorptiometry for body composition measurement in COPD. Eur Respir J. 2002;19(4):626–31.

19 BodyStat. BodyStat® 2017. Available from http://www.bodystat.com/ Accessed 2013 Nov 1.

20 Kyle UG, Genton L, Slosman DO, Pichard C. Fat-free and fat mass percentiles in 5225 healthy subjects aged 15 to 98 years. Nutrition. 2001;17(7–8):534–41.

21 Kyle UG, Pirlich M, Lochs H, Schuetz T, Pichard C. Increased length of hospital stay in underweight and overweight patients at hospital admission: a controlled population study. Clin Nutr. 2005;24(1):133–42.

22 Mura M, Porretta MA, Bargagli E, Sergiacomi G, Zompatori M, Sverzellati N, et al. Predicting survival in newly diagnosed idiopathic pulmonary fibrosis: a 3-year prospective study. Eur Respir J. 2012;40(1):101–9.
23 Nakatsuka Y, Handa T, Kokosi M, Tanizawa K, Puglisi S, Jacob J, et al. The clinical significance of body weight loss in idiopathic pulmonary fibrosis patients. Respiration. 2018;96(4):338–47.
24 Pugashetti J, Graham J, Boctor N, Mendez C, Foster E, Juarez M, et al. Weight loss as a predictor of mortality in patients with interstitial lung disease. Eur Respir J. 2018;52(3):1801289.
25 Sun T, Liu J, Zhao DW. Efficacy of N-acetylcysteine in idiopathic pulmonary fibrosis: a systematic review and meta-analysis. Medicine. 2016;95:1–7.
26 Gologanu D, Ionita D, Gartonea T, Stanescu C, Bogdan MA. Body composition in patients with chronic obstructive pulmonary disease. Maedica. 2014;9(1):25–32.
27 Vestbo J, Prescott E, Almdal T, Dahl M, Nordestgaard BG, Andersen T, et al. Body mass, fat-free body mass, and prognosis in patients with chronic obstructive pulmonary disease from a random population sample: findings from the Copenhagen City Heart Study. Am J Respir Crit Care Med. 2006;173(1):79–83.
28 Patel S, Nolan C, Barker R, Jones S, Maddocks M, George P, et al. Body composition and mortality in idiopathic pulmonary fibrosis (IPF): a prospective cohort study. Eur Respir J. 2018:PA2056.
29 Jensen B, Moritoyo T, Kaufer-Horwitz M, Peine S, Norman K, Maisch MJ, et al. Ethnic differences in fat and muscle mass and their implication for interpretation of bioelectrical impedance vector analysis. Appl Physiol Nutr Metab. 2019;44(6):619–26.
30 Cederholm T, Bosaeus I, Barazzoni R, Bauer J, Van Gossum A, Klek S, et al. Diagnostic criteria for malnutrition: an ESPEN Consensus Statement. Clin Nutr. 2015;34(3):335–40.
31 Tynan C, Hasse JM. Current nutrition practices in adult lung transplantation. Nutr Clin Pract. 2004;19(6):587–96.
32 Joppa P, Tkacova R, Franssen FM, Hanson C, Rennard SI, Silverman EK, et al. Sarcopenic obesity, functional outcomes, and systemic inflammation in patients with chronic obstructive pulmonary disease. J Am Med Dir Assoc. 2016;17(8):712–8.
33 Öztürk ZA, Türkbeyler İH, Abiyev A, Kul S, Edizer B, Yakaryılmaz FD, et al. Health-related quality of life and fall risk associated with age-related body composition changes; sarcopenia, obesity and sarcopenic obesity. Intern Med J. 2018;48(8):973–81.
34 Gonzalez M, Pastore CA, Orlandi SP, Heymsfield SB. Obesity paradox in cancer: new insights provided by body composition. Am J Clin Nutr. 2014;99(5):999–1005.
35 Jouneau S, Kerjouan M, Rousseau C, Lederlin M, Llamas-Guttierez F, De Latour B, et al. What are the best indicators to assess malnutrition in idiopathic pulmonary fibrosis patients? A cross-sectional study in a referral center. Nutrition. 2019;62:115–21.
36 Autore K, Black T, Klesen M, Richards T, Gibson K, Kaminski N, et al. Evaluating nutritional status of patients with idiopathic pulmonary fibrosis: a prospective pilot study using the mini nutrition assessment short form. A42. Interstitial Lung Dis. Epidemiol. eval. pathog. Philadelphia, Pennsylvania: American Thoracic Society; 2013. p. A1461.
37 Norman G. Biostatistics: the bare essentials. 4th ed. Shelton, Connecticut: Pmph-Usa Ltd.; 2013.
38 Tanimura K, Sato S, Sato A, Tanabe N, Hasegawa K, Uemasu K, et al. Accelerated loss of antigravity muscles is associated with mortality in patients with COPD. Respiration. 2020;99(4):298–306.