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Highlights

- Malnutrition is very frequent in idiopathic pulmonary fibrosis (IPF) patients.
- Low fat-free mass index (FFMI) assessed by bioimpedance analysis (BIA) is reported in 28% of patients.
- Body mass index (BMI) and mid-arm circumference (MAC) are independently associated with low FFMI.
- A two-step nutritional assessment based on BMI, MAC and BIA should be routinely performed in IPF patients.

What are the best indicators to assess malnutrition in idiopathic pulmonary fibrosis patients? A cross-sectional study in a referral centre

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Running title: malnutrition in idiopathic pulmonary fibrosis

ABSTRACT

Background & aims: Little is known about the indicators to assess malnutrition in patients with idiopathic pulmonary fibrosis (IPF). This study aimed to determine: i) the prevalence of malnutrition in IPF patients, ii) the nutritional indicators predictive of low fat-free mass (FFM) as measured by bioimpedance analysis; iii) the IPF patients' characteristics associated with low FFM. *Methods:* The IPF patients were consecutively recruited in a referral centre for Rare Pulmonary Diseases. Malnutrition was defined as a fat-free mass index (FFMI) = FFM (kg)/(height (m)²) <17 (men) or <15 (women). Nutritional assessment included body mass index (BMI), mid-arm circumference (MAC), triceps skinfold thickness, analogue food intake scale, and serum albumin and transthyretin. Primary endpoint: FFMI. Statistics: area under the receiver operating characteristic curve (AUC) assessed low FFMI prediction from nutritional indicators. Multivariable logistic regression: variables associated with low FFMI. *Results:* Eighty-one patients were consecutively recruited. Low FFMI prevalence was 28% (23/81). BMI AUC was 0.91 [95% CI, 0.84–0.97] and MAC AUC was 0.85 [0.76–0.94]. Multivariable analysis associated BMI (Odds ratio (OR) 0.26 [95% confidence interval (CI) 0.12 – 0.54], P=0.0003), male gender (OR 0.02 [0.00 – 0.33], P=0.005), and smoking (OR 0.10 [0.01 – 0.75], P=0.024) with a lower risk of malnutrition. *Conclusion:* Malnutrition occurred in nearly one third of IPF patients. Malnutrition screening should become systematic, based on BMI and MAC that are good clinical indicators of low FFMI. We propose a practical approach to screen malnutrition in IPF patients.

Keywords: malnutrition; lean body mass; food intake; bioelectrical impedance analysis; interstitial lung disease.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, and irreversible lung disease with a poor prognosis and a median survival after diagnosis of 3–5 years (1-3). IPF is the first aetiology of chronic idiopathic interstitial pneumonia in adults, and is associated with several comorbidities (4). Malnutrition, defined as low body mass index (BMI) or low fat-free mass (FFM) (5-8), is an independent predictor of mortality in patients with chronic obstructive pulmonary disease (COPD), another chronic, progressive, and irreversible lung disease. FFM is the nutritional indicator the best correlated with COPD patient's survival (7). Although BMI is widely used to assess nutritional status, it is an insensitive detector of impaired FFM in COPD patients (7, 9). Bioelectrical impedance analysis (BIA) is the simplest and most accurate method for assessing body composition in clinical practice (9, 11-13). Pulmonary rehabilitation improves the FFM of COPD patients (14). The prognosis for IPF patients with a low BMI (15) or low BMI plus respiratory parameters (16), and low FFM (17) is poor. However, to our knowledge, little is known regarding the nutritional assessment of IPF patients. The IPF management guidelines do not cover nutritional status assessment (2, 18) or the nutritional criteria for assessing disease stage and prognosis (2). Therefore it is needed to determine the best indicators for assessing IPF patients' nutritional status. In this cross-sectional study in consecutive IPF patients, we aim to assess the prevalence of malnutrition; to identify the most reliable clinical and biochemical nutritional indicators (BMI, weight loss, low energy intake, mid-arm circumference, triceps skinfold, serum albumin and transthyretin) for predicting low FFM diagnosed by BIA; and, using multivariate analysis, to identify the demographic, respiratory, and nutritional variables associated with low FFM. Our results should provide practical advice for detecting early stage malnutrition in IPF patients, form the basis for future prospective randomized controlled trials on IPF patient nutrition, and, at best, should contribute to elaborate nutritional recommendations in future IPF guidelines.

PATIENTS AND METHODS

Study design

This single-centre cross-sectional study used prospective data collection. Patients were recruited from several general hospitals and private physicians, and assessed at Rennes University Hospital (CHU Rennes).

Study population

The patients were recruited between May and December 2016 at a French tertiary referral centre for IPF: the Competence Centre for Rare Pulmonary Diseases ('Centre de Compétences Maladies Pulmonaires Rares'), Department of Respiratory Medicine, Rennes University Hospital (CHU Rennes), Rennes, France. We collected data from all consecutive patients with stable IPF, as defined in multidisciplinary discussions (2, 18) who had been without infection or exacerbation in the eight weeks preceding their first appointment. This study was approved by the hospital Ethic Committee (n°17.53).

Clinical and biological assessment of nutritional status

The nutritional status of all patients was assessed by a single pulmonologist physician (SJ). This initial medical consultation included assessment of weight, height, mid-arm circumference (MAC; tape measure) and triceps skinfold thickness (TSF; adipometer). Body mass index was calculated as: $\text{weight (kg)} / (\text{height (m)})^2$. Mid-arm muscular circumference (MAMC) (cm) was calculated as: $\text{MAC (cm)} - (\pi \times \text{TSF (cm)})$. Food intake was systematically assessed with the ten-point analogue visual scale of the Simplified Evaluation of Food Intake® (SEFI®), as previously described (19). Patients moved the cursor on the scale to answer the question: 'How much do you presently eat, ranging from 'nothing at all' (far left

of the scale) to ‘as usual’ (far right side of the scale)?’ Results were expressed as a number between 0 and 10. Nutritional biological parameters of all patients (serum albumin and transthyretin) and CRP were also measured.

Bioelectrical impedance analysis (BIA)

Body composition, including FFM, fat mass, total body water, extracellular and intracellular water, and 50-kHz phase angle, were measured with a multifrequency bioimpedance generator/analyser (Quadscan 4000, Bodystat Ltd, Isle of Man, UK). Briefly, patients lay supine with the palms of their hands facing inwards and areas of skin on the backs of their left hand, left wrist, left foot, and left ankle were cleaned with 70 % ethanol and four adhesive electrodes (3M Red Dot T; 3M Health Care, Borken, Germany) were placed on them. An 0.8 mA electrical current at frequencies of 5, 50, 100, and 200 kHz produced by the bioimpedance generator/analyser was used to measure whole-body resistance (R) and reactance (Xc) (11). Phase angles were calculated from: $\text{phase angle } (^{\circ}) = \arctan(Xc/R) \times (180/\pi)$. Fat-free mass index (FFMI) was calculated as: $\text{fat-free mass (kg)} / (\text{height (m)})^2$. FFMI was considered to be low if it was below 17 in men or below 15 in women, as in COPD patients (8, 20). The body fat mass index (BFMI) was calculated as: $\text{fat mass (kg)} / (\text{height (m)})^2$.

Respiratory and other data collection

Demographic (gender, age) and clinical data (disease duration, comorbidities, current drug use, tobacco use, performance of surgical lung biopsy), pulmonary function test (PFT) and six-minute walk test (6MWT) parameters, were collected from the hospital electronic medical database. Dyspnoea was assessed using the New York Health Association (NYHA) scale.

PFT and 6MWT were performed according to international guidelines (21, 22). The gender, age and physiology (GAP) index was calculated as proposed by Ley et al. (23).

Statistical analysis

Descriptive statistics are expressed as means \pm standard deviations (SD) or medians and interquartile ranges for continuous data, according to their distribution, and as the number of patients (with the percentage in parenthesis, followed immediately by the counts for the numerator/denominator) for categorical data. ROC curves were used to analyse the association of each nutritional variable with low FFM and to find the best cut-off associated with low FFM by the Youden method. ROC curves were analysed with their AUCs and 95 % confidence intervals (CIs). The discriminative power of the AUC was defined as: $0.90 \leq \text{AUC} \leq 1.0$, excellent; $0.80 \leq \text{AUC} < 0.90$, good; $0.70 \leq \text{AUC} < 0.80$, fair; $0.60 \leq \text{AUC} < 0.70$, poor; $0.50 \leq \text{AUC} < 0.60$, failure (24). We analysed the FFM with χ^2 tests (or Fisher's exact test when appropriate) for categorical data, and Student's *t*-test (or Mann-Whitney-Wilcoxon / Kruskal Wallis test when appropriate) for continuous data. Multivariable logistic regression analysis adjusted for factors with P values of <0.2 in univariate analysis was performed with backward stepwise elimination of all variables that did not contribute (P value ≥ 0.05). The adjusted Odds ratio of continuous variables was expressed for 1-point increases. Sensitivity, specificity, positive predictive value and negative predictive value, and their 95 % CIs were calculated according to the Youden method. Statistics were computed with SAS software V9.4 (SAS Institute Inc., Cary, NC, USA), and two-tailed P values of <0.05 were considered statistically significant.

RESULTS

Patients' clinical and demographics characteristics

The study included 81 patients (72 (88%) men) with IPF whose clinical characteristics are shown in **Table 1**. The mean age was 74.4 ± 8.6 years. Of these, 41 were taking antifibrotic medication at inclusion: 18 (32%) patients with nintedanib (mean duration - 597 ± 635 days; range 54 - 1765 days) and 23 (28%) with pirfenidone (mean duration - 449 ± 267 days; range 20 - 1049 days). The remaining 40 patients (49%) were either taking no antifibrotic medication because they were newly diagnosed ($n=20$ (25%)), did not tolerate or refuse antifibrotic medication, or their disease was too severe to be treated (i.e. $FVC < 50\%$ pred and/or $TLCO < 30\%$ pred).

Prevalence of malnutrition in IPF patients

In the 81 IPF patients the prevalence of malnutrition based on BIA, i.e. low FFM, was 28% (23/81) (**Table 2**). This prevalence was lower using other definitions: 4% (3/81) based on $BMI < 21$, 5% (4/81) based on MAC (< 250 mm in women and < 260 mm in men), and 9% (7/81) based on MMAC (< 190 mm in women and < 240 mm in men).

Relationship between fat-free mass and clinical and biological nutrition assessment parameters

Low FFMI was significantly associated with lower values for BMI, MAC, TSF, and hence MAMC (**Table 2**). The sensitivity, specificity, positive predictive value, and negative predictive value, defining the capacity of $BMI < 21$ for predicting low FFMI were respectively: 13%, 100%, 100%, and 74%. Lower FFMI was associated with a lower 50 kHz phase angle (25) and a higher percentage of fat mass. Patients with low FFMI were older, more frequently women, non-smokers, had a lower TLCO, and were less likely to be diagnosed using surgical lung biopsy (**Table 1**). Symptoms (dyspnoea, cough, digital clubbing) or IPF drug therapy were not associated with a low FFMI. Neither were changes in serum albumin

and serum transthyretin. The variables significantly associated with a reduced risk of low FFMI in multivariable logistic regression were BMI, male gender, and smoking. The capacity of MAC to predict low FFMI was assessed by replacing BMI with MAC in the multivariable model. Two variables were then significantly associated with less risk of low FFMI: MAC (OR 0.48 [0.32 – 0.70], $P=0.0002$), and male gender (OR 0.06 [0.01 – 0.46], $P=0.0062$). We further tested the predictive values of BMI and MAC for low FFMI. The area under the receiver operating characteristic curve assessing low fat-free mass index (FFMI) prediction by BMI was: 0.91 [95% CI, 0.84–0.97] (**Figure 1**), and the area for MAC was 0.85 [0.76–0.94] (**Figure 2**), indicating their excellent (BMI) and good (MAC) discriminative powers for low FFMI. An IPF patient with a $BMI \geq 25$ and a $MAC \geq 30$ cm was 100% likely to have a normal FFMI (**Table 4**). MAMC (AUC = 0.79, 95% CI, 0.69–0.90) and phase angle (AUC = 0.72, 0.61–0.84) were both fair predictors of FFMI loss.

Relationship between food intake, nutritional parameters, and IPF drug use

As reduced food intake is a well-known indicator of malnutrition, we assessed the factors associated with decreased food intake as indicated by the SEFI®. Patients with an SEFI® analogue score of <7 had a lower TLCO ($34.4 \pm 13.6\%$) than those with a SEFI® score ≥ 7 ($46.0 \pm 14.9\%$, $P=0.0028$), suggesting a link between decreased food intake and disease severity. Patients with a SEFI® analogue score <7 had lower values for MAC (28.3 ± 2.7 vs. 29.9 ± 2.5 cm, $P=0.01$), MAMC (26.3 ± 2.6 vs. 27.6 ± 2.3 cm, $P=0.025$), and phase angle (4.6 ± 1.0 vs. 5.2 ± 0.9 degrees, $P=0.012$) than those with a SEFI® score ≥ 7 , suggesting a more impaired nutritional status when energy intake is decreased. However, FFMI (17.7 ± 3.3 vs. 18.2 ± 2.3) and the percentage of patients with low FFMI (8/27 (30%) vs. 15/54 (28%)) were not statistically different in patients with SEFI® score <7 or ≥ 7 . Patients on pirfenidone ($6.9 \pm$

2.4) tended to report a lower SEFI® analogue score than patients on nintedanib (7.4 ± 2.7) or who were untreated (8.2 ± 2.3) ($P=0.0516$).

DISCUSSION

In this cross-sectional study, nearly one third (28%) of the IPF patients were malnourished, as defined by a low FFMI based on BIA. Decreased BMI and MAC, female gender, and never-smoking were strong predictors of low FFM. As a low FFMI has been suggested to affect IPF prognosis (17), a systematic nutritional assessment should be routinely recommended for IPF patients.

To our knowledge, this is the first study to determine, in IPF patients, if usual nutritional indicators could predict low FFMI measured by BIA. Measuring BMI with a cut-off of <21 , as recommended for COPD patients (8, 14, 20), is an insensitive method for diagnosing malnutrition, and largely underestimates the problem. It indicated that only 4% were malnourished, while a low FFMI derived from BIA diagnoses 28%, indicating that 87% of patients with low FFMI having $BMI \geq 21$ were false negatives. This poor sensitivity of $BMI < 21$ has been reported for COPD patients, for whom BIA is the most sensitive method for diagnosing malnutrition (9, 20). However, when choosing the right cut-offs, BMI is excellent, and MAC good, at predicting low FFMI. The most discriminative cut-off for BMI was 25.4 with excellent sensitivity and negative predictive value, but the specificity and positive predictive values were poor because it produced many false positives. $MAC < 295$ mm and a combination of BMI and MAC gave similar predictive profiles. We believe that these results will prove useful in daily clinical practice.

Our data indicate that malnutrition is common in IPF patients: nearly one third of them were malnourished. This is important because some studies on IPF patients suggested that a low BMI, alone (15) or combined with respiratory parameters (16), and low FFM derived from

BIA (17), are associated with a poor prognosis. But none of them assessed the prevalence of malnutrition, even based on BMI<21 or low FFMI. Alakhras *et al.* carried out a retrospective analysis of a US cohort of IPF patients and reported the relationship between BMI and mortality (15). Patients with a BMI ≥ 30 had a better survival rate than those with BMIs < 25 and 25-30. A retrospective Japanese study on 65 patients with IPF found that a one-point increase in BMI over 12 months was associated with 10% fewer deaths (16). A recent study of 44 Japanese IPF patients (17) evaluated the prognosis value of FFMI. The FFMI (hazard ratio (HR): 0.64, 95% CI: 0.43–0.94, P=0.02) and percentage predicted FVC (HR: 0.96, 95% CI: 0.93–0.99, P=0.008) were significant predictors of survival. Nutritional status was not correlated with respiratory parameters such as percentage predicted FVC, percentage predicted TLCO, or 6MWT (15, 17). We found that the percentage predicted TLCO was significantly lower in IPF patients with a low FFMI. It is now clearly needed to determine whether the prognostic prediction could be improved by combining nutritional and respiratory parameters. A low serum albumin was independently associated with increased mortality in 1269 patients with idiopathic interstitial pneumonia on the waiting list for lung transplantation in the US (26). The clinical profiles of the patients included in these studies differed from those of our patients. In Kishaba *et al.* study, most of the patients (74%) were treated with prednisone alone or prednisone plus ciclosporin (16). In Nishiyama *et al.* study, the patients had lower BMIs, only one had been diagnosed as IPF with a surgical lung biopsy, a lower TLCO, but young patients and those treated with anti-fibrotics (pirfenidone or nintedanib), or on long-term oxygen therapy were excluded (17). All those diagnosed with idiopathic interstitial pneumonia before the 2011 guidelines for IPF were published (2) had more severe disease and were eligible to lung transplant (26). Our cross-sectional study did not assess the relationship between FFMI and prognosis. A longitudinal study is needed to assess the impact of FFMI on survival according to disease severity, and therapy (oxygen supplements or anti-

fibrotic medications), in normal clinical practice. Nevertheless, the link between the loss of FFM and prognosis and illness severity emphasises the value of using BIA for managing patients with chronic diseases like IPF.

As expected, those patients with decreased FFMI were relatively old. The fact that patients diagnosed by surgical lung biopsy were less likely to have a low FFMI could be explained by their early diagnosis as they did not have to wait for there to be honeycombing on the chest CT-scan (27, 28), indicating more severe disease at the time of nutritional screening. We have no clear explanation why women and non-smokers are so likely to lose FFMI. The mechanisms underlying malnutrition in IPF patients remain unclear. As reported in COPD patients (29, 30), anorexia, insulin resistance, inflammation, and hypogonadism could all be involved. However, we found no link between food intake or C-reactive protein (CRP) concentration and FFMI. Nevertheless, the mean CRP concentration in our IPF patients (8.2 ± 12.1 mg/L) was higher than those of COPD patients (3-4 mg/L), who are known to suffer from systemic inflammation (31, 32).

We focussed specifically on antifibrotic therapy, but found no difference in the nutritional status of untreated patients and those treated with pirfenidone or nintedanib. However, patients on pirfenidone reported a slight decrease in food intake; this needs to be confirmed. BIA was chosen as the reference method for assessing FFM because it is easy to use for measuring body composition at the bedside or in outpatients (11-13), and has been well validated as an accurate measure of FFM and prognosis assessment in COPD patients (14). Our experience in this study confirmed the ease-of-use of BIA; all the measurements on all patients were obtained by a single physician (SJ) who had never used BIA before.

Finally, this study has some limitations. Weight loss was not taken into account as a nutritional parameter, because many data were missing. They were all based on patients' recall and so could be not considered as precise objective data. A longitudinal study is needed

to assess the predictive value of weight loss for assessing FFMI loss and disease prognosis.

We used the FFMI cut-off values recommended for COPD patients. Nishiyama *et al.* used the median of FFMI to split their 44 IPF patients (17). The cut-off was 16.6 kg/m² for both genders, which is quite similar to the COPD cut-offs we used: women <15 and men <17.

However, more studies are needed to determine the optimal cut-off for defining malnutrition in IPF patients.

We conclude that malnutrition (i.e. low FFMI measured by BIA) is highly prevalent (nearly one third) in IPF patients. Therefore, malnutrition screening should become systematic, based on BMI and MAC that are good clinical indicators of low FFMI. Based on these indicators sensitivity, specificity, positive predictive value, and negative predictive value (**Figures 1 and 2**, and **Table 4**), we propose a two-step assessment for malnutrition in IPF patients: 1) first step: measure BMI and MAC; if BMI ≥ 25 and MAC ≥ 300 mm, patient is likely not malnourished; if BMI <21 or MAC <295 mm, the patient is likely malnourished: dietician intervention is needed. 2) For all other situations, go to the second step: FFMI measurement by BIA: malnutrition if FFMI <15 (women) or <17 (men). Future studies should assess whether nutritional intervention targeted to FFM, e.g. pulmonary rehabilitation, could change IPF patient outcome.

Statement of authorship

All authors should have made substantial contributions: SJ and RT conceived, and designed the study, analysed, interpreted the data, and drafted the article; SJ, MK, ML, SG, and LV collected the data; CR analysed the data; BD conceived and designed the study; all authors approved the final version to be submitted.

Conflict of interest statement

Stéphane Jouneau has received fees, funding or reimbursement for national and international conferences, boards, expert or opinion groups, research projects over the past 5 years from Actelion, AIRB, Astra Zeneca, BMS, Boehringer, Chiesi, Gilead, GSK, LVL, Mundipharma, Novartis, Pfizer, Roche, Savara-Serendex. Ronan Thibault designed the Simplified Evaluation of Food Intake® (SEFI®) (Knoë, le Kremlin Bicêtre, France) tool, and received royalties.

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1 **Table 1- Clinical and demographic characteristics of patients with idiopathic pulmonary fibrosis (IPF).**

Variable	All patients (n=81)	Low FFMI (n=23)	Normal FFMI (n=58)	Odds ratio [95% confidence interval]	P value
Age (years)	74.4 ± 8.6 (42.0; 68.0; 76.0; 80.0; 89.0)	77.5 ± 6.8 (59.0; 74.0; 78.0; 83.0; 86.0)	73.1 ± 9.0 (42.0; 68.0; 75.0; 79.0; 89.0)	1.07 [1.00 – 1.15]	0.0375
Gender					
Female	10 (12.3%)	8 (34.8%)	2 (3.4%)	Reference	0.0005
Male	71 (87.7%)	15 (65.2%)	56 (96.6%)	0.07 [0.01 – 0.35]	
Smoking status					
Never	31 (38.3%)	13 (56.5%)	18 (31.0%)	Reference	0.0333
Yes	50 (61.7%)	10 (43.5%)	40 (69.0%)	0.35 [0.13 – 0.94]	
Cough					
No	25 (30.9%)	6 (26.1%)	19 (32.8%)	Reference	0.5578
Yes	56 (69.1%)	17 (73.9%)	39 (67.2%)	1.38 [0.47 – 4.07]	
Dyspnea (NYHA stages)					
I	7 (8.6%)	3 (13.0%)	4 (6.9%)	Reference	0.5224
II	16 (19.8%)	3 (13.0%)	13 (22.4%)	0.31 [0.04 – 2.17]	
III	43 (53.1%)	14 (60.9%)	29 (50.0%)	0.64 [0.13 – 3.28]	
IV	15 (18.5%)	3 (13.0%)	12 (20.7%)	0.33 [0.05 – 2.37]	
Digital clubbing					
No	53 (65.4%)	13 (56.5%)	40 (69.0%)	Reference	0.2883
Yes	28 (34.6%)	10 (43.5%)	18 (31.0%)	1.71 [0.63 – 4.62]	

Variable	All patients (n=81)	Low FFMI (n=23)	Normal FFMI (n=58)	Odds ratio [95% confidence interval]	P value
FVC (% pred)	81.4 ± 20.2 (25.0; 68.5; 82.0; 96.0; 128.0)	83.9 ± 21.1 (44.0; 68.0; 82.0; 100.0; 124.0)	80.4 ± 19.9 (25.0; 69.0; 79.0; 95.0; 128.0)	1.01 [0.98 – 1.03]	0.4886
TLCO (% pred)	42.3 ± 15.4 (14.0; 33.0; 41.0; 54.0; 72.0)	36.2 ± 13.8 (14.0; 26.0; 35.0; 39.0; 69.0)	44.6 ± 15.5 (18.0; 35.0; 43.0; 56.0; 72.0)	0.96 [0.92 – 1.00]	0.0404
GAP index	4.5 ± 1.5 (2.0; 3.0; 4.0; 5.0; 8.0)	4.7 ± 1.5 (2.0; 3.0; 5.0; 6.0; 7.0)	4.5 ± 1.5 (2.0; 3.0; 4.0; 5.0; 8.0)	1.10 [0.80 – 1.53]	0.4753
GAP class					
1	24 (29.6%)	7 (30.4%)	17 (29.3%)	Reference	0.1756
2	39 (48.1%)	8 (34.8%)	31 (53.4%)	0.63 [0.19 – 2.03]	
3	18 (22.2%)	8 (34.8%)	10 (17.2%)	1.94 [0.54 – 6.99]	
Time since diagnosis (days)	626.4 ± 796.1 (2.0 ; 119.0 ; 376.0 ; 712.0; 3967.0)	765.3 ± 1022.9 (23.0 ; 191.0 ; 499.0 ; 778.0 ; 3967.0)	571.3 ± 689.0 (2.0 ; 74.0 ; 354.0 ; 703.0 ; 2945.0)	1.00 [1.00 – 1.00]	0.2646
Surgical lung biopsy: No	61 (75.3%)	21 (91.3%)	40 (69.0%)	Reference	
Yes	20 (24.7%)	2 (8.7%)	18 (31.0%)	0.21 [0.04 – 1.00]	0.0355
Cancer					
No	73 (90.1%)	21 (91.3%)	52 (89.7%)	Reference	
Yes	8 (9.9%)	2 (8.7%)	6 (10.3%)	0.83 [0.15 – 4.42]	1.0

Variable	All patients (n=81)	Low FFMI (n=23)	Normal FFMI (n=58)	Odds ratio [95% confidence interval]	P value
Cardiovascular comorbidities*					
No	28 (34.6%)	9 (39.1%)	19 (32.8%)	0.76 [0.28 – 2.06]	0.5866
Yes	53 (65.4%)	14 (60.9%)	39 (67.2%)		
IPF drug					
Nintedanib	18 (22.2%)	3 (13.0%)	15 (25.9%)	0.47 [0.11 – 1.92]	0.4211
Pirfenidone	23 (28.4%)	8 (34.8%)	15 (25.9%)	1.24 [0.42 – 3.71]	
None	40 (49.4%)	12 (52.2%)	28 (48.3%)	Reference	

2 Qualitative variables: number (%). Quantitative variables: mean \pm standard deviation (min; Q1; median ; Q3; max). FFMI, fat-free mass index;

3 FVC, forced vital capacity; GAP index, the gender, age and physiology index; TLCO, carbon monoxide diffusion; % pred; percentage of

4 predicted values. Missing data: FVC, n=1; TLCO, n=12.

5 *Cardiovascular comorbidities included high blood pressure, history of stroke, myocardial infarction, atherosclerosis, etc...

6

7 Table 2- Nutritional assessment of patients with idiopathic pulmonary fibrosis (IPF) (n=81).

Variable	All patients (n=81)	Low FFMI (n=23)	Normal FFMI (n=58)	Odds ratio [95% confidence interval]	P value
Clinical parameters					
Weight (kg)	73.5 ± 11.4 (41.6 ; 64.0 ; 73.0 ; 82.0 ; 95.0)	60.7 ± 6.5 (41.6 ; 57.4 ; 61.0 ; 65.0 ; 72.0)	78.6 ± 8.6 (61.0 ; 73.0 ; 77.0 ; 86.0 ; 95.0)	0.69 [0.58 – 0.82]	<0.0001
Body mass index	26.3 ± 3.3 (17.3 ; 23.9 ; 26.0 ; 29.0 ; 35.3)	23.2 ± 2.0 (17.3 ; 21.9 ; 23.5 ; 24.5 ; 27.2)	27.6 ± 2.9 (22.2 ; 25.7 ; 27.5 ; 29.7 ; 35.3)	0.42 [0.27 – 0.64]	<0.0001
Body mass index < 21					
No	78 (96.3%)	20 (87.0%)	58 (100.0%)	Reference	
Yes	3 (3.7%)	3 (13.0%)	0 (0.0%)	19.98 [0.63 – 635.32]	0.0208
SEFI® score	7.7 ± 2.5 (1.0 ; 5.1 ; 8.6 ; 10.0 ; 10.0)	7.8 ± 2.8 (1.0 ; 5.0 ; 9.5 ; 10.0 ; 10.0)	7.6 ± 2.4 (2.5 ; 5.1 ; 8.0 ; 10.0 ; 10.0)	1.03 [0.85 – 1.26]	0.4560
SEFI® score < 7					
No	54 (66.7%)	15 (65.2%)	39 (67.2%)	Reference	
Yes	27 (33.3%)	8 (34.8%)	19 (32.8%)	1.09 [0.40 – 3.03]	0.8617
Mid-arm circumference (cm)	29.4 ± 2.7 (21.0 ; 27.5 ; 29.0 ; 31.0 ; 35.0)	27.2 ± 2.0 (21.0 ; 26.0 ; 27.0 ; 28.5 ; 31.0)	30.3 ± 2.4 (24.5 ; 29.0 ; 30.0 ; 32.0 ; 35.0)	0.50 [0.35 – 0.70]	<0.0001
TSF (mm)	7.1 ± 2.3	5.9 ± 2.0	7.6 ± 2.2	0.66 [0.51 – 0.87]	0.0017

Variable	All patients (n=81)	Low FFMI (n=23)	Normal FFMI (n=58)	Odds ratio [95% confidence interval]	P value
	(3.0 ; 5.0 ; 7.0 ; 8.0 ; 14.0)	(3.0 ; 4.0 ; 6.0 ; 7.0 ; 10.0)	(4.0 ; 6.0 ; 8.0 ; 9.0 ; 14.0)		
MAMC (mm)	271.5 ± 24.8 (197.4 ; 256.2 ; 270.6 ; 292.3 ; 328.0)	253.1 ± 21.4 (197.4 ; 238.6 ; 249.3 ; 269.3 ; 300.6)	278.8 ± 22.2 (226.2 ; 264.9 ; 279.6 ; 294.3 ; 328.0)	0.95 [0.92 – 0.97]	<0.0001
Bioimpedance analysis					
Resistance 50 kHz	510.3 ± 89.6 (380.0 ; 452.0 ; 493.0 ; 542.0 ; 937.0)	597.7 ± 99.9 (484.0 ; 539.0 ; 572.0 ; 635.0 ; 937.0)	475.7 ± 55.8 (380.0 ; 446.0 ; 468.0 ; 502.0 ; 688.0)	1.03 [1.01 – 1.04]	<0.0001
Reactance 50 kHz	44.2 ± 9.0 (20.0 ; 39.0 ; 44.4 ; 50.6 ; 79.0)	46.4 ± 6.7 (33.8 ; 40.8 ; 46.2 ; 52.0 ; 57.4)	43.3 ± 9.6 (20.0 ; 37.5 ; 43.3 ; 50.0 ; 79.0)	1.04 [0.98 – 1.10]	0.1632
50 kHz phase angle	5.0 ± 1.0 (2.8 ; 4.3 ; 5.0 ; 5.6 ; 8.9)	4.5 ± 0.8 (3.2 ; 3.9 ; 4.7 ; 5.1 ; 5.7)	5.2 ± 1.0 (2.8 ; 4.4 ; 5.3 ; 5.8 ; 8.9)	0.41 [0.22 – 0.76]	0.0033
Fat-free mass (%)	68.5 ± 6.4 (49.4 ; 66.2 ; 69.6 ; 72.7 ; 81.6)	64.1 ± 7.8 (49.4 ; 55.7 ; 67.3 ; 70.5 ; 74.1)	70.3 ± 4.7 (59.8 ; 67.3 ; 69.9 ; 73.3 ; 81.6)	0.84 [0.77 – 0.93]	0.0019
Fat-free mass (kg)	50.7 ± 9.9 (21.1 ; 45.0 ; 52.3 ; 57.8 ; 66.5)	39.2 ± 7.4 (21.1 ; 33.0 ; 41.3 ; 45.2 ; 50.0)	55.2 ± 6.5 (36.7 ; 51.5 ; 54.5 ; 60.1 ; 66.5)	0.70 [0.59 – 0.83]	<0.0001

Variable	All patients (n=81)	Low FFMI (n=23)	Normal FFMI (n=58)	Odds ratio [95% confidence interval]	P value
Fat (%)	31.5 ± 6.4 (18.4 ; 27.3 ; 30.4 ; ; 33.8 ; 50.6)	35.9 ± 7.8 (25.9 ; 29.5 ; 32.7 ; ; 44.3 ; 50.6)	29.7 ± 4.7 (18.4 ; 26.7 ; 30.1 ; 32.7 ; 40.2)	1.19 [1.08 – 1.31]	0.0013
Fat mass (kg)	22.8 ± 4.6 (14.2 ; 19.4 ; 23.1 ; ; 26.5 ; 34.2)	21.5 ± 4.3 (14.9 ; 18.4 ; 21.2 ; ; 23.8 ; 31.4)	23.4 ± 4.7 (14.2 ; 19.9 ; 23.7 ; 26.6 ; 34.2)	0.91 [0.81 – 1.02]	0.0909
Fat mass index	8.3 ± 2.0 (4.3 ; 7.0 ; 8.1 ; 9.6 ; 13.8)	8.3 ± 2.2 (5.2 ; 6.9 ; 7.6 ; 9.8 ; 13.8)	8.3 ± 1.9 (4.3 ; 7.0 ; 8.3 ; 9.6 ; 13.7)	1.00 [0.79 – 1.28]	0.9708
Total body water (%)	55.7 ± 4.9 (45.2 ; 51.8 ; 55.6 ; ; 58.8 ; 66.7)	55.9 ± 6.0 (45.2 ; 51.6 ; 56.1 ; ; 59.4 ; 66.7)	55.6 ± 4.4 (47.1 ; 51.8 ; 55.3 ; 58.6 ; 65.9)	1.01 [0.92 – 1.12]	0.8033
Extracellular water (%)	24.3 ± 2.1 (20.3 ; 23.0 ; 24.1 ; ; 25.2 ; 33.2)	24.9 ± 1.8 (22.0 ; 23.6 ; 24.7 ; ; 26.3 ; 28.4)	24.0 ± 2.2 (20.3 ; 22.5 ; 23.7 ; 25.0 ; 33.2)	1.24 [0.97 – 1.57]	0.0706
Intracellular water (%)	30.7 ± 3.0 (18.6 ; 29.5 ; 31.3 ; ; 32.7 ; 36.1)	30.2 ± 4.1 (23.9 ; 25.9 ; 31.4 ; ; 33.5 ; 35.9)	30.9 ± 2.5 (18.6 ; 29.7 ; 31.2 ; 32.7 ; 36.1)	0.93 [0.79 – 1.08]	0.4389
Body cell mass (kg)	32.3 ± 5.5 (14.8 ; 29.9 ; 33.6 ; ; 36.1 ; 41.8)	26.3 ± 4.8 (14.8 ; 21.2 ; 28.7 ; ; 30.1 ; 32.2)	34.7 ± 3.7 (19.9 ; 33.1 ; 34.9 ; 37.1 ; 41.8)	0.63 [0.51 – 0.78]	<0.0001

Biological parameters

Variable	All patients (n=81)	Low FFMI (n=23)	Normal FFMI (n=58)	Odds ratio [95% confidence interval]	P value
Serum albumin	41.9 ± 3.0 (35.8 ; 39.9 ; 42.3 ; 43.9 ; 47.6)	41.8 ± 3.1 (35.8 ; 40.2 ; 42.4 ; 44.3 ; 46.5)	42.0 ± 3.0 (35.9 ; 39.8 ; 42.3 ; 43.8 ; 47.6)	0.98 [0.84 – 1.15]	0.8099
Serum transthyretin	0.3 ± 0.1 (0.1 ; 0.2 ; 0.2 ; 0.3 ; 0.4)	0.3 ± 0.1 (0.1 ; 0.2 ; 0.2 ; 0.3 ; 0.4)	0.3 ± 0.1 (0.1 ; 0.2 ; 0.3 ; 0.3 ; 0.4)	1.02 [0.40 – 2.61]	0.9749
C reactive protein	8.2 ± 12.1 (1.0 ; 1.7 ; 3.6 ; 8.7 ; 61.6)	7.1 ± 10.1 (1.0 ; 1.5 ; 2.5 ; 8.8 ; 38.7)	8.6 ± 12.8 (1.0 ; 1.8 ; 4.4 ; 8.7 ; 61.6)	0.99 [0.95 – 1.03]	0.3563

8 Qualitative variables: number (%). Quantitative variables: mean ± standard deviation (min; Q1; median ; Q3; max). FFMI, fat-free mass index ;
9 MAMC, mid-arm muscular circumference; SEFI®, Simplified Evaluation of Food Intake®; TSF, triceps skinfold thickness. Missing data: serum
10 transthyretin, n=3.

Table 3– Logistic regression multivariable analysis of factors associated with malnutrition, defined by low fat-free mass index (n = 81). The Odds ratio for continuous variables (body mass index) is given for 1-point increases.

Variables	Odds Ratio [95% confidence interval]	P value
Body mass index	0.26 [0.12 – 0.54]	0.0003
Male gender	0.02 [0.00 – 0.33]	0.0055
Tobacco use	0.10 [0.01 – 0.75]	0.0243

Fat-free mass index was calculated as: fat-free mass (kg)/(height (m)²); below 17 was considered to be low or impaired for men and below 15 for women, as for COPD patients (8, 20).

Table 4- Value of body mass index (BMI) and mid-arm circumference (MAC) for predicting low fat-free mass index (FFMI) in idiopathic pulmonary fibrosis (IPF) patients (n=81).

Variable	Low FFMI	Normal FFMI	Patients (n)
BMI < 25 and/or MAC < 30	23	25	48
BMI ≥ 25 and MAC ≥ 30	0	33	33
Patients (n)	23	58	81

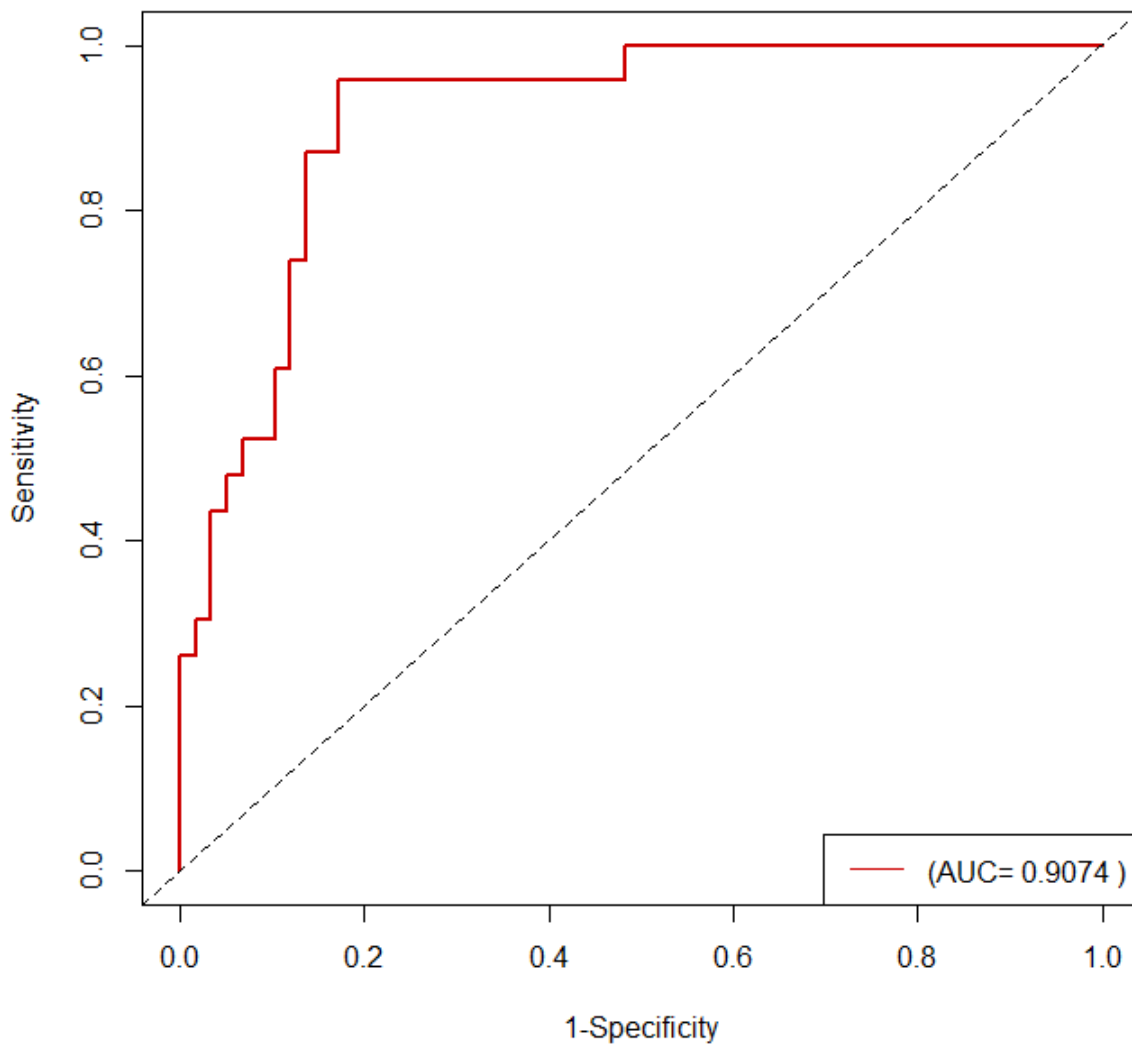
Fat-free mass index (FFMI) was determined by bioimpedance analysis, calculated as: fat-free mass (kg)/(height (m)²), and considered to be low or impaired (< 17 in men) and (<15 in women) as for COPD patients (8, 20). Sensitivity was 100 % for a BMI < 25 and/or CMB < 30, (23/23; 95 % confidence interval (CI) 88-100%), while specificity was 57 % (33/58; 95 % CI 43–70 %), positive predictive value was 48 % (23/48; 95 % CI 33–63 %) and the negative predictive value was 100 % (33/33; 95 % CI 91–100 %). The BMI and MAC cutoffs associated with low FFMI were assessed by the Youden method.

Figure legends

Figure 1- Area under the receiver operating characteristic curve (AUC) assessing body mass index (BMI) prediction of a low fat-free mass index (FFMI) (n=81). FFMI was determined by bioelectrical impedance analysis, and calculated as: fat-free mass (kg)/(height (m)²). FFMI was considered low when it was <17 in men or <15 in women (8, 20). A low BMI was associated with a lower fat-free mass index. AUC=0.91 [95% confidence interval (CI), 0.84–0.97]. The sensitivity, specificity, positive and negative predictive values for a BMI <25.4 were: 96%, 22/23, [95% CI, 78–100], 79%, 46/58, [67–89], 65%, 22/34, [47–80], and 98%, 46/47, [89–100]. The BMI cut-off associated with low FFMI was assessed by the Youden method.

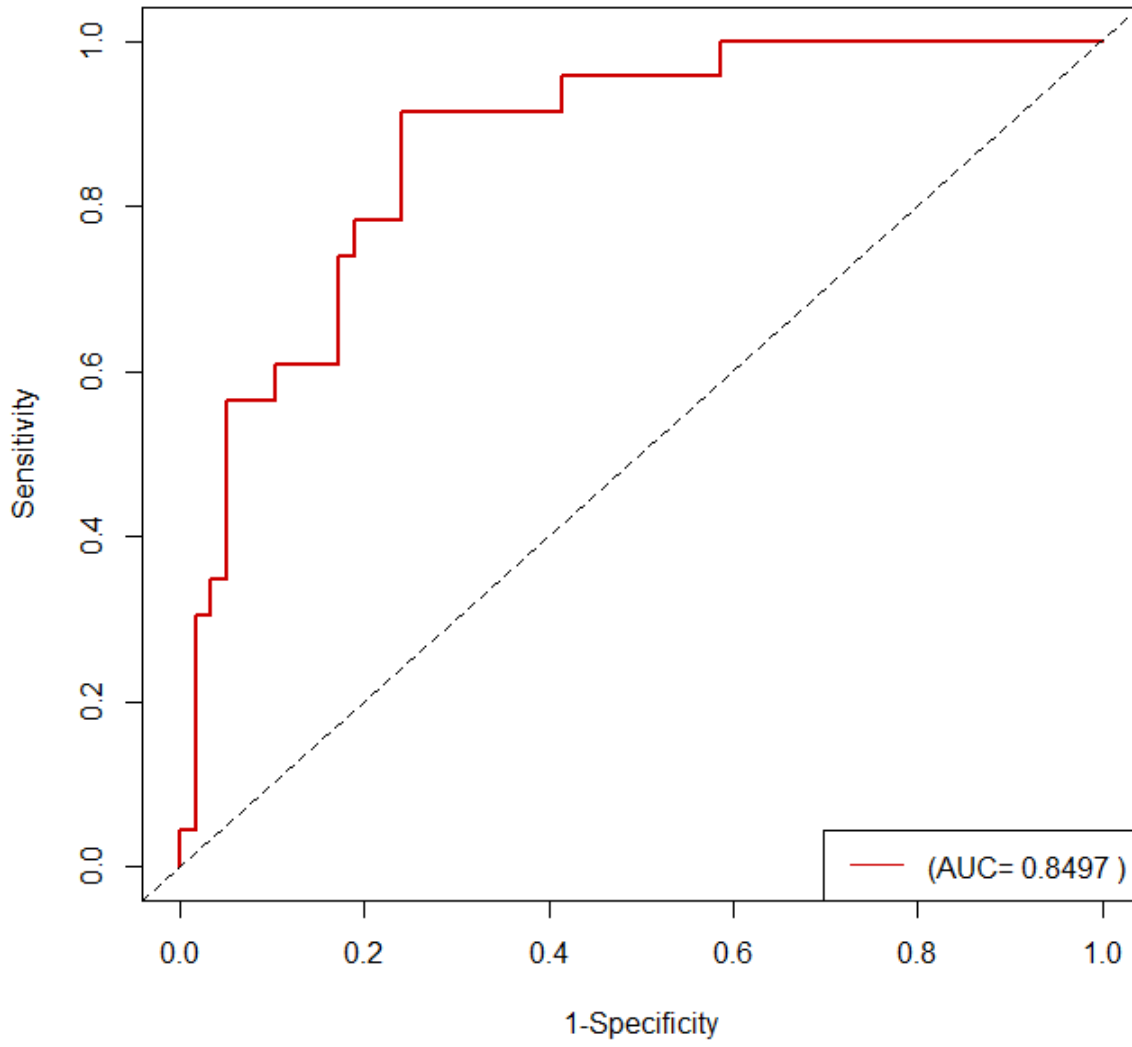
Figure 2- Area under the receiver operating characteristic curve (AUC) assessing mid-arm circumference (MAC) predictions of a low fat-free mass index (FFMI) (n=81). FFMI was determined by bioelectrical impedance analysis (fat-free mass (kg)/(height (m)²). FFMI was considered to be low if it was <17 in men or <15 in women (8, 20). A low MAC was associated with a low fat-free mass index. AUC=0.85 [95% confidence interval (CI), 0.76–0.94]. The sensitivity, specificity, positive and negative predictive values of a MAC <295 mm were: 91%, 21/23, [95% CI, 72–99], 66%, 38/58, [52–78], 51%, 21/41, [35–67], and 95%, 38/40, [83–99]. The MAC cut-off associated with a low FFMI was assessed by the Youden method.

Figure 1



ACCEI

Figure 2



ACCEI