



Contents lists available at ScienceDirect

## Nutrition

journal homepage: [www.nutritionjrn.com](http://www.nutritionjrn.com)

## Applied nutritional investigation

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



Stéphane Jouneau M.D., Ph.D.<sup>a,b</sup>, Mallorie Kerjouan M.D.<sup>a</sup>, Chloé Rousseau M.Sc.<sup>c</sup>,  
 Mathieu Lederlin M.D., Ph.D.<sup>d,e</sup>, Francisco Llamas-Gutierrez M.D.<sup>f</sup>, Bertrand De Latour M.D.<sup>g</sup>,  
 Stéphanie Guillot M.D.<sup>h</sup>, Laurent Vernhet Ph.D., Pharm.D.<sup>b</sup>, Benoit Desrues M.D., Ph.D.<sup>a,i</sup>,  
 Ronan Thibault M.D., Ph.D.<sup>j,k,\*</sup>

<sup>a</sup> Department of Respiratory Medicine, Competence Centre for Rare Pulmonary Diseases, CHU Rennes, Univ Rennes, Rennes, France

<sup>b</sup> IRSET, Research Institute for Environmental and Occupational Health UMR1085, Univ Rennes, Rennes, France

<sup>c</sup> Centre d'Investigation clinique, INSERM 1414, CHU Rennes, Rennes University Hospital, Rennes, France

<sup>d</sup> Department of Radiology, CHU Rennes, Rennes University Hospital, Rennes, France

<sup>e</sup> LTSI, INSERM U1099, Rennes University Hospital, Rennes, France

<sup>f</sup> Department of Histopathology, CHU Rennes, Rennes University Hospital, Rennes, France

<sup>g</sup> Department of Thoracic Surgery, CHU Rennes, Rennes University Hospital, Rennes, France

<sup>h</sup> Department of Pulmonary Function Testing, CHU Rennes, Rennes University Hospital, Rennes, France

<sup>i</sup> Chemistry, Oncogenesis and Stress Signalling, INSERM U1242, Centre Eugène Marquis, Rennes, France

<sup>j</sup> Unité de Nutrition, CHU Rennes, Rennes University Hospital, Rennes, France

<sup>k</sup> INRA, INSERM, Univ Rennes, Nutrition Metabolisms and Cancer, NuMeCan, Rennes, France

## ARTICLE INFO

## Article History:

Received 31 March 2018

Received in revised form 15 July 2018

Accepted 15 December 2018

## Keywords:

Malnutrition

Lean body mass

Food intake

Bioelectrical impedance analysis

Interstitial lung disease

## ABSTRACT

**Objectives:** Little is known about the indicators to assess malnutrition in patients with idiopathic pulmonary fibrosis (IPF). This study aimed to determine the following: 1) the prevalence of malnutrition in IPF patients; 2) the nutritional indicators predictive of low fat-free mass (FFM) as measured by bioimpedance analysis; 3) the IPF patients' characteristics associated with low FFM.

**Methods:** The IPF patients were consecutively recruited in a referral center for rare pulmonary diseases. Malnutrition was defined as a fat-free mass index (FFMI) = FFM (kg) / (height [m]<sup>2</sup>) <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. The primary endpoint was FFMI. Area under the receiver operating characteristic curve (AUC) assessed low FFMI prediction from nutritional indicators. Multivariable logistic regression determined variables associated with low FFMI.

**Results:** Eighty-one patients were consecutively recruited. Low FFMI prevalence was 28% (23 of 81). BMI AUC was 0.91 (95% confidence interval [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% CI, 0.12–0.54],  $P=0.0003$ ), male sex (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.

**Conclusions:** Malnutrition occurred in nearly one-third of IPF patients. Malnutrition screening should become systematic based on BMI and MAC, which are good clinical indicators of low FFMI. We propose a practical approach to screen malnutrition in IPF patients.

© 2018 Elsevier Inc. All rights reserved.

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

\* Corresponding author. Tel.: +33 2 99 28 96 46; Fax: +33 2 99 28 24 34.

E-mail address: [ronan.thibault@chu-rennes.fr](mailto:ronan.thibault@chu-rennes.fr) (R. Thibault).

## 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 to 5 y [1–3]. IPF is the leading cause 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 that 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 [9,10–12]. Pulmonary rehabilitation improves the FFM of COPD patients [13]. The prognosis for IPF patients with a low BMI [14] or low BMI plus respiratory parameters [15] and low FFM [16] 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 [2,17] 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 aimed 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, contribute to elaborate nutritional recommendations in future IPF guidelines.

## Materials and methods

### Study design

This single-center 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 center for IPF: the Competence Centre for Rare Pulmonary Diseases (Centre de Compétences Maladies Pulmonaires Rares) in the Department of Respiratory Medicine at Rennes University Hospital (CHU Rennes) in Rennes, France. We collected data from all consecutive patients with stable IPF, as defined in multidisciplinary discussions [2,17], who had been without infection or exacerbation in the 8 wk preceding their first appointment. This study was approved by the hospital ethics committee (no. 17.53).

### Clinical and biological assessment of nutritional status

The nutritional status of all patients was assessed by a single pulmonologist physician (S.J.). 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 weight (kg) / (height [m]<sup>2</sup>). Mid-arm muscular circumference (MAMC) (cm) was calculated as: MAC (cm) – ( $\pi \times$  TSF [cm]). Food intake was systematically assessed with the 10-point analog visual scale of the Simplified Evaluation of Food Intake (SEFI), as previously described [18]. 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 C-reactive protein (CRP) were also measured.

### Bioelectrical impedance analysis

Body composition, including FFM, fat mass, total body water, extracellular and intracellular water, and 50 kHz phase angle, were measured with a multi-frequency bioimpedance generator/analyzer (Quadscan 4000, Bodystat Ltd, Isle of Man, UK). Briefly, patients lay supine with the palms of their hands facing inward; 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 or analyzer was used to measure whole-body resistance (R) and reactance (Xc) [10]. Phase angles were calculated from: phase angle (°) =  $\arctan(Xc/R) \times (180/\pi)$ . Fat-free mass index (FFMI) was calculated as fat-free mass (kg) / (height [m]<sup>2</sup>). FFMI was considered to be low if it was <17 in men or <15 in women, as in COPD patients [8,19]. The body fat mass index (BFMI) was calculated as fat mass (kg) / (height [m]<sup>2</sup>).

### Respiratory and other data collection

Demographic (sex, age) and clinical data (disease duration, comorbidities, current drug use, tobacco use, performance of surgical lung biopsy) and pulmonary function test (PFT) and 6-min walk test (6MWT) parameters were collected from the hospital electronic medical database. Dyspnea was assessed using the New York Health Association scale. PFT and 6MWT were performed according to international guidelines [20,21]. The sex, age, and physiology (GAP) index was calculated as proposed by Ley et al. [22].

### Statistical analysis

Descriptive statistics are expressed as means  $\pm$  SD or median and interquartile range 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 and denominator) for categorical data. Receiver operative characteristic curves were used to analyze the association of each nutritional variable with low FFM and to find the best cutoff associated with low FFM by the Youden method. Receiver operative characteristic curves were analyzed with their AUCs and 95% confidence intervals (CIs). The discriminative power of the AUC was defined as 0.90  $\leq$  AUC  $\leq$  1.0, excellent; 0.80  $\leq$  AUC < 0.90, good; 0.70  $\leq$  AUC < 0.80, fair; 0.60  $\leq$  AUC < 0.70, poor; 0.50  $\leq$  AUC < 0.60, failure [23]. We analyzed the FFM with  $\chi^2$  tests (or Fisher 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*  $\geq$  0.05). The adjusted OR 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 version 9.4 (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  $\pm$  8.6 y. Of these, 41 were taking antifibrotic medication at inclusion: 18 patients (32%) with nintedanib (mean duration 597  $\pm$  635 d; range 54–1765 d) and 23 (28%) with pirfenidone (mean duration 449  $\pm$  267 d; range 20–1049 d). The remaining 40 patients (49%) were taking no antifibrotic medication either because they were newly diagnosed (*n* = 20 [25%]), they did not tolerate or refuse antifibrotic medication, or their disease was too severe to be treated (i.e., forced vital capacity [FVC] < 50% of predicted value [pred] or carbon monoxide diffusion [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 of 81) (Table 2). This prevalence was lower using other definitions: 4% (3 of 81) based on BMI < 21, 5% (4 of 81) based on MAC (<250 mm in women and <260 mm in men), and 9% (7 of 81) based on MAMC (<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,

**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% CI)	P
Age (y)	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
Sex					
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)	
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 (d)	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
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	

CI, confidence interval; FFMI, fat-free mass index; FVC, forced vital capacity; GAP index, the gender, age and physiology index; max, maximum; min, minimum; NYHA, New York Heart Association; TLCO, carbon monoxide diffusion; % pred; percentage of predicted values.

Qualitative variables: number (%).

Quantitative variables: mean ± SD (min; Q1; median; Q3; max).

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

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

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

Variable	All patients ( <i>n</i> = 81)	Low FFMI ( <i>n</i> = 23)	Normal FFMI ( <i>n</i> = 58)	Odds ratio (95% CI)	<i>P</i>
<b>Clinical parameters</b>					
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				Reference	
No	78 (96.3%)	20 (87.0%)	58 (100.0%)		
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				Reference	
No	54 (66.7%)	15 (65.2%)	39 (67.2%)		
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 (3.0, 5.0, 7.0, 8.0, 14.0)	5.9 ± 2.0 (3.0, 4.0, 6.0, 7.0, 10.0)	7.6 ± 2.2 (4.0, 6.0, 8.0, 9.0, 14.0)	0.66 (0.51–0.87)	0.0017
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
<b>Bioimpedance analysis</b>					
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
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
<b>Biological parameters</b>					
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

CI, confidence interval; FFMI, fat-free mass index; MAMC, mid-arm muscular circumference; max, maximum; min, minimum; SEFI, Simplified Evaluation of Food Intake; TSF, triceps skinfold thickness.

Qualitative variables: number (%).

Quantitative variables: mean ± SD (min; Q1; median; Q3; max).

Missing data: serum transthyretin, *n* = 3.

**Table 3**

Logistic regression multivariable analysis of factors associated with malnutrition, defined by low fat-free mass index ( $n = 81$ )

Variables	Odds ratio (95% CI)	P
Body mass index	0.26 (0.12–0.54)	0.0003
Male sex	0.02 (0.00–0.33)	0.0055
Tobacco use	0.10 (0.01–0.75)	0.0243

CI, confidence interval; COPD, chronic obstructive pulmonary disease.

The odds ratio for continuous variables (body mass index) is given for 1-point increases.

Fat-free mass index was calculated as fat-free mass (kg) / (height [m]<sup>2</sup>); <17 was considered to be low or impaired for men and <15 for women, as for COPD patients [8,19].

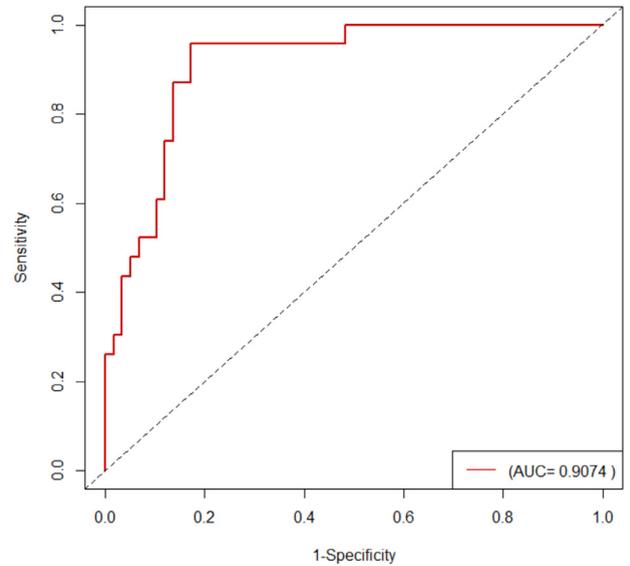
positive predictive value, and negative predictive value, defining the capacity of BMI < 21 for predicting low FFMI, were, respectively, 13%, 100%, 100%, and 74%. Lower FFMI was associated with a lower 50 kHz phase angle [24] and a higher percentage of fat mass. Patients with low FFMI were older, more often women, non-smokers, had a lower TLCO, and were less likely to be diagnosed using surgical lung biopsy (Table 1). Symptoms (dyspnea, cough, digital clubbing) and IPF drug therapy were not associated with a low FFMI. Neither were changes in serum albumin and serum trans-thyretin. The variables significantly associated with a reduced risk of low FFMI in multivariable logistic regression were BMI, male sex, and smoking (Table 3). 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 sex (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 FFMI prediction by BMI was 0.91 (95% CI, 0.84–0.97) (Fig. 1), and the area for MAC was 0.85 (0.76–0.94) (Fig. 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; 95% CI, 0.61–0.84) were both fair predictors of FFMI loss.

#### Relationship among food intake, nutritional parameters, and IPF drug use

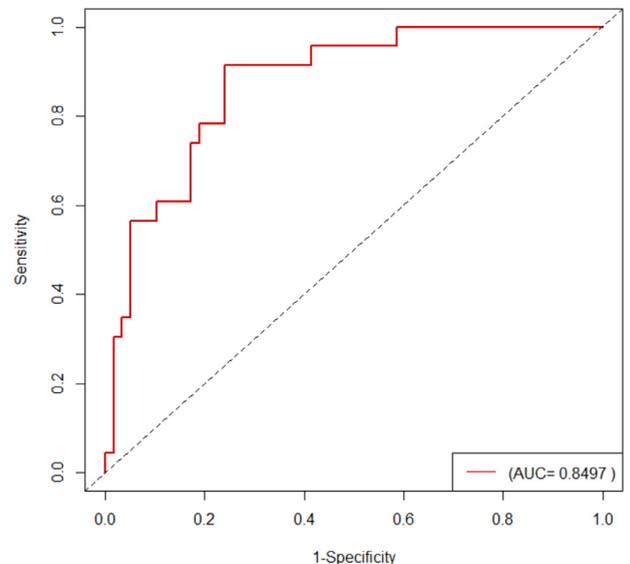
Because reduced food intake is a well-known indicator of malnutrition, we assessed the factors associated with decreased food intake as indicated by the SEFI. Patients with a SEFI score <7 had a lower TLCO ( $34.4\% \pm 13.6$ ) than those with a SEFI score  $\geq 7$  ( $46.0\% \pm 14.9$ ,  $P = 0.0028$ ), suggesting a link between decreased food intake and disease severity. Patients with a SEFI analogue score <7 had lower values for MAC ( $28.3 \pm 2.7$  versus  $29.9 \pm 2.5$  cm,  $P = 0.01$ ), MAMC ( $26.3 \pm 2.6$  versus  $27.6 \pm 2.3$  cm,  $P = 0.025$ ), and phase angle ( $4.6 \pm 1.0$  versus  $5.2 \pm 0.9$  degrees,  $P = 0.012$ ) than those with a SEFI score  $\geq 7$ , suggesting a more impaired nutritional status when energy intake is decreased. However, FFMI ( $17.7 \pm 3.3$  versus  $18.2 \pm 2.3$ ) and the percentage of patients with low FFMI (8 of 27 [30%] versus 15 of 54 [28%]) were not statistically different in patients with SEFI score <7 or  $\geq 7$ . Patients on pirfenidone ( $6.9 \pm 2.4$ ) tended to report a lower SEFI analogue score than patients on nintedanib ( $7.4 \pm 2.7$ ) or who were untreated ( $8.2 \pm 2.3$ ) ( $P = 0.0516$ ).

#### Discussion

In this cross-sectional study, nearly one-third (28%) of the IPF patients were malnourished, as defined by a low FFMI based on



**Fig. 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]<sup>2</sup>). FFMI was considered low when it was <17 in men or <15 in women [8,19]. 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, and positive and negative predictive values for a BMI < 25.4 were 96%, 22 out of 23 (95% CI, 78–100); 79%, 46 out of 58 (95% CI, 67–89); 65%, 22 out of 34 (95% CI, 47–80); and 98%, 46 out of 47 (95% CI, 89–100). The BMI cutoff associated with low FFMI was assessed by the Youden method.



**Fig. 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]<sup>2</sup>)). FFMI was considered to be low if it was <17 in men or <15 in women [8,19]. 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, and positive and negative predictive values of a MAC < 295 mm were 91%, 21 out of 23 (95% CI, 72–99); 66%, 38 out of 58 (95% CI, 52–78); 51%, 21 out of 41 (95% CI, 35–67); and 95%, 38 out of 40 (95% CI, 83–99). The MAC cutoff associated with a low FFMI was assessed by the Youden method.

BIA. Decreased BMI and MAC, female sex, and never smoking were strong predictors of low FFM. Because a low FFMI has been suggested to affect IPF prognosis [16], a systematic nutritional assessment should be routinely recommended for IPF patients.

**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
<b>Patients (n)</b>	<b>23</b>	<b>58</b>	<b>81</b>

CI, confidence interval; COPD, chronic obstructive pulmonary disease.

Fat-free mass index (FFMI) was determined by bioimpedance analysis, calculated as fat-free mass (kg) / (height [m]<sup>2</sup>), and considered to be low or impaired (<17 in men and <15 in women), as for COPD patients [8,19].

Sensitivity was 100% for a BMI < 25 or MAC < 30, (23 of 23; 95% CI 88–100); specificity was 57% (33 of 58; 95% CI 43–70), positive predictive value was 48% (23 of 48; 95% CI 33–63), and negative predictive value was 100% (33 of 33; 95% CI 91–100). The BMI and MAC cutoffs associated with low FFMI were assessed by the Youden method.

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 cutoff of <21, as recommended for COPD patients [8,13,19], is an insensitive method for diagnosing malnutrition and largely underestimates the problem. Indeed, it indicated that only 4% were malnourished, whereas 28% of patients were diagnosed as malnourished by measuring FFMI by BIA, indicating that 87% of patients with low FFMI having BMI ≥ 21 were false négatives. This poor sensitivity of BMI < 21 has been reported for COPD patients, for whom BIA is the most sensitive method for diagnosing malnutrition [9,19]. However, when choosing the right cutoffs, BMI is excellent and MAC good at predicting low FFMI. The most discriminative cutoff 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 [14] or combined with respiratory parameters [15], and low FFM derived from BIA [16] 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. [14] carried out a retrospective analysis of a US cohort of IPF patients and reported the relationship between BMI and mortality. Patients with a BMI ≥ 30 had a better survival rate than those with BMIs < 25 and 25 to 30. A retrospective Japanese study on 65 patients with IPF found that a 1-point increase in BMI over 12 mo was associated with 10% fewer deaths [15]. A recent study of 44 Japanese IPF patients [16] evaluated the prognosis value of FFMI. The FFMI (hazard ratio, 0.64; 95% CI, 0.43–0.94; *P* = 0.02) and percentage predicted FVC (hazard ratio, 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 [14,16]. We found that the percentage predicted TLCO was significantly lower in IPF patients with a low FFMI. It is now clearly necessary 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 United States [25]. The clinical profiles of the patients included in these studies differed from those of our patients. In the study by Kishaba et al. [15], most of the patients (74%) were treated with prednisone alone or prednisone plus

ciclosporin. In the study by Nishiyama et al. [16], the patients had lower BMI and TLCO, and only one patient has been diagnosed as IPF with a surgical lung biopsy [16]. In addition, young patients and those treated with antifibrotics (pirfenidone or nintedanib) or on long-term oxygen therapy were excluded [16]. All those diagnosed with idiopathic interstitial pneumonia before the 2011 guidelines for IPF were published [2] had more severe disease and were eligible for lung transplant [25]. 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 antifibrotic medications), in normal clinical practice. Nevertheless, the link between the loss of FFM and prognosis and illness severity emphasizes 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 because they did not have to wait for there to be honeycombing on the chest computed tomography scan [26,27], 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 [28,29], anorexia, insulin resistance, inflammation, and hypogonadism could all be involved. However, we found no link between food intake or 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 [30,31].

We focused 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 FFMI because it is easy to use for measuring body composition at the bedside or in outpatients [10–12] and has been well validated as an accurate measure of FFM and prognosis assessment in COPD patients [13]. Our experience in this study confirmed the ease of use of BIA; all the measurements on all patients were obtained by a single physician (S.J.) 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 cutoff values recommended for COPD patients. Nishiyama et al. [16] used the median of FFMI to split their 44 IPF patients. The cutoff was 16.6 kg/m<sup>2</sup> for both genders, which is quite similar to the COPD cutoffs we used: women <15 and men <17. However, more studies are needed to determine the optimal cutoff 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, which are good clinical indicators of low FFMI. Based on these indicators' sensitivity, specificity, positive predictive value, and negative predictive value (Figs. 1 and 2, 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, the patient is likely not malnourished; if BMI < 21 or MAC < 295 mm, the patient is likely malnourished, and dietitian intervention is needed. 2) For all other situations, go to the second step, which is FFMI measurement by BIA. Malnutrition is determined if FFMI < 15 (women) or FFMI < 17 (men). Future studies should assess

whether nutritional intervention targeted to FFM, such as pulmonary rehabilitation, could change IPF patient outcome.

## Acknowledgments

The authors thank the Association pour l'aide aux insuffisants respiratoires de Bretagne (AIRB) for providing the bioelectrical impedance analyzer and Dr. Owen Parkes for the English language editing of the manuscript.

## References

- [1] Ley B, Collard HR, King Jr. TE. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011;183:431–40.
- [2] 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;183:788–824.
- [3] Strand MJ, Sprunger D, Cosgrove GP, Fernandez-Perez ER, Frankel SK, Huie TJ, et al. Pulmonary function and survival in idiopathic vs secondary usual interstitial pneumonia. *Chest* 2014;146:775–85.
- [4] Raghu G, Amatto VC, Behr J, Stowasser S. Comorbidities in idiopathic pulmonary fibrosis patients: a systematic literature review. *Eur Respir J* 2015;46:1113–30.
- [5] Chailleux E, Laaban JP, Veale D. Prognostic value of nutritional depletion in patients with COPD treated by long-term oxygen therapy: data from the ANTADIR observatory. *Chest* 2003;123:1460–6.
- [6] Landbo C, Prescott E, Lange P, Vestbo J, Almdal TP. Prognostic value of nutritional status in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;160:1856–61.
- [7] Schols AM, Broekhuizen R, Weling-Scheepers CA, Wouters EF. Body composition and mortality in chronic obstructive pulmonary disease. *Am J Clin Nutr* 2005;82:53–9.
- [8] 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;173:79–83.
- [9] Thibault R, Le Gallic E, Picard-Kossovsky M, Darmaun D, Chambellan A. Assessment of nutritional status and body composition in patients with COPD: comparison of several methods. *Rev Mal Respir* 2010;27:693–702.
- [10] Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Gomez JM, et al. Bioelectrical impedance analysis—part I: review of principles and methods. *Clin Nutr* 2004;23:1226–43.
- [11] Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Manuel Gomez J, et al. Bioelectrical impedance analysis—part II: utilization in clinical practice. *Clin Nutr* 2004;23:1430–53.
- [12] Thibault R, Genton L, Pichard C. Body composition: why, when and for who? *Clin Nutr* 2012;31:435–47.
- [13] Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of chronic obstructive lung disease. Available at: <http://www.goldcopd.com>. Accessed February 19, 2019.
- [14] Alakhras M, Decker PA, Nadrous HF, Collazo-Clavell M, Ryu JH. Body mass index and mortality in patients with idiopathic pulmonary fibrosis. *Chest* 2007;131:1448–53.
- [15] Kishaba T, Nagano H, Nei Y, Yamashiro S. Body mass index-percent forced vital capacity-respiratory hospitalization: new staging for idiopathic pulmonary fibrosis patients. *J Thorac Dis* 2016;8:3596–604.
- [16] 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;22:480–5.
- [17] Cottin V, Crestani B, Valeyre D, Wallaert B, Cadranel J, Dalphin JC, et al. Diagnosis and management of idiopathic pulmonary fibrosis: French practical guidelines. *Eur Respir Rev* 2014;23:193–214.
- [18] Thibault R, Goujon N, Le Gallic E, Clairand R, Sebillé V, Vibert J, et al. Use of 10-point analogue scales to estimate dietary intake: a prospective study in patients nutritionally at-risk. *Clin Nutr* 2009;28:134–40.
- [19] Schols AM, Soeters PB, Dingemans AM, Mostert R, Frantzen PJ, Wouters EF. Prevalence and characteristics of nutritional depletion in patients with stable COPD eligible for pulmonary rehabilitation. *Am Rev Respir Dis* 1993;147:1151–6.
- [20] Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *Eur Respir J* 2005;26:319–38.
- [21] ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002;166:111–7.
- [22] Ley B, Ryerson CJ, Vittinghoff E, Ryu JH, Tomassetti S, Lee JS, et al. A multidimensional index and staging system for idiopathic pulmonary fibrosis. *Ann Intern Med* 2012;156:684–91.
- [23] Swets JA. Measuring the accuracy of diagnostic systems. *Science* 1988;240:1285–93.
- [24] Thibault R, Makhlof AM, Mulliez A, Cristina Gonzalez M, Kekstas G, Kozjek NR, et al. Fat-free mass at admission predicts 28-day mortality in intensive care unit patients: the international prospective observational study Phase Angle Project. *Intensive Care Med* 2016;42:1445–53.
- [25] Zisman DA, Kawut SM, Lederer DJ, Belperio JA, Lynch 3rd JP, Schwarz MI, et al. Serum albumin concentration and waiting list mortality in idiopathic interstitial pneumonia. *Chest* 2009;135:929–35.
- [26] Lee JW, Shehu E, Gjonbrataj J, Bahn YE, Rho BH, Lee MY, et al. Clinical findings and outcomes in patients with possible usual interstitial pneumonia. *Respir Med* 2015;109:510–6.
- [27] Yamauchi H, Bando M, Baba T, Kataoka K, Yamada Y, Yamamoto H, et al. Clinical course and changes in high-resolution computed tomography findings in patients with idiopathic pulmonary fibrosis without honeycombing. *PLoS One* 2016;11:e0166168.
- [28] Eid AA, Ionescu AA, Nixon LS, Lewis-Jenkins V, Matthews SB, Griffiths TL, et al. Inflammatory response and body composition in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;164:1414–8.
- [29] Evans WJ, Morley JE, Argiles J, Bales C, Baracos V, Guttridge D, et al. Cachexia: a new definition. *Clin Nutr* 2008;27:793–9.
- [30] Agusti A, Edwards LD, Rennard SI, MacNee W, Tal-Singer R, Miller BE, et al. Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. *PLoS One* 2012;7:e37483.
- [31] Groenewegen KH, Postma DS, Hop WC, Wielders PL, Schlosser NJ, Wouters EF, et al. Increased systemic inflammation is a risk factor for COPD exacerbations. *Chest* 2008;133:350–7.