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**Malnutrition and decreased food intake at diagnosis are associated with hospitalization
and mortality of idiopathic pulmonary fibrosis patients**

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Short title: Malnutrition and IPF outcomes

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Highlights

1. The prevalence of malnutrition at idiopathic pulmonary fibrosis (IPF) is frequent (26%).
2. Malnutrition and decreased food intake at IPF diagnosis are associated with increased hospitalization and mortality but not acute exacerbation of IPF.
3. In multivariable analysis, baseline higher gender-age-physiology (GAP) scores, lower BMI, and decreased food intake (Self Evaluation of Food Intake (SEFI)® score) were independently associated with all-cause hospitalization and mortality rates during follow-up.

ABSTRACT

Introduction and aims: Malnutrition is frequent in patients with idiopathic pulmonary fibrosis (IPF). We examined the relationship between malnutrition at diagnosis and all-cause hospitalization, survival, and acute exacerbation in newly diagnosed IPF patients. **Methods:** In this prospective cohort study, the nutritional status of 153 consecutive newly-diagnosed IPF outpatients was evaluated by measuring body mass index (BMI), fat-free mass index (FFMI) with bioelectrical impedance analysis, and food intake with the Self Evaluation of Food Intake (SEFI)®. Diagnosis was taken as the baseline date and malnutrition was defined as an FFMI below 17 (men) or 15 kg/m² (women). To determine the factors associated with all-cause hospitalization and mortality, univariate Cox regression analyses were performed and variables with P<0.2 were included in a stepwise multivariable analysis. **Results:** A quarter (26%; 40/153) of the patients were suffering from malnutrition at baseline, which was more frequent (62%) in patients whose BMI was <25 kg/m². Patients whose baseline FFMI was low were more likely to be hospitalized (Hazard Ratio (HR)=1.98 [95% confidence interval, 1.15; 3.41], P=0.0139) and/or die (HR=1.79 [1.11; 2.89], P=0.0165), but their acute exacerbation rate was similar to that of patients with normal FFMI. Decreased food intake (SEFI®<7) at baseline was associated with all-cause hospitalization (P=0.003) and mortality (P<0.0001) during follow-up. Baseline higher gender-age-physiology (GAP) scores (HR=1.24 [1.01;1.52], P=0.0434 ; HR=1.71 [1.37;2.14], P<0.0001, respectively), lower BMI (HR=0.89 [0.83;0.96], P=0.003 ; HR=0.89 [0.82; 0.96], P=0.003), and decreased food intake (SEFI® score) (HR=0.81 [0.71;0.93], P=0.003 ; HR=0.72 [0.64;0.81], P<0.0001), but not FFMI, were independently associated with all-cause hospitalization and mortality rates during follow-up. **Conclusions:** Malnutrition and decreased food intake at IPF diagnosis are associated with all-cause hospitalization and mortality. Future studies will determine whether dedicated

interventions to improve food intake and nutritional status could improve outcomes for IPF patients.

Keywords: Appetite; weight; body composition; interstitial lung disease; nintedanib; pirfenidone.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, and irreversible lung disease with a poor prognosis (1). It is also the major cause of chronic idiopathic interstitial pneumonia in adults (2). We previously used the fat-free mass index (FFMI), measured by bioelectrical impedance analysis (BIA), to define malnutrition, as did for chronic obstructive pulmonary disease (COPD) (3) to show that nearly one third of IPF patients are malnourished (4). Malnutrition may have a negative impact on IPF prognosis. An initial study of 44 Asian patients with IPF found that a low fat-free mass (FFM), assessed by BIA, was associated with increased mortality (5). Although the BMI is a simple, widely used marker of nutritional status, its value for predicting IPF outcome is still debated (5-10). It is not sensitive enough to diagnose malnutrition: patients with a normal BMI (21-25 kg/m²) can have an increased fat mass and a decreased FFM that it is not detected by BMI alone, leading to underestimated malnutrition rates (4, 11). BIA, which measures body composition, including fat mass, muscle mass and FFM, is a more accurate diagnostic tool and is recommended by the “The Global Leadership Initiative on Malnutrition” (GLIM) as a phenotypic criterion of malnutrition diagnosis (12).

The GLIM recommends assessing nutritional status by integrating five criteria defining malnutrition: BMI, weight loss, loss of muscle mass (by BIA) or muscle function, plus reduced food intake or an inflammatory disease such as IPF. The GLIM advocates using semi-quantitative methods to assess food intake (12). We have found that a 10-point visual analogue scale of food intake, the “Self-Evaluation of Food Intake” (SEFI®) is a simple tool that correlates well with malnutrition for hospital in-patients and out-patients (13), and primary care patients (14). The relationship between GLIM-evaluated malnutrition and the clinical outcome of IPF has never been assessed. This prospective observational study was done to determine whether malnutrition (defined by the etiologic factor “IPF, a chronic

disease”, and either one of two etiologic criteria: low FFMI or low BMI) and food intake, at baseline, could predict the clinical outcome of IPF (hospitalization, death, acute exacerbation) for a large population of Caucasian patients. We also assessed the evolution of their nutritional status during follow-up.

PATIENTS AND METHODS

Study design and patient recruitment

This single-centre cohort study used prospective data. Data for all newly diagnosed IPF patients referred to the Competence Centre for Rare Pulmonary Diseases (tertiary ILD Centre), Department of Respiratory Medicine, Rennes University Hospital, Rennes, France by general hospitals and private pulmonologists in Brittany between May 1, 2016 and December 31, 2019, were included.

Study population

Data for all the patients were collected when their IPF was diagnosed (baseline) and during follow-up (1, 15). Unstable patients who had suffered a respiratory infection or exacerbation in the eight weeks prior to diagnosis were excluded. This study was approved by the Rennes CHU Ethics Committee (n°17.53).

Clinical and biological assessment of nutritional status

The nutritional status of all patients at diagnosis was assessed prospectively by a pulmonologist (SJ) or a specialist outpatient clinic nurse by measuring weight, height, mid-arm circumference (MAC) and triceps skinfold thickness (TSF). BMI was calculated as: $\text{weight (kg)} / \text{height (m)}^2$. Malnutrition was defined as a BMI $<21 \text{ kg/m}^2$, as recommended for COPD patients (3, 16, 17). Mid-arm muscle circumference (MAMC) (cm) was calculated as: $\text{MAC (cm)} - (\pi * \text{TSF (cm)})$. Food intake was systematically assessed with the Simple

Evaluation of Food Intake (SEFI)[®] ten-point analogue scale (French version) (www.sefi-nutrition.com) (13). The result, between 0 and 10, is shown on the reverse side of the ruler. As shown previously (13, 14), the SEFI[®] score below 7 indicates a reduced food intake. We measured serum albumin (g/l), transthyretin (g/l), and C-reactive protein (CRP) (mg/l) as markers of malnutrition and inflammation.

Bioelectrical impedance analysis (BIA)

Body composition was measured with a multifrequency bioimpedance generator/analyser (Quadscan 4000, Bodystat Ltd, Isle of Man, UK)(4, 18) and the FFMI was calculated as: fat-free mass (kg)/height (m)². Malnutrition was defined as an FFMI below the 25th percentile (<17 kg/m² for men, <15 kg/m² for women) as recommended for COPD patients (3, 17) and by international guidelines (12). The body fat mass index (BFMI) was calculated as: fat mass (kg)/height (m)².

Outcomes, respiratory and other data collection

Outcomes, including all-cause hospitalization (date of the first unscheduled admission), survival (death or transplantation), and acute exacerbation of IPF (AEIPF) were assessed on December 31, 2019 to ensure a follow-up of at least 12 months for the most recently included patient. Survival was defined as the time from initial diagnosis to death (19), with right-censoring at the time of lung transplantation or at the end of the observation period for those individuals who were alive and transplant-free.

We collected demographic (gender, age) and clinical data (disease duration, comorbidities, current drug and/or tobacco use, any surgical lung biopsy), pulmonary function test (PFT) and six-minute-walk test (6MWT) at baseline and during follow-up from the hospital medical database. Dyspnoea was assessed using the New York Health Association (NYHA) scale.

PFT and 6MWT were performed according to international guidelines (20, 21). The gender, age and physiology (GAP) scores and indices were calculated as proposed by Ley et al (22).

Statistical analysis

Descriptive statistics are given as means \pm standard deviations (SD) or medians and interquartile ranges for continuous data and as the number of patients (percentages, numerator/denominator counts) for categorical data. We analysed the FFM with χ^2 tests (or Fisher's exact test) for categorical data, and Student's *t*-test (or Mann–Whitney–Wilcoxon test) for continuous data. Mixed models were used to analyse the evolution of weight, BMI, and FFMI for those patients with two or more evaluations.

Survival analyses included right censorship. Hazard ratios were calculated using a Cox model. Univariate Cox regression analyses were performed and significant variables ($p < 0.2$) were then included in a multivariate analysis, which was followed by backward stepwise elimination. Univariate and multivariate analyses were performed for all-cause hospitalization and survival. All statistics were calculated with SAS V9.4 software (SAS Institute Inc., Cary, NC, USA), and two-tailed *P* values of <0.05 were considered statistically significant.

RESULTS

Patient characteristics

The clinical characteristics of the 153 patients with IPF (22% (34/153) women; 38% (58/153) never-smokers) at diagnosis are shown in **Table 1**. The first 22 patients with BIA at baseline had already been included in a cross-sectional study.(4) The overall mean age was 72.4 ± 8.1 years. The low FFMI of 26.1% (40/153) of the patients indicated that they were malnourished. The mean FFMI of the women was 14.6 ± 2.2 kg/m² and that of the men was

19.2±2.2 kg/m². Those IPF patients with a low FFMI were older, more often female and never-smokers; they also had lower DLCO and higher GAP scores (**Table 1**).

The overall BMI at diagnosis was 26.8±4.0 kg/m² (**Table 2**) and patients with a low FFMI had a significantly lower BMI (22.7±2.7) than did those with a normal FFMI (28.3±3.4 kg/m², $P<0.0001$). All 7 patients whose BMI was <21 kg/m² had a low FFMI. More than two-thirds of patients with a low FFMI (28/40, 70.0%) had a normal BMI (≥ 21 and <25 kg/m²), and 5 (12.5%) were overweight (BMI ≥ 25 kg/m²). As previously shown, the mid-arm muscular circumference (MAMC) of patients with a low FFMI (26.3±2.5 cm) was smaller than that of patients with a normal FFMI (30.5±2.8 cm, $P<0.0001$). (4) The serum albumin, transthyretin and CRP concentrations of IPF patients with low and normal FFMI did not differ significantly.

Malnutrition at baseline and clinical outcomes

The mean follow-up time was 26 months (± 13), during which time 55 patients were hospitalized, 52 patients died and none was transplanted. Low-FFMI IPF patients were hospitalized earlier (survival probability without hospitalization: 23.8% [6.3; 47.6]) than were normal-FFMI patients (survival: 59.3% [45.4; 70.8]; HR=2.29 [1.33; 3.93], $P=0.0021$) (**Figure 1A**). The mortality rate of low-FFMI patients was higher (survival: 30.0% [7.4; 57.3]) than that of normal-FFMI patients (52.6% [36.4; 66.4], HR=1.83[1.04; 3.21]) (**Figure 1B**) but their AEIPF was not higher than that of normal-FFMI patients (**Figure 1C**). Outcomes are shown in **Table 3**.

The patients with a BMI of <21 kg/m² were more likely to die (survival: 38.1% [6.1; 71.6]) than were those whose BMI was ≥ 21 kg/m² (47.6% [33.0; 60.8], HR=2.96[1.06; 8.30]) (**Figure 2A**); they were also hospitalized earlier (survival: BMI <21 kg/m²: 25.0% [1.2; 64.6]; BMI ≥ 21 kg/m²: 50.5% [37.2; 62.3], HR=3.51[1.26; 9.81]) and more frequently exposed to

AEIPF (survival: BMI <21 kg/m²: 41.7% [1.1; 84.3]; BMI >21 kg/m²: 73.1% [59.8; 82.6], HR=3.33[0.77; 14.32]). The mortality rates of patients with BMIs of <25 and ≥25 kg/m² were similar (**Figure 2B**).

Patients whose food intake was decreased (SEFI®<7) were more likely to be hospitalized (**Figure 3A**) and to die (**Figure 3B**) than were patients whose food intake was normal (SEFI® ≥7).

Evolution of nutritional status

Mean body weight loss was 1.86 kg per year ($P<0.0001$). The decreases in FFMI (0.43 kg/m²/year, $P<0.0001$), and BFMI (0.23 kg/m²/year, $P=0.0017$) were also significant, indicating that IPF patients lost both fat mass and FFM during the course of IPF. Antifibrotic drugs had no impact on any of the nutritional parameters (data not shown).

Factors associated with all-cause hospitalization

Univariate analysis indicated that hospitalized patients had higher GAP scores and lower FFMI, BMI, SEFI®, MAC, and BFMI values (**Table 4**); other variables were not significantly different. Multivariate analyses revealed that the GAP score (HR=1.24; 95% CI 1.01; 1.52; $P=0.0434$), BMI (HR=0.89; 95% CI 0.83; 0.96; $P=0.0033$), and food intake (SEFI® HR=0.81; 95% CI 0.71; 0.93; $P=0.0027$) were independently associated with all-cause hospitalization (**Table 4**).

Death risk factors

Univariate analysis (**Table 5**) indicated that patients who died had lower FFMI, BMI, FVC, DLCO, SEFI®, MAMC, BFMI, serum albumin and transthyretin values, higher GAP scores, cancer, and dyspnea, and were less frequently treated with antifibrotics. Multivariate analyses

found that the GAP score (HR=1.71; 95% CI 1.37; 2.14; $P<0.0001$), BMI (HR=0.89; 95% CI 0.82; 0.96; $P=0.0031$), and food intake (SEFI® HR=0.72; 95% CI 0.64; 0.81; $P<0.0001$) were independently associated with death (**Table 5**).

DISCUSSION

This prospective study shows that the clinical outcomes for malnourished IPF patients (low FFMI or BMI) and those whose food intake is decreased (SEFI® <7) at diagnosis are worse than those for patients whose FFMI or food intake are normal, with higher mortality and higher all-cause hospitalization rates but not higher acute IPF exacerbation rates. The mean annual weight loss was almost 2 kg per year. The factors independently associated with increased all-cause hospitalization and mortality were a high GAP score, low BMI, and low SEFI® score, but not FFMI.

This study included the largest cohort ever evaluated for the impact of malnutrition at diagnosis on the clinical outcomes of IPF patients.

All-cause hospitalization is a very important outcome for patients suffering from IPF; it results in reduced patient survival and greater demand on healthcare resources, with subsequent increased costs (23). In univariate analyses, but not multivariable analysis, baseline low FFMI was found as a valuable predictor of all-cause hospitalization and mortality during follow-up. Clearly, then, a systematic assessment of the nutritional status of IPF patients at diagnosis and during follow-up, including data on weight, height, BMI, food intake (SEFI®), and BIA is most important for detecting malnutrition and predicting clinical outcome (19, 24). Although a BMI <21 kg/m² is used to define malnutrition in chronic diseases, such as COPD (3, 16, 17), it is not sensitive enough to identify patients with a low FFMI (7/40 (17%) in this study). BIA should therefore be part of the systematic nutritional assessment of IPF patients. However, if BIA is not available, the nutritional assessment

should include the BMI, since our results indicate that almost two thirds of IPF patients with a BMI $<25 \text{ kg/m}^2$ are malnourished and those whose BMI is $<21 \text{ kg/m}^2$ are much more likely to die than patients with a BMI $\geq 21 \text{ kg/m}^2$. Malnourished IPF patients should be referred to clinical nutritionists for a dedicated management.

The choice of the cutoff of $<25 \text{ kg/m}^2$ to define the BMI as associated with worse outcomes was based on two reasons: i) our data distribution: indeed only seven patients had a BMI $<21 \text{ kg/m}^2$, and no patient with BMI $<21 \text{ kg/m}^2$ had a normal FFMI (Table 2); ii) our recent publication (8) reporting that IPF patients with a baseline BMI $<25 \text{ kg/m}^2$ or annualized weight loss of $>0\text{-}<5\%$ or $\geq 5\%$ may experience worse outcomes over 1 year *versus* those with a baseline BMI $\geq 25 \text{ kg/m}^2$ or no weight loss.

We find that decreased food intake is associated with a poor prognosis for IPF patients. A low food intake is now considered by the GLIM as an etiologic criterion of malnutrition diagnosis (12). The SEFI® is a simple, easy tool for assessing food intake (13) and malnutrition (14) in outpatients, inpatients, and in general/private practice (13, 14). Low food intake and increased short-term mortality have also been shown to be associated in a large cohort of hospitalized patients (25). Decreased food intake can be a marker of disease severity (25) and malnutrition (13, 14). IPF is a chronic inflammatory disease and sufferers are at risk of malnutrition due to the progressive depletion of muscle protein stores, leading to decreased fat-free mass reserves, and anorexia/reduced food intake.

Several studies have examined the relationship between malnutrition and mortality for Caucasian and Asian IPF patients (6, 9, 26). Nutritional status was assessed by measuring BMI or weight loss but the BMI provided contradictory results. Nakatsuka et al. found that a $>5\%$ weight loss was associated with poor survival and that a weight loss $>6.1\%$ was an independent predictor of mortality (26). We have also shown that the FVCs of IPF patients whose weight loss is $>5\%$ in the placebo group of INPULSIS trials declined faster than those

of patients whose weight loss was $\leq 5\%$ (7). But we found no association between weight loss and mortality (7). In the present study, the survival curves (Kaplan-Meier) of IPF patients who lost $>2\text{kg}$ and those who lost no weight or $< 2\text{ kg}$ were not statistically different (data not shown). These differences may be due to a lack of statistical power in our present data. To our knowledge, only one study on 44 Asian IPF patients has investigated the association between FFMI and mortality (5). The authors reported that patients with below-median FFMI values ($<16.6\text{ kg/m}^2$) survived less well than patients whose FFMI was above the median, but they did not use the validated cut-offs proposed by the GLIM (12). Our study of a large cohort of Caucasian patients clearly indicates the link between malnutrition at diagnosis and mortality in IPF patients.

The pathophysiological mechanisms underlying the relationship between IPF and malnutrition are not well understood. Malnutrition and loss of muscle mass could be due to the pulmonary disease itself, as the progression of IPF and dyspnoea reduces exercise capacity, muscle strength and overall physical activity (27, 28). These changes could exacerbate dyspnea, resulting in a vicious circle and greater malnutrition. Further research is needed to identify the molecular mechanisms mediating malnutrition in IPF patients.

Fewer of our low-FFMI patients were treated with antifibrotics than were those with a normal FFMI. Perhaps pulmonologists should consider these patients as having an unfavourable risk/benefit balance against therapy. Nintedanib and pirfenidone can have potent side effects, including anorexia, body weight loss, fatigue, diarrhoea or abdominal pain, and these adverse effects can influence a patient's nutritional status, increasing the severity of malnutrition (2, 10, 29-33). In contrast, recent findings indicate that nintedanib protects the lung function of malnourished IPF patients. Post-hoc analyses of INPULSIS trial data revealed that the FVC of placebo group patients who lost $>5\%$ body weight declined more than that of patients who lost $\leq 5\%$ body weight but that this decrease in lung function did not occur in the nintedanib-

1 treated patients (7). Similarly, the FVC of placebo group patients with a baseline BMI of <25
2 kg/m² decreased faster than that of patients with a baseline BMI of ≥25 kg/m² (7).
3

4 The strength of this study is that we used a global assessment of nutritional status as
5 recommended by the GLIM (12). Our database was built prospectively with very few missing
6 data. The pulmonologists, nutritionists, radiologists, scientists, PFT specialists, and nurses in
7 our IPF tertiary care centre facilitated all stages of the study, from design to analysis.
8
9 Nevertheless, this study has limitations. All the patients were from a single area, so the results
10 need to be confirmed for other IPF populations. Second, we collected no molecular biology
11 data (cytokines/chemokines) and so can only speculate about the pathophysiological
12 mechanisms driving malnutrition in IPF patients. To study the FFMI, we used the cut-off
13 points recommended by the GLIM consensus (12) rather than the ones used in COPD patients
14 to predict mortality (16/15 (3) or 17.0/14.62 kg/m² (17) for males/females, respectively). This
15 could have possibly slightly influenced our results. Finally, we did not record the causes of
16 death.
17

18 To conclude, malnutrition and decreased food intake at diagnosis are associated with all-cause
19 hospitalization and mortality in IPF patients. Further studies will determine whether dedicated
20 intervention to improve food intake and nutritional status could improve outcomes for IPF
21 patients.
22

23 **Statement of authorship**

24 All the authors made substantial contributions: SJ and RT conceived and designed the study.
25
26 SJ collected the data; SJ, CR, DLP, ML, EO, LV and RT analysed the data. SJ, LV and RT
27 wrote the manuscript to which the other authors added substantial modifications. All the
28 authors approved the final submitted version.
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Conflict of interest statement

Stéphane Jouneau has received fees, funding or reimbursement for national and international conferences, boards, expert or opinion groups, and research projects over the past 5 years from Actelion, AIRB, Astra Zeneca, Bellorophon Therapeutics, Biogen, BMS, Boehringer, Chiesi, Fibrogen, Gilead, GSK, LVL, Mundipharma, Novartis, Olam Pharm, Pfizer, Pliant Therapeutics, Roche, Savara-Serendex.

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The other authors disclose no conflict of interest.

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Table 1- Clinical and demographic characteristics of idiopathic pulmonary fibrosis (IPF) patients at diagnosis. Malnutrition is defined as a low FFMI: <17 kg/m² (men) and <15 kg/m² (women).

Variables	All patients (n=153)	Low FFMI (n=40)	Normal FFMI (n=113)	Odds ratio [95% confidence interval]	P value
Age (years)	72.4 ± 8.1 (50.3; 66.9; 73.6; 78.3; 88.8)	75.5 ± 6.4 (60.4; 70.5; 75.0; 80.5; 88.8)	71.3 ± 8.4 (50.3; 65.3; 72.5; 77.5; 85.9)	1.07 [1.02 – 1.13]	0.0059
Male	119 (77.8%)	22 (55.0%)	97 (85.8%)	0.20 [0.09 – 0.46]	0.0001
Smoker	95 (62.1%)	13 (32.5%)	82 (72.6%)	0.18 [0.08 – 0.40]	< 0.0001
Cough	93 (60.8%)	28 (70.0%)	65 (57.5%)	1.72 [0.80 – 3.73]	0.1675
Dyspnea (NYHA stages)					
I	25 (16.3%)	4 (10.0%)	21 (18.6%)	Reference	0.2644
II	53 (34.6%)	14 (35.0%)	39 (34.5%)	1.88 [0.55 – 6.46]	
III	65 (42.5%)	17 (42.5%)	48 (42.5%)	1.86 [0.56 – 6.20]	
IV	10 (6.5%)	5 (12.5%)	5 (4.4%)	5.25 [1.02 – 26.98]	
Digital clubbing	42 (27.5%)	12 (30.0%)	30 (26.5%)	1.19 [0.54 – 2.63]	0.6744
FVC (% pred)	81.7 ± 17.5 (42.0; 69.0; 82.0; 93.0; 132.0)	77.7 ± 20.1 (47.0; 64.5; 76.0; 87.0; 132.0)	83.1 ± 16.3 (42.0; 71.0; 85.0; 96.0; 122.0)	0.98 [0.96 – 1.00]	0.0941

Variables	All patients (n=153)	Low FFMI (n=40)	Normal FFMI (n=113)	Odds ratio [95% confidence interval]	<i>P</i> value
DLCO (% pred)	45.4 ± 16.8 (8.0; 36.0; 46.0; 57.0; 108.0)	37.3 ± 18.2 (8.0; 25.5; 38.0; 51.0; 73.0)	48.3 ± 15.3 (8.0; 40.0; 47.0; 57.0; 108.0)	0.96 [0.93 – 0.98]	0.0006
GAP index	3.9 ± 1.4 (0.0; 3.0; 4.0; 5.0; 8.0)	4.4 ± 1.4 (2.0; 3.0; 4.0; 5.5; 8.0)	3.7 ± 1.3 (0.0; 3.0; 4.0; 4.5; 8.0)	1.45 [1.09 – 1.92]	0.0100
GAP class					
1	59 (38.8%)	13 (32.5%)	46 (41.1%)	Reference	0.0292
2	74 (48.7%)	17 (42.5%)	57 (50.9%)	1.06 [0.46 – 2.40]	
3	19 (12.5%)	10 (25.0%)	9 (8.0%)	3.93 [1.32 – 11.70]	
Surgical lung biopsy	37 (24.2%)	6 (15.0%)	31 (27.4%)	0.47 [0.18 – 1.22]	0.1203
Cancer	10 (6.6%)	2 (5.1%)	8 (7.1%)	0.70 [0.14 – 3.46]	0.6646
Cardiovascular comorbidities*	106 (69.3%)	26 (65.0%)	80 (70.8%)	0.77 [0.36 – 1.65]	0.4953
Charlson comorbidity index	1.4 ± 1.4 (0.0; 0.0; 1.0; 2.0; 9.0)	1.3 ± 1.3 (0.0; 0.0; 1.0; 2.0; 4.0)	1.4 ± 1.4 (0.0; 0.0; 1.0; 2.0; 9.0)	0.97 [0.75 – 1.27]	0.8466
Corticosteroid use	8 (5.3%)	5 (12.5%)	3 (2.7%)	5.19 [1.18 ; 22.83]	0.0293
Antifibrotics during follow-up					
Yes	96 (62.7%)	20 (50.0%)	76 (67.3%)	0.49 [0.23 – 1.01]	0.0545

Variables	All patients (n=153)	Low FFMI (n=40)	Normal FFMI (n=113)	Odds ratio [95% confidence interval]	<i>P</i> value
No	57 (37.3%)	20 (50.0%)	37 (32.7%)	Reference	
Nintedanib	58 (37.9%)	13 (32.5%)	45 (39.8%)	0.53 [0.23 – 1.22]	0.1444
Pirfenidone	38 (24.8%)	7 (17.5%)	31 (27.4%)	0.42 [0.16 – 1.12]	
None	57 (37.3%)	20 (50.0%)	37 (32.7%)	Reference	

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

FVC, forced vital capacity; GAP index, the gender, age and physiology index; DLCO, diffusing lung capacity for carbon monoxide; % pred;

percentage of predicted values. Missing data: FVC, n=2; DLCO, n=2; GAP index and class, n=1; Cancer, n=2.

*Cardiovascular comorbidities included especially high blood pressure, history of stroke, myocardial infarction, atrial fibrillation.

Table 2- Nutritional status of idiopathic pulmonary fibrosis (IPF) patients at diagnosis. Malnutrition is defined as a low FFMI: <17 kg/m² (men) and <15 kg/m² (women).

Variables	All patients (n=153)	Low FFMI (n=40)	Normal FFMI (n=113)	Odds ratio [95% confidence interval]	<i>P</i> value
Clinical parameters					
Weight (kg)	75.5 ± 14.4 (41.4; 65.0; 75.0; 84.0; 115.0)	59.1 ± 7.4 (41.4; 54.5; 60.0 ; 64.0 ; 75.0)	81.3 ± 11.6 (55.0; 73.0; 81.5; 87.0; 115.0)	0.72 [0.63 – 0.81]	<0.0001
Body mass index (kg/m ²)	26.8 ± 4.0 (16.4;24.0; 27.1; 29.4; 38.3)	22.7 ± 2.7 (16.4; 21.1; 22.6 ; 24.2; 28.9)	28.3 ± 3.4 (22.2; 25.7; 28.4; 30.1; 38.3)	0.50 [0.39 – 0.64]	<0.0001
Body mass index < 21 kg/m ²					
No	146 (95.4%)	33 (82.5%)	113 (100.0%)	Reference	
Yes	7 (4.6%)	7 (17.5%)	0 (0.0%)	50.77 [2.33 – 1108.46]	0.0125
SEFI® score	9.0 ± 1.9 (0.0 8.0; 10.0; 10.0; 10.0)	8.9 ± 2.1 (0.0; 8.0; 10.0; 10.0; 10.0)	9.0 ± 1.8 (3.0; 8.0; 10.0; 10.0; 10.0)	0.95 [0.79 – 1.15]	0.6116
SEFI® score < 7					
No	131 (86.2%)	34 (85.0%)	97 (86.6%)	Reference	
Yes	21 (13.8%)	6 (15.0%)	15 (13.4%)	1.14 [0.41 – 3.18]	0.8005
Mid-arm circumference (cm)	31.0 ± 3.3 (23.0 ; 28.5 ; 31.0 ; 33.0; ; 40.0)	27.7 ± 2.3 (23.0; 26.0 ; 28.0 ; 29.0 ; 34.0)	32.2 ± 2.8 (27.0 ; 30.0 ; 32.0 ; 34.0 ; 40.0)	0.44 [0.33 – 0.59]	<0.0001

Variables	All patients (n=153)	Low FFMI (n=40)	Normal FFMI (n=113)	Odds ratio [95% confidence interval]	<i>P</i> value
TSF (mm)	5.0 ± 3.0 (1.0 ; 3.0 ; 4.0 ; 6.0 ; 19.0)	4.5 ± 2.7 (2.0 ; 3.0 ; 4.0 ; 5.0 ; 14.0)	5.2 ± 3.0 (1.0 ; 3.0 ; 4.0 ; 6.0 ; 19.0)	0.91 [0.79 – 1.05]	0.1943
MAMC (mm)	294.1 ± 33.4 (211.2 ; 270.6 ; 294.0 ; 315.3 ; 396.9)	262.8 ± 24.9 (211.2 ; 244.0 ; 265.2 ; 279.9 ; 330.6)	305.5 ± 28.4 (248.6 ; 284.9 ; 302.7 ; 323.7 ; 396.9)	0.93 [0.91 – 0.96]	<0.0001
Bioimpedance analysis					
50 kHz phase angle (degree)	5.5 ± 1.4 (3.3 ; 4.8 ; 5.4 ; 5.9 ; 17.1)	4.9 ± 0.8 (3.3 ; 4.3 ; 5.0 ; 5.5 ; 6.4)	5.7 ± 1.5 (3.7 ; 5.0 ; 5.5 ; 6.0 ; 17.1)	0.39 [0.24 – 0.65]	0.0003
BFMI (kg/m ²)	8.6 ± 2.6 (4.0 ; 6.9 ; 8.2 ; 10.1 ; 18.9)	8.0 ± 2.7 (4.0 ; 5.8 ; 7.4 ; 9.9 ; 14.7)	8.8 ± 2.6 (4.3 ; 7.1 ; 8.4 ; 10.3 ; 18.9)	0.88 [0.75 – 1.02]	0.0950
FFMI (kg/m ²)					
Women	14.6 ± 2.2 (10.4; 13.2; 14.7; 16.1; 19.5)	13.0 ± 1.4 (10.4; 11.9; 13.3; 14.3; 14.8)	16.4 ± 1.2 (15.1; 15.6; 16.1; 17.0; 19.5)	0.01 [0.00 ; 0.75]	0.0378
Men	19.2 ± 2.2 (14.2; 17.8; 19.5; 20.9; 25.1)	16.1 ± 0.7 (14.2; 16.0; 16.3; 16.6; 16.9)	19.9 ± 1.7 (17.0; 18.5; 20.0; 21.0; 25.1)	0.00 [0.00 ; 1.87]	0.0623

Variables	All patients (n=153)	Low FFMI (n=40)	Normal FFMI (n=113)	Odds ratio [95% confidence interval]	P value
Biological parameters					
Serum albumin (g/L)	43.2 ± 2.9 (34.3 ; 41.8 ; 43.5 ; 45.4 ; 49.8)	43.3 ± 2.5 (35.8 ; 42.4 ; 43.6 ; 45.3 ; 47.5)	43.2 ± 3.0 (34.3 ; 41.7 ; 43.4 ; 45.5 ; 49.8)	1.02 [0.90 – 1.16]	0.7534
Serum transthyretin (g/L)	0.2 ± 0.1 (0.1 ; 0.2 ; 0.3 ; 0.3 ; 0.4)	0.2 ± 0.1 (0.2 ; 0.2 ; 0.3 ; 0.3 ; 0.4)	0.3 ± 0.1 (0.1 ; 0.2 ; 0.3 ; 0.3 ; 0.4)	0.92 [0.46 – 1.84]	0.8054
C reactive protein (mg/L)	6.3 ± 13.0 (1.0 ; 1.5 ; 2.7 ; 6.2 ; 107.0)	3.4 ± 4.5 (1.0 ; 1.0 ; 2.0 ; 3.3 ; 25.9)	7.3 ± 14.7 (1.0 ; 1.9 ; 3.3 ; 7.1 ; 107.0)	0.92 [0.83 – 1.02]	0.0990

Qualitative variable: number (%). Quantitative variable: mean ± standard deviation (min; Q1; median; Q3; max). BFMI, body fat mass index ; FFMI, fat-free mass index; MAMC, mid-arm muscular circumference; SEFI®, Simple Evaluation of Food Intake®; TSF, triceps skinfold thickness. Missing data: SEFI®, n=1; TSF, n=3; MAMC, n=3; serum albumin, n=3; serum transthyretin, n=4; C reactive protein, n=4.

Table 3: Outcomes of patients with idiopathic pulmonary fibrosis (IPF) according to their fat-free mass index (FFMI). Malnutrition is defined as a low FFMI: $<17 \text{ kg/m}^2$ (men and $<15 \text{ kg/m}^2$ (women). No missing data.

Variables	All patients (n=153)	Low FFMI (n=40)	Normal FFMI (n=113)	<i>P</i> value
All cause-hospitalization	55 (35.9%)	22 (55.0%)	33 (29.2%)	0.0035
Death	52 (34.0%)	19 (47.5%)	33 (29.2%)	0.0358
Acute exacerbation of IPF	26 (17.0%)	8 (20.0%)	18 (15.9%)	0.5558

Table 4: Univariate and multivariate analyses of baseline factors associated with all-cause hospitalization. Logistic regression multivariate analysis followed by backward stepwise selection. Multivariate analysis identified two significant variables associated with all-cause hospitalization: FFMI and ICW (continuous variables).

Variables	N total	All-cause hospitalization	HR [CI95%]	Univariate P-value	Multivariate P-value
Age	153	55	1.00 [0.97 ; 1.04]	0.8398	
Male	119	44	1.22 [0.63 ; 2.37]	0.5527	
FVC (% predicted)	151	54	0.98 [0.96 ; 0.99]	0.0099	
DLCO (% predicted)	151	54	0.97 [0.95 ; 0.99]	0.0006	
GAP score	152	54	1.34 [1.09 ; 1.65]	0.0052	0.0434
Cancer	10	5	2.11 [0.83 ; 5.33]	0.1150	
Smoker	95	33	0.87 [0.50 ; 1.48]	0.5988	
Dyspnea (NYHA stage)	153	55		0.1397	
4	10	5	1		
1	25	10	0.47 [0.17 ; 1.36]		
2	53	17	0.35 [0.13 ; 0.93]		
3	65	23	0.35 [0.13 ; 0.90]		
Charlson comorbidity index	152	55	1.09 [0.92 ; 1.29]	0.3318	
Antifibrotic drug during follow-up	96	32	0.72 [0.42 ; 1.22]	0.2217	
Body mass index (kg/m ²)	153	55	0.90 [0.84 ; 0.97]	0.0055	0.0033
SEFI®	152	54	0.82 [0.72 ; 0.93]	0.0030	0.0027
MAC (cm)	153	55	0.92 [0.84 ; 1.00]	0.0410	
MAMC (mm)	150	55	0.99 [0.99 ; 1.00]	0.1469	
Phase angle (degree)	153	55	0.85 [0.65 ; 1.12]	0.2390	
Normal FFMI	113	33	0.44 [0.25 ; 0.75]	0.0027	
BFMI (kg/m ²)	153	55	0.87 [0.78 ; 0.98]	0.0261	
Serum albumin (g/L)	150	54	0.93 [0.84 ; 1.03]	0.1905	
Serum transthyretin (g/L)	149	53	0.66 [0.39 ; 1.13]	0.1330	
CRP (mg/L)	149	53	1.00 [0.98 ; 1.02]	0.9739	

BFMI, body fat mass index; DLCO, diffusing lung capacity for carbon monoxide; % pred, percentage of predicted values. FFMI, fat-free mass index; FVC, forced vital capacity; GAP score, gender, age and physiology score; MAMC, mid-arm muscular circumference; SEFI®, Simple Evaluation of Food Intake®; TSF, triceps

skinfold thickness.

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Table 5: Univariate and multivariate analyses of baseline factors associated with death.

Logistic regression multivariate analysis followed by backward stepwise selection.

Multivariate analysis identified three variables significantly associated with poorer survival:

high GAP score, low body mass index (BMI) and low score of the Simple Evaluation of Food Intake (SEFI)®.

Variables	N total	Death	HR [CI95%]	Univariate P-value	Multivariate P-value
Age	153	52	1.03 [0.99; 1.07]	0.1070	
Male	119	45	1.95 [0.88; 4.33]	0.1002	
FVC	151	50	0.96 [0.94; 0.98]	<0.0001	
DLCO	151	51	0.95 [0.94; 0.97]	<0.0001	
GAP score	152	51	1.91 [1.55; 2.35]	<0.0001	<0.0001
Cancer	10	6	3.46 [1.46; 8.24]	0.0049	
Smoker	95	29	0.72 [0.42; 1.25]	0.2498	
Dyspnea (NYHA stage)	153	52		0.0117	
4	10	7	1		
1	25	5	0.09 [0.06; 0.60]		
2	53	16	0.26 [0.11; 0.64]		
3	65	24	0.31 [0.13; 0.72]		
Digital clubbing	42	18	1.88 [1.06; 3.35]	0.0320	
Charlson comorbidity index	152	52	1.08 [0.90 ; 1.28]	0.4107	
Antifibrotic drug during follow-up	96	26	0.52 [0.30; 0.90]	0.0200	
BMI (kg/m ²)	153	52	0.88 [0.82; 0.95]	0.0010	0.0031
SEFI®	152	52	0.72 [0.64; 0.80]	<0.0001	<0.0001
MAMC (mm)	150	52	0.99 [0.98; 1.00]	0.0297	
Phase angle (degree)	153	52	0.80 [0.59; 1.08]	0.1481	
Normal FFMI	113	33	0.55 [0.31; 0.96]	0.0368	
BFMI (kg/m ²)	153	52	0.80 [0.70; 0.91]	0.0011	
Serum albumin (g/L)	150	51	0.87 [0.80; 0.96]	0.0048	
Serum transthyretin (g/L)	149	50	0.43 [0.25; 0.75]	0.0031	
CRP (mg/L)	149	51	1.01 [0.99; 1.03]	0.4982	

Qualitative variable: number (%). Quantitative variable: mean \pm standard deviation (min; Q1; median; Q3; max). BFMI, body fat mass index; BMI, body-mass index; CRP, C-reactive protein; DLCO: diffusing lung capacity for carbon monoxide; ECW, extracellular water; FVC, forced vital capacity; F, female; FFMI, fat-free mass index; GAP, gender – age – physiology; ICW, intracellular water; M, male; MAC, mid-arm circumference; MAMC, mid-arm muscular circumference; SEFI®, Simple Evaluation of Food Intake®; TBW, total body water; TSF, triceps skinfold thickness.

Figure legends

Figure 1- Kaplan-Meier curves of main clinical outcomes for patients with a low or

normal FFMI. A. All-cause hospitalization. B. Survival (mortality). C. Acute

exacerbation of IPF. Low-FFMI IPF patients (dotted line) were more frequently hospitalized and more likely to die – but did not have more acute exacerbation of IPF – than for normal FFMI patients (full line).

Figure 2- Kaplan-Meier curves of Survival (mortality) of IPF patients compared with

BMI cut-offs. The survival rate of patients with a BMI<21 was lower (38.1% [6.1; 71.6]) than that of patients with a BMI \geq 21 (47.6% [33.0; 60.8]) (Figure 2A). Patients with BMIs of < and \geq 25 had similar mortality rates (54.6% [37.6%;68.7%] versus 33.7% [12.2%;56.9%] respectively, Figure 2B).

Figure 3- Kaplan-Meier curves of all-cause hospitalization (3A) and mortality (3B) of

IPF patients whose food intake was low (SEFI® < 7) and normal (SEFI® \geq 7). More

patients with a SEFI® < 7 (dotted line) were hospitalized and died than were patients with SEFI® \geq 7 (full line).

Figure 1

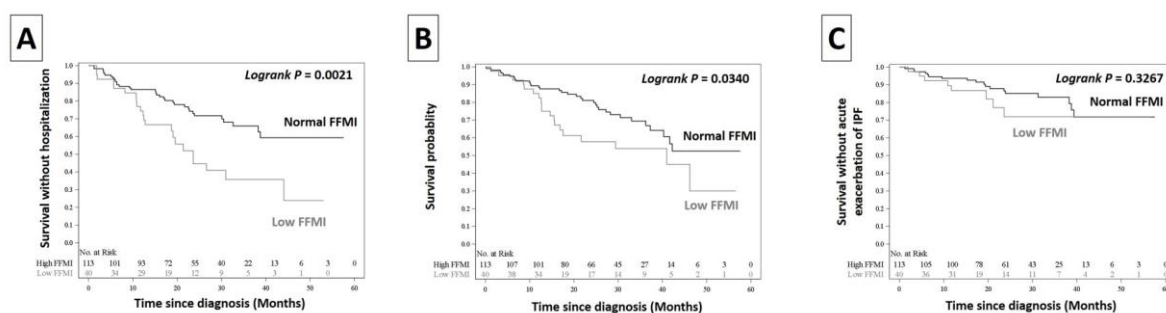


Figure 2

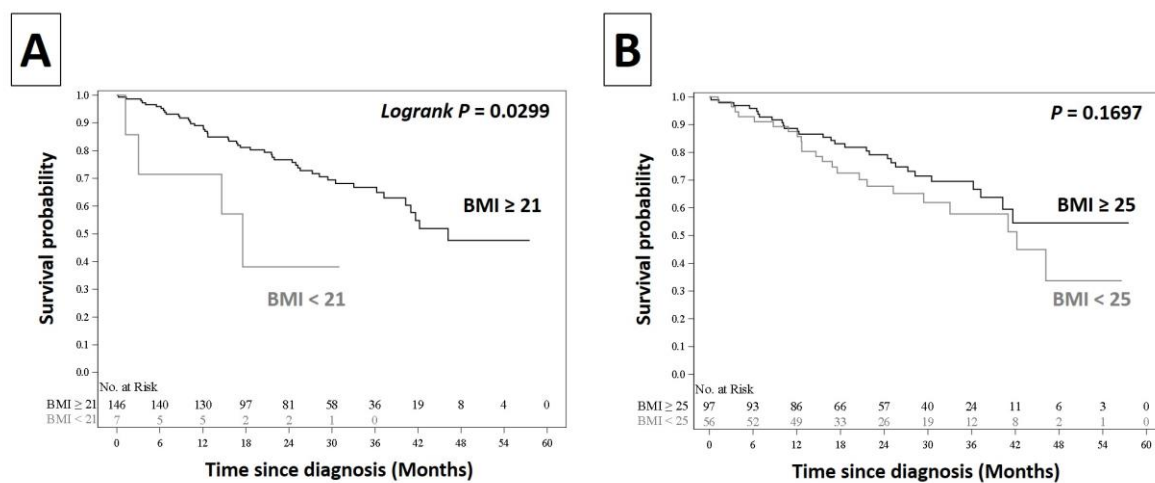
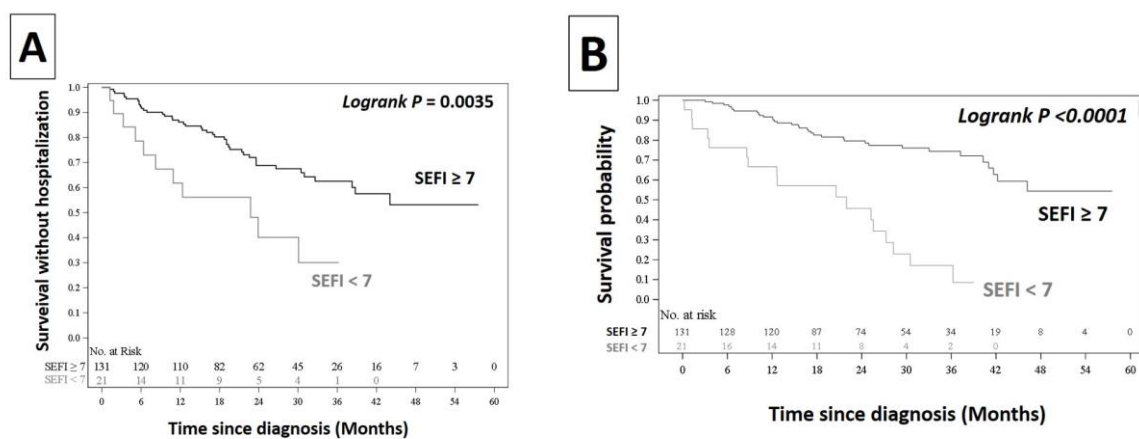


Figure 3





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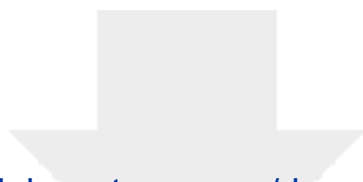
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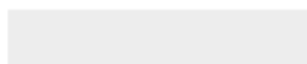




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