Early View

Original research article

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TITLE

Nutritional Assessment in Idiopathic Pulmonary Fibrosis: a Prospective Multicentre Study

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Keywords

Idiopathic pulmonary fibrosis, Nutrition, Nutritional Status, Sarcopenia

Take-home message

Patients with IPF at diagnosis are mainly normally nourished and obese, but early signs of nutritional and physical performance impairment can already be identified at this stage. Sarcopenia is identified only in a minority of cases; cachexia has not been observed.

Abstract

Background. Nutritional status (NS) impacts on quality of life and prognosis of patients with respiratory diseases including idiopathic pulmonary fibrosis (IPF). However, there is a lack of studies performing an extensive nutritional assessment of IPF patients. This study aims to investigate the NS and to identify nutritional phenotypes in a cohort of IPF patients at diagnosis.

Methods. Patients underwent a thorough pulmonary and nutritional evaluation including questionnaires on NS and physical activity, anthropometry, body impedance, dynamometry, 4-meter gait speed and blood tests.

Results. 90 IPF patients (78.9% males, mean age 72.7 years) were enrolled. The majority of patients were classified as Gender-Age-Physiology Index stage 2 (47, 52.2%) with an inactive lifestyle according to International Physical Activity Questionnaire score (39, 43.3%) and had mean forced vital capacity and diffusing capacity for carbon monoxide 86.5% and 54.2%, respectively. In regards to nutritional phenotypes, the majority of patients were normally nourished (67.8%, 95% Confidence Interval (CI):58.6-77.7), followed by non-sarcopenic obese (25.3%, 95%CI:16.1-35.2), sarcopenic (4.6%, 95%CI:0.0-14.5) and sarcopenic obese (2.3%, 95%CI:0.0-12.2). Among normally nourished, 49.2% showed early signs of nutritional and physical performance alterations, including body mass index ≥ 30 in 4.3%, history of weight loss $\geq 5\%$ in 11.9%, reduction of gait speed and hand grip strength in 11.9% and 35.6%, respectively. Low vitamin D values were observed in 56.3% of cases.

Conclusions. IPF patients at diagnosis are mainly normally nourished and obese, but early signs of nutritional and physical performance impairment can already be identified at this stage.

Introduction

Nutritional status has assumed increasing importance in the evaluation of chronic respiratory diseases, since their clinical course is often characterized by progressive reduction of physical activity, muscle deconditioning and sarcopenia.[1] Most of the evidence regarding nutritional status focused on chronic obstructive pulmonary disease (COPD), in which *Schols and colleagues* identified the importance of stratifying patients in specific nutritional phenotypes that had prognostic significance and could help prevention and intervention strategies.[2,3] The nutritional phenotypes identified by *Schols et al.* included obesity, sarcopenic obesity, sarcopenia and cachexia and required at least 3 items to be identified: 1) body mass index (BMI) and body circumferences; 2) bioelectrical impedance analysis (BIA); and 3) history of unintentional weight loss. This classification also aimed to provide criteria for high-quality nutritional assessment in real life and in future clinical trials.

Much less is known about the nutritional implications of other chronic respiratory diseases, such as idiopathic pulmonary fibrosis (IPF), a chronic, progressive interstitial lung disease with a poor prognosis and a median survival time ranging between three to five years.[4]

IPF and COPD may share some risk factors for an altered nutritional status, including smoking habit, systemic inflammation, progressive hypoxia, and sedentary lifestyle, except that in IPF these factors may develop and worsen in a shorter period of time given the rapid progression of the disease.[5] Preliminary studies on IPF also showed that nutritional status may influence disease outcomes, with lower BMI, body weight loss and vitamin D deficiency having a negative prognostic significance.[6,7,8]

To the best of our knowledge, there is a lack of studies performing a complete nutritional assessment of IPF patients from the time of diagnosis, evaluating not only single risk factors, but complete nutritional phenotypes. In order to identify these phenotypes, according to Schols and

colleagues, the nutritional assessment should include not only BMI and anthropometric measurements, but also an evaluation of body composition, muscle strength, physical performance and the impact of comorbid conditions.[3]

This study aims to investigate the nutritional status, defined as the set of nutritional (BIA, anthropometric measurements, blood exams and nutritional risk assessment tests) and physical performance (dynamometry, 4-meter gait speed and physical activity questionnaire) variables described both individually and lumped in nutritional phenotypes, in a cohort of IPF patients at the time of diagnosis.

Materials and Methods

Study design and participants

In this prospective, multicentre, observational, pilot study, we recruited consecutive IPF patients at the time of diagnosis over a 2-year period (December 2018-November 2020) from outpatient specialist clinics of 9 hospitals in Northern Italy (San Gerardo Hospital, Monza; G. Salvini Hospital, Garbagnate Milanese; San Giuseppe Hospital, Milan; San Paolo Hospital, Milan; San Matteo Hospital, Pavia; Spedali Civili, Brescia; San Martino Hospital, Genova; Ospedale di Circolo, Busto Arsizio; Ospedale Maggiore della Carità, Novara). This study received Ethics Committee approval and was registered on clinicaltrials.gov (NCT03770845 – NutriIPF study).

Patients were eligible for inclusion if they were older or equal to 40 years of age, received a diagnosis of IPF according to the ATS/ERS/JRS/ALAT 2018 guidelines [4] and gave written informed consent. Patients were excluded if they were affected by severe renal failure, defined as a glomerular filtration rate lower than 30ml/min, were in a New York Heart Association (NYHA) class IV (unable to carry on any physical activity without discomfort), had severe liver failure, defined as Child-Pugh score class C, had active solid or haematological tumors, had already received (currently or in the past) therapy with pirfenidone or nintedanib, were unable to walk, needed oxygen therapy at rest, and were already recruited in other interventional experimental protocols studying new drugs. All patients provided written informed consent at the time of enrollment. The study is reported according to STROBE guidelines.[9]

The study included two pneumological (T1 at IPF diagnosis and T3 after 6 months) and two nutritional visits (T2 and T4, to be performed within 3 weeks after T1 and T3, respectively). In this manuscript, we report results from T1 and T2.

The study visits were organized as follows: 1) during the first pneumological visit (T1) the following items were collected: past medical history, oxygen saturation, pulmonary functional tests (PFTs),

diffusing capacity for carbon monoxide (DLCO), six-minute walking test (6MWT) and Gender-Age-Physiology (GAP) score; 2) during the first nutritional assessment (T2) the following items were collected: anthropometric measurements; blood exams including liver function (transaminases, gamma-GT, total and fractionated bilirubin), renal function (creatinine, urea and urates), complete blood cell count, C-reactive protein, albumin, transferrin, vitamin D, total and fractionated cholesterol, sugar level, phosphorus, total calcium, ionized calcium and thyroid-stimulating hormone (TSH); questionnaires on nutritional status (Malnutrition Universal Screening Tool (MUST) and Mini Nutritional Assessment (MNA)) and on physical activity (International Physical Activity Questionnaire (IPAQ)); BIA; dynamometry and 4-meter gait speed test.

Procedures

PFTs and DLCO measurements were performed according to the ATS/ERS standardization using a dry spirometer.[10-12] 6MWT was performed according to the guidelines recommended by the ATS.[13]

The anthropometric assessment performed included weight, height, waist, arm and calf circumferences and triceps fold. BMI and muscle arm circumference were calculated.[14] Percentage of body weight loss or gain in the last 3 months was calculated, MUST and MNA questionnaires were administered in order to assess the patients' malnutrition risk.

Muscle strength was evaluated through hand grip strength for both dominant and non-dominant limbs: measurements were performed by hand-held dynamometer, repeated three times for each side and the best value was recorded.[15]

Physical performance was assessed by 4-meter gait speed test conducted along a 4-meter corridor. Walking speed was calculated by dividing the distance by the time needed to cover the distance (m/s).

BIA was performed using a standard tetra-polar technique with patients studied in the supine position with electrodes connected to the hands and feet.[16] Resistance (R) and capacitance (Xc) were directly measured in ohms (V) at 50 kHz and 800 mA. Phase angle measures using the BIA reflect the relative contributions of fluid (resistance) and cellular membranes (capacitance) of the body. It was calculated using the following equation: $(\text{resistance} / \text{capacitance}) \times (180/\pi)$. [17]

Fat-free mass index (FFMI) (kg/m^2) was calculated as $\text{FFM}/\text{height}^2$, skeletal muscle index (SMI) (kg/m^2) was calculated as $\text{SM}/\text{height}^2$, and body fat mass (BFM) was calculated as total body weight minus FFM and then BFM index (BFMI) was derived ($\text{BFMI } \text{kg}/\text{m}^2 = \text{BFM}/\text{height}^2$).

Outcomes

The primary study outcome was to determine the prevalence of different nutritional phenotypes in IPF patients at the time of diagnosis. Nutritional phenotypes were identified as reported in Table 1, and based on those previously applied in COPD and on consensus statements.[4,18] If it was not possible to identify a specific phenotype due to some unfulfilled criteria, we attributed the nutritional phenotype for which the greatest number of criteria were met. As a secondary analysis, normally nourished patients were divided into two groups, identifying a further phenotype defined as “normonourished with overweight”.

Secondary outcomes were to evaluate the prevalence of alterations of blood exams and BIA variables, the prevalence of reduced hand grip strength and gait velocity impairment, and the prevalence of reduced IPAQ, MNA and MUST scores.

Statistical analysis

Given the nature of this pilot study and the absence of evidences on the distribution of nutritional phenotypes at the time of IPF diagnosis, that could justify assumptions regarding the distribution

of the primary outcome, the sample size was set to 100 patients, to be enrolled consecutively. This choice satisfied both the need to reflect the real prevalence of nutritional phenotypes in the whole IPF population, and the potential for enlistment of participating centers in one year time span. In fact, considering the rarity of the disease (incidence rate about 5.5 x100,000 patients per year [19]) and the population served by participating centers (about 2.5 million people), the number of expected new cases of IPF would be roughly 140 over one year, and consequently our sample would cover more than 50% of such cases. However, the onset of COVID-19 pandemic in March 2020 interrupted most of the outpatient clinical activity in Northern Italy. Therefore, we decided to close the recruitment when 90% of the sample size was reached (90 patients), in order not to accumulate excessive delay on the planned study schedule (1 year).

For the purpose of evaluating the primary outcome, a descriptive analysis of the prevalence of each nutritional phenotype was performed within the study cohort. Multinomial simultaneous two-sided 95% confidence interval (CI) for each prevalence was estimated with Sison and Glaz approach for multinomial proportions.[20]

Summary statistical measures used to describe study population were mean and standard deviation (SD) for continuous data, frequencies and percentages for categorical variables. In this analysis, the proportion of missing data was low and therefore no imputation procedure was performed (Table E1).

Statistical significance was accepted at $p < 0.05$ and all tests were 2-tailed. Statistical analyses were performed with R, version 3.5.2. (R Project for Statistical Computing, <http://www.R-project.org>) and SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

Results

Study population

In the study period 131 consecutive patients with IPF were screened for study participation, 90 patients (21.1% women and mean age 72.7 ± 6.8 years) met inclusion criteria, provided consent to participate and, thus, were enrolled in the final cohort, Figure 1. The baseline clinical features of the study population are shown in Table 2. The majority of patients were former smokers (63, 70.0%) with an inactive lifestyle according to IPAQ score (39, 43.3%) and were classified as GAP stage 2 (47, 52.2%). The most frequently encountered comorbidities were systemic hypertension in 38 (42.2%) cases, other cardiovascular comorbidities in 26 (28.9%), and gastroesophageal reflux disease (GERD) in 23 (25.6%). Ten (11.1%) patients were on oral steroids (prednisone or methylprednisolone) prescribed before IPF diagnosis, while nobody participated in pulmonary rehabilitation programs.

Functional and physical performance indices

The majority of patients showed preserved FVC values, with mean (SD) FVC% of 86.5 (21.1), respectively, a mild TLC reduction and a moderate DLCO impairment (mean: 54.2%, SD: 18.4), Table 3. Mean (SD) distance walked at 6MWT was 408.2 (109.8) meters and 11 (12.2%) patients required oxygen supplementation during effort. Among the 87 patients that performed the assessment, at 4-meter gait speed, mean (SD) value was 1.11 (0.31) meters per second (m/s), and 69 (79.3%) patients showed gait velocity impairment (< 0.8 m/s). Regarding hand-held dynamometry values, mean (SD) hand grip strength for men and women was 31.9 (7.1) kg and 19.5 (5.0) kg, respectively. Twenty-nine (33.3%) and 17 (19.5%) patients showed intermediate (26-32 kg for men and 16-20 kg for women [21]) and weak (< 26 kg for men and < 16 kg for women [21]) grip strength, respectively.

Nutritional assessment and nutritional phenotypes

The nutritional assessment was performed in 87 patients. Mean (SD) BMI was 27.6 (4.0), with a predominance of patients in the overweight and non-sarcopenic obesity classes, 39 (44.8%) and 24 (27.6%) cases, respectively. Only about one fourth of cases (27.6%) showed normal weight and none was underweight. Anthropometric measurements are summarized in Table 4. Weight loss > 5% and weight gain > 5% in the 3 months prior to T2 were observed in 9 (10%) and 2 (2%) patients, respectively. Forty-eight per cent of patients showed an increased waist circumference (waist circumference > 102 cm in men and > 88 cm in women). When considering the joint distribution of increased waist circumference and BMI classes, 8.3%, 46.2% and 95.8% of patients in the normal weight, overweight and obese group, respectively, showed an increased, high or very high cardiovascular risk, Figure 2.

Mean (SD) mid-arm circumference and mid-arm muscle circumference values, indices of energy reserves and protein mass, were 30.2 (3.5) cm and 27.3 (3.5) cm, respectively, both in the normality range.

Nutritional risk assessment was performed through two screening tests: MUST and MNA. According to MUST score 4 (4.6%) patients were at medium risk (score = 1) and 7 (8.0%) at high risk of malnutrition (score $\geq$ 2), while using MNA questionnaire 13 (14.9%) cases were at risk of malnutrition (score 17-23.5) and 3 (3.5%) patients were malnourished (score < 17). Nine patients (10.3%) showed at least 5% weight loss in the 3 months prior to T2, all of them had a MUST score $\geq$ 1.

In regards to laboratory exams, 21 (24.1%) patients showed total cholesterol levels higher or equal to 200 mg/dL and LDL cholesterol was higher or equal to 115 mg/dL in 27 (31.0%) cases. Twenty-eight patients (31.1%) were on chronic statin treatment and their cholesterol levels were in the

normal range in the majority of cases (23 cases). Vitamin D deficiency (vitamin D < 20 ng/mL) and insufficiency (vitamin D between 20 and 30 ng/mL) were reported in 35 (40.2%) and 14 (16.1%) patients, respectively. Eight (9.2%) patients received chronic vitamin D supplementation and 4 of them showed insufficiency at blood exams. Unfortunately, information on vitamin D levels were missing for 24 patients (27.6%), therefore these evidences should be interpreted with caution, Table E1. Similarly, laboratory exams were not performed in up to 28% of patients in our cohort, however no alterations were observed in the other laboratory exams, Table E2.

BIA values are summarized in Table 4. Low FFMI (< 17 kg/m² in men and < 15 kg/m² in women), SMI (<8.87 kg/m² in men and <6.42 kg/m² in women) and BFMI (<1.7 kg/m² in men and <3.8 kg/m² in women) were identified in 4 (4.6%), 4 (4.6%) and 19 (21.8%) patients, respectively.

In 20 (23.0%) patients we observed a reduced phase angle (< 4°), marker of cell membrane function.

Regarding the primary outcome, nutritional phenotypes, the majority of patients were normally nourished (67.8%, 95%CI: 58.6 - 77.7), followed by non-sarcopenic obese (25.3%, 95%CI: 16.1 - 35.2), sarcopenic (4.6%, 95%CI: 0.0 - 14.5) and sarcopenic obese (2.3%, 95%CI: 0.00 - 12.16), Figure 3, Table E3. The majority of normally nourished patients showed early signs of nutritional and physical performance impairment including BMI ≥ 30 in 3.4% of cases, history of weight loss ≥ 5% in the prior 3 months in 11.9% of patients, reduction of gait speed in 11.9% of cases and a reduction of hand grip strength in 35.6% of patients, Figure 4.

Finally, when comparing patients who received oral steroids and those who did not, we did not observe any difference in nutritional phenotypes and main nutritional variables; while in regards to physical status, patients who received oral steroids had lower hand grip strength (mean (SD) 24.0 (8.1) vs 30 (8.2) Kg, p-value 0.03) and slower 4-meter gait speed (mean (SD) 0.9 (0.4) vs 1.1 (0.3) m/s, p-value 0.01) compared to those who did not.

Discussion

We report the complete nutritional assessment of a cohort of 87 consecutive patients with IPF at the time of diagnosis from 9 outpatient IPF clinics in Northern Italy.

In our cohort the majority of patients showed a normal nutritional status (67.8%), 25.3% were non-sarcopenic obese, while only a minority already showed sarcopenia (6.9% of cases, in 2 cases associated with hidden obesity) and none showed cachexia. Also considering the screening tests for nutritional risk assessment (MNA and MUST), only a minority of patients was malnourished (3.5%) or at high risk for malnutrition (8.0%), only 4.6% of patients showed reduced FFMI, another marker of malnutrition, at BIA, and 9 (10%) patients had a history of unintentional weight loss > 5%. Therefore, the prevalence of the characteristics that denote malnutrition, including depletion of muscle mass and/or fat mass and active weight loss, is low in our population.

Nevertheless, up to 49.2% of normally nourished patients showed early signs of nutritional and physical performance impairment, including being BMI ≥ 30 in 3.4% of cases, history of weight loss $\geq 5\%$ in the prior 3 months and reduction of gait speed both in 11.9% of patients, and reduction of hand grip strength in 35.6% of cases.

Our data are partially in contrast with those of other cohorts of IPF patients in which malnutrition was observed in up to 28% of cases.[8,22] This discrepancy may be due to the differences in study design, as previous studies included patients in advanced stages of the disease and without exclusion of severe comorbidities. However, recent studies showed that not only overt malnutrition is a negative prognostic factor for patients with IPF,[22] but also body weight loss, sarcopenia and reduced gait speed or hand grip strength are associated with poor clinical outcomes [23-26] or reduced quality of life.[27] These conditions were observed in a considerable percentage of our normally nourished patients. Furthermore, despite our study recruited patients at the time of diagnosis, only about one third of them was classified as GAP stage 1 at enrollment,

and up to 43% already reported an inactive lifestyle. Therefore, our results suggest two crucial considerations: first the importance of an early and comprehensive nutritional screening in patients with IPF, in order to promptly initiate nutritional and rehabilitation programs that may reduce nutritional and physical performance impairment; secondly, the importance of an early IPF diagnosis, as the introduction of a rehabilitation program or lifestyle modifications when the disease is already in a moderate-to-severe stage may be difficult and potentially worthless.

Although obesity was not associated with worse clinical outcomes as compared to malnutrition, this condition can be associated to complications during follow-up, including increased cardiovascular risk and ineligibility for lung transplant.[28]

The “obese phenotype” was identified in 28% of patients in our cohort. Furthermore, systemic hypertension was the most frequent comorbidity, observed in up to 42% of cases, and almost one third of patients had at least one cardiovascular comorbidity other than systemic hypertension. Furthermore, when considering anthropometric measurements such as waist circumference, 8.4% and 46.2% of patients in the normal weight and overweight classes showed an increase in cardiovascular risk. Our results overlap with prior observations that report a high prevalence of obesity and cardiovascular comorbidities in IPF patients.[27,29-30]

Low vitamin D values were observed in the great majority of cases, but only a minority of them were receiving supplementation. Since low serum vitamin D concentration was recently found to be a negative prognostic factor in patients with IPF, greater attention should be paid to investigating this deficit early in patient history.[31]

A few data are available on what should be included in a baseline nutritional evaluation of patients with IPF. Prior studies suggested to use anthropometric measurements as first step and BIA as second step to diagnose malnutrition,[8] while an expert panel recently considered a more extensive assessment to include nutrient intakes, energy expenditure, body composition,

laboratory data and body functions.[28] In our study, a complete evaluation of nutritional status, as suggested by *Schols and colleagues*,[3] allowed to identify early signs of nutritional and physical performance impairment, otherwise missed if only BMI and anthropometric measurements were considered. At an ordinary nutritional evaluation including only BMI and anthropometric measurements, patients with IPF at diagnosis may appear “well nourished”, however they deserve to be examined more accurately to rule out sarcopenia, physical performance impairment and cardiovascular risk factors. Therefore, we suggest to include in a nutritional evaluation for IPF patients both nutritional parameters (BIA, anthropometric measurements, laboratory exams) and indicators of physical performance, such as dynamometry and GAIT speed 4-meter.

Among the main strengths of our study we acknowledge: 1) the multicentric design, which included both university and non-university IPF referral hospitals from Northern Italy, that allowed us to enhance the generalizability of the results; 2) the choice to include only patients at time of diagnosis, before the introduction of antifibrotic therapies, that allowed us to describe patients at the beginning of disease trajectory and to start a prospective longitudinal data collection, that includes nutritional status.

Our study presents also some limitations: the recruitment period partially overlapped with COVID-19 pandemic, which hit Northern Italy with particular severity. This event prompted us to close the recruitment ahead of schedule in order not to accumulate excessive delay on the planned study schedule, as explained above. In a secondary analysis (Table E4), we compared IPF severity and physical performance indices between patients enrolled before and after the onset of the first COVID-19 outbreak (that we considered as March 1st). We observed no differences in nutritional variables and phenotypes and in physical performance indices, but the average GAP stage at enrollment rose from 2.2 (SD: 1.2) to 3.6 (SD: 1.3) (p-value <0.0001) after the outbreak, suggesting an indirect impact of pandemic on the access to healthcare services, and especially to outpatient

IPF clinics, that deserves further investigation. Furthermore, the criteria chosen excluded from the study IPF patients with severe renal, cardiac and liver failure and those in an advanced disease stage, therefore our results cannot be generalised to patients with such conditions. Finally, we used the terms nutritional status and malnutrition that do not have univocal and universally shared definitions.

In conclusion, IPF patients at diagnosis are mainly classified in the normally nourished and obese phenotype, however an extensive nutritional assessment identified early signs of nutritional and physical performance impairment, including sarcopenia, reduced gait speed or hand grip strength, in almost 50% of the cases. These findings may have a significant impact on patients management, therefore nutritional assessment should become routine clinical practice in patients with IPF. Future studies should evaluate the impact of nutritional intervention and physical training/rehabilitation personalized in accordance to the patient nutritional phenotype.

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Statement of Ethics

Our research complies with the guidelines for human studies and was conducted ethically in accordance with the [World Medical Association Declaration of Helsinki](#).

Disclosure Statement

The authors have no conflicts of interest to declare.

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- 30.

Figure 1. Study flow chart

Abbreviations. IPF= idiopathic pulmonary fibrosis; ILD= interstitial lung disease

Waist circumference	BMI (kg/m ²)		
	18.5-25	25-30	≥ 30
Men			
<102 cm	Low risk 19 (27.54%)	Increased risk 20 (28.99%)	High risk 1 (1.45%)
≥102 cm	Increased risk 0 (0.00%)	High risk 15 (21.74%)	Very high risk 14 (20.29%)
Women			
<88 cm	Low risk 3 (16.67%)	Increased risk 1 (5.56%)	High risk 0 (0.00%)
≥88 cm	Increased risk 2 (11.11%)	High risk 3 (16.67%)	Very high risk 9 (50.00%)

Figure 2. Cardiovascular risk in the study population, according to Body Mass Index (BMI) and waist circumference, evaluated at first nutritional visit (T2).

Abbreviations. BMI= body mass index

Figure 3. Prevalence of nutritional phenotypes (and 95% confidence interval) evaluated at first nutritional visit (T2). Panel A: classification based on 5 phenotypes, panel B: classification based on 6 phenotypes.

Figure 4. Criteria fulfilled among patients classified in the “normal nutritional status” phenotype

Abbreviations. BMI= body mass index; BFMI = body fat mass index; FFMI = fat free mass index; SMI = skeletal muscle mass index; M = male; F = female

Table 1. Criteria to identify nutritional phenotypes in study population.

Nutritional phenotypes	Parameters and cut-off
CACHEXIA	<ul style="list-style-type: none"> - BMI < 18.5 kg/m² - Involuntary weight loss > 5% in the last 3 months - FFMI < 17 kg/m² for males or < 15 kg/m² for females - SMI < 8.87 kg/m² for males or < 6.42 kg/m² for females - BFMI < 1.7 kg/m² for males or < 3.8 Kg/m² for females - Elevated serum C-reactive protein concentrations (CRP ≥ 5 mg/dL) and/or reduced serum concentrations of albumin (albumin < 3.2 g/dL)
SARCOPENIA	<ul style="list-style-type: none"> - BMI < 30 kg/m² - FFMI < 17 kg/m² for males or < 15 kg/m² for females - SMI < 8.87 kg/m² for males or < 6.42 kg/m² for females - BFMI ≥ 1.7 kg/m² for males or ≥ 3.8 kg/m² for females - Hand Grip < 30 kg for males or < 20 kg for females - Gait Speed (4 meter) < 0.8 m/sec
NORMAL NUTRITIONAL STATUS	<ul style="list-style-type: none"> - BMI between 18.5 and 24.9 Kg/m² (overweight if BMI ≥ 25 kg/m² and < 30 kg/m²) - FFMI ≥ 17 kg/m² for males or ≥ 15 kg/m² for females - BFMI between 1.7 kg/m² and 5.19 kg/m² for males or between 3.8 kg/m² and 8.19 Kg/m² for females - Hand Grip > 30 kg for males or > 20 kg for females - Gait Speed (4 meter) ≥ 0.8 m/sec - No involuntary weight loss > 5% in the last 3 months
NON-SARCOPENIC OBESITY	<ul style="list-style-type: none"> - BMI ≥ 30 kg/m² - Abdominal circumference > 102 cm for males or > 88 cm for females - FFMI ≥ 17 kg/m² for males or ≥ 15 kg/m² for females - SMI ≥ 8.87 kg/m² for males or ≥ 6.42 kg/m² for females - BFMI ≥ 8.3 kg/m² for males or ≥ 11.82 kg/m² for females - Hand Grip > 30 kg for males or > 20 kg for females - Gait Speed (4 meter) ≥ 0.8 m/sec
SARCOPENIC OBESITY	<ul style="list-style-type: none"> - BMI ≥ 30 kg/m² - Abdominal circumference: > 102 cm for males or > 88 cm for females - FFMI < 17 kg/m² for males or < 15 kg/m² for females - SMI < 8.87 kg/m² for males or < 6.42 kg/m² for females - BFMI ≥ 8.3 kg/m² for males or ≥ 11.82 Kg/m² for females - Hand Grip < 30 kg for males or < 20 kg for females - Gait Speed (4 meter) < 0.8 m/sec

Abbreviations. BMI = body mass index; FFMI = fat free mass index; BFMI = body fat mass index; SMI = skeletal muscle mass index.

Table 2. Demographics and clinical characteristics at baseline (T1).

	Population at T1
Patients, n	90
Demographic characteristics	
Female, N(%)	19 (21.1)
Age at enrolment	
Mean (SD)	72.7 (6.8)
Median (Q1-Q3)	73 (68 - 78)
Smoking history, N(%)	
Non-smoker	25 (27.8)
Active smoker	1 (1.1)
Ex-smoker	63 (70.00)
IPF stage	
GAP stage, N(%)	
1	26 (28.9)
2	47 (52.2)
3	16 (17.8)
Physical activity	
IPAQ, mean (SD)	
Mean (SD)	2089 (2977)
Median (Q1-Q3)	900 (262.5 - 2506)
IPAQ categories, N(%)	
<= 700 (inactive)	39 (43.3)
700 - 2519 (sufficiently active)	28 (31.1)
> 2519 (very active)	22 (24.4)
Comorbidities, N(%)	
Diabetes	10 (11.1)
Concomitant emphysema	6 (6.7)
Systemic hypertension	38 (42.2)
At least one cardiovascular comorbidity other than systemic hypertension *	26 (28.9)
Chronic liver disease	7 (7.8)
IBD	0 (0.0)
Dysthyroidism	5 (5.5)
Hyperthyroidism	2 (2.2)
Hypothyroidism	3 (3.3)
GERD	23 (25.6)
Osteoporosis	7 (7.8)
Previous solid neoplasm	14 (15.6)
Anxiety and depression	6 (6.7)
Therapies before IPF diagnosis, N(%)	
Chronic oral steroids	10 (11.1)
Prednisone 5mg daily	6 (6.7)
Prednisone 10mg daily	4 (4.4)
Median duration, weeks (Q1-Q3)	8 (5.75-10)

Abbreviations. SD= standard deviation; Q1= first quartile; Q3= third quartile; T1= first pneumological visit; GAP= Gender-Age-Physiology; IPAQ= international physical activity questionnaire; IBD= inflammatory bowel disease; GERD= gastro-esophageal reflux disease.

**including: arrhythmia, congestive heart failure, myocardial infarction, valvular heart disease, coronary artery disease and stroke*

Table 3. Pulmonary function tests at baseline (T1).

	Population at T1
Patients, n	90
Pulmonary function tests	
FEV1	
Mean (SD)	2.38 (0.67)
Median (Q1-Q3)	2.35 (1.93 - 2.78)
FEV1%	
Mean (SD)	93.63 (21.74)
Median (Q1-Q3)	92.40 (78.00 - 106.00)
FVC	
Mean (SD)	2.89 (0.81)
Median (Q1-Q3)	2.83 (2.38 - 3.43)
FVC%	
Mean (SD)	86.53 (21.07)
Median (Q1-Q3)	86.00 (72.30 - 100.00)
IT	
Mean (SD)	86.07 (11.60)
Median (Q1-Q3)	85.00 (79.50 - 89.00)
TLC	
Mean (SD)	4.75 (1.32)
Median (Q1-Q3)	4.67 (3.92 - 5.83)
TLC%	
Mean (SD)	77.03 (16.31)
Median (Q1-Q3)	77.50 (65.00 - 89.00)
DLCO	
Mean (SD)	6.16 (4.45)
Median (Q1-Q3)	4.66 (2.98 - 7.78)
DLCO%	
Mean (SD)	54.23 (18.36)
Median (Q1-Q3)	52.50 (39.40 - 66.00)

Abbreviations. T1: first pneumological visit; SD= standard deviation; Q1= first quartile; Q3= third quartile; FEV1= forced expiratory volume in the 1st second; FVC= forced vital capacity; IT= Tiffeneau Index; TLC= total lung capacity; DLCO= diffusing capacity for carbon monoxide.

Table 4. Anthropometric and bioelectrical impedance analysis measurements evaluated at T2.

	Males (N=69)	Females (N=18)	Total (N=87)
Anthropometric measurements			
Weight (kg)			
Mean (SD)	77.6 (12.2)	67.8 (12.1)	75.5 (12.8)
Median (Q1-Q3)	76.0 (70.4 - 83.0)	69.5 (55.3 - 78.0)	75.0 (69.0 - 82.0)
Height (m)			
Mean (SD)	1.7 (0.1)	1.5 (0.1)	1.7 (0.1)
Median (Q1-Q3)	1.7 (1.6 - 1.7)	1.5 (1.5 - 1.6)	1.7 (1.6 - 1.7)
BMI (Kg/m ²)			
Mean (SD)	27.3 (3.7)	28.9 (4.8)	27.6 (4.0)
Median (Q1-Q3)	26.4 (24.9 - 29.6)	30.0 (23.0 - 32.4)	26.9 (24.8 - 30.2)
Tricipital skinfold (mm)			
Mean (SD)	9.6 (4.5)	13.7 (4.2)	10.4 (4.7)
Median (Q1-Q3)	9.5 (7.0 - 12.5)	14.3 (12.6 - 16.0)	10.9 (7.5 - 13.5)
Mid-arm circumference (cm)			
Mean (SD)	30.2 (3.5)	30.5 (3.5)	30.2 (3.5)
Median (Q1-Q3)	30.0 (28.0 - 32.0)	30.0 (28.0 - 33.0)	30.0 (28.0 - 32.0)
Calf circumference (cm)			
Mean (SD)	36.4 (3.2)	36.4 (3.0)	36.4 (3.2)
Median (Q1-Q3)	37.0 (35.0 - 38.0)	36.5 (34.0 - 39.0)	37.0 (35.0 - 38.0)
Waist circumference (cm)			
Mean (SD)	99.9 (10.2)	97.6 (11.8)	99.4 (10.5)
Median (Q1-Q3)	99.0 (94.0 - 105.0)	103.3 (89.0 - 105.0)	100.0 (93.0 - 105.0)
Increased waist circumference*, n (%)	28 (40.6%)	14 (77.8%)	42 (48.3%)
Mid-arm muscle circumference (cm)			
Mean (SD)	27.3 (3.3)	27.4 (4.6)	27.3 (3.5)
Median (Q1-Q3)	26.6 (25.2 - 28.7)	26.8 (24.7 - 28.6)	26.6 (25.0 - 28.7)
Bioelectrical impedance analysis			
Resistance (ohms)			
Mean (SD)	371.2 (121.8)	438.6 (127.0)	385.3 (125.2)
Median (Q1-Q3)	406.0 (253.0 - 475.5)	482.5 (317.0 - 551.5)	416.9 (263.0 - 497.0)
Reactance			
Mean (SD)	33.6 (15.6)	37.2 (14.4)	34.3 (15.4)
Median (Q1-Q3)	37.0 (18.4 - 48.0)	42.5 (21.6 - 48.3)	37.0 (18.5 - 48.1)
Phase angle			
Mean (SD)	5.0 (1.2)	4.6 (0.9)	4.9 (1.1)
Median (Q1-Q3)	4.9 (4.1 - 5.8)	4.7 (3.9 - 5.0)	4.9 (4.1 - 5.7)
FFM (Kg)			
Mean (SD)	63.8 (11.5)	49.9 (12.9)	61.0 (13.0)
Median (Q1-Q3)	61.5 (55.0 - 69.1)	44.6 (40.1 - 62.0)	61.3 (53.6 - 67.3)
FFM index (Kg/m ²)			
Mean (SD)	23.6 (6.1)	21.9 (5.4)	23.3 (6.0)
Median (Q1-Q3)	22.7 (19.6 - 25.9)	19.7 (18.0 - 25.2)	22.2 (19.1 - 25.8)
SM mass (Kg)			
Mean (SD)	38.8 (11.8)	24.0 (8.0)	35.7 (12.6)

Median (Q1-Q3)	36.2 (28.8 - 47.0)	20.6 (17.8 - 31.0)	31.9 (27.0 - 46.1)
SM index (Kg/m ²)			
Mean (SD)	14.7 (4.0)	11.0 (3.4)	14.0 (4.1)
Median (Q1-Q3)	15.3 (10.7 - 17.5)	11.8 (7.7 - 13.1)	14.5 (10.1 - 17.2)
BFM (Kg)			
Mean (SD)	14.3 (10.7)	17.9 (11.5)	15.1 (10.9)
Median (Q1-Q3)	12.9 (5.1 - 22.5)	15.8 (6.6 - 29.2)	13.8 (5.6 - 22.5)
BFM index (Kg/m ²)			
Mean (SD)	5.8 (4.8)	8.0 (4.8)	6.2 (4.8)
Median (Q1-Q3)	5.0 (1.8 - 8.7)	8.2 (3.1 - 11.6)	5.3 (2.1 - 9.4)

Abbreviations. T2= first nutritional visit; SDI= standard deviation; Q1= first quartile; Q3= third quartile; BMI= body mass index; FFM= fat-free mass; SM= skeletal muscle; BFM= body fat mass.

** >102 cm Male, >88 cm Female*

SUPPLEMENTARY TABLES

Table E1. List of collected variables at T1 and T2, with missing values.

	n (%)
Baseline (T1), N=90	
Demographics and baseline	
Gender	0 (0.0%)
Birth date	0 (0.0%)
Age at enrolment	0 (0.0%)
Date of IPF diagnosis	0 (0.0%)
GAP stage	1 (1.1%)
GAP index	1 (1.1%)
Smoke	1 (1.1%)
Pack-year (only for smokers and ex-smokers)	6 (9.4%)
Physical activity	
IPAQ	1 (1.1%)
IPAQ categories	1 (1.1%)
Pulmonary function tests	
FEV1	4 (4.4%)
FEV1%	1 (1.1%)
FVC	6 (6.7%)
FVC%	1 (1.1%)
IT	4 (4.4%)
RV	28 (31.1%)
RV%	30 (33.3%)
TLC	13 (14.4%)
TLC%	12 (13.3%)
sRAW	52 (57.8%)
sRAW%	58 (64.4%)
DLCO	16 (17.8%)
DLCO%	2 (2.2%)
Hemogasanalysis	
pH	79 (87.8%)
pO2	80 (88.9%)
pCO2	80 (88.9%)
HCO3	85 (94.4%)
BE	86 (95.6%)
SatO2	1 (1.1%)
FiO2	1 (1.1%)
P/F	81 (90.0%)
6-minute walking test	
Metres	2 (2.2%)
Initial SatO2	3 (3.3%)
Final SatO2	2 (2.2%)
FiO2 - O2 L/min	2 (2.2%)
Breaks	2 (2.2%)

Comorbidities

Arrhythmia	0 (0.0%)
Congestive heart failure	1 (1.1%)
Myocardial infarction	0 (0.0%)
Valvular heart disease	0 (0.0%)
Coronary artery disease	0 (0.0%)
Solid neoplasm	0 (0.0%)
Dysthyroidism	0 (0.0%)
Hematologic neoplasm	0 (0.0%)
MRGE	0 (0.0%)
Osteoporosis	0 (0.0%)
Sleep apnea	0 (0.0%)
Stroke	0 (0.0%)
Dementia	0 (0.0%)
Other neuropathies	0 (0.0%)
COPD	0 (0.0%)
Anxiety an depression	0 (0.0%)
Chronic liver disease	0 (0.0%)
IBD	0 (0.0%)
Cirrhosis	0 (0.0%)
Pulmonary hypertension	1 (1.1%)
Vasculopathy	0 (0.0%)
Diabetes	0 (0.0%)
Hypertension	0 (0.0%)
At least one cardiovascular comorbidity*	1 (1.1%)

Therapies, before IPF diagnosis

Respiratory physical therapy	0 (0.0%)
Oral steroids	1 (1.1%)
Oral steroid type (only for patients with oral steroids)	1 (10.0%)
Pulmonary rehabilitation	0 (0.0%)

After 3 weeks (T2), N=87**Anthropometric measurements**

Weight	0 (0.0%)
Height	0 (0.0%)
BMI	0 (0.0%)
Tricipital skinfold	6 (6.9%)
Arm circumference	0 (0.0%)
Calf circumference	0 (0.0%)
Abdominal circumference	0 (0.0%)
Arm muscle circumference	5 (5.8%)

Nutritional risk screening

Weight 3 months before visit	2 (2.3%)
% weight loss or weight gain in 3 months	0 (0.0%)
MUST	0 (0.0%)
MNA	2 (2.3%)

Biochemical examination

Serum albumin	20 (23.0%)
Serum transferrin	25 (28.7%)
Hb	4 (4.6%)

HT	5 (5.8%)
Total cholesterol	16 (18.4%)
HDL	23 (26.4%)
LDL	26 (29.9%)
Serum creatinine	10 (11.5%)
Urea	18 (20.7%)
Uric acid	34 (39.1%)
AST	7 (8.1%)
ALT	7 (8.1%)
Gamma GT	15 (17.2%)
Total bilirubin	12 (13.8%)
Direct bilirubin	64 (73.6%)
Total calcium	20 (23.0%)
Ionized calcium	37 (42.5%)
Fasting blood glucose	14 (16.1%)
Serum phosphorous	34 (39.1%)
Vitamin D	24 (27.6%)
CRP	22 (25.3%)
TSH	23 (26.4%)

Bioelectrical impedance analysis

Resistance	1 (1.2%)
Reactance	3 (3.6%)
Phase angle	1 (1.2%)
FFM	2 (2.3%)
FFM index	2 (2.3%)
FFM index category	2 (2.3%)
SM mass	1 (1.2%)
SM index	1 (1.2%)
BFM	1 (1.2%)
BFM index category	1 (1.2%)

Dynamometry

Hand grip strength right hand	0 (0.0%)
Hand grip strength left hand	0 (0.0%)

Physical performance

GAIT speed 4-meter (m/s)	1 (1.2%)
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Abbreviations. T1: first pneumological visit; T2: first nutritional visit, IPAQ: international physical activity questionnaire, FEV1: forced expiratory volume in the 1st second, FVC: forced vital capacity, IT: Tiffeneau Index, RV: residual volume, TLC: total lung capacity, sRAW: specific airway resistance, DLCO: diffusing capacity for carbon monoxide, pH: potential of hydrogen, pO2: partial pressure of oxygen, pCO2: partial pressure of carbon dioxide, HCO3: hydrogen carbonate, BE: Base Excess, SatO2: oxygen saturation, FiO2: fraction of inspired oxygen, P/F: PaO2/FiO2 ratio, SatO2: oxygen saturation, GERD: gastro-esophageal reflux disease, COPD: chronic obstructive pulmonary disease, IBD: inflammatory bowel disease, MUST: malnutrition universal screening tool, MNA: mini nutritional assessment, Hb: hemoglobin, HT: haematocrit value, CRP: C-reactive protein, HDL: high-density lipoprotein, LDL: low-density lipoprotein, AST: aspartate transaminase, ALT: alanine transaminase, TSH: thyroid-stimulating hormone, FFM: fat-free mass, SM: skeletal muscle, BFM: body fat mass.

**including: arrhythmia, congestive heart failure, myocardial infarction, valvular heart disease , coronary artery disease and stroke.*

Table E2. Laboratory exams performed at T2.

	Population at T2
Patients still in follow-up	87
Biochemical examination	
Serum albumin (g/dl)	
Mean (SD)	5.3 (6.6)
Median (Q1-Q3)	4.1 (3.9 - 4.4)
Serum transferrin (µg/dl)	
Mean (SD)	239.6 (46.04)
Median (Q1-Q3)	237.5 (210.0 - 261.0)
Hb (g/dl)	
Mean (SD)	14.5 (1.4)
Median (Q1-Q3)	14.6 (13.6 - 15.6)
HT%	
Mean (SD)	43.8 (4.4)
Median (Q1-Q3)	44.3 (40.0 - 46.6)
CRP (mg/dL)	
Mean (SD)	1.4 (2.5)
Median (Q1-Q3)	0.5 (0.2 - 1.4)
Total cholesterol (mg/dl)	
Mean (SD)	173.1 (39.0)
Median (Q1-Q3)	176.0 (146.0 - 203.0)
HDL (mg/dl)	
Mean (SD)	51.3 (14.0)
Median (Q1-Q3)	50.0 (41.0 - 57.0)
LDL (mg/dl)	
Mean (SD)	106.9 (32.3)
Median (Q1-Q3)	111.0 (88.0 - 125.0)
Serum creatinine (mg/dl)	
Mean (SD)	1.0 (0.3)
Median (Q1-Q3)	1.0 (0.9 - 1.2)
Urea (mg/dl)	
Mean (SD)	43.3 (15.3)
Median (Q1-Q3)	40.0 (32.0 - 53.0)
AST (U/l)	
Mean (SD)	25.4 (8.6)
Median (Q1-Q3)	23.0 (20.0 - 28.0)
ALT (U/l)	
Mean (SD)	24.2 (13.6)
Median (Q1-Q3)	19.0 (14.5 - 30.0)
Gamma GT (U/l)	
Mean (SD)	44.5 (47.9)
Median (Q1-Q3)	29.0 (16.5 - 56.0)
Total bilirubin (mg/dl)	
Mean (SD)	0.8 (0.4)
Median (Q1-Q3)	0.7 (0.5 - 0.9)
Total calcium (mg/dl)	
Mean (SD)	9.0 (1.8)
Median (Q1-Q3)	9.4 (9.2 - 9.6)
Fasting blood glucose (mg/dl)	
Mean (SD)	102.8 (19.6)
Median (Q1-Q3)	98.0 (88.0 - 111.0)
Vitamin D (ng/dl)	
Mean (SD)	22.4 (14.3)

Median (Q1-Q3)	17.5 (12.2 - 31.0)
Vitamin D categories, N(%)	
Normal (≥ 30)	14 (16.1%)
Insufficient (20 - 30)	14 (16.1%)
Deficit (<20)	35 (40.2%)
TSH (mIU/l)	1.97 (1.3)
Mean (SD)	1.97 (1.3)
Median (Q1-Q3)	1.73 (1.0 - 2.5)

Abbreviations. T2: first nutritional visit, SD: standard deviation, Q1: first quartile, Q3: third quartile, Hb: hemoglobin, HT: haematocrit value, CRP: C-reactive protein, HDL: high-density lipoprotein, LDL: low-density lipoprotein, AST: aspartate transaminase, ALT: alanine transaminase, TSH: thyroid-stimulating hormone.

TABLE E3. Estimated distribution of nutritional phenotypes, using 5 or 6 classes

Phenotype	N patients*	Prevalence (95% Confidence Interval)
5 classes		
Cachectic	0	0.0% (0.0 - 9.9)
Sarcopenic	4	4.6% (0.0 - 14.5)
Normally nourished	59	67.8% (58.6 - 77.7)
Non-sarcopenic obese	22	25.3% (16.1 - 35.2)
Sarcopenic obese	2	2.3% (0.0 - 12.2)
6 classes		
Cachectic	0	0.0% (0.0 - 11.4)
Sarcopenic	4	4.6% (0.0 - 16.0)
Normally nourished	39	44.8% (34.5 - 56.2)
Normonourished with overweight	20	23.0% (12.6 - 34.4)
Non-sarcopenic obese	22	25.3% (14.9 - 36.7)
Sarcopenic obese	2	2.3% (0.0 - 13.7)

* Patients still in follow-up at the first nutritional assessment (T2).

TABLE E4. Comparison between IPF severity score at diagnosis and physical performance indices before and after the Italian lockdown due to COVID-19 pandemic.

	Visit date		Comparison, p-value
	Before March, 1 st 2020	After March, 1 st 2020	
GAP index			
Mean (SD)	2.21 (1.2)	3.60 (1.3)	<0.0001
Median (Q1-Q3)	2.0 (1.0 - 3.0)	3.00 (3.0 - 5.0)	
IPAQ			
Mean (SD)	2,031.9 (2,847.9)	2,353.4 (3,363.6)	0.8900
Median (Q1-Q3)	900.0 (205.0 - 2,715.0)	950.0 (262.5 - 2,220.0)	
4-meter gait speed (m/s)			
Mean (SD)	1.2 (0.3)	1.1 (0.3)	0.1520
Median (Q1-Q3)	1.3 (0.9 - 1.4)	1.05 (0.9 - 1.2)	
Hand Grip strenght (kg)			
Mean (SD)	30.2 (8.3)	28.6 (8.5)	0.3679
Median (Q1-Q3)	31.8 (24.4 - 35.8)	27.9 (23.4 - 34.1)	
BMI (Kg/m²)			
Mean (SD)	28.3 (4.1)	26.83 (3.8)	0.1195
Median (Q1-Q3)	27.3 (25.3 - 30.5)	26.20 (23.7 - 29.8)	
Percent weight loss (3 months)			
Mean (SD)	1.2 (2.7)	1.9 (4.1)	0.3505
Median (Q1-Q3)	0.0 (0.0 - 0.0)	0.0 (0.0 - 2.5)	
FFM index (Kg/m2)			
Mean (SD)	22.2 (4.7)	24.9 (7.0)	0.0314
Median (Q1-Q3)	21.4 (19.1 - 25.0)	23.8 (20.8 - 28.1)	
Nutritional phenotype - N(%)			0.8390
Sarcopenic	3 (6.5%)	1 (2.6%)	
Normonourished	29 (63.0%)	28 (71.8%)	
Non-sarcopenic obese	13 (28.3%)	9 (23.1%)	
Sarcopenic obese	1 (2.2%)	1 (2.6%)	

Abbreviations. T1: first pneumological visit; T2: first nutritional visit, SD: standard deviation, Q1: first quartile, Q3: third quartile, IPAQ: international physical activity questionnaire, GAP: Gender-Age-Physiology; FFM: fat-free mass; BMI: body mass index.