Nutritional assessment in idiopathic pulmonary fibrosis: a prospective multicentre study

Paola Faverio[1,19], Alessia Fumagalli[2,19], Sara Conti[3,4], Fabiana Madotto[3], Francesco Bini[5], Sergio Harari[6,7], Michele Mondoni[8], Tiberio Oggionni[9], Emanuela Barisione[10], Paolo Ceruti[11], Maria Chiara Papetti[5], Bruno Dino Bodini[5], Antonella Caminati[6], Angela Valentino[12], Stefano Centanni[8], Donatella Noè[13], Matteo Della Zoppa[9], Silvia Crotti[14], Marco Grosso[10], Samir Giuseppe Sukkar[15], Denise Modina[11], Marco Andreoli[16], Roberta Nicali[17], Giulia Suigo[18], Federica De Giacomi[1], Sara Busnelli[1], Elena Cattaneo[9], Lorenzo Giovanni Mantovani[3,4], Giancarlo Cesana[4], Alberto Pesci[1] and Fabrizio Luppi[1]

[1]Respiratory Unit, School of Medicine and Surgery, University of Milano Bicocca, San Gerardo Hospital, ASST Monza, Monza, Italy. [2]Pulmonary Rehabilitation Unit, Research Hospital of Casatenovo, Italian National Research Centre on Aging, Casatenovo, Italy. [3]Value-based Healthcare Unit, IRCCS Multimedica, Sesto San Giovanni, Italy. [4]Dept of Medicine and Surgery, Università degli Studi di Milano-Bicocca, Monza, Italy. [5]UOC Pneumologia, Ospedale G. Salvini, ASST Rhodense, Garbagnate Milanese, Italy. [6]UOC di Pneumologia e Terapia Semi-Intensiva Respiratoria – Servizio di Fisiopatologia Respiratoria ed Emodinamica Polmonare, Ospedale San Giuseppe, IRCCS Multimedica, Milan, Italy. [7]Depts of Medical Sciences, and Clinical Sciences and Community Health, San Giuseppe Hospital IRCCS Multimedica, University of Milan, Milan, Italy. [8]Respiratory Unit, Dept of Health Sciences, ASST Santi Paolo e Carlo, Università degli Studi di Milano, Milan, Italy. [9]Pulmonology Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. [10]UOC Pneumologia Interventistica, IRCCS Policlinico San Martino, Genoa, Italy. [11]UOC Pneumologia e Fisiopatologia Respiratoria, ASST Spedali Civili di Brescia, Brescia, Italy. [12]UOC di Diabetologia e Malattie Metaboliche, IRCCS Multimedica, Milan, Italy. [13]SSD Servizio Dietetico e Nutrizione Clinica, ASST Santi Paolo e Carlo, Milan, Italy. [14]Clinical Nutrition and Dietetics Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. [15]UOD Dietetica e Nutrizione Clinica, IRCCS Ospedale Policlinico San Martino, Genoa, Italy. [16]USD Servizio Dietetica e Nutrizione clinica, ASST di Brescia, Brescia, Italy. [17]UOC Pneumologia, Azienda Ospedaliero Universitaria Maggiore della Carità, Novara, Italy. [18]UO Pneumologia, Azienda Ospedaliera di Circolo, Busto Arsizio, Italy. [19]These authors contributed equally.

Corresponding author: Paola Faverio (paola.faverio@unimib.it)

Shareable abstract (@ERSpublications)
Patients with IPF at diagnosis are mainly normally nourished and obese but early signs of nutritional and physical performance impairment can already be identified. Sarcopenia is identified only in a minority of cases; cachexia has not been observed. https://bit.ly/3kZuRh2

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Abstract

Background Nutritional status impacts 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 aimed to investigate the nutritional status 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 nutritional status, and physical activity, anthropometry, body impedance, dynamometry, 4-m 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% 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 the normally nourished, 49.2% showed early signs of nutritional and physical performance alterations, including body mass index $\geqslant 30\ kg \cdot m^{-2}$ in 4.3%, history of weight loss ⩾5% in 11.9%, and 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 characterised by progressive reduction of physical activity, muscle deconditioning and sarcopenia [1]. Most of the evidence regarding nutritional status is 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 and colleagues included obesity, sarcopenic obesity, sarcopenia and cachexia, and required at least three 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 3 and 5 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 IP,F 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 [6–8].

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, 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 aimed to investigate the nutritional status, defined as the set of nutritional (BIA, anthropometric measurements, blood examinations and nutritional risk assessment tests) and physical performance (dynamometry, 4-m 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 nine 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, Genoa; Ospedale di Circolo, Busto Arsizio; and Ospedale Maggiore della Carità, Novara). This study received Ethics Committee approval and was registered at www.clinicaltrials.gov (identifier number NCT03770845; NutrIPF study).

Patients were eligible for inclusion if they were ⩾40-years of age, received a diagnosis of IPF according to the American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japan Respiratory Society/Latin American Thoracic Society 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 <30 $mL \cdot min^{-1}$; were in a New York Heart Association class IV (unable to carry out any physical activity without discomfort); had severe liver failure, defined as Child-Pugh score class C; had active solid or haematological tumours; were receiving or had already received therapy with pirfenidone or nintedanib; were unable to walk; needed oxygen therapy at rest; or were already recruited in other interventional experimental protocols studying new drugs. All patients provided written informed consent at the time of enrolment. The study is reported according to Strengthening the Reporting of Observational Studies in Epidemiology guidelines [9].

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

The study visits were organised 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 of the lung for carbon monoxide (D_{LCO}), 6-min walking test and Gender-Age-Physiology (GAP) score. 2) During the first nutritional assessment (T2), the following items were collected: anthropometric measurements; blood examinations including liver function (transaminases, γ-glutamyltransferase, and 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, ionised calcium and thyroid-stimulating hormone; 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-m gait speed test.

Procedures

PFTs and D_{LCO} measurements were performed according to the ATS/ERS standardisation using a dry spirometer [10–12]. A 6-min walking test 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, and 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-m gait speed test conducted along a 4-m corridor. Walking speed was calculated by dividing the distance by the time needed to cover the distance ($m \cdot s^{-1}$).

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 (X_c) were directly measured in ohms (Ω) at 50 kHz and 800 mA. Phase angle measures using the BIA reflect the relative contributions of fluid (R) and cellular membranes (X_c) of the body. It was calculated using the equation [17]:

$$\text{Phase angle} = \left(\frac{R}{X_c}\right) \times \left(\frac{180}{\pi}\right)$$

Fat-free mass index (FFMI) ($kg \cdot m^{-2}$) was calculated as:

$$\text{FFMI} = \frac{\text{fat-free mass}}{\text{height}^2}$$

Skeletal muscle index (SMI) ($kg \cdot m^{-2}$) was calculated as:

$$\text{SMI} = \frac{\text{skeletal muscle mass}}{\text{height}^2}$$

Body fat mass (BFM) was calculated as total body weight minus fat-free mass (FFM) and then body fat mass index (BFMI) was derived:

$$\text{BFMI} = \frac{\text{BFM}}{\text{height}^2}$$

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".

TABLE 1 Criteria to identify nutritional phenotypes in study population

Nutritional phenotypes	Parameters and cut-off
Cachexia	BMI <18.5 $kg \cdot m^{-2}$ Involuntary weight loss >5% in the last 3 months FFMI <17 $kg \cdot m^{-2}$ for males or <15 $kg \cdot m^{-2}$ for females SMI <8.87 $kg \cdot m^{-2}$ for males or <6.42 $kg \cdot m^{-2}$ for females BFMI <1.7 $kg \cdot m^{-2}$ for males or <3.8 $kg \cdot m^{-2}$ for females Elevated serum CRP concentrations ($\geqslant$5 $mg \cdot dL^{-1}$) and/or reduced serum concentrations of albumin (albumin <3.2 $g \cdot dL^{-1}$)
Sarcopenia	BMI <30 $kg \cdot m^{-2}$ FFMI <17 $kg \cdot m^{-2}$ for males or <15 $kg \cdot m^{-2}$ for females SMI <8.87 $kg \cdot m^{-2}$ for males or <6.42 $kg \cdot m^{-2}$ for females BFMI $\geqslant$1.7 $kg \cdot m^{-2}$ for males or $\geqslant$3.8 $kg \cdot m^{-2}$ for females Hand grip <30 kg for males or <20 kg for females Gait speed (4 m) <0.8 $m \cdot s^{-1}$
Normal nutritional status	BMI between 18.5 and 24.9 $kg \cdot m^{-2}$ (overweight if BMI $\geqslant$25 $kg \cdot m^{-2}$ and <30 $kg \cdot m^{-2}$) FFMI $\geqslant$17 $kg \cdot m^{-2}$ for males or $\geqslant$15 $kg \cdot m^{-2}$ for females BFMI between 1.7 $kg \cdot m^{-2}$ and 5.19 $kg \cdot m^{-2}$ for males or between 3.8 $kg \cdot m^{-2}$ and 8.19 $kg \cdot m^{-2}$ for females Hand grip >30 kg for males or >20 kg for females Gait speed (4 m) $\geqslant$0.8 $m \cdot s^{-1}$ No involuntary weight loss >5% in the last 3 months
Non-sarcopenic obesity	BMI $\geqslant$30 $kg \cdot m^{-2}$ Abdominal circumference >102 cm for males or >88 cm for females FFMI $\geqslant$17 $kg \cdot m^{-2}$ for males or $\geqslant$15 $kg \cdot m^{-2}$ for females SMI $\geqslant$8.87 $kg \cdot m^{-2}$ for males or $\geqslant$6.42 $kg \cdot m^{-2}$ for females BFMI $\geqslant$8.3 $kg \cdot m^{-2}$ for males or $\geqslant$11.82 $kg \cdot m^{-2}$ for females Hand grip >30 kg for males or >20 kg for females Gait speed (4 m) $\geqslant$0.8 $m \cdot s^{-1}$
Sarcopenic obesity	BMI $\geqslant$30 $kg \cdot m^{-2}$ Abdominal circumference >102 cm for males or >88 cm for females FFMI <17 $kg \cdot m^{-2}$ for males or <15 $kg \cdot m^{-2}$ for females SMI <8.87 $kg \cdot m^{-2}$ for males or <6.42 $kg \cdot m^{-2}$ for females BFMI $\geqslant$8.3 $kg \cdot m^{-2}$ for males or $\geqslant$11.82 $kg \cdot m^{-2}$ for females Hand grip <30 kg for males or <20 kg for females Gait speed (4 m) <0.8 $m \cdot s^{-1}$

BMI: body mass index; FFMI: fat-free mass index; BFMI: body fat mass index; SMI: skeletal muscle index; CRP: C-reactive protein.

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 evidence 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 centres in the 1-year time span. In fact, considering the rarity of the disease (incidence rate ~5.5 per 100 000 persons per year [19]) and the population served by participating centres (~2.5 million people), the number of expected new cases of IPF would be ~140 over 1 year, and consequently, our sample would cover >50% of such cases. However, the onset of the coronavirus disease 2019 (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 intervals for each prevalence were estimated with the Sison and Glaz [20] approach for multinomial proportions.

Summary statistical measures used to describe study population were mean±SD for continuous data and n (%) for categorical variables. In this analysis, the proportion of missing data was low and, therefore, no imputation procedure was performed (supplementary table E1).

Statistical significance was accepted at $p<0.05$ and all tests were two-tailed. Statistical analyses were performed with R, version 3.5.2 (R Project for Statistical Computing, 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 the 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 gastro-oesophageal reflux disease in 23 (25.6%). 10 (11.1%) patients were on oral steroids (prednisone or methylprednisolone) prescribed before IPF diagnosis, while nobody participated in pulmonary rehabilitation programmes.

Functional and physical performance indices

The majority of patients showed preserved forced vital capacity (FVC) values, with mean±SD FVC of 86.5±21.1% pred, a mild total lung capacity reduction and a moderate D_{LCO} impairment (54.2±18.4%) (table 3). Mean±SD distance walked in the 6-min walking test was 408.2±109.8 m and 11 (12.2%) patients required oxygen supplementation during effort. Among the 87 patients that performed the assessment, 4-m gait speed was 1.11±0.31 $m \cdot s^{-1}$ and 69 (79.3%) patients showed gait velocity impairment (<0.8 $m \cdot s^{-1}$).

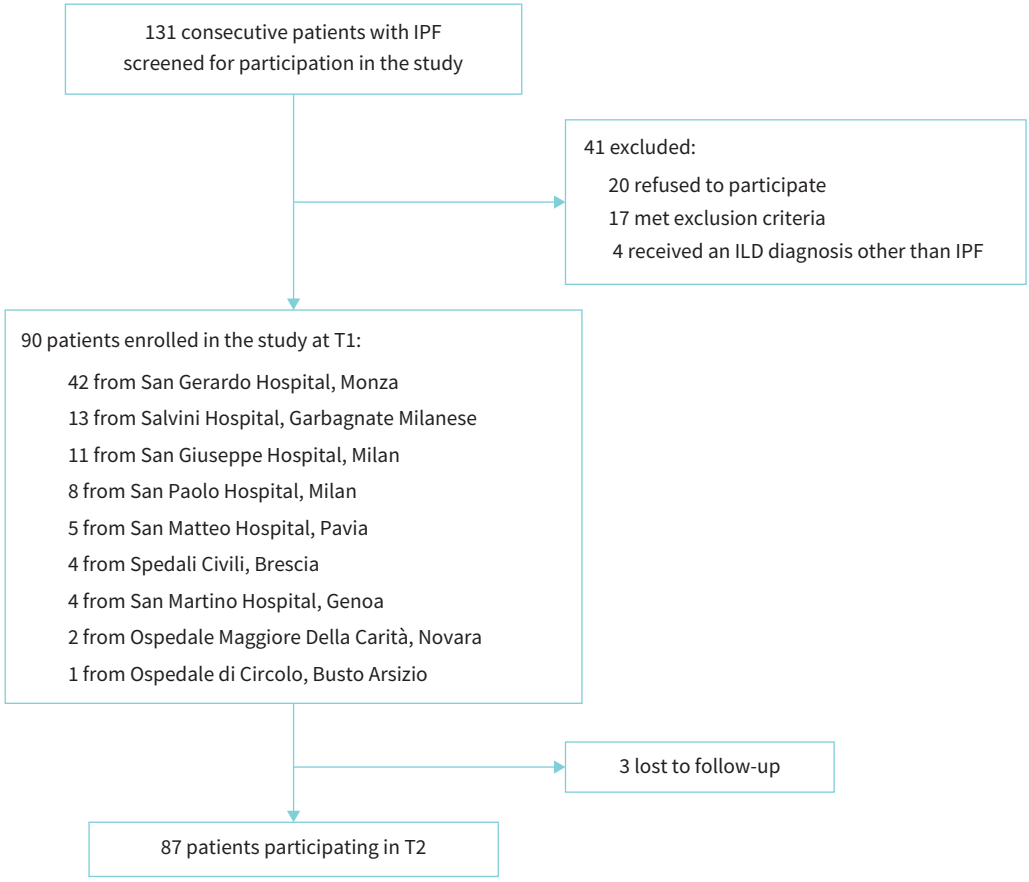

FIGURE 1 Study flow chart. ILD: interstitial lung disease; IPF: idiopathic pulmonary fibrosis.

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 (interquartile range)	73 (68–78)
Smoking history, n (%)	
Non-smoker	25 (27.8)
Active smoker	1 (1.1)
Ex-smoker	63 (70.00)
IPF GAP stage, n(%)	
1	26 (28.9)
2	47 (52.2)
3	16 (17.8)
Physical activity	
IPAQ score	
Mean±SD	2089±2977
Median (interquartile range)	900 (262.5–2506)
IPAQ category, 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)
GORD	23 (25.6)
Osteoporosis	7 (7.8)
Previous solid neoplasm	14 (15.6)
Anxiety and depression	6 (6.7)
Therapies before IPF diagnosis	
Chronic oral steroids, n (%)	10 (11.1)
Prednisone 5 mg daily	4 (4.4)
Prednisone 10 mg daily	6 (6.7)
Duration, weeks, median (interquartile range)	8 (5.75–10)

IPF: idiopathic pulmonary fibrosis; GAP: Gender-Age-Physiology; IPAQ: International Physical Activity Questionnaire; IBD: inflammatory bowel disease; GORD: gastro-oesophageal reflux disease. [#]: including arrhythmia, congestive heart failure, myocardial infarction, valvular heart disease, coronary artery disease and stroke.

Regarding hand-held dynamometry values, mean±SD hand grip strength for men and women was 31.9±7.1 and 19.5±5.0 kg, respectively. 29 (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 $kg \cdot m^{-2}$, with a predominance of patients in the overweight and non-sarcopenic obesity classes (39 (44.8%) and 24 (27.6%) cases, respectively). Only about a quarter of cases (27.6%) showed normal weight and none was underweight. Anthropometric measurements are summarised in table 4. Weight loss >5% and weight gain >5% in the 3 months prior to T2 were observed in nine (10%) and two (2%) patients, respectively. 48% of patients showed an increased waist circumference (waist circumference >102 cm in men and >88 cm in

TABLE 3 Pulmonary function tests at baseline (T1)

	Population at T1
Patients, n	90
FEV_1, L	
Mean±SD	2.38±0.67
Median (interquartile range)	2.35 (1.93–2.78)
FEV_1, % pred	
Mean±SD	93.63±21.74
Median (interquartile range)	92.40 (78.00–106.00)
FVC, L	
Mean±SD	2.89±0.81
Median (interquartile range)	2.83 (2.38–3.43)
FVC, % pred	
Mean±SD	86.53±21.07
Median (interquartile range)	86.00 (72.30–100.00)
FEV_1/FVC, %	
Mean±SD	86.07±11.60
Median (interquartile range)	85.00 (79.50–89.00)
TLC, L	
Mean±SD	4.75±1.32
Median (interquartile range)	4.67 (3.92–5.83)
TLC, % pred	
Mean±SD	77.03±16.31
Median (interquartile range)	77.50 (65.00–89.00)
D_{LCO}, mmol·min^{-1}·kPa^{-1}	
Mean±SD	6.16±4.45
Median (interquartile range)	4.66 (2.98–7.78)
D_{LCO}, % pred	
Mean±SD	54.23±18.36
Median (interquartile range)	52.50 (39.40–66.00)

FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; TLC: total lung capacity; D_{LCO}: diffusing capacity for carbon monoxide.

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 and 27.3±3.5 cm, respectively, both in the normal range.

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

In regards to laboratory examinations, 21 (24.1%) patients showed total cholesterol levels ⩾200 mg·dL^{-1} and low-density lipoprotein cholesterol was ⩾115 mg·dL^{-1} in 27 (31.0%) cases. 28 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 (<20 ng·mL^{-1}) and insufficiency (20–30 ng·mL^{-1}) were reported in 35 (40.2%) and 14 (16.1%) patients, respectively. Eight (9.2%) patients received chronic vitamin D supplementation and four of them showed insufficiency in blood examinations. Unfortunately, information on vitamin D levels was missing for 24 patients (27.6%); therefore, this evidence should be interpreted with caution (supplementary table E1). Similarly, laboratory examinationss were not performed in up to 28% of patients in our cohort; however, no alterations were observed in the other laboratory examinations (supplementary table E2).

BIA values are summarised in table 4. Low FFMI (<17 kg·m^{-2} in men and <15 kg·m^{-2} in women), SMI (<8.87 kg·m^{-2} in men and <6.42 kg·m^{-2} in women) and BFMI (<1.7 kg·m^{-2} in men and <3.8 kg·m^{-2} in women) were identified in four (4.6%), four (4.6%) and 19 (21.8%) patients, respectively. In 20 (23.0%) patients, we observed a reduced phase angle (<4°), a marker of cell membrane function.

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 (interquartile range)	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 (interquartile range)	1.7 (1.6–1.7)	1.5 (1.5–1.6)	1.7 (1.6–1.7)
BMI, $kg \cdot m^{-2}$			
Mean±SD	27.3±3.7	28.9±4.8	27.6±4.0
Median (interquartile range)	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 (interquartile range)	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 (interquartile range)	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 (interquartile range)	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 (interquartile range)	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 (interquartile range)	26.6 (25.2–28.7)	26.8 (24.7–28.6)	26.6 (25.0–28.7)
Bioelectrical impedance analysis			
Resistance, Ω			
Mean±SD	371.2±121.8	438.6±127.0	385.3±125.2
Median (interquartile range)	406.0 (253.0–475.5)	482.5 (317.0–551.5)	416.9 (263.0–497.0)
Reactance, Ω			
Mean±SD	33.6±15.6	37.2±14.4	34.3±15.4
Median (interquartile range)	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 (interquartile range)	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 (interquartile range)	61.5 (55.0–69.1)	44.6 (40.1–62.0)	61.3 (53.6–67.3)
FFMI, $kg \cdot m^{-2}$			
Mean±SD	23.6±6.1	21.9±5.4	23.3±6.0
Median (interquartile range)	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 (interquartile range)	36.2 (28.8–47.0)	20.6 (17.8–31.0)	31.9 (27.0–46.1)
SMI, $kg \cdot m^{-2}$			
Mean±SD	14.7±4.0	11.0±3.4	14.0±4.1
Median (interquartile range)	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 (interquartile range)	12.9 (5.1–22.5)	15.8 (6.6–29.2)	13.8 (5.6–22.5)
BFMI, $kg \cdot m^{-2}$			
Mean±SD	5.8±4.8	8.0±4.8	6.2±4.8
Median (interquartile range)	5.0 (1.8–8.7)	8.2 (3.1–11.6)	5.3 (2.1–9.4)

T2: first nutritional visit; BMI: body mass index; FFM: fat-free mass; FFMI: fat-free mass index; SM: skeletal muscle; SMI: skeletal muscle index; BFM: body fat mass; BFMI: body fat mass index. [#]: >102 cm for males and >88 cm for females.

Waist circumference, cm	BMI, kg·m^{-2} 18.5–25	25–30	≥30
	Men		
< 102	Low risk 19 (27.54%)	Increased risk 20 (28.99%)	High risk 1 (1.45%)
≥102	Increased risk 0 (0.00%)	High risk 15 (21.74%)	Very high risk 14 (20.29%)
	Women		
<88	Low risk 3 (16.67%)	Increased risk 1 (5.56%)	High risk 0 (0.00%)
≥88	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).

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 and supplementary table E3). The majority of normally nourished patients showed early signs of nutritional and physical performance impairment, including BMI ⩾30 kg·m^{-2} in 3.4% of cases, history of weight loss

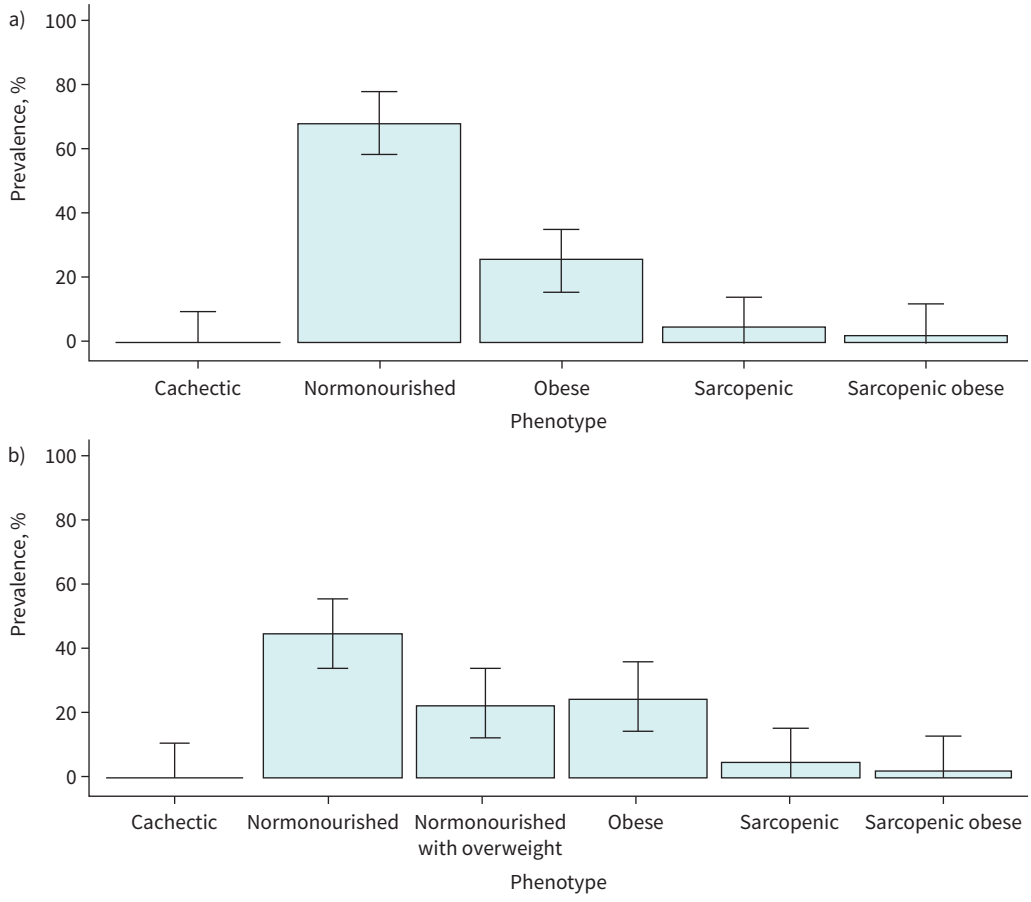

FIGURE 3 Prevalence of nutritional phenotypes evaluated at first nutritional visit (T2). a) Classification based on five phenotypes. b) Classification based on six phenotypes. Error bars represent 95% confidence intervals.

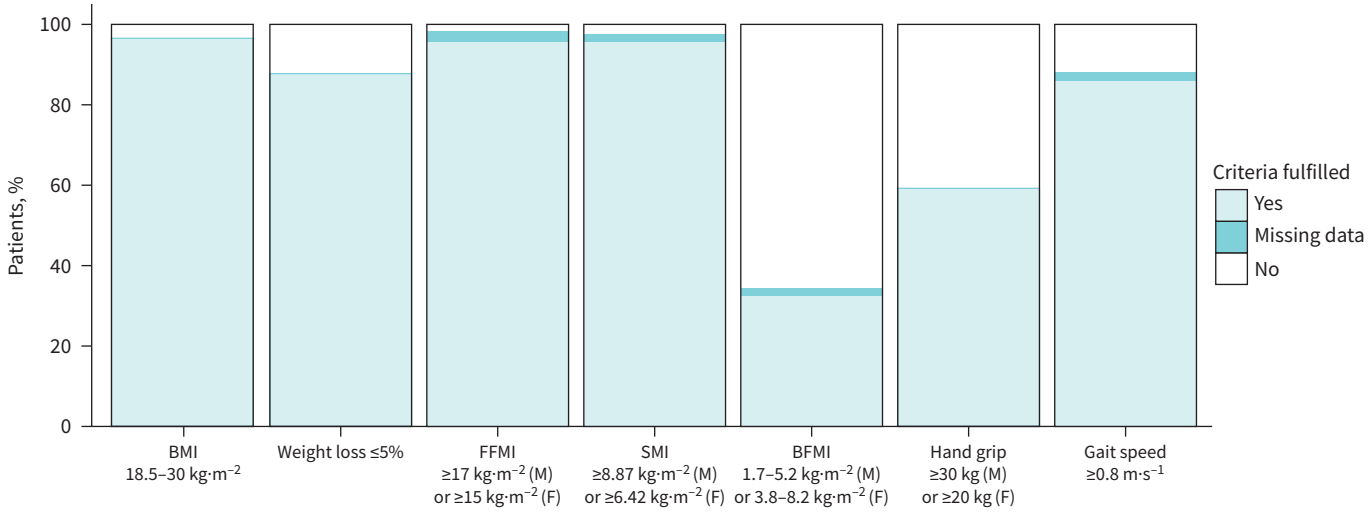

FIGURE 4 Criteria fulfilled among patients classified in the "normal nutritional status" phenotype. BMI: body mass index; FFMI: fat-free mass index; M: male; F: female; SMI: skeletal muscle index; BFMI: body fat mass index.

⩾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 *versus* 30±8.2 kg, p=0.03) and slower 4-m gait speed (0.9±0.4 *versus* 1.1±0.3 m·s^{-1}, p=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 nine 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 two 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 nine (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 kg·m^{-2} in 3.4% of cases, history of weight loss ⩾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 that our study recruited patients at the time of diagnosis, only about one third of them was classified as GAP stage 1 at enrolment, 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 programmes that

may reduce nutritional and physical performance impairment; secondly, the importance of an early IPF diagnosis, as the introduction of a rehabilitation programme 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. 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 concentrations were observed in the great majority of cases, but only a minority of these patients 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 Scholls *et al.* [3], allowed the identification of 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 including in a nutritional evaluation for IPF patients both nutritional parameters (BIA, anthropometric measurements and laboratory examinations) and indicators of physical performance, such as dynamometry and 4-m gait speed.

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, which allowed us to enhance the generalisability of the results; and 2) the choice to include only patients at the time of diagnosis, before the introduction of antifibrotic therapies, which allowed us to describe patients at the beginning of disease trajectory and to start a prospective longitudinal data collection, including nutritional status.

Our study also presents some limitations: the recruitment period partially overlapped with COVID-19 pandemic, which hit northern Italy with particular severity. This event prompted us to close recruitment ahead of schedule in order not to accumulate excessive delay on the planned study schedule, as explained above. In a secondary analysis (supplementary 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 1 March 2020). We observed no differences in nutritional variables and phenotypes, or in physical performance indices, but the average GAP stage at enrolment rose from 2.2±1.2 to 3.6±1.3 ($p<0.0001$) after the outbreak, suggesting an indirect impact of the 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", which 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 patient 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 personalised in accordance with the patient's nutritional phenotype.

Provenance: Submitted article, peer reviewed.

This study is registered at www.clinicaltrials.gov with identifier number NCT03770845.

Ethics statement: Our research complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Conflict of interest: P. Faverio reports personal fees from Boehringer Ingelheim and grants from Roche, outside the submitted work. A. Fumagalli has nothing to disclose. S. Conti has nothing to disclose. F. Madotto has nothing to disclose. F. Bini has nothing to disclose. S. Harari reports personal fees from Actelion, Roche and Boehringer Ingelheim, outside the submitted work. M. Mondoni has nothing to disclose. T. Oggionni has nothing to disclose. E. Barisione reports personal fees from Chiesi Farmaceutici, Boehringer Ingelheim and GlaxoSmithKline, outside the submitted work. P. Ceruti has nothing to disclose. M.C. Papetti has nothing to disclose. B.D. Bodini has nothing to disclose. A. Caminati reports personal fees from Roche and Boehringer Ingelheim, outside the submitted work. A. Valentino has nothing to disclose. S. Centanni has nothing to disclose. D. Noè has nothing to disclose. M. Della Zoppa has nothing to disclose. S. Crotti has nothing to disclose. M. Grosso reports personal fees from Chiesi Farmaceutici and Johnson & Johnson, outside the submitted work. S.G. Sukkar has nothing to disclose. D. Modina has nothing to disclose. M. Andreoli has nothing to disclose. R. Nicali has nothing to disclose. G. Suigo has nothing to disclose. F. De Giacomi has nothing to disclose. S. Busnelli has nothing to disclose. E. Cattaneo has nothing to disclose. L.G. Mantovani has nothing to disclose. G. Cesana has nothing to disclose. A. Pesci has nothing to disclose. F. Luppi reports lectures fee from Roche and from Boehringer Ingelheim.

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