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Original article

Malnutrition according to ESPEN consensus predicts hospitalizations and long-term mortality in rehabilitation patients with stable chronic obstructive pulmonary disease☆

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SUMMARY

Background: Nutritional disorders are frequent in patients with chronic pulmonary obstructive disease (COPD) and have negative health impacts. This study aimed to explore the value of the European Society of Clinical Nutrition and Metabolism (ESPEN) definition of malnutrition (and/or its individual components) to predict hospitalizations and mortality at 2 years, and to determine the prevalence of malnutrition in COPD patients referred to pulmonary rehabilitation.
Methods: The study was a prospective analysis of 118 patients with COPD free of exacerbations and/or hospital admissions in the previous two months. Main outcome variables were mortality, hospital admissions, and length of stay at 2-year follow-up; main covariates were malnutrition assessment according to the ESPEN definition and its components: unintentional weight loss, body mass index, and fat-free mass index (FFMI). Body composition was assessed by bioimpedance analysis. Kaplan-Meier survival curves and linear regression analyses were performed, adjusting for age and airflow obstruction as potential confounders.
Results: The observed prevalence of malnutrition was 24.6%. Malnutrition was associated with increased mortality risk (HR = 3.9 [95% CI: 1.4–10.62]). FFMI was independently associated with increased mortality (HR = 17.0 [95% CI: 2.24–129.8]), which persisted after adjustment for age and lung function (adjusted HR = 13.0 [95% CI: 1.67–101.7]). Low age-related body mass index was associated with increased risk of hospital admissions.
Conclusions: Malnutrition according to ESPEN criteria, highly prevalent in patients with stable COPD referred to pulmonary rehabilitation, was associated with 4 times greater mortality risk after 2 years. Low FFMI was associated with a 17-fold increase in mortality risk, suggesting independent predictive value.

☆ EM, DSR, and NDY wrote the manuscript; EMR, DSR, AA, and JMM prepared the literature review; EM, NDY, and EMP participated in data collection; XD, EM, DSR and ED did the data analysis; ED, JMM, DAR, and FE corrected the manuscript. All co-authors read and approved the final version of the manuscript.

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Abbreviations

BMI	Body mass index
BODE	Body mass index, Obstruction, Dyspnoea, and Exercise
BW	Body weight
COPD	Chronic obstructive pulmonary disease
DL_{CO}	Carbon monoxide diffusing capacity
EPIDOS	EPIDémiologie de l'OStéoporose study
ERS	European Respiratory Society
ESPEN	European Society of Clinical Nutrition and Metabolism
FEV_1	Forced expiratory volume in the first second
FFMI	Fat-free mass index
FVC	Forced vital capacity
GOLD	Global Initiative for Obstructive Lung Disease
Ht	Height
HR	Hazard ratio
mMRC	Modified Medical Research Council
MNA-SF	Mini-Nutritional Assessment-Short Form
OR	Odds ratio
R	Resistance
SD	Standard deviation
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TLC	Total lung capacity
UWL	Unintentional weight loss
WHO	World Health Organization
6MWT	6-min walk test

1. Introduction

Chronic obstructive pulmonary disease (COPD), the fourth leading cause of mortality in the world, is a major public health problem associated with a substantial economic burden [1]. The prevalence of malnutrition in patients with COPD ranges from 20% to 45%, depending on the population and the methods used for its diagnosis [2–5]. The main consequences of malnutrition include poor functional status, worsening health-related quality of life, increased hospitalization and increased mortality [6–10]. Although early detection and management of patients at risk of malnutrition can reverse the adverse effects, malnutrition is often underdiagnosed and, consequently, undertreated [11,12].

The Task Force of the European Respiratory Society (ERS), in its statement on nutritional assessment in COPD, recommends a systematic nutritional evaluation as part of the multidisciplinary management of patients [13]. The Task Force stratifies nutritional risk in a diagram based on the prospective evaluation of involuntary weight loss and body composition [13]. In the absence of an international definition of malnutrition, the European Society for Clinical Nutrition and Metabolism (ESPEN) proposed a unified, simple and reliable tool for malnutrition diagnosis to be applied in all age ranges and healthcare settings, regardless of the aetiology [14]. These new criteria have been supplemented with the ESPEN guidelines on clinical nutrition definitions and terminology [15].

To date, only two studies have applied the ESPEN criteria in patients with stable and exacerbated COPD; both of them report approximately 20% prevalence of malnutrition [16,17]. In hospitalized patients with COPD, the risk of mortality at 6 and 9 months was almost three times higher in patients fulfilling ESPEN criteria [16], but their usefulness to predict mortality and hospitalizations in patients with stable COPD has not yet been established.

COPD is a heterogeneous disease with numerous pulmonary and extrapulmonary manifestations. Within the last decade, many different patterns of clinical expression of COPD have been described, including the exacerbator phenotype, one of the COPD phenotypes with clinical, prognostic and therapeutic consequences [17]. Acute exacerbations have a negative impact on the natural history of the disease [18]; moreover, impairment of peripheral and respiratory muscles in patients with COPD results in a higher susceptibility to multiple exacerbations. Reports showing that more than 20% of the patients with moderate COPD frequently present exacerbations while close to 40% of patients with severe or very severe COPD do not [19,20,21] suggests an individual susceptibility. The exacerbator phenotype together with the patient's clinical condition (e.g., infections with multi-drug resistant strains, hypercapnia, mechanical ventilation) contribute to our understanding that hospitalized patients for acute exacerbations have substantial differences that must be considered when studying COPD comorbidities (e.g., malnutrition).

Based on these considerations, the aim of this study was to determine if the ESPEN criteria (and/or its individual components) are prognostic factors of mortality and hospital admissions in patients with stable COPD in a 2-year follow-up period and secondly, to detect rates of malnutrition in COPD patients referred to pulmonary rehabilitation.

2. Methods

This was a prospective cohort study carried out according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations [22]. Participants were consecutive patients with a confirmed diagnosis of COPD referred to the Pulmonary Rehabilitation unit of a university hospital between June 2015 and February 2016. Patients with exacerbations and/or all-cause hospital admissions in the previous two months were excluded. All patients were routinely screened for malnutrition risk, using the Mini-Nutritional Assessment Short Form (MNA-SF) [23], and the ESPEN diagnostic criteria were applied in at-risk patients (MNA-SF $\leq$11). Two approaches were used to diagnose malnutrition: 1) body mass index (BMI) $<$ 18.5 Kg/m^2 and/or 2) unintentional weight loss ($>$10% in indefinite time or $>$5% in the last 3 months) together with low BMI ($<$20 Kg/m^2 in patients younger than 70 years and $<$22 Kg/m^2 in those aged $\geq$70 years) or fat-free mass index (FFMI) ($<$17 Kg/m^2 in men and $<$15 Kg/m^2 in women) [14].

Main outcome variables were the ESPEN components (age-related BMI, unintentional weight loss, and sex-specific FFMI), as well as mortality, number of hospital admissions and length of stay obtained from electronic medical records during a 2-year follow-up period. For analysis purposes, the number of admissions and days of stay during the follow-up period were categorized in dichotomous variables: $\geq$2 hospitalizations and/or $\geq$10 days of hospital stay in the follow-up period.

Parameters of body composition were assessed by bioimpedance analysis (Bodystat 1500, Bodystat Ltd, Isle of Man, British Isles) as previously described [24]. Fat-free mass was estimated using sex-specific regression equations for patients with

COPD [25]. Measures were expressed in Kg and as a percentage of the European population reference values [26].

Twelve other variables were collected: age, sex, smoking history, severity of airflow obstruction according to Global Initiative for Obstructive Lung Disease (GOLD) criteria [27], dyspnoea evaluated with the modified scale of the Medical Research Council (mMRC), estimated exercise capacity with distance travelled in the 6-min walk test (6MWT), the multidimensional BODE (Body mass index, Obstruction, Dyspnoea, and Exercise capacity) index, and respiratory function tests including forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), total lung capacity (TLC), airway resistance and carbon monoxide diffusing capacity (DL_{CO}) [28].

National and international research ethics guidelines were followed, including the Deontological Code of Ethics, the Helsinki Declaration and the Spanish Privacy Law on personal data (Organic Law 15/1999, of December 13, Protection of Data of Personal character). The study was approved by the local Ethics Committee and the participants gave their written consent before the inclusion of the study. Patients with malnutrition received nutritional support and dietary advice.

2.1. Statistical analysis

The categorical variables were reported with their absolute values and percentages; the quantitative variables were expressed with the mean and standard deviation (SD), or with the median and 25th and 75th percentiles (P_{25} and P_{75}, respectively) if they did not follow a normal distribution. The assumption of normality was analysed using normality charts and the Kolmogorov–Smirnov test corrected with the Lilliefors test. Chi-square test, Student t test for independent samples, Mann-Whitney U test, and one-way analysis of variance (ANOVA), were used for the bivariate analyses, according to the nature of the variables. For continuous variables, mean differences were indicated with 95% confidence intervals (95% CI). Pearson (r) or Spearman (ρ) correlation coefficients were calculated, as appropriate. Linear regression analysis was used to determine the association between variables (exposure) related to the nutritional evaluations: risk of malnutrition according to MNA-SF and definition of malnutrition according to ESPEN basic diagnosis and each of its components (involuntary weight loss, age-related BMI and sex-specific FFMI). Adjustments were made for possible confounding factors (age and severity). To compare overall survival between the four ESPEN malnutrition groups, the Kaplan-Meier survival curves were plotted and compared using the log-rank test. For the contrasts, a p-value <0.05 was established for statistical significance. Statistical analysis was performed using STATA 15.0 software (Stata Corp, College Station, Texas, USA).

3. Results

Of 151 consecutive patients referred to pulmonary rehabilitation in the study period, 27 (17.9%) had recently experienced a COPD exacerbation or required hospitalization, and 6 patients (<4%) declined to participate in the study; therefore, the final sample was 118 patients (mean age 66.6 ± 9 years, 80.5% men). More than 75% of patients had severe or very severe airflow obstruction, and all of them were community-dwelling. Baseline description of participants is summarized in Table 1. The MNA-SF identified 61 (51.7%) patients at risk of malnutrition, of which 29 (24.6%) were diagnosed as malnourished according to the ESPEN definition. No significant differences were observed in age, sex, or smoking history between patients with and without malnutrition according to ESPEN criteria. Prevalence of malnutrition was associated with severity of airflow obstruction: 17.4% in patients with moderate obstruction versus 37.9% in the group of patients with severe or very severe obstruction.

Table 1
Baseline description of participants (n = 118).

	Total sample (n = 118)
Age (years)	66.6 (SD 9.0)
Sex (men)	95 (80.5%)
Body mass index (Kg/m^2)	26.2 (SD 6.4)
Smoking history	
Smoker	49 (41.5%)
Past smoker	69 (58.5%)
Severity of airflow obstruction (according to GOLD)	
Moderate	27 (22.9%)
Severe	49 (41.5%)
Very severe	42 (35.6%)
BODE index	2.7 (SD 1.8)

BODE: Body-mass index, airflow Obstruction, Dyspnoea, and Exercise; **GOLD:** Global Initiative for Chronic Obstructive Lung Disease; **% pred.:** percentage of predicted value.

Table 2 describes the main differences between COPD patients with and without malnutrition in the variables commonly collected during evaluation for referral to pulmonary rehabilitation. Malnutrition was significantly associated with greater severity in the parameters of respiratory function (except FVC) and body composition, as well as a worse prognosis according to the BODE index. No significant differences between groups were found in the dyspnoea scale or distance travelled in the 6MWT.

In the first year of follow-up, mortality was 3.4% (n = 4), and increased to 12.7% (n = 15) in the second year. Of the 15 patients who died, 9 (~60%) were malnourished according to ESPEN criteria; average age at the time of death was 74.1 years (SD 8.1). As shown in Table 3, mortality was significantly associated with age, severity symptoms (dyspnoea, exercise capacity), and body composition. No statistical differences in the respiratory function were observed, except in the DLco; however, when obstruction severity was categorized according to GOLD criteria, mortality was significantly higher in the group with very severe COPD. A significant difference between the survival curves at 2 years of follow-up was observed for the malnutrition and non-malnutrition groups (Fig. 1). A more detailed analysis by proportional hazard models is summarized in Table 4, which presents the associations of the ESPEN basic diagnosis of malnutrition and each of its individual components (involuntary weight loss, low age-related BMI and low sex-specific FFMI) with mortality, admissions and hospital stay.

Malnutrition according to ESPEN basic diagnosis was associated with an increased risk of 2-year mortality (HR 3.85, 95% CI 1.4–10.62, p = 0.009). The analysis was repeated using the MNA-SF screening test and each component of the definition. MNA-SF scores ≤11 showed a similar association (HR 3.96, 95% CI: 1.12–14.03, p = 0.033). Among the components of the ESPEN definition, the association with mortality risk was 17 times higher for low FFMI (HR 17.06, 95% CI: 2.24–129.82, p = 0.006); 6.4 times higher for involuntary weight loss + low sex-specific FFMI (HR 6.39, 95% CI: 2.18–18.69, p = 0.001); and 3 times higher for low age-related BMI (HR 3.19 95% CI: 1.16–8.79, p = 0.025). These associations remained significant after adjusting for age and lung function: low FFMI (HR 13.03, 95% CI: 1.67–101.71, p = 0.014); and involuntary weight loss + low sex-specific FFMI (HR 4.8, 95% CI: 1.53–15.07, p = 0.007).

Sixty-two patients (66.9%) required at least one hospital admission during the 2-year follow-up. The total number of days spent in the hospital during this period was significantly higher in patients with malnutrition: median (P_{25}, P_{75}) of 18 (1, 53.5) days in malnourished patients, compared to in front of 9 (3, 20.5) days in patients without malnutrition (p = 0.041). A low age-related BMI was associated with a higher risk of hospital admissions (HR 2.59,

Table 2
Clinical characteristics of the study participants according to malnutrition as defined by the ESPEN consensus (n = 118).

	Total sample (n = 118)	No malnutrition (n = 89)	Malnutrition (n = 29)	Mean differences (95% CI)	p-value
Age (years)	66.6 (SD 9.0)	66.5 (SD 8.5)	66.8 (SD 10.4)	−0.3 (−4.1 to −3.5)	0.878
Dyspnoea (mMRC scale)	2.2 (SD 0.9)	2.1 (SD 0.8)	2.3 (SD 1.1)	−0.2 (−0.6 to 0.3)	0.455
Respiratory function test					
%FEV_1/FVC	45.5 (SD 12.8)	48.5 (SD 12.1)	35.6 (SD 9.6)	12.8 (7.7–17.9)	**<0.001**
FEV_1 (% pred.)	37.3 (SD 13.4)	39.6 (SD 13.0)	29.2 (SD 10.9)	9.3 (3.9–14.8)	**0.001**
FVC (% pred.)	62.8 (SD 17.6)	61.1 (SD 13.9)	66.2 (SD 28.3)	−6.2 (−16.9 to 4.4)	0.242
TLC (% pred.)	103.3 (SD 22.6)	99.7 (SD 20.8)	118.4 (SD 25.7)	−15.6 (−25.9 to −5.4)	**0.003**
DL_{CO} (% pred.)	43.2 (SD 18.3)	47.2 (SD 18.1)	26.7 (SD 9.1)	18.3 (12.3–24.4)	**<0.001**
Six-minute walking distance (m)	397.6 (SD 122.8)	401.0 (SD 118.7)	387.1 (SD 119.1)	13.9 (−38.3 to 66.1)	0.599
BODE index	2.7 (SD 1.8)	2.5 (SD 1.7)	3.4 (SD 2.2)	−0.9 (−1.7 to −0.2)	**0.019**
Body mass index (Kg/m^2)	26.2 (SD 6.4)	28.3 (SD 5.9)	19.8 (SD 3.0)	8.5 (6.8–10.1)	**<0.001**
Bioimpedance body composition					
Fat-free mass (Kg)	47.1 (SD 10.0)	49.3 (SD 10.2)	40.1 (SD 4.7)	9.3 (6.5–12.0)	**<0.001**
Fat-free mass (% pred.)	87.7 (SD 16.3)	91.9 (SD 16.0)	74.7 (SD 8.2)	17.2 (12.7–21.7)	**<0.001**
Fat mass (Kg)	26.2 (SD 12.4)	29.4 (SD 11.5)	16.5 (SD 8.2)	12.9 (9.0–16.8)	**<0.001**
Fat mass (% pred.)	145.6 (SD 73.7)	162.7 (SD 72.9)	93.5 (SD 47.7)	69.2 (45.8–92.6)	**<0.001**
Water (L)	38.2 (SD 8.1)	39.8 (SD 8.5)	33.2 (SD 4.0)	4.8 (4.3–8.9)	**<0.001**
Water (% body weight)	53.6 (SD 8.3)	51.5 (SD 7.3)	60.1 (SD 7.9)	−8.6 (−11.8 to −5.5)	**<0.001**
Fat-free mass index (Kg/m^2)	16.9 (SD 3.1)	17.8 (SD 3.0)	14.0 (SD 1.2)	3.6 (2.9–4.4)	**<0.001**
Fat mass index (Kg/m^2)	9.4 (SD 4.2)	10.5 (SD 3.9)	5.7 (SD 2.6)	4.8 (3.6–6.1)	**<0.001**

Bold indicate p values <0.05.
BODE: Body mass index, Obstruction, Dyspnoea, and Exercise capacity; **DL_{CO}:** carbon monoxide diffusing capacity; **FEV_1:** forced expiratory volume in the first second; **FVC**: forced vital capacity; **TLC:** Total lung capacity; **% pred.:** percentage of predicted value; **mMRC:** Modified Medical Research Council.

95% CI: 1.07–6.3, p = 0.035) and overall, BMI < 18.5 Kg/m^2 was associated with higher risk of ≥2 hospital admissions (HR 3.55, 95% CI 1.04–12.05, p = 0.042) during the 2-year follow-up. These associations remained statistically significant when variables were adjusted by age, but were lost when adjusted for both age and lung function. A hospital stay >10 days during the study period was associated only with low age-related BMI (HR 2.84, 95% CI: 1.15–7.03, p = 0.024); an association that persisted when adjusted for age, but not when adjusted for both age and lung function.

4. Discussion

Our study establishes the association of the ESPEN consensus definition of malnutrition and its individual components with key prognostic variables (mortality and hospitalization) in a two-year follow-up period and describes the prevalence of malnutrition in patients with stable COPD referred to pulmonary rehabilitation.

The 24.5% prevalence of malnutrition in patients with COPD that we obtained using the ESPEN definition is in line with previous studies. De Blasio et al. [17] reported a prevalence of 19.8% in rehabilitation patients with stable COPD, and 48.1% in patients with very severe airflow obstruction, very close to the 45.2% observed in our group of patients with greater airflow obstruction. Notably, Ingadottir et al. [16] reported a prevalence of malnutrition among inpatients with COPD exacerbations that was very similar to that observed in our sample of stable patients: 11% and 13.7%, respectively, in patients with moderate airflow obstruction and 90% and 86.1%, respectively, when the obstruction was severe or very severe. These data add insight to the complex interaction between nutrition status and disease progression. Until not very long ago, the natural history of

Table 3
Main clinical differences between survivors and non survivors at 2-year follow-up.

	Survivors (n = 103)	Non survivors (n = 15)	Mean differences (95% CI)	p-value
Age (years)	65.7 (SD 8.8)	72.7 (SD 8.1)	7.0 (2.2–11.7)	**0.004**
Dyspnoea (mMRC scale)	2.1 (SD 0.8)	2.3 (SD 1.1)	0.5 (0.03–1.0)	**0.037**
Respiratory function test				
%FEV_1/FVC	45.8 (SD 12.2)	43.7 (SD 16.8)	−2.1 (−9.1 to 4.9)	0.557
FEV_1 (% pred.)	39.6 (SD 13.0)	29.2 (SD 10.9)	−4.8 (−14.7 to 0.5)	0.195
FVC (% pred.)	61.1 (SD 13.9)	66.2 (SD 28.3)	−6.9 (−16.5 to 2.7)	0.157
TLC (% pred.)	99.7 (SD 20.8)	118.4 (SD 25.7)	−5.5 (−19.9 to 8.8)	0.447
DL_{CO} (% pred.)	47.2 (SD 18.1)	26.7 (SD 9.1)	13.4 (−24.8 to −2.0)	**0.022**
Six-minute walking distance (m)	401.0 (SD 118.7)	387.1 (SD 119.1)	−130.8 (−193.9 to 67.7)	**<0.001**
BODE index	2.5 (SD 1.7)	3.4 (SD 2.2)	1.9 (−2.8 to 0.9)	**<0.001**
Body mass index (Kg/m^2)	28.3 (SD 5.9)	19.8 (SD 3.0)	−4.4 (−7.9 to −1.0)	**0.013**
Bioimpedance body composition				
Fat-free mass (Kg)	49.3 (SD 10.2)	40.1 (SD 4.7)	−7.4 (−10.7 to −4.2)	**<0.001**
Fat-free mass (% pred.)	91.9 (SD 16.0)	74.7 (SD 8.2)	−12.6 (−21.2 to −3.9)	**0.005**
Fat mass (Kg)	29.4 (SD 11.5)	16.5 (SD 8.2)	−7.1 (−13.7 to −0.4)	**0.038**
Fat mass (% pred.)	162.7 (SD 72.9)	93.5 (SD 47.7)	−45.8 (−71.6 to −20.0)	**0.001**
Water (L)	39.8 (SD 8.5)	33.2 (SD 4.0)	−5.2 (−8.0 to −2.4)	**0.001**
Water (% body weight)	51.5 (SD 7.3)	60.1 (SD 7.9)	3.9 (0.6–8.4)	0.089
Fat-free mass index (Kg/m^2)	17.8 (SD 3.0)	14.0 (SD 1.2)	−2.3 (−3.2 to −1.2)	**<0.001**
Fat mass index (Kg/m^2)	10.5 (SD 3.9)	5.7 (SD 2.6)	−2.1 (−4.3 to 0.0)	0.063

Bold indicate p values <0.05.
BODE: Body mass index, Obstruction, Dyspnoea, and Exercise capacity; **DL_{CO}:** carbon monoxide diffusing capacity; **FEV_1:** forced expiratory volume in the first second; **FVC**: forced vital capacity; **TLC:** Total lung capacity; **% pred.:** percentage of predicted value; **mMRC:** Modified Medical Research Council.

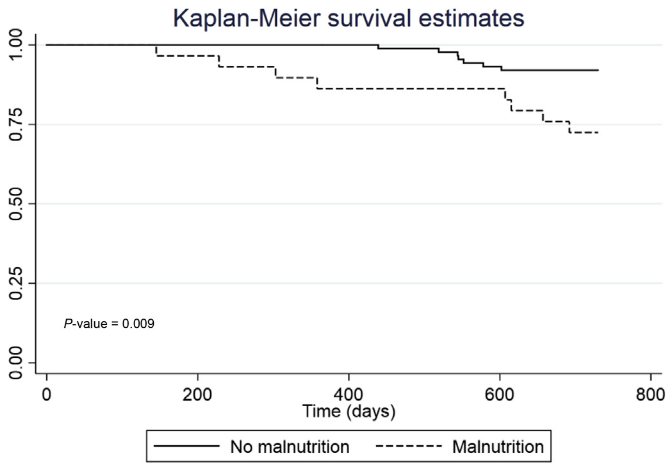

Fig. 1. Survival curve according to malnutrition as defined by the ESPEN criteria.

COPD was restricted to describing changes in airflow limitation, but extrapulmonary manifestations in COPD do not necessarily show a parallel progression with obstruction severity [29].

Many extrapulmonary manifestations have a negative impact on overall outcomes, as in the case of low BMI and FFMI values [30]. A strong association between FFMI and some parameters of cardiopulmonary, respiratory, and muscle function has been previously described: the FFMI has a mild to moderate positive correlation with handgrip strength ($r = 0.331$, $p = 0.007$) [31] and a moderately positive correlation with total caloric expenditure ($r = 0.548$, $p < 0.001$) [32], 6MWT distance ($\rho = 0.52$, $p < 0.01$), and maximal inspiratory pressure ($\rho = 0.47$, $p < 0.01$) [33]. Moreover, Ingadottir et al. [16] suggest that FFMI could be used independently of weight loss to diagnose malnutrition in patients hospitalized with COPD, as low FFMI was associated with a severe or very severe stage of disease (OR 4.767, 95% CI 2.029 to 11.2). In their study, unintentional weight loss was associated with the greatest increase in risk of mortality at 6 and 9 months, compared to other ESPEN criteria: OR 3.884 (95% CI 1.138 to 13.26) and 2.955 (95% CI 0.892 to 9.785), respectively.

Weight loss is one of the strongest indicators of health status in older people [34]. The scientific community agrees that weight loss should be considered independently of its speed, magnitude and aetiology [14], but there is no agreement about the amount of weight variation that should cause clinical concern [35,36]. Conversely, in our study, weight loss alone was not associated with increased risk of mortality in our stable COPD patients, but FFMI was a significant factor (HR 17.06, 95% CI 2.24 to 129.8) overall and after adjustments for age and pulmonary function. In contrast, according to our unpublished data (manuscript under review), the FFMI alone was not associated to long-term mortality in 181 community-dwelling healthy older women included in the EPIDOS-Toulouse cohort [37].

The use of BMI alone may have limited value for diagnosing malnutrition. In our sample, patients with overweight and obesity showed no significant differences in baseline characteristics (age, physical state, comorbidity) or survival, and therefore were analysed as a single group. Although the influence of BMI on mortality remains controversial, most authors agree that a BMI range of

Table 4
Hazard ratios of mortality and odds ratios of admissions and length of stay in 2-year follow-up (dependent variables) according to nutritional risk and malnutrition as defined by the ESPEN consensus and by its specific components (independent variables). Crude analysis and adjusted results (n = 118).

	n	Crude analysis			Model 1 Adjusted for age			Model 2 Adjusted for age and obstruction severity			Model 3 Adjusted for age and diffusing capacity		
		HR	CI 95%	p	HR	CI 95%	p	HR	CI 95%	p	HR	CI 95%	p
Mortality at 2 years													
At nutritional risk (MNA-SF ≤11)	61	3.96	1.12 to 14.03	**0.033**	3.75	1.05 to 13.3	**0.041**	3.25	0.88 to 11.96	0.77	1.62	0.41 to 6.47	0.489
ESPEN basic diagnosis	29	3.85	1.4 to 10.62	**0.009**	3.76	1.36 to 10.39	**0.011**	2.62	0.88 to 7.83	0.85	2.58	0.74 to 8.96	0.136
BMI <18.5 Kg/m^2	12	2.42	0.68 to 8.59	0.170	3.21	0.9 to 11.49	0.073	1.9	0.48 to 7.48	0.357	1.16	0.24 to 5.64	0.853
UWL + age-related BMI	15	1.73	0.49 to 6.12	0.397	1.9	0.53 to 6.73	0.322	1.9	0.48 to 7.48	0.357	1.41	0.29 to 6.84	0.667
UWL + sex-related FFMI	31	6.39	2.18 to 18.69	**0.001**	6.38	2.17 to 18.71	**0.001**	4.8	1.53 to 15.07	**0.007**	6.34	1.61 to 25.09	**0.008**
UWL	50	1.13	0.41 to 3.1	0.820	0.92	0.33 to 2.57	0.881	0.93	0.33 to 2.59	0.888	1.01	0.29 to 3.48	0.99
Low age-related BMI	27	3.19	1.16 to 8.79	**0.025**	3.09	1.12 to 8.54	**0.030**	2.29	0.77 to 6.83	0.138	1.21	0.33 to 4.5	0.774
Low sex-related FFMI	57	17.06	2.24 to 129.8	**0.006**	15.54	2.04 to 118.6	**0.008**	13.03	1.67 to 101.71	**0.014**	9.38	1.19 to 74.0	**0.034**
	n	OR	CI 95%	p	OR	CI 95%	p	OR	CI 95%	p	OR	CI 95%	p
Hospital admissions (≥2)													
At nutritional risk (MNA-SF ≤11)	61	1.86	0.84 to 4.12	0.126	1.89	0.85 to 4.19	0.119	1.28	0.53 to 3.07	0.579	1.46	0.57 to 3.76	0.431
ESPEN basic diagnosis	29	1.81	0.76 to 4.32	0.183	1.82	0.76 to 4.36	0.180	1.13	0.42 to 3.03	0.804	1.28	0.42 to 3.88	0.664
BMI <18.5 Kg/m^2	12	3.55	1.04 to 12.05	**0.042**	3.43	1 to 11.75	**0.049**	2.02	0.56 to 7.31	0.284	2.82	0.67 to 11.8	0.156
UWL + age-related BMI	15	1.11	0.35 to 3.51	0.860	1.09	0.34 to 3.48	0.879	0.74	0.21 to 2.55	0.631	0.56	0.12 to 2.63	0.466
UWL + sex-related FFMI	31	1.29	0.54 to 3.07	0.564	1.29	0.54 to 3.07	0.567	0.85	0.31 to 2.29	0.745	1.14	0.4 to 3.301	0.806
UWL	50	0.66	0.29 to 1.48	0.309	0.69	0.3 to 1.56	0.369	0.69	0.29 to 1.64	0.398	0.52	1.93 to 1.41	0.199
Low age-related BMI	27	2.59	1.07 to 6.3	**0.035**	2.63	1.08 to 6.42	**0.034**	1.75	0.67 to 4.61	0.254	1.53	0.48 to 4.91	0.468
Low sex-related FFMI	57	1.93	0.87 to 4.25	0.103	1.99	0.9 to 4.41	0.090	1.47	0.63 to 3.46	0.377	1.89	0.72 to 4.95	0.195
Hospital stay (>10 days)													
At nutritional risk (MNA-SF ≤11)	61	1.83	0.8 to 4.2	0.155	1.84	0.8 to 4.22	0.152	1.15	0.46 to 2.89	0.77	0.98	0.36 to 2.61	0.961
ESPEN basic diagnosis	29	1.6	0.65 to 3.96	0.307	1.61	0.65 to 3.97	0.305	0.85	0.3 to 2.4	0.764	0.76	0.24 to 2.43	0.640
BMI <18.5 Kg/m^2	12	3.08	0.91 to 10.37	0.070	3.08	0.91 to 10.47	0.070	1.66	0.45 to 6.13	0.445	1.94	0.47 to 8.03	0.358
UWL + age-related BMI	15	0.97	0.29 to 3.31	0.966	0.97	0.29 to 3.3	0.962	0.6	0.16 to 2.24	0.443	0.33	0.06 to 1.87	0.211
UWL + sex-related FFMI	31	1.14	0.46 to 2.83	0.780	1.14	0.46 to 2.83	0.781	0.63	0.22 to 1.8	0.388	0.73	0.24 to 2.24	0.581
UWL	50	0.65	0.28 to 1.52	0.319	0.66	0.28 to 1.55	0.340	0.64	0.26 to 1.61	0.345	0.36	0.12 to 1.06	0.063
Low age-related BMI	27	2.84	1.15 to 7.03	**0.024**	2.85	1.15 to 7.07	**0.024**	1.79	0.66 to 4.82	0.250	1.23	0.38 to 4.05	0.729
Low sex-related FFMI	57	2.21	0.96 to 5.08	0.063	2.24	0.97 to 5.16	0.060	1.6	0.65 to 3.93	0.309	1.57	0.58 to 4.23	0.374

BMI: body mass index; **CI**: Confidence interval; **ESPEN:** European Society of Clinical Nutrition and Metabolism; **FFMI:** fat-free mass index; **HR:** hazard ratio; **MNA-SF:** Mini-nutritional Assessment Short Form**; OR:** odds ratio; **UWL:** unintentional weight loss (>10% indefinite time or >5% in the last 3 months). **Model 1:** adjustment for age; **Model 2:** adjustment for age and obstruction severity; significant HR ($p < 0.05$) indicated in bold.

25–30 kg/m^2 would be protective [38]. Low BMI was not associated with higher risk of mortality; this observation raises questions about the ESPEN definition's use of BMI <18.5 Kg/m^2 as the cut-off point for malnutrition in a disease characterized by wasting (such as COPD). In our study, 12 patients had BMI <18.5 Kg/m^2, but no greater mortality was observed.

The ERS Task Force [13] and the updated (2018) GOLD criteria [27] recommend nutritional interventions in selected patients (level of evidence B). Given that nutritional interventions are most effective when combined with exercise programs [13], and that a clinical trial of a 4-month exercise program obtained better results in the study group that also received nutritional supplementation [39], the addition of nutritional interventions within rehabilitation programs may improve both physical performance and health status.

From the opposite perspective, malnutrition and limited mobility are bidirectionally linked. Therefore, the early identification of patients with malnutrition will help the multidisciplinary team to establish realistic objectives, select therapeutic strategies, and provide patients and caregivers with more accurate information.

Several methodological limitations must be taken into consideration when interpreting the results of this study. First, there was no sample size calculation to determine outcomes because the BELLEPOC cohort consists of stable COPD patients followed up after referral to a pulmonary rehabilitation program (PPR). The general objective of this prospective study is to assess functional outcomes, adherence and prognosis after completing the PPR; sample size was based on improvements in functional outcomes (exercise capacity and muscle function). Second, we would highlight a possible selection bias, as samples from rehabilitation settings are drawn from patients preselected for their potential to follow a rehabilitation program and cannot be considered representative of the entire population of patients with COPD. Despite the progressive increase in the prevalence of COPD in women, there are differences regarding phenotype, symptoms, and comorbidities; these distinct features need to be considered to boost success of therapeutic interventions (including attendance to pulmonary rehabilitation) [40,41]. Third, bioimpedance analysis is not the gold-standard tool to assess muscle mass, but is an alternative method of estimating fat and lean body mass for research and clinical use, according to international consensus [42]. These considerations, together with the frequent comorbidities in this population, could act as confounding factors. In addition, although the MNA-SF is a validated screening tool for malnutrition, some societies recommend the use of the full version to improve the specificity of results [43].

The quality and accuracy of anthropometric measurements should also be considered. In all cases, height and weight were systematically collected during all follow-up visits; however, factors such as osteoporotic changes or vertebral deformities were not taken into account. Some authors point out the difficulties of obtaining reliable one-year weight loss information from the clinical history. In this sense, a strength of our study is the consistent protocol for objective measurement of body weight and height as part of the annual respiratory function testing of all of the study participants in the Respiratory Diseases Department of a single centre.

5. Conclusions

The prevalence of malnutrition in patients with stable COPD referred to pulmonary rehabilitation according to ESPEN criteria is high (22%) and is associated with a nearly 4-fold increased risk of mortality in a 2-year follow-up period. A low FFMI value was associated with a 17-fold increase in mortality risk, suggesting its potential use as a predictive factor, independently of the other ESPEN components (BMI and unintentional weight loss). Future research is needed to validate these findings in prospective longitudinal studies in other settings and in larger samples with subpopulations of patients with COPD, in order to determine potential differences according to phenotypical profiles.

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Conflict of interest

All authors declare they do not have any financial and personal relationships with other persons or organizations that could inappropriately influence their work.

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