

The Impact of Malnutrition on COPD Outcomes: Role of Mini-Nutritional Assessment (Mna) in Predicting Acute Exacerbations in Patients with Highly Complex COPD and Its Clinical and Prognostic Implications

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Article

The Impact of Malnutrition on Copd Outcomes: Role of Mini-Nutritional Assessment (Mna) in Predicting Acute Exacerbations in Patients With Highly Complex Copd and its Clinical and Prognostic Implications

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Abstract: Background: Current management of COPD is predominantly focused on respiratory aspects. A multidimensional assessment including nutritional assessment, quality of life and disability provides a more reliable perspective of the true complexity of COPD patients. Methods: Prospective observational study of 120 elderly COPD patients at high risk of acute exacerbations. The Mini-Nutritional Assessment (MNA) was administered in addition to the usual respiratory assessment. The primary outcome was a composite of moderate or severe acute exacerbations during 52 weeks of follow-up. Results: The median MNA Short Form (SF) score was 11 (8-12), 39 participants (32.50%) had normal nutritional status, 57 (47.5%) were at risk of malnutrition and 24 (20%) were malnourished. Our multivariate linear logistic models showed that the MNA score was associated with dyspnea and respiratory symptoms severity assessed by the Modified British Medical Research Council (mMRC) and the COPD Assessment Test (CAT) score, with spirometric variables, in particular with the severity of airflow limitation based on the value of FEV1 and with poorer QoL as assessed by the EQ-5D-3 questionnaire. Cox regression analysis according to nutritional status based on the MNA score showed that COPD participants "at risk of malnutrition" and "malnourished" had a higher risk of moderate to severe acute exacerbations with a hazard ratio (HR) of 3.54 (p=0.002) and 8.20 (p=0.0001), respectively. Conclusion: Our study confirms the importance of assessing nutritional status in elderly COPD patients and its prognostic value.

Keywords: malnutrition; mini nutritional assessment (MNA); chronic obstructive pulmonary disease (COPD); acute exacerbation of COPD (AECOPD); quality of life; frailty; multimorbidity

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a major global health problem characterized by persistent airflow limitation and chronic systemic inflammation, with a significant impact on the patient's overall health and well-being [1].

Over the past few decades, there has been sustained research activity in the area of malnutrition, poor quality of life (QoL), and impaired autonomy in activities of daily living (ADLs) in COPD

patients. This new area of interest adds relevant information to the comprehensive assessment and management of elderly multimorbid COPD patients, who are poorly represented in clinical trials.

Malnutrition, often suspected because of low body mass index, is a common problem in COPD patients, with prevalence ranging from 17% to 47.2%, pooled prevalence of 30.0% and the pooled prevalence of at-risk for malnutrition in patients with COPD was 50.0% ([2–4]. The term malnutrition refers to a condition characterized by an imbalance in energy, protein, or other nutrients that leads to adverse effects on body composition, physical function, and clinical outcomes [5]. In patients with one or more chronic diseases, such as COPD, malnutrition is a major risk factor for the development of sarcopenia [6]. Poor nutritional status is a major negative determinant of muscle energetics, exercise tolerance and ultimately worsening respiratory symptoms in COPD [7]. There is no validated gold-standard diagnostic tool to evaluate malnutrition in COPD; the Mini Nutritional Assessment (MNA) is a widely used questionnaire able to provide the physician of several information about the nutritional status of elderly people. Recent studies show a significant correlation between the nutritional status of COPD patients evaluated by the MNA and the progression and prognosis of the disease [8] and with the subjective perception of dyspnea [9]. Currently, evidence suggests that the MNA has a predictive value for various health-related outcomes, including morbidity and mortality [10] but despite the potential of MNA in identifying malnutrition and its associated adverse outcomes in COPD patients, no studies to date have explored the impact of nutritional intervention guided by the MNA on COPD outcomes.

Malnutrition, especially in the elderly, has an intricate relationship with impaired autonomy in ADLs, ultimately leading to a poor QoL; COPD subjects, often in the more advanced stages of disease, show increasing difficulty in performing ADLs as evidenced by studies that have found impaired self-reported ADL task performance [11–13]. This progressive impairment may be due to several factors: the limitation of physical abilities brought on by breathlessness, fatigue, and reduced exercise tolerance that is a common feature of COPD [14,15]; the reduced lean mass, respiratory muscular mass, limited ventilatory response and dynamic hyperinflation [7,16]; the psychological impact of the physical decline [17]. Malnutrition-related worsening of lung function and respiratory symptoms may have a negative impact on quality of life (QoL) [18], with implications for exacerbation frequency, hospital admissions and mortality [19,20].

All these factors may have potentially relevant implications on COPD outcomes, especially on rate and severity of exacerbations, periods where symptoms become worse, when patients have a greater level of dependence on others for ADLs., experiencing an acute increase in functional impairment, requiring assistance for even basic needs [21,22]. Despite this, there is limited data on the role of poor nutritional status and its secondary effects on limitations in ADLs and reduced autonomy on clinical outcomes in COPD. So, the aim of the present study was to evaluate the impact of malnutrition, as assessed by the administration of the Mini-Nutritional Assessment (MNA), in a cohort of highly complex elderly COPD patients, as a potential prognostic indicator of COPD outcomes.

2. Materials and Methods

We consecutively recruited 120 patients with COPD who were referred to the “Internal Medicine and Stroke Care” Unit and Cardiovascular Risk” Unit of the Department of Promoting Health, Maternal-Infant. Excellence and Internal and Medicine (Promise) of the Policlinico Paolo Giaccone of the University of Palermo from 01/09/2021 to 01/01/2024. This ad interim analysis belongs to the ongoing MACH (Multidimensional Approach for COPD and High complexity) Trial which is registered on ClinicalTrial.gov Platform (NCT04986332) and was approved by Institutional review board (Comitato Etico Palermo 1; *Approval Ref N. 04/2021*).

The objectives and the materials and methods and main outcomes of the MACH Study have been described elsewhere [23].

Each participant considered in the present analysis underwent a 12-month follow-up, as follows:

- For participants admitted during hospitalization, a reassessment was performed at 3, 6 and 12 months after discharge at “COPD and Cardiovascular Risk” outpatient Unit in which information on both moderate and severe acute COPD exacerbation that led to hospitalization and mortality was collected;

- For outpatients referred to “COPD and Cardiovascular Risk” ambulatory, information on moderate and severe acute COPD exacerbation that led to hospitalization was retrospectively collected the day after the last moderate or severe AECOPD and follow-up continued since 12-month follow-up was completed;

2.1. COPD Evaluation and Outcomes

The diagnosis of COPD was made according to the current GOLD report “Global Strategy for Prevention, Diagnosis and Management of COPD” [1]. For participants with previously diagnosed COPD, only spirometry tests performed within six months from enrolment were collected. Participants who met all inclusion criteria and had never performed a pulmonary function test, spirometry was performed in the outpatient clinic as soon as participants were considered clinically stable and free from a respiratory tract infection. Spirometric measurements were performed using the POXY FX desktop spirometer (COSMED Srl, Rome, Italy). The procedures for Forced Vital Capacity (FVC) manoeuvres were performed according to the statement “Standardization of Spirometry 2019 Update of American Thoracic Society/European Respiratory Society” [24] and for the comparison of measured values to the healthy population were used the Global Lung Initiative (GLI) reference equation for spirometry [25]. Assessment of symptoms through the Modified British Medical Research Council (mMRC) and COPD Assessment Test (CAT™) were performed under stable COPD conditions. The primary outcome of the study was a composite of moderate or severe COPD exacerbation during the 12-months follow-up.

2.2. Administration of Questionnaires

One specifically trained research assistant administered the following questionnaires:

1. **Mini Nutritional Assessment (MNA):** MNA includes anthropometric measurements, global assessment, dietary questionnaire, and subjective assessment. According to developers' instructions, the MNA administration utilizes a two-step approach, the screening step, and the global assessment step. Subsequently, based on MNA-Total Score (MNA-TS), patients are classified as “malnourished”, “at risk of malnutrition” or “normal nutritional status”. the “global assessment step” of the MNA should only be administered in patients not reaching the screening threshold. For the purpose of this study we evaluated both procedures of MNA questionnaire.
2. **Barthel Index:** The evaluation of activities of daily living is essential in gaining insight into the functional capacity and independence of COPD patients. Barthel Index plays a crucial role in assessing the functional status of these individuals [26]. The Barthel Index, formerly the Maryland Disability Index, was codified by English nurse Barthel in the 1950s. serves as an ordinal scale and It consists of 10 items examining ADLs. Each item is assigned an arbitrary score of 5, 10, 15 points (maximum 100). The sum indicates the degree of autonomy in carrying out daily activities [27]. For the purpose of this study, the cut-off points suggested by Shah et al [28] were used and allow to interpret the Barthel Index score as follows: a total score ranging between 0-20 implies “total dependency”, 21-60 indicates “severe dependency”, 61-90 indicates “moderate dependency”, and 91-99 suggests “slight dependency”. A score of 100 denotes complete independence from external assistance.
3. **EuroQoL 5D 3 level (EQ-5D-3L):** EQ-5D-3L is a simple questionnaire that explore the QoL and the health status [29]. Euro-QoL-5D-3L (EQ-5D-3L) is a widely used generic health-related QoL (HRQoL) instrument that measures individuals' health status across five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. It provides a descriptive profile of health and allows for the calculation of an overall index score [29]. Studies using EQ-5D-3L in COPD patients have consistently found that they experience significant impairments in several dimensions of health: key findings in COPD patients include decreased mobility due to breathlessness, limitations in self-care activities, and difficulties in performing usual activities. Furthermore, COPD patients often report moderate to severe levels of pain/discomfort and anxiety/depression, which can significantly impact their overall HRQoL [30,31]. For the purpose of this study, the Italian population-based set value was used to calculate the EQ-5D-3L Index Value [32]; License agreement number: 159432, march 2021;

2.3. Statistical Analysis

Statistical analysis of quantitative and qualitative data, including descriptive statistics, was performed for all data collected. Variables were evaluated using histogram and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk test) to determine distribution. Continuous data are defined as the mean $\pm$ standard deviation or median (interquartile range, IR) if normally distributed or non-normally distributed, respectively. Categorical variables are expressed as frequency counts and percentages. Kruskal-Wallis test was performed to assess any significant differences in the distribution of continuous variable between the three different groups based on MNA, both Short Form and Total Score. Subsequently, pairwise comparisons were performed using Dunn's (1964) procedure. A Bonferroni correction for multiple comparisons was made with statistical significance accepted at the $p < .0016$ level. Multivariate linear regression model was performed to assess the relationship between the dependent variable (mMRC scale, CAT, Barthel Index, EQ-5D-3L index value) and independent variable (MNA-SF and MNA-TS), adjusting data for age, gender (Female as reference category), CAT score (<10 points as reference variable) and GOLD class (Class 1 as reference variable). The interpretation of the goodness-of-fit of the regression models was made with the coefficient of determination (R^2) [31]. The Cox proportional hazards regression was used to assess the ability of both MNA indices to predict the primary outcome. Cox regression models were adjusted for confounder variables, age, sex (female as reference group), CAT score (<10 points as reference variable) and GOLD class (Class 1 as reference variable). A two-tailed p -value <0.05 was considered significant and a 95% confidence interval (CI) was reported. Statistical analysis was performed using STATA Statistical Software, version 17 (Stata-Corp, College Station, TX-USA).

3. Results

All 120 participants completed the study procedures. Sixteen participants died during the study, six from cardiovascular complications and the remaining ten from a lower respiratory tract infection complicated by respiratory failure.

3.1. Demographic and Anthropometric Variables of Enrolled Participants.

The baseline characteristics of the study participants are presented in Table 1. Of the 120 enrolled participants, the mean age (SD) was 72.08 years (6.07) and 62.5% were males. The majority of participants were overweight (34.17%) and the baseline functional impairment due to dyspnea measured through mMRC scale were 2-to-3 out of 4. Finally, our cohort was characterized by a moderate-severe COPD (GOLD class II, 51.67%). According to the inclusion criteria of " ≥ 2 moderate exacerbations or ≥ 1 leading to hospitalisation", all COPD participants belonged to the "E" group, as recently proposed by the 2024 GOLD report.

Table 1. Demographic, anthropometric and COPD-related variables at the baseline.

Variable	Count (%)	Mean $\pm$ SD
Male, n (%)	72 (62.5)	
Age (years), median (IR)		73 (67-79)
Former smoker (yes), n (%)	75 (62.50)	
Active smoker (yes), n (%)	45 (37.50)	
Environmental risk factors (yes), n (%)	37 (30.83)	
BMI (Kg/m ²), mean $\pm$ SD		27.8 (24.2-31.2)
Obesity Class according to BMI	Underweight, n (%)	4 (3.33)
	Optimal weight, n (%)	32 (26.67)
	Overweight, n (%)	41 (34.17)
	Class I obesity, n (%)	30 (25)
	Class II obesity, n (%)	9 (7.5)
	Class III obesity, n (%)	4 (3.33)

mMRC, n (%)	0	5 (4.17)
	1	25 (20.83)
	2	32 (26.67)
	3	39 (32.5)
	4	19 (15.83)
CAT, mean ± SD		15.94 ± 7.95
FVC (Lt), mean ± SD		2.33 ± 0.72
FVC (% predicted), median (IR)		72 (60-86)
FEV ₁ (Lt/sec), median (IR)		1.4 (1.01-1.85)
FEV ₁ (% predicted), mean ± SD		58.33 ± 18.90
FEV1/FVC, median (IR)		0.63 (0.54-0.68)
COPD-GOLD class, n (%)	GOLD 1E	14 (11.67)
	GOLD 2E	62 (51.67)
	GOLD 3E	38 (31.67)
	GOLD 4E	6 (5)
Inhaled bronchodilators, n (%)	LAMA	22 (18.33)
	LABA+ICS	20 (16.67)
	LABA+LAMA	37 (30.83)
	LABA+LAMA+ICS	41 (34.17)
LTOT, n (%)		39 (32.50)
Outpatient enrollment, n(%)		70 (58.33)

Table 1: Data are presented as mean value ± SD; BMI: Body Mass Index; mMRC: modified Medical Research Council; CAT: COPD Assessment Test; FVC: Forced Vital Capacity; FEV₁: Forced Expiratory Volume in the 1st second; COPD: Chronic Obstructive Pulmonary Disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease; LAMA: long-acting muscarinic antagonist; LABA: long-acting β-agonist; ICS: inhaled corticosteroid; LTOT: Long-Term Oxygen Therapy; Class obesity are defined as: “Underweight” for BMI<18.5 kg/m²; “Optimal weight” for BMI ranging from 18.5 to 24.9 kg/m²; “Overweight” for BMI ranging from 25 to 29.9 kg/m²; “Class I Obesity” for BMI ranging from 30.0 to 34.9 kg/m²; “Class II Obesity” for BMI ranging from 35 to 39.9 kg/m²; “Class III Obesity” for BMI ≥ 40.0 kg/m²; .

3.2. Distribution of Multidimensional Tests

The median value (IR) of Barthel Index was 90 (77.5-100) and according to Shah et Al cut-off, the level of functional disability of our cohort were: 44 participants (33.67%) were “none”, 17 (14.17%) were “slight dependent”, 42 (35%) were “moderate dependent”, 17 (14.17%) were “severe dependent”. The median value (IR) of MNA-SF was 11 (8-12) and according to “screening score”, 39 participants (32.50%) had a normal nutritional status, 57 (47.5%) were at risk of malnutrition and 24 (20%) were malnourished. The median value (IR) of MNA-TS was 22.5 (18.25-24.5) and according to “Malnutrition Indicator Score”, 45 participants (37.50%) had a normal nutritional status, 62 (51.67%) were at risk of malnutrition and 13 (10.83%) were malnourished. Finally the median (IR) of EQ-5D-3L Index score was 0.82 (0.72-0.89) out of 1.

3.3. Results of the Spearman’s Analysis

A Spearman’s analysis was performed to assess the relationship between MNA indices, the clinical-spirometric parameters of COPD severity, the multidimensional assessment (BI and EQ-5D-3L), Age and BMI. Table 2 shows the results of Spearman’s correlation analysis. Our results clearly show that MNA, both Short form and Total Score, are correlated with the breathlessness severity assessed by the mMRC and CAT, with spirometric variables, specifically with the severity of airflow

limitation based on the value of FEV₁. Also, they were correlated with QoL measured with EQ-5D-3L and with the degree of independence (only MNA-TS).

Table 2. Spearman's correlation analysis.

	<i>mMRC</i>	<i>CAT</i>	<i>FVC (%)</i>	<i>FEV₁ (%)</i>	<i>Barthel Index</i>	<i>EQ-5D-3L</i>	<i>Age</i>	<i>BMI</i>	<i>MNA-SF</i>	<i>MNA-TS</i>
<i>MNA-SF</i> ρ	-0,380***	-0,414***	0,247*	-0,312***	0.147	0,424***	-0.07	0.140	--	0.831***
<i>MAN-TS</i> ρ	0,398***	0,448***	0.126	-0,267**	0,224**	0.494***	-0.02	0.132	0.831***	--

Table 3: mMRC: modified Medical Research Council; CAT: COPD Assessment Test; FVC: Forced Vital Capacity; FEV₁: Forced Expiratory Volume in the 1st second; EQ-5D-3L: EuroQol 5D 3 level; BMI: Body Mass Index; MNA-SF: Mini Nutritional Assessment – Short Form; MNA-TS: Mini Nutritional Assessment – Total Score;. *** p<0,001; ** p<0,01; * p<0.05;

3.4. Results of the Kruskal-Wallis Test

Kruskal-Wallis results are presented in table 3. mMRC, CAT, FVC, FEV₁, EQ-5D-3L scores were statistically significantly different between the different nutritional status based on MNA-SF: “normal nutritional status” (n:39), “risk of malnutrition” (n:57) and “malnourished” (n:24). The post hoc analysis revealed statistically significant differences in: 1) mMRC distribution of “normal nutritional status” and “at risk of malnutrition” vs. “malnourished”; same findings were documented for CAT and EQ-5D-3L distributions; 2) For FVC and FEV₁, statistically significant differences were found between “normal nutritional status” and “malnourished”; mMRC, CAT, FVC/FEV₁, BI and EQ-5D-3L scores were also statistically significantly different between the different nutritional status based on MNA-TS: “normal nutritional status” (n:45), “risk of malnutrition” (n:62) and “malnourished” (n:13). The post hoc analysis revealed statistically significant differences in: 1) mMRC and CAT distribution of “normal nutritional status” and “at risk of malnutrition” vs. “malnourished”; 2) For FVC/FEV₁ and BI, statistically significant differences were found between “normal nutritional status” and “malnourished”; 3) between all group for EQ-5D-3L distribution;

Table 3. Results of Kruskal-Wallis test according to MNA risk class of malnutrition..

	<i>Mini-Nutritional Assessment Short Form</i>				<i>Mini-Nutritional Assessment Total Score</i>			
	Normal (1) (n=39)	At risk (2) (n=57)	Malnourished (3) (n=24)	<i>p value</i>	Normal (1) (n=45)	At risk (2) (n=62)	Malnourished (3) (n=13)	<i>p value</i>
Age	71 (66-78)	74 (68-80)	73.5 (66-79.5)	NS	74 (67-78)	73 (67-80)	71 (70-78)	NS
BMI	27.5 (24.2-30.9)	28.7 (24.5-31.2)	25.7 (22-33.5)	NS	28.3 (24.6-31.1)	27.5 (24.1-31.2)	25.1 (21.6-34.15)	NS
mMRC	2 (1-3)	3 (2-3)	3 (2-4)	1 vs 2-3, <i>p</i> <0.01	2 (1-3)	3 (2-3)	3 (3-4)	1 vs 2-3, <i>p</i> <0.01
CAT score	11 (5-15)	18 (13-22)		1 vs 2-3, <i>p</i> <0.001	13 (6-17)	17 (11-22)	23 (16-28)	1 vs 2-3, <i>p</i> <0.001
FVC (%)	77.5 (65-91.5)	75 (60-86)	62 (56-73)	1 vs 3, <i>p</i> =0.019	75 (61-88.5)	71.5 (58-87)	71 (59-78)	NS
FEV ₁ (%)	66 (51-78)	59 (40-68)	50 (39-59)	1 vs 3, <i>p</i> =0.01	62 (49-74)	58 (44-68)	44 (34-55)	NS

FVC/FEV ₁	0.65 (0.59-0.69)	0.62 (0.51-0.68)	0.62 (0.58-0.65)	NS	0.65 (0.59-0.69)	0.63 (0.54-0.68)	0.52 (0.45-0.62)	1 vs 3, <i>p</i> =0.002
Barthel Index	95 (85-100)	90 (75-100)	92.5 (67.5-100)	NS	95 (85-100)	92.5 (80-100)	75 (45-90)	1 vs 3, <i>p</i> =0.015
EQ-5D-3L	0.88 (0.81-0.92)	0.78 (0.7-0.88)	0.72 (0.52-0.82)	1 vs 2-3, <i>p</i> <0.01	0.88 (0.81-0.9)	0.78 (0.72-0.87)	0.56 (0.37-0.72)	All comparison <i>p</i> <0.001
MNA-SF	12 (12-14)	10 (9-11)	7 (5.5-7)	All comparison <i>p</i> <0.0001	12 (11-14)	10 (8-11)	6 (5-7)	All comparison <i>p</i> <0.001
MNA-TS	25 (24-27)	22 (19.5-23.5)	17.25 (15.25-18.5)	All comparison <i>p</i> <0.0001	25 (24-27)	20 (18-22.5)	15 (14-16)	All comparison <i>p</i> <0.0001

Table 2: Data are presented as median (interquantile range); BMI: Body Mass Index; mMRC: modified Medical Research Council; CAT: COPD Assessment Test; FVC: Forced Vital Capacity; FEV₁: Forced Expiratory Volume in the 1st second; MNA-SF: Mini Nutritional Assessment – Short Form; MNA-TS: Mini Nutritional Assessment – Total Score; EQ-5D-3L: EuroQol 5D 3 level; NS: No significant;.

3.5. Multivariate Linear Regression Analysis

Table 4 shows our multiple regression analysis, performed to predict mMRC (model 1), CAT score (model 2) BI (model 3) and EQ-5D-3L Index value (model 4) from MNA indices, adjusting data for confounding variables. Regression coefficient (β), R² and adjusted R² (aR²) are shown below in table 4. Supplementary Table 3 shows all of the regression analysis with the confounding variables. Both MNA-SF and MNA-TS were predictors of breathlessness severity assessed by the mMRC and CAT, with QoL measured with EQ-5D-3L and with the degree of independence assessed through BI.

Table 4. Multiple regression results for mMRC (model 1), CAT (model 2), BI (model 3) and EQ-5D-3L (model 4).

	<i>Model</i> 1.1	<i>Model</i> 1.2	<i>Model</i> 2.1	<i>Model</i> 2.2	<i>Model</i> 3.1	<i>Model</i> 3.2	<i>Model</i> 4.1	<i>Model</i> 4.2
R ²	0.273	0.292	0.220	0.275	0.173	0.238	0.222	0.314
aR ²	0.235	0.254	0.179	0.237	0.129	0.198	0.181	0.277
	<i>β coefficient</i>							
MNA-SF	- 0.135***	-	- 1.075***	-	1.424*	-	0.273***	-
MNA-TS	-	- 0.095***	-	- 0.844***	-	1.605***	-	0.231***

Table 3. * *p*<0.05; ** *p*<0.01; *** *p*<0.001; An increase of 1 point is intended for continuous variables, except for model 4 (0.1-point increase); R²: coefficient of determination; aR²: adjusted R²; MNA-SF: Mini Nutritional Assessment – Short Form; MNA-TS: Mini Nutritional Assessment – Total Score, mMRC: modified Medical Research Council; CAT: COPD Assessment Test; BI: Barthel Index.

3.6. Cox Regression Analysis

Cox regression analysis according to the nutritional status (Table 5), based on MNA score, showed that COPD participants “at risk of malnutrition” and “malnourished” were at higher risk of moderate-to-severe acute exacerbations during the 52 weeks of follow-up (respectively Hazard Ratio (HR) (95% CI): 3.547 (1.59-7.913), $p=0.002$; 8.207 (3.105-21.695), $p=0.0001$). For multivariate Cox regression computed with MNA-SF and MNA-TS as ordinal variables and the confounding variables, see Supplementary Table 5.1 and Table 5.2. Also, when computed as continuous variables, a one-point increase of MNA-SF and MNA-TS respectively reduced the risk of our primary outcome «moderate-to-severe acute exacerbations at 52 weeks from enrollment», of 21% and 14%, respectively. (HR: 0.79 (0.70-0.89); HR: 0.86 (0.80-0.93), $p<0.0001$). For multivariate Cox regression model computed with MNA-SF and MNA-TS as continuous variables, see Supplementary Material (Table 6.1 and Table 6.2).

Table 5. Results of multivariate Cox regression analysis according to the nutritional status (MNA score).

	Normal nutritional status	At risk of malnutrition	Malnourished
MNA-Short Form	Group reference	4.01 (1.48-10.85)	7.47 (2.63-21.21)
MNA-Total Score	Group reference	3.54 (1.59-7.91)	8.20 (3.10-21.69)

Table 5: Results are presented as Hazard Ratio with 95% confidence intervals (CIs) and P values. MNA: Mini Nutritional Assessment.

4. Discussion

The main results of the analysis presented in this study firstly demonstrates that in elderly subjects with COPD and a high burden of comorbidities, assessment of nutritional status by systematic administration of the Mini Nutritional Assessment (MNA) questionnaire allows the identification of a subgroup of subjects whose poorer nutritional status is significantly associated with breathlessness severity and respiratory symptoms assessed by the mMRC and CAT, with spirometric variables, specifically with the severity of airflow limitation based on the value of FEV1, with poorer QoL assessed through the EQ-5D-3 questionnaire and with a lower degree of independence assessed by the Barthel Index. In other words, a group of patients with COPD and higher levels of frailty may be identified. Our data also show that in highly complex elderly COPD subjects, nutritional status assessed by MNA is correlated with severity of airflow limitation (FEV1, FVC/FEV1), clinical severity (mMRC, CAT score), and quality of life (EQ-5D-3L index score), which are significantly correlated with each other. Finally, our study through Cox regression analysis suggests that COPD participants "at risk of malnutrition" and "malnourished" according to nutritional status based on MNA score have a higher risk of moderate to severe acute exacerbations with hazard ratio (HR) of 3.54 ($p=0.002$) and 8.20 ($p=0.0001$) respectively along one year of follow-up.

Malnutrition is a common finding in patients with COPD [2-4,33]. The prevalence is very variable, ranging from 17% to 47.2%, due to the different types of patients in which it is assessed and the different diagnostic criteria used, but it is clear that the more severe the disease, the higher the risk of malnutrition and sarcopenia. In our study 47.5% of subjects have been classified at risk of malnutrition and 20 were malnourished, data consistent with available evidence, confirming the relevance of this issue. Of note, the mean BMI of our sample is 27.8, and only the 3.3% of the total population can be classified as underweight according to BMI levels demonstrating the need for an additional routine nutritional screening to detect poor nutritional status in COPD. Our Spearman's correlation analysis, shown in Table 2, shows that both BMI and age are not correlated with the results of the MNA questionnaire in our population, and the Kruskal-Wallis test (Table 3) confirms no significant differences in BMI levels or age in relation to the different results of the MNA. On the other hand, the results of the Kruskal-Wallis test according to the MNA risk class of malnutrition showed progressively lower lung function and higher clinical severity for worsening nutritional status. Another important issue is that the prevalence of malnutrition is reported to be influenced by geographical regions, which may reflect the negative impact of social and economic factors in developing countries [4], but also removing this additional determinant, even in a high-income country such as Italy, the relevance of this aspect and its potential consequences for the natural history of the disease cannot be underestimated.

The clinical implications of poor nutritional status in people with COPD are strictly related to the pathophysiology of the disease [7,34], which often leads to a disease-related energy imbalance with a hypercatabolic state also induced by low-grade systemic inflammation, tissue hypoxia, and ultimately muscle wasting and atrophy. All these events can be further amplified by aging and polytherapy. Our data seem to confirm a closer correlation of all items considered with lung function in COPD.

Our sample of 120 elderly subjects followed for 12 months provides evidence of a closer relationship between nutritional status, as assessed by the MNA and respiratory function, severity of respiratory symptoms, quality of life. Similar results have been provided by Fekete et al in 50 subjects in Hungary, but using the Malnutrition Universal Screening Tool (MUST) and bioelectrical impedance analysis (BIA) as screening tools [18]. This is not an intervention study, but our study suggests that targeted strategies to improve nutritional status in elderly COPD may have a relevant prognostic value. As recommended by the latest GOLD report [1], a combination of exercise, specific interventions to control respiratory and systemic inflammation, and targeted nutritional support may be used to prevent all the negative effects of the development of pulmonary cachexia. Future development may consider the use of nutritional supplements for this category of subjects, such as oral supplementation with ketone bodies, as already proposed for subjects with heart failure [35]. Over dietary intervention, exercise, especially in comorbid patients where cardiovascular, metabolic and respiratory disorders coexist, is recognized as the better intervention strategy to reverse some of the skeletal muscle abnormalities typical of COPD patients [36,37], being the most effective non-pharmacological intervention to improve exercise capacity and dyspnea. Systemic inflammation and oxidative stress that have been postulated to be aetiological factors of muscle dysfunction in COPD, may be also a therapeutic target through an integrated approach combining nutrition, exercise and drugs. The MACH (Multidimensional Approach for COPD and High Complexity) Study, of which these represent preliminary data, will also evaluate these aspects in an ongoing intervention arm of the study.

Only a few studies have attempted to determine the prognostic role of malnutrition, with greater heterogeneity of results showing increased mortality in malnourished COPD patients, two in stable COPD [19,38] and two during acute exacerbations [39,40]. These papers adopted the European Society of Clinical Nutrition and Metabolism (ESPEN) criteria for identifying clinical malnutrition [41], or the Global Leadership Initiative on Malnutrition (GLIM) criteria [42] giving a relevant role to BMI, which in our sample appears to be an inaccurate parameter for COPD subjects. No studies to date have provided information on the risk of acute exacerbations during a 12-months of follow-up according to a screening-based use of MNA in identifying a subgroup of subjects with poor nutritional status. In our analysis, the condition of "at risk of malnutrition" is associated to a hazard ratio (HR) of 3.54 ($p=0.002$) of moderate to severe acute exacerbations along one-year follow-up and the "malnourished" status have an HR of 8.20 ($p=0.0001$).

Our study has some limitations, first of all the reliability of MNA as a screening tool in COPD; data shows that the measurement tool influenced the malnutrition prevalence and the at-risk for malnutrition prevalence among patients with COPD [4]. To date, there is a lack of gold-standard diagnostic tool to evaluate malnutrition in COPD. Since malnutrition is a very complex subject, the attempt to validate a world-wide gold standard for malnutrition is challenging and this assumption is more and more valid for COPD. MNA is one of the widely used test worldwide and the present analysis in our opinion could be useful to validate its use in elderly high-complex COPD subjects. Second, our sample consisted of very complex COPD patients with a high degree of comorbidities [23], so our results may not be generalizable to the entire clinical spectrum of COPD. Given this, this category of patients with the highest level of frailty is the one that may benefit more from a multidimensional assessment, which needs to include a validated tool for screening nutritional status. Thirdly, the use of a screening tool such as the MNA is subject to the judgement of the operator and requires the active co-operation of the patients, the information provided may be subjectively transmitted and subjectively received, which reduces the reproducibility of the data.

5. Conclusions

In elderly COPD patients at high risk of exacerbations, systematic screening for malnutrition using MNA identifies categories of patients at different risk of acute exacerbations: the poorer the

nutritional status, the higher the risk. Inadequate nutritional health is significantly associated with a worse clinical profile, lung function and perceived quality of life. BMI per se may not be an accurate parameter of good/bad nutritional status in COPD.

Our study confirms the importance of a multidimensional assessment in elderly patients with a high burden of comorbidities, as several determinants have a strong influence on the clinical course of respiratory disease. In particular, the MNA assessment may also provide prognostic value; subjects at risk of malnutrition or with overt malnutrition in our analysis have a higher risk of moderate to severe acute exacerbations.

Poor nutritional status should merit being subjected to a targeted clinical pathway that addresses all clinical and social vulnerabilities leading to malnutrition with an individualized treatment plan.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

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References

1. 2024 GOLD Report Available online: <https://goldcopd.org/2024-gold-report/> (accessed on 28 February 2024).
2. Mete, B.; Pehlivan, E.; Gülbaş, G.; Günen, H. Prevalence of Malnutrition in COPD and Its Relationship with the Parameters Related to Disease Severity. *Int J Chron Obstruct Pulmon Dis* **2018**, *13*, 3307–3312, doi:10.2147/COPD.S179609.
3. Soler, J.J.; Sánchez, L.; Román, P.; Martínez, M.A.; Perpiñá, M. Prevalence of malnutrition in outpatients with stable chronic obstructive pulmonary disease. *Arch Bronconeumol* **2004**, *40*, 250–258, doi:10.1016/s1579-2129(06)70095-7.
4. Deng M.; Lu Y.; Zhang Q.; Bian Y.; Zhou X.; Hou, G. Global prevalence of malnutrition in patients with chronic obstructive pulmonary disease: Systemic review and meta-analysis. *Clin Nutr* **2023**, *42*, 848–858, doi: 10.1016/j.clnu.2023.04.005.
5. Sieber C.C. Malnutrition and sarcopenia. *Aging Clin Exp Res* **2019**, *31*, 793–798. doi: 10.1007/s40520-019-01170-1.
6. Cruz-Jentoft A.J.; Bahat G.; Bauer J.; Boirie Y.; Bruyère O.; Cederholm T.; Cooper C.; Landi F.; Rolland Y.; Sayer A.A.; et al. Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), and the Extended Group for EWGSOP2. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* **2019**, *48*, 16–31. doi: 10.1093/ageing/afy169
7. Tramontano, A.; Palange, P. Nutritional State and COPD: Effects on Dyspnoea and Exercise Tolerance. *Nutrients* **2023**, *15*, 1786. <https://doi.org/10.3390/nu15071786>
8. Kaluźniak-Szymanowska, A.; Krzyżmińska-Siemaszkó, R.; Wiczerowska-Tobis, K.; Deskur-Śmielecka, E. Optimal Assessment of Nutritional Status in Older Subjects with the Chronic Obstructive Pulmonary Disease—A Comparison of Three Screening Tools Used in the GLIM Diagnostic Algorithm. *Int J Environ Res Public Health* **2022**, *19*, 1025, doi:10.3390/ijerph19031025.
9. Scichilone N.; Paglino G.; Battaglia S.; Martino L.; Interrante A.; Bellia V. The mini nutritional assessment is associated with the perception of dyspnoea in older subjects with advanced COPD. *Age Ageing* **2008**, *37*, 214–7. doi: 10.1093/ageing/afm143.
10. Guigoz, Y. The Mini Nutritional Assessment (MNA) Review of the Literature—What Does It Tell Us? *J Nutr Health Aging* **2006**, *10*, 466–485; discussion 485–487.
11. Fried, T.R.; Frago, C.A.V.; Rabow, M.W. Caring for the Older Person With Chronic Obstructive Pulmonary Disease. *JAMA* **2012**, *308*, 1254–1263, doi:10.1001/jama.2012.12422.

12. Ozsoy, I.; Ozcan Kahraman, B.; Acar, S.; Ozalevli, S.; Akkoclu, A.; Savci, S. Factors Influencing Activities of Daily Living in Subjects With COPD. *Respir Care* **2019**, *64*, 189–195, doi:10.4187/respcare.05938.
13. Nakken, N.; Janssen, D.J.A.; Wouters, E.F.M.; van den Bogaart, E.H.A.; Muris, J.W.M.; de Vries, G.J.; Bootsma, G.P.; Gronenschild, M.H.M.; Delbressine, J.M.L.; van Vliet, M.; et al. Changes in Problematic Activities of Daily Living in Persons with COPD during 1 Year of Usual Care. *Aust Occup Ther J* **2020**, *67*, 447–457, doi:10.1111/1440-1630.12664.
14. Lahaije, A.J.M.C.; van Helvoort, H. a. C.; Dekhuijzen, P.N.R.; Heijdra, Y.F. Physiologic Limitations during Daily Life Activities in COPD Patients. *Respir Med* **2010**, *104*, 1152–1159, doi:10.1016/j.rmed.2010.02.011
15. Simon, K.M.; Carpes, M.F.; Corrêa, K.S.; dos Santos, K.; Karloh, M.; Mayer, A.F. Relationship between Daily Living Activities (ADL) Limitation and the BODE Index in Patients with Chronic Obstructive Pulmonary Disease. *Rev Bras Fisioter* **2011**, *15*, 212–218.
16. Silva, C.S.; Nogueira, F.R.; Porto, E.F.; Gazzotti, M.R.; Nascimento, O.A.; Camelier, A.; Jardim, J.R. Dynamic Hyperinflation during Activities of Daily Living in COPD Patients. *Chron Respir Dis* **2015**, *12*, 189–196, doi:10.1177/1479972315576143.
17. Zareifopoulos, N.; Bellou, A.; Spiropoulou, A.; Spiropoulos, K. Prevalence, Contribution to Disease Burden and Management of Comorbid Depression and Anxiety in Chronic Obstructive Pulmonary Disease: A Narrative Review. *COPD* **2019**, *16*, 406–417, doi:10.1080/15412555.2019.1679102.
18. Fekete, M.; Fazekas-Pongor, V.; Balazs, P.; Tarantini, S.; Szollosi, G.; Pako, J.; Nemeth, A.N.; Varga, J.T. Effect of Malnutrition and Body Composition on the Quality of Life of COPD Patients. *Physiol Int* **2021**, doi:10.1556/2060.2021.00170.
19. Marco, E.; Sánchez-Rodríguez, D.; Dávalos-Yerovi, V.N.; Duran, X.; Pascual, E.M.; Muniesa, J.M.; Rodríguez, D.A.; Aguilera-Zubizarreta, A.; Escalada, F.; Duarte, E. Malnutrition According to ESPEN Consensus Predicts Hospitalizations and Long-Term Mortality in Rehabilitation Patients with Stable Chronic Obstructive Pulmonary Disease. *Clin Nutr* **2019**, *38*, 2180–2186, doi:10.1016/j.clnu.2018.09.014.
20. Schwartz, D.B. Malnutrition in Chronic Obstructive Pulmonary Disease. *Respir Care Clin N Am* **2006**, *12*, 521–531, doi:10.1016/j.rcc.2006.09.001.
21. Anzueto, A. Impact of Exacerbations on COPD. *Eur Respir Rev* **2010**, *19*, 113–118, doi:10.1183/09059180.00002610.
22. Erhabor, G.E.; Adeniyi, B.; Arawomo, A.O.; Akinwalere, O.; Adetona, G.; Fagbohun, F.T.; Aigbirior, J.; Erhabor, J.O. Acute Exacerbation of COPD: Clinical Perspectives and Literature Review. *West Afr J Med* **2021**, *38*, 1129–1142.
23. Di Raimondo, D.; Pirera, E.; Pintus, C.; De Rosa, R.; Profita, M.; Musiari, G.; Siscaro, G.; Tuttolomondo, A. The Role of the Cumulative Illness Rating Scale (CIRS) in Estimating the Impact of Comorbidities on Chronic Obstructive Pulmonary Disease (COPD) Outcomes: A Pilot Study of the MACH (Multidimensional Approach for COPD and High Complexity) Study. *J Pers Med* **2023**, *13*, 1674, doi:10.3390/jpm13121674.
24. Graham, B.L.; Steenbruggen, I.; Miller, M.R.; Barjaktarevic, I.Z.; Cooper, B.G.; Hall, G.L.; Hallstrand, T.S.; Kaminsky, D.A.; McCarthy, K.; McCormack, M.C.; et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. *Am J Respir Crit Care Med* **2019**, *200*, e70–e88, doi:10.1164/rccm.201908-1590ST.
25. Quanjer, P.H.; Stanojevic, S.; Cole, T.J.; Baur, X.; Hall, G.L.; Culver, B.H.; Enright, P.L.; Hankinson, J.L.; Ip, M.S.M.; Zheng, J.; et al. Multi-Ethnic Reference Values for Spirometry for the 3–95-Yr Age Range: The Global Lung Function 2012 Equations. *Eur Respir J* **2012**, *40*, 1324–1343, doi:10.1183/09031936.00080312.
26. van Dam van Isselt, E.F.; Spruit, M.; Groenewegen-Sipkema, K.H.; Chavannes, N.H.; Achterberg, W.P. Geriatric Rehabilitation for Patients with Advanced Chronic Obstructive Pulmonary Disease: A Naturalistic Prospective Cohort Study on Feasibility and Course of Health Status. *Chron Respir Dis* **2014**, *11*, 111–119, doi:10.1177/1479972314529674.
27. Wylie, C.M.; White, B.K. A Measure of Disability. *Archives of Environmental Health: An International Journal* **1964**, *8*, 834–839, doi:10.1080/00039896.1964.10663764.
28. Shah, S.; Vanclay, F.; Cooper, B. Improving the Sensitivity of the Barthel Index for Stroke Rehabilitation. *J Clin Epidemiol* **1989**, *42*, 703–709, doi:10.1016/0895-4356(89)90065-6.
29. Rabin, R.; de Charro, F. EQ-5D: A Measure of Health Status from the EuroQol Group. *Ann Med* **2001**, *33*, 337–343, doi:10.3109/07853890109002087.
30. Boros, P.W.; Lubiński, W. Health State and the Quality of Life in Patients with Chronic Obstructive Pulmonary Disease in Poland: A Study Using the EuroQoL-5D Questionnaire. *Pol Arch Med Wewn* **2012**, *122*, 73–81, doi:10.20452/pamw.1177.
31. Lin, F.-J.; Pickard, A.S.; Krishnan, J.A.; Joo, M.J.; Au, D.H.; Carson, S.S.; Gillespie, S.; Henderson, A.G.; Lindenauer, P.K.; McBurnie, M.A.; et al. Measuring Health-Related Quality of Life in Chronic Obstructive Pulmonary Disease: Properties of the EQ-5D-5L and PROMIS-43 Short Form. *BMC Med Res Methodol* **2014**, *14*, 78, doi:10.1186/1471-2288-14-78.

32. Finch, A.P.; Meregaglia, M.; Ciani, O.; Roudijk, B.; Jommi, C. An EQ-5D-5L Value Set for Italy Using Videoconferencing Interviews and Feasibility of a New Mode of Administration. *Soc Sci Med* **2022**, *292*, 114519, doi:10.1016/j.socscimed.2021.114519.
33. Kaluźniak-Szymanowska A.; Krzyminińska-Siemaszkó R.; Deskur-Śmielecka E.; Lewandowicz M.; Kaczmarek B.; Wieczorowska-Tobis K. Malnutrition, Sarcopenia, and Malnutrition-Sarcopenia Syndrome in Older Adults with COPD. *Nutrients* **2021**, *14*, 44. doi: 10.3390/nu14010044.
34. Verduri A.; Cline E.; Carter B.; Hewitt J. Impact of Frailty on Symptom Burden in Chronic Obstructive Pulmonary Disease. *J Clin Med* **2024**, *13*, 984. doi: 10.3390/jcm13040984.
35. Berg-Hansen K.; Gopalasingam N.; Christensen K.H.; Ladefoged B.; Andersen M.J.; Poulsen S.H.; Borlaug B.A.; Nielsen R.; Møller N.; Wiggers H. Cardiovascular Effects of Oral Ketone Ester Treatment in Patients With Heart Failure With Reduced Ejection Fraction: A Randomized, Controlled, Double-Blind Trial. *Circulation* **2024**, *149*, 1474-1489. doi: 10.1161/CIRCULATIONAHA.123.067971.
36. Di Raimondo D.; Musiari G.; Miceli G.; Arnao V.; Pinto A. Preventive and Therapeutic Role of Muscle Contraction Against Chronic Diseases. *Curr Pharm Des* **2016**, *22*, 4686-4699. doi: 10.2174/1381612822666160510125011.
37. Di Raimondo D.; Tuttolomondo A.; Musiari G.; Schimmenti C.; D'Angelo A.; Pinto A. Are the Myokines the Mediators of Physical Activity-Induced Health Benefits? *Curr Pharm Des* **2016**, *22*, 3622-47. doi: 10.2174/1381612822666160429121934.
38. Dávalos-Yerovi, V.; Marco, E.; Sánchez-Rodríguez, D.; Duran, X.; Meza-Valderrama, D.; Rodríguez, D.A.; Muñoz, E.; Tejero-Sánchez, M.; Muns, M.D.; Guillén-Solà, A.; et al. Malnutrition According to GLIM Criteria Is Associated with Mortality and Hospitalizations in Rehabilitation Patients with Stable Chronic Obstructive Pulmonary Disease. *Nutrients* **2021**, *13*, 369. <https://doi.org/10.3390/nu13020369>.
39. de Araújo B.E.; Kowalski V.; Leites G.M.; da Silva Fink J.; Silva F.M. AND-ASPEN and ESPEN consensus, and GLIM criteria for malnutrition identification in AECOPD patients: a longitudinal study comparing concurrent and predictive validity. *Eur J Clin Nutr* **2022**, *76*, 685-692. doi: 10.1038/s41430-021-01025-x.
40. Perrot L.; Greil A.; Boirie Y.; Farigon N.; Mulliez A.; Costes F.; Caillaud D. Prevalence of sarcopenia and malnutrition during acute exacerbation of COPD and after 6 months recovery. *Eur J Clin Nutr* **2020**, *74*, 1556-1564. doi: 10.1038/s41430-020-0623-6.
41. Cederholm T.; Bosaeus I.; Barazzoni R.; Bauer J.; Van Gossum A.; Klek S.; Muscaritoli M.; Nyulasi I.; Ockenga J.; Schneider S.M.; et al. Diagnostic criteria for malnutrition - An ESPEN Consensus Statement. *Clin Nutr* **2015**, *34*, 335-40. doi: 10.1016/j.clnu.2015.03.001.
42. Cederholm T.; Jensen G.L.; Correia M.I.T.D.; Gonzalez M.C.; Fukushima R.; Higashiguchi T.; Baptista G.; Barazzoni R.; Blaauw R.; Coats A.; et al. GLIM Core Leadership Committee; GLIM Working Group. GLIM criteria for the diagnosis of malnutrition - A consensus report from the global clinical nutrition community. *Clin Nutr* **2019**, *38*, 1-9. doi: 10.1016/j.clnu.2018.08.002.

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