Unintentional weight loss is reflected in worse one-year clinical outcomes among COPD outpatients

Yde, Søren Kveiborg; Mikkelsen, Sabina; Brath, Mia Solholt Godthaab; Holst, Mette

Published in:
Clinical Nutrition

DOI (link to publication from Publisher):
10.1016/j.clnu.2023.09.012

Publication date:
2023

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (APA):
Yde, S. K., Mikkelsen, S., Brath, M. S. G., & Holst, M. (2023). Unintentional weight loss is reflected in worse one-year clinical outcomes among COPD outpatients. *Clinical Nutrition*, *42*(11), 2173-2180. https://doi.org/10.1016/j.clnu.2023.09.012

Clinical Nutrition 42 (2023) 2173–2180

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Unintentional weight loss is reflected in worse one-year clinical outcomes among COPD outpatients

Søren Kveiborg Yde [a], Sabina Mikkelsen [a, b], Mia Solholt Godthaab Brath [a, c], Mette Holst [a, b, 1, *]

[a] Department of Clinical Medicine, Aalborg University, Sdr. Skovvej 15, 9000 Aalborg, Denmark
[b] Centre for Nutrition and Intestinal Failure, Department of Gastroenterology, Aalborg University Hospital, Sdr. Skovvej 5.1, 9000 Aalborg, Denmark
[c] Department of Respiratory Diseases, Aalborg University Hospital, Mølleparkvej 4, 9000 Aalborg, Denmark

ARTICLE INFO

Article history:
Received 13 March 2023
Accepted 7 September 2023

Keywords:
COPD
Outpatients
Malnutrition
Clinical outcomes
Unintentional weight loss

SUMMARY

Rationale: Unintentional weight loss (UWL) is prevalent among patients with chronic obstructive pulmonary disease (COPD). However, little research has been done on UWL as an independent variable in terms of clinical outcome. The aim of this study was to investigate the association between BMI, UWL, and clinical outcome in terms of hospitalization, length of stay, exacerbations, mortality, and quality of life (QoL) within six months and one year in a hospital outpatient setting.

Methods: A prospective single-center cohort study enrolled 200 patients from the COPD outpatient clinic between October 2020 and May 2021 at a Danish Hospital. At baseline, data was collected using patients' electronic journals and a quantitative questionnaire was gathered with a patient-reported UWL of 5% of body weight within three months. At six months and one-year follow-ups, data was collected using the patients' medical journals and a telephonic interview with the EQ-5D-5L and SARC-F questionnaire and the number of non-hospitalization exacerbations since inclusion. Data were analyzed using logistic and Cox hazard regression analysis.

Results: A total of 187 patients were eligible for follow-up (mean age 69.2 years, 43.9% males, median BMI 26.8 kg/m^2), and the prevalence of UWL was 13.4%. UWL was associated with an almost trifold risk of >five days stay (OR = 2.94, p = 0.021). Additionally, UWL was associated with a worse QoL. A higher risk of exacerbation was found in the underweight patients (OR = 4.94, p = 0.014). No significant difference in mortality was found.

Conclusion: UWL as a solitary factor is associated with increased hospital length of stay and a worse QoL. The results provide further evidence that implementation of regular screening for UWL in addition to BMI might be beneficial to include in international COPD guidelines for outpatient settings.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a rapidly escalating global health threat, among the most prevalent disorders contributing to significant morbidity and mortality worldwide [1]. COPD is progressive, poorly reversible, and is characterized by persistent respiratory symptoms and airway obstruction, leading to severe dyspnea over time [1].

Many risk factors, such as malnutrition, low Body Mass Index (BMI), and loss of muscle mass, have been shown to affect the progression of the disease and outcome in terms of hospitalizations, exacerbations, and mortality [2–9]. Notably, malnutrition affects a substantial proportion of COPD patients, with a prevalence ranging from 20% to 45%, correlating with increased mortality risk [2]. Weight loss is a key component of malnutrition and is prevalent among patients with COPD [2–4], and has been established as an independent risk factor of mortality in COPD patients [4,5]. Additionally, patients with COPD, who exhibit low BMI and weight loss, experience more frequent hospital admissions for exacerbations

Abbreviations: COPD, chronic obstructive pulmonary disease; UWL, unintentional weight loss; BMI, Body Mass Index; QoL, quality of life; MRC, Medical Research Council; LOS, length of stay.

* Corresponding author. Centre for Nutrition and Intestinal Failure, Department of Gastroenterology, Aalborg University Hospital and Department of Clinical Medicine, Aalborg University, Denmark.
E-mail address: mette.holst@rn.dk (M. Holst).
[1] Permanent postal address: Visborggårdvej 4, 9200, Aalborg SV, Denmark

https://doi.org/10.1016/j.clnu.2023.09.012

and have an increased likelihood of subsequent exacerbations [6]. Similarly, a low BMI (<18.5) in patients with COPD has shown a three-fold increased mortality risk, while patients with a higher BMI consistently exhibit lower mortality risk [5]. Paradoxically, being overweight and even obese has been associated with lower mortality rates than underweight and normal weight patients with COPD, unlike in many other diseases [7].

Another critical dimension is the association between quality of life (QoL) and weight loss in patients with COPD, as a pronounced link between disease severity, malnutrition, and reduced QoL have been established [8,9]. Deterioration in QoL metrics over time independently increases the mortality risk in patients with COPD [8]. However, a notable gap exists in the literature regarding the nexus between unintentional weight loss (UWL) and QoL among Danish COPD outpatients. The need for systematic UWL screening in outpatient settings compounds this gap.

In the literature, there are different definitions of UWL, as seen in Christensen et al., a questionnaire-based investigation to test the prevalence of UWL, where UWL was defined as a decrease of a minimum of two kilos within three months [10]. The study found a noteworthy 21.5% prevalence of nutritional risk measured by UWL. Furthermore, it revealed that 13.5% were underweight, while 34.5% were obese, which indicates that nutritional screening and guidance are essential for both COPD patients who are underweight and obese [10]. The NRS-2002 nutrition screening tool, used systematically in hospitalized patients in Denmark, has shown a firm association with clinical outcomes. For this study, we re-analyzed the prevalence of nutritional risk using the 5% cut-off and found a prevalence of 13.5% [11–13]. Using the 5% UWL within 3 months as a primary and initial marker for malnutrition is a feasible and less time-consuming method [13].

We hypothesize that UWL may be an independent predictor for poorer clinical outcomes and QoL in outpatient settings and thus indicate the need for further screening and assessment.

The primary aim of this study is to investigate the association between UWL, BMI, and clinical outcomes in terms of hospitalizations, length of stay (LOS) when hospitalized, exacerbations, QoL, and mortality within six months and one year in patients visiting the COPD-outpatient clinic at a Danish University Hospital.

The secondary aim is to investigate whether potential subgroups may be more exposed to UWL and thus need increased attention to nutritional status. Achieving this will broaden the understanding of risk variables and the potential importance of implementing screening tools for specific patient categories to improve clinical outcomes.

2. Methods

2.1. Study population and study design

This prospective cohort study enrolled 200 patients and the cohort available for follow-up consists of 187 Danish outpatients from the Department of Respiratory Medicine at Aalborg University Hospital, North Denmark Region. The patients were enrolled between October 2020 and May 2021. Eligible patients were patients with a clinical diagnosis of COPD according to the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) guidelines, including also patients with Alpha-1-antitrypsin deficiency, who are seen by the same staff in the COPD clinic [1].

A spirometry was performed at enrollment, and the patient's body weight and height were measured. If no spirometry was performed at enrollment, the closest spirometry performed within six months of enrollment was used. Weight and height were used to calculate BMI (body mass (kg)/height $(m)^2$). Demographic variables (age, sex, smoking status) and COPD phenotypical variables were obtained: Emphysema, alpha-1-antitrypsin deficiency, and Asthma-COPD Overlap Syndrome (ACO). Pulmonary hypertension was noted if it had been verified by echocardiography or catheter measurement.

Additionally, at enrollment, patients were asked about their weight three months ago, and thus UWL within the last three months was obtained. Weight was checked in patient medical records to ensure if a wide discrepancy was seen between the informed and the last noted weight. For this follow-up study, UWL was defined as an unplanned weight loss of more than 5% of body weight [1,14].

All patient records were assessed for comorbidities, and the number of prescription medicines was noted. Charlson's Comorbidity Index (CCI) was used to stratify comorbidities [15]. Furthermore, the study highlighted whether patients were engaged in regional telemedicine that monitored weekly body weight, blood oxygen levels, and blood pressure. Information on any self-management plan and current treatment with oral nutritional supplementation was obtained.

Self-management plans are often used in COPD patients, wherein clinic staff provide training to recognize exacerbation symptoms. This enables patient to have the necessary medication at home, granting them the authority to initiate treatment with antibiotics or oral steroids upon experiencing exacerbation signs, even without a prior medical assessment.

2.2. Data collection

Patient medical records were assessed at the 6-month and 1-year follow-ups, and telephone interviews were conducted with all available patients. Patient records were assessed for all-cause somatic hospital admissions and admissions related to dyspnea, pneumonia, and COPD exacerbation. Data on admissions were collected through the common regional patient record database. Thus, hospitalizations at other regional hospitals were included. Psychiatric admissions were excluded.

Additionally, LOS was recorded for all admissions. Data on mortality were collected through the regional hospital personal registration number system. Medically educated research assistants obtained all patient record data.

In phone interviews, patients were asked if they had received any treatment for exacerbation of COPD that did not require hospital admission during the follow-up period, either through their general practitioner or using a self-management plan. The EuroQol EQ-5D-5L questionnaire was fulfilled at follow-up by telephone to assess the different QoL parameters: mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and VAS score on overall health [16]. The five variables each contain five different levels, with higher scores indicating worse outcomes, thus ranging from having no problems to having extreme problems in the dimension. Additionally, a SARC-F questionnaire was fulfilled to assess for sarcopenia [17]. All telephone interviews were performed by the same two researchers using the same manuscript of instructions with all patients.

2.3. Statistical analysis

All data were analyzed using STATA Version 17 (Stata Corp, College Station, TX, USA).

All continuous variables were assessed for normal distribution using the Shapiro-Wilks test. Mean and standard deviation (SD) were used and reported for parametric data, and median and interquartile ranges (IQR) were used and reported for non-parametric data. The clinical characteristics were reported with absolute numbers and percentages for the categorical variables.

The population was divided into groups having UWL and no UWL (NUWL). Dichotomous variables were analyzed using a Chi-square test, and continuous variables were analyzed using Student's t-test and Mann Whitney U test, respectively. Odds ratios (OR) were calculated using logistic regression analyses, and hazard ratios (HR) were calculated using Cox proportional hazard model regression analyses. Results were expressed with the ratio with a 95% confidence interval and p-value, and the models were adjusted for other variables in a multivariate analysis. A Kaplan Meier curve was used to plot survival with UWL as the primary variable. A p-value of <0.05 was considered statistically significant.

2.4. Sample size

For sample size, we consecutively enrolled 200 outpatients from the COPD clinic. It was anticipated that approximately 10% of the patients from the COPD clinic would not have the COPD diagnosis at enrollment or receive the COPD diagnosis during follow-ups as they would be newly referred patients, who were examined due to unspecified respiratory symptoms. The sample size was estimated to be at least 181 needed to be included based on the studies of Marco and Deutz. However, no quite suitable studies were found to match and thus inspire the number needed to achieve sufficient power [2,18].

2.5. Ethical considerations

All patients gave informed written consent to participate in the study and could withdraw their consent at any time during the study. The North Jutland Ethical Committee was approached for project review and had no concerns since the study was exempt from full application due to Danish legislation. The North Jutland data protection agency approved the project, application ID: 2020–119.

3. Results

3.1. Patient characteristics

Out of the 200 enrolled patients, 13 (6.5%) were excluded due to misdiagnosis (not meeting the criteria for COPD) after one year. At the 6-month follow-up, 37 patients did not respond or complete the telephone interview. At the 1-year follow-up, 43 patients did not respond or complete the telephone interview. Figure 1 shows the sample size development during follow-up.

As seen in Table 1, the baseline mean age of the eligible population was 69.2 years and consisted of 43.9% males. The majority (67.9%) had had a COPD diagnosis for more than five years. The median BMI was 26.8, and 25 (13.4%) had an UWL of more than 5% body weight at inclusion. Of the overall population, 11% received oral nutritional supplementation. Almost all patients (97.3%) were former smokers with a median of 37 pack-years. The population had a median CCI Score of 2. The median FEV1 was 41% and the median Medical Research Council (MRC) dyspnea score was 4. The prevalence of emphysema, pulmonary hypertension, and ACO was 78.1%, 24.6%, and 28.3%, respectively.

Table 1
Baseline characteristics of the study population.

	Total population (n = 187) N (%) or mean (±SD) or median [25. Quartile-75. Quartile]
Age (years)	69.2 (±9.9)
Male	82 (43.9%)
Body weight (kg)	76.2 [59.0–94.0]
BMI (kg/m^2)	26.8 [22.2–32.6]
BMI categories	
Underweight (<18.5)	25 (13.4%)
Normal (18.5–24.9)	53 (28.3%)
Overweight (BMI 25.0–29.9)	44 (23.6%)
Obese (BMI ≥30)	65 (34.8%)
FEV1 (% predicted, *n = 166*)	41.0 [30.0–55.0]
Mild	11 (6.6%)
Moderate	47 (28.3%)
Severe	68 (40.1%)
Very severe	40 (24.1%)
MRC dyspnea score	4.0 [3.0–5.0]
Charlson Comorbidity Index Score	2.0 [1.0–4.0]
Emphysema	146 (78.1%)
Alpha-1-antitrypsin deficiency	12 (6.4%)
ACO	53 (28.3%)
Pulmonary hypertension	46 (24.6%)
Time since diagnosis	
0–2 years	21 (11.2%)
2–5 years	39 (20.9%)
More than 5 years	127 (67.9%)
Smoking status	
Current	31 (16.6%)
Cessation	2 (1.1%)
Former	149 (79.7%)
Never smoked	5 (2.7%)
Pack years (years)	37.0 [25.0–50.0]
More than 5 prescription medicines	152 (81.7%)
Unintentional weight loss	25 (13.4%)
Participates in telemedicine	53 (28.9%)
Self-management plan	56 (30.1%)

BMI, body mass index; MRC, Medical Research Council; FEV1, forced expiratory volume in 1 s; ACO, asthma-COPD overlap syndrome.

3.2. Comparison of groups at follow-up

As shown in Table 2, the baseline characteristics of the population divided into UWL and NUWL were relatively similar with no significant differences for most descriptive variables. However,

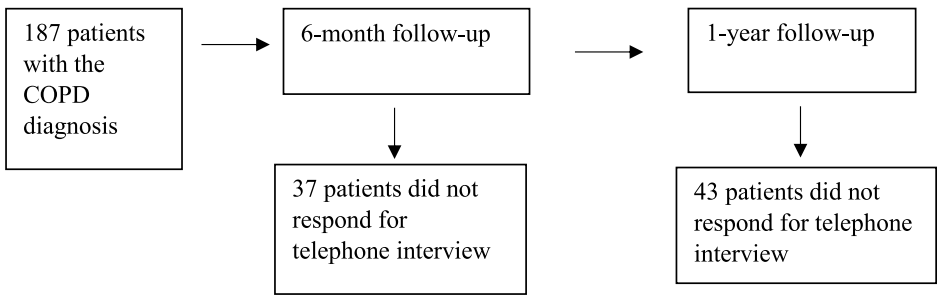

Fig. 1. Flow chart of the sample size development during follow-up.

Table 2
Baseline characteristics of the population divided into unintentional weight loss (UWL) and no unintentional weight loss (NUWL).

	UWL (n = 25)	NUWL (n = 162)	*p*-value
Age (years)	68.2 (±10.6)	69.3 (±9.8)	0.755[†]
Male	12 (48.0%)	70 (43.2%)	0.653[±]
Body weight (kg)	56.0 [47.9–78.0]	79.0 [65.0–95.0]	**0.004**[×]
BMI (kg/m^2)	18.6 [16.6–23.5]	27.8 [23.3–33.0]	**<0.001**[×]
BMI categories			**<0.001**[±]
Underweight (<18.5)	12 (48.0%)	13 (8.0%)	
Normal (18.5–24.9)	7 (28.0%)	46 (28.4%)	
Overweight (BMI 25.0–29.9)	2 (8.0%)	42 (25.9%)	
Obese (BMI ≥30)	4 (16.0%)	61 (37.7%)	
FEV1 (% predicted, *n = 166*)	40.1 (±18.8)	44.9 (±19.0)	0.259[×]
Mild	1 (4.5%)	10 (6.9%)	
Moderate	5 (22.7%)	42 (29.2%)	
Severe	7 (31.8%)	61 (42.4%)	
Very severe	9 (40.9%)	31 (21.5%)	
MRC dyspnea score	5.0 [3.0–5.0]	4.0 [3.0–5.0]	0.140[×]
Charlson Comorbidity Index Score	2.0 [1.0–5.0]	2.0 [1.0–3.0]	0.419[×]
Emphysema	23 (92.0%)	130 (80.1%)	0.071[±]
Alpha-1-antitrypsin deficiency	0 (0.0%)	12 (7.4%)	0.160[±]
ACO	5 (20.0%)	48 (29.6%)	0.320[±]
Pulmonary hypertension	4 (16.0%)	42 (25.9%)	0.283[±]
Time since diagnosis			0.318[±]
0–2 years	1 (4.0%)	20 (12.4%)	
2–5 years	4 (16.0%)	35 (21.6%)	
More than 5 years	20 (80.0%)	107 (66.1%)	
Smoking status			0.659[±]
Current	4 (16.0%)	27 (16.7%)	
Cessation	0 (0.0%)	2 (1.2%)	
Former	20 (80.0%)	129 (79.6%)	
Never smoked	1 (4.0%)	4 (2.5%)	
Pack years (years)	36.5 [20.0–52.0]	37.0 [25.0–50.0]	0.698[×]
More than 5 prescription medicines	22 (88.0%)	130 (80.1%)	0.383[±]
Self-management plan	9 (36.0%)	47 (29.2%)	0.490[±]

Data are expressed as mean (±SD) if normally distributed, as median [25. Quartile-75. Quartile] if non-normally distributed, or n (%).
Bold numbers indicate significant p-values <0.05.
BMI, body mass index; MRC, Medical Research Council; FEV1, forced expiratory volume in 1 s; ACO, asthma-COPD overlap syndrome.
[±] = chi-squared test; [×] = Mann-Whitney U test; [†] = T-test.

there was a significant difference in median BMI, with the UWL group having a significantly lower value of 18.6 kg/m^2 compared to the NUWL group's 27.8 kg/m^2 ($p = 0.0001$). Similarly, the body weight was significantly lower ($p = 0.004$).

As shown in Table 3, at 6-month follow-up, there was no apparent difference between the two groups in clinical regarding admissions, the number of admissions, days admitted, exacerbations, or mortality. At 1-year follow-up, a trend towards higher prevalence in the UWL was found on most parameters such as admission to hospital and median LOS.

In Table 4, a significant difference between the groups was seen regarding of self-care, usual activities, and pain/discomfort. The UWL group had a significantly higher score indicating a worse outcome than the NUWL group. The EQ5D-VAS score was lower in the UWL group than the NUWL, indicating lower QoL. No difference was found in the overall SARC-F score.

Table 3
Comparison of clinical outcomes at 6-month follow-up and 1-year follow up in relation to whether the patients had an unintentional weight loss (UWL) and no unintentional weight loss (NUWL) at baseline.

	UWL 6 months follow-up (n = 25)	NUWL 6 months follow-up loss (n = 162)	*p*-value	UWL 1-year follow-up (n = 25)	NUWL 1-year follow-up loss (n = 162)	*p*-value
Hospital admission	13 (52.0%)	57 (36.8%)	0.147[±]	17 (68.0%)	78 (48.2%)	0.065[±]
Admission with primary diagnosis[a]	6 (24.0%)	27 (16.7%)	0.371[±]	10 (40%)	46 (28.4%)	0.238[±]
Number of admissions, all-cause[b]	1.0 [1.0–3.0]	1.0 [1.0–2.0]	0.335[×]	2.0 [1.0–3.0]	2.0 [1.0–3.0]	0.224[×]
Number of admissions, primary diagnosis[b]	0.6 (±0.8)	0.8 (±1.1)	0.914[×]	1.0 [0.0–2.0]	1.0 [0.0–1.0]	0.617[×]
LOS, all-cause[b]	6.7 [2.0–9.3]	2.3 [2.0–5.6]	0.165[×]	5.0 [3.5–7.0]	3.0 [2.0–6.0]	0.068[×]
LOS, primary diagnosis[b]	5.5 [2.0–7.0]	3.0 [2.0–4.0]	0.327[×]	6.2 [2.7–9.0]	3.5 [2.0–6.5]	0.203[×]
Exacerbation not requiring admission[c]	10 (47.6%)	52 (38.8%)	0.443[±]	13 (65.0%)	65 (51.6%)	0.264[±]
Number of exacerbations[c]	1.5 [1.0–2.0]	1.0 [1.0–3.0]	0.967[×]	2.0 [2.0–3.0]	2.0 [1.0–4.0]	0.487[×]
Number of deaths	2 (8.0%)	17 (10.5%)	0.701[±]	3 (12.0%)	24 (14.8%)	0.709[±]

Data are expressed as mean (±SD) if normally distributed, as median [25. Quartile-75. Quartile] if non-normally distributed, or n (%).
UWL, unintentional weight loss; NUWL, no unintentional weight loss; LOS, length of stay.
[±] = chi-squared test; [×] = Mann-Whitney U test.
[a] Primary diagnosis was defined as either COPD exacerbation, pneumonia or dyspnea.
[b] Number of admissions and length of stay are based on the patients that had a hospital admission.
[c] Data for exacerbation only included patients that completed the interview and excluded mortalities (No. patients at 6-month follow-up n = 150, and one-year follow-up n = 144).

Table 4
Results of the EQ-5D-5L and SARC-F questionnaire between the two groups at 1-year follow-up.

	UWL (n = 20)	NUWL (n = 124)	*p*-value
EQ-5D-5L			
Mobility	2.8 (±1.0)	2.4 (±1.2)	0.110[×]
Self-care	2.7 (±1.4)	2.0 (±1.1)	**0.017**[×]
Usual activities	3.3 (±1.1)	2.7 (±1.2)	**0.036**[†]
Pain/discomfort	2.6 (±0.9)	2.0 (±1.1)	**0.012**[×]
Anxiety/depression	1.5 [1.0–3.0]	1.0 [1.0–2.0]	0.267[×]
Overall health (0–100)	46.8 (±21.8)	50.9 (±20.5)	0.406[†]
SARC-F overall score	3.2 (±2.1)	3.1 (±2.5)	0.699[×]

Data are expressed as mean (±SD) if normally distributed or as median [25. Quartile-75. Quartile] if non-normally distributed, or n (%).
UWL, unintentional weight loss; NUWL, no unintentional weight loss.
Bold numbers indicate significant p-values <0.05.
[×] = Mann-Whitney U test; [†] = T-test.

As shown in Table 5, no significant difference was seen with either UWL or BMI at 6-month and one-year follow-up when comparing hospital admission when adjusted for age, FEV1, and comorbidities. Regarding LOS, a trifold risk of having a LOS of more than five days was found in the UWL group (OR 2.94, $p = 0.021$). This remained significant after adjustment for age, FEV1, and comorbidities (OR 3.41, $p = 0.021$). A tendency to an increased risk of a LOS of more than ten days was found among the UWL group (OR 2.32, $p = 0.233$). There was no significant difference between the groups regarding hospitalization with the primary diagnosis. Among the underweight patients, an increased risk of exacerbation was found (OR 4.94, $p = 0.014$) but after the adjustment for comorbidities, this association was not significant (OR 3.95, $p = 0.056$).

During the follow-up period, 27 deaths were recorded (14.4%). In the UWL group, three had died (12%), and in the NUWL, 24 had died (14.8%). As seen in Table 5, the hazard ratios of the Cox regression analyses showed a tendency towards a lower mortality risk with UWL and with low and high BMI. Still, none of the results were statistically significant (p > 0.05). The first mentioned is also shown in the Kaplan-Meier plot that showed no significant difference in mortality (p = 0.718) (Fig. 2).

4. Discussion

This study investigated the association between UWL, BMI, and clinical outcomes regarding hospitalization, LOS, exacerbations, QoL, and mortality in 187 Danish COPD outpatients. The main findings of this prospective cohort study were that 13.4% of patients that experienced UWL had a significantly lower BMI than the NUWL group and showed significantly increased risk

Table 5
Logistic regression and Cox hazard model regression of clinical outcomes. Odds ratios and hazard ratios are presented unadjusted in a crude analysis and adjusted for age, age and FEV1 as well as age, FEV1 and comorbidities.

	Unadjusted			Adjusted for age			Adjusted for age and FEV1			Adjusted for age, FEV1 and comorbidities		
	OR	95%CI	*p*	OR	95%CI	*p*	OR	95%CI	*p*	OR	95%CI	*p*
Hospital admission at 6 months												
Unintentional weight loss	1.86	0.80–4.36	0.151	1.93	0.82–4.56	0.132	1.61	0.63–4.13	0.321	1.39	0.52–3.66	0.511
Underweight	1.94	0.72–5.22	0.191	2.11	0.77–5.77	0.148	1.79	0.58–5.56	0.315	1.56	0.49–4.96	0.451
Obese	2.17	0.99–4.72	0.052	2.57	1.14–5.79	**0.022**	2.91	1.13–7.51	**0.027**	2.50	0.96–6.55	0.062
Hospital admission at 1-year follow-up												
Unintentional weight loss	2.29	0.94–5.60	0.070	2.41	0.98–6.00	0.057	2.07	0.79–5.42	0.139	1.88	0.71–5.01	0.205
Underweight	1.66	0.64–4.33	0.300	1.84	0.69–4.90	0.221	1.57	0.54–4.61	0.405	1.43	0.48–4.25	0.519
Obese	1.52	0.73–3.16	0.260	1.85	0.86–3.96	0.114	1.98	0.83–4.68	0.121	1.75	0.73–4.21	0.209
LOS (> 5 days) at 6-month follow-up (n = 23)												
Unintentional weight loss	3.55	1.29–9.78	**0.014**	3.63	1.31–10.06	**0.013**	4.95	1.63–15.02	**0.005**	4.52	1.46–13.97	**0.009**
Underweight	1.96	0.53–7.16	0.310	2.08	0.56–7.68	0.273	1.99	0.49–8.09	0.335	1.82	0.44–7.46	0.408
Obese	1.42	0.48–4.21	0.523	1.61	0.52–4.91	0.407	1.58	0.43–5.73	0.490	1.46	0.40–5.34	0.571
LOS (> 5 days) at 1-year follow-up (n = 35)												
Unintentional weight loss	2.94	1.18–7.37	**0.021**	3.03	1.20–7.65	**0.019**	3.97	1.44–10.94	**0.008**	3.41	1.20–9.68	**0.021**
Underweight	2.02	0.68–6.00	0.203	2.13	0.71–6.36	0.117	2.21	0.67–7.32	0.194	1.92	0.57-6-53	0.296
Obese	0.78	0.30–2.05	0.616	0.86	0.32–2.30	0.763	0.89	0.28–2.83	0.847	0.76	0.23–2.46	0.645
LOS (> 10 days) at 6-month follow-up (n = 8)												
Unintentional weight loss	2.26	0.43–11.88	0.335	2.21	0.42–11.68	0.349	2.27	0.33–15.52	0.403	2.01	0.28–14.31	0.485
Underweight	2.22	0.29–16.73	0.440	2.12	0.28–16.22	0.468	1.35	0.16–11.22	0.779	1.24	0.15–10.54	0.842
Obese	1.23	0.20–7.67	0.822	1.14	0.18–7.35	0.892	0.46	0.04–5.81	0.552	0.45	0.04–5.62	0.531
LOS (> 10 days) at 1-year follow-up (n = 12)												
Unintentional weight loss	2.32	0.58–9.22	0.233	2.35	0.58–9.39	0.225	3.43	0.78–15.10	0.103	3.06	0.68–13.85	0.146
Underweight	0.83	0.15–4.63	0.836	0.86	0.15–4.79	0.861	0.92	0.15–5.59	0.925	0.81	0.13–5.07	0.824
Obese	0.63	0.16–2.47	0.507	0.67	0.16–2.72	0.571	0.37	0.06–2.23	0.280	0.33	0.05–1.99	0.226
Exacerbation at 6-month follow-up (n = 62)												
Unintentional weight loss	1.43	0.57–3.61	0.445	1.58	0.62–4.05	0.341	1.10	0.39–3.13	0.858	1.08	0.38–3.09	0.890
Underweight	1.26	0.44–3.60	0.663	1.39	0.48–4.03	0.549	1.32	0.41–4.28	0.647	1.31	0.40–4.25	0.657
Obese	0.82	0.36–1.85	0.629	0.99	0.42–2.31	0.976	1.30	0.50–3.36	0.591	1.27	0.49-3-31	0.622
Exacerbation at 1-year follow-up (n = 78)												
Unintentional weight loss	1.74	0.65–4.66	0.268	1.82	0.68–4.90	0.236	1.26	0.42–3.82	0.684	1.12	0.36–3.45	0.848
Underweight	4.94	1.38–17.65	**0.014**	5.04	1.41–18.09	**0.013**	4.06	1.00–16.40	**0.049**	3.95	0.97–16.12	0.056
Obese	1.95	0.84–4.50	0.118	2.15	0.91–5.09	0.082	2.58	0.96–6.92	0.060	2.39	0.88–6.46	0.087
Mortality (n = 27)	**HR**	**95%CI**	***p***	**HR**	**95%CI**	***p***	**HR**	**95%CI**	***p***	**HR**	**95%CI**	***p***
Unintentional weight loss	0.80	0.24–2.66	0.718	0.84	0.25–2.79	0.773	1.00	0.29–3.45	0.999	0.96	0.28–3.32	0.947
Underweight	1.04	0.36–3.06	0.937	1.17	0.40–3.43	0.781	1.04	0.33–3.27	0.946	0.99	0.31–3.13	0.985
Obese	0.64	0.25–1.62	0.345	0.80	0.31–2.10	0.655	0.78	0.24–2.53	0.684	0.76	0.23–2.45	0.640

Bold numbers indicate significant p-values <0.05.
Variables are divided into unintentional weight loss (UWL) and low and high BMI groups compared to normal BMI.
OR, odds ratio; 95%CI, 95% confidence interval; *p*, p-value; LOS, length of stay; HR, hazard ratio. Underweight = BMI <18.5; Obese = BMI ≥30.

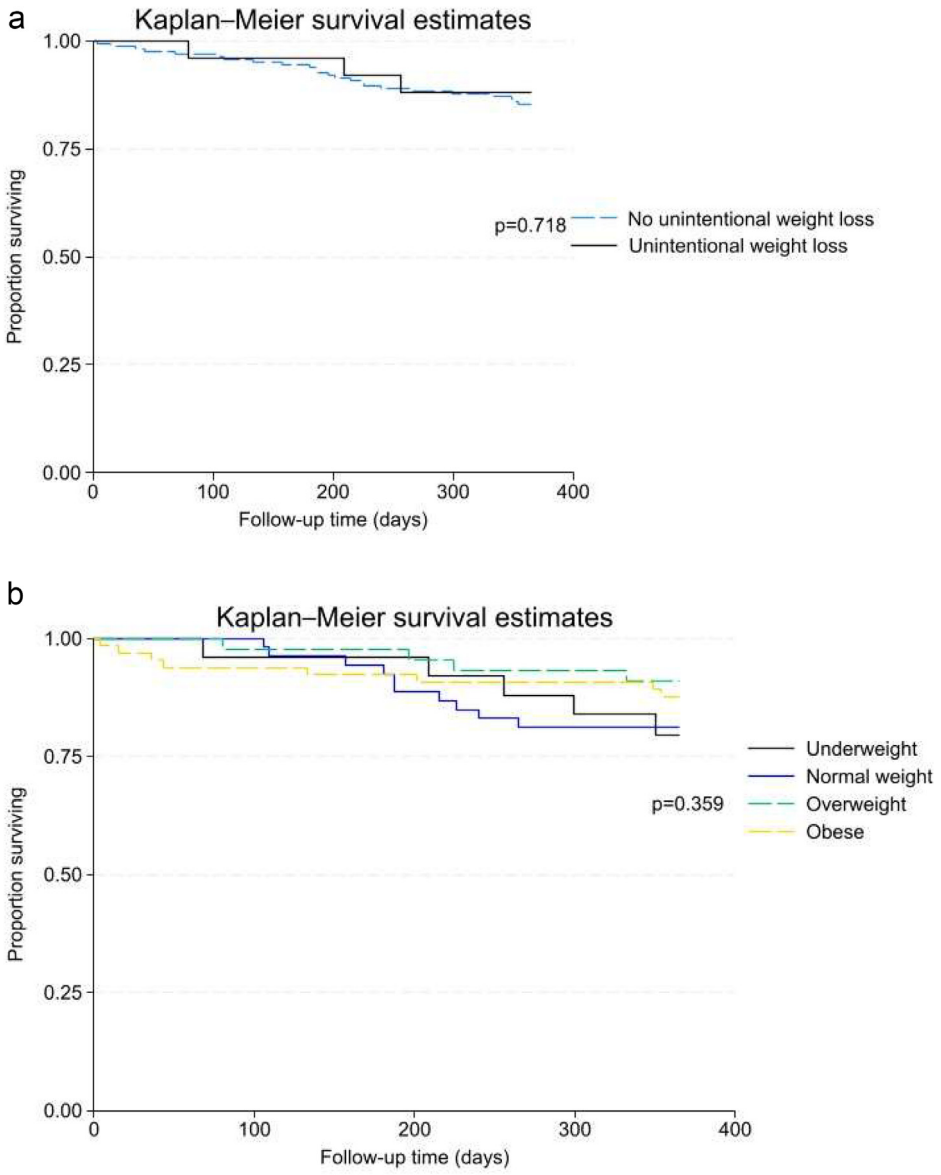

Fig. 2. (a) Kaplan-Meier cumulative survival plot comparing unintentional weight loss and no unintentional weight loss. (b) Kaplan-Meier cumulative survival plot comparing BMI groups.

regarding LOS on hospitalizations and exacerbations. Furthermore, a significant difference was seen in QoL with the EQ-5D-5L questionnaire. No significant difference was found for mortality. In terms of hospitalization, this study showed a trend toward a higher risk of hospital admission during the follow-up period among the UWL patients (OR 2.29, $p = 0.070$). A potential explanation could be a difference in comorbidities between those with UWL and those without since even though there was no significant difference in hospitalization between the groups, the odds for hospitalization remained higher in the UWL patients after adjustment for comorbidities from CCI score (OR 2.12, $p = 0.107$). The present study did not find any difference between BMI groups or UWL, solely looking at admissions due to the primary diagnosis. As for exacerbations as an outcome variable, a possible explanation for the results could be that one-third of the population had a self-management plan which has been shown to prevent and reduce hospital admissions in patients with COPD [19]. However, no difference was found between those having a self-management plan and UWL or not ($p = 0.490$).

In terms of LOS, no difference was found between BMI groups, unlike a study that found a longer LOS among underweight patients [2]. However, a difference in LOS was found in those with UWL with an almost trifold increased risk of a LOS of more than five days during the follow-up period (OR 2.94, $p = 0.021$). This remained significant after adjusting for age and FEV1 ($p = 0.008$) and was found at both 6-month and 1-year follow-ups. Looking at LOS of more than ten days, a tendency to a higher risk among UWL patients was still found but not significant (OR 2.32, $p = 0.233$). A limitation of this result was that the sample size of patients became very small (n = 12) and allowed for a more considerable variance within the data. A possible explanation could be a higher prevalence of comorbidities in the UWL group. However, as shown in Table 1, no significant difference in CCI score was present between the UWL and NUWL groups. Few other studies have compared LOS with UWL as an independent variable in patients with COPD. A recent study found a significantly higher risk of LOS over ten days in malnourished patients but found no difference with UWL as an independent variable alone [2]. The discrepancy remains unclear as they had a similar sample size.

However, they compared over a 2-year follow-up period, and their population might have less severe COPD as the mean MRC in their study was 3.1, and our population had a median of 4. Additionally, they had a 45% prevalence of weight loss compared to 13.4% in the current study. Another study also found malnutrition as a risk factor for increased LOS in COPD patients [20].

In the current study, having a non-hospital-requiring exacerbation during follow-up had a prevalence of about 50%. The analysis showed a significantly higher risk among the underweight patients (OR 4.94, $p = 0.014$) and a tendency to a slightly higher prevalence among those with UWL. A possible explanation for the former could be that 30.1% of the population had the self-management plans mentioned earlier, and the prevalence of self-management plans among BMI groups was highest in the underweight category (44%). Previous literature has shown that patients with COPD with self-management plans might have difficulties separating an onset of acute exacerbation from day-to-day worsening of symptoms, including exacerbations [19,21]. Therefore, the results might be blurred as the subgroup with a medical self-treatment plan was more likely to have experienced an exacerbation (OR 5.22, $p < 0.000$). Previous literature on this is sparse, so further research is required to establish a difference.

UWL was also associated with poorer QoL. Most variables in the EQ-5D-5L questionnaire showed worse scores for the UWL group, with significant differences in self-care, usual activities, and pain/discomfort. Other studies have shown an improvement in QoL parameters by nutritional intervention, which, combined with the current study's results, emphasize the importance of screening and clinical assessment of weight loss and malnutrition in COPD outpatients [9,22]. However, these studies were conducted in a Vietnamese population in which the prevalence of UWL was as high as 80% of the patients with COPD. The transferability of these findings to a developed Western country is arguable.

The finding of no increased mortality risk with UWL or for BMI groups is contrary to many previous studies on COPD patients that showed increased mortality in patients with low BMI [2,4,5,23,24] and UWL [4]. Part of the explanation behind this discrepancy could be that the follow-up period in this study needed to be longer to show a statistically significant difference between the groups compared with earlier studies that had decade-long follow-ups. Similarly, this study's prevalence of mortality ($n = 27$) is limited. A hypothesis could be that COPD medication therapy has changed over the years since some of these studies present data that are quite old, although the studies were recently published [2,5,24]. In addition, geographical and societal differences in health care could impact the availability of COPD medication, affecting the outcome and disease progression. This hypothesis may be one of many potential explanations for the discrepancy. However, a recent study with a similar sample size found no increased mortality with UWL [2]. However, this is not described in the literature regarding nutritional status elsewhere [19,21].

Previous studies have investigated the so-called obesity paradox in recent years, where overweight and obesity were positive predictors for survival in patients with COPD [25,26]. Our study showed a similar tendency; the overweight and obese patients had the lowest hazard ratio compared to normal weight. However, this finding was not statistically significant. In their prospective cohort study, Smulders et al. also found that obesity was associated with increased survival and a positive predictor for severe exacerbation frequency [26]. Our study found a slightly higher risk of mild to moderate exacerbation among obese patients but not significant (OR 1.95, $p = 0.118$). However, when looking at LOS, a trend towards the lowest risk was found among obese patients, indicating that a high BMI might benefit some clinical outcome parameters in patients with COPD.

The prevalence of 13.4% UWL in this cohort is relatively low compared to other studies. Reports of UWL in a COPD population span from 6% to 45%, depending on the cohort's COPD severity, setting, and definition of weight loss [2,4]. Given the disease severity of our population, part of the explanation behind the low prevalence could be that 11.2% of the population received oral nutritional supplementation. In addition, a significantly lower BMI was found in the subgroup that experienced UWL, consistent with other literature that also shows an overrepresentation of low BMI in the patients that experience UWL [4]. It could have been interesting to investigate further the underlying mechanisms by including inflammatory biomarkers such as C-Reactive Protein, white blood cell count, or albumin to enlighten any potential differences across the population subgroups.

There are some potential limitations to consider regarding this study. The prevalence of UWL was lower than expected at 13.4%, which made the UWL sample somewhat small. However, studies with similar or smaller sample sizes could still show significant outcome differences [2,6]. In addition, a longer follow-up could likely reveal more significant outcome differences, especially in terms of mortality, as other large studies with up to decade-long follow-ups reveal varying differences in mortality [4,5,23]. Nevertheless, the follow-up period revealed significant differences in other outcomes, such as LOS, exacerbations, and the EQ-5D-5L questionnaire.

The methods used in the study are generally well-researched and validated, but some methodological limitations must still be considered. First, the UWL parameter was obtained at inclusion as patient-reported data, which could spark debate about validity. However, patient-reported weight loss is generally considered reliable and used in other large studies with significant results [4,27]. Furthermore, 29% of the study population participated in ongoing regional telemedicine that involves weekly measurements of body weight, which enhances the accuracy of self-reported weight loss. Second, the questionnaires used were the standardized, well-validated QoL questionnaire EQ-5D-5L and the SARC-F questionnaire, which is a commonly used screening tool for sarcopenia, even though some limitations are present in the latter. A newly published meta-analysis showed that the reliability of the SARC-F as a screening tool is limited due to low sensitivity [28]. This may be further aggravated by the low sample of patients with UWL after one year and the invisibility of nutrition support and training other than COPD rehabilitation.

Additionally, both questionnaires were cross-sectional, and a prospective study of QoL parameters in the population could have provided further knowledge.

The current study's findings provide further evidence that clinical screening and assessment of BMI and weight loss in COPD patients offer essential information that can be used to identify specific populations at risk of poorer clinical outcomes regarding hospitalizations and QoL. Current international guidelines, including the GOLD guidelines and the National Institute of Health Excellence (NICE) guidelines, have started incorporating recommendations for regular screening of BMI and potential malnutrition [1]. However, the results of the current study, along with other studies, indicate that UWL as a solitary factor is an important parameter to use for early screening as well that should be included in future clinical guidelines for patients with COPD – not only in the older people as the NICE guidelines currently recommend. UWL is accessible in the busy outpatient clinic, where time with the patients is short. Furthermore, nutritional intervention for patients experiencing weight loss seems advisable [29]. Anabolic steroid treatment has also been studied in COPD patients as a potential treatment for muscle wasting and poor pulmonary function. However, the results are mixed and are currently not generally recommended as a treatment option [30,31].

Based on the results of the present study, more research is required over a more extended period and with a larger sample to potentially highlight clinical outcome differences further.

5. Conclusion

The study found a prevalence of 13.4% UWL with a significantly lower body weight among those with UWL. In follow-up within six and twelve months, a significantly higher risk of an extended LOS on admissions was found in those with UWL. UWL was also associated with a poorer QoL. BMI<18,5 was associated with an increased risk of exacerbation. No significant difference was found for mortality. These findings provide additional evidence that the identification of UWL should be implemented early to intervene with nutritional assessment and support to prevent poorer clinical outcomes.

Funding

This research did not receive any funding.

Conflict of interest

None.

Acknowledgements

M. Holst made the conceptualization, design, supervision and project administration. S. K. Yde and M. Holst shared the overall data collection from patients. S. Mikkelsen, S. K. Yde, and M. S. G. Brath were responsible for the data management. M. S. G. Brath validated the acquisition of medical data. S. Mikkelsen and S. K. Yde did the statistical analysis and interpretation of data. S. K. Yde wrote the original draft of the manuscript, and all authors contributed to - and approved the final edition.

References

[1] Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. Am J Respir Crit Care Med 2017;195:557–82. https://doi.org/10.1164/rccm.201701-0218PP.

[2] Marco E, Sánchez-Rodríguez D, Dávalos-Yerovi VN, Duran X, Pascual EM, Muniesa JM, et al. Malnutrition according to ESPEN consensus predicts hospitalizations and long-term mortality in rehabilitation patients with stable chronic obstructive pulmonary disease. Clin Nutr 2019;38:2180–6. https://doi.org/10.1016/j.clnu.2018.09.014.

[3] McDonald MLN, Wouters EFM, Rutten E, Casaburi R, Rennard SI, Lomas DA, et al. Body mass index and mortality in chronic obstructive pulmonary disease: a meta-analysis. Respir Med 2002;20:1–9. https://doi.org/10.1007/s11136-012-0322-4.

[4] Kwan HY, Maddocks M, Nolan CM, Jones SE, Patel S, Barker RE, et al. The prognostic significance of weight loss in chronic obstructive pulmonary disease-related cachexia: a prospective cohort study. J Cachexia Sarcopenia Muscle 2019;10:1330–8. https://doi.org/10.1002/jcsm.12463.

[5] Wada H, Ikeda A, Maruyama K, Yamagishi K, Barnes PJ, Tanigawa T, et al. Low BMI and weight loss aggravate COPD mortality in men, findings from a large prospective cohort: the JACC study. Sci Rep 2021;11:1–9. https://doi.org/10.1038/s41598-020-79860-4.

[6] Hallin R, Koivisto-Hursti UK, Lindberg E, Janson C. Nutritional status, dietary energy intake and the risk of exacerbations in patients with chronic obstructive pulmonary disease (COPD). Respir Med 2006;100:561–7. https://doi.org/10.1016/j.rmed.2005.05.020.

[7] Schols AMWJ, Broekhuizen R, Weling-Scheepers CA, Wouters EF. Body composition and mortality in chronic obstructive pulmonary disease. Am J Clin Nutr 2005;82:53–9. https://doi.org/10.1093/ajcn/82.1.53.

[8] Domingo-Salvany A, Lamarca R, Ferrer M, Garcia-Aymerich J, Alonso J, Félez M, et al. Health-related quality of life and mortality in male patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2002;166:680–5. https://doi.org/10.1164/rccm.2112043.

[9] Nguyen HT, Collins PF, Pavey TG, Nguyen NV, Pham TD, Gallegos DL. Nutritional status, dietary intake, and health-related quality of life in outpatients with COPD. Int J COPD 2019;14:215–26. https://doi.org/10.2147/COPD.S181322.

[10] Christensen T, Mikkelsen S, Geisler L, Holst M. Chronic obstructive pulmonary disease outpatients bear risks of both unplanned weight loss and obesity. Clin Nutr ESPEN 2022;49:246–51. https://doi.org/10.1016/j.clnesp.2022.04.010.

[11] Kondrup J, Ramussen HH, Hamberg O, Stanga Z, Camilo M, Richardson R, et al. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. Clin Nutr 2003;22:321–36. https://doi.org/10.1016/S0261-5614(02)00214-5.

[12] Tangvik R, Henriksen J, Øyen J, Tell GS, Nilsen RM, Eisman JA, et al. The nutritional strategy: four questions predict morbidity, mortality and health care costs. Clin Nutr 2013;33:634–41. https://doi.org/10.1016/j.clnu.2013.09.008.

[13] Cederholm T, Jensen GL, Correia MITD, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition – a consensus report from the global clinical nutrition community. J Cachexia Sarcopenia Muscle 2019;10:207–17. https://doi.org/10.1002/jcsm.12383.

[14] Cederholm T, Bosaeus I, Barazzoni R, Bauer J, Van Gossum A, Klek S, et al. Diagnostic criteria for malnutrition - an ESPEN consensus statement. Clin Nutr 2015;34:335–40. https://doi.org/10.1016/j.clnu.2015.03.001.

[15] Medical C. A new method of classifying prognostic in longitudinal studies : development. J Chron Dis 1987;40:373–83.

[16] Altawalbeh SM, Almomani BA, Alefan Q, Mohammad Momany S, Al-Share QY. The influence of adverse drug effects on health-related quality of life in chronic obstructive pulmonary disease patients. Int J Pharm Pract 2022;30:457–65. https://doi.org/10.1093/ijpp/riac052.

[17] Ida S, Kaneko R, Murata K. SARC-F for screening of sarcopenia among older adults: a meta-analysis of screening test accuracy. J Am Med Dir Assoc 2018;19:685–9. https://doi.org/10.1016/j.jamda.2018.04.001.

[18] Deutz NE, Ziegler TR, Matheson EM, Matarese LE, Tappenden KA, Baggs GE, et al. Reduced mortality risk in malnourished hospitalized older adult patients with COPD treated with a specialized oral nutritional supplement: sub-group analysis of the NOURISH study. Clin Nutr 2021;40:1388–95. https://doi.org/10.1016/j.clnu.2020.08.031.

[19] Pinnock H, Steed L, Jordan R. Supported self-management for COPD: making progress, but there are still challenges. Eur Respir J 2016;48:6–9. https://doi.org/10.1183/13993003.00576-2016.

[20] Hoong JM, Ferguson M, Hukins C, Collins PF. Economic and operational burden associated with malnutrition in chronic obstructive pulmonary disease. Clin Nutr 2017;36:1105–9. https://doi.org/10.1016/j.clnu.2016.07.008.

[21] Jordan RE, Majothi S, Heneghan NR, Blissett DB, Riley RD, Sitch AJ, et al. Supported self-management for patients with moderate to severe chronic obstructive pulmonary disease (COPD): an evidence synthesis and economic analysis. Health Technol Assess (Rockv) 2015;19:1–515. https://doi.org/10.3310/hta19360.

[22] Janssen MF, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res 2013;22:1717–27. https://doi.org/10.1007/s11136-012-0322-4.

[23] Prescott E, Almdal T, Mikkelsen KL, Tofteng CL, Vestbo J, Lange P. Prognostic value of weight change in chronic obstructive pulmonary disease: results from the Copenhagen City Heart Study. Eur Respir J 2002;20:539–44. https://doi.org/10.1183/09031936.02.00532002.

[24] Cao C, Wang R, Wang J, Bunjhoo H, Xu Y, Xiong W. Body mass index and mortality in chronic obstructive pulmonary disease: a meta-analysis. PLoS One 2012;7. https://doi.org/10.1371/journal.pone.0043892.

[25] Stoll P, Foerster S, Virchow JC, Lommatzsch M. Overweight is a predictor of long-term survival in hospitalised patients with exacerbations of COPD. Respir Med 2016;116:59–62. https://doi.org/10.1016/j.rmed.2016.05.016.

[26] Smulders L, van der Aalst A, Neuhaus EDET, Polman S, Franssen FME, van Vliet M, et al. Decreased risk of COPD exacerbations in obese patients. COPD J Chronic Obstr Pulm Dis 2020;17:485–91. https://doi.org/10.1080/15412555.2020.1799963.

[27] Haverkort EB, De Haan RJ, Binnekade JM, Van Bokhorst-De Van Der Schueren MAE. Self-reporting of height and weight: valid and reliable identification of malnutrition in preoperative patients. Am J Surg 2012;203:700–7. https://doi.org/10.1016/j.amjsurg.2011.06.053.

[28] Voelker SN, Michalopoulos N, Maier AB, Reijnierse EM. Reliability and concurrent validity of the SARC-F and its modified versions: a systematic review and meta-analysis. J Am Med Dir Assoc 2021;22:1864–1876.e16. https://doi.org/10.1016/j.jamda.2021.05.011.

[29] Collins PF, Elia M, Stratton RJ. Nutritional support and functional capacity in chronic obstructive pulmonary disease: a systematic review and meta-analysis. Respirology 2013;18:616–29. https://doi.org/10.1111/resp.12070.

[30] Daga MK, Khan NA, Malhotra V, Kumar S, Mawari G, Hira HS. Study of body composition, lung function, and quality of life following use of anabolic steroids in patients with chronic obstructive pulmonary disease. Nutr Clin Pract 2014;29:238–45. https://doi.org/10.1177/0884533614522832.

[31] Sharma S, Arneja A, McLean L, Duerksen D, Leslie W, Sciberras D, et al. Anabolic steroids in COPD: a review and preliminary results of a randomized trial. Chron Respir Dis 2008;5:169–76. https://doi.org/10.1177/1479972308092350.