Evaluation of nutritional status and physical performance in patients with chronic obstructive pulmonary disease

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This dissertation was made at the Department of Internal Medicine, Division of Pulmonary Medicine, Dubrava University Hospital, Zagreb, Croatia

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LIST OF SYMBOLS AND ABBREVIATIONS

AMA	arm muscle area
ATS	American Thoracic Society
AUC	area under the curve
BIA	bioelectric impedance analysis
BMI	body mass index
BMC	bone mineral content
BMD	bone mineral density
BODE	B: body mass index; O: airflow obstruction; D: dyspnoea; E: exercise capacity (explained at p. 9)
CAT	COPD Assessment Test
CC	calf circumference
cm	centimetre
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
CT	computed tomography
DEXA	dual energy X-ray absorptiometry
DLCO	diffusing capacity of the lung for carbon monoxide
DLCO/VA	diffusing capacity of the lung for carbon monoxide per litre of alveolar volume
EQ-5D-5L	EuroQol questionnaire
ERS	European Respiratory Society
FEV_1	forced expiratory volume in one second
FEV_1/FVC	ratio of forced expiratory volume in one second to forced vital capacity
FFM	fat-free mass
FFMI	fat-free mass index
FM	fat mass
FMI	fat mass index
FVC	forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HADS	Hospital Anxiety and Depression Scale
hsCRP	high-sensitivity C-reactive protein
ICS	inhaled corticosteroids

keV	kiloelectron volt
kg	kilogram
kg/m^2	kilogram per square meter
kPa	kilopascal
LABA	long-acting beta2-agonists
LAMA	long-acting muscarinic antagonists
LM	lean soft tissue mass
LMI	lean mass index
LTOT	long-term oxygen therapy
m	metre
MAMC	mid-arm muscle circumference
4MGS	4-metre gait speed
ml	millilitre
µM	micromolar (micromoles per litre)
mmHg	millimetre of mercury
mMRC	modified Medical Research Council dyspnoea scale
MNA	Mini Nutritional Assessment
MRI	magnetic resonance imaging
m/s	metre per second
MUAC	mid-upper arm circumference
6MWD	6-minute walk distance
6MWT	6-minute walk test
NIV	non-invasive ventilation
nmol/L	nanomoles per litre
pO_2	partial pressure of oxygen in arterial blood
pCO_2	partial pressure of carbon-dioxide in arterial blood
pred.	predicted
RF_{CSA}	rectus femoris cross-sectional area
RV	residual volume
RV/TLC	ratio of residual volume to total lung capacity
s	seconds
SABA	short-acting beta2-agonists
SAMA	short-acting muscarinic antagonists
SAM	StepWatch Activity Monitor®

$SatO_2$	arterial oxygen saturation
SD	standard deviation
SpO_2	peripheral capillary oxygen saturation
TLC	total lung capacity
TSF	triceps skin fold
VAS	visual analogue scale
VC	vital capacity
WHO	World Health Organization

1. INTRODUCTION AND BACKGROUND

1.1. Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory lung disorder characterised by permanent, progressive, and poorly reversible airflow limitation leading to chronic respiratory symptoms - cough, expectoration and dyspnoea. Together with asthma COPD is the most common chronic respiratory disease [1]. According to the World Health Organization (WHO) COPD was the fourth leading cause of death in 2004, after ischaemic heart disease, cerebrovascular disease and lower respiratory infections, and it was estimated that by 2030 it will become the third leading cause of death worldwide [2]. With around 384 million patients in the world, global prevalence of 11.7% in adult population and around three million deaths annually, COPD is a leading cause of morbidity and mortality worldwide and represents a significant socioeconomic burden [1, 3, 4]. Additionally, the global prevalence and burden of COPD are projected to increase in the coming decades due to the continued high exposure to risk factors, especially tobacco smoking, and the ageing of the world's population [5].

1.1.1. Risk factors

COPD results from a complex interaction between long-term cumulative exposure to noxious gases and particles, combined with different host factors. Cigarette smoking is the leading environmental risk factor for COPD, especially in high- and middle-income countries, and is also the most studied. Cigarette smokers have a higher prevalence of respiratory symptoms, accelerated lung function decline and a greater COPD mortality rate than non-smokers [6]. Other types of tobacco (e.g. pipe, cigar, water pipe) and marijuana smoking, as well as passive exposure to cigarette smoke also represent risk factors for COPD [7, 8, 9].

Occupational exposure to organic and inorganic dusts, chemicals and fumes is associated with airflow limitation and respiratory symptoms, but is often under-appreciated as a risk factor for COPD [10]. In low-income countries exposure to indoor air pollution as a result of the broad use of coal and biomass fuels for cooking, heating and other household needs is an important

risk factor for COPD, especially for non-smoking women [11]. Outdoor air pollution in urban and industrial areas is recognised as harmful to individuals with pre-existing lung disease, but its role in the development of COPD is less clear.

Genetics may play a role in the susceptibility to COPD in individuals with environmental exposures. The best documented genetic risk factor is a severe hereditary deficiency of alpha-1 antitrypsin, a major circulating inhibitor of serine proteases [12]. Other host factors that may predispose to the development of COPD include frequent and/or severe lower respiratory infections during childhood [13], low birth weight [14], asthma and airway hyper-responsiveness [15], chronic bronchitis with mucus hypersecretion [16], lower socioeconomic status [17], and HIV infection [18].

Age is often considered a risk factor for COPD, although it is not clear whether age really represents an independent risk factor or it actually reflects the cumulative exposures to environmental factors throughout one's life [19]. COPD prevalence and mortality were higher in men for a long time, but recent studies from developed countries report an equal prevalence of COPD in men and women, probably reflecting the increase in cigarette smoking among women in the last decades [20].

1.1.2. Pathogenesis and pathophysiology

Prolonged or repeated inhalation of toxic particles and gases in a genetically predisposed individual leads to the development of chronic inflammation in the lungs. Increased numbers of macrophages, activated neutrophils, and different subtypes of lymphocytes can be found in peripheral airways, lung parenchyma, and the pulmonary vessels of patients with COPD [21]. In some patients who demonstrate clinical overlap with asthma there may also be increased numbers of eosinophils in the airways. All these inflammatory cells, together with epithelial cells are involved in the production and release of multiple inflammatory mediators (e.g. proinflammatory cytokines, chemoattractants, growth factors), oxidants and different types of proteinases (e.g. elastase, cathepsin G, proteinase 3, matrix metalloproteinase) leading to various aspects of tissue damage [22]. Oxidative stress and protease-antiprotease imbalance may have a key role in driving lung inflammation and parenchymal tissue destruction resulting in the development of emphysema and the reduction of gas-exchanging surface of the lung [23]. On the other hand, excessive defence and repair mechanisms result in lung

remodelling, inflammatory and/or fibrous thickening and narrowing of small bronchioles leading to progressive airflow limitation and hyperinflation [24].

Clinically these pathological and pathophysiological changes manifest as exertional dyspnoea, reduced exercise tolerance, the development of hypoxemia and hypercapnia. Mucus hypersecretion with chronic productive cough is present in patients with chronic bronchitis without airflow limitation as well as a substantial number of COPD patients who have chronic bronchitis phenotype, and is caused by the increased number of goblet cells and hypertrophy of the submucosal glands in the airways as a result of chronic irritation by the noxious agents, additionally stimulated by several inflammatory mediators [16].

Interestingly, lung inflammation with its deleterious consequences persists even after smoking cessation, possibly through the involvement of autoantigens and lung microbiome [25]. The intensity of lung inflammation is further enhanced during COPD exacerbations triggered by respiratory infections and environmental factors, leading to reduced expiratory flow, increased hyperinflation, and worsening of respiratory symptoms [26]. Furthermore, pulmonary hypertension may develop late in the course of COPD as a result of hypoxic vasoconstriction, structural changes of the small pulmonary arteries, as well as the loss of the pulmonary capillary bed in emphysema, and may additionally worsen respiratory symptoms [27].

1.1.3. Symptoms

Chronic and progressive dyspnoea is the most common symptom of COPD, and a major cause of a disability [28]. Patients with severe and very severe COPD may experience dyspnoea even at rest or on minimal exertion. Dyspnoea is sometimes accompanied by wheezing and chest tightness.

Chronic cough is often the first symptom of COPD, and may be productive or unproductive. Regular production of sputum for three or more months in two consecutive years in the absence of any other condition that may explain it is the seminal definition of chronic bronchitis, which may precede the development of airflow limitation [29]. Patients producing large volume of sputum may have underlying bronchiectasis, and those with persistently purulent sputum, even when clinically stable, may have chronic bronchial infection [30].

In advanced stages of COPD additional extrapulmonary manifestations of the disease can be expected including fatigue, weight loss, skeletal muscle wasting and dysfunction, symptoms of depression and anxiety [31, 32]. Cardiovascular complication of COPD is cor pulmonale that may lead to right-sided heart failure manifesting with hepatomegaly, peripheral oedema and ascites.

1.1.4. Diagnosis and severity assessment

1.1.4.1. Spirometric criteria

COPD should be considered and post-bronchodilator spirometry should be performed in any patient who has dyspnoea, chronic cough or sputum production, and/or a history of exposure to risk factors [5]. While the screening spirometry in the general population is not recommended, performing spirometry in individuals with chronic respiratory symptoms and/or risk factors is indicated [5].

Spirometry should be performed after the administration of an adequate dose of a short-acting inhaled bronchodilator (10-15 minutes after inhalation of 400 mcg of salbutamol or 30-45 minutes after 160 mcg of ipratropium), and the measured parameters forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) should be compared with the predicted values for height, age, sex, and race [33]. A post-bronchodilator ratio of $FEV_1/FVC < 0.70$ confirms the presence of persistent airflow limitation, and is required to establish the diagnosis of COPD in a person with symptoms consistent with COPD and/or risk factors [5].

The classification of the severity of airflow limitation according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) is presented in **Table 1** [5].

Besides the presence and severity of the spirometric abnormalities, COPD assessment should consider patient's symptoms, exacerbation history and future risk, and the presence of comorbidities [5].

Table 1. Classification of airflow limitation severity in COPD based on post-bronchodilator spirometry with $FEV_1/FVC < 0.70$ [5].

GOLD 1	Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3	Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4	Very severe	$FEV_1 < 30\%$ predicted

Abbreviations: COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity.

1.1.4.2. Assessment of symptoms severity

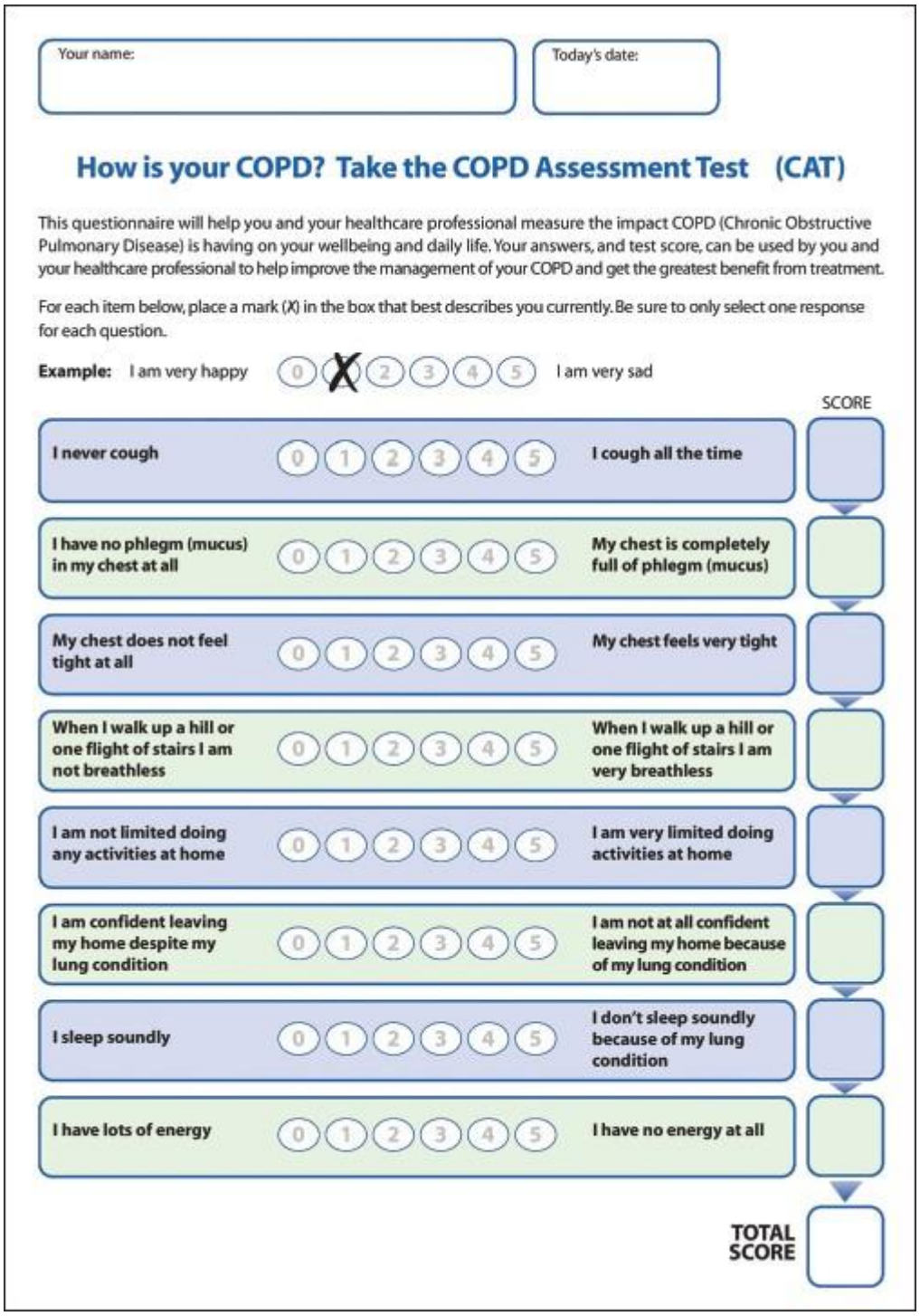
Breathlessness is a very common symptom in patients with COPD, and together with airflow limitation is a predictor of mortality [34]. A simple, useful, and widely used measure of breathlessness is the modified Medical Research Council (mMRC) dyspnoea scale (grades 0-4) [35, 36], which is depicted in **Table 2**.

Table 2. Modified Medical Research Council (mMRC) dyspnoea scale [35].

mMRC grade 0	I only get breathless with strenuous exercise.
mMRC grade 1	I get short of breath when hurrying on the level or walking up a slight hill.
mMRC grade 2	I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking at my own pace on the level.
mMRC grade 3	I stop for breath after walking about 100 meters or after a few minutes on the level.
mMRC grade 4	I am too breathless to leave the house or I am breathless when dressing or undressing.

However, breathlessness is only one of the symptoms in COPD, which is a far more complex disease with respiratory and extrapulmonary manifestations. Due to the need for a more complete assessment of respiratory symptoms in COPD and their impact on activities of daily

living several comprehensive, disease-specific health status questionnaires were developed, one of them being the COPD Assessment Test (CAT™) (COPD Assessment Test and the CAT logo are trademarks of the GlaxoSmithKline group of companies). This is an 8-item measure of health status impairment in COPD with a score that ranges from 0-40 (**Figure 1**). The CAT™ has been extensively used as a research method, but it is also suitable for the assessment of symptom burden in COPD patients in everyday clinical practice [37].


Your name:

Today's date:

How is your COPD? Take the COPD Assessment Test (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy 0 X 2 3 4 5 I am very sad

SCORE

I never cough	0 1 2 3 4 5	I cough all the time
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	My chest is completely full of phlegm (mucus)
My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless
I am not limited doing any activities at home	0 1 2 3 4 5	I am very limited doing activities at home
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition
I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition
I have lots of energy	0 1 2 3 4 5	I have no energy at all

TOTAL SCORE

Figure 1. COPD Assessment Test (CAT™) [37].

1.1.4.3. COPD exacerbations - assessment of risk

COPD exacerbations are very heterogeneous events in terms of aetiology and clinical presentation. The European Respiratory Society (ERS) and the American Thoracic Society (ATS) task force defined COPD exacerbation as an increase in patient's baseline dyspnoea, cough, and/or sputum production that usually requires a change in therapy [38]. Another proposed definition of COPD exacerbation is sustained worsening of the patient's condition from the stable state and beyond normal day-to-day variations that is acute in onset and may warrant additional treatment in a patient with underlying COPD [39].

Published data suggest that approximately 70% of exacerbations are caused by respiratory infections, namely infections with aerobic bacteria (40–60%), respiratory viruses (about 30%), and atypical bacteria (5–10%) [40, 41]. Polymicrobial aetiology was demonstrated in as much as 33% of exacerbations, being particularly important in the most severe cases [26]. Environmental factors, including low temperature and air pollution are considered causative for approximately 10% of exacerbations, depending on season and geographical settings [42]. Multifactor aetiology is not uncommon, e.g. a combination of infective and environmental factors or already mentioned polymicrobial infections [26]. Furthermore, noncompliance with respiratory medication and/or abrupt withdrawal of therapy is responsible for a certain proportion of exacerbations [43]. However, in some cases the aetiology remains unknown.

When referring to a severity of COPD exacerbations, the most popular classification is based on healthcare utilisation. According to that classification "mild" exacerbations are self-managed by the patient at home by increasing the usual COPD medication (short acting bronchodilators and/or inhaled corticosteroids [ICS]), "moderate" exacerbations are treated with antibiotics and/or oral corticosteroids in the outpatients settings, while "severe" ones require hospitalisation or emergency room visit [44].

Exacerbations have a negative impact on patient's health-related quality of life and prognosis, they accelerate lung function decline, and severe exacerbations also bring significant mortality risk [45, 46]. Therefore it is important to assess the risk of future exacerbations in order to reduce it with an appropriate treatment strategy.

Exacerbations become more frequent and more severe as COPD progresses and FEV_1 declines, but regardless of the COPD severity the best predictor of future exacerbations is a history of previous exacerbations [47]. Frequent exacerbator phenotype is usually defined by

≥ 2 exacerbations per year, and the main predictor of frequent exacerbator status in the following year among all grades of COPD severity is a history of frequent exacerbations in the previous year [48].

Recent studies suggest that a baseline blood eosinophil count may serve as a marker of exacerbation risk in COPD patients with a history of moderate/severe exacerbations, and may predict the usefulness of ICS in addition to bronchodilators in reducing the exacerbation rate [49]. Although the results of a post-hoc analysis of some clinical trials have suggested the beneficial effect of ICS therapy in patients with blood eosinophil level ≥ 2% [49], a cut-off threshold for blood eosinophils in predicting future exacerbations risk is still to be determined.

1.1.4.4. Additional investigations

In the clinical assessment of a patient with COPD several additional investigations are frequently performed, although they are not necessary to establish a diagnosis of COPD. **Chest radiograph** (colloquially called a **chest X-ray**) may demonstrate some radiological changes associated with COPD and resulting lung hyperinflation (e.g. hyperlucency of the lungs, flattening of the diaphragm, increased retrosternal airspace and intercostal spaces), but its greatest value is in establishing the presence of other pulmonary, pleural, cardiac and skeletal diseases.

Computed tomography (CT) of the chest is not routinely recommended in the management of COPD, but it may be useful in the differential diagnosis, when concomitant pathology is suspected (e.g. bronchiectasis, lung cancer, combined pulmonary fibrosis and emphysema), as well as in the evaluation of the distribution of emphysema when lung volume reduction procedures are considered [50].

Body plethysmography with lung volumes measurement is a preferred method for the assessment of lung hyperinflation, which commonly accompanies expiratory airflow limitation in patients with COPD contributing to the severity of dyspnoea. Lung hyperinflation is characterised by the increase in end-expiratory lung volume, residual volume (RV), total lung capacity (TLC), and/or ratio of residual volume to total lung capacity (RV/TLC), and the values >120% of the predicted are considered clinically important, although these ‘‘cut-offs’’ remain arbitrary [51].

Diffusing capacity of the lung for carbon monoxide (DLCO) is expected to be decreased in patients with emphysema where a gas-exchanging surface of the lung is reduced. Measurement of DLCO may be particularly useful in patients with breathlessness that seems out of proportion to the degree of airflow limitation [5].

In patients with clinical signs suggestive of respiratory failure **pulse oxymetry** should be used to measure peripheral capillary oxygen saturation (SpO_2). In case of a resting stable $SpO_2 \leq$ 92% **arterial blood gases** sampling is required in order to assess eligibility for long-term oxygen therapy (LTOT) [52]. Arterial blood gases assessment is also indicated in hospitalised patients with severe COPD exacerbations for oxygen titration during supplemental oxygen therapy, as well as in the evaluation of a need for mechanical ventilation.

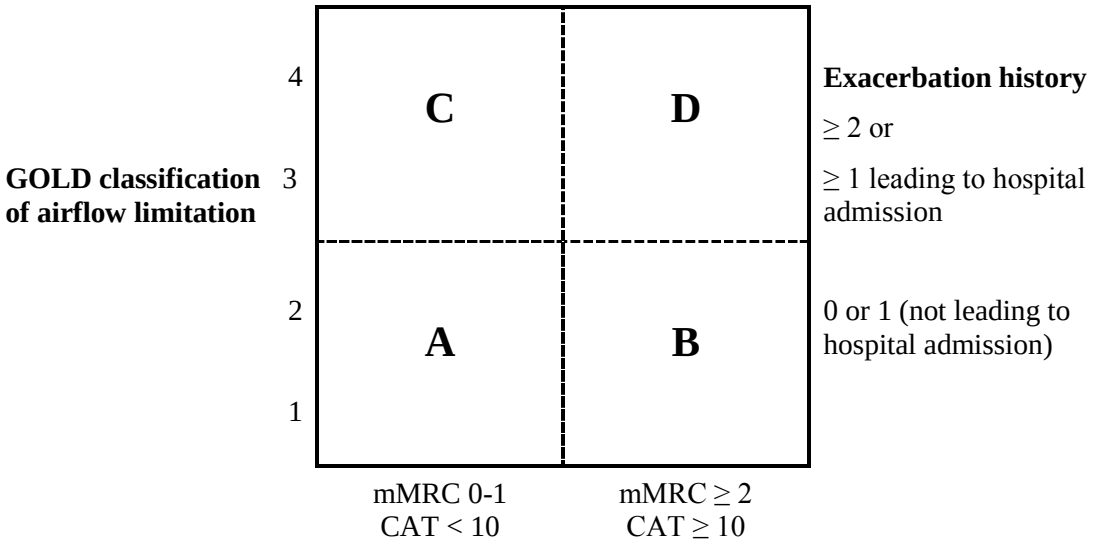
Exertional dyspnoea is a common symptom in COPD that usually leads to the reduction in exercise capacity and physical activity. Since the impairment in physical performance has been recognised as a negative prognostic factor in COPD [53], **exercise testing** and **objective measurement of physical activity** may be useful in a comprehensive assessment of COPD severity. However, these are still underperformed in everyday clinical practice because their determination is time consuming, and remains largely reserved for research purposes. The exceptions are walking tests, mainly **incremental shuttle walk test** and **6-minute walk test (6MWT)**, which are also in clinical use mostly to evaluate the effectiveness of pulmonary rehabilitation. Different methods of assessing physical performance will be discussed in more detail in section 1.3.

BODE index is a multidimensional 10-point scale that is used to predict long-term outcomes in COPD, in particular the risk of death [34]. In the calculation of BODE index four factors are evaluated: body mass index (BMI) (B); airflow obstruction (O), evaluated by the FEV_1; severity of dyspnoea (D), assessed by the mMRC dyspnoea scale; and exercise capacity (E), measured by the 6-minute walk distance (6MWD).

1.1.5. Classification of COPD

The most widely used classification of COPD is the one given by the GOLD [54], which takes into consideration patient's symptoms based on the mMRC dyspnoea scale (**Table 2**) [35] and/or the CAT™ score (**Figure 1**) [37], severity of airflow limitation assessed by the spirometry (**Table 1**), and the risk of exacerbations based on previous exacerbation history.

Using these parameters patients are classified into one of the four categories – A, B, C or D (**Figure 2**), which determines a severity of the diseases, impact on patient's health status, the risk of future events (exacerbations, hospitalisations, deaths) and serves as a guide in a therapy [54].



Patient category	Characteristics	Spirometric classification	Exacerbations per year	CAT	mMRC
A	Low risk, less symptoms	GOLD 1-2	0-1	< 10	0-1
B	Low risk, more symptoms	GOLD 1-2	0-1	≥ 10	≥ 2
C	High risk, less symptoms	GOLD 3-4	≥ 2 / ≥ 1 hosp.	< 10	0-1
D	High risk, more symptoms	GOLD 3-4	≥ 2 / ≥ 1 hosp.	≥ 10	≥ 2

Figure 2. Classification of COPD according to the GOLD guidelines 2011-2016 [54].

Abbreviations: CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease; hosp: hospitalised exacerbation; mMRC: modified Medical Research Council dyspnoea scale.

The novelty of the GOLD 2017 in comparison to the GOLD 2011-2016 is that the ABCD categorisation is now determined only by the symptoms severity and exacerbation history,

while the degree of airflow limitation (spirometric grade 1 to 4) should be presented separately (e.g. GOLD grade 3, group D) (**Figure 3**) [5]. According to the GOLD 2017 spirometry is no longer needed neither for the classification of COPD patients, nor for the initial therapeutic strategy; however, its role in the diagnosis, prognosis and follow-up is still irreplaceable [5].

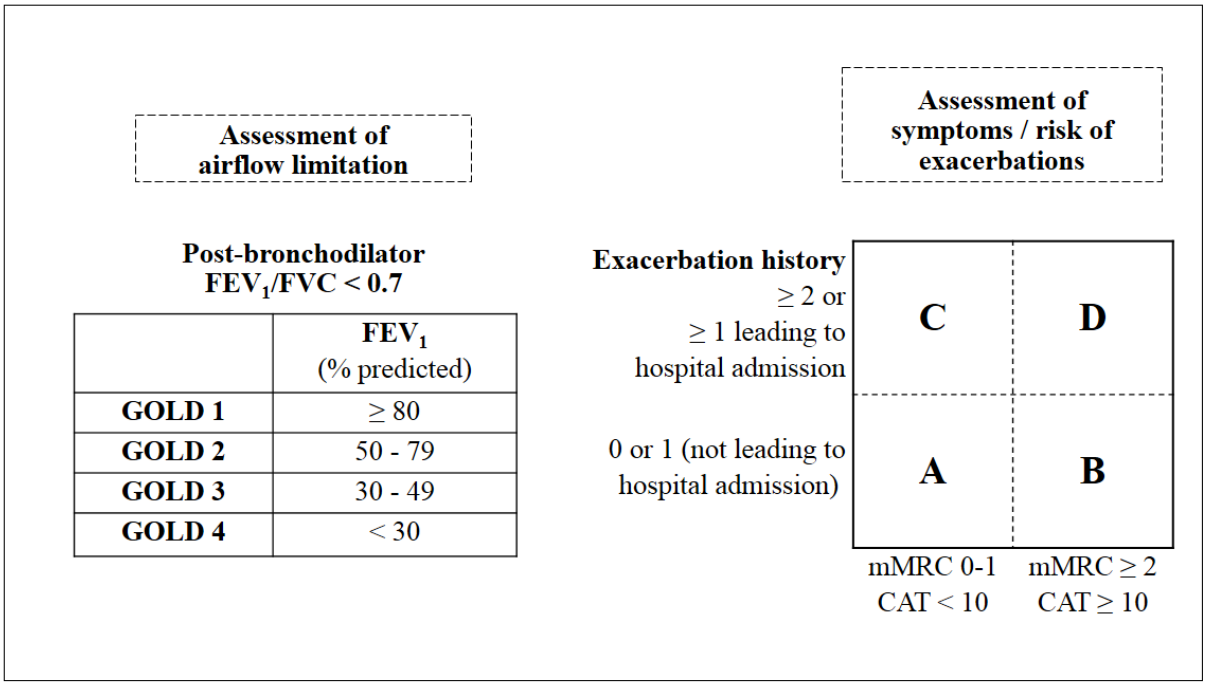


Figure 3. Classification of COPD according to the GOLD guidelines 2017 [5]. **Abbreviations**: CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in one second; GOLD: Global Initiative for Chronic Obstructive Lung Disease; mMRC: modified Medical Research Council dyspnoea scale.

However, it is now widely recognised that COPD is a very complex disease with a significant heterogeneity in clinical presentation and disease progression, and the term "phenotype" has recently become more common when referring to different clinical forms of COPD [55]. A group of international experts has defined COPD phenotypes as "those attributes of the disease that either alone or combined describe the differences between individuals with COPD regarding parameters that have clinical significance (symptoms, exacerbations,

response to therapy, progression rate of the disease, or death)" [55]. Established on the premise that the phenotypes enable the classification of patients into distinct prognostic and therapeutic subgroups, in recent years some national respiratory societies, e.g. Spanish and Czech respiratory societies, have developed guidelines for the diagnosis and treatment of COPD based on phenotypes [56, 57].

Spanish guidelines propose four distinct phenotypes: (A) non-exacerbator, with emphysema or chronic bronchitis; (B) mixed COPD-asthma; (C) exacerbator with emphysema; (D) exacerbator with chronic bronchitis (**Figure 4**) [56].

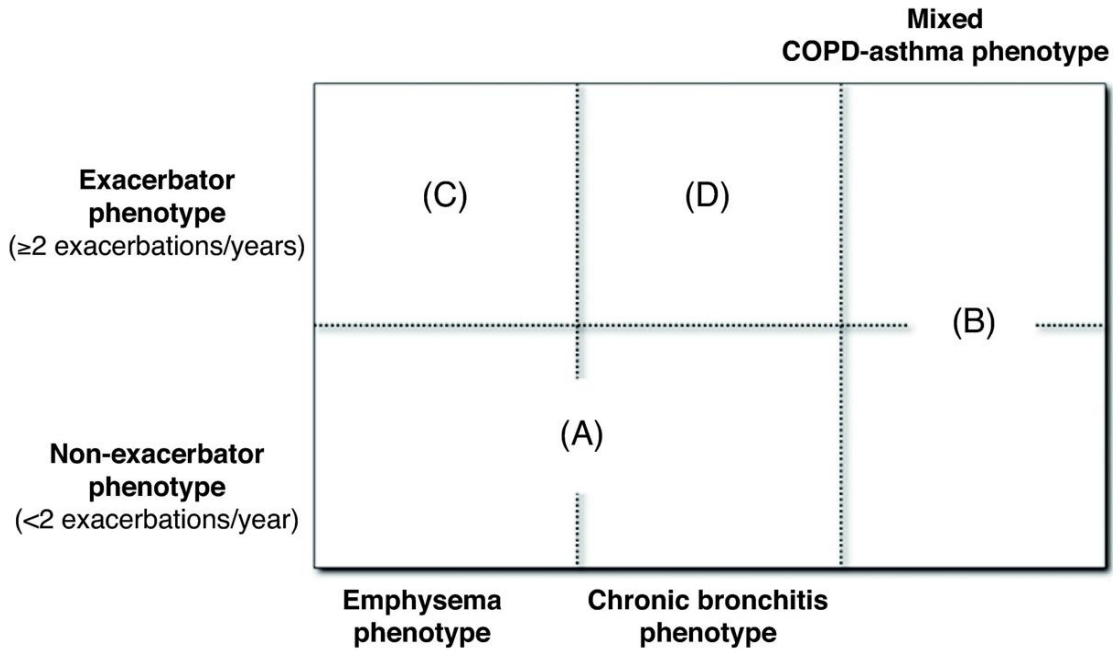


Figure 4. COPD clinical phenotypes according to the Spanish guidelines [56].

The emphysema phenotype includes COPD patients with clinical / radiological / functional diagnosis of emphysema who present dyspnoea and exercise intolerance as predominant symptoms [56]. Furthermore, chronic bronchitis is defined as the presence of productive cough or expectoration for more than three months a year during more than two consecutive years [58]. The mixed COPD-asthma phenotype is characterised by the symptoms of increased variability of airflow accompanied by the incompletely reversible airflow obstruction and increased bronchodilator responsiveness [59]. For the clinical identification of mixed COPD-asthma phenotype 2 major diagnostic criteria or 1 major and 2 minor criteria should be met - **Table 3** [60]. The exacerbator phenotype includes COPD patients who appear with two or more moderate or severe exacerbations a year requiring treatment with systemic

corticosteroids and/or antibiotics, and this phenotype may coexist with the three previous phenotypes [56].

Table 3. Major and minor criteria for establishing the diagnosis of mixed COPD-asthma phenotype in COPD [60].

Major criteria
Very positive bronchodilator test (increase in FEV_1 >15% and >400 ml)
Eosinophilia in sputum
Personal history of asthma
Minor criteria
High levels of total IgE
Personal history of atopy
Positive bronchodilator test on at least two occasions (increase of FEV_1 >12% and >200 ml)

Abbreviations: FEV_1: forced expiratory volume in one second; IgE: immunoglobulin E.

Similarly to Spanish guidelines, Czech COPD guidelines distinguish bronchitic phenotype, emphysematic phenotype, overlap COPD + asthma, and frequent-exacerbation phenotype, but apart from them they propose two additional phenotypes, namely pulmonary cachexia phenotype and overlap COPD + bronchiectasis [57]. Pulmonary cachexia phenotype is characterised by the decrease in body weight (BMI <21 kg/m^2), and particularly in fat-free mass (FFM) (fat-free mass index [FFMI] <16 kg/m^2 in men, <15 kg/m^2 in women) [57]. Overlap COPD + bronchiectasis phenotype includes COPD patients with radiological confirmation of bronchiectasis by the high-resolution CT scan, and clinically they are recognised by the chronic purulent expectoration, lower or no smoking burden, younger age, history of prolonged/recurrent respiratory infections and episodic haemoptysis [57]. Occasionally different phenotypes may occur simultaneously in an individual patient (e.g. emphysematic phenotype and cachexia, or bronchitic phenotype with frequent exacerbations) [57].

1.1.6. Treatment of COPD

Treatment of COPD includes different pharmacologic and non-pharmacologic therapeutic interventions with the main objectives to reduce symptoms, prevent exacerbations, delay the natural progression of the disease, and to improve the health-related quality of life.

Since smoking has a deleterious effect in the development and progression of COPD, all patients who continue to smoke should be strongly encouraged to quit, and if needed, pharmacotherapy for **smoking cessation** may be included (e.g. nicotine replacement products, varenicline, bupropion) [61].

Influenza and pneumococcal vaccinations are recommended for all COPD patients as a part of general non-pharmacologic measures [5].

Inhaled bronchodilators are the mainstay of the pharmacologic treatment of COPD. By combining bronchodilators of different classes the degree of bronchodilation may increase with a lower risk of side-effects compared to increasing the dose of a single bronchodilator [62]. Short-acting inhaled bronchodilators, namely short-acting beta2-agonists, SABA (e.g. salbutamol) and short-acting muscarinic antagonists, SAMA (e.g. ipratropium) are used as symptom-relieving treatment usually on an as-needed basis, and as monotherapy they are sufficient only in oligosymptomatic patients with mild COPD [5]. Patients with moderate, severe and very severe COPD require prolonged bronhchodilation, which can be achieved with long-acting muscarinic antagonists, LAMA (e.g. tiotropium, umeclidinium, aclidinium, glycopyrronium) and/or long-acting beta2-agonists, LABA (e.g. formoterol, salmeterol, indacaterol, olodaterol) [63]. When used on a regular basis long-acting inhaled bronchodilators exhibit many clinical benefits – they improve lung function (increase FEV_1), reduce resting and dynamic lung hyperinflation, alleviate dyspnoea, reduce exacerbation rate, and improve exercise tolerance, health status and quality of life [64]. However, so far there is no evidence that these drugs affect lung function decline, disease progression and mortality.

Corticosteroids are efficient anti-inflammatory drugs that have been used in COPD for a long time, but in recent years their indications have become more restricted due to potential adverse effects and the evidence of benefit only in a selected group of patients with distinct clinical phenotypes [65]. The current guidelines recommend the treatment with ICS in association with LABA for COPD patients with a history of frequent exacerbations despite appropriate treatment with long-acting bronchodilators, and for patients with features of both

asthma and COPD, i.e. athma-COPD overlap syndrome [5, 56, 57]. It has been suggested that the presence of sputum and blood eosinophilia may serve as a predictor of response to ICS in COPD [49]. ICS in a combination with LABA reduce exacerbation rate, and improve lung function and health status in selected COPD patients, though there is no evidence of survival benefit or effect on long-term FEV_1 decline [65, 66].

Systemic corticosteroids are not recommended in the treatment of stable COPD; however, a short course (≤ 14 days) of systemic corticosteroids is indicated in COPD exacerbations, preferably orally administered rather than intravenously even in hospitalised patients [67]. There is evidence to support treatment of COPD exacerbations with systemic corticosteroids in reducing the risk of early relapse, shortening recovery time and length of hospital stay, and improving lung function and symptoms [68].

Methylxanthines (e.g. theophylline, aminophylline) are non-selective phosphodiesterase inhibitors with a weak bronchodilator and anti-inflammatory activity, and some additional effects of which clinical relevance is still not clear, such as a potential to increase respiratory muscle activity and reverse corticosteroid resistance [69, 70]. Theophylline is given orally as slow-release preparations in stable COPD, and aminophylline is given intravenously in exacerbations, but their use is constantly declining because of a relatively small therapeutic effect, significant interactions with commonly used medications and frequent side effects, especially in elderly persons [69].

Roflumilast, a selective phosphodiesterase-4 inhibitor is a relatively new drug with a variety of anti-inflammatory effects, and besides some improvement in lung function its main clinical benefit is a reduction of moderate and severe exacerbations [71]. As part of a combination regimen with long-acting bronchodilators, roflumilast is indicated in the treatment of patients with severe to very severe COPD (FEV_1 <50% predicted) associated with chronic bronchitis and a history of exacerbations [71].

Regarding **antibiotics** there is evidence supporting their use in COPD exacerbations with clinical signs of a bacterial infection, e.g. increased sputum purulence [72], as well as in severe exacerbations requiring invasive or noninvasive mechanical ventilation [73]. Antibiotic therapy in COPD exacerbations reduces the risk of short-term mortality and treatment failure, and increases the time between exacerbations [74]. The choice of the antibiotic should be based upon local bacterial sensitivity patterns [67].

Although there is still some controversy in the preventive antibiotic use in stable COPD, there is evidence of the effectiveness of prolonged intermittent use of some antibiotics (e.g. azithromycin, moxifloxacin) in decreasing the exacerbation rate in patients with an increased risk of exacerbations [75, 76]. However, due to potential side-effects and the development of bacterial resistance the candidates for the preventive antibiotic therapy should be strictly selected among patients with severe COPD and signs of chronic bronchial infection (e.g. chronic bronchitis phenotype with permanently purulent sputum, carriers of bronchiectasis) who experience recurrent infective exacerbations despite adequate therapy [56].

Mucolytic agents (e.g. N-acetylcysteine, carbocysteine) are recommended as additional therapy in patients with chronic bronchitis phenotype and frequent exacerbations [5, 56]. There is evidence that the treatment with mucolytics may produce a small reduction in the frequency of exacerbations and a small effect on the overall quality of life, especially in patients not receiving ICS [77].

Candidates for **alpha-1 antitrypsin augmentation therapy** are patients with severe hereditary alpha-1 antitrypsin deficiency (serum levels of alpha-1 antitrypsin <11.0 μM), established emphysema, postbronchodilator FEV_1 between 30-65% predicted or if they experience a rapid decline in lung function (ΔFEV_1 >120 ml/year) [78].

Pharmacologic treatment algorithms suggested by the GOLD 2017 guidelines are presented in **Figure 5** [5].

Pulmonary rehabilitation has a central place in the non-pharmacologic treatment of COPD, and among others includes structured and supervised exercise training, education, and behavioural change, all designed to improve the physical and psychological condition of a patient [79]. It is indicated for patients who have decreased exercise tolerance, exertional dyspnoea or fatigue, and/or impairment of activities of daily living [80]. Pulmonary rehabilitation should be considered (a) at diagnosis, (b) at discharge following hospitalisation for an exacerbation, and (c) when symptoms are progressively deteriorating despite optimal pharmacologic therapy [5]. The evidence for improvement in exercise endurance, dyspnoea, functional capacity, and quality of life is stronger for pulmonary rehabilitation than for almost any other therapy in COPD [80, 81]. Despite previous evidence that pulmonary rehabilitation after an exacerbation may also reduce readmissions and mortality, more recent studies have failed to show the benefit on these outcomes [81].

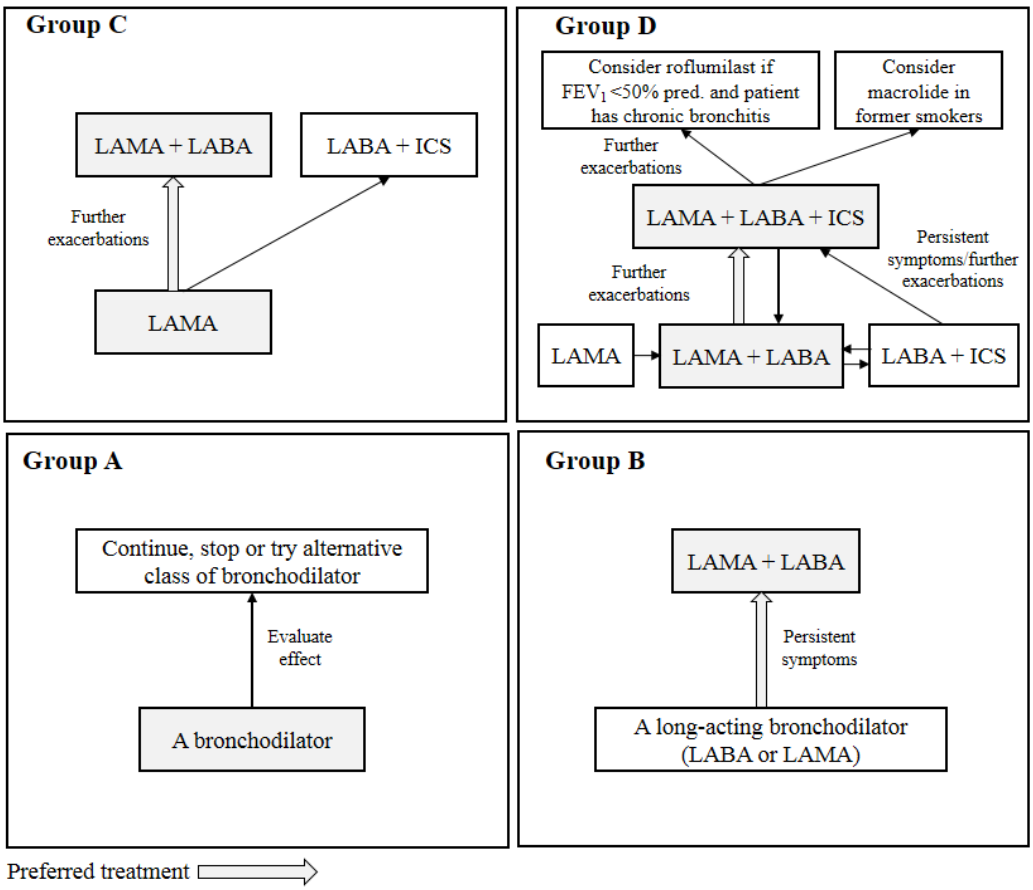


Figure 5. Pharmacologic treatment algorithms for A-D GOLD categories of COPD [5].
Abbreviations: FEV_1: forced expiratory volume in one second; ICS: inhaled corticosteroids; LABA: long-acting beta2-agonists; LAMA: long-acting muscarinic antagonists.

Nutritional supplementation is indicated in malnourished patients with COPD based on the evidence of positive effects on weight gain, FFM, fat-mass (FM), respiratory muscle strength, exercise tolerance and the health-related quality of life [82].

In patients with severe chronic respiratory failure **LTOT** improves survival [83]. LTOT is recommended for stable COPD patients with partial pressure of oxygen in arterial blood (pO_2) ≤ 7.3 kPa (55 mmHg) or arterial oxygen saturation ($SatO_2$) ≤ 88% confirmed twice over a three week period in resting condition [5]. For COPD patients with pulmonary hypertension, peripheral oedema suggesting congestive cardiac failure, or polycythemia (haematocrit > 55%) LTOT is indicated if pO_2 ≤ 8.0 kPa (60 mmHg) [5].

Non-invasive ventilation (NIV) in the form of non-invasive positive pressure ventilation is the standard of care for patients hospitalised for severe COPD exacerbations with respiratory

failure [5]. It has been proven that in these patients NIV improves oxygenation and respiratory acidosis, reduces the need for intubation and invasive ventilation, decreases length of hospital stay, and reduces in-hospital complications (e.g. ventilator associated pneumonia) and mortality [84]. However, the evidence of survival benefit and lower readmission rate when using NIV at home is not as conclusive, but it may be considered in selected patients with very severe COPD and persistent daytime hypercapnia (i.e. partial pressure of carbon-dioxide in arterial blood (pCO_2) ≥ 52 mmHg) after hospitalisation [5, 85]. On the other hand, in patients with both COPD and obstructive sleep apnoea there is strong evidence in favour of using continuous positive airway pressure (CPAP) as an intervention that improves survival and reduces the risk of hospitalisation [86].

Interventional bronchoscopy and **surgery** may be considered in selected COPD patients. In patients with advanced emphysema and significant hyperinflation lung volume reduction may be achieved by the surgical methods (e.g. **lung volume reduction surgery**, **bullectomy**) or bronchoscopic methods (e.g. **placement of endobronchial valves** or **lung coils**) [87, 88]. A selection of a method depends on several factors including lung function, extent and pattern of emphysema, presence of interlobar collateral ventilation (i.e. fissure integrity), availability of a certain method, and patient and providers preferences [5].

Lung transplantation remains an option for patients with end-stage COPD without significant comorbid conditions. Criteria for the referral for lung transplantation include COPD with progressive disease course despite maximal treatment, not a candidate for endoscopic or surgical lung volume reduction, BODE index of 5 to 6, pCO_2 > 6.6 kPa (50 mmHg) and/or pO_2 < 8 kPa (60 mmHg), and FEV_1 < 25% predicted [89]. Criteria for listing include at least one of the following: BODE index ≥ 7, FEV_1 < 15-20% predicted, ≥ 3 severe exacerbations during the preceding year, one severe exacerbation with acute hypercapnic respiratory failure, moderate to severe pulmonary hypertension [89].

1.1.7. Comorbidities and extrapulmonary manifestations of COPD

Patients with COPD often suffer from other chronic medical conditions. Although respiratory symptoms dominate in the clinical presentation of COPD, and maximum efforts are directed toward their reduction, concomitant diseases may aggravate clinical manifestations of COPD and worsen its prognosis. Comorbidities that are most frequently reported include ischaemic

heart disease, heart failure, systemic and pulmonary hypertension, metabolic syndrome, diabetes mellitus, dyslipidaemia, osteoporosis, obstructive sleep apnoea, lung cancer, anaemia, weight loss, skeletal muscle wasting and/or dysfunction, and psychological disorders such as depression and anxiety [90, 91]. In a study by Mapel et al. [92] patients with COPD had an average of 3.7 comorbidities compared to 1.8 for the control subjects, and only 6% of COPD patients did not have any other chronic medical condition. COPD and many of reported comorbidities often share the same risk factors, the most important being tobacco smoking and ageing. However, such a high incidence of different comorbidities in COPD cannot be attributed only to the common predisposing factors, and there is increasing evidence that chronic low-grade systemic inflammation, chronic hypoxia, and sedentary lifestyle play an important role in the pathogenesis of comorbidities in patients with COPD [93]. Inflammatory response in COPD is not limited only to the lungs, but there is also a certain level of systemic inflammation, both during exacerbations and in stable periods, which in a significant number of cases may be attributed to the chronic bronchial infection [94]. Consequently, it has been suggested that a chronic systemic inflammation may be the common pathway linking COPD and comorbidities, and that in fact many comorbidities may actually be considered systemic/extrapulmonary manifestations of COPD [95].

Furthermore, some COPD medications may contribute to certain concomitant diseases, e.g. ICS increase the risk of pneumonia, and when used in high doses may predispose to cataracts and osteoporosis, bronchodilators may contribute to tachyarrhythmias, inhaled anticholinergics may predispose to glaucoma and urinary retention, while systemic corticosteroids affect different tissues and organs increasing the risk of osteoporosis, diabetes, hypertension, muscle dysfunction, and adrenal insufficiency [90].

The presence of comorbidities often worsen clinical presentation of COPD with a negative impact in terms of quality of life, exacerbations, hospitalisations and mortality [91]. Therefore, as part of the comprehensive care of patients with COPD an additional effort should be made for an early diagnose and appropriate treatment of each concomitant medical condition, which generally does not differ from the management in subjects without COPD.

1.2. Evaluation of nutritional status and body composition in COPD

One of the systemic manifestations of COPD is a change in the nutritional status, namely body weight and body composition alterations, which reflect a complex interaction between

the effects of genetics, lifestyle and disease on muscle, bone and fat tissue [96]. Malnutrition arises from a combination of inflammation and a disturbed nutrient balance involving the intake of energy (calories), proteins, carbohydrates, fats, vitamins, minerals and other nutrients required to maintain the normal structure of human organs and their functioning [97, 98]. By definition the malnourished state includes both undernutrition (lack of nutrients) and overnutrition (excess of nutrients), resulting with health problems in both situations [97, 98]. However, the narrower sense of the term malnutrition refers to undernutrition, and in clinical practice it is more often used in that context.

Back in 1968, Filley et al. [99] already distinguished two contrasting types of COPD patients, i.e. the emphysematous type ("pink puffer") and the bronchial type ("blue bloater") that besides the differences in the respiratory and cardiovascular features also exhibit distinct body habitus. More recent scientific research on this topic has shown that body weight and body composition variables represent a continuous spectrum, and that nutritional abnormalities in COPD patients are predictors of outcome independent of lung function impairment [96].

The BMI, calculated as weight/height squared (kg/m^2) is the most commonly used anthropometric parameter in the assessment of nutritional status in adults. The WHO suggests the following BMI classification: underweight (<18.5 kg/m^2), normal weight (≥18.5, <25 kg/m^2), overweight (≥25, <30 kg/m^2), and obese (≥30 kg/m^2) [100]. However, studies on COPD frequently use a BMI <20 or <21 kg/m^2 to define underweight, since a higher mortality was observed in COPD patients with BMI below these values [101, 102]. The cut-off BMI <21 kg/m^2 for underweight patients with COPD is also recommended by the ATS/ERS [103].

Body composition is more informative than BMI, but it is highly influenced by many biological factors, such as age, gender, genetics, ethnicity, dietary intake, physical activity, and the presence of disease [104]. Information on human body composition can be collected at five distinct levels of increasing complexity: atomic, molecular, cellular, tissue, and whole-body level (**Figure 6**) [105]. At the atomic level six chemical elements (oxygen, hydrogen, carbon, nitrogen, calcium, and phosphorus) account for over 98% of the body mass [105]. At the molecular level the human body is composed of water, lipids, proteins, glycogen, and minerals, while at the cellular level it can be divided into cell mass, extracellular fluids, and extracellular solids [105]. Furthermore, four main body components at the tissue level are skeletal muscles, bones, adipose tissue, and internal organs [105]. Nevertheless, in clinical practice the most widely used approach to estimate body composition is a two-compartment model of body composition, in which the body is divided into FM and FFM [104]. On a tissue

level the FFM comprises skeletal muscles, bones and internal organs, while on a molecular level it consists of water (approximately 73%), proteins (20%), minerals (7%), and a small amount of carbohydrates (mainly glycogen and glucose) [104, 106]. The lean body mass and the FFM are usually used as synonyms, while the lean soft tissue mass (LM) represents bone-free FFM. On the other hand, the main component of the FM on a tissue level is adipose tissue with reserves of a body fat, which chemically mainly consists of triglycerides. Adipose tissue can be classified as two main types: subcutaneous (adipose tissue directly underneath the skin), and internal adipose tissue, which is further subdivided into visceral (adipose tissue surrounding the internal organs), and nonvisceral internal adipose tissue (e.g. adipose tissue in bone marrow, interstitial adipose tissue between muscle fibres, and retro-orbital, paravertebral and intra-articular adipose tissue) [106].

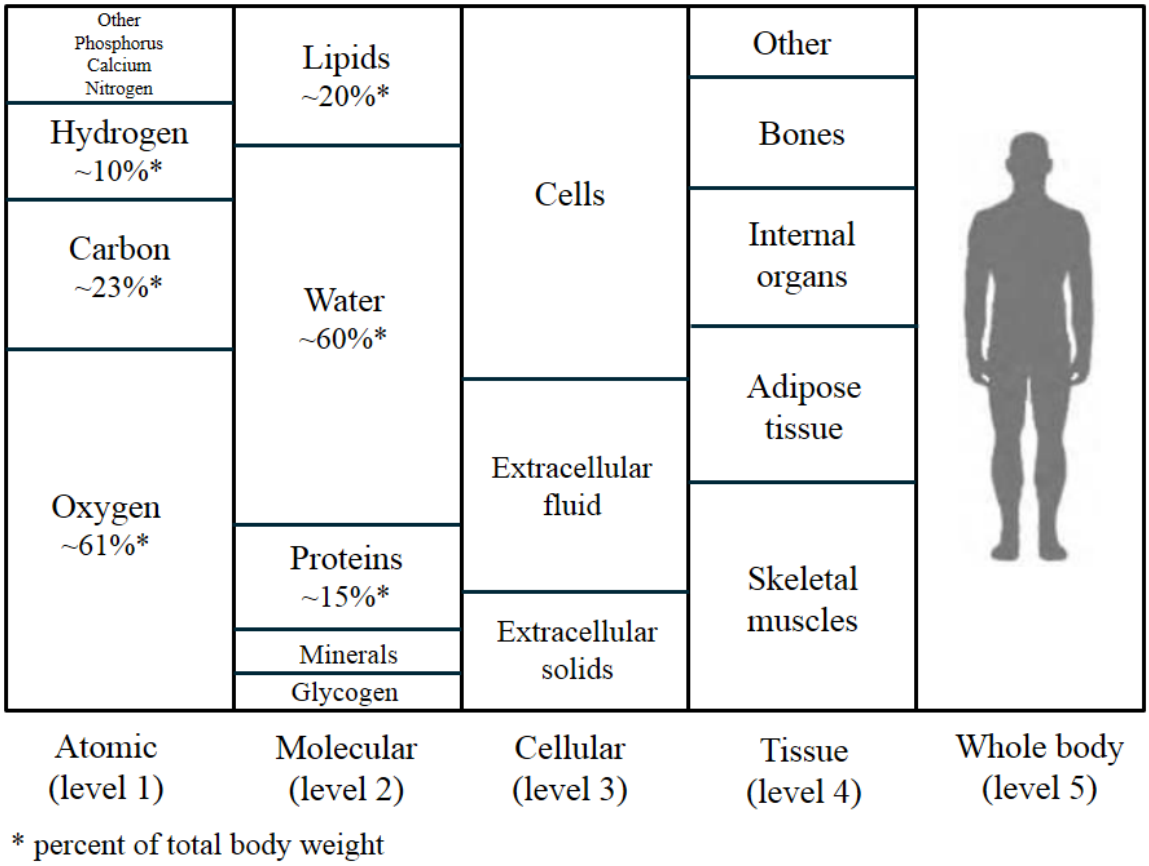


Figure 6. Five-level body composition model. Adapted from references 104 and 105.

In the assessment of nutritional status and body composition different methods may be applied depending on the population studied and the purpose of the investigation:

1) **Questionnaires** [107] – ESPEN, the European Society for Clinical Nutrition and Metabolism, recommends several questionnaires as screening tools to detect undernourished patients: MUST (Malnutrition Universal Screening Tool), NRS-2002 (Nutritional Risk Screening), and MNA (Mini Nutritional Assessment). Methods to assess dietary intake include food frequency questionnaires, 1-7 day food records, and 24-hour dietary recalls.

2) **Anthropometry** [100, 104] – includes direct measurements of different anthropometric variables (e.g. height, weight, circumferences of the waist, hips, upper arm, forearm, thigh and calf, skinfold thickness at specific anatomic locations) followed by the calculation of more complex anthropometric parameters using specific equations. Anthropometric instruments are portable and inexpensive, procedures are non-invasive and minimal training is required.

3) **Bioelectric impedance analysis (BIA)** [104, 108] – it is one of the most frequently used methods for estimating body composition due to its relatively low cost, ease of use, portability, and safety (not recommended for participants with a pacemaker). It measures the impedance or resistance to a small alternating electrical current as it travels through the body's water pool. Skeletal muscles have both a large volume and low resistance owing to the high electrolyte content, while adipose tissue and bones have poor conductance properties, and consequently most of the current in a whole-body BIA measure flows through skeletal muscles. An estimation of the total body water should allow calculation of the FFM based on the assumption that all the water in the body is in the FFM, and that 73% of the FFM is water. Moreover, FM can be determined by subtracting FFM from total body mass. The disadvantage of BIA is its reference-method dependence; that is, BIA resistance measures must be mathematically transformed into the body composition component of interest using prediction equations, which are population specific. Furthermore, BIA measures are dependent on hydration status, which reduces the reliability of this method in some clinical situations (e.g. recent food/fluids consumption, recent exercise, dehydration, congestive heart failure, renal insufficiency, diuretic therapy, dialysis).

4) **Dual energy X-ray absorptiometry (DEXA)** [104, 108] – this method is more exact than BIA and enables determination of three components of the human body: bone mineral content (BMC) with bone mineral density (BMD), bone-free FFM (i.e. LM), and FM in addition to

their regional distribution. The basic physical principle behind DEXA is the measurement of the transmission of a low-photon (~40 keV) and a high-photon (~80 keV) X-ray through the body. The intensity of the X-ray is attenuated when passing through the body, but the level of attenuation differs for different tissues, which enables body composition estimation based on complex mathematical equations. This method is relatively quick (≤ 15 min for the whole-body scan), non-invasive, precise, and reproducible. DEXA is considered the gold standard technique for the diagnosis of osteopenia and osteoporosis. Disadvantages include a small dose of radiation (equivalent to that received on a transcontinental flight or between 1 and 10% of a chest radiograph), and a limitation by the subject's weight and size (must fit into the scanning field).

5) **CT** and **magnetic resonance imaging (MRI)** [104, 108] – these are the most accurate methods available for in vivo quantification of body composition at the tissue level. CT and MRI allow for the estimation of adipose tissue, skeletal muscle, and are the only methods available for the measurement of internal organs. Routine use of these imaging techniques is limited by access and cost, so they are now mostly used in body composition research.

6) **Isotope dilution techniques** [108] – total body water can be measured by several isotope dilution techniques using water labelled with the isotope of oxygen (^{18}O) or hydrogen (^{2}H or ^{3}H). Assuming that the hydration of FFM is relatively constant in healthy subjects (i.e. total body water/FFM = 0.732), measurement of total body water allows for the evaluation of FFM and FM. This method is mainly used in body composition research.

7) **Laboratory assessment** [109, 110] – includes identification of different nutrients and metabolites in biological specimens (e.g. blood, urine, saliva, hair, adipose tissue), which ideally reflect dietary exposures and nutritional status. Many nutritional biomarkers are available, however their clinical utility in the nutritional assessment may be limited due to numerous factors that affect the metabolism of each nutrient. Albumin, prealbumin, transferrin, and retinol-binding protein have been suggested as markers of protein status.

Albumin is a serum protein synthesized by the liver, it is a negative acute phase reactant, which levels decrease during the acute phase response (e.g. inflammation, infection, metabolic stress, trauma, post-operative state), and besides that its serum concentration is affected by many other factors (e.g. hydration status, liver disease, nephrotic syndrome, burns and other protein losing states, pregnancy) [110, 111]. Because of its relatively large body pool size (more than 50% is located extravascularly), and a long half-life (14-20 days), serum

albumin levels do not reflect acute changes in protein intake, but it may be considered a marker of chronic nutritional status [110].

Prealbumin is also a negative acute phase reactant, but its advantage over albumin is a shorter half-life (2-3 days) and a smaller body pool, so it is expected to respond more rapidly to changes in nutrient intake [110].

Transferrin is involved in iron transport, and its levels increase in iron deficiency, which limits its usefulness in protein status assessment [110].

Retinol-binding protein forms retinol-circulating complex together with prealbumin and retinol, and as a marker of protein status generally has similar characteristics as prealbumin [110].

Since malnutrition may also affect the immune system, several immunological tests (e.g. **total lymphocyte count**, **delayed cutaneous hypersensitivity testing**) may be applied as a functional measure of nutritional status [98].

1.3. Evaluation of physical performance in COPD

Physical activity can be defined as any bodily movement produced by skeletal muscles that results in energy expenditure, and includes different kinds of activities, such as domestic, occupational and leisure-time activities [112]. **Exercise** is a subset of physical activity that is planned, structured, repetitive and purposeful with an objective to improve or maintain **physical fitness** and **exercise capacity** - the maximum amount of physical exertion that a person can sustain [112, 113]. Furthermore, **activities of daily living** are another subset of physical activity that includes a set of basic, everyday tasks required for personal self-care and independent living [114].

Patients with COPD are markedly less physically active compared with age-matched healthy individuals, which becomes more evident with increasing COPD severity [115, 116]. Reduced exercise capacity and low physical activity in COPD have been related to multiple negative outcomes including poor health-related quality of life, increased exacerbation risk, and higher mortality [117-120]. For this reason, it is important to assess physical performance, quantify physical activity, and to employ additional effort in their improvement. In the evaluation of physical performance different methods are used, depending on the clinical settings, purpose of the investigation, and availability of financial resources.

Cardiopulmonary exercise testing is incremental, symptom-limited exercise testing, which is performed on a cycle ergometer or a treadmill in a specially equipped laboratory, and includes measurement of different cardiovascular and respiratory parameters [121]. Cardiopulmonary exercise testing allows a valid and comprehensive assessment of cardiopulmonary function capability.

The most commonly employed field walking tests are the **6MWT**, **incremental shuttle walk test**, and **endurance shuttle walk test**, which are proven to be a valid and reliable measure of exercise capacity for people with chronic respiratory diseases [122].

The **6MWT** [122, 123] is a self-paced test of walking capacity in which subjects are asked to walk as far as possible in 6 minutes along a flat corridor between two cones spaced 30 metres apart. The test includes measurement of pulse and SpO_2 by the continuous pulse oximetry, rating levels of baseline and post-test dyspnoea and fatigue according to the Borg scale, and most importantly recording of the total distance walked expressed in metres (i.e. 6-minute walk distance - 6MWD).

The **incremental shuttle walk test** [122] is an externally paced maximal exercise test in which the speed of walking is controlled by a series of pre-recorded signals, and the total distance walked is recorded. The participant is required to walk between two cones spaced 10 metres apart with gradual increase in the speed of walking until he cannot keep up with the set pace, or becomes too breathless or too tired to continue.

The **endurance shuttle walk test** [122] is an adaptation of the incremental shuttle walk test designed to assess endurance exercise capacity. Subjects are asked to walk for as long as possible at a constant pace that is a predetermined percentage of maximum walking performance as assessed by the incremental shuttle walk test. The primary outcome of the endurance shuttle walk test is time (expressed in minutes and seconds), although it can also be expressed as distance completed.

Several other simple field tests are available for a rapid assessment of physical performance, such as the **gait speed test**, **timed chair stand test**, and **timed up and go test**.

Gait speed is easily measured and enables the assessment of walking functional mobility. There are different versions of gait speed test, which differ in a distance walked and whether the usual or maximum speed is measured. In the original **4-metre gait speed (4MGS) test** [124] the participant walks 4 metre distance at his usual pace, and if needed he is allowed to use his normal walking aid (e.g. cane). Briefly, the 4 m distance is marked out on the floor

with tape, the participant is positioned with his toes just touching the start line, timing with the stopwatch starts when the participant begins to move and stops when his/her first foot completely crosses the 4-m line. The test is repeated without rest, and the faster of the two times is used to calculate 4MGS expressed in m/s. The 4MGS was proven to be a reliable and valid indicator of functional impairment in patients with COPD, and it correlates well with exercise capacity, dyspnoea and the health-related quality of life [124].

The **timed chair stand test** [125] was developed for the assessment of lower limb muscle strength in older people. There are several variants of this test – either to measure the time that a participant needs to rise 10 (original test), 1 or 5 times from a standard height chair (46 cm) with arms folded across the chest, or to measure the number of stands from a chair in 30 seconds (i.e. **30-second chair stand test**) [126] or in a 1 minute period (i.e. **sit-to-stand test**) [127].

The **timed up and go test** [128] is a reliable and valid test for quantifying functional mobility of frail elderly people. The participant is observed and timed while he rises from an arm chair, walks 3 metres at normal pace, turns, walks back, and sits down again. Use of a walking aid is permitted in this test.

Physical performance is directly related to a peripheral muscle mass, strength and endurance, which all often become impaired with the progression of COPD [129]. Muscle mass and its surrogate indicators, namely FFM and LM, can be quantified using one of the methods for body composition analysis (e.g. **anthropometry**, **BIA**, **DEXA**), as explained in the previous section. Additionally, in the assessment of regional limb muscle mass several other techniques are available, such as **CT**, **MRI** and **ultrasonography**, which have been used to assess quadriceps size in patients with COPD [129]. On the other hand, muscle function is evaluated by the measurement of muscle strength and/or endurance with different methodologies depending on whether muscle contraction is isometric or isokinetic, voluntary or involuntary (i.e. muscle contraction in response to an electrical or magnetic stimulation of a peripheral nerve) [129]. In the studies investigating muscle function in patients with COPD, **isometric quadriceps maximal voluntary contraction strength**, and the **handgrip strength** are most commonly measured [130, 131].

Assessment of overall physical activity is complex, and on the one hand includes widely available, low-cost methods, such are **questionnaires** and **pedometers**, and on the other hand

more accurate, sophisticated and expensive methods, such are **accelerometers** and **doubly labelled water method** [132].

Physical activity questionnaires and **diaries** are inexpensive and easy to use research instruments that are commonly used in epidemiological studies and large clinical trials to evaluate the different aspects of physical activity [133]. Among 104 available questionnaires that measure physical activity in elderly and chronically ill populations, 15 were developed for use in patients with COPD [134]. The main limitation is their lack of accuracy due to recall bias [133].

Pedometers or **step counters** are small, lightweight, portable and relatively inexpensive devices that measure the number of steps that a person creates in a given period of time [132]. They are usually worn on the waist and designed to detect vertical movements of the hips while walking, although some newer models of pedometers in the form of bracelet detect arm swing during walking. With some additional information including the average step length, height and weight of the subject pedometers may also roughly estimate distance walked and energy expenditure [132]. Nevertheless, their main disadvantage is that they tend to be less accurate and generally underestimate activity in individuals with slower walking speed, which makes them impractical for use in patients with advanced COPD who usually walk very slowly [135]. Furthermore, pedometers are not able to detect other forms of physical activity such are cycling, swimming and static exercise, what might be an issue when assessing physical activity in patients in early stage of COPD who still do some recreational sport activities.

Accelerometers or **activity monitors** are portable electronic devices worn on the body (usually on the waist, wrist, upper arm, or ankle) that measure quantity and intensity of bodily motion by detecting acceleration, and convert it to vector magnitude units (the vectorial sum of activity counts in different directions) [132, 135]. Accelerometers can detect movements along one axis (uni-axial accelerometers, which provide information similar to pedometers, but with the advantage of assessing acceleration in addition to simply detecting steps), two axes (bi-axial accelerometers) or three axes (tri-axial accelerometers) [132]. Some activity monitors have additional sensors for measuring other physiological functions (e.g. heart rate, skin temperature), which increases their accuracy in the estimation of daily physical activity and energy expenditure [132]. Reliability and validity of accelerometers, especially new ones with improved technology is generally high, which was also confirmed in several studies with COPD patients [135-137]. When measuring physical activity in daily life recommendation for

the number of assessment days is not straightforward and it depends on the population studied, but it is usually suggested that between 4 and 12 measurement days are needed to obtain accurate data [135].

Doubly labelled water method provides an indirect assessment of total energy expenditure by the body over a period of time [132]. The technique is based on the ingestion of water labelled with the hydrogen isotope ^{2}H known as deuterium (i.e. $^{2}H_2O$), and with the oxygen isotope ^{18}O (i.e. $H_2{}^{18}O$) in a known ratio [138]. The deuterium is eliminated through the urine, whereas the ^{18}O is eliminated through the urine and CO_2, and by measuring their elimination rates in the urine one can estimate the CO_2 production, which further enables the calculation of energy expenditure [138]. Although this method is considered a "gold standard" for measuring the caloric cost of physical activity, its main drawback is that it actually does not allow separation of energy expenditure linked to physical activity and energy expenditure linked to basal metabolism and diet-induced metabolism, which needs to be taken into account when using this method in different study populations [132].

1.4. Background for the presented research

Respiratory symptomatology predominates in the clinical presentation of COPD, and for a long time it has been the main focus of diagnostic assessment and therapeutic efforts. However, extrapulmonary manifestations of COPD are increasingly being recognised as important determinants of disease severity and prognosis, and in the last two decades have become the subject of extensive scientific research [95]. Among common systemic manifestations of COPD are nutritional alterations and shifts in body composition, i.e. changes in the FFM, FM and BMC [96, 139]. Body weight loss and/or FFM depletion (defined as a FFMI <15 kg/m^2 for women and <16 kg/m^2 for men) are observed in 20-40% of COPD patients, with increasing prevalence in advanced stages of the disease, especially in women [140-142]. Different forms of nutritional depletion and body composition abnormalities have been described in COPD patients – cachexia (reduction in both body weight and FFM), semistarvation (reduction in body weight with normal FFM), and muscle atrophy (reduction in FFM with normal body weight) [143]. It is of clinical importance that skeletal muscle mass waste, reflected in the reduction of LM and FFM, together with low body weight have been recognised as predictors of increased disability and mortality in

COPD [142, 144]. Additionally, a low FFMI is a strong predictor of mortality even in the COPD population with a normal BMI [143].

Loss of skeletal muscle mass (i.e. sarcopenia) is closely linked to COPD-related limb muscle dysfunction, which besides muscle fibre atrophy includes different structural and functional alterations of peripheral muscle, such as a reduced muscle capillarisation, muscle fibre type shifting from type I to II, reduced mitochondrial density and function, decreased muscle oxidative/aerobic capacity, enhanced muscle protein turnover, low mechanical efficiency and high resting energy expenditure [129]. Peripheral skeletal muscle dysfunction, as most frequently evidenced by a reduction in quadriceps strength and endurance, is demonstrable in one-third of COPD patients (even in those with mild disease), and associated with many important clinical implications including exercise intolerance, reduced quality of life, and increased health care use and mortality [129, 130, 145]. Although all mechanisms underlying the development of peripheral muscle wasting and dysfunction are not yet known, some contributing factors have been identified: deconditioning due to physical inactivity, inflammation (chronic low-grade systemic inflammation with additional increase in the inflammatory response during exacerbations), hypoxia, hypercapnia with tissue acidosis, local and systemic oxidative stress, corticosteroid therapy, smoking, vitamin D deficiency, low levels of anabolic hormones (e.g. testosterone), impaired energy balance (as a result of inadequate dietary intake and/or elevated energy expenditure due to increased work of breathing), ageing, etc. [129]. Many of these factors actually interfere with the muscle protein metabolism by reducing contractile protein synthesis and/or triggering its degradation, which ultimately leads to muscle atrophy and weakness [129].

In contrast to severe COPD, in which weight loss and skeletal muscle mass wasting/dysfunction are frequent findings, patients with mild-to-moderate COPD often tend to be overweight or obese with coexisting metabolic syndrome [146, 147]. There is some evidence of increasing prevalence of overweight and obesity in COPD – in the study by Eisner et al. [146] there were 20% overweight and 54% obese patients in a COPD cohort with a mean FEV_1 58%, and in the study by Cecere et al. [148] 32% of patients were overweight (mean FEV_1 50%) and 38% obese (mean FEV_1 55%). In patients who are overweight or obese a higher FM is associated with slower walking speed, greater likelihood of functional limitation and increased cardiovascular risk, while higher lean mass-to-fat mass ratio is related to the faster walking speed and less limitation [146, 149, 150].

Physical activity together with many other factors (e.g. age, gender, genetics, ethnicity, dietary intake, different diseases and medications) affect body composition, but their relation is complex: body composition is influenced by exercise capacity and physical activity, and vice versa, changes in the body composition (e.g. muscle mass waste or gain, fat tissue increase) may have significant impact on physical performance [151-153]. There is strong evidence that COPD patients have a lower level and intensity of daily physical activity compared to age-matched healthy controls, and even compared to patients with other chronic diseases [115, 154]. Although physical inactivity may be present even in a mild disease, it becomes more common with increasing COPD severity so that sedentary lifestyle is one of the characteristics of advanced COPD [116, 155]. In most patients physical performance is limited by the two cardinal symptoms – dyspnoea and/or fatigue. Factors contributing to exercise intolerance may be divided into three main categories [79]:

1) Ventilatory limitation - includes airflow limitation, dynamic hyperinflation, pulmonary gas exchange abnormalities, respiratory muscle dysfunction;

2) Cardiac dysfunction - includes cardiovascular deconditioning, right ventricular overload/hypertrophy/failure as a result of an elevated pulmonary vascular resistance, compromised left ventricular filling due to right ventricular hypertrophy and interventricular septal shifting, tachyarrhythmias;

3) Peripheral muscle dysfunction - discussed previously.

In addition, exercise tolerance and physical activity may also be influenced by other factors, such as poor motivation, coexistence of anxiety/depression, sociodemographic factors (e.g. socioeconomic status, education level, ethnicity), environmental conditions (e.g. weather, climate, geographical location), day of the week etc. [132].

Low physical activity and exercise intolerance have multiple negative clinical implications in COPD – they are associated with functional limitation and disability, impaired health-related quality of life, increased exacerbation risk, higher hospital admission rate, occurrence of anxiety and depression, and increased mortality [117-120, 156-158].

Although the clinicians are increasingly becoming aware of the importance of physical activity, exercise capacity and nutritional status in patients with COPD, in clinical practice these are rarely assessed because their determination is time consuming and requires special equipment. However, the evaluation of physical performance and body composition would

improve overall medical care of COPD patients and enable detection of those who would benefit most from the pulmonary rehabilitation program and nutritional counselling.

Nutrition, metabolism and physical activity have been the topic of intense scientific research in many chronic diseases including COPD, but previous studies have mainly investigated either physical performance or nutritional status and their independent association with COPD severity and prognosis [118, 142, 155]. The main aim of the present study was to investigate the relationship between nutritional status and physical performance in COPD, and to assess the differences in the nutritional status and body composition in patients with poor and normal physical performance.

2. HYPOTHESIS

The hypothesis of the present research is that COPD patients with poor physical performance have deficient nutritional status. This hypothesis is supported by the previous observations that patients with COPD often have reduced physical activity / exercise capacity, and that nutritional abnormalities and body composition changes are common extrapulmonary manifestations of this disease.

3. AIMS AND PURPOSE OF THE RESEARCH

General aim

To compare nutritional status / body composition in COPD patients with poor and normal physical performance assessed by the 6MWD, gait speed and daily physical activity

Specific aims

1) To identify factors associated with malnutrition in patients with COPD

2) To evaluate physical performance in patients with different forms of nutritional abnormality

3) To evaluate the association between physical activity and severity of COPD assessed by the lung function, symptoms severity and exacerbation frequency

4) To evaluate the correlation between daily physical activity and simple tests of muscle function/mass

5) To evaluate the association between physical activity, body composition and health-related quality of life

6) To evaluate the association between physical activity, body composition and anxiety/depression

4. MATERIALS AND METHODOLOGY

4.1. Subjects

A cross-sectional observational study was conducted in outpatients with moderate to very severe COPD in the Dubrava University Hospital, Zagreb, Croatia, from February 2015 to June 2016. Patients' participation in the study was on a voluntary basis, and the participants met the following **inclusion criteria**:

- Age ≥ 40 years
- Documented COPD history ≥ 1 year in accordance with the criteria set by the GOLD [54]
- Smokers or ex-smokers with smoking history ≥ 10 pack-years
- Post-bronchodilator spirometry with $FEV_1/FVC < 0.70$, and $FEV_1 < 80\%$ predicted
- Clinically stable (without exacerbations) for at least 3 months prior to enrolment

The **exclusion criteria** were concomitant diseases and conditions that might influence nutritional status and/or physical performance:

- Unstable cardiac disease (symptomatic ischaemic heart disease, heart failure, uncontrolled arrhythmias)
- Peripheral artery disease with intermittent claudication
- Limitation in walking due to neurological or osteomuscular disorder
- Active malignant disease
- COPD exacerbation within three months prior to enrolment
- Asthma
- Active respiratory disease other than COPD
- End-stage renal disease
- Decompensated liver cirrhosis
- Uncontrolled diabetes
- Uncontrolled thyroid pathology
- Dementia
- Sustained systemic corticosteroid therapy

The study was approved by the Ethics Committee of the Dubrava University Hospital, Zagreb, and by the Ethics Committee of the School of Medicine, University of Zagreb. Each participant gave written informed consent.

4.2. Study design

Two study visits were scheduled within 7±2 days. At the first visit all protocol-related procedures and measurements were performed including demographic and clinical data collection, pulmonary function tests, nutritional assessment, and physical performance evaluation. Tests of physical performance preceded the lung function tests.

4.2.1. Demographic and clinical data

Age, sex, smoking history expressed by pack-years, treatment and duration of COPD were recorded, along with the number of COPD exacerbations in the previous year. Based on the medical history and electronic health care database the information was obtained on moderate COPD exacerbations that required treatment with antibiotics and/or oral corticosteroids in the outpatient settings, and severe exacerbations that required hospitalisations. Comorbidities were evaluated according to the Charlson index [159]. The mMRC dyspnoea scale (**Table 2**) [36] and CAT™ (**Figure 1**) [37] were used for the assessment of symptoms severity. Psychological status was evaluated by the Hospital Anxiety and Depression Scale (HADS), a fourteen item scale of which seven items are related to anxiety and the remaining seven to depression [160]. The Anxiety and Depression subscale scores enable classification into four groups: "normal" (0-7), "mild" (8-10), "moderate" (11-14), and "severe" (15-21). Health-related quality of life was assessed with the EuroQol questionnaire (EQ-5D-5L) that includes the visual analogue scale (VAS), descriptive system and calculation of index values [161].

4.2.2. Pulmonary function tests

Pre- and post-bronchodilator spirometry, single-breath DLCO measurement, and body plethysmography with lung volumes (Vmax Series Software Version 20-7, VIASYS Healthcare Inc., SensorMedics Corporation, USA) were performed according to standards set by the ATS/ERS using established reference values [33, 162, 163]. The following lung function parameters in absolute and percent predicted values were recorded: FEV_1, FVC, FEV_1/FVC ratio, DLCO, diffusing capacity of the lung for carbon monoxide per litre of alveolar volume (DLCO/VA), vital capacity (VC), TLC, RV, RV/TLC ratio.
Patients were classified as GOLD grade 2, 3 or 4 according to the severity of airflow limitation based on the post-bronchodilator FEV_1 (**Table 1**) [5]. The GOLD guidelines 2011-2016 [54] were applied for ABCD categorisation with respect to the post-bronchodilator FEV_1, exacerbation history, and symptoms severity assessed by the mMRC dyspnoea scale and the CAT™ score (**Figure 2**).

Arterial blood gases were determined in subjects under resting conditions breathing room air (RAPIDLAB 348 pH/Blood Gas Analyzer, Siemens Medical Solutions Diagnostics, USA).

4.2.3. Nutritional assessment

Body weight was measured to the nearest 0.1 kg, height to the nearest 0.5 cm and expressed in meters, and the BMI was calculated as weight/height squared (kg/m^2). The subjects were categorised into four groups based on the BMI: underweight (<21 kg/m^2), normal weight (≥ 21, <25 kg/m^2), overweight (≥ 25, <30 kg/m^2), and obese (≥ 30 kg/m^2). The choice of a cut-off <21 kg/m^2 for underweight is in line with the recommendation given by the ATS/ERS based on previous studies reporting a higher mortality in COPD patients with BMI <21 kg/m^2 [101-103].

Additional anthropometric measurements and calculations were performed by routine methods [100, 164, 165]: waist, hip, and calf circumference (CC) (cm); waist-to-hip ratio; mid-upper arm circumference (MUAC) (cm); triceps skin fold (TSF) (measured in mm with the Harpenden Skinfold Caliper, British Indicators LTD, England); mid-arm muscle circumference (MAMC) calculated by the equation MAMC (cm) = MUAC (cm) – 0.314 x

TSF (mm); arm muscle area (AMA) calculated by the equation AMA (cm^2) = [MUAC (cm) – 0.314 x TSF (mm)]^2 / (4 x 3.14). Measurements of the MUAC, TSF and CC were taken on the right side of the body. All anthropometric measurements were performed twice, except for the TSF, which was measured in triplicate, and the mean values were recorded.

Body composition was assessed by the DEXA total body scan (Lunar PRODIGY Primo, enCORE Software version 11.1, GE Healthcare), as previously described in section 1.2., and the following parameters were obtained: LM (kg), FFM (kg), FM (kg), fat proportion (%), BMC (kg), BMD (g/cm^2), and the T-score. Additionally, the lean mass index (LMI), the FFMI, and the fat mass index (FMI) were calculated by dividing the LM, FFM, and FM, respectively, by height squared and expressed in kg/m^2.

For rapid clinical assessment of nutritional status the MNA questionnaire was used, and patients were stratified in three categories according to the MNA score: "normal nutritional status" (24-30 points), "at risk of malnutrition" (17-23.5 points), and "malnourished" (<17 points) [166].

Venous blood samples were collected and analysed for the following biomarkers using commercially available assays: total lymphocyte count (Siemens ADVIA 2120i, Siemens Healthcare Diagnostics [Shanghai], Walpole, NJ, USA), serum albumin (Beckman Coulter AU2700 plus, Miami, USA), prealbumin (Beckman Coulter AU680, Miami, USA), high-sensitivity C-reactive protein (hs-CRP) (Beckman Coulter AU2700 plus, Miami, USA), and 25-hydroxyvitamin D (Siemens ADVIA Centaur XP, Siemens Healthcare Diagnostics [Shanghai], Walpole, NJ, USA). All samples were analysed at the central laboratory of the Dubrava University Hospital.

4.2.4. Physical performance and muscle function assessment

In the evaluation of physical performance and peripheral muscle function seven different methods were used.

The 30-second chair stand test [126] and the timed up and go test [128] were performed as previously described in section 1.3. The timed up and go test was repeated with some rest in between if needed, and the faster of the two times was recorded.

The maximal handgrip strength (kg) was measured with a handheld dynamometer (KERN MAP 80K1, Version 1.2 08/2012, KERN & Sohn GmbH, Germany) in a sitting position while the hand was unsupported with the elbow at 90° flexion and the underarm and wrist in neutral positions [167]. The highest of the six measurements (three with each hand) was used in the analysis.

Ultrasound measurement of quadriceps rectus femoris cross-sectional area (RF_{CSA}) was done by the radiologist using a B-mode ultrasonography with an 8 MHz, 5.6 cm linear transducer array (General Electric Logiq E9, General Electric Company, WI, USA) according to a technique described by Seymour et al. [168]. Briefly, the patient was in a supine position with the rested right leg supported in passive extension, and the transducer was placed perpendicular to the long axis of the thigh on its superior aspect, three-fifths of the distance along a line from the anterior superior iliac spine to the superior patellar border. RF_{CSA} was calculated using a planimetric technique after the echogenic line of the rectus femoris was outlined manually on a frozen image, and the average of the three consecutive measurements was recorded.

The 4MGS was measured as previously described in section 1.3. [124].

The 6MWT was performed according to the ATS guidelines as previously explained in section 1.3. [123], and the measured 6MWD was used in the analysis. During both walk tests the subjects were allowed to use their usual walking aids (e.g. cane), and those with chronic respiratory insufficiency (SpO_2 < 90% at rest breathing room air) were provided with supplemental oxygen from a portable oxygen cylinder that was carried by the examiner during the tests.

At the end of the first visit the patients were supplied with the StepWatch Activity Monitor® (SAM) (Modus Health IIc, Washington DC, USA), an ankle-worn accelerometer for the assessment of physical activity. The SAM does not provide on-instrument feedback of steps walked, and its accuracy in detecting steps has been previously demonstrated in subjects with a range of activity levels, including patients with COPD [118, 137]. Patients were instructed to wear the SAM during 7±2 consecutive days except while washing and sleeping, to perform physical activity as usual, and to return the device at the second study visit when the data were downloaded. The days of the study visits, as well as no-wear days (< 8 hours of wear time) were excluded from the analysis, and the average daily step count was recorded.

4.3. Statistical analysis

Descriptive statistics were used to describe the study population. Categorical variables are presented as absolute numbers (percentages), and continuous variables as means ± standard deviations (SD), or medians (1^{st} quartile; 3^{rd} quartile) in the case of non-normal distribution. For each measure of physical performance (6MWD, 4MGS, daily physical activity) the results were divided in the "poor" and "normal" group with cut-offs of 350 m for the 6MWD, 0.8 m/s for the 4MGS and the median for the average daily step count in line with previous studies [124, 169, 170]. Demographic, clinical and nutritional variables were compared between the "poor" and "normal" group. Categorical variables were compared with the Chi square or Fisher's test, while the Student's t or Mann-Whitney U test were used for comparison of continuous variables. The association between independent variables and "poor" physical performance was assessed using univariate and multivariate stepwise logistic regression analysis. Variables showing a p-value <0.1 in the univariate analysis were included in the multivariate models. The correlation between variables was analysed by Pearson's or Spearman's rank correlation tests. All the tests were conducted at a significance level of $\alpha = 0.05$. The SPSS version 20 software (IBM Corp., Armonk, NY) was used for all the analyses.

5. RESULTS

5.1. Patients' characteristics

A total of 112 patients were recruited, and one was excluded because of non-compliance, leaving 111 patients for analysis. The patients' characteristics are presented in **Table 4**. The study population was comprised of 76 (68.5%) men and 35 (31.5%) women, and the mean ± SD age was 67.7 ± 7.8 years (range 48-88 years). There were 39 (35%) smokers and 72 (65%) ex-smokers with a cumulative smoking history of 43.9 ± 24.8 pack-years.

On average, patients had been treated for COPD 9.1 ± 7.4 years, and 42 (37.8%) patients had had at least one moderate or severe COPD exacerbation in the previous year (mean number of moderate/severe exacerbations was 1.2 ± 1.4, maximum 8). According to the pulmonary function tests the average patient had moderately severe airflow obstruction (mean post-bronchodilator FEV_1 48.9 ± 15.0% pred., FEV_1/FVC 0.43 ± 0.11), lung hyperinflation (TLC 110.5 ± 24.6% pred., RV 159.5 ± 62.2% pred., RV/TLC 55.0 ± 13.2%, RV/TLC 134.5 ± 31.6% pred.), mild-to-moderate decrease in diffusing capacity (DLCO 50.5 ± 19.3% pred., DLCO/VA 70.3 ± 22.9% pred.), and mild hypoxemia (pO_2 9.2 ± 1.4 kPa, SatO2 93.2 ± 3.7%). Regarding symptoms severity the mean CAT score was 17.9 ± 6.4 and mMRC dyspnoea grade 2.0 ± 1.0.

The Charlson comorbidity index was 1.8 ± 1.0, while the mean HADS scores on anxiety and depression were within the normal range. The health-related quality of life of the study population was impaired with an EQ-5D-5L index value of 0.7 ± 0.2, and EQ-5D-5L VAS score of 57.9 ± 15.2.

GOLD categorisation of the study population is depicted in **Figure 7.** According to the severity of airflow obstruction the most prevalent were GOLD 2 (47%) and GOLD 3 (42%) categories, and when symptoms and exacerbations were considered the majority of patients were in the GOLD groups B (29%) and D (61%). Frequency of the different therapies used in the study population are presented in **Figure 8**. LABA, LAMA and SABA were the most commonly used COPD medications.

Table 4. Baseline characteristics of the study population (n = 111).

Demographic and clinical parameters		Pulmonary function	
Age, years	67.7 ± 7.8	Post FVC, % pred.	90.8 ± 19.0
Sex		Post FEV_1, % pred.	48.9 ± 15.0
Male Female	76 (68.5) 35 (31.5)	Post FEV_1/FVC	0.43 ± 0.11
Smoking history, pack-years	43.9 ± 24.8	VC, % pred.	85.1 ± 19.1
Treated for COPD, years	9.1 ± 7.4	TLC, % pred.	110.5 ± 24.6
COPD exacerbations in the previous year	1.2 ± 1.4	RV, % pred.	159.5 ± 62.2
mMRC dyspnoea scale	2.0 ± 1.0	RV/TLC, %	55.0 ± 13.2
CAT score	17.9 ± 6.4	RV/TLC, % pred.	134.5 ± 31.6
Charlson comorbidity index	1.8 ± 1.0	DLCO, % pred.	50.5 ± 19.3
HADS Anxiety score	6.8 ± 4.1	DLCO/VA, % pred.	70.3 ± 22.9
HADS Depression score	7.3 ± 3.5	pO_2, kPa	9.2 ± 1.4
EQ-5D-5L index value	0.7 ± 0.2	pCO_2, kPa	5.6 ± 0.7
EQ-5D-5L VAS	57.9 ± 15.2	$SatO_2$, %	93.2 ± 3.7

Data are presented as means ± standard deviation or numbers (%), as appropriate.

Abbreviations: CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; DLCO: diffusing capacity of the lung for carbon monoxide; DLCO/VA: diffusing capacity of the lung for carbon monoxide per litre of alveolar volume; EQ-5D-5L: EuroQol questionnaire; FEV_1: forced expiratory volume in one second; FEV_1/FVC: ratio of forced expiratory volume in one second to forced vital capacity; FVC: forced vital capacity; HADS: Hospital Anxiety and Depression Scale; mMRC: modified Medical Research Council; pCO_2: partial pressure of carbon-dioxide in arterial blood; pO_2: partial pressure of oxygen in arterial blood; Post: post-bronchodilator; pred: predicted; RV: residual volume; RV/TLC: ratio of residual volume to total lung capacity; $SatO_2$: arterial oxygen saturation; TLC: total lung capacity; VAS: visual analogue scale; VC: vital capacity.

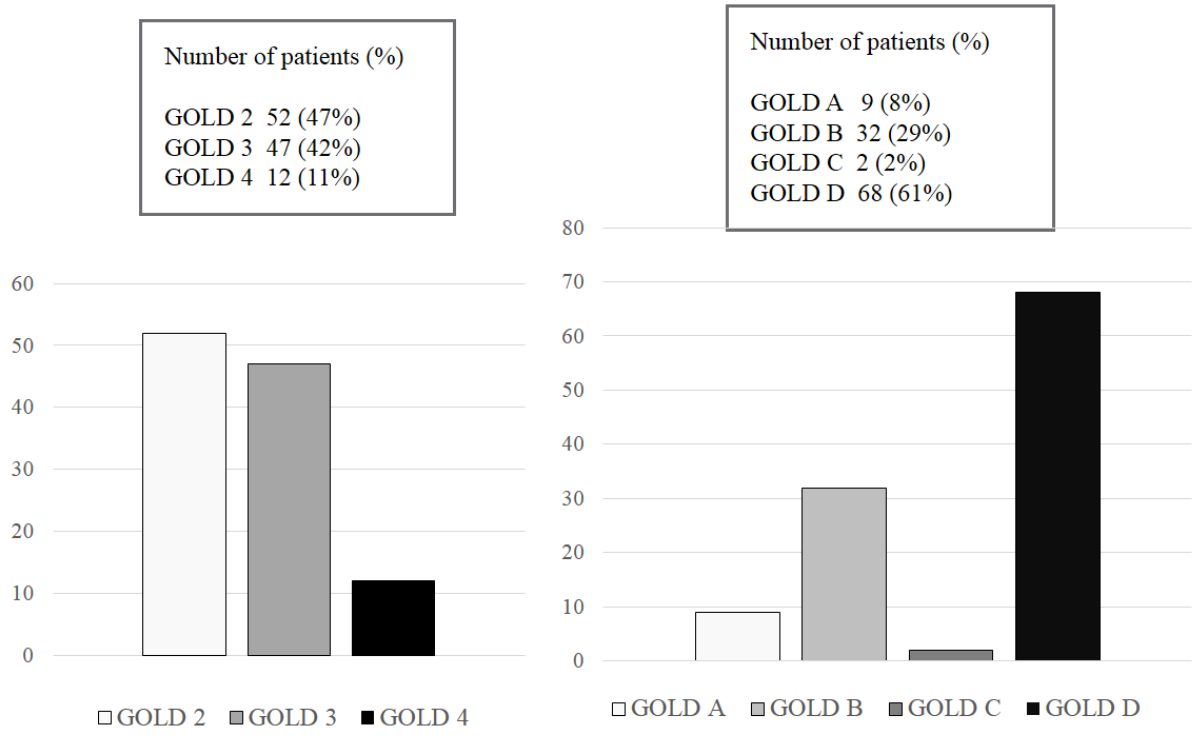


Figure 7. GOLD categorisation of the study population.

Abbreviations: GOLD: Global Initiative for Chronic Obstructive Lung Disease.

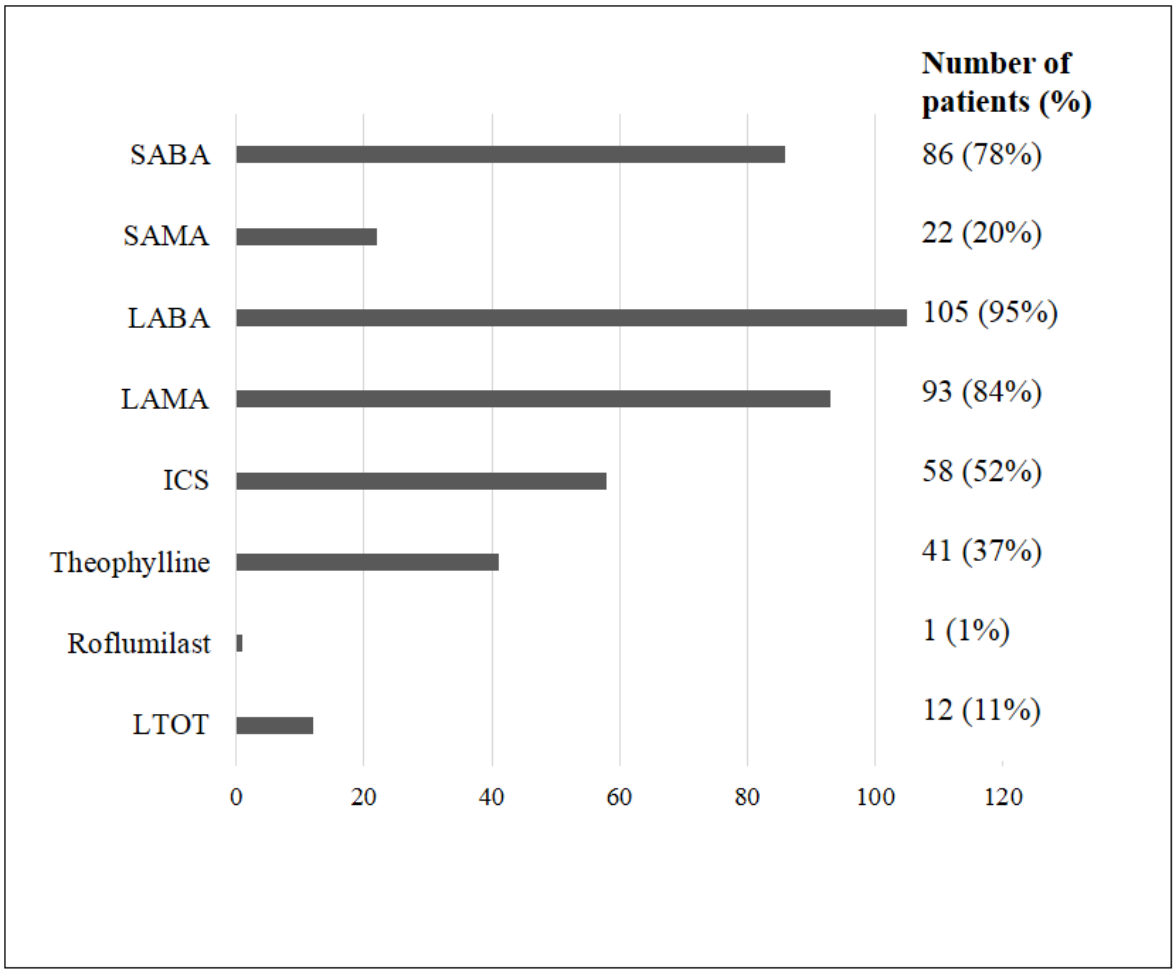


Figure 8. Frequency of different therapeutic options in the study population.

Abbreviations: ICS: inhaled corticosteroids; LABA: long-acting beta2-agonists; LAMA: long-acting muscarinic antagonists; LTOT: long-term oxygen therapy; SABA: short-acting beta2-agonists; SAMA: short-acting muscarinic antagonists.

5.2. Physical performance of the study population

The results of the physical performance and muscle function tests for the study population are presented in **Table 5**. On average, in the 6MWT patients achieved 376 ± 119 m (range 78-627 m), and 0.89 ± 0.22 m/s (range 0.33-1.35 m/s) in the 4MGS. The average daily step count for the study population was 8059 ± 4757 steps/day, but ranged from extremely poor (minimum 220 steps/day) to excellent (maximum 23342 steps/day).

A very strong correlation was found between the 6MWD and the 4MGS (Pearson coefficient $r = 0.852$, $p<0.001$). The correlation between physical activity and the 6MWD was strong ($r = 0.681$, $p<0.001$), while the correlation between physical activity and the 4MGS was moderate ($r = 0.451$, $p<0.001$).

The mean number of rises in the 30-second chair stand test was 11 ± 3, while the mean result in the timed up and go test for the study population was 10.3 ± 3.3 s. The rest of the variables related to muscle function can be found in **Table 5.**

Table 5. Physical performance and muscle function tests results for the study population.

Parameter	
6-minute walk distance, m	376 ± 119
4-metre gait speed, m/s	0.89 ± 0.22
Physical activity, steps/day	8059 ± 4757
30-second chair stand test, number of rises	11 ± 3
Timed up and go test, s	10.3 ± 3.3
Handgrip strength – right hand, kg	30.7 ± 10.1
Handgrip strength – left hand, kg	29.1 ± 9.2
Rectus femoris cross-sectional area, cm^2	6.0 ± 1.8

Data are presented as means ± standard deviation.

5.3. Nutritional status of the study population

The mean BMI was 27.1 ± 5.8 kg/m^2, and MNA score 24.0 ± 3.3. The stratification of the study population based on the BMI and MNA scores is depicted in **Figure 9**.

Fig 9A. Nutritional status of the study population assessed by the body mass index

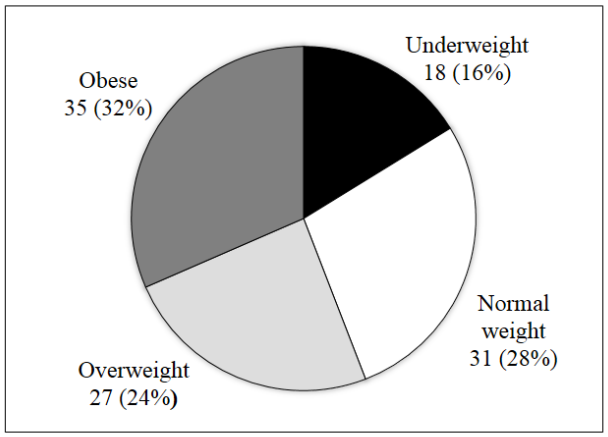


Fig 9B. Nutritional status of the study population assessed by the Mini Nutritional Assessment questionnaire

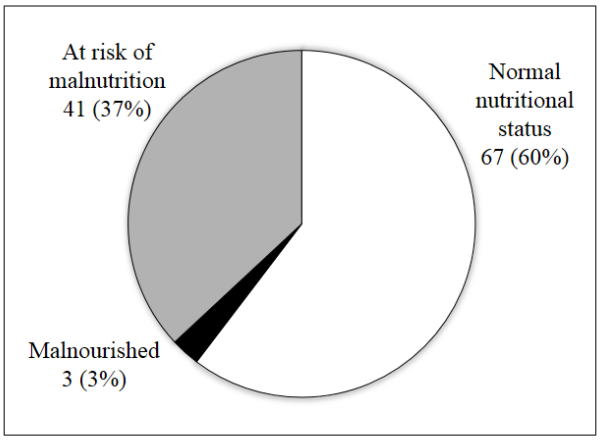


Figure 9. Nutritional status of the study population assessed by the body mass index (**Fig 9A**) and the Mini Nutritional Assessment questionnaire (**Fig 9B**). Data are presented as number of patients (%) for each category.

The average values of the anthropometric measurements, MNA score, DEXA parameters and laboratory findings of the study population are presented in **Table 6**. Mean serum vitamin D concentration was 40.0 ± 18.2 nmol/L, and 86 patients (77%) were vitamin D deficient (serum vitamin D level < 50 nmol/L).

The mean FFMI for the study population was 18.3 ± 2.7 kg/m^2, and FFM depletion (FFMI <15 kg/m^2 for women, <16 kg/m^2 for men,) was more prevalent in women (37%) than in men (4%) – **Figure 10**.

Table 6. Nutritional parameters of the study population.

Anthropometric measurements and MNA score		DEXA and laboratory parameters	
Body mass index, kg/m^2	27.1 ± 5.8	Lean mass index, kg/m^2	17.4 ± 2.6
		Fat-free mass index, kg/m^2	18.3 ± 2.7
Waist circumference, cm	97.3 ± 15.2	Fat mass index, kg/m^2	8.8 ± 4.1
Hip circumference, cm	99.4 ± 10.0	Fat proportion, %	30.9 ± 9.7
Waist-to-hip ratio	1.0 ± 0.1	Bone mineral content, kg	2.6 ± 0.6
Calf circumference, cm	35.6 ± 4.2	Bone mineral density, g/cm^2	1.1 ± 0.1
Mid-upper arm circumference, cm	29.8 ± 4.5	T-score	-1.0 ± 1.5
Triceps skin fold, mm	16.8 ± 8.0	Lymphocyte count, x10^9/L	2.0 ± 0.7
Mid-arm muscle circumference, cm	24.5 ± 3.2		
Arm muscle area, cm^2	48.6 ± 12.5	Albumin, g/L	46.2 ± 3.4
MNA score	24.0 ± 3.3	Prealbumin, g/L	21.7 ± 4.7
		hs-CRP, mg/L	6.9 ± 11.3
		Vitamin D, nmol/L	40.0 ± 18.2

Data are presented as means ± standard deviation.

Abbreviations: DEXA: dual energy X-ray absorptiometry; hs-CRP: high-sensitivity C-reactive protein; MNA: Mini Nutritional Assessment.

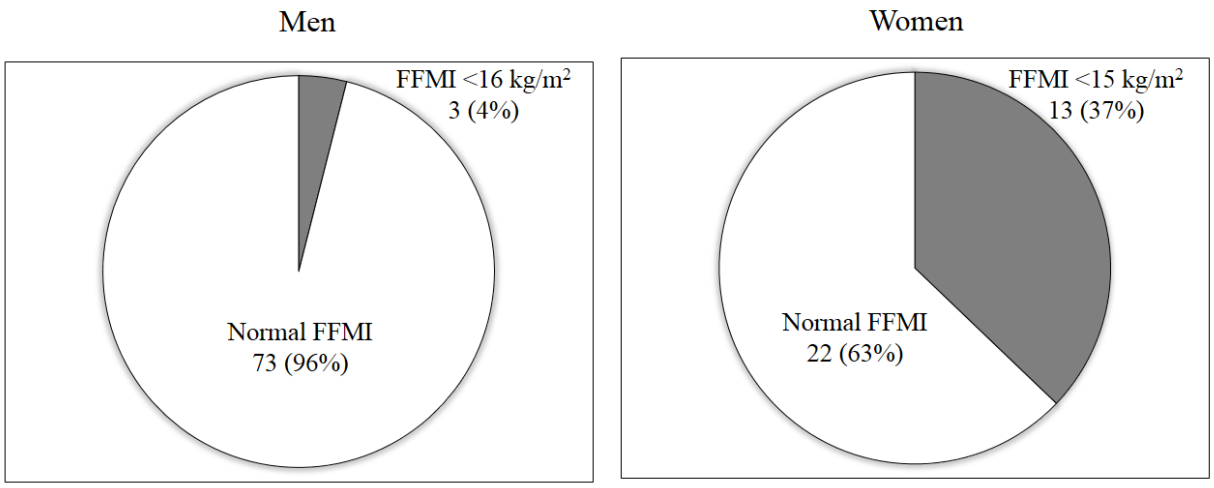


Figure 10. Prevalence of reduced fat-free mass index (FFMI) in male and female patients. Data are presented as number of patients (%).

5.4. Comparison of patients with poor and normal exercise capacity

Fifty-three (48%) patients had poor exercise capacity defined by the 6MWD ≤ 350 m, and in comparison to those with normal exercise capacity (6MWD > 350 m) they were significantly older, had worse lung function, a higher CAT score and a higher mMRC dyspnoea level ($p<0.05$) (**Table 7**). Additionally, they had been treated longer for COPD, had more exacerbations, worse health-related quality of life, as well as a higher HADS Depression score ($p<0.05$). There was a higher proportion of women in the group of patients with 6MWD ≤ 350 m than in the group with 6MWD > 350 m. Patients with poor exercise capacity also had a significantly slower gait speed and lower daily step counts (**Table 7**).

Comparison of nutritional parameters is presented in **Table 8**. Patients with low exercise capacity had a lower LMI, FFMI, BMC, BMD, and T-score ($p<0.05$). Among anthropometric measurements they had a significantly smaller CC, MUAC, MAMC and AMA. Furthermore, they had a lower MNA score, as well as lower serum albumin and prealbumin levels ($p<0.05$).

The factors that were independently and significantly related to low exercise capacity in the multivariate analysis were age, previous exacerbations, RV/TLC ratio, DLCO/VA, and mMRC dyspnoea level (**Table 9**). The multivariate model showed good goodness-of-fit (P-value of 0.608 in the Hosmer-Lemeshow test) and a good predictive power (area under the curve [AUC] = 0.922; $p<0.001$) (**Figure 11**).

Table 7. Characteristics of patients with poor and normal exercise capacity based on the 6-minute walk distance (6MWD).

Parameter	Patients with 6MWD ≤ 350 m (n=53)	Patients with 6MWD > 350 m (n=58)	p-value
Age, years	70.1 ± 7.5	65.5 ± 7.4	**0.002***
Sex Male Female	 30 (56.6) 23 (43.4)	 46 (79.3) 12 (20.7)	**0.010***
Smoking history, pack-years	41.5 ± 24.2	46.2 ± 25.3	0.325
Treated for COPD, years	12.1± 7.4	6.3 ± 6.3	**<0.001***
COPD exacerbations in the previous year	1.8 ± 1.5	0.7 ± 1.0	**<0.001***
mMRC dyspnoea scale	2.6 ± 0.8	1.4 ± 0.7	**<0.001***
CAT score	20.9 ± 5.9	15.2 ± 5.7	**<0.001***
Post FVC, % pred.	87.6 ± 20.3	93.8 ± 17.5	0.087
Post FEV_1, % pred.	43.2 ± 13.6	54.1 ± 14.5	**<0.001***
TLC, % pred.	115.4 ± 28.3	106.2 ± 20.1	0.051
RV, % pred.	177.6 ± 66.4	143.6 ± 53.9	**0.004***
RV/TLC, %	60.5 ± 13.3	50.2 ± 11.2	**<0.001***
DLCO/VA, % pred.	63.4 ± 21.3	76.6 ± 22.8	**0.002***
pO_2, kPa	8.7 ± 1.6	9.7 ± 1.2	**0.001***
pCO_2, kPa	5.7 ± 0.8	5.5 ± 0.6	0.108
Charlson comorbidity index	1.8 ± 1.1	1.7 ± 1.0	0.946
HADS Anxiety score	7.6 ± 4.3	6.1 ± 3.8	0.055
HADS Depression score	8.5 ± 3.7	6.2 ± 3.0	**<0.001***
EQ-5D-5L index value	0.7 ± 0.2	0.8 ± 0.1	**<0.001***
EQ-5D-5L VAS	51.9 ± 15.0	63.4 ± 13.4	**<0.001***
4MGS, m/s	0.74 ± 0.18	1.04 ± 0.14	**<0.001***
6MWD, m	274 ± 78	469 ± 59	**<0.001***
Physical activity, steps/day	5366 ± 3080	10519 ± 4703	**<0.001***

Data are presented as means ± standard deviation or numbers (%), as appropriate.

***** statistically significant ($p < 0.05$)

Abbreviations: CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; DLCO/VA: diffusing capacity of the lung for carbon monoxide per litre of alveolar volume; EQ-5D-5L: EuroQol questionnaire; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; HADS: Hospital Anxiety and Depression Scale; 4MGS: 4-metre gait speed; mMRC: modified Medical Research Council; 6MWD: 6-minute walk distance; pCO_2: partial pressure of carbon-dioxide in arterial blood; pO_2: partial pressure of oxygen in arterial blood; Post: post-bronchodilator; pred: predicted; RV: residual volume; RV/TLC: ratio of residual volume to total lung capacity; TLC: total lung capacity; VAS: visual analogue scale.

Table 8. Comparison of nutritional status between patients with poor and normal exercise capacity based on the 6-minute walk distance (6MWD).

Parameter	Patients with 6MWD ≤ 350 m (n=53)	Patients with 6MWD > 350 m (n=58)	p-value
Body mass index, kg/m^2	26.6 ± 6.3	27.6 ± 5.3	0.388
Waist circumference, cm	95.3 ± 15.4	99.1 ± 14.9	0.190
Hip circumference, cm	98.5 ± 10.3	100.3 ± 9.7	0.343
Waist-to-hip ratio	1.0 ± 0.1	1.0 ± 0.1	0.242
Calf circumference, cm	34.5 ± 4.1	36.5 ± 4.2	**0.013***
Mid-upper arm circumference, cm	28.8 ± 4.6	30.7 ± 4.2	**0.026***
Triceps skin fold, mm	16.6 ± 8.3	17.0 ± 7.8	0.776
Mid-arm muscle circumference, cm	23.6 ± 3.2	25.3 ± 3.0	**0.003***
Arm muscle area, cm^2	45.0 ± 12.1	51.8 ± 12.1	**0.004***
Lean mass index, kg/m^2	16.7 ± 2.6	18.0 ± 2.4	**0.006***
Fat-free mass index, kg/m^2	17.6 ± 2.8	19.0 ± 2.5	**0.006***
Fat mass index, kg/m^2	8.9 ± 4.4	8.6 ± 3.8	0.662
Fat proportion, %	32.0 ± 10.2	29.9 ± 9.2	0.266
Bone mineral content, kg	2.4 ± 0.6	2.7 ± 0.6	**0.003***
Bone mineral density, g/cm^2	1.07 ± 0.1	1.15 ± 0.1	**0.002***
T-score	-1.4 ± 1.4	-0.7 ± 1.5	**0.013***
MNA score	23.1 ± 3.5	24.9 ± 2.9	**0.004***
Lymphocyte count, x10^9/L	1.9 ± 0.7	2.0 ± 0.7	0.359
Albumin, g/L	45.4 ± 3.0	46.8 ± 3.6	**0.026***
Prealbumin, g/L	20.6 ± 4.8	22.7 ± 4.5	**0.017***
hs-CRP, mg/L	7.8 ± 13.1	6.1 ± 9.5	0.415
Vitamin D, nmol/L	39.1 ± 16.5	40.9 ± 19.7	0.605

Data are presented as means ± standard deviation.

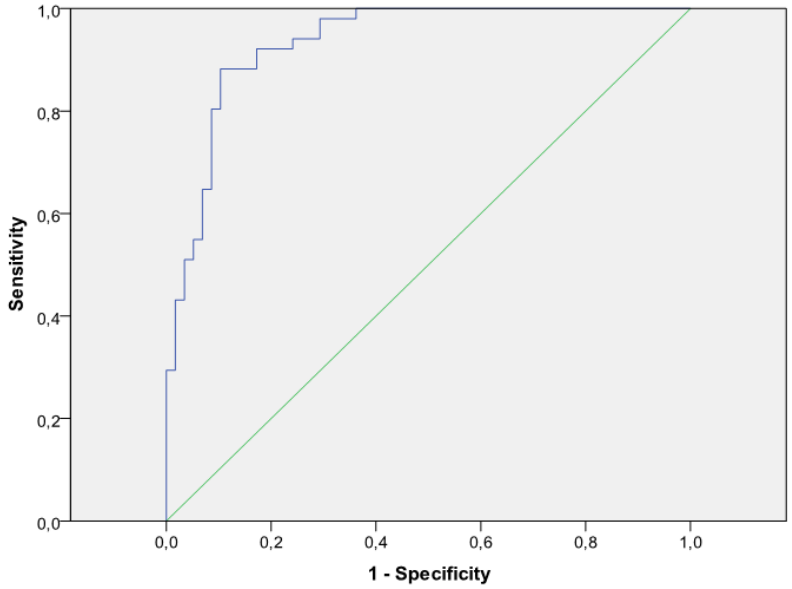
***** statistically significant ($p < 0.05$)

Abbreviations: hs-CRP: high-sensitivity C-reactive protein; MNA: Mini-Nutritional Assessment; 6MWD: 6-minute walk distance.

Table 9. Univariate and multivariate logistic regression analysis for the prediction of poor exercise capacity defined by the 6-minute walk distance ≤ 350 m.

	Univariate		Multivariate	
Variable	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Age (years)	1.086 (1.029-1.147)	0.003	1.229 (1.090-1.385)	<0.001
Sex (female)	2.939 (1.274-6.780)	0.011		
Previous exacerbations	4.384 (1.898-10.168)	0.001	4.216 (1.064-16.700)	0.040
FEV_1 (% pred.)	0.983 (0.963-1.003)	0.089		
RV/TLC (%)	1.079 (1.038-1.182)	0.001	1.026 (1.002-1.052)	0.007
DLCO/VA (% pred.)	0.973 (0.955-0.991)	0.003	0.939 (0.899-0.980)	0.007
HADS Depression score	2.138 (0.981-4.596)	0.050		
CAT score	1.181 (1.095-1.275)	<0.001		
EQ-5D-5L index value	0.007 (0.001-0.102)	0.001		
mMRC dyspnoea scale	9.382 (3.690-23.851)	0.001	7.389 (2.600-20.994)	<0.001
MNA	0.835 (0.735-0.908)	0.005		
FFMI (kg/m^2)	0.814 (0.700-0.954)	0.008		
LMI (kg/m^2)	0.809 (0.691-0.947)	0.008		
BMD (g/cm^2)	0.010 (0.001-0.230)	0.004		
pO_2 (kPa)	0.809 (0.772-0.820)	0.001		
Albumin (g/L)	0.873 (0.772-0.988)	0.032		
Prealbumin (g/L)	0.904 (0.831-0.984)	0.020		
Arm muscle area (cm^2)	0.954 (0.923-0.987)	0.006		
Calf circumference (cm)	0.889 (0.808-0.978)	0.016		

Abbreviations: BMD: bone mineral density; CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; CI: confidence interval; DLCO/VA: diffusing capacity of the lung for carbon monoxide per litre of alveolar volume; EQ-5D-5L: EuroQol questionnaire; FEV_1: forced expiratory volume in one second; FFMI: fat-free mass index; HADS: Hospital Anxiety and Depression Scale; LMI: lean mass index; mMRC: modified Medical Research Council; MNA: Mini-Nutritional Assessment; 6MWD: 6-minute walk distance; OR: odds ratio; pO_2: partial pressure of oxygen in arterial blood; pred: predicted; RV/TLC: ratio of residual volume to total lung capacity.



AUC	SE	95% CI	p-value
0.922	0.023	0.885 to 0.976	<0.001

Figure 11. Receiver operating characteristic analysis of significant variables derived from the multivariate logistic regression model and their capacity to predict poor exercise capacity defined by the 6-minute walk distance ≤ 350 m. The model includes age, moderate/severe exacerbations in the previous year, ratio of residual volume to total lung capacity (RV/TLC), diffusing capacity of the lung for carbon monoxide per litre of alveolar volume (DLCO/VA), and mMRC dyspnoea level.

Abbreviations: AUC: area under the curve; CI: confidence interval; SE: standard error.

5.5. Comparison of patients with slow and normal gait speed

Thirty-six (32%) patients had slow gait speed defined by the 4MGS < 0.8 m/s. When compared to those with normal gait speed, patients with slow gait speed were significantly older, had a longer history of COPD, worse lung function, more frequent exacerbations, and a higher symptom burden assessed by the CAT and the mMRC dyspnoea scale ($p<0.05$) (**Table 10**). Moreover, patients with slow gait speed had worse health-related quality of life based on the results in the EuroQol questionnaire, and a higher HADS Depression score ($p<0.05$). Women were more prevalent in the group of patients with 4MGS < 0.8 m/s than in the group with 4MGS ≥ 0.8 m/s. In addition, patients with slow gait speed had a significantly worse exercise capacity (i.e. shorter 6MWD) and lower daily step counts (**Table 10**).

Comparison of nutritional parameters is presented in **Table 11**. Patients with slow gait speed had a lower LMI, FFMI, BMC, BMD, T-score, and a lower MNA score ($p<0.05$). Anthropometric assessment has revealed a significantly smaller CC, MAMC and AMA in patients with 4MGS < 0.8 m/s.

Table 10. Characteristics of patients with slow and normal gait speed based on the 4-metre gait speed (4MGS) test.

Parameter	**Patients with 4MGS < 0.8 m/s** (n=36)	**Patients with 4MGS ≥ 0.8 m/s** (n=75)	**p-value**
Age, years	70.0 ± 8.2	66.6 ± 7.4	**0.032***
Sex Male Female	 18 (50.0) 18 (50.0)	 58 (77.3) 17 (22.7)	**0.004***
Smoking history, pack-years	40.6 ± 24.1	45.5 ± 25.1	0.333
Treated for COPD, years	12.7± 8.2	7.3 ± 6.3	**0.001***
COPD exacerbations in the previous year	1.9 ± 1.7	0.9 ± 1.1	**<0.001***
mMRC dyspnoea scale	2.7 ± 0.9	1.6 ± 0.7	**<0.001***
CAT score	20.8 ± 5.8	16.6 ± 6.3	**0.001***
Post FVC, % pred.	86.1 ± 22.1	93.1 ± 17.1	0.102
Post FEV_1, % pred.	42.3 ± 15.1	52.1 ± 14.0	**0.001***
TLC, % pred.	115.4 ± 31.1	108.2 ± 20.8	0.157
RV, % pred.	179.4 ± 69.8	150.1 ± 56.3	**0.021***
RV/TLC, %	61.1 ± 14.9	52.1 ± 11.4	**0.001***
DLCO/VA, % pred.	61.5 ± 22.1	74.5 ± 22.3	**0.005***
pO_2, kPa	8.7 ± 1.7	9.5 ± 1.3	**0.013***
pCO_2, kPa	5.7 ± 0.8	5.5 ± 0.7	0.141
Charlson comorbidity index	1.8 ± 1.2	1.7 ± 0.9	0.547
HADS Anxiety score	7.3 ± 3.9	6.6 ± 4.2	0.411
HADS Depression score	8.3 ± 3.8	6.8 ± 3.3	**0.033***
EQ-5D-5L index value	0.6 ± 0.2	0.8 ± 0.1	**<0.001***
EQ-5D-5L VAS	50.6 ± 14.1	61.4 ± 14.6	**<0.001***
4MGS, m/s	0.65 ± 0.14	1.01 ± 0.13	**<0.001***
6MWD, m	251 ± 85	436 ± 81	**<0.001***
Physical activity, steps/day	5340 ± 3356	9364 ± 4794	**<0.001***

Data are presented as means ± standard deviation or numbers (%), as appropriate.

***** statistically significant ($p < 0.05$)

Abbreviations: CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; DLCO/VA: diffusing capacity of the lung for carbon monoxide per litre of alveolar volume; EQ-5D-5L: EuroQol questionnaire; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; HADS: Hospital Anxiety and Depression Scale; 4MGS: 4-metre gait speed; mMRC: modified Medical Research Council; 6MWD: 6-minute walk distance; pCO_2: partial pressure of carbon-dioxide in arterial blood; pO_2: partial pressure of oxygen in arterial blood; Post: post-bronchodilator; pred: predicted; RV: residual volume; RV/TLC: ratio of residual volume to total lung capacity; TLC: total lung capacity; VAS: visual analogue scale.

Table 11. Comparison of nutritional status between patients of with slow and normal gait speed based on the 4-metre gait speed (4MGS) test.

Parameter	Patients with 4MGS < 0.8 m/s (n=36)	Patients with 4MGS ≥ 0.8 m/s (n=75)	p-value
Body mass index, kg/m^2	26.3 ± 6.0	27.5 ± 5.7	0.300
Waist circumference, cm	94.3 ± 14.6	98.7 ± 15.3	0.150
Hip circumference, cm	98.0 ± 10.1	100.1 ± 9.9	0.293
Waist-to-hip ratio	1.0 ± 0.1	1.0 ± 0.1	0.257
Calf circumference, cm	33.9 ± 4.2	36.4 ± 4.1	**0.004***
Mid-upper arm circumference, cm	28.6 ± 4.4	30.4 ± 4.4	0.051
Triceps skin fold, mm	16.7 ± 8.2	16.9 ± 7.9	0.870
Mid-arm muscle circumference, cm	23.4 ± 3.0	25.0 ± 3.1	**0.009***
Arm muscle area, cm^2	44.1 ± 11.3	50.7 ± 12.6	**0.009***
Lean mass index, kg/m^2	16.3 ± 2.4	17.9 ± 2.5	**0.002***
Fat-free mass index, kg/m^2	17.2 ± 2.5	18.8 ± 2.6	**0.002***
Fat mass index, kg/m^2	9.0 ± 4.4	8.7 ± 3.9	0.678
Fat proportion, %	32.6 ± 10.8	30.1 ± 9.2	0.208
Bone mineral content, kg	2.3 ± 0.6	2.7 ± 0.6	**0.009***
Bone mineral density, g/cm^2	1.05 ± 0.1	1.14 ± 0.1	**0.002***
T-score	-1.5 ± 1.4	-0.8 ± 1.5	**0.017***
MNA score	22.5 ± 3.6	24.8 ± 2.9	**0.001***
Lymphocyte count, x10^9/L	1.9 ± 0.7	2.0 ± 0.7	0.314
Albumin, g/L	45.5 ± 3.2	46.5 ± 3.5	0.155
Prealbumin, g/L	21.0 ± 5.1	22.0 ± 4.5	0.275
hs-CRP, mg/L	8.5 ± 15.3	6.1 ± 8.9	0.302
Vitamin D, nmol/L	38.9 ± 17.5	40.6 ± 18.6	0.642

Data are presented as means ± standard deviation.

***** statistically significant ($p < 0.05$)

Abbreviations: hs-CRP: high-sensitivity C-reactive protein; 4MGS: 4-metre gait speed; MNA: Mini-Nutritional Assessment.

5.6. Comparison of patients with poor and normal physical activity

Fifty-six (50%) patients had poor physical activity defined by the daily step count ≤ 7128 steps/day, and in comparison to those with normal physical activity they were significantly older, had a longer history of COPD, more frequent exacerbations, worse lung function, more severe respiratory symptoms based on the CAT score and mMRC dyspnoea level, and worse health-related quality of life ($p<0.05$). They also had a slower gait speed and a shorter 6MWD (**Table 12**).

Comparison of nutritional parameters is presented in **Table 13**. Among anthropometric measurements patients with low physical activity had a significantly smaller CC, MAMC and AMA, and when analysing body composition they had a lower LMI and FFMI ($p<0.05$). Furthermore, they had a significantly lower MNA score, as well as lower serum prealbumin and vitamin D levels ($p<0.05$).

The factors that were independently and significantly related to low physical activity in the multivariate analysis were age, DLCO/VA, and mMRC dyspnoea level (**Table 14**). The multivariate model was well calibrated (P-value of 0.331 in the Hosmer-Lemeshow test) and showed a good predictive power (AUC = 0.840; $p<0.001$) (**Figure 12**).

Table 12. Characteristics of patients with poor and normal physical activity based on the average daily step count.

Parameter	Patients with ≤ 7128 steps/day (n=56)	Patients with > 7128 steps/day (n=55)	p-value
Age, years	69.3 ± 7.1	66.1 ± 8.1	**0.026***
Sex Male Female	 37 (66.1) 19 (33.9)	 39 (70.9) 16 (29.1)	 0.538
Smoking history, pack-years	42.0 ± 24.5	45.9 ± 25.2	0.415
Treated for COPD, years	11.0 ± 7.3	7.1 ± 7.0	**0.006***
COPD exacerbations in the previous year	1.6 ± 1.6	0.8 ± 1.0	**0.002***
mMRC dyspnoea scale	2.5 ± 1.0	1.5 ± 0.6	**<0.001***
CAT score	20.0 ± 6.1	15.8 ± 6.1	**0.001***
Post FVC, % pred.	87.3 ± 20.7	94.5 ± 16.6	**0.046***
Post FEV_1, % pred.	43.5 ± 14.6	54.5 ± 13.5	**<0.001***
TLC, % pred.	115.4 ± 28.0	105.8 ± 20.1	**0.043***
RV, % pred.	176.1 ± 69.7	143.2 ± 49.2	**0.006***
RV/TLC, %	58.5 ± 14.4	51.5 ± 11.0	**0.005***
DLCO/VA, % pred.	64.2 ± 21.2	76.5 ± 23.2	**0.004***
pO_2, kPa	8.9 ± 1.6	9.6 ± 1.2	**0.006***
pCO_2, kPa	5.7 ± 0.8	5.4 ± 0.5	**0.033***
Charlson comorbidity index	1.8 ± 1.1	1.7 ± 0.9	0.450
HADS Anxiety score	7.0 ± 4.3	6.6 ± 4.0	0.579
HADS Depression score	7.8 ± 3.5	6.8 ± 3.5	0.108
EQ-5D-5L index value	0.7 ± 0.2	0.8 ± 0.2	**0.001***
EQ-5D-5L VAS	54.0 ± 16.4	61.8 ± 13.0	**0.006***
4MGS, m/s	0.82 ± 0.22	0.97 ± 0.19	**<0.001***
6MWD, m	316 ± 110	437 ± 95	**<0.001***
Physical activity, steps/day	4403 ± 1662	11781 ± 3912	**<0.001***

Data are presented as means ± standard deviation or numbers (%), as appropriate.

***** statistically significant ($p < 0.05$)

Abbreviations: CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; DLCO/VA: diffusing capacity of the lung for carbon monoxide per litre of alveolar volume; EQ-5D-5L: EuroQol questionnaire; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; HADS: Hospital Anxiety and Depression Scale; 4MGS: 4-metre gait speed; mMRC: modified Medical Research Council; 6MWD: 6-minute walk distance; pCO_2: partial pressure of carbon-dioxide in arterial blood; pO_2: partial pressure of oxygen in arterial blood; Post: post-bronchodilator; pred: predicted; RV: residual volume; RV/TLC: ratio of residual volume to total lung capacity; TLC: total lung capacity; VAS: visual analogue scale.

Table 13. Comparison of nutritional status between patients of with poor and normal physical activity based on the average daily step count.

Parameter	Patients with ≤ 7128 steps/day (n=56)	Patients with > 7128 steps/day (n=55)	p-value
Body mass index, kg/m^2	26.6 ± 6.0	27.7 ± 5.6	0.313
Waist circumference, cm	96.5 ± 15.0	98.1 ± 15.5	0.589
Hip circumference, cm	98.9 ± 10.0	99.9 ± 10.0	0.581
Waist-to-hip ratio	1.0 ± 0.1	1.0 ± 0.1	0.748
Calf circumference, cm	34.7 ± 3.9	36.5 ± 4.4	**0.028***
Mid-upper arm circumference, cm	29.1 ± 4.4	30.4 ± 4.5	0.132
Triceps skin fold, mm	16.7 ± 8.5	16.9 ± 7.5	0.884
Mid-arm muscle circumference, cm	23.9 ± 2.8	25.1 ± 3.5	**0.045***
Arm muscle area, cm^2	46.1 ± 10.7	51.1 ± 13.8	**0.033***
Lean mass index, kg/m^2	16.8 ± 2.5	17.9 ± 2.5	**0.027***
Fat-free mass index, kg/m^2	17.7 ± 2.6	18.9 ± 2.7	**0.026***
Fat mass index, kg/m^2	8.8 ± 4.3	8.8 ± 3.8	0.977
Fat proportion, %	31.3 ± 10.8	30.5 ± 8.6	0.673
Bone mineral content, kg	2.5 ± 0.6	2.6 ± 0.6	0.176
Bone mineral density, g/cm^2	1.09 ± 0.1	1.13 ± 0.1	0.074
T-score	-1.3 ± 1.5	-0.8 ± 1.5	0.072
MNA score	23.3 ± 3.4	24.7 ± 3.0	**0.022***
Lymphocyte count, x10^9/L	1.9 ± 0.7	2.1 ± 0.7	0.210
Albumin, g/L	46.0 ± 2.8	46.4 ± 3.9	0.537
Prealbumin, g/L	20.7 ± 4.2	22.7 ± 5.1	**0.032***
hs-CRP, mg/L	7.0 ± 9.3	6.9 ± 13.2	0.961
Vitamin D, nmol/L	34.7 ± 16.2	45.5 ± 18.6	**0.001***

Data are presented as means ± standard deviation.

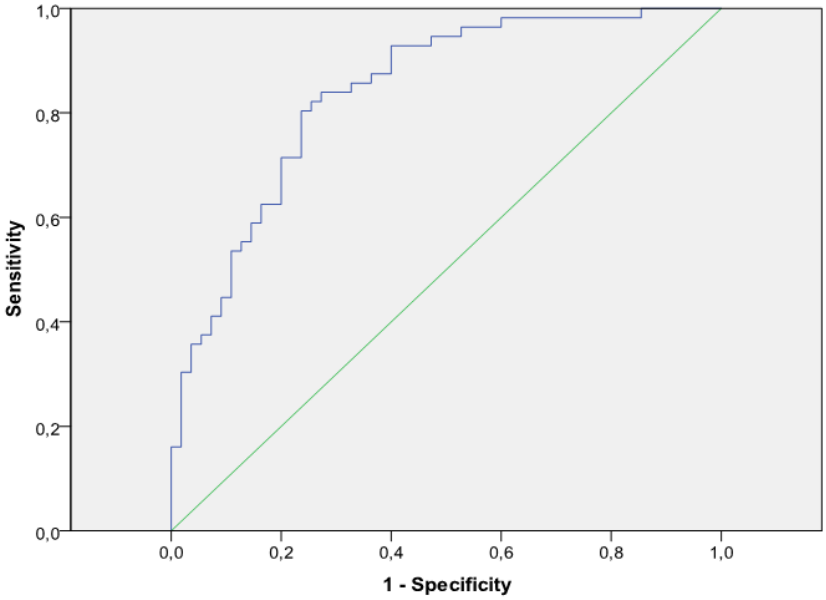
***** statistically significant ($p < 0.05$)

Abbreviations: hs-CRP: high-sensitivity C-reactive protein; MNA: Mini-Nutritional Assessment.

Table 14. Univariate and multivariate logistic regression analysis for the prediction of poor physical activity defined by the daily step count ≤ 7128 steps/day.

Variable	Univariate		Multivariate	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Age (years)	1.059 (1.006-1.115)	0.029	1.086 (1.013-1.163)	0.021
Previous exacerbations	2.636 (1.192-5.826)	0.017		
FEV_1 (% pred.)	0.979 (0.959-1.000)	0.049		
RV/TLC (%)	1.014 (1.000-1.027)	0.044		
DLCO/VA (% pred.)	0.975 (0.957-0.983)	0.006	0.975 (0.953-0.997)	0.026
HADS Depression score	1.300 (0.612-2.760)	0.049		
CAT score	1.117 (1.045-1.194)	<0.001		
EQ-5D-5L index value	0.023 (0.002-0.258)	0.001		
mMRC dyspnoea scale	5.177 (2.543-10.546)	0.001	4.332 (2.124-8.833)	<0.001
MNA	0.870 (0.769-0.983)	0.026		
FFMI (kg/m^2)	0.850 (0.734-0.984)	0.029		
LMI (kg/m^2)	0.844 (0.724-0.983)	0.030		
BMD (g/cm^2)	0.074 (0.004-1.317)	0.076		
pO_2 (kPa)	0.680 (0.512-0.902)	0.007		
Prealbumin (g/L)	0.914 (0.841-0.994)	0.035		
Vitamin D (nmol/L)	0.964 (0.942-0.987)	0.003		
Arm muscle area (cm^2)	0.967 (0.937-0.998)	0.036		
Calf circumference (cm)	0.074 (0.004-1.317)	0.076		

Abbreviations: BMD: bone mineral density; CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; CI: confidence interval; DLCO/VA: diffusing capacity of the lung for carbon monoxide per litre of alveolar volume; EQ-5D-5L: EuroQol questionnaire; FEV_1: forced expiratory volume in one second; FFMI: fat-free mass index; HADS: Hospital Anxiety and Depression Scale; LMI: lean mass index; mMRC: modified Medical Research Council; MNA: Mini-Nutritional Assessment; OR: odds ratio; pO_2: partial pressure of oxygen in arterial blood; pred: predicted; RV/TLC: ratio of residual volume to total lung capacity.



AUC	SE	95% CI	p-value
0.840	0.037	0.766 to 0.913	<0.001

Figure 12. Receiver operating characteristic analysis of significant variables derived from the multivariate logistic regression model and their capacity to predict poor physical activity defined by the daily step count ≤ 7128 steps/day. The model includes age, diffusing capacity of the lung for carbon monoxide per litre of alveolar volume (DLCO/VA) and mMRC dyspnoea level.

Abbreviations: AUC: area under the curve; CI: confidence interval; SE: standard error.

5.7. Evaluation of factors associated with malnutrition in patients with COPD

Eighteen (16%) patients were underweight (BMI < 21 kg/m^2) and in comparison to patients with BMI ≥ 21 kg/m^2 they had more severe lung hyperinflation (i.e. higher TLC, RV, and RV/TLC), and more pronounced reduction in lung diffusing capacity (i.e. lower DLCO/VA) ($p<0.05$) (**Table 15**). Underweight patients also had more severe airflow limitation (i.e. lower FEV_1), however this difference did not reach statistical significance ($p=0.058$).

There were no significant differences between underweight patients and the rest of the study population regarding age, sex ratios, smoking history, COPD duration, symptoms severity, frequency of COPD exacerbations, comorbidities, psychological status, and health-related quality of life (**Table 15**).

Table 15. Comparison of clinical and lung function parameters between underweight patients (body mass index [BMI] < 21 kg/m^2) and patients with BMI ≥ 21 kg/m^2.

Parameter	Patients with BMI < 21 kg/m^2 (n=18)	Patients with BMI ≥ 21 kg/m^2 (n=93)	p-value
Age, years	66.2 ± 7.4	68.0 ± 7.8	0.625
Sex Male Female	 10 (55.6) 8 (44.4)	 66 (71.0) 27 (29.0)	0.198
Smoking history, pack-years	39.9 ± 25.8	44.7 ± 24.6	0.419
Treated for COPD, years	7.6 ± 8.2	9.4 ± 7.3	0.197
COPD exacerbations in the previous year	1.4 ± 2.2	1.2 ± 1.2	0.514
mMRC dyspnoea scale	2.3 ± 1.0	1.9 ± 0.9	0.138
CAT score	18.6 ± 6.2	17.8 ± 6.5	0.651
Post FVC, % pred.	91.2 ± 21.3	90.8 ± 18.7	0.737
Post FEV_1, % pred.	43.0 ± 16.0	50.1 ± 14.7	0.058
TLC, % pred.	129.7 ± 16.0	106.7 ± 24.3	**<0.001***
RV, % pred.	208.2 ± 61.5	149.9 ± 57.9	**<0.001***
RV/TLC, % pred.	152.8 ± 32.2	130.9 ± 30.3	**0.004***
DLCO/VA, % pred.	47.7 ± 13.7	74.7 ± 21.8	**<0.001***
Charlson comorbidity index	1.6 ± 0.9	1.8 ± 1.1	0.472
HADS Anxiety score	5.9 ± 4.1	6.9 ± 4.1	0.507
HADS Depression score	7.3 ± 2.4	7.3 ± 3.7	0.803
EQ-5D-5L index value	0.7 ± 0.2	0.7 ± 0.2	0.885
EQ-5D-5L VAS	55.3 ± 15.0	58.4 ± 15.3	0.447

Data are presented as means ± standard deviation or numbers (%), as appropriate.

***** statistically significant (p <0.05)

Abbreviations: BMI: body mass index; CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; DLCO/VA: diffusing capacity of the lung for carbon monoxide per litre of alveolar volume; EQ-5D-5L: EuroQol questionnaire; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; HADS: Hospital Anxiety and Depression Scale; mMRC: modified Medical Research Council; Post: post-bronchodilator; pred: predicted; RV: residual volume; RV/TLC: ratio of residual volume to total lung capacity; TLC: total lung capacity; VAS: visual analogue scale.

5.8. Evaluation of physical performance in patients with different forms of nutritional abnormality

The average values for the 4MGS, 6MWD and daily step count for patients in four BMI categories – underweight (BMI <21 kg/m^2), normal weight (BMI ≥21, <25 kg/m^2), overweight (BMI ≥25, <30 kg/m^2) and obese (BMI ≥30 kg/m^2) are presented in **Table 16**.

No significant differences were observed in the physical performance between patients in different BMI categories.

Table 16. Physical performance of the study population in relation to the nutritional status.

Parameter	**Underweight patients*** (n=18)	**Patients with normal weight #** (n=31)	**Overweight patients §** (n=27)	**Obese patients $** (n=35)	**p-value**
4MGS, m/s	0.85 ± 0.23	0.90 ± 0.24	0.88 ± 0.24	0.92 ± 17	0.728
6MWD, m	348 ± 140	379 ± 115	386 ± 123	379 ± 112	0.759
Physical activity, steps/day	7104 ± 5356	8074 ± 4701	9295 ± 5383	7582 ± 3909	0.412

Data are presented as means ± standard deviation.

* BMI <21 kg/m^2

BMI ≥21, <25 kg/m^2

§ BMI ≥25, <30 kg/m^2

$ BMI ≥30 kg/m^2

Abbreviations: BMI: body mass index; 4MGS: 4-metre gait speed; 6MWD: 6-minute walk distance.

5.9. Association between physical activity and severity of COPD

The association between physical activity expressed as a daily step count and selected parameters related to the severity of COPD (i.e. lung function parameters, symptoms severity scores, frequency of exacerbations) was evaluated using the Spearman correlation analysis (**Table 17, Figure 13**).

A strong negative and a moderate positive correlation was observed between daily step count and the mMRC dyspnoea level (Spearman correlation coefficient rho = -0.664, p<0.001), and the FEV_1 (rho = 0.467, p<0.001), respectively (**Fig 13A** and **13B**). The correlation for the RV/TLC was moderate, negative (rho = -0.400, p<0.001) (**Fig 13C**), and for the DLCO/VA weak, positive (rho = 0.312, p=0.001) (**Fig 13D**). Previous exacerbations and the CAT score both showed weak negative correlation with daily step count (**Fig 13E** and **13F**).

Table 17. Correlations between daily step count and parameters of COPD severity.

	Daily step count
	Spearman correlation coefficient rho, p-value
Post FEV_1, % pred.	**0.467, p<0.001***
RV/TLC, %	**-0.400, p<0.001***
DLCO/VA, % pred.	**0.312, p=0.001***
COPD exacerbations in the previous year	**-0.308, p=0.001***
mMRC dyspnoea level	**-0.664, p<0.001***
CAT score	**-0.372, p<0.001***

***** statistically significant (p <0.05)

Abbreviations: CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; DLCO/VA: diffusing capacity of the lung for carbon monoxide per litre of alveolar volume; FEV_1: forced expiratory volume in one second; mMRC: modified Medical Research Council; Post: post-bronchodilator; pred: predicted; RV/TLC: ratio of residual volume to total lung capacity.

Fig 13A. Correlation between the mMRC dyspnoea level and daily step count
rho = -0.664, p<0.001

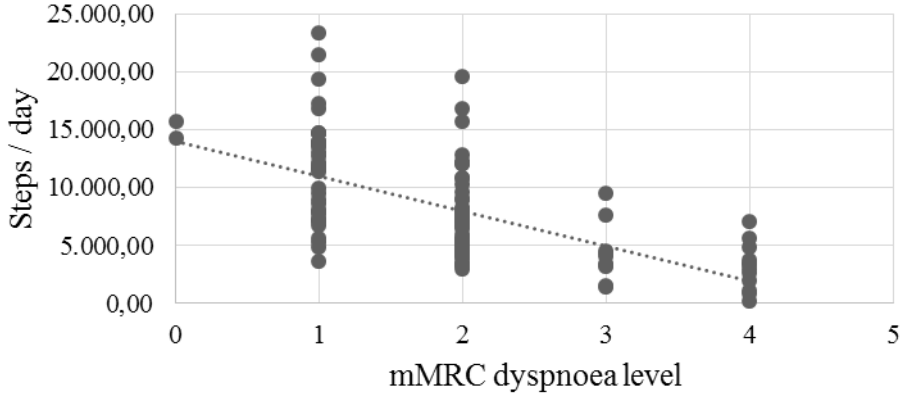
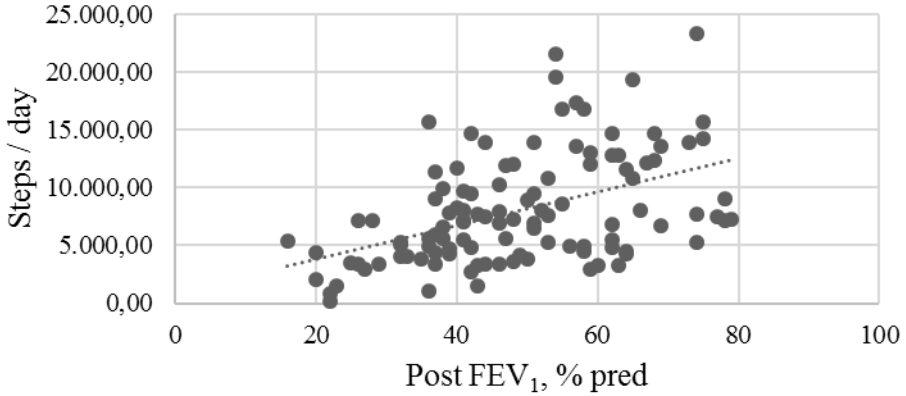


Fig 13B. Correlation between the post FEV_1 and daily step count
rho = 0.467, p<0.001



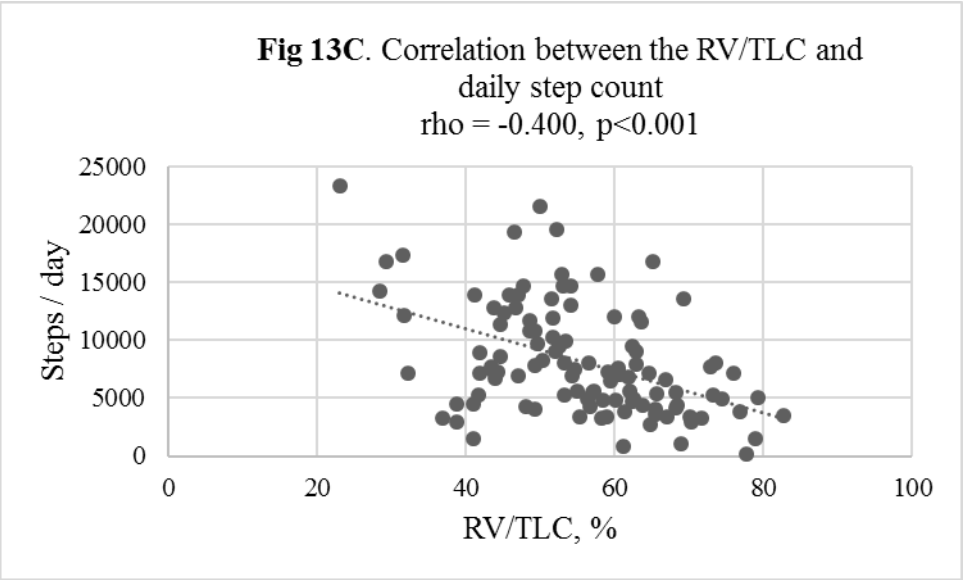


Fig 13C. Correlation between the RV/TLC and daily step count
rho = -0.400, p<0.001
Steps / day
25000
20000
15000
10000
5000
0
0
20
40
60
80
100
RV/TLC, %

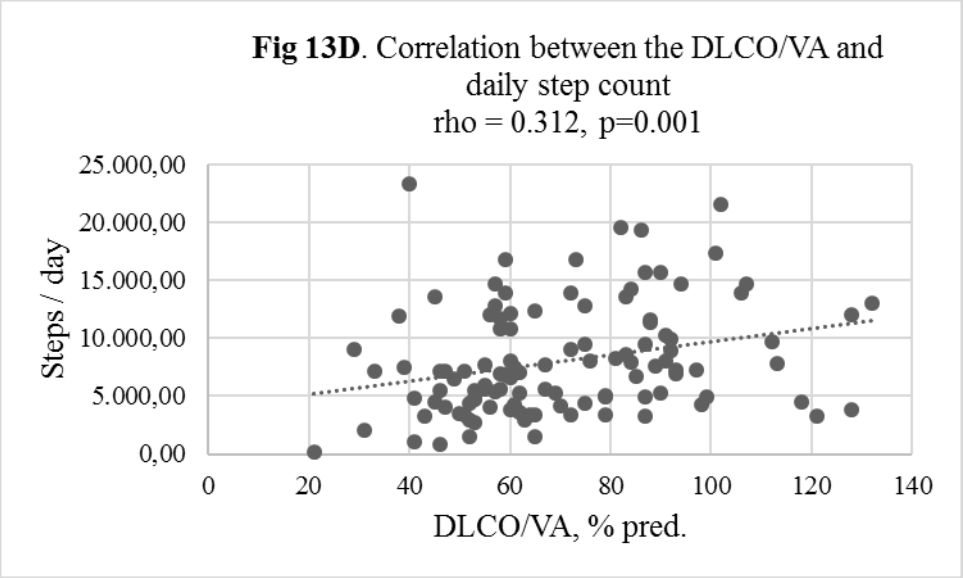
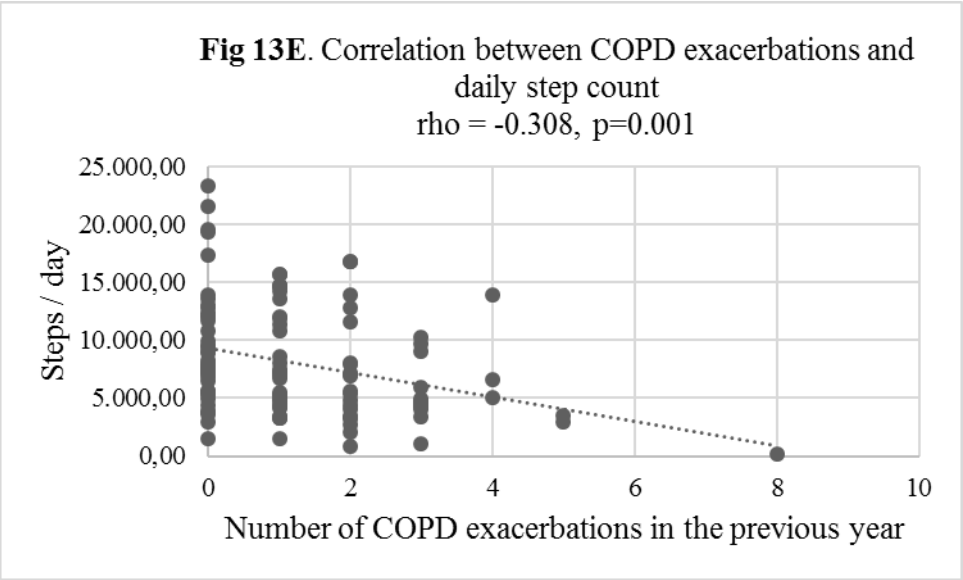


Fig 13D. Correlation between the DLCO/VA and daily step count
rho = 0.312, p=0.001
Steps / day
25.000,00
20.000,00
15.000,00
10.000,00
5.000,00
0,00
0
20
40
60
80
100
120
140
DLCO/VA, % pred.



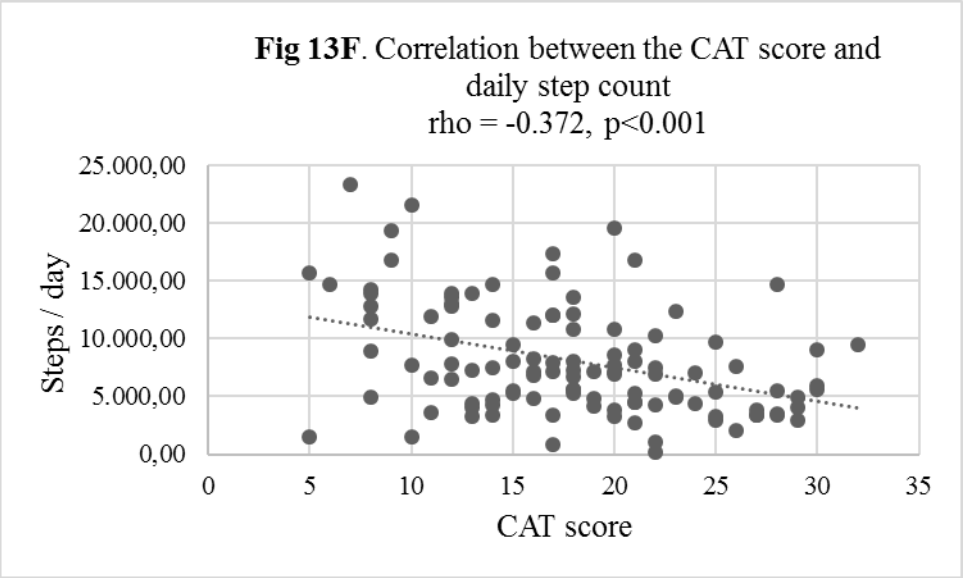


Figure 13. Correlations between daily step count and parameters of COPD severity.

Abbreviations: CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; DLCO/VA: diffusing capacity of the lung for carbon monoxide per litre of alveolar volume; FEV_1: forced expiratory volume in one second; mMRC: modified Medical Research Council; Post: post-bronchodilator; pred: predicted; RV/TLC: ratio of residual volume to total lung capacity.

5.10. Correlation between physical activity and simple tests of muscle function / mass

The results of the Spearman correlation analysis for physical activity expressed as a daily step count and simple tests of muscle function (4MGS, 6MWD, 30-second chair stand test, timed up and go test, handgrip strength) and several indicators of muscle mass (FFMI, CC, AMA, RF_{CSA}) are presented in **Table 18** and **Figure 14**.

A strong correlation was found between daily step count and the 6MWD (rho = 0.684, p<0.001) (**Fig 14A**), and a moderate correlation between daily step count and the 4MGS (rho = 0.464, p<0.001) (**Fig 14B**). The correlation for the 30-second chair stand test was moderate, positive (rho = 0.402, p<0.001) (**Fig 14C**), and for the timed up and go test moderate, negative (rho = -0.463, p<0.001) (**Fig 14D**). Furthermore, the FFMI and daily physical activity showed a weak correlation (rho = 0.210, p=0.027) (**Fig 14E**).

No significant correlations were found between daily step count and the handgrip strength, CC, AMA and $RF_{CSA,}$ respectively (**Table 18**).

Table 18. Correlations between daily step count and parameters of muscle function / mass.

	Daily step count
	Spearman correlation coefficient rho, p-value
4-metre gait speed, m/s	**0.464, p<0.001***
6-minute walk distance, m	**0.684, p<0.001***
30-second chair stand test, number of rises	**0.402, p<0.001***
Timed up and go test, s	**-0.463, p<0.001***
Handgrip strength, kg	0.129, p=0.176
Fat-free mass index, kg/m^2	**0.210, p=0.027***
Calf circumference, cm	0.167, p=0.080
Arm muscle area, cm^2	0.163, p=0.088
Rectus femoris cross-sectional area, cm^2	0.134, p=0.161

***** statistically significant (p <0.05)

Fig 14A. Correlation between the 6MWD and daily step count
rho = 0.684, p<0.001

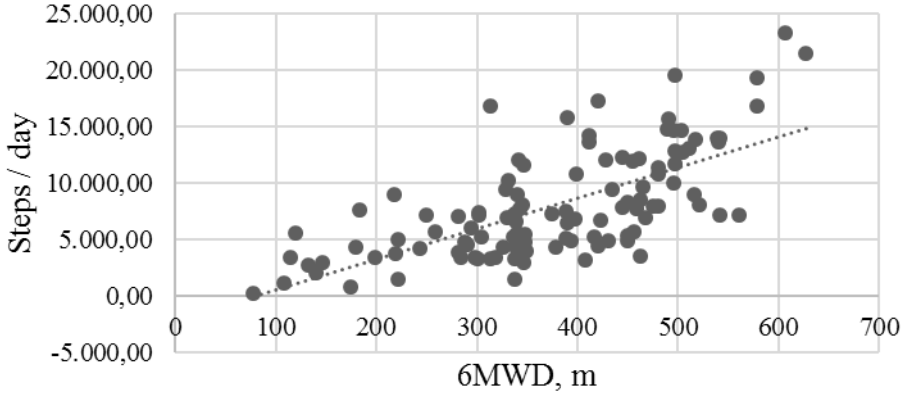


Fig 14B. Correlation between the 4MGS and daily step count
rho = 0.464, p<0.001

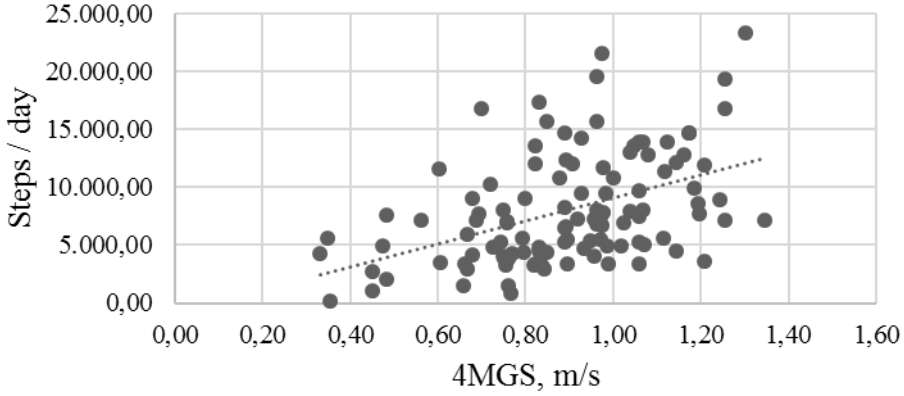
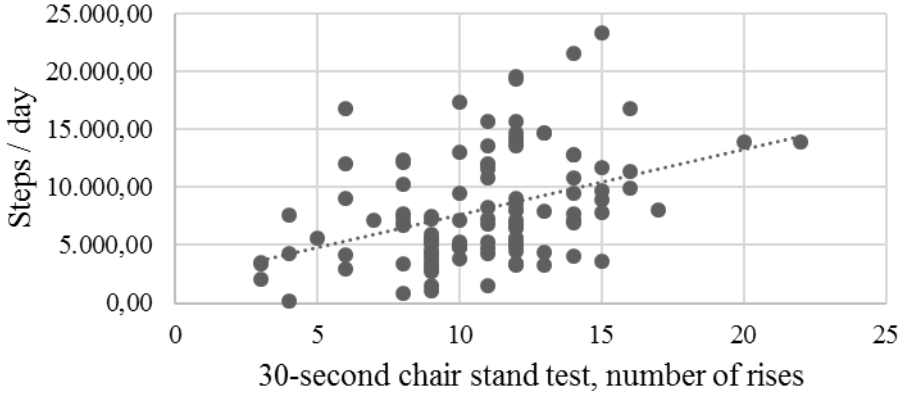
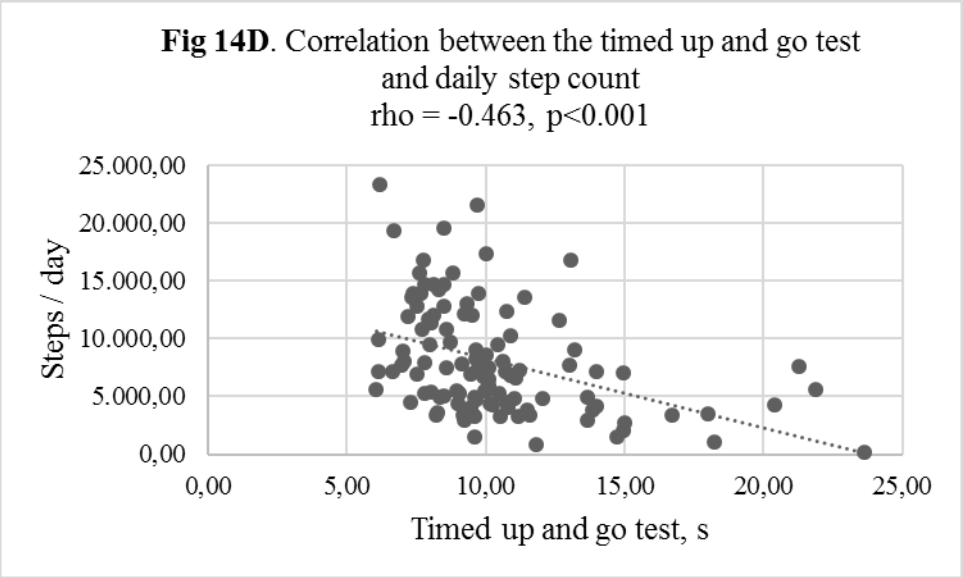


Fig 14C. Correlation between the 30-second chair stand test and daily step count
rho = 0.402, p<0.001





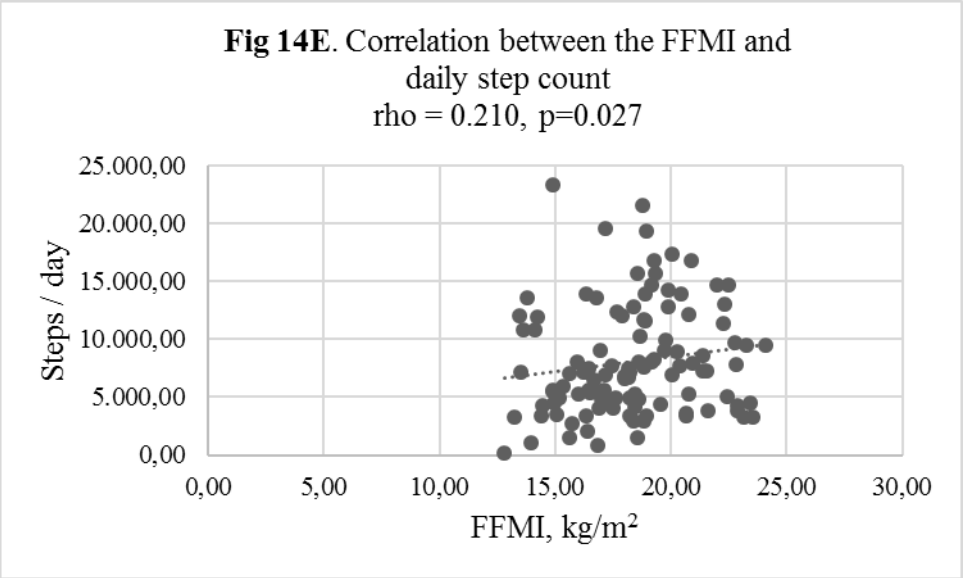


Figure 14. Significant correlations between daily step count and parameters of muscle function / mass.

Abbreviations: FFMI: fat-free mass index; 4MGS: 4-metre gait speed; 6MWD: 6-minute walk distance.

5.11. Association between physical activity, body composition and health-related quality of life

The Spearman rank correlation test was used to determine the association between physical activity, FFMI and health-related quality of life, which was assessed with the EQ-5D-5L index value and the EQ-5D-5L VAS (**Table 19**).

Physical activity expressed as a daily step count showed a moderate positive correlation with the EQ-5D-5L index value (rho = 0.403, p<0.001) (**Fig 15A**), and a weak positive correlation with the EQ-5D-5L VAS score (rho = 0.308, p=0.001) (**Fig 15B**).

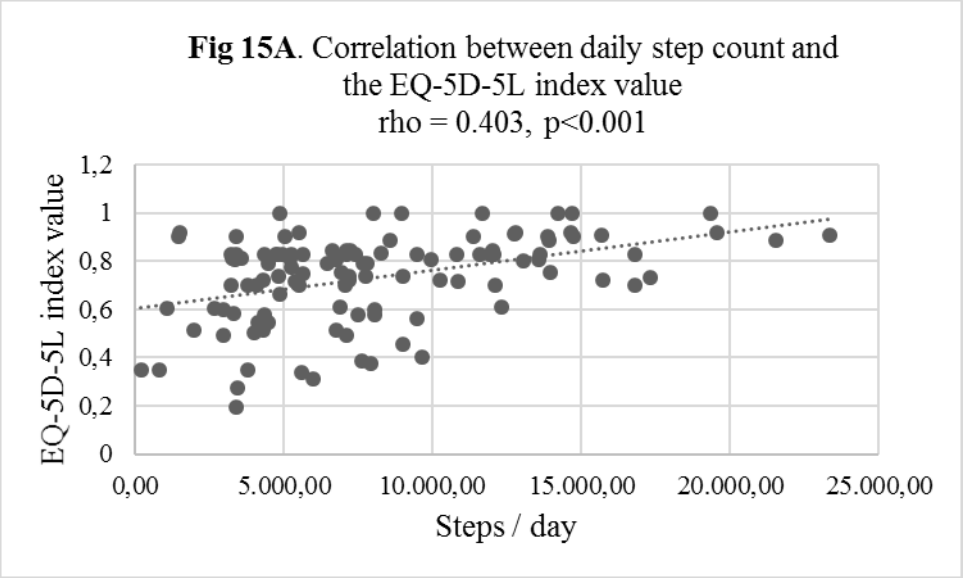
No correlation was found between FFMI and the health-related quality of life measures (**Table 19**).

Table 19. Correlations between physical activity, fat-free mass index and health-related quality of life measures.

	EQ-5D-5L index value	EQ-5D-5L VAS
	Spearman correlation coefficient rho, p-value	Spearman correlation coefficient rho, p-value
Physical activity, steps/day	**0.403, p<0.001***	**0.308, p=0.001***
Fat-free mass index, kg/m^2	0.115, p=0.231	0.148, p=0.121

***** statistically significant (p <0.05)

Abbreviations: EQ-5D-5L: EuroQol questionnaire; VAS: visual analogue scale.



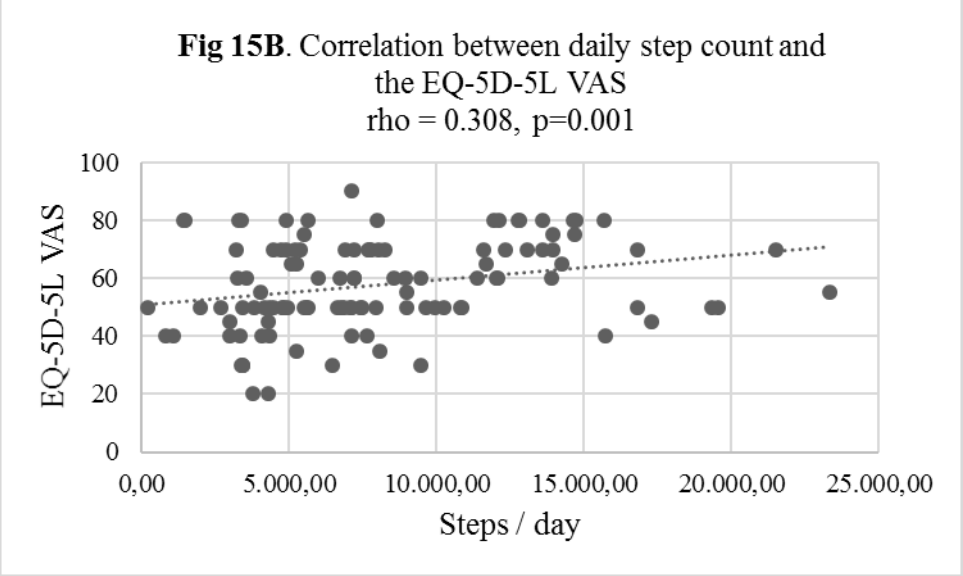


Figure 15. Correlations between physical activity and the health-related quality of life measures.

Abbreviations: EQ-5D-5L: EuroQol questionnaire; VAS: visual analogue scale.

5.12. Association between physical activity, body composition and anxiety / depression

Based on the HADS Anxiety score, 42 (38%) patients had some degree of anxiety (HADS Anxiety score ≥ 8): 26 (23%) patients scored in the range of mild anxiety, 8 (7%) moderate, and 8 (7%) severe anxiety. Regarding symptoms of depression, 48 (43%) patients manifested clinically significant depression (HADS Depression score ≥ 8): 26 (23%) mild, 19 (17%) moderate, and 3 (3%) severe depression.

No significant correlations were found between daily step count and HADS Anxiety score and HADS Depression score, respectively (**Table 20**). Similarly, there were no correlations between FFMI and measures of anxiety/depression.

Table 20. Correlation between physical activity, fat-free mass index and psychological status.

	HADS Anxiety score	HADS Depression score
	Spearman correlation coefficient rho, p-value	Spearman correlation coefficient rho, p-value
Physical activity, steps/day	-0.003, p=0.975	-0.168, p=0.077
Fat-free mass index, kg/m^2	-0.109, p=0.255	-0.089, p=0.353

Abbreviations: HADS: Hospital Anxiety and Depression Scale.

6. DISCUSSION

The results of the presenting study indicate that in the population of ambulatory patients with moderate to very severe COPD, patients with poor physical performance have deficient nutritional status, which manifested dominantly with lower parameters of muscle/bone tissue and serum protein levels. There were no significant differences in the BMI and parameters related to fat tissue between patients with poor and normal physical performance. In the multivariate analysis the variables that were independently and significantly associated with poor exercise capacity were older age, previous exacerbations, lung hyperinflation, reduced lung diffusion capacity and dyspnoea level; and likewise, older age, reduced lung diffusion capacity and dyspnoea level were independently associated with poor physical activity. However, none of the nutritional parameters were identified as independently related to poor physical performance.

6.1. Discussion regarding the general aim of the research

Comparison of nutritional status / body composition in COPD patients with poor and normal physical performance

Patients with COPD apart from respiratory symptoms often develop extrapulmonary manifestations of the disease, some of them being nutritional alterations and body composition changes [96, 139]. Furthermore, physical inactivity is highly prevalent in patients with COPD, which is closely associated not only with the ventilatory limitation, but also with the peripheral muscle loss and dysfunction [115, 129].

The general aim of the presenting research was to compare nutritional status and body composition in COPD patients with poor and normal physical performance, which was assessed in three different ways – evaluation of exercise capacity by the 6MWD, measurement of gait speed by the 4MGS test, and objectively measured physical activity expressed as average daily step count. According to our results patients with poor physical performance determined by any of these three methods had deficient nutritional status in terms of reduced MNA score and several indicators of skeletal muscle mass – lower LMI and FFMI, as well as smaller CC, MAMC and AMA (**Table 8, 11, 13**). Additionally, patients with

poor exercise capacity (i.e. 6MWD ≤ 350 m) and those with slow gait speed (i.e. 4MGS < 0.8 m/s) also had reduced DEXA parameters of bone tissue (i.e. BMC, BMD, T-score) (**Table 8** and **11**), which might have been influenced by a higher proportion of women in both "poor exercise capacity" and "slow gait speed" groups compared to the respective "normal" groups (**Table 7** and **10**). Namely, women are more prone to increased loss of bone tissue with ageing than men, especially in the postmenopausal period [171].

Although patients with poor physical activity (i.e. ≤ 7128 steps/day) also had lower BMD and T-score in comparison to patients with normal physical activity, this trend did not reach statistical significance (p=0.07), what is somewhat surprising considering that a significant difference was observed in the serum concentration of vitamin D, which is very important in bone metabolism. Patients with poor physical activity had significantly lower mean serum vitamin D concentration (**Table 13**), nevertheless, the causal relationship between vitamin D and physical activity level in this research could not be established because of the cross-sectional study design, but the association might be bidirectional. Namely, vitamin D may improve physical performance, especially in the elderly population, through its function in musculoskeletal system [172, 173]. On the other hand, patients with more outdoor physical activities have more sun exposure that stimulates the production of vitamin D in the skin, which is the main source of vitamin D in humans. It is of note, however, that although patients with normal physical activity had significantly higher serum vitamin D levels, even 77% of study population was vitamin D deficient (serum vitamin D concentration < 50 nmol/L), and the mean vitamin D levels for the entire study population as well as in all "poor" and "normal" physical performance groups were constantly in the range of deficiency (**Table 6, 8, 11, 13**), which is consistent with the previously reported high prevalence of vitamin D deficiency in the general elderly population [173, 174].

Serum proteins may give additional information on nutritional status, and in this study albumin and prealbumin levels were explored. Since both proteins belong to the negative acute phase reactants, the concentration of which fall during inflammation [111], serum levels of hs-CRP were also determined as a measure of systemic inflammation. Patients with poor exercise capacity had significantly lower serum albumin and prealbumin concentrations, and patients with poor physical activity had lower prealbumin levels (**Table 8** and **13**). No relation was found between hs-CRP and physical performance.

It is important to note that there were no differences in the BMI, FMI, fat proportion, waist and hip circumference, waist-to-hip ratio and TSF between patients with poor and normal

physical performance (**Table 8, 11, 13**), which suggests that nutritional differences that were observed in relation to physical performance are mainly reserved to the muscle/bone mass and protein status, and not to the fat tissue. This is not surprising having in mind the central role of the musculoskeletal system in body movements. These results are also in line with previously published studies using BIA in the body composition evaluation in COPD patients that found a positive correlation between FFMI and the 6MWD [153, 175]. However, the advantage of this research is that in the assessment of nutritional status several different methods were used - anthropometry, serum biomarkers, MNA questionnaire, and most importantly the DEXA, which is considered a reference method for the measurement of body composition in the clinical settings and is superior to more accessible and more used BIA [176].

Besides nutritional parameters the comparison of patients with poor and normal physical performance also included demographic variables and parameters related to the lung disease, health-related quality of life and psychological status. Irrespective of which method was used in the assessment of physical performance (6MWD, 4MGS or daily step count), patients with poor physical performance were older, had worse lung function (i.e. more severe airflow obstruction manifested as the lower FEV_1, lung hyperinflation demonstrated by the higher RV and RV/TLC, reduced lung diffusion capacity, more pronounced hypoxemia), higher symptom burden, more frequent exacerbations, and worse health-related quality of life (**Table 7, 10, 12**). These data are consistent with the findings of other authors, who reported higher prevalence of physical inactivity with increasing COPD severity [116, 155], and related physical inactivity / exercise intolerance to multiple negative clinical consequences including functional limitation, impaired health-related quality of life, higher exacerbation and hospital admission rate, and increased mortality [117-120, 156].

In order to detect which variables are independently associated with poor physical performance, we performed the multivariate analysis. Two multivariate models were built, the first one with poor exercise capacity (i.e. 6MWD $\leq$ 350 m) as a dependent variable, and the second one with poor physical activity (i.e. $\leq$ 7128 steps/day) as a dependent variable. Since a very strong correlation was found between 6MWD and 4MGS, which is in accordance with previously published data [169, 177], separate multivariate analysis for slow gait speed was not justified and therefore not performed. The variables that were independently and significantly associated with poor exercise capacity in the first multivariate model were older age, previous exacerbations, lung hyperinflation, reduced lung diffusion capacity and increased level of dyspnoea. Similarly, the second multivariate model identified older age,

decreased lung diffusion capacity and higher dyspnoea level as independently associated with poor physical activity. Although several nutritional parameters (e.g. MNA score, FFMI, LMI, AMA, prealbumin) showed a significant association with poor physical performance in the univariate analysis, after adjusting for age, sex, and parameters of lung function and symptoms severity in the multivariate models this significance was lost and finally none of the nutritional parameters were independently associated with poor physical performance. This suggests that age, air trapping, gas transfer and dyspnoea have a stronger relation to physical performance, and that the body composition alterations observed in patients with different levels of physical performance are secondary and influenced by other factors, probably related to the disease itself and to the process of ageing.

6.2. Discussion regarding the specific aims of the research

6.2.1. Factors associated with malnutrition in patients with COPD

Although the term malnutrition includes both undernutrition and overnutrition (as previously explained in section 1.2.), here it has been used in its narrow sense of meaning referring to the undernutrition and underweight. Reduced body weight and low BMI, largely attributed to the loss of skeletal muscle mass, have long been recognised as independent predictors of health-care use and mortality in COPD [101, 102, 142]. On the other hand, for patients with COPD being overweight or obese seems to have a protective effect on survival. Namely, overweight and obese COPD patients have a lower risk of all-cause mortality when compared not only to underweight patients, but also to those with normal weight, which was named "obesity paradox" [101, 102, 178].

As it was explained in section 1.2., studies on COPD frequently use a BMI <20 or <21 kg/m^2 when defining underweight instead of <18.5 kg/m^2 (recommended by the WHO for the general population), since a higher mortality has been observed in COPD patients below these values [101, 102]. The cut-off BMI <21 kg/m^2 for underweight patients with COPD is also recommended by the ATS/ERS [103], and it was applied in the presenting research.

We identified only 18 (16%) underweight patients, while the proportion of overweight and obese patients was quite high (24% and 32%, respectively) (**Figure 9A**). Furthermore, FFM depletion, defined as FFMI <16 kg/m^2 for men and <15 kg/m^2 for women, was detected in 4%

of male and 37% of female patients in our study population (**Figure 10**). According to the previously published data underweight and FFM depleted patients make up 20-40% of the COPD population, with increasing prevalence in advanced stages of disease, especially in women [140-142]. Lower prevalence of underweight in our population may be explained by the fact that the study was conducted in outpatients with the mean postbronchodilator FEV_1 49% and the majority of patients were in the GOLD 2 and 3 category of airflow limitation (**Figure 7**). Due to the study design and exclusion criteria the most fragile patients with very severe COPD who are bedridden or extremely inactive could not have been included in this research, and in such population a prevalence of underweight is expected to be higher.

On the other hand, a high proportion of overweight/obese patients in our research concurs with some previous studies that reported a rising prevalence of overweight and obesity in COPD, especially in mild-to-moderate disease – in the study by Eisner et al. [146] in a COPD cohort with a mean FEV_1 58% there were 20% overweight and 54% obese patients, and in the study by Cecere et al. [148] 32% of patients were overweight (mean FEV_1 50%) and 38% obese (mean FEV_1 55%).

When underweight patients were compared with the rest of the study population, the parameters that were significantly different between them were TLC, RV, RV/TLC (higher in underweight) and DLCO/VA (lower in underweight) (**Table 15**), which suggests more severe lung hyperinflation and reduction in lung diffusion capacity. Although imaging techniques (e.g. chest CT scan) were not used in our study and therefore the degree of emphysema could not have been precisely measured, lung function measurements reflecting lung hyperinflation and decreased lung diffusion capacity provide a good estimate of the extent of emphysema [179]. Our results are in accordance with previously published data indicating that low body weight in COPD is related to the degree of emphysema [180]. In our study underweight patients also had more severe airflow limitation (i.e. lower FEV_1), however this difference did not reach statistical significance ($p=0.058$).

Due to the small number of underweight patients the multivariate analysis in prediction of malnutrition would not be conclusive and was therefore not performed.

6.2.2. Physical performance in patients with different forms of nutritional abnormality

Based on the previous observations suggesting bidirectional relation between physical performance and nutritional status, we explored and compared the physical performance of COPD patients in different BMI categories (underweight, normal weight, overweight, and obese). Contrary to some of the existing evidence, the differences in the 6MWD, 4MGS and daily step count between patients in different BMI categories in our study were not significant (**Table 16**). On the other hand, Ischaki et al. [175] found a positive correlation between 6MWD and both BMI and FFMI. In addition, in the study by Lan et al. [181] underweight patients with COPD had impaired exercise capacity, and the additional strengths of this study are that it was conducted in a lung function-matched patients (the mean FEV_1 was similar in the underweight, normal-weight, and overweight group) and that in the assessment of exercise capacity cardiopulmonary exercise test was used instead of 6MWT. In our research underweight patients also had the worst exercise capacity (i.e. the lowest mean 6MWD), though this trend did not reach statistical significance.

Regarding gait speed, Abbatecola et al. [150] showed in a population of older COPD patients that participants with the slowest gait speed apart from being older and having worse lung function, also had higher BMI and FM, as well as lower lean-to-fat ratio. Additionally, among body composition markers FM was the only independent determinant of walking speed [150]. However, due to the methodological differences in the study design a comparison of the results of this study and our study is limited. Firstly, Abbatecola et al. [150] calculated the gait speed by dividing 6MWD by time, and we performed 4MGS test. Secondly, the population in a study by Abbatecola et al. [150] were patients admitted for pulmonary rehabilitation and in general their mobility was better (the mean values for the three walking speed tertiles were 0.93, 1.1 and 1.43 m/s, respectively) than in our study population (mean walking speed 0.89 m/s, range 0.33-1.35 m/s). Thirdly, in the body composition analysis Abbatecola et al. [150] used BIA instead of DEXA that was used in our study, and they used absolute values for FM and FFM, while we calculated FMI and FFMI by dividing the FM and FFM, respectively, by height squared.

When it comes to physical activity, Monteiro et al. [182] demonstrated worse physical activity in the daily life in obese COPD patients compared to underweight and normal-weight patients. In our study obese and underweight patients had the lowest daily step count, and

overweight patients the highest, nevertheless, these differences were not statistically significant.

6.2.3. Association between physical activity and severity of COPD

It is well established that low physical activity is common in patients with COPD, what becomes even more evident with increasing severity of the disease, as discussed previously in sections 1.3. and 1.4. [115, 116, 155]. In order to investigate the association between physical activity and the severity of COPD in our patients, we looked for a correlation between daily step count and several parameters of lung function, symptoms severity scores and exacerbation frequency (**Table 17**).

Existing evidence supports the association between physical activity and various lung function indicators of respiratory limitation in COPD, which includes airflow limitation, static and dynamic lung hyperinflation, reduced lung diffusion capacity with subsequent pulmonary gas exchange abnormalities, and respiratory muscle dysfunction [137, 183-187]. In line with previous studies our results indicate significant correlations between daily step count and several parameters of lung function – the correlation was moderate positive in the case of FEV_1, indicator of airflow limitation (**Fig 13B**); moderate negative in the case of RV/TLC, marker of lung hyperinflation (**Fig 13C**); and weak positive for the DLCO/VA, representing lung diffusion capacity (**Fig 13D**).

We also found a strong negative correlation between daily step count and the mMRC dyspnoea grade, which concurs with previously published data repeatedly demonstrating that physical activity is affected by the level of exertional breathlessness [137, 183].

Furthermore, previous findings suggest linear relationship between self-reported walking time and CAT score, a measure of symptom severity in COPD [119]. In our study a weak negative correlation was observed between CAT score and objectively measured physical activity (**Fig 13F**).

Exacerbations are unfavourable events in the course of COPD with multiple negative implications. Existing evidence suggest a bidirectional relation between physical activity and COPD exacerbations. Namely, due to worsening in respiratory symptoms patients are less active during exacerbations and shortly thereafter, moreover, frequent previous exacerbations

have been recognised as predictors of reduced physical activity in the future [184, 189]. On the other hand, higher level of physical activity may be protective and may prolong the time until the next exacerbation [157, 190]. In accordance with the previously published data, we found a weak negative correlation between the number of moderate/severe exacerbations in the previous year and a daily step count (**Fig 13E**).

6.2.4. Correlation between physical activity and simple tests of muscle function / mass

The assessment of physical activity is time consuming and requires additional equipment, which makes it impractical for its implementation in routine clinical practice. Hence, one of the aims of the present research was to evaluate whether some simple and rapid tests of physical performance exhibit a good correlation with objectively measured physical activity, and may potentially serve as surrogate methods for assessing physical activity.

We found a strong positive correlation between daily step count and the 6MWD (**Fig 14A**), and a moderate positive correlation between daily step count and the 4MGS (**Fig 14B**). These results are in line with the findings of other authors demonstrating physical activity to be strongly related to the exercise capacity measured by the 6MWD on the one hand [183, 186, 187], and moderately related to the walking speed on the other [177, 191].

As it was discussed in section 1.3. 30-second chair stand test was developed for the assessment of lower extremity muscle strength in older people, while the timed up and go test is a reliable and valid method for quantifying mobility and balance in older people [126, 128]. Both tests are rapid and easy to perform, and we found that the 30-second chair stand test was in a moderate positive correlation with the daily step count (**Fig 14C**), and the timed up and go test in a moderate negative correlation (**Fig 14D**). These results contribute to the knowledge in this field, because there have not been any previously published studies investigating the correlation between physical activity and either of these two tests. The only comparable published data are for the sit-to-stand test, which is similar to the 30-second chair stand test with the main difference that the participant repeatedly rises from the chair without support from the hands for a duration of one minute instead of 30-seconds as in the 30-second chair stand test [126, 127]. In the study by van Gestel et al. [192] the number of stands in the sit-to-stand test showed moderate positive correlation with the daily step count in patients

with COPD. On the other hand, Albarrati et al. [193] demonstrated that the timed up and go test was inversely related to the 6MWD and FEV_1, and directly related to the quality of life assessed by the St. George's Respiratory Questionnaire and to the symptoms severity assessed by the CAT score. However, until now there has not been any data available on the correlation between the timed up and go test and objectively measured physical activity.

FFMI as an indicator of muscle and bone mass is expected to be related to physical performance. There are several studies available that explored the association between FFMI in patients with COPD and their exercise capacity measured by the 6MWD, and they found a positive correlation between them [153, 175]. However, the evidence on relation between FFMI and physical activity in patients with COPD is not so strong, because there is only one published study that investigated this subject and found a weak positive correlation between FFMI and physical activity level [191]. In accordance with this study, the FFMI and daily step count were also weakly correlated in our research (**Fig 14E**).

As it was previously discussed in section 1.4., peripheral muscle dysfunction is present in about one-third of patients with COPD, even in those with mild disease, and has been associated with multiple negative implications, including exercise intolerance, increased health care use, reduced quality of life and increased mortality [129, 130, 145]. We evaluated muscle function in our COPD patients by measuring handgrip strength, and as an alternative to measuring quadriceps strength we used ultrasound imaging of the quadriceps muscle with measurement of the RF_{CSA}. In contrast to some of the published data suggesting a weak to moderate correlation between handgrip strength / quadriceps strength and physical activity [186, 191, 194], we did not find significant correlations between daily step count and handgrip strength or RF_{CSA}, respectively (**Table 18**). We also explored the association between daily step count and two anthropometric parameters related to the limb muscle mass (CC and AMA), but nor here no significant correlations were found (**Table 18**). The absence of statistically significant relation between physical activity and previously mentioned parameters of muscle strength/mass (i.e. handgrip strength, $RF_{CSA,}$ CC, AMA) in our research may be explained by the fact that physical activity was expressed as a daily step count and did not take into account the intensity of the activity, which is an important part of the effect of physical activity in building muscle mass and strength.

6.2.5. Association between physical activity, body composition and health-related quality of life

For patients with COPD the tendency of adopting a sedentary lifestyle is rising with increasing severity of the lung disease, moreover, physical activity substantially decreases with time across all severity stages of COPD, and this decline is paralleled by a worsening of health status and quality of life. [115, 116, 155]. Esteban et al. [117] have demonstrated that a reduction in time spent engaging in physical activity or maintaining a low level of activity may impair health-related quality of life, whereas an increase in physical activity level over time can improve quality of life parameters. Furthermore, average daily step count and functional capacity have been recognised as independent determinants of a health-related quality of life in patients with COPD [195]. Our results are in accordance with the previously published data: physical activity expressed as a daily step count showed a positive correlation with the quality of life parameters - moderate correlation with the EQ-5D-5L index value (**Fig 15A**), and a weak correlation with the EQ-5D-5L VAS score (**Fig 15B**).

On the contrary, the existing evidence for the relation between the muscle mass depletion and quality of life in COPD is not as straightforward. Namely, in the study by Verhage et al. [196] FFMI reduction did not show correlation with the health status, while in the study by Mostert et al. [197] depletion of FFM irrespective of body weight was associated with the impairment of quality of life. In our study no correlation was found between the FFMI and the health-related quality of life measures (**Table 19**).

6.2.6. Association between physical activity, body composition and anxiety/depression

Based on the HADS score 38% of our study population had some degree of anxiety and 43% presented clinically significant depression. In the previously published studies the prevalence of depression in COPD patients ranged from 24% to 75%, depending on the severity of the pulmonary disease and the method used in the evaluation of psychological status [32, 198]. The existing evidence indicates that depressive COPD patients have worse lung function, greater dyspnoea, poorer quality of life, more exacerbations, and reduced exercise capacity

and physical activity [32, 158]. On the other hand, it has been suggested that increased anxiety in COPD patients was associated with higher levels of physical activity [199].

In our research patients with poor exercise capacity (6MWD ≤ 350 m) and those with slow gait speed (4MGS < 0.8 m/s) had significantly higher HADS Depression scores (**Table 7** and **10**). In contrast to the published data, patients with poor physical activity (daily step count ≤ 7128 steps/day) did not differ from the normal activity group in the symptomatology of depression (**Table 12**). Equally, the level of anxiety was not different in patients with poor physical performance determined by any of the three methods (i.e. 6MWD, 4MGS, and daily step count) (**Table 7**, **10** and **12**).

In line with these results, there were no significant correlations between daily step count and HADS Anxiety score and HADS Depression score, respectively (**Table 20**). Similarly, no correlations were found between the FFMI and measures of anxiety/depression in our study population (**Table 20**).

Our data confirm that depression and anxiety are common problems in patients with COPD, however, these are complex disorders influenced by many factors, and their association with physical performance was only partially demonstrated in our research.

6.3. Study limitations

Several study limitations need to be addressed. Firstly, physical activity was assessed by measuring steps walked throughout the day and not a distance walked or energy expenditure. Because the step length of a person is related to a body height and legs length, the same distance walked by people of a different height may translate into a different number of steps. However, the same activity monitor that was used in our research has already been validated and proven accurate at measuring physical activity in patients with COPD, and it has been applied in multiple studies, including studies with populations other than COPD patients resulting in nearly 200 peer-reviewed publications [118, 137, 200].

Secondly, for each patient physical activity was assessed during 7±2 consecutive days and the study was conducted from February 2015 to June 2016, which included different seasons. Although according to some previously published data there is a trend of lower activity during

periods of the year with poor weather and lower temperatures, the seasonal variations of physical activity were not taken into account in this research [132, 201].

Finally, the analysis of physical performance and nutritional status was not carried out separately for men and women. Even though the proportions of women in the “poor exercise capacity” and “slow gait speed” groups were higher than in the corresponding “normal” groups, female sex did not show significance in the multivariate analysis. Additionally, no association was found between female sex and poor physical activity, thus differences in the physical performance and accompanying alterations in the nutritional status of the study population cannot be ascribed to the variations in gender distribution.

7. CONCLUSIONS

1) In the population of patients with moderate to very severe COPD physical performance was assessed in three different ways – exercise capacity evaluated by the 6MWD, gait speed measured by the 4MGS test, and objectively measured physical activity expressed as average daily step count. Patients with poor physical performance determined by any of these three methods had deficient nutritional status in terms of reduced MNA scores and several indicators of skeletal muscle mass – lower LMI and FFMI, and smaller CC, MAMC and AMA.

2) Patients with poor exercise capacity (i.e. 6MWD ≤ 350 m) and those with slow gait speed (i.e. 4MGS < 0.8 m/s) had significantly lower DEXA parameters of bone tissue - BMC, BMD, and T-score. Patients with poor physical activity (i.e. ≤ 7128 steps/day) also had reduced BMD and T-score, however, this trend did not reach statistical significance (p=0.07).

3) Patients with poor exercise capacity had significantly lower serum albumin and prealbumin concentrations, and patients with poor physical activity had lower prealbumin and vitamin D levels.

4) Vitamin D deficiency (serum vitamin D concentration < 50 nmol/L) was present in 77% of the study population and the mean vitamin D levels for the entire study population as well as in all "poor" and "normal" physical performance groups were constantly in the range of deficiency.

5) Irrespective of which method was used in the assessment of physical performance (6MWD, 4MGS or daily step count), patients with poor and normal physical performance did not differ in the BMI, FMI, fat proportion and fat mass-related anthropometric measurements (e.g. TSF, waist and hip circumference, waist-to-hip ratio). This suggests that the observed nutritional differences between patients at different levels of physical performance are mainly limited to the muscle/bone mass and protein status, and not to the fat tissue.

6) Apart from the aforementioned nutritional differences, patients with poor physical performance were older, had worse lung function (i.e. more severe airflow obstruction manifested as the lower FEV_1, lung hyperinflation demonstrated by the higher RV and RV/TLC, reduced lung diffusion capacity, more pronounced hypoxemia), higher symptom

burden (i.e. higher CAT score and mMRC dyspnoea level), more frequent exacerbations, and worse health-related quality of life (i.e. lower EQ-5D-5L index value and VAS score).

7) Based on the results of the multivariate analysis, variables that were independently and significantly associated with poor exercise capacity were older age, previous exacerbations, lung hyperinflation, reduced lung diffusion capacity and higher dyspnoea level. Similarly, older age, reduced lung diffusion capacity and higher dyspnoea level were also independently associated with poor physical activity. However, none of the nutritional parameters showed an independent relation to physical performance in our study. This suggests that age and parameters associated with ventilatory limitation (i.e. air trapping, compromised gas exchange and dyspnoea) have a stronger relation to physical performance, and that the body composition alterations in patients with poor physical performance are secondary and influenced by other factors, most likely by the disease itself and by the process of ageing.

8) In our study population only 16% of patients were underweight (BMI <21 kg/m^2) while the proportion of overweight (BMI ≥25, <30 kg/m^2) and obese patients (BMI ≥30 kg/m^2) was relatively high (24% and 32%, respectively). When compared to the rest of the study population, underweight patients had more severe lung hyperinflation (i.e. higher TLC, RV, and RV/TLC) and reduced lung diffusion capacity (i.e. lower DLCO/VA).

9) Patients in different BMI categories did not show significant differences in the 6MWD, 4MGS or daily step count.

10) Regardless of body weight, 37% of female patients and 4% of male patients in our study population were FFM depleted (FFMI <15 kg/m^2 for women and <16 kg/m^2 for men).

11) Physical activity expressed as a daily step count showed significant correlations with several parameters of lung function – the correlation was moderate positive in the case of FEV_1, indicator of airflow limitation; moderate negative in the case of RV/TLC, marker of lung hyperinflation; and weak positive for the DLCO/VA, representing lung diffusion capacity. The strongest negative correlation was found between daily step count and the mMRC dyspnoea level. Exacerbations in the previous year and the CAT score both showed weak negative correlation with daily step count.

12) Several simple and rapid tests of muscle function/mass demonstrated significant correlation with objectively measured physical activity. A strong correlation was found

between daily step count and the 6MWD, and a moderate correlation between daily step count and the 4MGS, the 30-second chair stand test, and the timed up and go test, respectively. Furthermore, the FFMI and daily step count showed a weak correlation.

13) Physical activity showed a positive correlation with the quality of life parameters – moderate correlation with the EQ-5D-5L index value, and a weak correlation with the EQ-5D-5L VAS score.

14) No correlation was found between the FFMI and the health-related quality of life measures.

15) Based on the HADS 38% of our COPD patients had some degree of anxiety and 43% manifested clinically significant depression. Patients with poor exercise capacity and those with slow gait speed had significantly higher HADS Depression scores. However, patients with poor physical activity did not differ from the normal activity group in the psychological status, and consequently no significant correlations were found between physical activity and measures of anxiety/depression.

16) No correlations were observed between the FFMI and measures of anxiety/depression in our study population.

8. ABSTRACT

Physical inactivity and skeletal muscle mass wasting are frequent findings in patients with chronic obstructive pulmonary disease (COPD). The aim of the study was to compare nutritional status and body composition in COPD patients with poor and normal physical performance, which was assessed in three different ways – exercise capacity evaluated by the 6-minute walk test, gait speed measured by the 4-metre gait speed test and physical activity expressed as average daily step count. In the population of 111 patients with moderate to very severe COPD, those with poor physical performance were older, had worse lung function, higher symptom burden, more frequent exacerbations, worse health-related quality of life, and deficient nutritional status, which manifested dominantly with lower parameters of muscle/bone tissue and serum protein levels. There were no significant differences in the body-mass index and parameters related to fat tissue. In the multivariate analysis the variables that were independently and significantly associated with poor exercise capacity were older age, previous exacerbations, lung hyperinflation, reduced lung diffusion capacity and higher dyspnoea level. Likewise, older age, reduced lung diffusion capacity and dyspnoea level were independently associated with poor physical activity. However, none of the nutritional parameters were independently related to poor physical performance.

Keywords: chronic obstructive pulmonary disease; nutritional status; body composition; physical activity; exercise capacity; gait speed; lung function.

Evaluation of nutritional status and physical performance in patients with chronic obstructive pulmonary disease (Zinka Matković, 2018)

9. SAŽETAK

Tjelesna neaktivnost i gubitak skeletne mišićne mase su česti u bolesnika s kroničnom opstrukcijskom bolešću pluća (KOPB). Cilj istraživanja je bio usporediti nutritivni status i tjelesni sastav u KOPB bolesnika sa smanjenom i normalnom fizičkom sposobnošću koja je procijenjena na tri različita načina – tjelesnom kondicijom na temelju 6-minutnog testa hoda, brzinom hoda mjerenom testom brzine hoda na 4 metra i tjelesnom aktivnošću izraženom prosječnim dnevnim brojem koraka. U populaciji od 111 bolesnika s umjereno teškim do vrlo teškim KOPB-om, bolesnici sa smanjenom fizičkom sposobnošću su bili stariji, imali lošiju plućnu funkciju, izraženije simptome, češće egzacerbacije, slabiju kvalitetu života i lošiji nutritivni status što se u prvom redu manifestiralo nižim vrijednostima parametara mišićno-koštane mase i nižim vrijednostima serumskih proteina. Nije bilo značajne razlike u indeksu tjelesne mase niti u parametrima koji se odnose na masno tkivo. Multivarijantnom analizom je utvrđeno da su starija dob, prethodne egzacerbacije, hiperinflacija pluća, smanjen difuzijski kapacitet pluća i viši stupanj zaduhe nezavisno i statistički značajno povezani sa smanjenom tjelesnom kondicijom. Jednako tako su starija dob, smanjen difuzijski kapacitet pluća i viši stupanj zaduhe bili nezavisno povezani sa smanjenom tjelesnom aktivnošću. Nijedan nutritivni parametar nije pokazao nezavisnu povezanost sa smanjenom fizičkom sposobnošću.

Ključne riječi: kronična opstrukcijska bolest pluća; nutritivni status; tjelesni sastav; tjelesna aktivnost; tjelesna kondicija; brzina hoda; plućna funkcija.

Procjena nutritivnog statusa i fizičke sposobnosti bolesnika s kroničnom opstrukcijskom bolešću pluća (Zinka Matković, 2018.)

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11. CURRICULUM VITAE

Zinka Matković was born on December 26, 1978 in Varaždin, Croatia. She studied medicine at the University of Zagreb, School of Medicine 1997-2003, and after obtaining a MD degree in 2003 she interned at the General Hospital Varaždin. In 2004 she worked as a scientific assistant at the University Hospital for Infectious Diseases "Dr. Fran Mihaljević", Zagreb, and in the same year she enrolled into the postgraduate study "Biomedicine and Health Sciences" at the University of Zagreb, School of Medicine. Since 2005 she has been a staff physician at the Dubrava University Hospital, Zagreb, Department of Internal Medicine, Division of Pulmonary Medicine, where she completed residency in internal medicine (2005-2009) and subspecialisation in respiratory medicine (2011-2013). She has participated as a sub-investigator in several asthma and COPD clinical trials. As a recipient of an ERS/SEPAR (European Respiratory Society / Spanish Society of Pneumology and Thoracic Surgery) fellowship in 2010-2011 she joined the research group at the Hospital Clinic Barcelona, Barcelona, Spain to collaborate in the COPD line of research under the supervision of Dr. Marc Miravitlles. In 2013 she obtained the European diploma in adult respiratory medicine after passing the HERMES (Harmonised Education in Respiratory Medicine for European Specialists) examination. Her publications are listed below.

11.1. List of publications by Zinka Matković

Scientific and professional papers:

1. Matković Z. Attention deficit / hyperactivity disorder. Acta Med 2003;29:47-56.
2. Baršić B, Krajinović V, Matković Z. Catheter-associated urinary tract infections. Medix 2004;53:31-4.
3. Matkovic Z, Zivkovic V, Korica M, Plavec D, Pecanic S, Tudoric N. Efficacy and safety of Astragalus membranaceus in the treatment of patients with seasonal allergic rhinitis. Phytother Res 2010;24:175-81.
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10. Matkovic Z, Miravitlles M. Chronic bronchial infection in COPD. Is there an infective phenotype? Respir Med 2013;107:10-22.
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13. Aliberti S, Reyes LF, Faverio P, et al. Global initiative for meticillin-resistant Staphylococcus aureus pneumonia (GLIMP): an international, observational cohort study. Lancet Infect Dis 2016;16:1364-76.

14. Matkovic Z, Cvetko D, Rahelic D, et al. Nutritional status of patients with chronic obstructive pulmonary disease in relation to their physical performance. COPD 2017;14: 626-34.

Chapter in a book:

1. Matkovic Z, Miravitlles M. Acute exacerbations of chronic bronchitis and chronic obstructive pulmonary disease. In: Blasi F, Dimopoulos G, eds. Textbook of Respiratory and Critical Care Infections. New Delhi: Jaypee Brothers Medical Publishers; 2014: 86-101.

Abstracts for conferences:

1. Matkovic Z, Pecanic S, Plavec D, Tudoric N. Efficacy and safety of HMC with Astragalus membranaceus (AM) in the treatment of seasonal allergic rhinitis (SAR). XXVII Congress of the European Academy of Allergology and Clinical Immunology, 2008.
2. Matkovic Z, Piskac-Zivkovic N, Tudoric N. Switch from intravenous to oral antibiotic therapy in hospitalized patients with non-severe community acquired pneumonia. European Respiratory Society Annual Congress, 2010.
3. Matkovic Z, Miravitlles M, Soler N, et al. Predictors of poor outcome in severe hospitalised COPD exacerbations. European Respiratory Society Annual Congress, 2011.
4. Matkovic Z. Impact of chronic bronchial infection in COPD. 46. Annual Meeting of Croatian Pulmonologists, 2013.
5. Matkovic Z, Cvetko D, Rahelic D, et al. Evaluation of nutritional status, disease severity and anxiety/depression in COPD patients with different exercise capacity. European Respiratory Society Annual Congress, 2016.
6. Matkovic Z, Cvetko D, Rahelic D, et al. Physical activity in patients with COPD and its association with disease severity, quality of life and anxiety/depression. Submitted for the European Respiratory Society Annual Congress, 2018.