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Original article

Coexistence of malnutrition, frailty, physical frailty and disability in patients with COPD starting a pulmonary rehabilitation program

L. ter Beek^{a, b, c, *}, H. van der Vaart^b, J.B. Wempe^b, W.P. Krijnen^{a, d}, J.L.N. Roodenburg^c, C.P. van der Schans^{a, e, f}, H. Jager-Wittenaar^{a, c}

^a Hanze University of Applied Sciences, Research Group Healthy Ageing, Allied Health Care and Nursing, Petrus Driessenstraat 3, 9714 CA, Groningen, the Netherlands

^b University of Groningen, University Medical Center Groningen, Department of Pulmonary Diseases and Tuberculosis, Center for Rehabilitation, PO Box 30.002, Haren, 9750 RA, Groningen, the Netherlands

^c University of Groningen, University Medical Center Groningen, Department of Maxillofacial Surgery, PO Box 30.001, 9700 RB, Groningen, the Netherlands

^d University of Groningen, Faculty of Science and Engineering, Groningen, the Netherlands

^e University of Groningen, University Medical Center Groningen, Department of Rehabilitation Medicine, Groningen, the Netherlands

^f University of Groningen, University Medical Center Groningen, Health Psychology Research, Groningen, the Netherlands

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SUMMARY

Background & aims: Malnutrition, frailty, physical frailty, and disability are common conditions in patients with chronic obstructive pulmonary disease (COPD). Insight in the coexistence and relations between these conditions may provide information on the nature of the relationship between malnutrition and frailty. Such information may help to identify required interventions to improve the patient's health status. We therefore aimed to explore whether malnutrition, frailty, physical frailty, and disability coexist in patients with COPD at the start of pulmonary rehabilitation.

Methods: For this cross-sectional study, from March 2015 to May 2017, patients with COPD were assessed at the start of a pulmonary rehabilitation program. Nutritional status was assessed with the Scored Patient-Generated Subjective Global Assessment (PG-SGA) based Pt-Global app. Frailty was assessed by the Evaluative Frailty Index for Physical activity (EFIP), physical frailty by Fried's criteria, and disability by the Dutch version of World Health Organization Disability Assessment Schedule 2.0 (WHODAS). These variables were dichotomized to determine coexistence of malnutrition, frailty, physical frailty, and disability. Associations between PG-SGA score and respectively EFIP score, Fried's criteria, and WHODAS score were analyzed by Pearson's correlation coefficient. Two tailed P-values were used, and significance was set at $P < 0.05$.

Results: Of the 57 participants included (age 61.2 ± 8.7 years), malnutrition and frailty coexisted in 40%. Malnutrition and physical frailty coexisted in 18%, and malnutrition and disability in 21%. EFIP score and PG-SGA score were significantly correlated ($r = 0.43$, $P = 0.001$), as well as Fried's criteria and PG-SGA score ($r = 0.37$, $P = 0.005$).

Conclusions: In this population, malnutrition substantially (40%) coexists with frailty. Although the prevalence of each of the four conditions is quite high, the coexistence of all four conditions is limited (11%). The results of our study indicate that nutritional interventions should be delivered by health care professionals across multiple disciplines.

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Abbreviations: EFIP, Evaluative Frailty Index for Physical activity; WHODAS, World Health Organization Disability Assessment Schedule; PR, Pulmonary Rehabilitation.

* Corresponding author. Hanze University of Applied Sciences, Research Group Healthy Ageing, Allied Health Care and Nursing, Petrus Driessenstraat 3, 9714 CA, Groningen, the Netherlands.

E-mail addresses: l.ter.beek@pl.hanze.nl (L. ter Beek), h.van.der.vaart@umcg.nl (H. van der Vaart), j.b.wempe@umcg.nl (J.B. Wempe), w.p.krijnen@pl.hanze.nl (W.P. Krijnen), c.p.van.der.schans@pl.hanze.nl (C.P. van der Schans), ha.jager@pl.hanze.nl (H. Jager-Wittenaar).

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1. Introduction

Malnutrition, frailty, physical frailty, and disability are common conditions in patients with chronic obstructive pulmonary disease (COPD). Prevalence of these conditions in patients with COPD is reported to be 11%–62% for malnutrition, 22%–58% for frailty, 7%–65% for physical frailty, and 13%–50% for disability, respectively. These prevalence rates are broad, mainly due to the different instruments used in the various studies, and differences in COPD subpopulations studied, such as outpatients, hospitalized patients, and elderly patients [1–8].

Malnutrition has been defined as “a state resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat-free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease” [9]. Frailty is considered a multidimensional clinical state, in which an individual's vulnerability for dependency or mortality is increased when exposed to a stressor, due to a lack of reserve capacity [10]. The multidimensionality of frailty is characterized by the inclusion of physical, psychological, and social domains. Various determinants of frailty have been identified within each of these domains [11]. In contrast, physical frailty is a unidimensional construct, first operationalized by Fried et al., and described as being at risk for falls, hospitalizations, disability, and death [12]. Frailty and physical frailty both are considered risk factors for disability [10]. In the International Classification of Functioning, Disability, and Health, disability is described as “a difficulty in functioning at the body, person or societal levels in one or more life domains, as experienced by an individual with a health condition in interaction with contextual factors” [13]. In approximately 50% of disabled older adults, disability develops chronically and progressively in association with underlying severity of disease, comorbidity and frailty, whereas in the other 50%, disability develops acutely or catastrophically [14].

Hence, these conditions may overlap, since all are to a large extent defined by a decrease in muscle mass, functional performance, and adverse clinical outcome. Furthermore, these conditions share social, demographic, and cognitive risk factors [15,16]. However, the underlying mechanisms differ, as malnutrition is primarily caused by an imbalance between nutritional intake and nutritional requirements, and frailty is predominantly caused by immobility, ageing and psychosocial impediments. In community-dwelling older adults and geriatric outpatients, malnutrition has been associated with physical frailty [17,18]. In clinical populations, including patients with chronic diseases, this relationship has not yet been explored, and thus it is unclear to which extent malnutrition, frailty, physical frailty, and disability coexist in clinical populations.

Although several prevalence rates of malnutrition in patients with COPD are reported, few studies reported specifically on the prevalence of malnutrition in patients with COPD in a pulmonary rehabilitation (PR) program. These prevalence rates vary from 11 to 40%, which is mostly related to the use of different assessment methods [1,19,20]. Malnutrition may be either a cause or a consequence of frailty, physical frailty, and disability. Insight in the coexistence and correlation between these conditions in patients with COPD, may help to identify required interventions to improve the patient's health status. Therefore, we aimed to assess the prevalence and coexistence of malnutrition, frailty, physical frailty, and disability in patients with COPD at the start of PR.

2. Materials and methods

2.1. Study design

This observational study is part of a larger longitudinal study. In the current study, baseline data were used in a cross-sectional analysis. Patients with COPD under the care of the Center for Rehabilitation of the University Medical Center Groningen (UMCG) were assessed in the first of their nine-week PR program, from March 2015 to May 2017. In this program, patients with COPD participated in a tailored multimodal intervention, which included exercise training, dietary counseling, education on symptom-management, and behavior change therapy [21]. The patients were assessed by a dietitian/researcher who has experience in working with patients participating in PR, with the assistance of trained nutrition and dietetics undergraduate students. All researchers were trained in performing the functioning measurements by experienced physiotherapists and in performing the PG-SGA by an expert in the PG-SGA, to ensure consistent and accurate measurements of these measurements and instrument. The study measurements were performed outside routine care, except for body weight and bio-electrical impedance analysis, which were included in routine care.

Inclusion criteria for this study were: aged ≥ 40 years old; able to understand and speak the Dutch language; diagnosed with COPD and staged GOLD 1–4 by a pulmonary physician; no severe cognitive disabilities reported in medical history; no palliative treatment; no wheelchair dependency; no contra-indication for physical exercise; no skin problems. Time of diagnosis did not exclude any participant. Patients that aimed to lose weight were excluded, since intentional weight loss has a different physiological pathway than disease-related weight loss.

The Medical Ethical Committee of the UMCG gave permission to conduct this study according to the Dutch law regarding patient-based medical research (WMO) obligation (reference 2014/432). Patient data were processed and electronically stored according to the Declaration of Helsinki – Ethical principles for medical research involving human subjects and informed consent was obtained from each participant. This study was registered in the Dutch Trial Register (NTR5107).

2.2. Measurements

Demographics and spirometry [FEV_1 (L), FEV_1 (% predicted), and FEV_1/FVC (%)] were measured at the start of PR. The content of the PR and type of rehabilitation program was assessed in a multidisciplinary meeting. Body mass index (BMI) was calculated, i.e., dividing actual measured weight by actual measured length². Fat-free mass index (FFMI) was calculated from the raw data generated by bio-electrical impedance analysis (Bodystat QuadScan 4000), using Rutten's prediction equation [22].

Nutritional status was assessed with the Scored Patient-Generated Subjective Global Assessment (PG-SGA) based Pt-Global app [23]. The PG-SGA is one of the few instruments covering all domains of the malnutrition definition and is a validated nutritional assessment tool in patients with COPD participating in PR [24,25]. The PG-SGA includes four boxes that were designed to be completed by the patient. Patients completed these boxes in the presence of the researcher(s), and if the patient was in need of assistance to fill out the box, this help was provided. Box 1 addresses the history of weight loss: percentage weight loss in the past month or past six months, and changes in weight in the past

two weeks; Box 2 evaluates changes in food intake in the past month; Box 3 addresses presence of nutrition impact symptoms (NIS) in the past two weeks; and Box 4 evaluates activities and function in the past month. In case of missing items in any box, the box's score was taken as '0'. In addition to this patient-generated component of the PG-SGA, the second component is completed by the professional. This professional component includes worksheets addressing scoring of weight loss, diseases/conditions that increase nutritional requirements, metabolic stress, and physical examination of body composition. The point score is used for screening and triaging of patients, with a score of four to eight points indicating that intervention is required by a dietitian in conjunction with a nurse or physician as indicated by symptoms. A score of nine points or higher indicates a critical need for improved symptom management and/or nutrient intervention options. The PG-SGA Category serves to categorize patients as well nourished (A), suspected/moderate malnutrition (B), or severe malnutrition (C). The scoring of the PG-SGA has been described in detail in a review on the use of the PG-SGA [26].

Frailty was assessed by the Evaluative Frailty Index for Physical activity (EFIP). EFIP is a questionnaire containing 50 items on domains of physical functioning (19 items), psychological functioning (8 items), social functioning (7 items), and general health (16 items). Total frailty score can range from 0 to 1. The cut-off point for frailty was set at >0.25 , in accordance with the original study [27]. In case of a missing item, the score was considered 0. If > 5 items were missing, the subject was excluded from the analysis.

Physical frailty was assessed by Fried's criteria, in which one point was given for each of the following criteria: unintentional weight loss, (muscle) weakness, poor endurance and energy (exhaustion), slowness, and low physical activity level. No points implied physically non-frail. One or two points were categorized as physically pre-frail, and three or more points as physically frail [12]. Unintentional weight loss of ≥ 4.5 kg (10 pounds) or $\geq 5\%$ in the last year prior to study measurement was scored as one point. When the patient could not remember the weight from 12 months ago, the weight from 6 months was used. Weakness was assessed by handgrip strength in kilograms: the highest attempt was used from three right and three left side attempts, stratified for gender and BMI, and if this was below the cut-off it was scored as one point [12]. Exhaustion was assessed by asking: 'Do you have a low energy level or do you feel tired?', if the answer was 'yes', it was scored as one point. Slowness was assessed by the 4 meter walking speed test, and stratified for gender and length, and if this was below the cut-off it was scored as one point [12]. Low physical activity level was measured by asking 'Are you active for at least 30 min per day in such a manner that you start feeling warm or start sweating?' if the answer was 'no', it was scored as one point. Patients with more than one item missing on the Fried's criteria were excluded from the analysis.

Disability was assessed by the Dutch version of World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) [28]. The WHODAS contains 36 items in the following domains: Understanding & Communicating; Getting around; Self-care; Getting along with people; Domestic Life activities; Participation in society. Scoring was performed using a 5 point scale: non, mild, moderate, severe, and extreme/cannot do. Disability was defined as a score of 41 out of 100 or higher, which is the cut-off value for the worst scoring 10% percentile of the population [29] and has been used as cut-off point for moderate up to severe and extreme disability [8]. Missing data were handled as instructed by the WHODAS manual, i.e. missing data were replaced by the mean of the other scores within the domain, limited to a maximum of 30% missings [29]. If more than 30% of the WHODAS data were missing, the participant was excluded from the analysis. Scores were

calculated without scores for work or study, since most of the patients did not work or study [29].

2.3. Statistical analyses

The categorical variables gender, social status, smoking status, GOLD classification, nutritional status, frailty status, physical frailty status, and disability status were presented as numbers and percentages. The continuous variables age, BMI, spirometry, FFMI, EFIP score, Fried's score, and WHODAS score were normally distributed and presented as mean and standard deviation (SD). The PG-SGA score, as an ordinal variable, was presented as median and interquartile range. To determine coexistence of malnutrition, frailty, physical frailty, and disability, the data were dichotomized into affected/not affected, based on the described cut-off points. Associations between PG-SGA score and respectively EFIP score, Fried's criteria score, and WHODAS score were analyzed by Pearson's correlation coefficient. Two tailed P-values were used, and significance was set at $P < 0.05$. Data were analyzed using IBM SPSS version 23.0 (SPSS Inc., Chicago, IL, USA).

3. Results

In total, 202 consecutive patients were asked to participate in the study, and 106 patients gave informed consent. Fig. 1 shows the inclusion procedure applied. Out of 106 patients, 17 did not enter the rehabilitation program, and an additional 11 patients were not included in the study, because of non-verified diagnosis of COPD ($N = 5$), having second thoughts about expected burden from participation in the study ($N = 4$), or logistic reasons ($N = 2$). Out of 78 participants, 17 were excluded from the analysis because they aimed to lose weight. Of the remaining 61 participants, 4 were excluded because of missing data on malnutrition, frailty, physical frailty, or disability. The remaining 57 participants were included in the analysis. Table 1 shows the characteristics of the study population. Fifty-one percent of the participants were female, mean age was 61.2 ± 8.7 years, and mean FEV₁ (% pred) was $36.11 \pm 14.68\%$. Mean BMI was 23.2 ± 4.6 kg/m² and mean FFMI was 16.2 ± 2.2 kg/m². Of the 57 participants, 37 (65%) lived with a partner.

Of all participants, 46% percent (26/57) were categorized as malnourished (PG-SGA Stage B or C). The median PG-SGA score of all participants was 7 (IQR: 4–11.5) points. In all participants, the highest median score per PG-SGA Box or Worksheet was found in Box 3: 2 (IQR: 0–5) points. The most frequently reported nutrition impact symptoms in Box 3 were lack of appetite ($N = 17$), fatigue ($N = 17$), feel full quickly ($N = 16$), and dry mouth ($N = 12$). The mean (SD) EFIP score of all participants was 0.34 ± 0.11 points. In total, 83% of the participants were frail, 4% were pre-frail, 28% were physically frail, and 63% were physically pre-frail. Mean (SD) WHODAS score of all participants was 38.1 ± 13.6 points, and 33% were disabled. In six patients (11%), malnutrition, frailty, physical frailty, and disability coexisted, whereas six (11%) patients did not have any of these conditions. Fig. 2 shows the coexistence of the four conditions.

3.1. Coexistence between malnutrition and frailty

Malnutrition and frailty coexisted in 40% (23/57) of the participants. Of all 47 frail participants, 49% were malnourished, and of all malnourished participants, 89% (23/26) were frail. The EFIP score and PG-SGA score were significantly correlated ($N = 57$, $r = 0.43$, $P = 0.001$), as seen in Fig. 3. Frail participants scored more frequently on problems in the domain of general health: 50% (16/32). Of all points, 43% (6/14) were scored in the social domain, 32%

Fig. 1. Flow chart of inclusion procedure.

(12/38) in the domain of physical function, and 31% (5/16) in the psychological domain.

3.2. Coexistence between malnutrition and physical frailty

Malnutrition and physical frailty coexisted in 18% (10/57). Of all physically frail participants, 63% (10/16) were malnourished. In contrast, of all malnourished participants, 39% (10/26) were physically frail. Fried's criteria score and PG-SGA score were significantly correlated ($N = 57$, $r = 0.37$, $P = 0.005$). Physically frail participants scored most frequently on low activity (88%; 14/16) and exhaustion (94%; 15/16). Of all 57 participants, 23 scored on unintentional weight loss.

3.3. Coexistence between malnutrition and disability

Malnutrition and disability coexisted in 21% (12/57). Of all disabled participants, 63% (12/19) were malnourished, whereas of malnourished participants, 46% (12/26) were disabled. The

WHODAS score and PG-SGA score did not significantly correlate ($N = 57$, $r = 0.19$, $P = 0.163$). Disabled participants scored most frequently on the domain of 'domestic life activities' (86% of maximum score), followed by the domain of 'getting around' (65% of maximum score), and 'participation in society' (60% of maximum score).

4. Discussion

Our study is the first study exploring the relations between malnutrition, frailty, physical frailty, and disability in patients with COPD. In this population, malnutrition and frailty substantially coexist. Although the prevalence of each of the four conditions is quite high, the coexistence of all four conditions is limited.

In this study, we found that a very large majority of patients with COPD at the start of a PR program is frail (83%). This is a remarkable finding, as frailty is considered a geriatric syndrome [30], and the mean age of our patients was only 61 years. The mean age of other COPD study populations that were studied for

Table 1
Characteristics of the population studied (n = 57).

	N (%)
Age (years), mean±SD ^a	61.2 ± 8.7
Gender	
Male	28 (49)
Female	29 (51)
Social status	
Living alone	19 (33)
With partner	37 (65)
Missing	1 (2)
BMI ^b (kg/m ²), mean ± SD	23.2 ± 4.6
Spirometry ^c	
FEV ₁ (L)	1.01 ± 0.48
FEV ₁ (% predicted)	36.1 ± 14.7
FEV ₁ /FVC (%)	35.3 ± 10.4
FFMI ^d (kg/m ²), mean ± SD	16.2 ± 2.2
Smoking	
Current smoker	15 (32)
Never smoker	1 (2)
Former smoker	38 (67)
Missing	3
GOLD ^e	
1	1
2	10
3	23
4	23
Nutritional status	
PG-SGA ^f Stage A	31 (54)
PG-SGA Stage B/C	26 (46)
PG-SGA score, median (IQR)	7 (4–11.5)
Frailty	
Pre-frail	2 (4)
(EFIP score ^g 0.2–0.25)	
Frail	47 (83)
(EFIP score >0.25)	
EFIP score, mean ± SD	0.34 ± 0.11
Physical frailty (Fried)	
Pre-frail (1–2 points)	36 (63)
Frail (3–5 points)	16 (28)
Disability	
No/mild disability	38 (67)
(WHODAS ^h < 41)	
Disability	19 (33)
(WHODAS 41–100)	
WHODAS score, mean ± SD	38.1 ± 13.6

^a Standard deviation.

^b Body mass index.

^c FEV₁: forced expiratory volume in the first second; FVC: forced vital capacity.

^d Fat-free mass index.

^e Disease classification according to the Global Initiative for Chronic Obstructive Lung Disease.

^f The Scored Patient-Generated Subjective Global Assessment.

^g The Evaluative Frailty Index for Physical activity.

^h World Health Organization Disability Assessment Schedule 2.0.

prevalence of frailty, has been reported to be 10–15 years older [3,4]. This finding may be related to various consequences of COPD being a systemic disease. These patients experience problems in various domains, which not only concern physical, but cognitive, social, and psychological aspects as well [31]. Being the most prominent symptom in COPD, dyspnea can heavily impact social relations and can result in psychological stress, since patients experience barriers to engage in activities and relationships [32]. Furthermore, low oxygen saturation may result in cognitive disabilities [33], which may hinder patients in finding solutions for obstacles in daily activities, such as grocery shopping and cooking, but also in personal relationships. Furthermore, inflammation activity may also play a role in high prevalence of frailty in this COPD population [12]. Moreover, COPD is a disease that is caused by cigarette smoke, which can result in ‘collateral damage’ or

Fig. 2. Proportional Venn diagram of the coexistence of malnutrition, physical frailty, frailty and disability in patients with COPD (n = 57).

Fig. 3. Scatter plot of PG-SGA score and EFIP score with a horizontal line at PG-SGA score 9 (cut-off for critical need for improved symptom management and/or nutrition intervention options) and vertical line at EFIP score 0.25 (cut-off for frailty).

comorbidities from smoking, that may contribute to the high prevalence of frailty in our patients [34]. In addition, people who smoke often have a lower level of education and income [35], and as result may have limited means to pursue a healthy lifestyle, i.e., exercise, healthy diet, each contributing to a higher risk of frailty as well. Nevertheless, we do not know whether our patients had a low level of income or education. Previous studies in patients with COPD reported prevalence rates of frailty up to 58%, which is much lower than the prevalence found in our study. This might be caused by differences between the COPD populations that differed regarding clinical stability and disease stage, as well as the different parameters used to assess frailty [3,4,36,37]. Frailty in patients with other chronic diseases, such as end stage renal disease, is reported to be 37% up to 67%, depending on the parameters used [38].

With more than one-quarter being physically frail, the prevalence of this specific subtype of frailty in the studied group of patients with COPD is substantial. This finding is comparable to the prevalence found in a prospective cohort study in patients with COPD participating in PR [39]. The construct of physical frailty is based on factors that closely relate to muscle mass and muscle

function, i.e., weakness, slowness, exhaustion, poor endurance, weight loss. The high prevalence of 28% of physical frailty reported in our study may be explained by common disease symptoms in patients with COPD, such as inadequate intake of protein and energy, limited physical activity, and inflammation. These symptoms are likely to enhance muscle wasting, which is commonly present in patients with COPD, and which is closely related to physical frailty [12].

However, the patients in our study population had a normal BMI and borderline normal FFMI. This finding is in line with results on body composition in other studies in patients with COPD in a PR program [19,20]. Although BMI and FFMI were within normal ranges in our study population, substantial loss of muscle mass may have occurred. For example, a patient currently weighing 70 kg at a length of 1.73 m, has a BMI of 23.4 kg/m². However, this patient may have lost 7 kg (10% of total body weight) in one month, e.g., during exacerbation, indicating severe loss, which is known to be accompanied by loss of muscle mass [9]. Of all participants in our study, 40% reported to have experienced unintentional weight loss of ≥ 4.5 kg or $\geq 5\%$ in the last year prior to study measurement.

To the best of our knowledge, thus far no studies have addressed the coexistence of, or the association between malnutrition and frailty, although previous studies have addressed the association between malnutrition and physical frailty in community-dwelling older adults and in general hospital populations [15,17]. In our study, malnutrition and frailty coexisted in 40% of the patients and malnutrition and physical frailty coexisted in 18%. The fairly substantial correlations found between PG-SGA score and EFIP score ($r = 0.43$) and Fried's criteria ($r = 0.37$) imply that we need to determine whether malnutrition impacts on frailty and physical frailty in this population, and to what extent. Malnutrition, frailty, and physical frailty are multidimensional constructs, based on various different contributing factors, and therefore it is more difficult to interpret their relations. The contributing factors generate a deeper insight into the patient's needs with regard to the construct, so that health care professionals can provide individualized care. Furthermore, EFIP scores for frailty in our participants ranged between 0 and 0.6 (on a scale of 0–1), which means that the range was quite small. This small range underlines that our participants were a specific subgroup, i.e., severe deconditioned COPD patients starting a PR program. From this finding we can speculate that malnutrition and frailty may influence each other. The significant association between malnutrition and physical frailty has previously been confirmed in a systematic review and meta-analysis on malnutrition and physical frailty in community-dwelling adults [36]. Studies reported a strong association between physical frailty and (risk for) malnutrition, but no interchangeability, similar to our findings [40]. This may be explained by the difference in underlying biological mechanisms. Malnutrition is primarily caused by an imbalance between nutritional intake or uptake and nutritional need [9], whereas physical frailty is primarily caused by immobility and ageing [12,41].

The findings of our study have several implications for clinical practice. Malnutrition may be a risk factor for frailty and physical frailty, but on the other hand malnutrition might also be a consequence of frailty and physical frailty. If we address nutrition impact symptoms that may lead to malnutrition and frailty, such as nausea, fatigue, pain, and lack of appetite, we may be able to prevent or treat frailty. With regard to the chronic lung disease population, it has been recommended to use instruments for screening or assessment of (physical) frailty that detect both characteristics and risk factors for malnutrition, such as significant loss of muscle mass or decreased food intake [42]. As loss of muscle due to malnutrition may contribute to frailty, and the cognitive and psychosocial impairments that often occur in frail patients may hinder the

treatment of malnutrition, these obstacles need to be addressed to successfully treat malnutrition and possible frailty and disability. Studies have reported on successful nutritional and exercise interventions in malnourished COPD patients, such as dietary counseling, nutritional supplements and high intensity exercise training [43,44]. The results of our study indicate that nutritional interventions, such as intake of sufficient protein combined with resistance training or prescription of anti-emetic drugs, should be delivered by health care professionals across multiple disciplines. Future studies need to determine whether these interventions improve frailty status and prevent disability in patients with COPD. Since malnutrition is a multidimensional condition, it may require adequate care from different health care professionals such as dietitians, nurses, physiotherapists, psychologists, and physicians.

Our study has some limitations that need to be addressed. First, our study had a cross-sectional design with a relatively small sample. Therefore, we cannot establish any causal relations between the conditions. Second, our study population consisted of COPD patients referred for tertiary rehabilitation, and the results may not generalize to the whole group of patients with COPD, limiting generalizability. Third, the EFIP questionnaire that we used has been validated in a sample of community-dwelling elderly and elderly living in a residential care facility, all aged 65 years old or older, and not in COPD patients. However, frailty is not disease-specific, but instead is considered a general lack of reserve capacity [10]. Therefore we considered the use of the EFIP appropriate in the current study. Some of the items included in the EFIP are not, or less discriminating in COPD patients, such as the item 'COPD/breathing problems' and the use of 'more than 4 drugs'. Nevertheless, the EFIP is the Dutch adaptation of the 'accumulation of deficits' Frailty Index by Mitnitski et al., and the method of deficit accumulation is reported to be the most appropriate method to evaluate frailty [11,27].

In conclusion, since malnutrition and frailty coexist in a substantial proportion of patients with COPD starting a PR program, there is a strong need to create more awareness of their correlation and their potential impact on each other. Therefore we recommend to implement systematic nutritional assessment and triaging for interdisciplinary interventions. Future research should be of longitudinal design, studying effectiveness of interventions and the possibly dynamic relation between malnutrition and frailty, both in patients with COPD that are starting PR and in those who are receiving other types of care.

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CrediT authorship contribution statement

L. ter Beek: Conceptualization, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Project administration.

H. van der Vaart: Conceptualization, Methodology, Resources, Validation, Writing – review & editing.

J.B. Wempe: Conceptualization, Methodology, Resources, Writing – review & editing, Visualization.

W.P. Krijnen: Formal analysis, Writing – review & editing.

J.L.N. Roodenburg: Conceptualization, Methodology, Writing – review & editing, Supervision.

C.P. van der Schans: Conceptualization, Methodology, Writing – review & editing, Supervision.

H. Jager-Wittenaar: Conceptualization, Methodology, Validation, Writing – review & editing, Visualization, Supervision.

Conflict of Interest

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References

- [1] Ng MGS, Kon SSC, Canavan JL, Clark AL, Nolan CM, Jones SE, et al. Prevalence and effects of malnutrition in COPD patients referred for pulmonary rehabilitation. *Eur Respir J* 2013;42:5107.
- [2] Luo Y, Zhou L, Li Y, Guo S, Li X, Zheng J, et al. Fat-free mass index for evaluating the nutritional status and disease severity in COPD. *Respir Care* 2016;61:680–8.
- [3] Kusunose M, Oga T, Nakamura S, Hasegawa Y, Nishimura K. Frailty and patient-reported outcomes in subjects with chronic obstructive pulmonary disease: are they independent entities? *BMJ Open Respir Res* 2017;4:e000196. 2017-000196. eCollection 2017.
- [4] Park SK, Richardson CR, Holleman RG, Larson JL. Frailty in people with COPD, using the national health and nutrition evaluation survey dataset (2003–2006). *Heart Lung* 2013;42:163–70.
- [5] Limpawattana P, Putraveephong S, Inthasuwana P, Boonsawat W, Theerakulpisut D, Chindaprasit J. Frailty syndrome in ambulatory patients with COPD. *Int J Chronic Obstr Pulm Dis* 2017;12:1193–8.
- [6] Valenza MC, Torres-Sánchez I, Cabrera-Martos I, Rodríguez-Torres J, González-Jiménez E, Muñoz-Casabonn T. Physical activity as a predictor of absence of frailty in subjects with stable COPD and COPD exacerbation. *Respir Care* 2016;61:212–9.
- [7] Martinez CH, Richardson CR, Han MK, Cigolle CT. Chronic obstructive pulmonary disease, cognitive impairment, and development of disability: the health and retirement study. *Ann Am Thorac Soc* 2014;11:1362–70.
- [8] de Pedro-Cuesta J, Alberquilla A, Virues-Ortega J, Carmona M, Alcalde-Cabero E, Bosca G, et al. ICF disability measured by WHO-DAS II in three community diagnostic groups in Madrid, Spain. *Gac Sanit* 2011;25(Suppl 2):21–8.
- [9] Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. *Clin Nutr* 2017;36:49–64.
- [10] Morley JE, Vellas B, van Kan GA, Anker SD, Bauer JM, Bernabei R, et al. Frailty consensus: a call to action. *J Am Med Dir Assoc* 2013;14:392–7.
- [11] de Vries NM, Staal JB, van Ravensberg CD, Hobbelen JS, Olde Rikkert MG, Nijhuis-van der Sanden MW. Outcome instruments to measure frailty: a systematic review. *Ageing Res Rev* 2011;10:104–14.
- [12] Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;56:M146–56.
- [13] Leonardi M, Bickenbach J, Ustun TB, Kostanjsek N, Chatterji S, MHADIE Consortium. The definition of disability: what is in a name? *Lancet* 2006;368:1219–21.
- [14] Ferrucci L, Guralnik JM, Simonsick E, Salive ME, Corti C, Langlois J. Progressive versus catastrophic disability: a longitudinal view of the disablement process. *J Gerontol A Biol Sci Med Sci* 1996;51:M123–30.
- [15] Boulos C, Salameh P, Barberger-Gateau P. Malnutrition and frailty in community dwelling older adults living in a rural setting. *Clin Nutr* 2016;35:138–43.
- [16] Jeejeebhoy KN. Malnutrition, fatigue, frailty, vulnerability, sarcopenia and cachexia: overlap of clinical features. *Curr Opin Clin Nutr Metab Care* 2012;15:213–9.
- [17] Wei K, Nyunt MSZ, Gao Q, Wee SL, Ng TP. Related and distinct syndrome prevalence and association among community-dwelling older adults: Singapore longitudinal ageing studies. *J Am Med Dir Assoc* 2017;18:1019–28.
- [18] Kurku M, Meijer RI, Lonterman S, Muller M, de van der Schueren MAE. The association between nutritional status and frailty characteristics among geriatric outpatients. *Clin Nutr ESPEN* 2018;23:112–6.
- [19] Günay E, Kaymaz D, Selçuk NT, Ergün P, Sengül F, Demir N. Effect of nutritional status in individuals with chronic obstructive pulmonary disease undergoing pulmonary rehabilitation. *Respirology* 2013;18:1217–22.
- [20] Marco E, Sánchez-Rodríguez D, Dávalos-Yerovi VN, Duran X, Pascual EM, Muniesa JM, et al. Malnutrition according to ESPEN consensus predicts hospitalizations and long-term mortality in rehabilitation patients with stable chronic obstructive pulmonary disease. *Clin Nutr* 2019;38:2180–6.
- [21] Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med* 2013;188. e13–e64.
- [22] Rutten EP, Spruit MA, Wouters EF. Critical view on diagnosing muscle wasting by single-frequency bio-electrical impedance in COPD. *Respir Med* 2010;104:91–8.
- [23] Sealy MJ, Haß U, Ottery FD, van der Schans CP, Roodenburg JLN, Jager-Wittenaar H. Translation and cultural adaptation of the scored patient-generated subjective global assessment (PG-SGA): an interdisciplinary nutritional instrument appropriate for Dutch cancer patients. *Cancer Nurs* 2018;41:450–62.
- [24] Sealy MJ, Nijholt W, Stuiver MM, van der Berg MM, Roodenburg JL, van der Schans CP, et al. Content validity across methods of malnutrition assessment in patients with cancer is limited. *J Clin Epidemiol* 2016;76:125–36.
- [25] Bauer J, Egan E, Clavarino A. The scored patient-generated subjective global assessment is an effective nutrition assessment tool in subjects with chronic obstructive pulmonary disease. *Clin Nutr ESPEN* 2011;6. e27–e30.
- [26] Jager-Wittenaar H, Ottery FD. Assessing nutritional status in cancer: role of the patient-generated subjective global assessment. *Curr Opin Clin Nutr Metab Care* 2017;20:322–9.
- [27] de Vries NM, Staal JB, Olde Rikkert MG, Nijhuis-van der Sanden MW. Evaluative frailty index for physical activity (EFIP): a reliable and valid instrument to measure changes in level of frailty. *Phys Ther* 2013;93:551–61.
- [28] Garin O, Ayuso-Mateos JL, Almansa J, Nieto M, Chatterji S, Vilagut G, et al. Validation of the “World health organization disability assessment Schedule, WHODAS-2” in patients with chronic diseases. *Health Qual Life Outcomes* 2010;8:51. 7525–8–51.
- [29] Üstün TB, Kostanjsek N, Chatterji S, Rehm J. WHODAS 2.0 manual. Malta. World Health Organization; 2010.
- [30] Rockwood K, Mitnitski A. Frailty defined by deficit accumulation and geriatric medicine defined by frailty. *Clin Geriatr Med* 2011;27:17–26.
- [31] Brien SB, Stuart B, Dickens AP, Kendrick T, Jordan RE, Adab P, et al. Independent determinants of disease-related quality of life in COPD – scope for nonpharmacologic interventions? *Int J Chronic Obstr Pulm Dis* 2018;13:247–56.
- [32] Blinderman CD, Homel P, Billings JA, Tennstedt S, Portenoy RK. Symptom distress and quality of life in patients with advanced chronic obstructive pulmonary disease. *J Pain Symptom Manag* 2009;38:115–23.
- [33] Liesker JJ, Postma DS, Beukema RJ, ten Hacken NH, van der Molen T, Riemersma RA, et al. Cognitive performance in patients with COPD. *Respir Med* 2004;98:351–6.
- [34] Kojima G, Iliffe S, Jivraj S, Liljas A, Walters K. Does current smoking predict future frailty? The English longitudinal study of ageing. *Age Ageing* 2018;47:126–31.
- [35] Maralani V. Understanding the links between education and smoking. *Soc Sci Res* 2014;48:20–34.
- [36] Galizia G, Cacciatore F, Testa G, Della-Morte D, Mazzella F, Langellotto A, et al. Role of clinical frailty on long-term mortality of elderly subjects with and without chronic obstructive pulmonary disease. *Ageing Clin Exp Res* 2011;23:118–25.
- [37] Bernabeu-Mora R, Garcia-Guillamon G, Valera-Novella E, Giménez-Giménez LM, Escolar-Reina P, Medina-Mirapeix F. Frailty is a predictive factor of readmission within 90 days of hospitalization for acute exacerbations of chronic obstructive pulmonary disease: a longitudinal study. *Ther Adv Respir Dis* 2017;11:383–92.
- [38] Kojima G. Prevalence of frailty in end-stage renal disease: a systematic review and meta-analysis. *Int Urol Nephrol* 2017;49:1989–97.
- [39] Maddocks M, Kon SS, Canavan JL, Jones SE, Nolan CM, Labey A, et al. Physical frailty and pulmonary rehabilitation in COPD: a prospective cohort study. *Thorax* 2016;71:988–95.
- [40] Verlaan S, Ligthart-Melis GC, Wijers SL, Cederholm T, Maier AB, de van der Schueren MAE. High prevalence of physical frailty among community-dwelling malnourished older adults-A systematic review and meta-analysis. *J Am Med Dir Assoc* 2017;18:374–82.
- [41] Laur CV, McNicholl T, Valaitis R, Keller HH. Malnutrition or frailty? Overlap and evidence gaps in the diagnosis and treatment of frailty and malnutrition. *Appl Physiol Nutr Metab* 2017;42:449–58.
- [42] Luckhardt T, Thannickal VJ. Measures of frailty in chronic lung diseases. *Ann Am Thorac Soc* 2017;14:1266–7.
- [43] Collins PF, Stratton RJ, Elia M. Nutritional support in chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Am J Clin Nutr* 2012;95:1385–95.
- [44] van de Boel C, Rutten EPA, van Helvoort A, Franssen FME, Wouters EFM, Schols AMWJ. A randomized clinical trial investigating the efficacy of targeted nutrition as adjunct to exercise training in COPD. *J Cachexia Sarcopenia Muscle* 2017;8:748–58.