Disease-related malnutrition and nutritional assessment in clinical practice

ter Beek, Lies

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

Submitted

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ABSTRACT

Background We 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 Our study is the first study exploring the relations between malnutrition, frailty, physical frailty, and disability in patients with COPD. 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 interdisciplinary (nutritional) interventions are indicated.

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% to 62% for malnutrition, 22%-58% for frailty, 7%-65% for physical frailty, and 13% to 50% for disability, respectively, depending on the various instruments used and specific COPD subpopulation 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 seem to be overlapping, 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. 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, as example of a chronic disease, may help to identify required interventions to improve the patient's health status. Adequate interventions may reverse frailty and disability in patients with COPD. Therefore, we aimed to assess the

prevalence and coexistence of malnutrition, frailty, physical frailty, and disability in patients with COPD at the start of a pulmonary rehabilitation program (PR).

METHODS

Study design

For this observational study, patients with COPD under the care of the Center for Rehabilitation of the University Medical Center Groningen (UMCG), were assessed at the start of PR, from March 2015 to May 2017. In this program, patients with COPD participate in a tailored multimodal intervention, which includes exercise training, dietary counselling, education, and behavior change therapy.[19]

Inclusion criteria for this study were: aged ≥40 years; 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 wheel-chair dependency; no contra-indication for physical exercise; no skin problems. 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. This study was registered in the Dutch Trial Register ('Dutch Trial Register') with registration number NTR5107.

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, dividing actual measured weight by actual measured length^2. Fat-free mass index (FFMI) was calculated from the raw data generated by bio-electrical impedance analyses (Bodystat QuadScan 4000), using Rutten's prediction equation.[20]

Nutritional status was assessed with the Scored Patient-Generated Subjective Global Assessment (PG-SGA) based Pt-Global app.[21] The PG-SGA is one of the few instruments covering all domains of the malnutrition definition.[22] The PG-SGA includes four Boxes to be completed by the patient. 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, its Box score was taken as '0'. In addition to this patient-generated part of the PG-SGA, the second part is completed by the professional. This professional part addresses metabolic stress, comorbidities and physical examination of body composition. The point score is used for screening and triaging of patients, whereas 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 elsewhere.[23]

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. [24] 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] Weight loss was assessed as present in case of unintentional weight loss of ≥4.5 kg (10 pounds) or ≥5% in the last year prior to study measurement. 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 score was used from three right and three left side attempts, stratified for gender and BMI. Exhaustion was assessed by asking: 'Do you have a low energy level or do you feel tired?' Slowness was assessed by 4 meter walking speed, recalculated into 15 ft and stratified for gender and length. Low physical activity level was measured by asking 'Are you active for at least 30 minutes per day in such a manner that you start feeling warm or start sweating?'. Patients with more than one item missing on the Fried's criteria were excluded from the analyses.

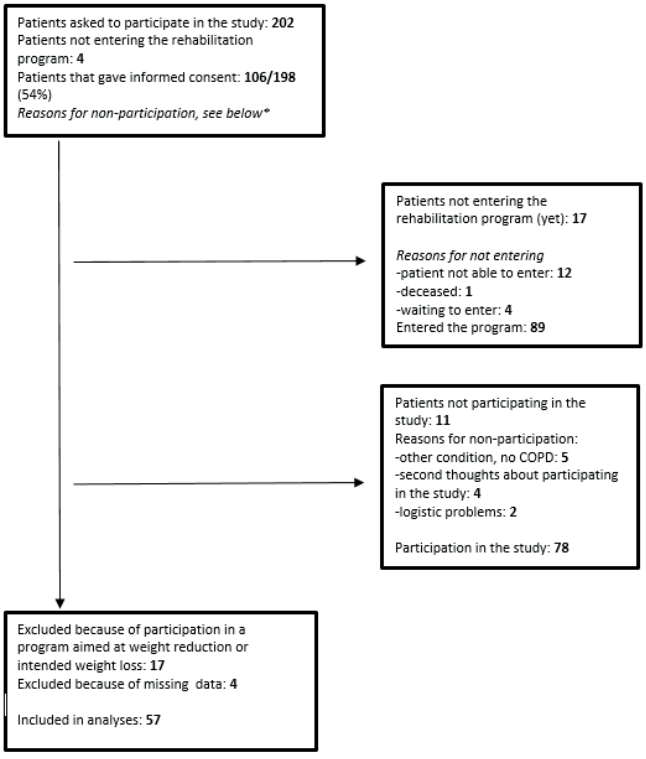
Disability was assessed by the Dutch version of World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0).[25] The WHODAS contains 36 items in the following domains: Understanding & Communicating; Getting around; Self-care; Getting along with people; Domestic Life activities; Participation 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 [26] 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.[26] If more than 30% of the WHODAS data were missing, the participant was excluded from the analyses. Scores were calculated without scores for work or study, as most of the patients did not participate in work or study.[26]

Statistical analyses

Categorical variables were presented as numbers and percentages. Continuous variables were presented as mean (SD). 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).

RESULTS

In total, 202 consecutive patients were asked to participate in the study, and 106 patients gave informed consent. **Figure 1** shows the inclusion procedure applied.



*Reasons for non-participation (N=92)

No specific reason given	59
Perceived burden	20
Not interested	13

Figure 1 Flow chart of inclusion procedure

Out of 106 patients, 17 did not enter the rehabilitation program, and an additional 11 patients were not included in the study, because of no 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 analyses 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 taken for analyses. **Table 1** shows the baseline characteristics of the study population**.** Fifty-one percent of the participants were female, mean age was 61.2 ± 8.7 years, and mean FEV_1%pred was 36.11 ± 14.68

Table 1. Patient characteristics/Study population (n=57)

	N (%) or mean ± SD
Age mean SD	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	23.2 ± 4.6
Spirometry	
FEV_1 (L)	1.01 ± 0.48
FEV_1 (% predicted)	36.1 ± 14.7
FEV_1/FVC (%)	35.3 ± 10.4
FFMI	16.2 ± 2.2
Smoking	
Current smoker	15 (32)
Never smoker	1 (2)
Former smoker	38 (67)
Missing	3
GOLD	
1	1
2	10
3	23
4	23

Of all participants, 46% percent (26/57) was categorized as malnourished (PG-SGA Stage B or C). The median PG-SGA score of all participants was 7 (IQR: 4-11.5). In all participants, the highest median score per PG-SGA Box or Worksheet was found in Box 3: 2 (IQR: 0-5). 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). In total, 38% 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, 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. **Figure 2** visualizes the coexistence of the four conditions.

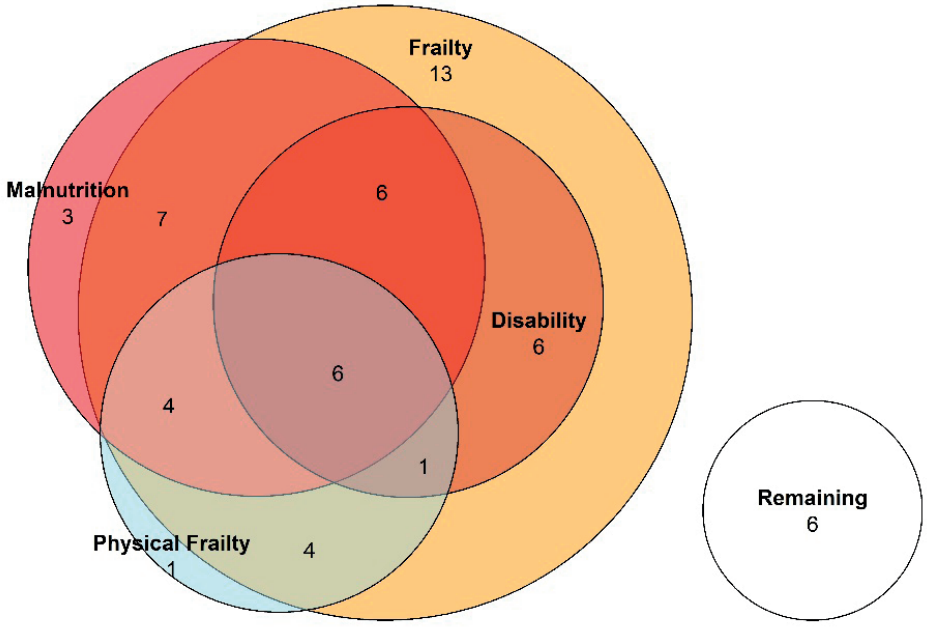


Figure 2 Proportional Venn diagram of the coexistence of malnutrition, physical frailty, frailty and disability in patients with COPD (n=57)

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) was frail. The EFIP score and PG-SGA score were significantly correlated (N=57, r=0.43, P=0.001), as visualized in **Figure 3**. Frail participants scored relatively most frequently on problems in the domain of general health: 50% (16/32). Forty-three % (6/14) of the points were scored in the social domain, 32% (12/38) in the domain of physical function, and 31% (5/16) in the psychological domain.

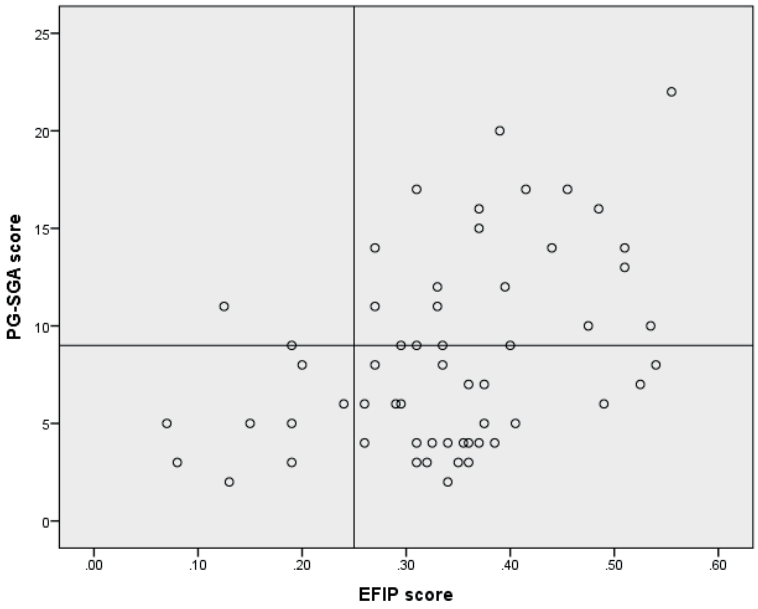


Figure 3 Scatter plot of correlation between PG-SGA score and EFIP score with lines at PG-SGA score 9 (cut-off for critical need for improved symptom management and/or nutrition intervention options) and EFIP score 0.25 (cut-off for frailty)

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).

Coexistence between malnutrition and disability

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

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 (40%). Although the prevalence of each of the four conditions is quite high, the coexistence of all four conditions is limited (11%).

In this study, we found that a very large majority of patients with COPD at the start of a pulmonary rehabilitation program is frail (83%). This is a remarkable finding, as frailty is considered a geriatric syndrome[27], and the mean age of our patients was only 61 years. 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 areas as well.[28] Dyspnea, the most prominent symptom in COPD, can heavily impact social relations and can result in psychological stress, since patients experience barriers to engage in activities and relationships.[29] Furthermore, low oxygen saturation may result in cognitive disabilities, [30] which may hinder patients in finding solutions for obstacles in daily activities, such as grocery shopping and cooking, but also in relationships. Another way COPD may be associated with frailty is by its inflammatory activity.[12] Moreover, COPD is a disease that is caused by cigarette smoke, which can result in 'collateral damage' or comorbidities from smoking, that may contribute to the high prevalence of frailty in our patients. In addition, people who smoke often have a lower level of education and income [31] 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. Previous studies in patients with COPD reported prevalence rates of frailty up to 58%, which is much lower than our results. This might be caused by differences between the patient groups, such as clinical stability and disease stage of the COPD patients included and the different parameters used.[3,4,32,33] 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. [34]

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 participating in pulmonary rehabilitation. [35] Other studies that evaluated physical frailty in patients with COPD reported prevalence rates varying from 7% up to 65%, depending on the specific subpopulation of patients with COPD and/or instrument used.[5,6] 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 is closely related to physical frailty.[12]

Several studies have addressed the association between malnutrition and physical frailty in studies on community-dwelling older adults and in general hospital populations.[15,17] To the best of our knowledge, thus far no studies have addressed the coexistence of, or the association between malnutrition and frailty. In our study, malnutrition and frailty coexisted in 40% of the patients malnutrition and physical frailty in 18% respectively. The fairly substantial correlations found between PG-SGA score and EFIP score (r=0.43) and Fried's criteria (r=0.37) respectively, 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, therefore it is more difficult to interpret their relations. The contributing factors give us a 'profile' of the patient with regard to the construct. Furthermore, EFIP scores for frailty in our participants ranged between 0 and 0.6 (on a scale of 0 to 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 rehabilitation 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.[36] 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[12,37]

Several implications for clinical practice follow from our study. Malnutrition may be hypothesized a risk factor for frailty and physical frailty, but on the other hand 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 reduce frailty. With regard to the chronic lung disease population, it has been recommended to use instruments that detect nutritional impairments which characterize (physical) frailty.[38] As loss of muscle due to malnutrition may contribute to frailty, and the cognitive and psychosocial impediments that often occur in frail patients may hinder the treatment of malnutrition, these obstacles need to be addressed to successfully treat malnutrition and possibly frailty and disability. Studies have reported on successful nutritional and exercise interventions in malnourished COPD patients, such as dietary counselling, nutritional supplements and high intensity exercise training.[39,40] The results of our study indicate that interdisciplinary (nutritional) interventions are required, and 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 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 size. 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 generalizable to the whole group of patients with COPD. 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 or older, and not in COPD patients. However, frailty is not a disease-specific condition, 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/problems breathing' 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.[11,24]

In conclusion, our study is the first to explore the relations between malnutrition, frailty, physical frailty, and disability in patients with COPD. Since malnutrition and frailty coexist in a substantial proportion of patients with COPD starting a pulmonary rehabilitation 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.

ACKNOWLEDGEMENTS

We acknowledge the World Health Organization for their permission to use the WHODAS 2.0.

We would like to thank our students from the Hanze University of Applied Sciences: Ellen Raeymaekers, Annelies Gilops, Robbin Bossen, Kevin Vangeel, Eline Holvoet, and Marije Rolsma for their help in collecting the data.

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