Respiratory Medicine 201 (2022) 106944

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Original Research

# Stability of distinct symptom experiences in patients with chronic obstructive pulmonary disease (COPD)

Vivi L. Christensen [a,*], Tone Rustøen [b,c], Magne Thoresen [d], Are M. Holm [e,f], Signe B. Bentsen [g]

[a] Department of Nursing and Health Sciences, Faculty of Health and Social Sciences, University of South-Eastern Norway, Drammen, Norway
[b] Institute of Health and Society, Department of Nursing Science, University of Oslo, Oslo, Norway
[c] Department of Research and Development, Division of Emergencies and Critical Care, Oslo University Hospital, Oslo, Norway
[d] Department of Biostatistics, Faculty of Medicine, University of Oslo, Oslo, Norway
[e] Department of Respiratory Medicine, Oslo University Hospital, Oslo, Norway
[f] Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway
[g] Department of Health and Caring Sciences, Western Norway University of Applied Sciences, Haugesund, Norway

ARTICLE INFO

*Keywords:*
Symptom burden
Subgroups
Longitudinal
Stability
Latent class analyses

ABSTRACT

*Purpose:* This study aimed to examine reclassification rates among classes of chronic obstructive pulmonary disease (COPD) patients based on their distinct symptom experiences and to assess how these subgroups differed in symptom scores and health-related quality of life (HRQoL) outcomes over one year. Moreover, we wished to assess how these subgroups differed in demographic and clinical characteristics at 12 months.

*Patients and methods:* This is a follow-up study of 267 patients with moderate, severe, and very severe COPD. Based on their distinct symptom experiences using the Memorial Symptom Assessment Scale (MSAS), three subgroups (i.e., "high", "intermediate", and "low") were identified at baseline. In the present study, transitions between the subgroups at three, six, nine, and 12 months were investigated and calculated as reclassification rates. Differences among the subgroups in symptom scores and HRQoL at each time point and demographic and clinical characteristics at 12 months were evaluated using analysis of variance with post hoc comparisons.

*Results:* Almost 65% were still in the "high" class after 12 months. At 12 months, pairwise comparisons for respiratory function measurements were not significantly different. Compared to the "intermediate" and "low" class, patients in the "high" class were more likely to be women and had significantly more comorbidities, reported a significantly higher number of symptoms at all time points, and worse HRQoL scores.

*Conclusion:* Our findings suggest that the pattern of a high symptom burden in COPD is consistent over time. The patients' individual symptom experiences should be the primary focus of treatment.

## 1. Introduction

Although shortness of breath is the most common symptom, patients with chronic obstructive pulmonary disease (COPD) may experience a wide range of symptoms [1,2] and co-occurrence of cough, dry mouth, lack of energy, feeling nervous, difficulty sleeping, pain, worrying, and difficulty concentrating have been reported [3–8]. This symptom burden is complex, and groups of patients have been identified based on their symptom experiences [9–11]. Analyzing the co-occurrence of multiple symptoms using cluster analysis may facilitate the development of targeted interventions to relieve the patients' symptom burden [12].

Our research group has previously found that ≥40% of COPD patients reported having 14 physical and psychological symptoms simultaneously. Three subgroups of COPD patients reported either low, intermediate, or high symptom experiences [13]. In cross-sectional studies there seems to be a degree of covariation of the symptoms experienced by patients with COPD [2,13]. However, due to varying instrument selection, the precise composition of these clusters is still uncertain, and there is a need to examine the stability of symptoms over time [2,5].

One longitudinal study assessed the stability of symptom clusters in severity and distress over time [14]. Four subgroups of symptoms were identified, including emotional problems, memory function decline, sleep alteration, and pain and unpleasant sensation. Notably, the study

* Corresponding author. Department of Nursing and Health Sciences, Faculty of Health and Social Sciences, University of South-Eastern Norway, Grønland 58, 3045, Drammen, Norway.
*E-mail address:* vivi.l.christensen@usn.no (V.L. Christensen).

https://doi.org/10.1016/j.rmed.2022.106944
Received 20 April 2022; Received in revised form 6 July 2022; Accepted 24 July 2022
Available online 9 August 2022

included two measurements with an interval of four weeks, which may not provide enough information on the stability of symptoms over longer periods.

Subgroups of patients with specific symptom experience patterns have been associated with defined clinical characteristics and lower health-related quality of life (HRQoL). Identifying such subgroups may indicate possible treatment opportunities [15–20].

In the current study we wished to ascertain whether the previous symptom-defined groups are stable over time and aimed to examine reclassification rates among these three latent classes of COPD based on the Memorial Symptom Assessment Scale (MSAS) [13–21]. We also aimed to assess how these subgroups differed in symptom scores and HRQoL outcomes at five different time points over 12 months. Moreover, we wished to assess how these subgroups differed in demographic and clinical characteristics at 12 months.

## 2. Material and methods

### 2.1. Design, population, and recruitment

This is a longitudinal study of COPD patients with distinct symptom experiences recruited from three outpatient clinics and one referral hospital in Norway. COPD patients who participated in the study, completed the MSAS related to their symptom experience at enrollment (baseline) and at three, six, nine, and 12 months after enrollment. The study procedures are described in detail elsewhere [13].

In brief, patients were included if they were ≥18 years of age; diagnosed with moderate, severe, or very severe COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification of airflow limitation in COPD [22]; able to read and understand Norwegian; and with no cognitive impairments as assessed by the nurse during the process of enrollment. Patients were excluded if they were receiving ongoing treatment for pulmonary infection, COPD exacerbation, or cancer diagnosis at enrollment.

Only patients who gave informed consent participated in the study. The study was approved by the hospital's Data Protection Officer (Reference no.: 09/5580) and the Regional Committees for Medical and Health Research Ethics (Reference no.: S-09102a).

### 2.2. Instruments

#### 2.2.1. Clinical characteristics at 12 months

Research nurses obtained information on body mass index (BMI), and smoking history at the different clinics. Comorbidities were evaluated through self-report. Patients completed information on comorbidities by using the Self-Administered Comorbidity Questionnaire (SCQ-19) [23], which includes 16 common medical conditions and three optional conditions. To obtain the total number of comorbidities, the 19 medical conditions were summed (range 0–19) [23].

**Lung function:** Spirometry was performed by the research nurses according to the guidelines of the European Respiratory Society [24]. Classification of severity of airflow limitation based on post-bronchodilator FEV1 in patients with FEV1/FVC <0.70 were defined as mild (FEV1 ≥80% predicted), moderate (FEV1 50%–79% predicted), severe (FEV1 30%–49% predicted), or very severe (FEV1 <30% predicted) COPD [22]. As supplementary measures, partial pressure of oxygen in the arterial blood (PaO2), number of acute exacerbations (i.e., number of prednisolone courses) during the last 12 months, the occurrence of chronic bronchitis (i.e., daily mucopurulent sputum over more than three months in at least two consecutive years), and presence of emphysema (i.e., based on the clinician's assumptions upon inclusion and chest configuration) were registered.

**Exercise capacity:** The 6-min walk test (6MWT) was used to measure exercise capacity. The 6MWT measures the exercise capacity with the distance walked to the closest meter. The 6MWT has shown satisfactory validity and reliability in studies including patients with COPD [25].

**Functional dyspnea:** To assess the patient's functional dyspnea the modified Medical Research Council Dyspnea Scale (mMRC) was used [26–28]. The mMRC is a 5-level rating scale from 0 (not troubled by breathlessness except during strenuous exercise) to 4 (too breathless to leave the house or breathless when dressing or undressing) that measures perceived disability based on the patients' perception of functional limitation with daily activities. The mMRC is a well-known scale in terms of assessing the patients' level of dyspnea [22]. The mMRC has shown satisfactory validity and reliability in studies including patients with COPD [26,27], but is insensitive to measure change in dyspnea [29,30].

#### 2.2.2. Multiple symptoms at baseline, and 3, 6, 9 and 12 months

To measure multiple symptoms the MSAS was used. The MSAS consists of a list of 32 common symptoms that are used to assess the multiple dimensions of a patient's symptom experience during the past week [21]. Patients are asked to indicate whether they had each symptom (i.e., occurrence) and to rate its frequency, severity, and distress. In the current study, the occurrence dimension of MSAS, was used to identify and follow three subgroups of patients at enrollment (baseline), and time points three, six, nine, and 12 months. Based on the symptom occurrence rates of the fourteen most common symptoms from the MSAS, the three subgroups were named "high", "intermediate", and "low". The symptoms were shortness of breath, lack of energy, feeling drowsy, dry mouth, cough, worrying, pain, feeling bloated, difficulty sleeping, feeling sad, problems with sexual interest or activity, feeling nervous, feeling irritable, and difficulty concentrating [13].

In addition, the MSAS total score and mean number of symptoms were calculated at the four time points. The three subscale scores; the psychological subscale (PSYCH), the physical subscale (PHYS), and the global distress index (GDI) were calculated at 12 months. The validity and reliability of the MSAS are well described in Portenoy's original work and have been used in several studies of COPD patients [3,4,29,31]. To our knowledge no sensitivity tests are performed.

#### 2.2.3. Health-related quality of life at baseline, and 3, 6, 9 and 12 months

The St. George's Respiratory Questionnaire (SGRQ) was used to examine HRQoL at enrollment (baseline), and three, six, nine, and 12 months. The questionnaire has 50 items with 76 weighted responses to measure HRQoL in patients with respiratory disease. The SGRQ consists of three components (i.e., symptoms, activity, and impact) as well as the SGRQ total score [32]. Each of the component scores as well as the total score can range from 0 to 100. Higher scores indicate worse HRQoL, and a change of 4 in the total score is considered a clinically meaningful change [33,34]. The SGRQ is a valid and reliable measure of HRQoL in COPD patients and is sensitive for change [33–35].

### 2.3. Statistical analyses

The latent class analyses (LCA) were based on fourteen symptoms from the MSAS that occurred in ≥40% of the patients at baseline. The three subgroups (i.e., latent classes) of patients with distinct symptom experiences have previously been described [13]. The "high" class included high occurrence rates of both physical and psychological symptoms, while the "intermediate" class included higher rates of physical symptoms and lower rates of psychological symptoms, and finally, the "low" class included lower rates of both physical and psychological symptoms. In the current study, we employed LCA independently at each time point with an initial restriction to three classes. We monitored the fit of the models and allowed for a different number of classes if this led to a considerably better fit. Based on the fitted models we investigated transitions between the classes and specifically calculated reclassification rates based on the classification at baseline. The LCA were made in the GLLAMM package in Stata, version 16 [37].

Differences among the three subgroups in demographic and clinical

characteristics at 12 months, and symptom scores and HRQoL for each time point (i.e., baseline, three, six, nine and 12 months) were evaluated using analysis of variance, Kruskal Wallis analyses, and chi-square analyses using IBM SPSS Statistics Version 26.0 (IBM Corp., Armonk, NY, USA). A p-value of $<0.05$ was considered statistically significant. Post hoc comparisons were made using the Bonferroni procedure.

## 3. Results

A total of 363 patients were asked to participate in the study. Sixteen patients did not meet the inclusion criteria and 55 declined to participate. Of the 292 patients enrolled, eight patients withdrew from the study and 17 patients did not return the questionnaires. The final sample consisted of 267 patients (response rate of 76.9%). Patients completed MSAS at baseline (n = 267), and at three (n = 233), six (n = 224), nine (n = 200), and 12 (n = 194) months after enrollment. No statistically significant differences were found at enrollment in age, gender, or number of comorbidities between patients who did and those who did not complete the questionnaire at 12 months. However, those who dropped out at 12 months had lower lung function at enrollment (baseline) than those who completed the study at 12 months.

### 3.1. Latent class analysis

A model with three latent classes fitted the data well for all time points, except for time-point six months where one of the groups became very small and a model with only two classes fitted the data considerably better. When assessing the patterns of the 14 symptoms used in the LCA at baseline, the probability of occurrence of each specific symptom seemed relatively constant across all time points. Based on the same assessment of occurrence probabilities, we considered the two fitted classes at six months to correspond to the "intermediate" and "high" class, respectively.

### 3.2. Reclassification rates from baseline and at 3, 6, 9, and 12 months

As shown in Table 1 and Fig. 1, for the patients who were classified with a "high" symptom burden at baseline, 64.7% were still in the "high" class at 12 months. For the patients who were classified as "low" at baseline, 81.8% were still "low" at 12 months, while none of them were reclassified as "high" (0.0%).

Finally, for the patients who were classified as intermediate at baseline, 76.3% were still in the "intermediate" class after six months while 43.7% were in the "intermediate" class at 12 months.

### 3.3. Differences in SGRQ and MSAS scores among the three subgroups at 3, 6, 9, and 12 months

As shown in Table 2, significant differences among the latent classes at three, six, nine and 12 months were found for the SGRQ symptom, activity, and impact scores as well as the total score. Significant differences were found in the expected direction at three, six, and nine months (i.e., "low" < "intermediate" < "high"). At 12 months, patients in the low class had significantly lower SGRQ symptoms, activity, impact, and total scores, compared to patients in the "intermediate" and "high" classes.

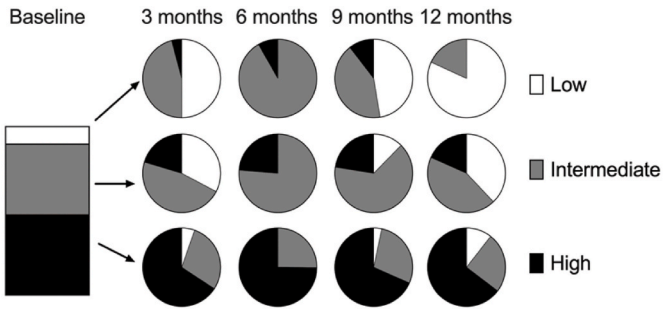


**Fig. 1.** Illustration of the reclassification rates from baseline to 3, 6, 9, and 12 months.

For the MSAS scores at 12 months, significant differences were found in the mean number of symptoms among the classes (i.e., "high" = 19.37 ± 5.37 > "intermediate" = 10.46 ± 3.41 > "low" = 4.92 ± 2.46). Significant differences among the classes in the GDI, PHYS, PSYCH subscale, and MSAS total score had the same pattern (i.e., "low" < "intermediate" < "high").

### 3.4. Differences in patient characteristics among the subgroups at 12 months

Demographic and clinical characteristics at 12 months are presented in Table 3. The only respiratory measure that differed between the classes in the pairwise comparisons, was the mMRC dyspnea scale in the way that patients in the "high" and "intermediate" class reported significantly more functional dyspnea compared to patients in the "low" class.

In pairwise comparisons, patients in the "high" class were more likely to be female compared with patients in the "low" and "intermediate" classes. Compared with the "low" and "intermediate" class, patients in the "high" class had a significantly higher number of comorbidities. When compared with the "low" class, patients in the "intermediate" class had significantly lower BMI.

### 3.5. Probability of occurrence of the 14 MSAS symptoms at baseline and 12 months

Probability of occurrence for the 14 MSAS symptoms in the three latent classes at baseline and 12 months is presented in Fig. 2. At 12 months, the most common symptom was shortness of breath with the highest probability of occurrence for all of the three classes. Lack of energy was the second most common symptom in the "intermediate"

**Table 1**
Reclassification rates from baseline to 3, 6, 9, and 12 months.

| Class | Baseline | 3 months | | | 6 months | | | 9 months | | | 12 months | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n = 267 | n = 233 | | | n = 224 | | | n = 200 | | | n = 194 | | |
| | | L | I | H | L | I | H | L | I | H | L | I | H |
| **Low** | 28 (10.5%) | 50.0% | 45.8% | 4.2% | | 91.7% | 8.3% | 47.4% | 42.1% | 10.5% | 81.8% | 18.2% | 0.0% |
| **Intermediate** | 112 (41.9%) | 32.7% | 46.9% | 20.4% | | 76.3% | 23.7% | 12.4% | 65.2% | 22.5% | 37.9% | 43.7% | 18.4% |
| **High** | 127 (47.6%) | 5.4% | 28.8% | 65.8% | | 25.2% | 74.8% | 3.3% | 28.3% | 68.5% | 10.6% | 24.7% | 64.7% |

**Notes:** The table gives reclassification rates from baseline to the subsequent time points. Notice that the number of patients varies over the time course.
The Baseline column gives the distribution of the patients between the three classes at baseline. The remaining part of the table gives re-classification rates. As an example, among those who were classified as belonging to the "Low" class at baseline, 50% were still in "Low" after three months, while 45.8% of them were reclassified as belonging to the "Intermediate" class. In the same way, among those who were classified as "Low" at baseline, 81.8% were still "Low" after 12 months, while none of them were reclassified as "High".

**Table 2**
Differences in SGRQ and MSAS scores among the three latent classes at 3, 6, 9, and 12 months.

| SGRQ and MSAS scores | Mean (SD), number of observations | | | Statistics and Post Hoc Contrast |
|---|---|---|---|---|
| | Low (0) | Intermediate [1] | High [2] | |
| **3 months (n = 233)** | | | | |
| **SGRQ scores** Symptom component | 46.4 (21.5), n = 50 | 59.6 (20.6), n = 88 | 68.5 (18.8), n = 94 | F = 19.850, p < 0.001 0 < 1<2 |
| Activity component | 56.0 (23.2), n = 46 | 72.7 (21.3), n = 81 | 75.6 (17.6), n = 86 | F = 14.875, p < 0.001 0 < 1 = 2 |
| Impact component | 30.6 (22.4), n = 48 | 43.5 (19.2), n = 84 | 53.6 (17.8), n = 88 | F = 21.951, p < 0.001 0 < 1<2 |
| SGRQ total score | 41.1 (20.5), n = 46 | 55.6 (17.2), n = 79 | 63.3 (15.2), n = 85 | F = 24.722, p < 0.001 0 < 1<2 |
| **MSAS scores** Number of MSAS symptoms (0-32) | 5.4 (3.4), n = 50 | 11.9 (3.5), n = 89 | 21.2 (5.4), n = 94 | F = 237.939, p < 0.001 0 < 1<2 |
| MSAS total score | 0.3 (0.2), n = 50 | 0.8 (0.3), n = 89 | 1.4 (0.4), n = 94 | F = 182. 450, p < 0.001 0 < 1<2 |
| **6 months (n = 224)** | | | | |
| **SGRQ scores** Symptom component | | 52.8 (23.1), n = 119 | 69.3 (20.2), n = 101 | F = 2.764, p < 0.001 |
| Activity component | | 65.5 (24.5), n = 105 | 76.6 (18.6), n = 92 | F = 7.909, p = 0.001 |
| Impact component | | 35.6 (20.8), n = 117 | 53.1 (19.2), n = 96 | F = 1.160, p < 0.001 |
| SGRQ total score | | 49.0 (20.1), n = 103 | 63.5 (15.9), n = 91 | F = 5.309, p < 0.001 |
| **MSAS scores** Number of MSAS symptoms (0-32) | | 6.8 (3.8), n = 122 | 19.5 (5.8), n = 102 | F = 22.828, p < 0.001 |
| MSAS total score | | 0.4 (0,3), n = 122 | 1.3 (0.0), n = 102 | F = 28.224, p < 0.001 |
| **9 months (n = 200)** | | | | |
| **SGRQ scores** Symptom component | 39.1 (29.6), n = 23 | 55.1 (20.9), n = 91 | 70.5 (18.5), n = 85 | F = 24.183, p < 0.001 0 < 1<2 |
| Activity component | 52.8 (28.4), n = 19 | 67.2 (22.6), n = 81 | 76.5 (18.1), n = 80 | F = 10.489, p < 0.001 0 < 1<2 |
| Impact component | 25.2 (18.9), n = 20 | 39.1 (19.0), n = 87 | 54.3 (19.2), n = 82 | F = 24.387, p < 0.001 0 < 1<2 |
| SGRQ total score | 36.3 (21.9), n = 18 | 51.3 (17.5), n = 80 | 64.5 (15.5), n = 79 | F = 24.561, p < 0.001 0 < 1<2 |
| **MSAS scores** Number of MSAS symptoms (0-32) | 2.6 (2.2), n = 23 | 10.0 (3.6), n = 92 | 21.0 (5.6), n = 85 | F = 219.403, p < 0.001 0 < 1<2 |
| MSAS total score | 0.1 (0.1), n = 23 | 0.6 (0.2), n = 92 | 1.4 (0.5), n = 85 | F = 161.937, p < 0.001 0 < 1<2 |
| **12 months (n = 194)** | | | | |
| **SGRQ scores** Symptom component | 43.0 (24.5), n = 60 | 64.8 (18.4), n = 61 | 70.2 (17.6), n = 69 | F = 31.582, p < 0.001 0 < 1 = 2 |
| Activity component | 54.4 (28.0), n = 52 | 74.3 (21.8), n = 57 | 76.1 (15.5), n = 57 | F = 15.830, p < 0.001 0 < 1 = 2 |
| Impact component | 29.9 (21.8), n = 58 | 44.0 (20.3), n = 58 | 52.2 (18.1), n = 64 | F = 19.018, p < 0.001 0 < 1 = 2 |
| SGRQ total score | | 57.6 (17.6), n = 55 | 39.9 (22.9), n = 52 | 62.8 (14.0), n = 56 | F = 22.548, p < 0.001 0 < 1 = 2 |
| **MSAS scores** Number of MSAS symptoms (0-32) | 4.92 (2.46), n = 60 | 10.46 (3.41), n = 63 | 19.15 (5.4), n = 71 | F = 209.585, p < 0.001 0 < 1<2 |
| Global Distress Index | 0.20 (0.2), n = 59 | 0.80 (0.36), n = 57 | 1.74 (0.66), n = 60 | 174.028, p < 0.001 0 < 1<2 |
| PHYS subscale score | 0.27 (0.25), n = 60 | 0.81 (0.33), n = 63 | 1.28 (0.56), n = 71 | F = 98.745, p < 0.001 0 < 1<2 |
| PSYCH subscale score | 0.19 (0.29), n = 60 | 0.54 (0.35), n = 63 | 1.73 (0.60), n = 71 | F = 218.295, p < 0.001 0 < 1<2 |
| MSAS total score | 0.29 (0.18), n = 60 | 0.67 (0.24), n = 63 | 1.29 (0.49), n = 71 | F = 145.219, p < 0.001 0 < 1<2 |

**Note:** At 6 months, the "low" class was not defined.
**Abbreviations:** HRQoL, Health Related Quality of Life; MSAS, Memorial Symptoms Assessment Scale; PHYS, physical; PSYCH, psychological; SD, standard deviation; SGRQ, St George Respiratory Questionnaire.

and the "high" classes.

## 4. Discussion

This study is the first to report reclassification rates in three latent classes of patients with COPD based on their distinct symptom experiences at 12 months. We found that 65% of the patients in the "high" class at baseline remained, and continually reported, a higher number of symptoms after 12 months. Regarding the patients in the "low" class, as many as 82% were still in the "low" class after 12 months, while none of these patients were reclassified as "high" (Table 1 and Fig. 1). Due to the relatively stable classes, the latent classes are presumed to capture the patients with the same symptom burden throughout time. Surprisingly, only two classes were found at six months (i.e., "high" and "intermediate"). We have no explanation for this, and seasonal variance is not a likely explanation since we included patients regardless of the seasons.

Furthermore, patients in the "high" class reported a probability of occurrence over 90% in several of the psychological symptoms, such as worrying, feeling sad, and feeling nervous (Fig. 2). At 12 months, these patients reported a significantly higher number of physical and psychological symptoms, varying from 19.15 ± 5.4 and up to 21.0 ± 5.6 compared to the "intermediate" and "low" classes (Table 2). Interestingly, a significantly higher fraction of the patients in the "high" class were women (66.2%) compared to the "low class" (Table 3). Conversely, in the "low class", a significantly higher proportion were men. These patients were reporting a significantly lower number of symptoms, varying from 2.6 ± 2.2 and 5.4 ± 3.4, as well as fewer comorbidities, and less functional dyspnea (Tables 2 and 3). These findings may suggest that female patients with COPD consistently tend to report a higher symptom burden compared to men. Over the last decades, the prevalence of women diagnosed with COPD has increased along with the reporting of more severe COPD symptoms [38,39]. According to previous research, women with COPD are particularly vulnerable to psychological impairment [40]. Taken together, these observations suggest that more attention should be given to symptoms in women with COPD.

The symptom with the highest probability of occurrence in all three classes at 12 months, was shortness of breath measured using MSAS. This finding is not surprising since airway obstruction is part of the definition of COPD, and shortness of breath is a highly rated and burdensome symptom known to increase among COPD patients with

**Table 3**
Differences in demographic and clinical characteristics among the three latent classes after 12 months.

| Characteristics | Low (0) n = 60 (30.9%) | Intermediate [1] n = 63 (32.5%) | High [2] n = 71 (36.6%) | Statistics and Post Hoc Contrast |
|---|---|---|---|---|
| | Mean (SD) | Mean (SD) | Mean (SD) | |
| Age (years) | 66.2 (8.4) | 63.8 (9.1) | 65.5 (8.5) | F = 1.250, p = 0.289 |
| Number of years smoking *(n = 102)* | 44.3 (9.5) | 37.3 (11.2) | 41.7 (14.7) | F = 2.923, p = 0.058 |
| Number of comorbidities – SCQ *(n = 187)* | 1.3 (1.3) | 2.0 (1.7) | 3.3 (2.2) | KW, p < 0.001 0 and 1 < 2 |
| BMI (kg/m$^2$) *(n = 134)* | 25.7 (4.3) | 23.5 (4.1) | 24.4 (4.3) | F = 3.195, p = 0.044 0 > 1 |
| $FEV_1$ (liters) *(n = 154)* | 1.2 (0.6) | 1.1 (0.6) | 1.0 (0.5) | KW, p = 0.320 |
| $FEV_1$% predicted *(n = 132)* | 42.9 (18.3) | 40.7 (20.4) | 47.3 (19.6) | F = 1.334, p = 0.254 |
| $FEV_1$/FVC *(n = 154)* | 0.5 (0.1) | 0.4 (0.1) | 0.5 (0.1) | F = 0.253, p = 0.267 |
| $PaO_2$ (kPa) *(n = 143)* | 9.7 (1.5) | 9.5 (1.4) | 9.4 (1.4) | F = 0.484, p = 0.618 |
| 6MWT (meters) *(n = 124)* | 435.5 (119.9) | 387.8 (142.6) | 402.4 (103.4) | F = 1.542, p = 0.218 |
| mMRC dyspnea scale (0–4) | 1.9 (1.4) | 2.6 (1.4) | 2.7 (1.1) | KW, p < 0.001 0 < 1 and 2 |
| Acute exacerbations in last 12 months *(n = 156)* | 1.0 (2.1) | 1.2 (1.6) | 1.1 (1.7) | KW, p = 0.367 |
| | **% (n)** | **% (n)** | **% (n)** | |
| Gender (female) | 43.3 [26] | 46.0 [29] | 66.2(47) | $\chi^2$ = 8,421, p = 0.015 0 < 2 |
| Emphysema (% yes) *(n = 117)* | 28.7 [23] | 35.0 [28] | 36.3 [29] | $\chi^2$ = 0.555, p = 0.758 |
| Chronic bronchitis (% yes) *(n = 116)* | 19.4 [7] | 34.9 [15] | 30.3 [36] | $\chi^2$ = 2339 p = 0.311 |
| GOLD classification *(n = 126)* Moderate Severe Very severe | 31.1 [14] 35.6 [16] 31.1 [14] | 29.3 [12] 26.8 [11] 41.5 [17] | 42.9 [18] 31.0 [13] 26.2 [11] | KW, p = 0.402 |

**Abbreviations:** BMI, body mass index; COPD, chronic obstructive pulmonary disease; $FEV_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; kg, kilogram; kPa, kilopascal; m$^2$, square meter; KW, Kruskal-Wallis test; mMRC, modified Medical Research Council Dyspnea Scale; $PaO_2$, partial pressure of oxygen in blood; 6MWT, 6-min walk test; SD, standard deviation.

increasing stages of the disease [5]. However, findings from our research group suggest that COPD patients report variations in their symptom burden based on their stage of disease [13]. In addition, research suggests COPD patients in a terminal stage of disease may experience a higher symptom burden compared to cancer patients, possibly because COPD patients often live longer with their disease burden [41,42]. Prolonged shortness of breath has previously been associated with symptoms such as fatigue, sleep disturbance, depression, anxiety, pain, and a higher number of comorbidities, as well as being a significant predictor of mortality in COPD [43–45].

The second most common symptom in the "intermediate" and the "high" classes were lack of energy, which may be related to fatigue. Linked to lack of energy is also feeling drowsy, and in the present study, the probability of occurrence of feeling drowsy was high in all three classes at 12 months compared to baseline [13]. Drowsiness, or daytime sleepiness, may be caused by nocturnal respiratory disturbances in patients with more severe COPD symptoms [46] and is reported as a common symptom in COPD [47,48]. Difficulty sleeping was rated considerably lower, which may suggest that the symptom of drowsiness may occur due to the total burden and the high number of symptoms.

Pain in COPD is a common and significant problem that needs attention. Although pain was not rated the most occurrent symptom, in both "high" and "intermediate" class the symptom of pain occurred in 79% and 62% of the patients, respectively (Fig. 2). In our baseline study, the probability of occurrence of pain in the "high" and "intermediate" class were 66% and 49% [13]. This finding is consistent with previous research that confirms a stable prevalence of pain in patients with COPD over time [49]. Pain has been associated with several symptoms, comorbidities, depression, as well as increased mortality within 5 years in COPD patients [50]. Research also shows that chronic pain is common in patients with COPD and that it has a negative impact on mood, breathlessness, interference with daily activities, and quality of life, and should be included in the management of the disease [51].

Interestingly, patients in the "low" class reported more physical symptoms that may be more known as respiratory- or COPD-related symptoms. In the ranking of symptoms cough and dry mouth were rated top three. While cough is regarded as one of the first symptoms in the manifestation of COPD [22], dry mouth may occur due to high doses of anticholinergic medications. As this symptom is associated with decreased nutritional intake and malnutrition, assessment of this symptom is crucial [52].

Although findings from the baseline study showed significant differences in both severity stages of COPD and $FEV_1$% among all the three classes [13], no significant differences in pulmonary function were found between the classes at 12 months (Table 3). However, self-reported functional dyspnea using the mMRC dyspnea scale differed significantly among the classes at 12 months. Interestingly, the same pattern in pairwise comparisons among the three classes ("low" < "intermediate" and "high") was found at baseline [13]. Moreover, the number of comorbidities differed significantly among the latent classes, and patients in the "high" class reported the highest number. Common comorbidities in our study are back and neck pain (47%), depression (26%), headache (24%), osteoarthritis (19%), and heart disease (18%), which could potentially explain the high symptom burden in this class. Consistent with findings from the present study, COPD patients often suffer from several comorbidities [53,54]. In terms of understanding the COPD patient's symptoms, research highlights the influence of various comorbidities that need to be taken into consideration when caring for these patients [54]. Finally, the patients in the "low" class had significantly higher BMI compared to the "intermediate" class, being slightly within the overweight range. Higher BMI or being overweight has been associated with a better prognosis in COPD and with a lower risk of exacerbations [55,56].

Further, patients in the "high" class reported significantly lower scores on all the subscales of SGRQ and total score of MSAS at all time points and all the subscales of the MSAS at 12 months compared to the other classes. These findings show how the burden of multiple co-occurring symptoms has a strong impact on HRQoL. In addition, co-morbid conditions in COPD have been associated with worse HRQoL [57]. Results from the current study are consistent with previous research highlighting how patients with a higher symptom burden report significantly lower HRQoL and that the HRQoL is not necessarily dependent on specific clinical characteristics related to the diagnosis of COPD [13,15,58]. Individualized comprehensive symptom assessment is important to identify the patient's burden and to better meet their needs in coping with the disease.

In addition, we found significant decrements in HRQoL among all three classes at baseline and at 12 months. These findings suggest that the COPD patients' symptom burden is highly individual and not dependent of pulmonary function alone. Accordingly, research suggests that COPD patients experiencing dyspnea despite treatment may benefit

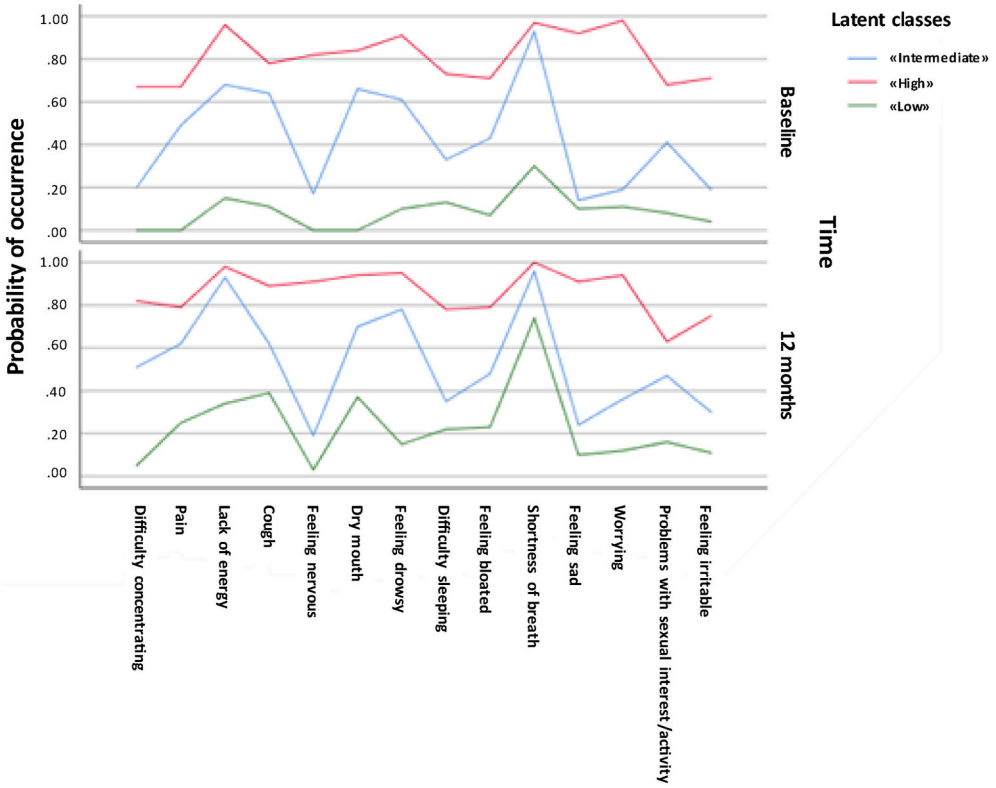


**Fig. 2.** Probability of occurrence for the 14 symptoms in the three latent classes at baseline and 12 months.

from an even more specific treatment regarding their symptoms [59].

## 5. Limitations

Some limitations need to be acknowledged. Although the MSAS includes 32 physical and psychological symptoms, COPD-related symptoms such as wheezing, chest pain, or chest pressure are not included in the list and could have contributed to more clarity in understanding the symptom experience of these patients [4]. However, using the original version of MSAS made us capable of comparing our results to other studies that also have used MSAS for measuring multiple symptoms.

Of the total number of patients included at baseline (n = 267), 46% had very severe COPD [13]. As these patients are only a minor part of the global COPD population, the classes identified in the current study may not generalize to all COPD patients. The patients who dropped out during the 12 months, had severe lung function ($FEV_1$% predicted) at the time of inclusion, compared to the patients who completed the follow-up period. It is uncertain if these patients would have affected the analyses and distribution of classes. On the other hand, no significant differences were found at baseline in age, gender, or number of comorbidities between the patients who did and did not drop out of the study during the 12 months. Finally, due to insufficient data on medications at 12 months, we were not able to assess if the use of medications may have differed among the classes.

## 6. Conclusion

The reclassification rates along with the MSAS- and SGRQ scores as well as the patient characteristics in the current study, provide meaningful information about the stability in COPD patients' symptom experience and underlines the importance of a broad and individualized symptom assessment. Our findings suggest that the symptom burden in COPD patients continues over time. The subgroup with the highest burden of symptoms was associated with a higher number of female patients and patients with a higher number of comorbidities. Shortness of breath, which is a problematic and frequent symptom, was the overall highest rated symptom in all the three classes. Findings from our study emphasize the importance of considering the patients' individual symptom experiences which should be the primary focus in treatment.

### Clinical implications

Multidimensional symptom assessments should be prioritized to better understand the patient's experience with the burden of disease and provide the specific treatment needed. Rehabilitation may be important to consider as it may help patients how to live with a higher symptom burden. Teaching patients when to contact medical help is of great importance and may also be a helpful strategy to better cope with the disease.

### Future research

Interventional studies are needed to determine if different symptom management strategies may help to relieve multiple co-occurring symptoms.

### Declaration of competing interest

The authors declare no competing interests. This study was funded by the South-Eastern Norway Regional Health Authority (2009055). Details reported at Clinical Trials: NCT01016587.

### Acknowledgments

We are grateful to all the patients and clinicians who contributed to this study, especially the research nurses Gunilla Solbakk, Mari-Ann Øvreseth, and Britt Drægni.

## References


[1] J. Sigurgeirsdottir, S. Halldorsdottir, R.H. Arnardottir, G. Gudmundsson, E. H. Bjornsson, COPD patients' experiences, self-reported needs, and needs-driven strategies to cope with self-management, Int. J. Chronic Obstr. Pulm. Dis. 14 (2019) 1033–1043.

[2] B.A. Jenkins, P. Athilingam, R.A. Jenkins, Symptom clusters in chronic obstructive pulmonary disease: a systematic review, Appl. Nurs. Res. 45 (2019) 23–29.

[3] J. Eckerblad, K. Todt, P. Jakobsson, M. Unosson, E. Skargren, M. Kentsson, et al., Symptom burden in stable COPD patients with moderate or severe airflow limitation, Heart Lung 43 (4) (2014) 351–357.

[4] C.D. Blinderman, P. Homel, J.A. Billings, S. Tennstedt, R.K. Portenoy, Symptom distress and quality of life in patients with advanced chronic obstructive pulmonary disease, J. Pain Symptom Manag. 38 (1) (2009) 115–123.

[5] O. Melhem, E. Savage, E. Lehane, Symptom burden in patients with chronic obstructive pulmonary disease, Appl. Nurs. Res. 57 (2021), 151389.

[6] V.L. Christensen, A.M. Holm, B. Cooper, S.M. Paul, C. Miaskowski, T. Rustoen, Differences in symptom burden among patients with moderate, severe, or very severe chronic obstructive pulmonary disease, J. Pain Symptom Manag. 51 (5) (2016) 849–859.

[7] C. Bausewein, S. Booth, M. Gysels, R. Kuhnbach, B. Haberland, I.J. Higginson, Understanding breathlessness: cross-sectional comparison of symptom burden and palliative care needs in chronic obstructive pulmonary disease and cancer, J. Palliat. Med. 13 (9) (2010) 1109–1118.

[8] S. Bentsen, D. Gundersen, J. Assmus, H. Bringsvor, A. Berland, Multiple symptoms in patients with chronic obstructive pulmonary disease in Norway, Nurs. Health Sci. 15 (3) (2013) 292–299.

[9] H.K. Koo, S.W. Park, J.W. Park, H.S. Choi, T.H. Kim, H.K. Yoon, et al., Chronic cough as a novel phenotype of chronic obstructive pulmonary disease, Int. J. Chronic Obstr. Pulm. Dis. 13 (2018) 1793–1801.

[10] F. Fei, J. Koffman, X. Zhang, W. Gao, Chronic obstructive pulmonary disease symptom cluster composition, associated factors, and methodologies: a systematic review, West. J. Nurs. Res. (2021), 193945921995773.

[11] P. Finamore, M.A. Spruit, J.M.G.A. Schols, R. Antonelli Incalzi, E.F.M. Wouters, D. J.A. Janssen, Clustering of patients with end-stage chronic diseases by symptoms: a new approach to identify health needs, Aging Clin. Exp. Res. 33 (2) (2021) 407–417.

[12] C. Miaskowski, A. Barsevick, A. Berger, R. Casagrande, P.A. Grady, P. Jacobsen, et al., Advancing symptom science through symptom cluster research: expert panel proceedings and recommendations, J. Natl. Cancer Inst.: J. Natl. Cancer Inst. 109 (4) (2017).

[13] V.L. Christensen, T. Rustøen, B.A. Cooper, C. Miaskowski, A.H. Henriksen, S. B. Bentsen, et al., Distinct symptom experiences in subgroups of patients with COPD, Int. J. Chronic Obstr. Pulm. Dis. 11 (2016) 1801–1809.

[14] C. Srirat, S. Hanucharurnkul, S. Aree-Ue, T. Junda, Similarity and stability of symptom cluster in severity and distress among persons with chronic obstructive pulmonary disease, Pac. Rim Int. J. Nurs. Res. 19 (2) (2015) 89–106.

[15] K.E. Lim, S.R. Kim, H.K. Kim, S.R. Kim, Symptom clusters and quality of life in subjects with COPD, Respir. Care 62 (9) (2017) 1203–1211.

[16] S. Park, C. Meldrum, J. Larson, Subgroup analysis of symptoms and their effect on functioning, exercise capacity, and physical activity in patients with severe chronic obstructive pulmonary disease, Heart Lung 42 (6) (2013) 465–472.

[17] H.Y. Yoon, S.Y. Park, C.H. Lee, M.K. Byun, J.O. Na, J.S. Lee, et al., Prediction of first acute exacerbation using COPD subtypes identified by cluster analysis, Int. J. Chronic Obstr. Pulm. Dis. 14 (2019) 1389–1397.

[18] L.M. Pinto, M. Alghamdi, A. Benedetti, T. Zaihra, T. Landry, J. Bourbeau, Derivation and validation of clinical phenotypes for COPD: a systematic review, Respir. Res. 16 (1) (2015) 50.

[19] J. Lopez Campos, V. Bustamante, X. Muñoz, E. Barreiro, Moving towards patient-centered medicine for COPD management: multidimensional approaches versus phenotype-based medicine–a critical view, COPD 11 (5) (2014) 591–602.

[20] S. Park, J. Larson, Symptom cluster, healthcare use and mortality in patients with severe chronic obstructive pulmonary disease, J. Clin. Nurs. 23 (17–18) (2014) 2658–2671.

[21] R.K. Portenoy, H.T. Thaler, A.B. Kornblith, J.M. Lepore, H. Friedlander-Klar, E. Kiyasu, et al., The Memorial Symptom Assessment Scale: an instrument for the evaluation of symptom prevalence, characteristics and distress, Eur. J. Cancer 30A (9) (1994) 1326–1336.

[22] S.C. GOLD, Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease - 2020 report, Global Initiative for Chroninc Obstructive Lung Disease, Inc [Internet]. 2021 Cited April 2020]. Available from: https://goldcopd.org/wp-content/uploads/2019/12/GOLD-2020-FINAL-ver1.2-03Dec19_WMV.pdf.

[23] O. Sangha, G. Stucki, M.H. Liang, A.H. Fossel, J.N. Katz, The Self-Administered Comorbidity Questionnaire: a new method to assess comorbidity for clinical and health services research, Arthritis Rheum. 49 (2) (2003) 156–163.

[24] P.H. Quanjer, G.J. Tammeling, J.E. Cotes, O.F. Pedersen, R. Peslin, J.C. Yernault, Lung volumes and forced ventilatory flows. Report working party standardization of lung function tests, European community for steel and coal. Official statement of the European respiratory society, Eur. Respir. J. Suppl. 16 (1993) 5–40.

[25] G.H. Guyatt, M.J. Sullivan, P.J. Thompson, E.L. Fallen, S.O. Pugsley, D.W. Taylor, et al., The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure, Can. Med. Assoc. J. 132 (8) (1985) 919–923.

[26] D.A. Mahler, C.K. Wells, Evaluation of clinical methods for rating dyspnea, Chest 93 (3) (1988) 580–586.

[27] J. Bestall, E. Paul, R. Garrod, R. Garnham, P. Jones, J. Wedzicha, Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease, Thorax 54 (7) (1999) 581–586.

[28] [28] ATS, Society AT, Force ERT. Standards for the Diagnosis and Management of Patients with COPD [Internet]. New York; 2004.

[29] J. Sandberg, M.J. Johnson, D.C. Currow, M. Ekström, Validation of the dyspnea exertion scale of breathlesess in people with life-limiting illness, J. Pain Symptom Manag. 56 (3) (2018) 430–435.

[30] C. Stenton, The MRC breathlessness scale, Occup. Med. 58 (3) (2008) 226–227.

[31] K. Theander, M. Hasselgren, K. Luhr, J. Eckerblad, M. Unosson, I. Karlsson, Symptoms and impact of symptoms on function and health in patients with chronic obstructive pulmonary disease and chronic heart failure in primary health care, Int. J. Chronic Obstr. Pulm. Dis. 9 (2014) 785–794.

[32] P.W. Jones, F.H. Quirk, C.M. Baveystock, The St george's respiratory questionnaire, Respir. Med. 85 (Suppl B) (1991) 25–31, discussion 3-7.

[33] P.W. Jones, Interpreting thresholds for a clinically significant change in health status in asthma and COPD, Eur. Respir. J. 19 (3) (2002) 398–404.

[34] E. Ståhl, A. Lindberg, S.A. Jansson, E. Ronmark, K. Svensson, F. Andersson, et al., Health-related quality of life is related to COPD disease severity, Health Qual. Life Outcome 3 (2005) 56.

[35] P.W. Jones, F.H. Quirk, C.M. Baveystock, P. Littlejohns, A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire, Am. Rev. Respir. Dis. 145 (6) (1992) 1321–1327.

[36] M.A. Puahm, G.H. Guyatt, R. Goldstein, J. Mador, D. McKim, E. Stahl, et al., Relative responsiveness of the chronic obstructive respiratory questionnaire, St Georges respiratory questionnaire and four other health related quality of life instruments with chronic lung disease, Respir. Med. 101 (2) (2007) 308–316.

[37] S. Rabe-Hesketh, A. Skrondal, A. Pickles, GLLAMM Manual. Manual UC Berkeley Division of Biostatistics Working Paper Series Working Paper Series, 2004. Working Paper 160.

[38] D.L. DeMeo, S. Ramagopalan, A. Kavati, A. Vegesna, M.K. Han, A. Yadao, et al., Women manifest more severe COPD symptoms across the life course, Int. J. Chronic Obstr. Pulm. Dis. 13 (2018) 3021–3029.

[39] E. Diaz-Guzman, D.M. Mannino, Epidemiology and prevalence of chronic obstructive pulmonary disease, Clin. Chest Med. 35 (1) (2014) 7–16.

[40] M.I. Pumar, C.R. Gray, J.R. Walsh, I.A. Yang, T.A. Rolls, D.L. Ward, Anxiety and depression-Important psychological comorbidities of COPD, J. Thorac. Dis. 6 (11) (2014) 1615–1631.

[41] M. Joshi, A. Joshi, T. Bartter, Symptom burden in chronic obstructive pulmonary disease and cancer, Curr. Opin. Pulm. Med. 18 (2) (2012) 97–103.

[42] T. Luckett, A. San Martin, D.C. Currow, M.J. Johnson, M.M. Barnes-Harris, J. L. Phillips, A systematic review and meta-analysis of studies comparing burden from lung cancer and chronic obstructive pulmonary disease, Palliat. Med. 34 (10) (2020) 1291–1304.

[43] C.R. Borge, A.K. Wahl, T. Moum, Association of breathlessness with multiple symptoms in chronic obstructive pulmonary disease, J. Adv. Nurs. 66 (12) (2010) 2688–2700.

[44] M. Parshall, R. Schwartzstein, L. Adams, R. Banzett, H. Manning, J. Bourbeau, et al., An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea, Am. J. Respir. Crit. Care Med. 185 (4) (2012) 435–452.

[45] R. Prudente, E.A.T. Franco, C.B. Mesquita, R. Ferrari, I. de Godoy, S.E. Tanni, Predictors of mortality in patients with COPD after 9 years, Int. J. Chronic Obstr. Pulm. Dis. 13 (2018) 3389–3398.

[46] C. Enz, S. Brighenti-Zogg, E.H. Steveling-Klein, S. Dürr, S. Maier, D. Miedinger, et al., Predictors of increased daytime sleepiness in patients with chronic obstructive pulmonary disease: a cross-sectional study, Sleep Disord. 2016 (2016), 1089196.

[47] S.A. Antoniu, A. Apostol, L.V. Boiculese, Extra-respiratory symptoms in patients hospitalized for a COPD exacerbation: prevalence, clinical burden and their impact on functional status, Clin. Res. J 13 (12) (2019) 735–740.

[48] A. Wajnberg, K. Ornstein, M. Zhang, K.L. Smith, T. Soriano, Symptom burden in chronically ill homebound individuals, J. Am. Geriatr. Soc. 61 (1) (2013) 126–131.

[49] L.M. Walke, A.L. Byers, M.E. Tinetti, J.A. Dubin, R. McCorkle, T.R. Fried, Range and severity of symptoms over time among older adults with chronic obstructive pulmonary disease and heart failure, Arch. Intern. Med. 167 (22) (2007) 2503–2508.

[50] S.B. Bentsen, A.M. Holm, V.L. Christensen, A.H. Henriksen, M.C. Småstuen, T. Rustøen, Changes in and predictors of pain and mortality in patients with chronic obstructive pulmonary disease, Respir. Med. 171 (2020), 106116.

[51] H. Lewthwaite, G. Williams, K.L. Baldock, M.T. Williams, Systematic review of pain in clinical practice guidelines for management of COPD: a case for including chronic pain? Healthcare (Basel) 7 (1) (2019).

[52] J. Nordén, A.M. Grönberg, I. Bosaeus, H.B. Forslund, L. Hulthén, E. Rothenberg, et al., Nutrition impact symptoms and body composition in patients with COPD, Eur. J. Clin. Nutr. 69 (2) (2015) 256–261.

[53] N.A. Negewo, V.M. McDonald, P.G. Gibson, Comorbidity in chronic obstructive pulmonary disease, Respir. Invest. 53 (6) (2015) 249–258.

[54] D.J. Maselli, S.P. Bhatt, A. Anzueto, R.P. Bowler, D.L. DeMeo, A.A. Diaz, et al., Clinical epidemiology of COPD: insights from 10 Years of the COPDGene study, Chest 156 (2) (2019) 228–238.

[55] F. Spelta, A.M. Fratta Pasini, L. Cazzoletti, M. Ferrari, Body weight and mortality in COPD: focus on the obesity paradox, Eat. Weight Disord. 23 (1) (2018) 15–22.

[56] Y.S. Jo, Y.H. Kim, J.Y. Lee, K. Kim, K.S. Jung, K.H. Yoo, et al., Impact of BMI on exacerbation and medical care expenses in subjects with mild to moderate airflow obstruction, Int. J. Chronic Obstr. Pulm. Dis. 13 (2018) 2261–2269.

[57] J. Sundh, G. Johansson, K. Larsson, A. Linden, C.G. Lofdahl, C. Janson, et al., Comorbidity and health-related quality of life in patients with severe chronic obstructive pulmonary disease attending Swedish secondary care units, Int. J. Chronic Obstr. Pulm. Dis. 10 (2015) 173–183.

[58] S.B. Bentsen, C. Miaskowski, T. Rustoen, Demographic and clinical characteristics associated with quality of life in patients with chronic obstructive pulmonary disease, Qual. Life Res. 23 (3) (2014) 991–998.

[59] J.B. Gruenberger, J. Vietri, D.L. Keininger, D.A. Mahler, Greater dyspnea is associated with lower health-related quality of life among European patients with COPD, Int. J. Chronic Obstr. Pulm. Dis. 12 (2017) 937–944.