# Symptom burden and its associations with clinical characteristics in patients with COPD: a clustering approach

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## Abstract

*Background* Symptom burden in patients with COPD is often under-recognised. In this cross-sectional analysis, we aimed to study the severity of a variety of (non-)respiratory symptoms in patients with and without COPD and to explore the associations between clusters based on symptom severity and other clinical characteristics.

*Methods* Characteristics were assessed in 538 patients with COPD from primary, secondary and tertiary care and 116 non-COPD participants. The severity of 20 symptoms was measured using a visual analogue scale (VAS), ranging from 0 mm (no symptom) to 100 mm (maximum severity). K-means cluster analysis was applied to symptom severity in the patient sample only.

*Results* People with COPD were comparable with non-COPD participants in terms of gender (58% *versus* 55% male, p=0.132) and age (64±9 years *versus* 63±6 years, p=0.552) and had a reduced forced expiratory volume in 1 s (57±23% predicted *versus* 111±17% predicted, p<0.001). The COPD group had higher VAS scores for most symptoms (p<0.05). The most severe symptoms in patients with COPD were dyspnoea, fatigue and muscle weakness while non-COPD participants mainly experienced insomnia and micturition. Three clusters were identified in the patient sample. Health status and care dependency differed between all clusters, while functional mobility, exacerbation history and lung function differed between cluster 1 and the other two clusters (p<0.05).

*Conclusions* People with COPD report a high burden of respiratory as well as non-respiratory symptoms. Cluster analysis demonstrated a co-occurrence of different levels of symptom severity, highlighting the heterogeneity of symptoms experience. Identifying clusters of patients with shared symptom experiences will help us to understand the impact of the disease and define integrated, multidimensional treatment strategies.

## Introduction

The most common respiratory symptoms associated with COPD include dyspnoea, cough and/or sputum production, which significantly impact patients' overall health status [1]. Therefore, respiratory symptoms play an important role in COPD disease management given that the classification and treatment of the disease is based on the patient's perceived symptom severity and previous history of exacerbations [2].

However, COPD is a complex disease with systemic manifestations and comorbidities contributing to different clinical phenotypes [3, 4]. Therefore, non-respiratory symptoms, such as fatigue, depressive feelings, insomnia and pain, are also highly common [5–7]. A median number of 13 psychological and physical symptoms have previously been identified in patients with COPD [8]. Shortness of breath, lack of

energy, difficulty sleeping, worrying, dry mouth, feeling nervous and feeling irritable were the most severe and burdensome symptoms [8]. Furthermore, high symptom burden was associated with low functional performance in this sample [9].

Despite the significant impact of respiratory as well as non-respiratory symptoms on patients' lives, they are often under-reported or under-recognised [10]. Understanding the heterogeneity of symptom occurrence together with symptom severity can help define adequate treatment strategies. FINAMORE et al. [11] identified three clusters based on symptom severity in patients with severe COPD, chronic heart failure or chronic renal failure and showed distinct patterns of symptoms, health status, care dependency and life-sustaining treatment preferences between clusters. However, to the best of our knowledge, cluster analysis based on the severity of respiratory and non-respiratory symptoms in a broad sample of patients with COPD has not been conducted before. Additionally, previous studies have not included a non-COPD control group, which would provide a better understanding of the symptom burden.

Therefore, we aimed to study 1) the symptom burden of a variety of respiratory and non-respiratory symptoms in patients with COPD and non-COPD participants and 2) the associations between clusters based on symptom severity and other clinical characteristics.

## Methods

Data were retrieved from the Chance study, an observational longitudinal study concerning the clinical, physiological and psychosocial determinants of health status in a broad sample of patients with COPD and non-COPD participants [12]. The Medical Ethical Committee of the Maastricht University Medical Centre (Maastricht, the Netherlands) approved the study (METC 11-3-070), which is registered at the Netherlands National Trial Register (NTR 3416).

### Study sample

People with COPD were recruited between April 2012 and September 2014 from eight general practices (GPs) (primary care) in the Southern part of the Netherlands, from the outpatient pulmonary clinic of the Maastricht University Medical Centre, the Netherlands (secondary care), and from Ciro, a centre of expertise for chronic organ failure in Horn, the Netherlands (tertiary care).

Non-COPD participants were recruited at the same GPs as the primary care patients with COPD. They were eligible if they had no history of respiratory diseases, heart failure, malignancies within the past 5 years or other clinically relevant disease that may influence health status according to the principal investigator. Details about other inclusion and exclusion criteria, recruitment and assessment have been described in the study protocol [12].

### Clinical characteristics

Demographic and clinical characteristics were assessed as described previously [12]. Functional mobility was assessed by the Timed Up and Go (TUG) test [13]. Health status was assessed by the COPD Assessment Test (CAT) [14].

### Symptom assessment

Participants were asked to rate the severity of 20 physical and psychological symptoms using a visual analogue scale (VAS): dyspnoea, fatigue, cough, muscle weakness, loss of appetite, insomnia, depression, anxiety, panic, pain, mouth complaints, itch, oedema, thirst, muscle cramps, restless legs, dizziness, chest pain, micturition during the day and micturition during the night [15]. VAS is a horizontal straight line, ranging from 0 mm (no symptoms) to 100 mm (maximum severity), where the distance in millimetres from the left side of the line to the point the patient marks represents the self-perceived severity of the symptom during the previous 2 weeks. A cut-off of ⩾30 mm was used to define a symptom as being present [16].

### Statistics

Continuous variables are described as mean±SD or median (interquartile range (IQR)), as appropriate. Categorical variables are reported as frequencies (n (%)).

Only participants with complete symptom assessment were included in the current analyses.

Cluster analysis was applied in the patient sample only. K-means cluster analysis was applied to symptom severity to partition observations into K clusters, in which each observation belongs to the cluster with the nearest mean [17]. The optimal number of clusters was chosen based on a graphical aid: each cluster was represented by a so-called silhouette, which is based on the comparison of its tightness and separation and

provides an evaluation of clustering validity. The silhouette approach shows which objects lie well within their cluster [18].

Symptoms and clinical characteristics between groups were compared using an independent sample t-test or Mann–Whitney U test, as appropriate. Chi-square test was used for categorical variables. Median symptom scores have been represented using a radar plot. Diagrams were constructed using GraphPad Prism 5 (GraphPad Software, La Jolla, CA, USA). Statistical analyses were performed using IBM SPSS statistics, version 28.0 (IBM Corp., Armonk, NY, USA). A p-value of $\leqslant 0.05$ was interpreted as statistically significant.

## Results

In total, 836 people volunteered to participate in the Chance study, of which 100 were patients with COPD from primary care, 100 were patients with COPD from secondary care, 518 were patients with COPD from tertiary care and 118 were non-COPD participants (table 1). Two non-COPD participants and 180 patients from tertiary care had to be excluded owing to missing data on at least one item on the symptom checklist. Patients from tertiary care with missing data were older and had worse health status compared to patients from tertiary care with complete data (supplementary table S1).

### COPD versus non-COPD participants

People with COPD were comparable to non-COPD participants in terms of gender distribution and mean age. Compared to non-COPD participants, patients with COPD had worse lung function, worse functional mobility and worse health status. A higher proportion of patients reported worse activity limitation due to breathlessness and were former smokers and care dependent (table 1).

Compared to non-COPD participants, patients with COPD had higher median symptom scores for most symptoms ($p < 0.05$), except for pain, dizziness and micturition during the day and night (table 2). The most prevalent symptoms in patients with COPD were dyspnoea (68%), fatigue (68%) and muscle weakness (53%) while non-COPD participants mainly complained about insomnia (16%) and daytime or night-time micturition (14%), although prevalences were generally low (table 3). Symptom burden overlapped between patients from the different care settings (supplementary figure S1).

### Clusters

Three clusters were identified demonstrating distinct patterns of symptom severity: cluster 1 had the least symptom burden, cluster 2 had medium symptom burden and cluster 3 had the highest symptom burden (figure 1). Dyspnoea and fatigue were the most prevalent symptoms in all clusters. In clusters 2 and 3, fatigue (88% and 94%, respectively), dyspnoea (83% and 86%, respectively) and muscle weakness (75% and 78%, respectively) were highly prevalent. People in cluster 3 reported the highest symptom scores for most symptoms compared to clusters 1 and 2, except for dyspnoea, fatigue, cough, muscle weakness and oedema, which were comparable between clusters 2 and 3 (figure 1a, table 2). Cluster 3 was characterised by an overall high symptom burden, with 11 symptoms present in at least 50% of the participants (figure 1b, table 3).

### Differences between clusters

Overall, participants reported increasingly worse outcomes from cluster 1 to 3 although the majority of the clinical characteristics were comparable between clusters 2 and 3 (table 1, figure 2). A higher proportion of participants in cluster 3 was female (table 1) and reported a history of myocardial infarction compared to clusters 1 and 2 (supplementary table S2). Health status and care dependency differed between all clusters, while functional mobility, exacerbation history and lung function differed between clusters 1 and 2 and clusters 1 and 3 (figure 2).

## Discussion

To the best of our knowledge, this study is the first cluster analysis based on the severity of various respiratory and non-respiratory symptoms in a broad sample of patients with COPD. The present study confirmed that patients with COPD may experience a high burden of respiratory as well as non-respiratory symptoms compared to non-COPD participants. Cluster analysis demonstrated a co-occurrence of different symptoms, highlighting the heterogeneity of symptom experience. Furthermore, increased symptom severity was associated with worse clinical characteristics.

### Symptom burden

In line with previous studies [5–8], the current study demonstrated a high symptom burden in patients with COPD. The most severe symptoms in non-COPD participants (insomnia and micturition) were reported by

**TABLE 1** Patient characteristics

| | Non-COPD participants | Patients with COPD | COPD *versus* non-COPD p-value | Cluster 1 | Cluster 2 | Cluster 3 | Cluster 1 *versus* cluster 2 p-value | Cluster 1 *versus* cluster 3 p-value | Cluster 2 *versus* cluster 3 p-value |
|---|---|---|---|---|---|---|---|---|---|
| Subjects, n | 116 | 538 | | 205 | 202 | 131 | | | |
| Male | 64 (55.4) | 313 (58.2) | 0.132 | 126 (61.5) | 123 (60.9) | 64 (48.9) | 0.906 | 0.023 | 0.031 |
| Age, years | 63.2±6.4 | 64.2±8.6 | 0.552 | 63.8±8.2 | 65.3±8.8 | 63.2±8.9 | 0.062 | 0.520 | 0.027 |
| $FEV_1$, % predicted | 111.0±17.1 | 57.0±22.6 | <0.001 | 62.4±22.9 | 51.9±21.4 | 56.1±22.0 | <0.001 | 0.013 | 0.081 |
| FVC, % predicted | 114.2±17.4 | 100.2±21.1 | <0.001 | 104.9±20.0 | 97.1±20.9 | 97.4±21.9 | <0.001 | 0.001 | 0.894 |
| $FEV_1/FVC$ | 0.79±0.05 | 0.45±0.14 | <0.001 | 0.47±0.14 | 0.42±0.13 | 0.46±0.14 | <0.001 | 0.541 | 0.006 |
| mMRC | | | <0.001 | | | | <0.001 | <0.001 | 0.275 |
| 0 | 81 (69.8) | 71 (13.3) | | 61 (29.9) | 4 (2.0) | 6 (4.6) | | | |
| 1 | 31 (26.7) | 118 (22.1) | | 67 (32.8) | 35 (17.4) | 16 (12.3) | | | |
| 2 | 3 (2.6) | 181 (33.8) | | 52 (25.5) | 81 (40.3) | 48 (36.6) | | | |
| 3 | 1 (0.9) | 96 (17.9) | | 3 (7.8) | 49 (24.4) | 31 (23.8) | | | |
| 4 | 0 (0.0) | 69 (12.9) | | 8 (3.9) | 32 (15.9) | 29 (22.3) | | | |
| CAT score | 7.5±5.6 | 19.2±7.5 | <0.001 | 13.8±6.5 | 21.7±5.4 | 23.9±6.4 | <0.001 | <0.001 | <0.001 |
| ⩾2 exacerbations in previous 12 months | – | 226 (42.0) | – | 54 (26.3) | 101 (50.0) | 71 (54.2) | <0.001 | <0.001 | 0.177 |
| ⩾1 hospitalisation in previous 12 months[#] | – | 156 (29.0) | – | 33 (16.1) | 77 (38.1) | 46 (35.1) | <0.001 | 0.003 | 0.065 |
| Former smoker | 72 (62.1) | 395 (73.6) | <0.001 | 158 (77.1) | 149 (74.1) | 88 (67.2) | 0.784 | 0.088 | 0.227 |
| LTOT | 0 (0.0) | 92 (17.1) | <0.001 | 25 (12.2) | 46 (22.8) | 21 (16.0) | 0.005 | 0.319 | 0.134 |
| TUG test, time (s) | 8.4±1.5 | 10.1±3.1 | <0.001 | 8.8±1.8 | 10.7±3.2 | 11.4±3.8 | <0.001 | <0.001 | 0.060 |
| Care dependent (CDS⩽68) | 0 (0.0) | 107 (20.3) | <0.001 | 16 (7.9) | 47 (23.7) | 44 (34.9) | <0.001 | <0.001 | 0.029 |
| Primary care | | 100 (18.6) | – | 66 (32.2) | 18 (8.9) | 16 (12.2) | <0.001 | <0.001 | 0.239 |
| Secondary care | | 100 (18.6) | | 37 (18.0) | 34 (16.8) | 29 (22.1) | | | |
| Tertiary care | | 338 (62.8) | | 102 (49.8) | 150 (74.3) | 86 (65.6) | | | |

Data are presented as mean±SD or n (%), unless otherwise indicated. Cluster 1: least symptom burden; cluster 2: medium symptom burden; cluster 3: high symptom burden. $FEV_1$: forced expiratory volume in 1 s; FVC: forced vital capacity; mMRC: modified Medical Research Council; CAT: COPD Assessment Test; LTOT: long-term oxygen therapy; TUG: Timed Up and Go test; CDS: Care Dependency Scale. [#]: due to COPD.

**TABLE 2** Symptom scores

| | Non-COPD participants | Patients with COPD | COPD *versus* non-COPD p-value | Cluster 1 | Cluster 2 | Cluster 3 | Cluster 1 *versus* cluster 2 p-value | Cluster 1 *versus* cluster 3 p-value | Cluster 2 *versus* cluster 3 p-value |
|---|---|---|---|---|---|---|---|---|---|
| Subjects, n | 116 | 538 | | 205 | 202 | 131 | | | |
| Dyspnoea | 0.0 (0.0–10.0) | 46.0 (25.8–61.3) | <0.001 | 27.0 (11.0–45.0) | 51.0 (37.0–66.3) | 57.0 (42.0–73.0) | <0.001 | <0.001 | 0.032 |
| Fatigue | 4.0 (0.0–16.5) | 47.0 (22.0–65.0) | <0.001 | 20.0 (3.5–36.0) | 55.0 (45.0–67.3) | 65.0 (47.0–74.0) | <0.001 | <0.001 | 0.001 |
| Cough | 0.0 (0.0–6.8) | 23.0 (0.0–50.0) | <0.001 | 4.0 (0.0–25.0) | 38.0 (10.0–60.3) | 46.0 (8.0–62.0) | <0.001 | <0.001 | 0.559 |
| Muscle weakness | 0.0 (0.0–5.8) | 35.5 (0.0–58.3) | <0.001 | 0.0 (0.0–18.0) | 49.0 (30.5–68.3) | 54.0 (36.0–67.0) | <0.001 | <0.001 | 0.425 |
| Loss of appetite | 0.0 (0.0–0.0) | 0.0 (0.0–19.0) | <0.001 | 0.0 (0.0–0.0) | 0.0 (0.0–19.0) | 13.0 (0.0–60.0) | <0.001 | <0.001 | <0.001 |
| Insomnia | 0.0 (0.0–14.8) | 0.0 (0.0–51.0) | 0.002 | 0.0 (0.0–12.0) | 0.0 (0.0–50.0) | 54.0 (31.0–71.0) | <0.001 | <0.001 | <0.001 |
| Depression | 0.0 (0.0–3.8) | 0.0 (0.0–29.0) | <0.001 | 0.0 (0.0–0.0) | 0.0 (0.0–21.3) | 45.0 (12.0–64.0) | <0.001 | <0.001 | <0.001 |
| Anxiety | 0.0 (0.0–0.0) | 0.0 (0.0–14.0) | <0.001 | 0.0 (0.0–0.0) | 0.0 (0.0–12.3) | 17.0 (0.0–53.0) | <0.001 | <0.001 | <0.001 |
| Panic | 0.0 (0.0–0.0) | 0.0 (0.0–0.0) | 0.006 | 0.0 (0.0–0.0) | 0.0 (0.0–0.0) | 0.0 (0.0–0.0) | 0.002 | <0.001 | <0.001 |
| Pain | 0.0 (0.0–10.0) | 0.0 (0.0–21.0) | 0.103 | 0.0 (0.0–0.0) | 0.0 (0.0–21.0) | 29.0 (0.0–67.0) | <0.001 | <0.001 | <0.001 |
| Mouth complaints | 0.0 (0.0–0.0) | 0.0 (0.0–12.0) | <0.001 | 0.0 (0.0–0.0) | 0.0 (0.0–22.3) | 0.0 (0.0–45.0) | <0.001 | <0.001 | 0.005 |
| Itch | 0.0 (0.0–0.0) | 0.0 (0.0–10.3) | 0.004 | 0.0 (0.0–0.0) | 0.0 (0.0–2.0) | 2.0 (0.0–49.0) | 0.154 | <0.001 | <0.001 |
| Oedema | 0.0 (0.0–0.0) | 0.0 (0.0–13.0) | <0.001 | 0.0 (0.0–0.0) | 0.0 (0.0–14.3) | 0.0 (0.0–34.0) | <0.001 | <0.001 | 0.010 |
| Thirst | 0.0 (0.0–0.0) | 0.0 (0.0–28.0) | <0.001 | 0.0 (0.0–0.0) | 0.0 (0.0–22.3) | 45.0 (0.0–67.0) | <0.001 | <0.001 | <0.001 |
| Muscle cramps | 0.0 (0.0–18.0) | 15.0 (0.0–49.0) | <0.001 | 0.0 (0.0–23.0) | 16.0 (0.0–42.3) | 56.0 (21.0–73.0) | <0.001 | <0.001 | <0.001 |
| Restless legs | 0.0 (0.0–7.0) | 0.0 (0.0–23.0) | 0.040 | 0.0 (0.0–0.0) | 0.0 (13.3) | 36.0 (0.0–66.0) | 0.017 | <0.001 | <0.001 |
| Dizziness | 0.0 (0.0–11.0) | 0.0 (0.0–17.0) | 0.264 | 0.0 (0.0–0.0) | 0.0 (0.0–12.3) | 26.0 (0.0–57.0) | 0.003 | <0.001 | <0.001 |
| Chest pain | 0.0 (0.0–0.0) | 0.0 (0.0–11.3) | <0.001 | 0.0 (0.0–0.0) | 0.0 (0.0–10.0) | 12.0 (0.0–44.0) | <0.001 | <0.001 | <0.001 |
| Micturition (night) | 0.0 (0.0–17.8) | 0.0 (0.0–35.0) | 0.172 | 0.0 (0.0–14.0) | 0.0 (0.0–30.8) | 47.0 (0.0–65.0) | 0.041 | <0.001 | <0.001 |
| Micturition (day) | 0 (0.0–14.8) | 0.0 (0.0–32.0) | 0.120 | 0.0 (0.0–6.0) | 0.0 (0.0–17.0) | 48.0 (0.0–67.0) | 0.327 | <0.001 | <0.001 |

Data presented as median symptom score (interquartile range), unless otherwise indicated. Cluster 1: least symptom burden; cluster 2: medium symptom burden; cluster 3: high symptom burden.
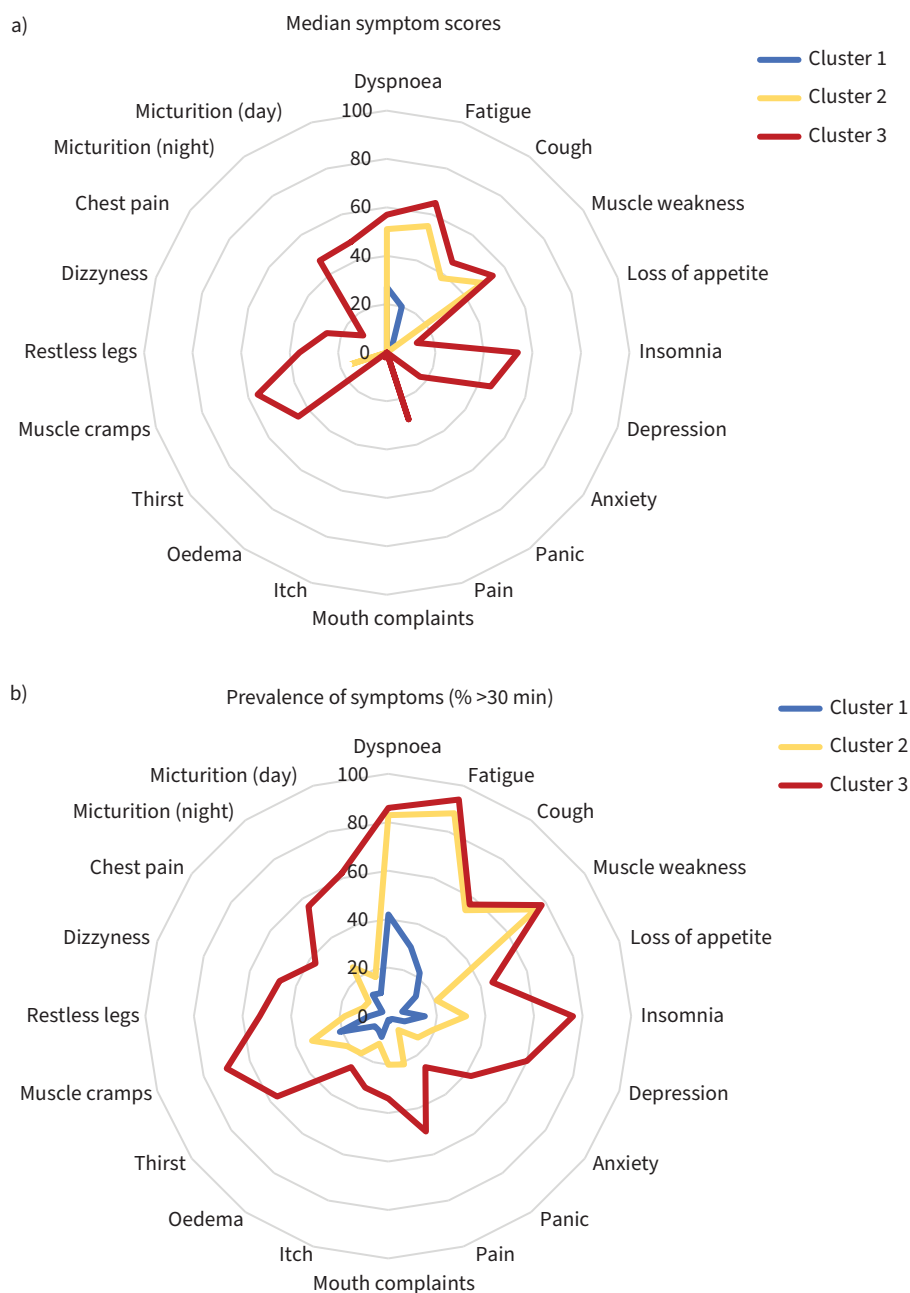
FIGURE 1 Spider plots stratified by the three clusters. Cluster 1 (least symptom burden), n=205; cluster 2 (medium symptom burden), n=202; cluster 3 (high symptom burden), n=131.

a minority of participants (16% and 14%, respectively) while patients with COPD predominantly reported dyspnoea, fatigue and muscle weakness (ranging between 53% and 68%). Especially in the medium and high symptom burden clusters (clusters 2 and 3), fatigue was the most prevalent symptom (88% and 94%, respectively) followed by dyspnoea (83% and 86%, respectively) and, remarkably, muscle weakness (75% and 78%, respectively). Muscle weakness as the third most important symptom might be explained by the high prevalence of fatigue. Indeed, participants described the sensation of fatigue as persistent overwhelming tiredness, severe lack of energy and physical weakness that worsens over time [19], suggesting a close association between fatigue and muscle weakness. Furthermore, multiple physical and psychological factors seem to be associated with fatigue [20] but little is known about the underlying determinants of fatigue in patients with COPD [21]. The current study underlines the need to understand

**TABLE 3** Prevalence of symptoms (VAS ⩾30 mm)

| | Non-COPD participants | Patients with COPD | COPD versus non-COPD p-value | Cluster 1 | Cluster 2 | Cluster 3 | Cluster 1 versus cluster 2 p-value | Cluster 1 versus cluster 3 p-value | Cluster 2 versus cluster 3 p-value |
|---|---|---|---|---|---|---|---|---|---|
| Subjects, n | 116 | 538 | | 205 | 202 | 131 | | | |
| Dyspnoea | 10 (8.6) | 367 (68.2) | <0.001 | 87 (42.4) | 168 (83.2) | 112 (85.5) | <0.001 | <0.001 | 0.571 |
| Fatigue | 15 (12.9) | 363 (67.5) | <0.001 | 62 (30.2) | 178 (88.1) | 123 (93.9) | <0.001 | <0.001 | 0.081 |
| Cough | 10 (8.6) | 229 (42.6) | <0.001 | 45 (22.0) | 109 (54.0) | 75 (57.3) | <0.001 | <0.001 | 0.555 |
| Muscle weakness | 13 (11.2) | 284 (52.8) | <0.001 | 30 (14.6) | 152 (75.2) | 102 (77.9) | <0.001 | <0.001 | 0.584 |
| Loss of appetite | 1 (0.9) | 114 (21.2) | <0.001 | 13 (6.3) | 42 (20.8) | 59 (45.0) | <0.001 | <0.001 | <0.001 |
| Insomnia | 19 (16.4) | 195 (36.2) | <0.001 | 32 (15.6) | 64 (31.7) | 99 (75.6) | <0.001 | <0.001 | <0.001 |
| Depression | 6 (5.2) | 130 (24.2) | <0.001 | 14 (6.8) | 38 (18.8) | 78 (59.5) | <0.001 | <0.001 | <0.001 |
| Anxiety | 6 (5.2) | 89 (16.5) | 0.002 | 4 (2.0) | 30 (14.9) | 55 (42.0) | <0.001 | <0.001 | <0.001 |
| Panic | 5 (4.3) | 51 (9.5) | 0.071 | 3 (1.5) | 14 (6.9) | 34 (26.0) | 0.006 | <0.001 | <0.001 |
| Pain | 15 (12.9) | 113 (21.0) | 0.047 | 5 (2.4) | 43 (21.3) | 65 (49.6) | <0.001 | <0.001 | <0.001 |
| Mouth complaints | 1 (0.9) | 89 (16.5) | <0.001 | 3 (1.5) | 41 (20.3) | 45 (34.4) | <0.001 | <0.001 | 0.004 |
| Itch | 6 (5.2) | 83 (15.4) | 0.003 | 18 (8.8) | 24 (11.9) | 41 (31.3) | 0.304 | <0.001 | <0.001 |
| Oedema | 6 (5.2) | 87 (16.2) | 0.002 | 15 (7.3) | 38 (18.8) | 34 (26.0) | <0.001 | <0.001 | 0.122 |
| Thirst | 5 (4.3) | 131 (24.3) | <0.001 | 14 (6.8) | 43 (21.3) | 74 (56.5) | <0.001 | <0.001 | <0.001 |
| Muscle cramps | 14 (12.1) | 201 (37.4) | <0.001 | 43 (21.0) | 66 (32.7) | 92 (70.2) | 0.008 | <0.001 | <0.001 |
| Restless legs | 12 (10.3) | 123 (22.9) | 0.003 | 17 (8.3) | 37 (18.3) | 69 (52.7) | 0.003 | <0.001 | <0.001 |
| Dizziness | 14 (12.1) | 94 (17.5) | 0.155 | 9 (4.4) | 23 (11.4) | 62 (47.3) | 0.009 | <0.001 | <0.001 |
| Chest pain | 3 (2.6) | 75 (13.9) | <0.001 | 6 (2.9) | 21 (10.4) | 48 (36.6) | 0.002 | <0.001 | <0.001 |
| Micturition (night) | 16 (13.8) | 145 (27.0) | 0.003 | 22 (10.7) | 50 (24.8) | 73 (55.7) | <0.001 | <0.001 | <0.001 |
| Micturition (day) | 17 (14.7) | 136 (25.3) | 0.014 | 20 (9.8) | 35 (17.3) | 81 (61.8) | 0.026 | <0.001 | <0.001 |

Data are presented as n (%), unless otherwise indicated. Cluster 1: least symptom burden; cluster 2: medium symptom burden; cluster 3: high symptom burden.
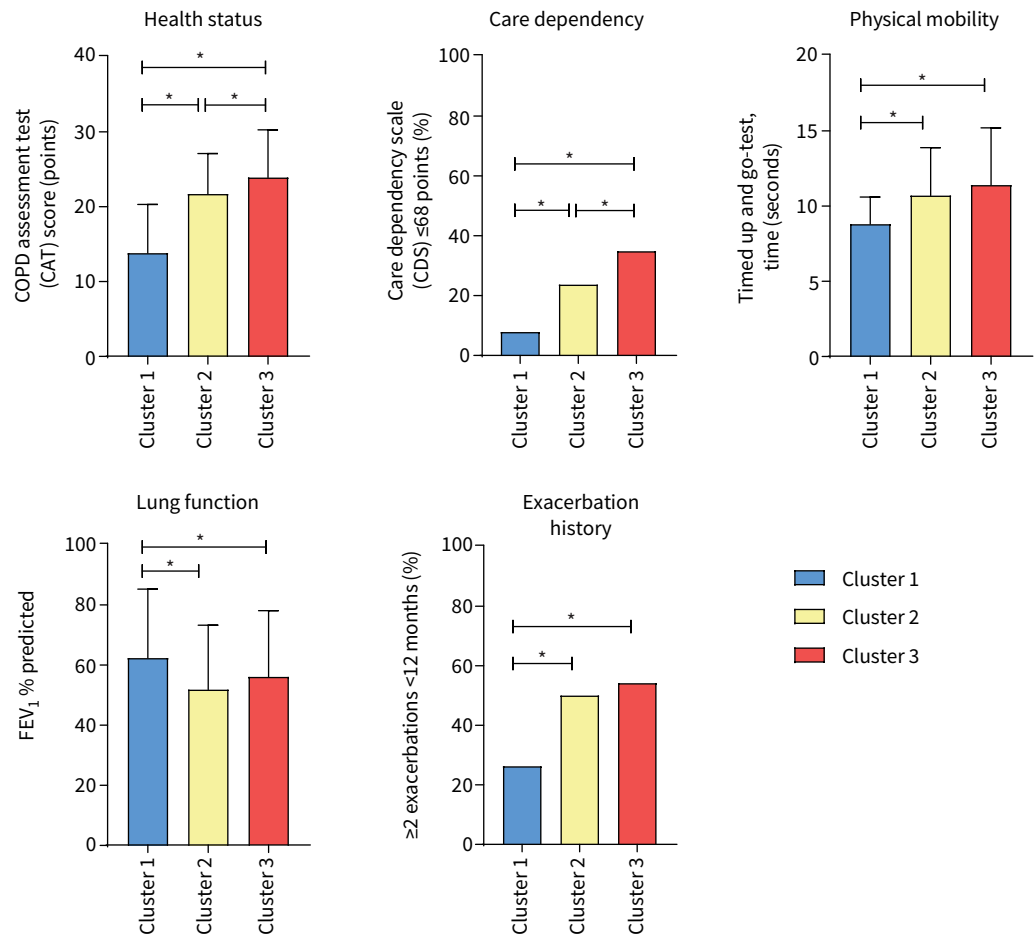
**FIGURE 2** Clinical characteristics stratified by the three clusters. Cluster 1 (least symptom burden), n=205; cluster 2 (medium symptom burden), n=202; cluster 3 (high symptom burden), n=131. CAT: COPD Assessment Test; CDS: Care Dependency Scale; $FEV_1$: forced expiratory volume in 1 s. *: $p \leqslant 0.05$

and target fatigue in COPD management to break the vicious circle of fatigue, inactivity, loss of muscle mass and muscle weakness.

In the current study, symptom burden seemed to be mainly driven by non-respiratory symptoms, underlining the need for comprehensive symptom assessment. Owing to the systemic effects and the complexity of the disease, it seems reasonable to include a broad variety of respiratory as well as non-respiratory symptoms in COPD disease management. However, in clinical practice, only disease-specific and respiratory measures (modified Medical Research Council scale or CAT) are used to classify patients as highly symptomatic [2]. However, as previously demonstrated, respiratory symptoms had only a limited contribution to the classification of patients as highly symptomatic, indicating that non-respiratory symptoms have an important impact on disease classification and treatment algorithms [22]. This study underlines the importance of a careful assessment of respiratory as well as non-respiratory symptoms in patients with COPD: classifying patients as highly symptomatic simply based on one measure or domain does not adequately reflect symptom experience. Furthermore, the current study underlined once again that lung function, *i.e.* forced expiratory volume in 1 s, cannot be used to accurately identify symptomatic patients [23, 24].

Participants in cluster 3 were characterised by overall worse outcomes. Therefore, broader assessment of unmet palliative care needs in these patients and integration of palliative care in disease-modifying treatment seems warranted [25]. Compared to clusters 1 and 2, a higher proportion of participants in cluster 3 were female, which might partly explain the high symptom burden. Indeed, the burden of COPD in women is increasing [26]. Compared to men with COPD, women experience a higher symptom burden and more impaired quality of life [26, 27]. Further research should focus on appropriate approaches to achieve adequate treatment strategies in women with COPD [26].

### Methodological considerations and recommendations

Comparing the current results with previous symptom cluster analysis is challenging because the composition of symptom clusters is inconsistent across studies owing to variations in study design, assessment tools and statistical approach [28, 29]. However, an advantage of the current study is the use of the highly sensitive VAS scale because patients' options are not limited to predefined descriptors or numbers. The number of symptoms can also be further extended. Additionally, qualitative studies are needed to provide a deeper patient-centred perspective of symptom experience in patients with COPD [28]. Although the current study included a broad sample of patients with COPD, two thirds of the patients were recruited from tertiary care, which may partly affect the external validity of the results. The analyses show that the care setting may only be partially relevant: 30.2% of the patients recruited in tertiary care ended up cluster 1 (least symptom burden), while 16% of the patients recruited in primary care ended up in cluster 3 (high symptom burden). Moreover, there was a lot of overlap in symptom burden between patients from all three care settings. Furthermore, the current study shows cross-sectional results demonstrating a snapshot of patients' symptom experience. Future studies are needed to assess the (in)stability of symptoms over time because considerable proportions of patients have previously reported daily, weekly and seasonal variability in their symptoms [1, 30]. However, a longitudinal study in patients with moderate to very severe COPD demonstrated that the pattern of high symptom burden is consistent over time [31], underlining the need to intervene in time. Unfortunately, physicians pay most attention to domains related to clinical features, such as cough, phlegm and dyspnoea, which were consequently most likely to be treated [7, 32].

The current study creates relevant awareness for clinical practice; clusters provide important insights into the clinical complexity of patients' symptom burden and highlight the need for multidimensional symptom management. For example, co-occurring fatigue and insomnia (cluster 3) require a different treatment approach to fatigue without co-occurring insomnia (cluster 2). To effectively treat co-occurring symptoms, healthcare professionals must perform comprehensive symptom assessment, including physical as well as psychological symptoms [33]. Once identified, an integrated treatment plan is needed to adequately address co-occurring symptoms and consequently reduce patients' symptom burden. Although several questionnaires are available for assessing symptoms, uptake is often limited in clinical practice, most likely due to a combination of lack of awareness, difficulty in incorporating questionnaires into practice flow, or lack of electronic medical record support for questionnaires [10]. A clinical decision support tool combining patient-reported symptom burden with guideline-based recommendations can improve multidimensional symptom assessment [34]. Furthermore, pulmonary rehabilitation might be an appropriate setting for integrating comprehensive symptom assessment and management [35].

### Conclusions

Cluster analysis demonstrated a co-occurrence of different symptom severity patterns, highlighting the heterogeneity of symptom experience in patients with COPD. Identifying clusters of patients with shared symptom experiences can help us to understand the impact of the disease and define integrated, multidimensional treatment strategies. Respiratory and non-respiratory symptoms should be assessed and considered routinely in the long-term treatment plan of patients with COPD.

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