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# Distinct pain profiles in patients with chronic obstructive pulmonary disease

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**Background:** Few studies have examined changes in the pain experience of patients with COPD and predictors of pain in these patients.

**Objectives:** The objectives of the study were to examine whether distinct groups of COPD patients could be identified based on changes in the occurrence and severity of pain over 12 months and to evaluate whether these groups differed on demographic, clinical, and pain characteristics, and health-related quality of life (HRQoL).

**Patients and methods:** A longitudinal study of 267 COPD patients with very severe COPD was conducted. Their mean age was 63 years, and 53% were females. The patients completed questionnaires including demographic and clinical variables, the Brief Pain Inventory, and the St Georges Respiratory Questionnaire at enrollment, and 3, 6, 9, and 12 months follow-up. In addition, spirometry and the 6 Minute Walk Test were performed. Latent class analysis was used to identify subgroups of patients with distinct pain profiles based on pain occurrence and worst pain severity.

**Results:** Most of the patients (77%) reported pain occurrence over 12 months. Of these, 48% were in the "high probability of pain" group, while 29% were in the "moderate probability of pain" group. For the worst pain severity, 37% were in the "moderate pain" and 39% were in the "mild pain" groups. Females and those with higher body mass index, higher number of comorbidities, and less education were in the pain groups. Patients in the higher pain groups reported higher pain interference scores, higher number of pain locations, and more respiratory symptoms. Few differences in HRQoL were found between the groups except for the symptom subscale.

**Conclusion:** Patients with COPD warrant comprehensive pain management. Clinicians may use this information to identify those who are at higher risk for persistent pain.

**Keywords:** chronic obstructive pulmonary disease, patient-reported outcomes, pain, pain occurrence, worst pain severity, latent profile analysis

## Introduction

Pain is a common symptom in patients with COPD, but there is a high variation in the estimates of both the occurrence and the severity of pain in individuals with COPD.<sup>1-5</sup> Across two studies,<sup>1,6</sup> the occurrence of pain ranged from 34% to 53% in patients with moderate COPD, from 24% to 31% in those with severe COPD, and from 16% to 42% in those with very severe COPD. Similarly, between 21% and 96% of COPD patients report pain with severity scores in the moderate to severe range.<sup>1-5</sup>

While cross-sectional studies provide insights about pain in COPD patients, only three studies have evaluated longitudinal changes in pain occurrence and severity.<sup>7-9</sup> In a community sample of COPD patients,<sup>7</sup> 46% reported pain at enrollment and 48% after two years. In another study,<sup>8</sup> the occurrence of pain was 74% before hospitalization

and decreased to 54% two weeks after discharge. Finally, in a sample of COPD patients admitted to hospice,<sup>9</sup> 82% had pain on admission and 28% had pain control within 24 hours. Across these three studies,<sup>7–9</sup> 16%–31% of the patients reported mild pain and 20%–63% reported moderate to severe pain. While these findings suggest that pain persists in COPD patients, none of these studies evaluated for changes in the occurrence and severity of pain and in patients at different stages of their disease. Therefore, longitudinal studies are needed to characterize changes over time in the occurrence and severity of pain in COPD patients in various stages of the disease.

Eight studies evaluated the relationships between demographic and clinical characteristic and pain in COPD patients.<sup>1,2,6,10–14</sup> While no sex and age differences were found in two studies,<sup>13,14</sup> in other studies females had a higher prevalence of pain.<sup>1</sup> Moreover, younger patients reported more severe pain.<sup>2,10</sup> Regarding the relationships between pain and body mass index (BMI) and comorbidities, previous findings are inconclusive. While three studies found no association between pain and BMI,<sup>10,13,14</sup> other studies of COPD patients found that pain was associated with higher BMI,<sup>12</sup> as well as with a higher number of comorbidities.<sup>6,12</sup> While no associations were found between lung function or smoking and pain in two studies,<sup>6,10</sup> in a recent study<sup>1</sup> patients with better lung function reported more severe pain. In addition, COPD patients with pain had lower levels of physical function.<sup>12</sup>

Health-related quality of life (HRQoL) provides insights into the disease as well as patients' health status.<sup>15–18</sup> Three studies have evaluated the relationship between pain and HRQoL in patients with COPD.<sup>6,13,19</sup> One study<sup>6</sup> found a significant association between pain occurrence and respiratory symptoms, while another study found a significant association between pain occurrence and pain severity, and overall health status,<sup>13</sup> by contrast, in another study<sup>19</sup> no association was found between worst pain severity and overall health status.

In several studies,<sup>1,10,11,20–22</sup> the authors commented that the occurrence, severity, and risk factors for pain in patients with COPD were rather heterogeneous. Although two studies reported changes over time in the occurrence and severity of pain,<sup>7,8</sup> neither of these studies evaluated demographic and clinical characteristics, and HRQoL associated with this variability. These limitations highlight the need for additional research on changes in and characteristics associated with the occurrence and severity of pain in patients with COPD. Therefore, the purposes of the present study were to examine whether distinct groups of COPD patients could be

identified based on changes in self-reports of pain occurrence and severity over 12 months and to evaluate whether these groups differed on a number of demographic, clinical, and pain characteristics, as well as HRQoL.

## Patients and methods

### Patients, settings, and study procedures

This longitudinal study is a follow-up study of 267 COPD patients ([ClinicalTrials.gov](https://clinicaltrials.gov) identification: NCT01016587).<sup>1</sup> In brief, patients were enrolled from three outpatient clinics and one referral hospital in the Norwegian Health Region Southeast from December 2009 until October 2012. A research nurse explained the purpose of the study at enrollment, and written informed consent was obtained from all patients. The inclusion criteria were >18 years of age; diagnosed with moderate (grade II), severe (grade III), or very severe (grade IV) COPD according to the Global Initiative for Chronic Obstructive Lung disease (GOLD);<sup>23</sup> able to read and understand Norwegian; and had no cognitive impairments. The patient's cognitive function was assessed by the nurse during the enrollment process. Exclusion criteria were receiving ongoing treatment for a pulmonary infection, COPD exacerbation, or cancer diagnosis at enrollment.

A total of 363 patients were asked to participate in this study. Of these, 16 did not meet the inclusion criteria and 55 declined to participate. Of the 292 patients who wanted to participate, eight withdrew from the study and 17 did not return the questionnaire at enrollment. The final sample for this study consisted of 267 patients (response rate 76.9%). To evaluate for the changes in pain occurrence and severity, patients completed questionnaires at enrollment (n=267), and at three (n=234), six (n=225), nine (n=202), and 12 (n=202) months after enrollment.

This study was approved by the privacy ombudsman at Oslo University Hospital, and recommended by the Regional Committees for Medical and Health Research Ethics (reference no S-09102a).

### Instruments

Patients completed all of the self-report questionnaires. Research nurse reviewed the patients' medical records for clinical data.

### Demographic and clinical characteristics

At enrollment, patients provided information on age, sex, education, and cohabitation. The research nurse collected data on BMI, smoking history, and number of years since diagnosis of COPD. Pack-years smoking was calculated as

the average number of cigarettes smoked per day divided by 20 and multiplied by the total number of years smoking.<sup>24</sup>

### Comorbidity

Comorbidities were assessed using the Self-Administered Comorbidity Questionnaire (SCQ-19),<sup>25</sup> which includes 16 common and three optional medical conditions. Patients were asked to indicate whether they had the comorbid condition (yes/no), if they received treatment for it (yes/no), and whether it limited their activities (yes/no). The SCQ total score can range from 0 to 57. A higher score indicates a more severe comorbidity profile.<sup>25</sup> The SCQ-19 has well-established validity and reliability with patients with chronic medical conditions.<sup>25</sup>

### Pain

Pain occurrence, worst pain severity, pain inference, and number of pain locations were examined using the Brief Pain Inventory (BPI).<sup>26</sup> Patients were asked to indicate whether they generally were bothered by pain (yes/no). If they were generally bothered by pain, they rated worst pain severity using a numeric rating scale (NRS) that ranged from 0 (no pain) to 10 (worst pain imaginable). In addition, patients rated how much pain interfered with general activity, mood, walking ability, normal work and housework, relations with other people, sleep, enjoyment of life using a NRS that ranged from 0 (does not interfere) to 10 (completely interferes). A total interference score was calculated as the mean of these seven items. Total number of pain locations was calculated using a body outline diagram. The body outline diagram is divided into 30 different areas. Each area that was marked was counted and summed to create the total number of pain locations. Scores could range from 0 to 30.<sup>27</sup> The Norwegian version of BPI has satisfactory validity and reliability and sensitivity to change in longitudinal studies.<sup>28,29</sup> The BPI was used in studies of COPD patients.<sup>1,10–13,22</sup>

### HRQoL

The St George's Respiratory Questionnaire (SGRQ) during the last three months was used to evaluate the overall HRQoL.<sup>30</sup> The total SGRQ score can range from 0 to 100, with higher scores indicating lower HRQoL.<sup>30,31</sup> The SGRQ is a valid and reliable measure of HRQoL in patients with COPD.<sup>32–34</sup>

### Lung function

At enrollment, patients underwent a spirometry. Data were collected on forced expiratory volume in one second (FEV<sub>1</sub>) and forced vital capacity (FVC), and predicted values were

calculated according to the guidelines of the European Respiratory Society.<sup>35</sup> FVC, FEV<sub>1</sub>, and FEV<sub>1</sub> as a percentage of the predicted value (FEV<sub>1</sub>% predicted) were used as measures of lung function. Disease severity was classified using the GOLD guidelines<sup>23</sup> and was graded as mild (FEV<sub>1</sub> ≥80% predicted), moderate (FEV<sub>1</sub> 50%–79% predicted), severe (FEV<sub>1</sub> 30%–49% predicted), or very severe (FEV<sub>1</sub> <30% predicted).

### Physical function

Physical function was evaluated using the 6 Minute Walk Test (6MWT).<sup>36,37</sup> Distance covered was measured to the closest meter. A greater distance indicates better physical function. The 6MWT has satisfactory validity and reliability in COPD patients.<sup>37,38</sup>

### Data analysis

In this study, patients who indicated that they were generally bothered by pain or who completed information on two of the four dimensions of the BPI (ie, intensity, location, interference, relief)<sup>26</sup> were categorized into the pain group.

The profile for pain across five assessments was evaluated. Because trajectory for pain across the assessments was complex, latent class analysis (LCA) for the occurrence rates, and latent profile analysis (LPA) for the severity ranges were performed rather than growth mixture modeling.<sup>39–42</sup> To accommodate expected serial covariation over time, covariances between adjacent assessments were included in the model (ie, baseline with three months, three months with six months, etc.). Patients who did not report pain at any of the five measurements were classified as the no pain group. These patients were not included in the LCA or LPA. Separate analyses were done for pain occurrence (LCA) and severity (worst pain; LPA) to identify groups of patients (ie, latent classes) with distinct pain experiences over the five assessments.

Estimation was carried out with full information maximum likelihood (FIML) with standard errors and a chi-square test that are robust to non-normality and non-independence of observations (estimator = multiple linear regression analysis). Model fit was evaluated using the Bayesian Information Criterion (BIC), entropy, the Vuong Lo Mendell Rubin (VLMR) likelihood ratio test for the K vs K-1 model, and latent class sizes (percentages) that were large enough to be reliable.<sup>43,44</sup> Missing data were accommodated with the use of FIML and the Expectation Maximization algorithm.

Mixture models such as LPA are known to produce solutions at local maxima. Therefore, our models were fit with from 1,000 to 2,400 random starts. This approach ensured

that the selected model was replicated many times and not due to a local maximum. The LPAs were conducted using Mplus Version 7.2.<sup>43</sup>

After identifying the latent class solution that best fits the data for each outcome, the patients who did not report pain at any of the five assessments were added in the subsequent analyses as the no pain group. Differences in demographic and clinical characteristics as well as HRQoL among the pain groups were evaluated using analysis of variance, chi-square tests, or Kruskal–Wallis tests using SPSS version 21.<sup>45</sup> A *p*-value of <0.05 was considered statistically significant. Multiple comparisons of differences between groups were Bonferroni adjusted.

## Results

### Patient characteristics

Of the 267 patients in this study, 52.8% were females, with a mean age of 63.2 (SD 9.0, range 37–84) years. A total of 24% were current smokers. The mean numbers of years since the diagnosis of COPD was 7.6 (SD 6.3, range 0–35). In addition, 31.1% of the patients had moderate COPD, 22.8% had severe COPD, while 46.1% had very severe COPD. Characteristics of the participants at enrollment are summarized in Table 1.

### LCA for pain occurrence

After removing patients who did not report any occurrence of pain across the five assessments, the LCA was performed. A 2-class solution fits the data best. The 2-class solution was selected because the BIC was smallest for the 2-class solution, the VLMR was significant for the 2-class but not for the 3-class solution, and because one of the classes in the 3-class solution was too small (14 cases, or 7% of the sample examined in the latent profile models) to be reliable (Table 2).

As shown in Figure 1, 62 patients (23.2%) did not report any pain across the five assessments (ie, no pain group). The largest group of patients (n=128; 47.9%), with the highest pain occurrence rates, was named the “high probability of pain” group. The second largest group (n=77; 28.8%) was named the “moderate probability of pain” group.

### Differences in demographic and clinical characteristics and HRQoL among the pain occurrence groups

As shown in Table 3, compared to the “no pain” group, patients in the “high probability of pain” group were more

**Table 1** Characteristics in the total sample at enrollment into the study (n=267)

Characteristics	Mean (SD)	Range
Age (years)	63.2 (9.0)	37–84
FEV <sub>1</sub> (liters)	1.0 (0.6)	0.2–2.9
FEV <sub>1</sub> % predicted	38.9 (19.3)	10.4–80.0
Number of years with COPD	7.6 (6.3)	0–35
Pack-years smoking	35.7 (22.3)	0.3–160
Number of comorbidities	2.3 (1.7)	0–11
BMI (kg/m <sup>2</sup> )	23.9 (4.6)	14.9–37.7
6MWT (meters)	378.8 (131.5)	36–720
	<b>n</b>	<b>(%)</b>
Sex		
Male	126	(47.2)
Female	141	(52.8)
Cohabitation		
Living with someone	175	(66.3)
Living alone	89	(33.7)
Education		
Primary	96	(36.8)
Secondary	136	(52.1)
University/college	29	(11.1)
Smoking		
Current	64	(24.0)
Previous	200	(74.9)
Never	3	(1.1)
Disease severity based on GOLD criteria		
Moderate	83	(31.1)
Severe	61	(22.8)
Very severe	123	(46.1)

**Abbreviations:** BMI, body mass index; FEV<sub>1</sub>, forced expiratory volume in one second; FEV<sub>1</sub>%, forced expiratory volume in one second as a percentage of the predicted value; GOLD, Global Initiative for Chronic Obstructive Lung Disease; 6MWT, 6 Minute Walk Test.

likely to be female; were less likely to have a university education; had a higher BMI; had a higher FEV<sub>1</sub>% predicted; and were less likely to have very severe COPD. In addition, these patients reported a higher number of comorbidities and a higher total SCQ score, and were more likely to report heart disease, headache, depression, osteoarthritis, back and neck pain, and disease of muscle and connective tissue. Compared to the “no pain” group, patients in the “moderate probability of pain” group reported a higher number of comorbidities and were more likely to report back and neck pain. Compared to the “moderate probability of pain” group, patients in the “high probability of pain” group reported more pain locations and a higher pain interference score. For the SGRQ symptom component, patients in the “high probability of pain” group had a significantly higher score than the patients in the “no pain” group. In addition, there was a significant difference in the SGRQ total score, but no significant pairwise group differences were found.

**Table 2** Latent class profile analysis solutions and fit indices for the 1-class through 3-class solutions for probability of occurrence of pain and severity of worst pain

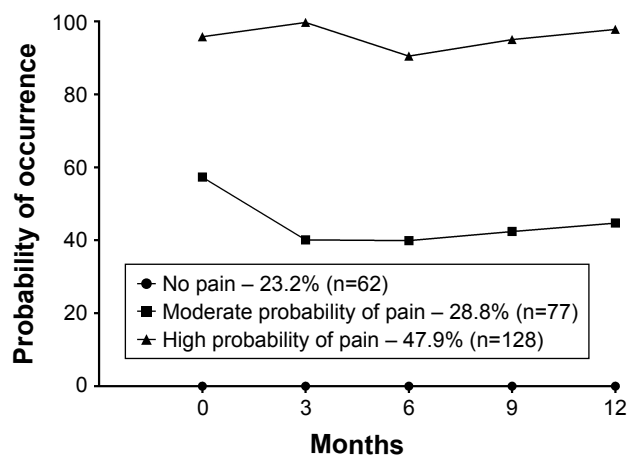
Model	LL	AIC	BIC	Entropy	VLMR
<b>Pain occurrence</b>					
1-class	-505.66	1,021.32	1,037.94	N/A	N/A
2-class <sup>a</sup>	-442.61	907.22	943.78	0.70	126.10*
3-class	-439.76	913.52	970.01	0.73	5.70 <sup>NS</sup>
<b>Pain severity</b>					
1-class	-1,541.10	3,110.20	3,156.58	N/A	N/A
2-class <sup>b</sup>	-1,492.67	3,025.35	3,091.61	0.68	96.85
3-class	-1,476.31	3,004.63	3,090.77	0.77	32.71 <sup>NS</sup>

**Notes:** \* $p < 0.0001$ . <sup>a</sup>The 2-class solution was selected for pain occurrence because the BIC for that solution was lower than the BIC for both the 1- and 3-class solutions. In addition, the VLMR was significant for the 2-class solution, indicating that 2-classes fit the data better than 1-class, but the VLMR was not significant for the 3-class solution, indicating that too many classes had been extracted. In addition, the 3-class solution resulted in a third, very small class (14 cases, 6.8% of the sample in the model) that is unlikely to generalize to other samples. <sup>b</sup>The 2-class solution was selected for pain severity because the BIC for that solution was lower than the BIC for the 1-class solution. In addition, the VLMR was significant for the 2-class solution, indicating that 2-classes fit the data better than 1-class, but the VLMR was not significant for the 3-class solution, indicating that too many classes had been extracted. In addition, the 3-class solution resulted in a third, very small class (9 cases, 4.6% of the sample in the model) that is unlikely to generalize to other samples.

**Abbreviations:** AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; LL, log-likelihood; N/A, not applicable; <sup>NS</sup>, not significant; VLMR, Vuong-Lo-Mendell-Rubin likelihood ratio test for the K vs K-1 model.

## LPA for worst pain severity

After removing patients who did not report any severity ratings for pain across the five assessments, the LPA of worst pain scores was performed. Again, a 2-class solution fits the data best. The 2-class solution was selected because the VLMR was significant for the 2-class but not for the 3-class solution and one of the classes in the 3-class solution was too small (9 cases, or 4% of the sample examined in the latent profile models) to be reliable (Table 2). In addition,



**Figure 1** Probability of pain occurrence in the two latent classes across five assessments.

although the BIC was slightly larger for the 2-class solution compared to the 3-class solution, the difference was trivial (3,091.61 compared to 3,090.77).<sup>46,47</sup> Therefore, the 3-class solution did not provide a better fit than the 2-class solution using the BIC as a criterion.

As shown in Figure 2, 64 patients (24.0%) reported worst pain scores of 0 across the five assessments (ie, no pain group). The largest group of patients (n=105, 39.3%) reported worst pain scores in the mild range (ie, mild pain group). The second largest group (n=98, 36.7%) reported worst pain scores in the moderate range (ie, moderate pain group).

## Differences in demographic and clinical characteristics and HRQoL among the worst pain severity groups

As shown in Table 4, compared to the “no pain” group, patients in the “moderate pain” group were more likely to be female, were less likely to have a university education, had a higher BMI, had a higher FEV<sub>1</sub> (liters) and FEV<sub>1</sub>% predicted, and were less likely to have very severe COPD. In addition, these patients reported a higher number of comorbidities and a higher SCQ score. They were more likely to report heart disease, headache, osteoarthritis, back and neck pain, and disease of muscle and connective tissue. Compared to the “no pain” group, the patients in the “mild pain” group reported a higher number of comorbidities, had a higher SCQ score, and were more likely to report back and neck pain. Compared to the “mild pain” group, patients in the “moderate pain” group reported more pain locations and higher pain interference score. There was a significant difference in SGRQ symptoms score ( $p=0.047$ ), but no significant pairwise group difference was found.

## Discussion

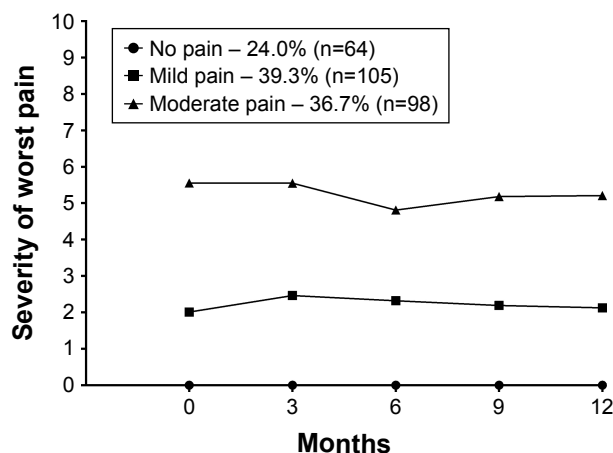
The present study is the first to identify specific groups of patients with COPD who are characterized by distinct trajectories of pain based on reports of occurrence and severity over a 12-month period. Using LCA, two distinct groups of pain could be identified among those COPD patients who reported pain, one with high probability and one with moderate probability of pain. A similar pattern was found when severity scores were used in the LPA. When analyzing the occurrence of pain, we found that 77% of the patients had pain at least once during the five assessments done over one year. Of these, 29% of the patients were in the “moderate probability of pain” group and 48% were

**Table 3** Differences in demographic and clinical characteristics, and health-related quality of life among the three latent pain groups based on probability of occurrence of pain

Characteristic	No pain (1)	Moderate probability of pain (2)	High probability of pain (3)	Statistics
	23.2% (n=62) Mean (SD)	28.8% (n=77) Mean (SD)	47.9% (n=128) Mean (SD)	
Age (years)	62.4 (8.5)	62.1 (8.4)	64.2 (9.6)	$F=1.56, p=0.213$
SCQ score (0–57)	2.4 (2.4)	3.7 (3.0)	6.4 (4.4)	$F=28.44, p<0.001, 3>1$ and 2
Number of comorbidities	1.3 (1.2)	2.0 (1.5)	3.0 (1.8)	$F=28.27, p<0.001, 3>2>1$
Number of years since diagnosis of COPD	7.3 (6.2)	7.2 (5.9)	8.1 (6.5)	$F=0.47, p=0.627$
BMI (kg/m <sup>2</sup> )	22.7 (4.2)	24.2 (4.7)	24.4 (4.6)	$F=3.20, p=0.043, 3>1$
FEV <sub>1</sub> (liters)	0.9 (0.6)	1.1 (0.6)	1.1 (0.6)	KW, $p=0.053$
FEV <sub>1</sub> % predicted	31.5 (16.8)	39.3 (19.0)	42.2 (19.8)	KW, $p=0.001, 3>1$ and 2
6MWT (meters)	386.9 (140.6)	394.2 (143.3)	364.3 (117.6)	$F=1.15, p=0.319$
Number of pain locations	N/A	1.7 (2.7)	6.0 (5.3)	$t=-7.49, p<0.001$
Pain inference (0–10)	N/A	1.4 (1.5)	3.5 (2.7)	$t=-6.68, p<0.001$
Symptoms (SGRQ, 0–100)	56.2 (21.6)	59.3 (20.3)	65.4 (19.7)	$F=4.82, p=0.012, 3>1$
Activity (SGRQ, 0–100)	70.3 (24.6)	70.5 (22.7)	70.7 (21.8)	$F=0.01, p=0.994$
Impact (SGRQ, 0–100)	40.1 (20.9)	43.8 (20.7)	48.3 (19.1)	$F=3.41, p=0.035^{\S}$
Total score (SGRQ, 0–100)	52.8 (20.1)	54.9 (18.2)	58.2 (17.3)	$F=1.79, p=0.170$
	% (n)	% (n)	% (n)	
Sex				$\chi^2=12.44, p=0.002, 3<1$
Male*	64.5 (40)	49.4 (38)	37.0 (48)	
Female	35.5 (22)	50.6 (39)	63.0 (80)	
Cohabitation				$\chi^2=3.84, p=0.156$
Lives alone	24.6 (15)	32.5 (25)	38.9 (49)	
Lives with someone	75.4 (46)	67.5 (52)	61.1 (77)	
Education				KW, $p=0.010, 3<1$
Primary	23.3 (14)	39.0 (30)	41.9 (52)	
Secondary	56.7 (34)	50.6 (39)	50.8 (63)	
University	20.0 (12)	10.4 (8)	7.3 (9)	
Smoking				$\chi^2=3.48, p=0.159$
Yes	96.8 (60)	100.0 (77)	99.2 (127)	
No	3.2 (2)	0.0 (0)	0.8 (1)	
Disease severity based on GOLD criteria				KW, $p=0.019, 3<1$
Moderate	16.2 (10)	35.0 (27)	36.0 (46)	
Severe	25.8 (16)	18.2 (14)	24.2 (31)	
Very severe	58.0 (36)	46.8 (36)	39.8 (51)	
Comorbid conditions				
Heart disease	10.2 (6)	12.9 (9)	25.9 (29)	$\chi^2=8.33, p=0.015, 3>1$
High blood pressure	29.3 (17)	23.6 (17)	34.8 (40)	$\chi^2=2.65, p=0.262$
Cancer	0.0 (0)	0.0 (0)	4.6 (5)	$\chi^2=6.10, p=0.061$
Diabetes	5.0 (3)	11.1 (8)	8.1 (9)	$\chi^2=1.62, p=0.454$
Ulcer or stomach disease	3.4 (2)	4.2 (3)	8.4 (9)	$\chi^2=2.23, p=0.360$
Bowel disease	1.7 (1)	4.3 (3)	6.5 (7)	$\chi^2=1.95, p=0.385$
Kidney disease	1.7 (1)	1.4 (1)	2.8 (3)	$\chi^2=0.44, p=0.861$
Liver disease	0.0 (0)	0.0 (0)	0.9 (1)	$\chi^2=1.20, p=1.000$
Anemia or other blood disease	0.0 (0)	2.9 (2)	1.9 (2)	$\chi^2=1.60, p=0.593$
Headache	8.5 (5)	22.9 (16)	32.4 (35)	$\chi^2=12.14, p=0.002, 3>1$
Depression	15.0 (9)	24.3 (17)	33.0 (37)	$\chi^2=6.76, p=0.036, 3>1$
Osteoarthritis	3.5 (2)	10.0 (7)	31.5 (35)	$\chi^2=24.37, p<0.001, 3>1$ and 2
Back and neck pain	8.5 (5)	43.1 (31)	68.7 (79)	$\chi^2=57.36, p<0.001, 3>2>1$
Rheumatoid arthritis	5.2 (3)	2.9 (2)	5.5 (6)	$\chi^2=0.72, p=0.727$
Disease of muscle/connective tissue	1.7 (1)	2.9 (82)	15.7 (17)	$\chi^2=13.47, p=0.001, 3>1$ and 2
Skin diseases	12.1 (7)	17.1 (12)	17.7 (20)	$\chi^2=0.96, p=0.638$

**Note:** \*Reference group. <sup>§</sup> indicates significant differences among the latent classes, but no significant pairwise group differences.

**Abbreviations:** BMI, body mass index; FEV<sub>1</sub>, forced expiratory volume in one second; FEV<sub>1</sub>%, forced expiratory volume in one second as a percentage of the predicted value; GOLD, Global Initiative for Chronic Obstructive Pulmonary Disease; KW, Kruskal–Wallis test; N/A, not applicable; SCQ, self-administered comorbidity questionnaire; SGRQ, St George Respiratory Questionnaire; 6MWT, 6 Minute Walk Test.



**Figure 2** Severity of worst pain in the two latent classes across five assessments.

in the “high probability of pain” group. Moreover, when analyzing pain severity, we found that the overall percentage of patients with pain scores in the mild and moderate range was 76%. This finding is higher than the 38% found in terminally ill COPD patients.<sup>5</sup> Taken together, our findings suggest that persistent pain is a significant problem for COPD patients.

In addition, we found that those who reported pain had less severe COPD as measured by FEV<sub>1</sub>% predicted. These findings are consistent with a previous study that found that patients with moderate COPD reported a higher pain prevalence rate and worse pain severity scores than patients with severe or very severe disease.<sup>3</sup> There may be several explanations for this somewhat unexpected finding. One potential explanation is that patients with more severe COPD are more likely to report respiratory phenomena (eg, chronic cough, sputum production, breathlessness, wheezing)<sup>10,48,49</sup> that are experienced as more severe and distressing than pain.

Despite the fact that the patients with higher probability of pain occurrence had less severe COPD as measured by FEV<sub>1</sub>% predicted, they reported more respiratory symptoms. This finding is consistent with a previous study.<sup>20</sup> In addition, in a qualitative study<sup>22</sup> it was found that COPD patients described their pain as “tying up their body” making it impossible to breathe, which in turn resulted in increased pain. This finding may be a confirmation of the notion that the sensation of pain and respiratory symptoms may be related.<sup>50</sup>

Regarding the specific descriptions of pain, our study showed that painful conditions including headache, heart diseases, osteoarthritis, back and neck pain, rheumatoid arthritis, and diseases of muscle and connective tissue were reported in relatively high percentages of patients in the two highest pain groups compared to the no pain groups. This finding is consistent with previous research.<sup>51</sup> It is conceivable

that some of these conditions may be causally related to the COPD. Headache may result from chronic hypoxemia.<sup>52</sup> In addition, osteoporosis-related vertebral fractures are common in COPD<sup>53</sup> and the resulting pain is often reported to be severe.<sup>54,55</sup> Moreover, the high rates of back and neck pain in the COPD patients could be explained by changes in respiratory function and remodeling of the thorax often associated with COPD.<sup>56,57</sup> The main muscles of respiration are the diaphragm and the intercostal muscles.<sup>58</sup> However, in patients with COPD, a range of muscles located in the neck (ie, sternocleidomastoid, scalene muscles, pectoralis major and minor) and back (erector spinae and levatores costarum) are overused,<sup>59</sup> which may lead to increased pain.<sup>56,57</sup> Also, there is evidence to suggest that the systemic inflammation associated with COPD may contribute to the sensation of pain.<sup>8,51</sup> Finally, the back and neck pain may be related to a higher BMI.<sup>11,13</sup> The BMIs of the patients in the “high probability of pain” (ie, 24–29) and “moderate pain” (ie, 25–29) groups are classified as overweight by the World Health Organization.<sup>60</sup> Moreover, being overweight is associated with increased pain in the elderly,<sup>61</sup> as well as with a number of painful musculoskeletal conditions (eg, osteoarthritis, and neck back, hip and knee pain).<sup>62,63</sup>

Additional factors are associated with reports of pain in patients with COPD. Compared to the “no pain” group, patients in the “high probability of pain” and “moderate pain” groups were more likely to be female, to report depression, and to have only a primary school education. Of note, painful musculoskeletal disorders (eg, back and neck pain, osteoarthritis) are more common in females.<sup>64–66</sup> In addition, population-based studies,<sup>67,68</sup> as well as previous studies of COPD patients,<sup>2,69</sup> found that females and depressed patients report higher occurrence and severity of pain. The reasons for this association are not clear. However, evidence suggests that sex differences in pain occurrence and severity may be explained by differences in sex steroid hormones.<sup>70</sup> While causal association between depression and pain is not clear, it may be of interest that the same neurological mechanisms are involved in the perception of both depression and pain.<sup>71,72</sup> Finally, why the occurrence and severity of pain was associated with a lower level of education is not clear, but our finding is consistent with a previous study.<sup>73</sup>

## Limitations

Some limitations need to be acknowledged. The exact etiologies for the pain and the use of pain medications were not evaluated. Our observations suggest that a detailed characterization of the causes of and treatment for pain should be evaluated in future studies. A further limitation of this study



**Table 4** Differences in demographic and clinical characteristics, and health-related quality of life among the three latent pain groups based on ratings of severity of worst pain

Characteristics	No pain (1) 24.0% (n=64)	Mild pain (2) 39.3% (n=105)	Moderate pain (3) 36.7% (n=98)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)	62.3 (8.4)	62.9 (8.4)	64.1 (10.0)	$F=0.84, p=0.432$
SCQ score (0–57)	2.3 (2.4)	4.0 (3.1)	6.9 (4.6)	$F=32.91, p<0.001, 3>2>1$
Number of comorbidities	1.2 (1.2)	2.2 (1.4)	3.2 (1.9)	$F=32.01, p<0.001, 3>2>1$
Number of years since diagnosis of COPD	7.3 (6.1)	7.7 (6.2)	7.8 (6.5)	$F=0.09, p=0.919$
BMI (kg/m <sup>2</sup> )	22.7 (4.1)	24.1 (4.6)	24.6 (4.7)	$F=3.62, p=0.028, 3>1$
FEV <sub>1</sub> (liters)	0.9 (0.6)	1.0 (0.5)	1.2 (0.6)	KW, $p=0.004, 3>1$
FEV <sub>1</sub> % predicted	31.1 (16.6)	37.6 (18.4)	45.3 (19.9)	KW, $p<0.001, 3>1$ and 2
6MWT (meters)	385.3 (139.8)	376.7 (130.6)	376.5 (128.2)	$F=0.09, p=0.918$
Number of pain locations	N/A	2.5 (3.0)	6.5 (5.7)	$t=-6.15, p<0.001$
Pain interference (0–10)	N/A	1.6 (2.0)	4.0 (2.6)	$t=-6.70, p<0.001$
Symptoms (SGRQ, 0–100)	57.0 (21.7)	60.9 (20.8)	65.2 (19.2)	$F=3.10, p=0.047^{\S}$
Activity (SGRQ, 0–100)	70.4 (24.3)	70.9 (21.7)	70.3 (22.7)	$F=0.02, p=0.982$
Impact (SGRQ, 0–100)	41.0 (21.3)	45.5 (20.5)	47.2 (18.9)	$F=1.77, p=0.173$
Total score (SGRQ, 0–100)	53.5 (20.2)	56.0 (18.6)	57.7 (16.5)	$F=0.92, p=0.399$
	% (n)	% (n)	% (n)	
Sex				$\chi^2=11.28, p=0.004, 3<1$
Male*	62.5 (40)	48.6 (51)	35.7 (35)	
Female	37.5 (24)	51.4 (54)	64.3 (63)	
Cohabitation				$\chi^2=3.08, p=0.216$
Lives alone	25.0 (16)	34.0 (35)	38.8 (38)	
Lives with someone	75.0 (47)	66.0 (68)	61.2 (60)	
Education				KW, $p=0.005, 3$ and $2<1$
Primary	22.5 (14)	39.4 (41)	43.2 (41)	
Secondary	56.5 (35)	53.9 (56)	47.4 (45)	
University	21.0 (13)	6.7 (7)	9.4 (9)	
Smoking				$\chi^2=3.51, p=0.185$
Yes	96.9 (62)	100.0 (105)	99.0 (97)	
No	3.1 (2)	0.0 (0)	1.0 (1)	
Disease severity based on GOLD criteria				KW, $p<0.001, 3<1$ and 2
Moderate	15.6 (10)	29.5 (31)	42.9 (42)	
Severe	25.0 (16)	18.1 (19)	26.5 (26)	
Very severe	59.4 (38)	52.4 (55)	30.6 (30)	
Comorbid conditions				
Heart disease	9.8 (6)	15.3 (15)	28.0 (23)	$\chi^2=8.74, p=0.012, 3>1$
High blood pressure	28.3 (17)	24.5 (24)	37.9 (33)	$\chi^2=4.08, p=0.132$
Cancer	0.0 (0)	1.0 (1)	5.0 (4)	$\chi^2=5.08, p=0.072$
Diabetes	4.8 (3)	7.1 (7)	12.0 (10)	$\chi^2=2.70, p=0.266$
Ulcer or stomach disease	3.3 (2)	6.1 (6)	7.6 (6)	$\chi^2=1.13, p=0.575$
Bowel disease	1.7 (1)	3.1 (3)	8.8 (7)	$\chi^2=4.73, p=0.107$
Kidney disease	1.7 (1)	1.0 (1)	3.8 (3)	$\chi^2=1.65, p=0.532$
Liver disease	0.0 (0)	1.0 (1)	0.0 (0)	$\chi^2=1.45, p=1.000$
Anemia or other blood disease	0.0 (0)	1.1 (1)	3.7 (3)	$\chi^2=3.26, p=0.195$
Headache	8.2 (5)	22.9 (22)	36.2 (29)	$\chi^2=15.14, p<0.001, 3>1$
Depression	16.1 (10)	25.3 (24)	34.1 (29)	$\chi^2=6.07, p=0.048^{\S}$
Osteoarthritis	3.4 (2)	13.7 (13)	34.5 (29)	$\chi^2=24.70, p<0.001, 3>1$ and 2
Back and neck pain	8.2 (5)	49.0 (48)	71.3 (62)	$\chi^2=57.62, p<0.001, 3>2>1$
Rheumatoid arthritis	5.0 (3)	1.0 (1)	8.6 (7)	$\chi^2=5.76, p=0.051$
Disease of muscle/connective tissue	1.7 (1)	5.4 (5)	17.1 (14)	$\chi^2=12.50, p=0.002, 3>1$ and 2
Skin disease	11.7 (7)	18.6 (18)	16.7 (14)	$\chi^2=1.32, p=0.562$

**Notes:** \*Reference group; <sup>§</sup> indicates significant differences among the latent classes, but no significant pairwise group differences.

**Abbreviations:** BMI, body mass index; FEV<sub>1</sub>, forced expiratory volume in one second; FEV<sub>1</sub>%, forced expiratory volume in one second as a percentage of the predicted value; GOLD, Global Initiative for Chronic Obstructive Pulmonary Disease; KW, Kruskal–Wallis test; N/A, not applicable; SCQ, self-administered comorbidity questionnaire; SGRQ, St George Respiratory Questionnaire; 6MWT, 6 Minute Walk Test.

is that approximately 50% of our patients had very severe COPD and were recruited from a tertiary referral hospital. Hence, the results from the present study may not generalize to all COPD patients. Strengths of the study include its high response rate and the large sample of COPD patients evaluated, particularly those COPD patients in the more severe stages of the disease.<sup>6,11,13</sup>

## Conclusion and clinical implications

Our study demonstrates a high occurrence of pain in COPD patients and that this pain persists over time and is often associated with certain comorbidities. The results from this study suggest that more effective interventions are needed to manage pain in COPD patients, particularly among the overweight and poorly educated women in the milder disease groups of COPD. Clinicians may be able to use this information to identify patients who are at higher risk for more severe and persistent pain.

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## Disclosure

The authors report no conflicts of interest in this work.

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