Original Article

ISSN: 1735-0344 *Tanaffos 2022; 21(2): 167-178*

TANAFFOS

Chronic Pain in Patients with Chronic Obstructive Pulmonary Disease: A Cross Sectional Study

Malek Chaabouni, Walid Feki, Nadia Moussa, Najla Bahloul, Samy Kammoun

Department of Pulmonology, Hedi Chaker Hospital, Sfax, Tunisia.

Received: 14 January 2021
Accepted: 10 September 2021

Correspondence to: Chaabouni M
Address: Boite postale n°2, bureau de poste 15 Novembre, route Lafrane km 0,5, 3089 Sfax – Tunisie
Email address: chaabouni.malek@gmail.com

Background: Many individuals with chronic obstructive pulmonary disease (COPD) report suffering from chronic pain, which affects their quality of life. This study aimed to determine the prevalence, characteristics and impact of chronic pain in patients with COPD, and to explore its possible predictive and aggravating factors.

Materials and Methods: It was a cross-sectional study. Male individuals with COPD responded to a questionnaire, including mMRC, CAT, Brief Pain Inventory (BPI) (composed of Worst pain, Pain Severity Score (PSS) and Pain Interference Score (PIS)), and Hospital Anxiety and Depression Scale. Patients were divided into group 1 (G1) with chronic pain, and group 2 (G2) without chronic pain.

Results: Sixty eight patients were included. The general prevalence of chronic pain was 72.1% (CI95%:10.7%). The most common site of pain was the chest (54.4%). Analgesics were used in 38.8%. Patients from G1 had more hospital admissions in the past (OR=6.4[1.7–23.4]). Three variables were associated to pain in the multivariate analysis: socio-economic level (OR=4.6[1.1–19.2]), hospital admissions (OR=0.087[0.017–0.45]), and CAT (OR=0.18[0.05– 0.72]). Dyspnea was associated to PIS ($p<0.005$). A correlation was found between PSS and PIS ($r=0.73$). Six patients (8.8%) retired because of pain. Patients who had CAT≥10 were more in G1 (OR=4.9[1.6–15.7]). CAT was correlated to PIS ($r=0.5$). G1 demonstrated higher anxiety scores ($p<0.05$). There was a moderate positive correlation between depression symptoms and PIS ($r=0.33$).

Conclusion: Pain should be systematically assessed in COPD patients, regarding its high prevalence. New guidelines should take into consideration pain management to ameliorate patients' quality of life.

Key words: Anxiety; Chronic pain; COPD; Depression; Quality of Life

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of morbidity and mortality (1). Around 251 million people suffered from COPD in 2016 according to the World Health Organization (WHO). Its prevalence is increasing simultaneously with the rising trend of smoking prevalence in developing countries and the aging of the population in developed countries (2).

COPD is more than just an airways disease (3). In fact, it may generate a systemic inflammatory process responsible of extra-pulmonary disorders. Other chronic conditions related to smoking and aging co-exist with COPD and may aggravate its morbidity (4). It seems that the chronic inflammation is responsible of the co-occurrence of COPD and comorbidities (3,5).

The most common symptoms of COPD are productive cough and dyspnea. The latter becomes crippling in advanced stages of the pathology obliging patients to leave their workplace, limiting their daily-life activities, and consequently generating anxiety and depression (6). However, other symptoms exist but remain neglected by patients and under- diagnosed by physicians.

Pain, defined by the International Association for the Study of Pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage", is a very frequent symptom in cardiac pulmonary diseases. Its existence may further reduce the patients' daily-life activities and negatively affect their quality of life (QoL). It has been more and more evaluated in patients with COPD. Its prevalence varied between 32% to 66% from one study to another (7,8). This variation was due to differences in pain definition and study design between the different papers (7–9). Our study aimed to determine the prevalence and characteristics of chronic pain in patients with COPD and its impact on different aspects of life-quality, and to explore its possible predictive and aggravating factors.

MATERIALS AND METHODS

Study design

This was an observational cross-sectional survey study. It was conducted at the department of pulmonology of Hedi Chaker Hospital in Sfax (Tunisia) between November 1st, 2019 and December 31th, 2019.

To achieve a power of 80% and a level of significance of 5%, the minimum number of patients that should be recruited was calculated using the following formula:

$$n=\frac{1.96^2 p(1-P)}{(\frac{p}{5})^2}$$

Using data from a previous meta-analysis investigating chronic pain in patients with COPD in which the prevalence of chronic pain reached 60% in high quality studies (7), we took p=0.6 and obtained n=64 participants.

The study was approved by the South Committee of Protection of Persons.

Patients

All male individuals with COPD (confirmed by spirometry) who attended outpatient clinics during the study period were included after informed consent. Patients having diabetes or a cognitive impairment that interfered with the completion of the questionnaire, as well as those undergoing an exacerbation or suffering from an acute pain were excluded from the study.

Questionnaires

Patients were asked about demographics, professional status (current position and the reason of retirement and/or job conversion), habits (smoking, alcohol, and drugs), different comorbidities and their number, and past hospital admissions and exacerbations. Dyspnea was assessed using the modified Medical Research Council dyspnea scale (mMRC). Health- related quality of life (HRQoL) was evaluated adopting the Arabic version of the COPD Assessment Test (CAT) (10). Then, patients were classified according to the refined ABCD assessment tool (ABCD). Height and weight were measured to deduct the Body Mass Index (BMI). Patients were distributed according to the WHO BMI Classification.

Chronic pain was defined as persistent or recurrent pain lasting longer than 3 months (11). The prevalence of chronic pain was determined, and then patients were divided into 2 groups:

- Group 1 (G1): Patients who had chronic pain.
- Group 2 (G2): Patients without chronic pain.

Patients from G1 precised if they used any type of analgesics in the last month. Then, they responded to the Arabic short version of the Brief Pain Inventory (BPI) (12). It is a pain assessment questionnaire which has been previously validated in patients with COPD (13). It allows those who had pain in the last 24 hours to mark their pain location(s) on front/back body diagrams and to rate the severity of their pain at its "worst," "least" "average," and "now", using a scale 0-10. Pain Severity Scale (PSS) is the average of these items. It enables them also to precise the types of pain treatment they were receiving and the amount of relief it provided, and to assess the degree to which their pain interferes with

seven daily life items; including general activity, mood, walking ability, work/housework, relations with others, sleep, and enjoyment of life; using a scale 0-10; to finally calculate their average which corresponds to Pain Interference Scale (PIS).

In addition, G1 participants completed the Arabic version of the Neuropathic Pain Diagnostic Questionnaire (DN4) (14) which is designed to screen out neuropathic pain (15). The test is composed of 10 items: 3 about pain description (Burning, Painful cold, Electric shocks), 4 about associated symptoms (Tingling, Pins and needles, Numbness, Itching), and 3 about physical examination (Hypoesthesia to touch, Hypoesthesia to pinprick, pain caused or increased by brushing). It is considered positive when the score is ≥ 4. All these items were evaluated for each pain location apart, then, a mean score was calculated for each patient. NPL refers to the number of pain locations per patient in G1. Symptoms of Anxiety and Depression were measured with the Arabic version of the Hospital Anxiety and Depression Scale (HADS) (16,17). The HADS is divided into an Anxiety subscale (HADS-A) and a Depression subscale (HADS-D) both containing seven items, rated 0–3, giving a possible maximum score of 21 for each subscale. Patients were classified as: non-cases (≤ 7), doubtful cases (8 or 9), and definite cases (≥ 10).

Spirometry

All participants who had spirometries older than one year were invited to repeat a new one. Spirometry was performed, according to international guidelines (18), before and 15 minutes after administering 400 µg of salbutamol. Collected data were: Forced Expiratory Volume in 1 second (FEV1), Forced Vital Capacity (FVC), Post bronchodilator FEV1/FVC ratio (FEV1/FVC), and FEV1 % predicted to determine the GOLD Classification of airflow limitation severity (GOLD Classification).

Statistical Analysis

Data were analyzed using SPSS 23.0 software. Observed values of categorical variables were presented as well as frequencies and confidence interval (CI). The sample size was enough to assume normality for quantitative variables. The mean and standard deviation (SD) were calculated for each quantitative variable. Chi square test was used to compare frequencies between different categories, when the conditions were verified. In the opposite case, Fisher exact test was the option. Odds ratio (OR) was calculated when a significant link between two categorical variables was identified. Levene's test was employed to assess the homogeneity of variance when means are to compare. Independent sample T-test was adopted to compare the means of 2 groups when variances are equal. When there were more than two groups to compare, one factor ANOVA test was used for the same purpose. Welch test was used when variances are unequal. Correlations between normal quantitative variables were studied using Pearson correlation coefficient (r). A p-value ≤ 0.05 was considered statistically significant. Variables associated to chronic pain with a p ≤ 0.2 were included in the multivariate stepwise regression analysis, in which those who had p≤0.05 were considered as significantly associated. Then the R^2 of the regression model was calculated, and the OR and its CI were also determined for each variable.

RESULTS

Participants

Among the 80 patients who responded to inclusion criteria, 12 were excluded and 68 completed all the questionnaire and were finally included (Figure 1).

Patient Characteristics

The mean age of the participants was 67.9. Forty eight (70.6%) lived in urban areas. The majority of participants were currently retired (77.9%) and their socio-economic level was generally low (67.6%). Nineteen participants were illiterate (27.9%) and one reached university. Thirty one (45.6%) had at least one comorbidity (Table 1).

Most common comorbidities were hypertension and ischemic heart disease. Pulmonary comorbidities were bronchiectasis and tuberculosis (both with 7.4%) and one case of obstructive sleep apnea (Table 2).

The majority of patients (80.9%) were admitted in hospital at least once. Participants were not dyspnoeic (mMRC stage 0) in 23.5%. The biggest number of patients was mMRC stage IV (32.4%). The average CAT was 20.4, with 49 patients (72.1%) having CAT ≥10. The

majority of patients were normal weight (55.9%). Only one patient suffered from obesity. Only 4 patients were classified Mild stage. Participants were mostly at severe stage (38.2%). Moderate and Very severe had both 27.9% of the recruited population. Anxiety were detected in 6 patients (8.8%). As for depressive symptoms, they were present in 13 patients (19.1%) with 8 definite cases (11.8%) (Table 3).

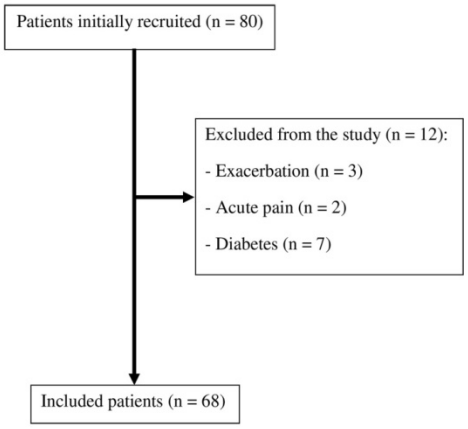

Figure 1. Inclusion process

Table 2. Comorbidities

Comorbidity	Frequency N(%)
Ischemic heart disease	8 (11.8)
Valvular heart disease	3 (4.4)
Arrhythmia	1 (1.5)
Hypertension	9 (13.2)
Bronchiectasis	5 (7.4)
Pulmonary tuberculosis	5 (7.4)
Obstructive sleep apnea	1 (1.5)
Osteoarthritis	2 (2.9)
Non broncho-pulmonary cancer	2 (2.9)

Moreover, dyspnea was associated to anxiety ($p < 0.001$), and depression ($p<0.001$). Higher HADS scores were observed in severe mMRC grades. In addition to that, a positive moderate correlation was found between CAT and both HADS subscales: HADS-A ($p<0.001$, $r=0.53$) and HADS-D ($p<0.001$, $r=0.39$).

Chronic Pain

The general prevalence of chronic pain was 72.1% with a CI of 10.7%. Forty nine patients who reported chronic pain formed G1, and the other nineteen were in G2. Twenty two pain locations were identified. The most common reported location was the chest (54.4%), followed by knee (16.2%), shoulders (14.7%), and then low back (13.2%). Locations which were expressed by more than two patients were marked on figure 2.

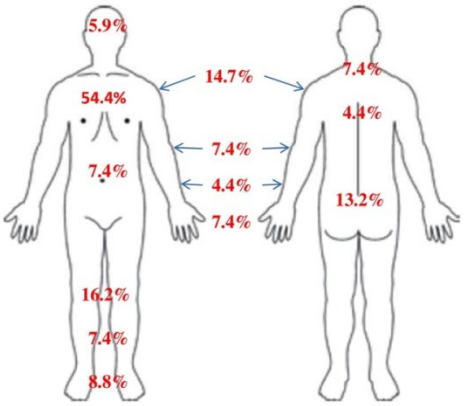

Figure 2. Most common pain locations

The mean NPL was 2.5 ± 1.5 with 7 locations as a maximum. BPI Worst pain had 5.8±3.5 as an average. Headache caused the highest Worst pain average with 9±1.2. The mean chest pain at its worst was 4.7±3.4. The average score of PSS was 3±2.2. It was the highest in headache with 6.1±1.4. Chest pain had a mean of 2.1±1.7 (Table 4).

Analgesics were used in 38.8%, of which 16.3% was paracetamol usage. Mean pain relief was 82.5% and 83.3% for paracetamol. The most demanding pain location was headache. All patients suffering from them were taking analgesics. Patients with chest pain used pain medication in 6.8%. Average PIS was 3±2.7. The item that had the highest mean was Mood with 4±3.9, then walking ability with 3.7±4.1. Pain interfered also with: General activities; 3.2±3.7; Work/Housework: 3.1±3.9; Enjoyment of life: 2.6±3.6; Sleep: 2.2±3.2; and the Relations with others: 1.2±2.5. Headache interfered the most with daily life with a mean of 3.7±1.1. As for chest pain, it interfered with an average of 2±2.7 (Table 4).

Old fractures were responsible of pain in 6 patients (8.8%). Other diagnosed pain etiologies were osteoarthritis, spinal disc herniation, inguinal hernia (2.9% each), cancer in one patient, and other origins. DN4 was positive in 3 cases (4.4%). Pain predictive factors The 2 groups were similar in terms of demographics, habits and comorbidities, and BMI ($p>0.05$) (Table 1).

Patients from G1 had a bit more exacerbations and hospital admissions during the last year without a significant p-value (p>0.05). Hospital admissions were significantly more frequent in G1 (p<0.01) with an OR=6.4 [1.7–23.4]. Dyspnea severity was not significantly different between the 2 groups. They were compared again after dividing mMRC grades to those < 2 (0, I) and those ≥ 2 (II, III, IV). But, still no difference was revealed (p>0.05). Furthermore, those who had chest pain were compared to those who did not, and it appeared that dyspnea severity was not associated to the presence of chest pain (p=0.19). The majority of G1 (81.6%) were classified B and D, while only 52.6% of G2 were in the same disease groups. Yet, no significant difference was found between the 2 groups (p>0.05). Although all patients who had Mild airflow limitation were in G1, lung function was the same in the 2 groups (p>0.05) (Table 3).

Six variables were included in the multivariate regression analysis (socio-economic level, WHO BMI Classification, hospital admissions, CAT, dyspnea and GOLD). Three remained after the stepwise regression (R^2=0.88): socio-economic level: p=0.034, OR=4.6 [1.1–19.2]; hospital admissions: p=0.004, OR=0.087 [0.017–0.45]; and CAT: p=0.015, OR=018 [0.05–0.72].

Pain aggravating factors

Age, BMI and lung function were not correlated neither to NPL, nor to BPI scores. Significantly higher PIS levels were observed in severe dyspnea ≥ II (p<0.005), and both B and D groups (p<0.001) (Table 5). A moderate positive association was found between NPL and Worst pain (p=0.004, r=0.41) and PSS (p=0.001, r=0.47).

Impact of chronic pain

NPL was positively moderately linked to PIS (p=0.011, r=0.36). Additionally, a positive strong correlation was found between Worst pain and PIS (p<0.001, r=0.6). Moreover, the association of PSS to PIS was positively very strong (p<0.001, r=0.7).

Six patients retired because of pain, which represents 8.8% of the studied population.

All job conversions were not caused by chronic pain.

Patients who had CAT ≥10 represent 81.6% of G1 (Table 3). They were 4.9 times more likely to be in G1 with a significant p-value (OR=4.9 [1.6–15.7]). CAT was positively moderately correlated to PIS (p<0.001, r=0.5), and patients with severe CAT ≥10 had higher PIS (p>0.001) (Table 5). G1 demonstrated higher HADS-A scores (p<0.05) (Table 3). There was a moderate positive correlation between depression symptoms and PIS (p<0.05, r=0.33) (Table 5).

Table 1. Patient characteristics

		Total	G1	G2	p
Age (years)		67.9 ± 8.2	68.2 ± 8.7	67.3 ± 6.7	0.7
Geographic origin	Urban	48 (70.6)	33 (67.3)	15 (78.9)	0.35
	Rural	20 (29.4)	16 (32.7)	4 (21.1)	
Retired		53 (77.9)	39 (79.6)	14 (73.7)	0.6
Education	Illiterate	19 (27.9)	14 (28.6)	5 (26.3)	0.66*
	Primary school	33 (48.5)	25 (51)	8 (42.1)	
	Secondary school	15 (21.1)	9 (18.4)	6 (31.6)	
	University	1 (1.5)	1 (2)	0	
Socio-economic level	Low	46 (67.6)	36 (73.5)	10 (52.6)	0.1
	Moderate	22 (32.4)	13 (26.5)	9 (47.4)	
Cigarettes smoking	Non-smoker	1 (1.5)	1 (2)	0	0.84
	Former smoker	44 (64.7)	32 (65.3)	12 (63.2)	
	Current smoker	23 (33.8)	16 (32.7)	7 (36.8)	
	PY	60.8 ± 32.3	62.2 ± 32.2	57.4 ± 33	0.59
Neffa **		12 (17.6)	10 (20.4)	2 (10.5)	0.34
Alcohol		8 (11.8)	5 (10.2)	3 (15.8)	0.68*
Drugs		0	0	0	1
Comorbidities		31 (45.6)	22 (44.9)	9 (47.4)	0.85
WHO BMI Classification	Underweight	15 (22.1)	7 (15.2)	7 (36.8)	0.08*
	Normal weight	38 (55.9)	29 (63)	8 (42.1)	
	Pre-obesity	14 (20.6)	10 (21.7)	3 (15.8)	
	Obesity class I	1 (1.5)	0	1 (5.3)	
		22.4±4.1	22.6±3.8	21.8±4.8	0.47

*Fisher exact test; G1: Group 1; G2: Group 2; PY: Pack-Year; WHO: World Health Organization; BMI: Body Mass Index; ** A local smokeless tobacco

Table 3. Disease characteristics

		Total	G1	G2	p
Long-term oxygen therapy		8 (11.8)	4 (8.2)	4 (21.1)	0.21
Past hospital admissions		55 (80.9)	44 (89.8)	11 (57.9)	**0.003**
Number of hospital admissions during the last year		0.43±0.1	0.45±0.89	0.37±0.76	0.73
Number of exacerbations during the last year		1.4±0.2	1.6±2.3	1±1	0.1
mMRC	0	16 (23.5)	9 (18.4)	7 (36.8)	0.24*
	I	9 (13.2)	6 (12.2)	3 (15.8)	
	II	5 (7.4)	4 (8.2)	1 (5.3)	
	III	16 (23.5)	15 (30.6)	1 (5.3)	
	IV	22 (32.4)	15 (30.6)	7 (36.8)	
	< II	25 (36.8)	15 (30.6)	10 (52.6)	0.09
	≥ II	43 (63.2)	34 (69.4)	9 (47.4)	
CAT	< 10	19 (27.9)	9 (18.4)	10 (52.6)	**0.005**
	≥ 10	49 (72.1)	40 (81.6)	9 (47.4)	
		20.4 ± 11.8	22.2 ± 10.3	15.8±14.2	0.09
ABCD	A	14 (20.6)	6 (12.2)	8 (42.1)	0.06*
	B	23 (33.8)	19 (38.8)	4 (21.1)	
	C	4 (5.9)	3 (6.1)	1 (5.3)	
	D	27 (39.7)	21 (42.9)	6 (31.6)	
Spirometry	FEV1 (L)	1.25 (0.56)	1.24±0.55	1.29±0.6	0.74
	FEV1 % predicted	44.4±19.1	44.3±19.7	44.6±17.8	0.96
	FVC (L)	2.39±0.78	2.4±0.79	2.37±0.78	0.88
	FEV1/FVC	51.4±10.2	51±10.2	52.4±10.3	0.61
GOLD	Mild	4 (6.2)	4 (8.7)	0	0.12*
	Moderate	19 (27.9)	9 (19.6)	9 (47.4)	
	Severe	26 (38.2)	19 (41.3)	6 (31.6)	
	Very severe	19 (27.9)	14 (30.4)	4 (21.1)	
Anxiety	Non-cases	62 (91.2)	44 (89.8)	18 (94.7)	1*
	Doubtful cases	5 (7.4)	4 (8.2)	1 (5.3)	
	Definite cases	1 (1.5)	1 (2)	0	
	HADS-A	3.9±2.8	4.4±2.7	2.7±2.7	0.027
Depression	Non-cases	55 (80.9)	39 (79.6)	16 (84.2)	0.4*
	Doubtful cases	5 (7.4)	5 (10.2)	0	
	Definite cases	8 (11.8)	5 (10.2)	3 (15.8)	
	HADS-D	4.1±4.6	4.1±4.7	4.2±4.4	0.92

*Fisher exact test; G1: Group 1; G2: Group 2; mMRC: The modified Medical Research Council dyspnea scale; CAT: COPD Assessment Test; ABCD: The refined ABCD assessment tool; FEV1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; FEV1/FVC: Post bronchodilator FEV1/FVC ratio; GOLD: Global Initiative for Chronic Obstructive Lung Disease Classification of airflow limitation severity; HADS-A: Hospital Anxiety and Depression Scale – Anxiety sub-scale; HADS-D: Hospital Anxiety and Depression Scale – Depression sub-scale

Table 4. Prevalence of different pain locations and their BPI scores

Location	N	Prevalence [CI] (%)	Mean Worst pain ± SD	Mean PSS ± SD	Mean PIS ± SD
Head	4	5.9 [5.6]	9±1.2	6.1±1.4	3.7±1.1
Chest	44	54.4 [11.8]	4.7±3.4	2.1±1.7	2±2.7
Abdomen	5	7.4 [6.2]	7.2±0.8	2.3±1.2	2.2±3.4
Neck	5	7.4 [6.2]	5.8±2.7	2.9±1.7	1.7±1.9
Shoulders	10	14.7 [8.4]	3.7±3.5	1.7±1.4	0.4±0.5
Top of the back	3	4.4 [4.9]	4.7±5	2.9±2.5	1.1±1.1
Elbows	5	7.4 [6.2]	3.4±3.1	1.8±1.4	0.9±1.3
Forearms	3	4.4 [4.9]	1.7±1.5	0.7±0.1	0.5±0.5
Hands	5	7.4 [6.2]	4.6±4.2	3±3.2	1.7±2.7
Low back	9	13.2 [8.1]	4.4±3	2.2±1.2	1.2±1.3
Knees	11	16.2 [8.8]	5±2.9	2.3±1.2	1.9±2.3
Legs	5	7.4 [6.2]	3.2±3	2.3±2.8	1.1±1.5
Feet	6	8.8 [6.7]	4.1±3.1	2.7±2.3	1.1±1.3

BPI: Brief Pain Inventory; N: Number of patients; CI: Confidence Interval; SD: Standard Deviation; PSS: Pain Severity Scale; PIS: Pain Interference Scale

Table 5. Pain aggravating factors and its impact

		NPL	Worst pain	PSS	PIS
Age (years)	p	0.52	0.36	0.99	0.84
	r	-0.1	-0.13	-0.001	-0.03
BMI	p	0.19	0.51	0.74	0.51
	r	0.19	0.1	-0.05	0.1
WHO BMI Classification	Underweight	1.4±1.1	5.4±4.6	2.9±2.2	2.9±2.5
	Normal weight	2.7±1.7	6±3.2	3.2±2.3	3.1±2.8
	Pre-obesity	2.6±1.2	6.5±3.9	3±1.9	3.3±3
	P	0.15	0.83	0.92	0.97
mMRC	0	1.7±0.9	3±3.7	1.5±1.6	0.8±1.3
	I	3±2	8±2.6	3.5±2.1	2.4±2.3
	II	2±1.4	6.8±2.8	4±1.7	3±2.2
	III	2.7±1.7	6.7±3.2	3.5±2.2	4.1±2.8
	IV	2.6±1.5	5.5±3.6	3±2.4	3.3±3
	P	0.41	0.048	0.19	0.016
	< II (0,I)	2.2±1.5	5±4.1	2.3±2	1.4±1.9
	≥ II (II,III,IV)	2.6±1.6	6.1±3.3	3.3±2.2	3.6±2.8
	P	0.42	0.3	0.14	0.003
CAT	p	0.18	0.25	0.09	< 0.001
	r	0.2	0.17	0.25	0.5
	<10	1.7±0.7	4.1±4.2	2±2	0.7±0.7
	≥10	2.7±1.6	6.2±3.3	3.2±2.2	3.5±2.7
	P	0.008	0.11	0.14	< 0.001
ABCD	A	1.8±0.8	5±4.9	2.5±2.3	0.9±0.8
	B	2.5±1.3	6.8±3.1	3.6±2.1	4.1±2.8
	C	1.3±0.6	2.3±2.1	1±0.7	0.1±0.2
	D	2.8±1.9	5.6±3.4	2.9±2.2	3±2.6
	P	0.07	0.18	0.22	< 0.001
FEV1 (L)	p	0.4	0.89	0.44	0.49
	r	0.13	0.02	-0.12	-0.1
FEV1 % predicted	p	0.46	0.99	0.47	0.5
	r	0.11	0.002	-0.11	-0.1
FVC (L)	p	0.48	0.92	0.84	0.51
	r	0.11	-0.02	-0.03	-0.1
FEV1/FVC	p	0.73	0.66	0.18	0.62
	r	0.05	0.07	-0.2	-0.08
GOLD	Mild	3.3±2.1	6.3±4.2	2.8±1.7	3.1±3.2
	Moderate	2.4±1.3	5.3±3.5	2.3±1.7	2.3±2.9
	Severe	2.6±1.6	6.7±3.1	3.7±2.3	3.1±2.6
	Very severe	2.2±1.7	5.4±4.2	3±2.4	3.6±2.9
	P	0.71	0.71	0.47	0.75
HADS-A	p	0.24	0.98	0.23	0.16
	r	0.17	0.004	0.18	0.21
	Non-cases	2.4±1.4	5.8±3.6	2.9±2	2.9±2.7
	Doubtful cases	4±2.4	5.8±4	2.9±3.5	3.7±3.4
	Definite cases	1	8	6.5	2
	P	0.08	0.83	0.27	0.82
HADS-D	p	0.14	0.11	0.22	0.02
	r	0.21	0.23	0.18	0.33
	Non-cases	2.3±1.3	5.5±3.4	2.9±2	2.6±2.6
	Doubtful cases	3.6±1.8	6.8±4.3	3.6±2.4	4.2±2.5
	Definite cases	3±2.6	7±4	3.6±3.2	4.4±3.5
	P	0.13	0.55	0.66	0.22

NPL : Number of Pain Locations per patient; PSS: Pain Severity Scale; PIS: Pain Interference Scale; mMRC: The modified Medical Research Council dyspnea scale; CAT: COPD Assessment Test; ABCD: The refined ABCD assessment tool; FEV1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; FEV1/FVC: Post bronchodilator FEV1/FVC ratio; GOLD: Global Initiative for Chronic Obstructive Lung Disease Classification of airflow limitation severity; HADS-A: Hospital Anxiety and Depression Scale – Anxiety sub-scale; HADS-D: Hospital Anxiety and Depression Scale – Depression sub-scale

DISCUSSION

Our findings confirmed the high prevalence of chronic pain in patients with COPD, determined its characteristics. Our study succeeded to explore the possible predictive factors of pain, particularly the history of hospital admission, low socio-economic level, and high CAT, and to highlight its heavy impact on QoL and mental health.

Chronic pain in patients with COPD is under-diagnosed and under-estimated in guidelines (9). Studies have found that pain prevalence is much higher in COPD than in the general population (19–22). While Roberts et al. (23) reported that it is more common in COPD than in other chronic diseases, others found a higher prevalence in patients with chronic heart failure (24) and lung cancer (25). Pain prevalence varies from one study to another due to differences in pain definition and study design including assessment instruments, and sampling size, context (stable, end of life) and source (7–9). Most of papers did not clearly define what type of pain are they investigating (acute, sub-acute, or chronic). The meta-analysis conducted by van Dam van Isselt et al. (7) suggested it ranged from 21% to 72.1%, and more precisely from 32% to 60% in high-quality studies, whereas a systematic review by Lee et al. showed it was 66% (CI 95%: 44–85%) in moderate to very severe COPD (8). More recent publications found rates between 37% and 81.2% (21,26–31). In our study, 72.1% of patients suffered from chronic pain.

The most common reported pain locations were low back (26 – 47.4%), shoulders (7 – 46.2%) and neck (9 – 40.5%), and chest (17.5 – 54%) (24,26,32). These pain locations were also frequent in our study but with different rates. Although rare, Headaches were responsible of severe pain with the highest impact. NPL was the same when COPD was compared to comorbidities (19). However, Roberts et al. found that it was the same compared to general population (23), but different results showing a higher NPL in COPD patients were found by HajGhanbari et al. (22). The mean of the second NPL, which was estimated as 3.1 ± 0.4, was positively correlated with BPI scores.

Christensen et al. (26) found a mean NPL of 5.5 ± 4.9 and a positive correlation to worst pain and PSS. In our study, NPL was lower than that (2.5±1.5) and influenced BPI likewise.

Some studies compared pain severity in patients with COPD to control groups: it was higher for COPD patients in two studies (21,22) and no difference was found in Bentsen et al's study (19). Different scores are used to quantify pain severity. In our study, we chose to use the BPI. Although Worst pain score was relatively high, mean PSS was mild to moderate. Our results were quite similar to the findings of other studies that used BPI (30,33,34). We found a strong positive correlation between PSS and PIS which corresponds to literature (26,27,32). Pain severity impacts its interference with daily life. There has been no previous study that worked on pain management interventions in patients with COPD (7,9). Studies described that pain management was based mainly on pain medication (27,34,35) and physiotherapy (19,23,27). Analgesics were used in 49% in Bentsen et al's study (19) 68% in Chen et al's survey (27), and 38.8% in ours. Christensen et al. (26) listed the types of painkillers and it was paracetamol in 16 patients, NSAID in 12 patients, and opioids in 34 participants out of 157 who had pain, which corresponds almost to 10%, 8% and 21% respectively. Janssen et al. (28) reported that 27.8% of patients with chest pain resorted to analgesics. Our study showed a 16.3% paracetamol usage. None of our patients underwent conventional physiotherapy sessions, which could be explained by a selection bias which is the socio-economic level of our sample. Pain relief was quantified only by Christensen et al. (26) and it was 41.6%, while our study concluded to 82.5%.

The literature did not confirm that age was associated to the presence of pain in patients with COPD (29–32). Conflicting results were found about pain severity and age (21,33). Our findings did not link age and pain in anyway. Smoking status was not matched to pain in the majority

of studies (26,30,31). Andenæs et al. (21) have different results with smoking as a risk factor of pain and higher pain severity in smokers. Smoking in our study was the same between the 2 groups and was not correlated to BPI scores. Many papers highlighted a significant association between the presence (21,23,29) or the number (19,26) of comorbidities and pain. Yet, some studies, like ours, could not prove it (32,36). Obesity is a risk factor for musculoskeletal pain (37), especially osteoarthritis (38,39). Besides, reports concluded sometimes that BMI was associated to pain (20,22,31), and other times not (27,29,30). In our study, this relationship was not confirmed. Pain was not associated to the number of exacerbations and hospital admissions during last year in our study, as well as in literature (26,29,40). A complex relationship exists between pain and dyspnea (41). They both activate common cerebral areas with other unpleasant feelings (42–46). A hypothesis suggested that chronic stimulation may produce changes in the perception of pain (22). The literature was mostly in favor of higher dyspnea severity in patients with chronic pain (30,33,34). However, Christensen et al. (26) argued that severe breathlessness accommodates patients to pain with a "response shift" (47). Another hypothesis said that air hunger may induce analgesia (48). The difference between the two groups was not significant in our study and pain severity was not associated to mMRC. Looking to literature, some reports chose a specific part of COPD patients, depending on the severity of airflow limitation. Multiple studies did not find a significant correlation between spirometry results or GOLD Classification and pain (23,32,36). Then, van Dam van Isselt et al. (7) discovered a strong positive correlation between lung function and pain in the meta-analysis. It means that pain was more prevalent in moderate than severe GOLD stages. More recent studies (26,31) confirmed this result. This finding was maybe due to selection bias. Indeed, patients suffering from pain in advanced COPD would more likely die or be unable to participate due to symptoms severity (7) Another possible explanation could be that the importance of respiratory symptoms in advanced stages pushes pain discomfort to the background (26,31). Besides, some studies highlighted that lung function was positively correlated to both BPI scores (22,26).

Our findings underlined the gravity of pain burden as 8.8% of the studied population retired because of pain. The decline of general activity and the impact on relations with others worsen the social impact of COPD (49). In addition, pain interfered with sleep. It was also reported by another paper (36). That interference was mild to moderate in our study. It could be related to other factors which also interfered with pain (26). In fact, respiratory symptoms often cause sleep disturbance (50). It is also known that sleep disorders are frequent in COPD (51). Mood and enjoyment of life, two psychological sub-domains of the PIS, were moderately affected by pain. Consequently, PIS was correlated to depression according to Christensen et al. (26) and our study. Several reports brought out pain impact on HRQoL (22,29,32). Our results showed that patients with CAT ≥10 were 4.9 times at risk to develop pain with a CI 95%: 1.6 – 15.7. PIS was significantly higher in the same group of patients. Borge et al. (32) found an anxiety-pain relationship, whereas it was not found in other papers (26,30). Our results showed more anxiety symptoms in those having pain. As for depression, many studies (23,26,49) reported its association with pain in COPD. Results from our survey showed a significant moderate positive correlation of PIS with HADS-D, although the difference was not significant between the 2 groups.

Bearing in mind that, in our study, mMRC and CAT were also correlated to HADS, it was not easy to conclude to what extent pain interference could be held accountable for depression symptoms. Pain interacted with dyspnea, QoL decline and psychological distress, yet, our findings did not confirm the nature of the association.

Our study demonstrated some limits that need to be acknowledged. The study was cross-sectional which is

perfect to determine the prevalence of chronic pain in patients with COPD. Yet, this design is not suitable to determine the exact causality of predictive factors of pain or its impact. Moreover, our report just described pain origins which are already diagnosed and did not investigate the other etiologies of pain.

Our study succeeded to determine the prevalence and characteristics of chronic pain in patients with COPD and to describe the particularities of their chronic disease. It explored the possible predictive and aggravating factors of chronic pain and confirmed its high impact on QoL and professional life. It determined some associations that need prospective studies to be validated. COPD and pain has been a hot topic in personalized respiratory medicine. The prevalence of chronic pain in patients with COPD is a red flag that urges clinicians to detect it and scientists to further investigate its causes and results. Larger prospective studies would be interesting to analyze various factors interacting with chronic pain and to test appropriate management protocols.

Acknowledgments

The authors would like to thank the staff members of the Department of Pulmonology for their contribution to the realization of this study, and all the patients who accepted to participate in it.

REFERENCES

1. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. ***Lancet*** 2012;380(9859):2095-128.
2. Lopez AD, Shibuya K, Rao C, Mathers CD, Hansell AL, Held LS, et al. Chronic obstructive pulmonary disease: current burden and future projections. ***Eur Respir J*** 2006;27(2):397-412.
3. Nussbaumer-Ochsner Y, Rabe KF. Systemic manifestations of COPD. ***Chest*** 2011;139(1):165-73.
4. Mannino DM, Higuchi K, Yu TC, Zhou H, Li Y, Tian H, et al. Economic Burden of COPD in the Presence of Comorbidities. ***Chest*** 2015;148(1):138-50.
5. Rochat T. BPCO: une maladie associée à une inflammation systémique [COPD: a disease with systemic inflammation]. ***Rev Mal Respir*** 2012;29(4):537-44.
6. Miravitlles M, Worth H, Soler Cataluña JJ, Price D, De Benedetto F, Roche N, Godtfredsen NS, van der Molen T, Löfdahl CG, Padullés L, Ribera A. Observational study to characterise 24-hour COPD symptoms and their relationship with patient-reported outcomes: results from the ASSESS study. ***Respir Res*** 2014;15(1):122.
7. van Dam van Isselt EF, Groenewegen-Sipkema KH, Spruit-van Eijk M, Chavannes NH, de Waal MW, Janssen DJ, et al. Pain in patients with COPD: a systematic review and meta-analysis. ***BMJ Open*** 2014;4(9):e005898.
8. Lee AL, Harrison SL, Goldstein RS, Brooks D. Pain and its clinical associations in individuals with COPD: a systematic review. ***Chest*** 2015;147(5):1246-58.
9. Lewthwaite H, Williams G, Baldock KL, Williams MT. Systematic Review of Pain in Clinical Practice Guidelines for Management of COPD: A Case for Including Chronic Pain? ***Healthcare (Basel)*** 2019;7(1):15.
10. Al-Moamary MS, Al-Hajjaj MS, Tamim HM, Al-Ghobain MO, Al-Qahtani HA, Al-Kassimi FA. The reliability of an Arabic translation of the chronic obstructive pulmonary disease assessment test. ***Saudi Med J*** 2011;32(10):1028-33.
11. Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, Cohen M, et al. A classification of chronic pain for ICD-11. ***Pain*** 2015;156(6):1003-7.
12. Ballout S, Noureddine S, Huijer HA, Kanazi G. Psychometric evaluation of the arabic brief pain inventory in a sample of Lebanese cancer patients. ***J Pain Symptom Manage*** 2011;42(1):147-54.
13. Chen YW, HajGhanbari B, Road JD, Coxson HO, Camp PG, Reid WD. Reliability and validity of the Brief Pain Inventory in individuals with chronic obstructive pulmonary disease. ***Eur J Pain*** 2018;22(10):1718-26.
14. Chatila N, Pereira B, Maarrawi J, Dallel R. Validation of a New Arabic Version of the Neuropathic Pain Diagnostic Questionnaire (DN4). ***Pain Pract*** 2017;17(1):78-87.
15. Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J, et al. Comparison of pain syndromes associated

with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). ***Pain*** 2005;114(1-2):29-36.

16. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. ***Acta Psychiatr Scand*** 1983;67(6):361-70.
17. Terkawi AS, Tsang S, AlKahtani GJ, Al-Mousa SH, Al Musaed S, AlZoraigi US, et al. Development and validation of Arabic version of the Hospital Anxiety and Depression Scale. ***Saudi J Anaesth*** 2017;11(Suppl 1):S11-S18.
18. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. ***Eur Respir J*** 2005;26(2):319-38.
19. Bentsen SB, Rustøen T, Miaskowski C. Prevalence and characteristics of pain in patients with chronic obstructive pulmonary disease compared to the Norwegian general population. ***J Pain*** 2011;12(5):539-45.
20. de Miguel-Díez J, López-de-Andrés A, Hernandez-Barrera V, Jimenez-Trujillo I, Del Barrio JL, Puente-Maestu L, et al. Prevalence of Pain in COPD Patients and Associated Factors: Report From a Population-based Study. ***Clin J Pain*** 2018;34(9):787-94.
21. Andenæs R, Momyr A, Brekke I. Reporting of pain by people with chronic obstructive pulmonary disease (COPD): comparative results from the HUNT3 population-based survey. ***BMC Public Health*** 2018;18(1):181.
22. HajGhanbari B, Holsti L, Road JD, Darlene Reid W. Pain in people with chronic obstructive pulmonary disease (COPD). ***Respir Med*** 2012;106(7):998-1005.
23. Roberts MH, Mapel DW, Hartry A, Von Worley A, Thomson H. Chronic pain and pain medication use in chronic obstructive pulmonary disease. A cross-sectional study. ***Ann Am Thorac Soc*** 2013;10(4):290-8.
24. Janssen DJ, Spruit MA, Uszko-Lencer NH, Schols JM, Wouters EF. Symptoms, comorbidities, and health care in advanced chronic obstructive pulmonary disease or chronic heart failure. ***J Palliat Med*** 2011;14(6):735-43.
25. Claessens MT, Lynn J, Zhong Z, Desbiens NA, Phillips RS, Wu AW, et al. Dying with lung cancer or chronic obstructive pulmonary disease: insights from SUPPORT. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments. ***J Am Geriatr Soc*** 2000;48(S1):S146-53.
26. Christensen VL, Holm AM, Kongerud J, Bentsen SB, Paul SM, Miaskowski C, et al. Occurrence, Characteristics, and Predictors of Pain in Patients with Chronic Obstructive Pulmonary Disease. ***Pain Manag Nurs*** 2016;17(2):107-18.
27. Chen YW, Camp PG, Coxson HO, Road JD, Guenette JA, Hunt MA, et al. Comorbidities That Cause Pain and the Contributors to Pain in Individuals With Chronic Obstructive Pulmonary Disease. ***Arch Phys Med Rehabil*** 2017;98(8):1535-43.
28. Janssen DJ, Wouters EF, Parra YL, Stakenborg K, Franssen FM. Prevalence of thoracic pain in patients with chronic obstructive pulmonary disease and relationship with patient characteristics: a cross-sectional observational study. ***BMC Pulm Med*** 2016;16:47.
29. Xiao T, Zhou X, He Y, Chen Y, Qiu H, Zhang S, et al. Pain problems for patients with mild and moderate chronic obstructive pulmonary disease - a community-based study in Shanghai. ***J Pain Res*** 2017;10:2247-52.
30. Lee AL, Goldstein RS, Brooks D. Chronic Pain in People With Chronic Obstructive Pulmonary Disease: Prevalence, Clinical and Psychological Implications. ***Chronic Obstr Pulm Dis*** 2017;4(3):194-203.
31. Bentsen SB, Miaskowski C, Cooper BA, Christensen VL, Henriksen AH, Holm AM, et al. Distinct pain profiles in patients with chronic obstructive pulmonary disease. ***Int J Chron Obstruct Pulmon Dis*** 2018;13:801-11.
32. Borge CR, Wahl AK, Moum T. Pain and quality of life with chronic obstructive pulmonary disease. ***Heart Lung*** 2011;40(3):e90-101.
33. Borge CR, Wahl AK, Moum T. Association of breathlessness with multiple symptoms in chronic obstructive pulmonary disease. ***J Adv Nurs*** 2010;66(12):2688-700.
34. Lohne V, Heer HC, Andersen M, Miaskowski C, Kongerud J, Rustøen T. Qualitative study of pain of patients with chronic obstructive pulmonary disease. ***Heart Lung*** 2010;39(3):226-34.
35. White P, White S, Edmonds P, Gysels M, Moxham J, Seed P, et al. Palliative care or end-of-life care in advanced chronic

obstructive pulmonary disease: a prospective community survey. ***Br J Gen Pract*** 2011;61(587):e362-70.

36. Bentsen SB, Gundersen D, Assmus J, Bringsvor H, Berland A. Multiple symptoms in patients with chronic obstructive pulmonary disease in Norway. ***Nurs Health Sci*** 2013;15(3):292-9.
37. Deere KC, Clinch J, Holliday K, McBeth J, Crawley EM, Sayers A, et al. Obesity is a risk factor for musculoskeletal pain in adolescents: findings from a population-based cohort. ***Pain*** 2012;153(9):1932-38.
38. Heidari B. Knee osteoarthritis prevalence, risk factors, pathogenesis and features: Part I. ***Caspian J Intern Med*** 2011;2(2):205-12.
39. Plotnikoff R, Karunamuni N, Lytvyak E, Penfold C, Schopflocher D, Imayama I, et al. Osteoarthritis prevalence and modifiable factors: a population study. ***BMC Public Health*** 2015;15:1195.
40. Bentsen SB, Rustøen T, Miaskowski C. Differences in subjective and objective respiratory parameters in patients with chronic obstructive pulmonary disease with and without pain. ***Int J Chron Obstruct Pulmon Dis*** 2012;7:137-43.
41. Lansing RW, Gracely RH, Banzett RB. The multiple dimensions of dyspnea: review and hypotheses. ***Respir Physiol Neurobiol*** 2009;167(1):53-60.
42. von Leupoldt A, Sommer T, Kegat S, Eippert F, Baumann HJ, Klose H, et al. Down-regulation of insular cortex responses to dyspnea and pain in asthma. ***Am J Respir Crit Care Med*** 2009;180(3):232-8.
43. Evans KC, Banzett RB, Adams L, McKay L, Frackowiak RS, Corfield DR. BOLD fMRI identifies limbic, paralimbic, and cerebellar activation during air hunger. ***J Neurophysiol*** 2002;88(3):1500-11.
44. Peiffer C, Poline JB, Thivard L, Aubier M, Samson Y. Neural substrates for the perception of acutely induced dyspnea. ***Am J Respir Crit Care Med*** 2001;163(4):951-7.
45. Banzett RB, Mulnier HE, Murphy K, Rosen SD, Wise RJ, Adams L. Breathlessness in humans activates insular cortex. ***Neuroreport*** 2000;11(10):2117-20.
46. Casey KL. Forebrain mechanisms of nociception and pain: analysis through imaging. ***Proc Natl Acad Sci U S A*** 1999;96(14):7668-74.
47. Schwartz CE, Sprangers MA. Methodological approaches for assessing response shift in longitudinal health-related quality-of-life research. ***Soc Sci Med*** 1999;48(11):1531-48.
48. Nishino T. Dyspnea and its interaction with pain. ***J Anesth*** 2011;25(1):157-61.
49. Lee AL, Harrison SL, Goldstein RS, Brooks D. An exploration of pain experiences and their meaning in people with chronic obstructive pulmonary disease. ***Physiother Theory Pract*** 2018;34(10):765-72.
50. Klink ME, Dodge R, Quan SF. The relation of sleep complaints to respiratory symptoms in a general population. ***Chest*** 1994;105(1):151-4.
51. Mieczkowski B, Ezzie ME. Update on obstructive sleep apnea and its relation to COPD. ***Int J Chron Obstruct Pulmon Dis*** 2014;9:349-62.