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Clinical outcomes of chronic obstructive pulmonary disease phenotypes. One center prospective study

Abstract

Introduction: The clinical outcome of different chronic obstructive pulmonary disease (COPD) phenotypes is still unclear.
Objectives: This study was designed to detect the effect of different COPD phenotypes on disease outcomes.
Material and methods: One hundred stable COPD patients were included. They were divided into 3 phenotypes; 45 patients in exacerbator phenotype, 37 patients in non-exacerbator, and 18 patients in asthma COPD overlap (ACO) phenotype. Patient demographics, respiratory symptoms, grading of COPD, co-morbidities, spirometry, six minute walk test, and systemic inflammatory markers were measured. Also, exacerbation frequency and severity were assessed throughout the study period.
Results: COPD Assessment Test (CAT) score was significantly higher in exacerbator phenotype versus the other phenotypes(14.7 $\pm$ 1.5; $p = 0.04$).In addition, about 60% and 42% of exacerbator phenotype were in Global Initiative for Chronic Obstructive Lung Disease (GOLD) class D and C respectively which were significantly higher than the other phenotypes($p = 0.001$), while 58% and 50% of non-exacerbator and ACO patients respectively were in class B of GOLD. Twenty eight percent of patients of ACO had no comorbidity and this was significantly higher versus the other phenotypes ($p = 0.03$), while 40% of non-exacerbator had one comorbidity ($p = 0.003$) and 86% of exacerbator had ≥ 2 comorbidities ($p = 0.002$). COPD comorbidity index was significantly higher in exacerbator phenotype (2.5 $\pm$ 0.8; $p = 0.01$). Although patients of exacerbator phenotype had more and severe form of exacerbations than the other phenotypes, no significant difference in in-hospital outcome was found ($p = 0.3$).
Conclusions: Exacerbator phenotype has worse disease outcome than those of non-exacerbator and ACO phenotypes. These results support the need for more treatment options to alleviate the morbidity of COPD especially among exacerbator phenotype.

Key words: COPD severity, co-morbidity, exacerbation

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Introduction

Chronic obstructive pulmonary disease (COPD) is a prevalent, preventable and treatable disorder that is specified by constant respiratory features and limitation of airflow that is owing to airway and or alveolar flaws that is created by notable exposure to toxic particles or gases [1]. It is a complex disease and heterogeneous and has multicomponent elements so the concept of phenotype-emerged, and the traditional concept of pink puffers and blue bloaters, is now being replaced by a variety of different phenotypes [2].

The phenotyping phase occurs as a result of clinical necessity to group patients with similar presentation and/or behavior to provide them for the best quality health treatment, customize the therapeutic plan for the patient in terms of symptoms control, disease progression, the state of health, and the quality of life [3].

Some research studies have examined specific phenotype frequencies and features, but limited ones are available to address the effect of these phenotypes on clinical outcomes [4–6]. So, this study was carried out to highlight on outcomes of these phenotypes purposing to intensify the lines of treatment available for those with the worst outcomes.

Aim of the work

To appraise the impact of different COPD phenotypes on disease outcomes as regard disease severity, inflammatory burden, comorbidity, and exacerbation.

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Material and methods

This study was a prospective study that included 100 patients with stable COPD who attending the out-patients chest clinic at Cardiothoracic Minia University hospital during the period between October 2018 to December 2019. All patients were diagnosed according to the GOLD definition of COPD with a post-bronchodilator forced vital capacity/volume in the first second (FVC/FEV_1) ratio of < 0.7 [1]. Stable COPD was identified by a failure of hospitalization, urgent care visits, and changes in medications within 4 weeks before the study. Exclusion criteria included patients suffering acute COPD exacerbation within 1 month before the study, combined COPD and interstitial lung disease, patients with a history of pulmonary tuberculosis, and COPD patients on domiciliary long-term oxygen therapy. The Protocol to the study was accepted by the research ethics committee of Minia faculty of medicine. The research character was explained to all patients. In all patients, a verbal consent was obtained.

A full detailed history was taken from all patients included chest symptoms, dyspnea scale using the modified Medical Research Council (mMRC) scale [7], COPD Assessment Test (CAT) score [8]. Besides, assessment of the presence of comorbidities as diabetes mellitus (DM), arterial hypertension, ischemic heart disease were based on physician-based diagnosis and medications used for them. Evaluation of anxiety and or depression using the Hamilton Anxiety Rating scale [9] and Patient Health Questionnaire [10]. COPD cO-morbidity TEst (COTE) was also calculated. It is a score which include 5 categories of diseases which are cardiovascular diseases, metabolic diseases, musculoskeletal diseases, psychological diseases and oncologic diseases. The patient is scored 1 if at least one of the diseases belonging to that category is present, the total score is the sum of scores accounted to each category with the range from 0 to 5 [11].

Spirometry was performed using a 2130 spirometer (V_{max}, Sensormedia, USA), which was calibrated daily. Results were obtained for FVC, FEV_1, and FEV_1/FVC ratio. Post bronchodilation test was done following 400 mcg of salbutamol inhalation.

Body mass index, 6-minute walk test, and BODE index (Body mass index, Obstruction, Dyspnea, Exercise capacity) [12] were calculated. Peripheral capillary oxygen saturation (Sp_{O2}) on room air was also detected.

A chest X-ray was done to each patient and a high-resolution computed tomography chest was done to detect the type and distribution of emphysema in some cases.

Complete blood count in addition to inflammatory markers in the form of, C-reactive protein (CRP), and serum fibrinogen were assayed. Blood samples were collected, centrifuged within 2 hours of sampling and the serum was frozen and stored at –20°C until analyzed for measurement of CRP by enzyme immunoassay kits supplied by European Authorized Representative (normal value: 1–6 mg/L) [13].

Serum fibrinogen was assayed using Human Fibrinogen ELIZA kits, the United States of America (normal value: 1.25–100 ng/mL) [14].

All patients offered telephone follow up and or on outpatient visit clinic till the end of the study period for assessment the following; frequency and severity of exacerbation, hospitalization for exacerbation, and outcome of hospital stay. The follow up period is determined from the point of inclusion of the patient till the end of the study (December 2019) and this period is ranged from 6–12 months.

Under Spanish guidelines for COPD [15], the studied patients were classified into the following 3 phenotypes; exacerbator group (I): 45 patients with frequent exacerbations (34 with chronic bronchitis and 11 with emphysema predominant). Those with two exacerbations or one exacerbation that needs hospitalization in a year, 3 months/year with cough and expectoration for 2 successive years were that of frequent exacerbator with chronic bronchitis predominant, while those with frequent exacerbation without chronic bronchitis and with radiological (chest x-ray or computed tomography) diagnosis of emphysema were those of frequent exacerbator with emphysema. Non-exacerbator group (II); 37 patients (32 with chronic bronchitis and 5 with emphysema), these patients had < 2 exacerbations per year. Finally, 18 patients with asthma COPD overlap (ACO) group (III). ACO patients were diagnosed based on the presence of 2 major criteria or 1 major 2 minor criteria.

Major criteria were as the following: a) A personal asthma history. b) Positive bronchodilator test with increase FEV_1 > 15% and > 400 mL. c) Fractional exhaled nitric oxide > 40 in parts per billion (ppb). Minor criteria were: a) Elevated IgE in blood; b) Personal history of atopy; c) Positive post-bronchodilator test with an increase of FEV_1 > 12% and > 200 m/l in at least 2 different occasions. All patients were diagnosed according to the presence of 2 major criteria.

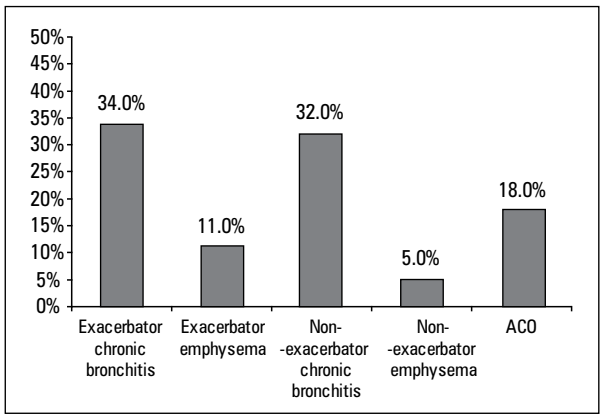

Figure 1. Distribution of each phenotypes of chronic obstructive pulmonary disease. ACO — asthma COPD overlap

Statistical analysis

Data were collected and entered using Statistical Package of Social Science, version 22. Parametric quantitative data were presented by mean and standard deviation, while qualitative data were presented by numbers and percentages. Chi-square and Fischer exact tests were used to compare qualitative data. One Way Analysis of Variance (ANOVA) was used to compare more than two means followed by post Hoc analysis when the results were found significant using Least Significant Difference (LSD) test. The confidence interval was set to 95% and the margin of error accepted was set to 5%; $p < 0.05$ was considered statistically significant.

Results

One hundred COPD patients were involved in the study. A summary of the distribution of each phenotype is presented in Figure 1. Patients with chronic bronchitis were more than those of emphysema in both exacerbator and non-exacerbator phenotypes (34 *vs* 11 patients and 32 *vs* 5 patients respectively).

It was found that patients of the exacerbator and nob-exacerbator phenotypes were significantly older than ACO patients, male gender was more in exacerbator and non-exacerbator phenotypes. Regarding respiratory symptoms, wheezes are the only symptom that was significantly predominant in ACO ($p = 0.01$) with a nearby similar distribution of other chest symptoms in all phenotypes. On analysis of spirogram results, both of FEV_1/FVC and FEV_1% predicted were lower in exacerbator phenotype ($p = 0.001$ for both), while 6-minute walk distance (6MWD) and SpO_2 showed similar values in all phenotypes. On analysis of post hoc test results, it was found that ACO patients were younger and most of them were females, while their spirometry readings were less affected than the other phenotypes (Table 1).

CAT was significantly higher in exacerbator than ACO. Interpretation of post hoc findings reveal that CAT score was lower in ACO patients by a significant degree than the other phenotypes. In addition, more than half of the exacerbator group of GOLD class D while non-exacerbator and ACO cases were more in class B ($p = 0.001$) (Table 2).

Although higher values of all inflammatory indices in the exacerbator phenotype than the others, no significant difference was found ($p > 0.05$; Table 3).

As regard comorbidities encountered in different COPD phenotypes, about one third and one forth of ACO and non- exacerbator phenotypes respectively had no comorbidity with a significant value for ACO patients in comparison to exacerbator phenotype only (Table 4). On the other hand, 40% of non-exacerbator suffered from one comorbidity only ($p = 0.003$), while 85% of the exacerbator phenotype had 2 or more comorbidities which was highly significant among them than the other 2 phenotypes ($p = 0.002$). Referring to psychological comorbidities, anxiety and depression were the predominant ones in all phenotypes with a higher significance only for anxiety among exacerbator phenotype (62.2%, $p = 0.02$).

Traditionally, comorbidity found in COPD patients has been evaluated using a non-disease specific score such as the Charlson comorbidity score [16]. Latest time, Divo et al. [11], elaborated an index unique to COPD, COPD Comorbidity Test, or COTE index that includes those comorbidities that impact survival in patients with COPD. We found a higher significant score for exacerbators in comparison with the other phenotypes (mean COTE score = 2.7 ± 0.8, with 95% CI: 2.35–3.04; 2.3 ± 0.9, 95% CI: 1.99–2.60 and 1.9 ± 0.9 with 95% CI: 1.68–2. 11, $p = 0.01$ for exacerbator, non-exacerbator and ACO respectively) (Figure 2).

Exacerbations are described as acute aggravation of respiratory symptoms that lead to further treatment and they are classified into mild, moderate and severe according to the treatment affordable for each type as issued by GOLD [1]. Referring to COPD exacerbations that the studied patients suffered (Table 5), ten patients missed to be followed, only 2 exacerbator patients out of 45 had no exacerbations thought the study period which was significant for them than the other phenotypes. Regarding the severity of exacerbations,

Table 1. Summary of demography, clinical and spirometry results among COPD phenotypes

Variable	Exacerbator (I)	Non-exacerbator (II)	ACO (III)	P-value		
	n = 45	n = 37	n = 18			
Age [years]	63.9 ± 8.2	62.1 ± 7	57.8 ± 7.3		0.019	
				I vs II	I vs III	II vs III
				0.294	0.008	0.039
Male, n (%)	40 (88.8%)	34 (91.8%)	6 (33.3%)		0.001	
Female, n (%)	5 (11.1%)	3 (8.1%)	12 (66.7%)			
				I vs II	I vs III	II vs III
				0.648	< 0.001	< 0.001
Dyspnea, n (%)	24 (54.5%)	28 (73.7%)	10 (55.6%)		0.160	
mMRC score						
Grade 1	1 (4.2%)	1 (3.6%)	1 (5.6%)		0.97	
Grade 2	13 (54.2%)	15 (53.6%)	5 (66.7%)			
Grade 3	10 (41.7%)	12 (42.9%)	4 (27.8%)			
Cough, n (%)	34 (77.3%)	32 (84.2%)	18 (100%)		0.08	
Wheezes, n (%)	21 (47.7%)	16 (42.1%)	15 (83.3%)		0.01	
				I vs II	I vs III	II vs III
				0.756	0.007	0.004
FEV_1/FVC (actual)	49.9 ± 11.1	54.8 ± 9.3	60.3 ± 8.4		0.001	
				I vs II	I vs III	II vs III
				0.036	0.001	0.039
FEV_1 (%, pred.)	37.2 ± 12.9	38.2 ± 9.6	49.2 ± 12.6		0.001	
				I vs II	I vs III	II vs III
				0.697	0.001	0.001
6MWD [m]	267.1 ± 50.5	272.4 ± 46.1	270.2 ± 49.2		0.86	
Resting SpO_2 [%]	92.2 ± 3.3	94.3 ± 3.5	93.3 ± 2.9		0.28	

Some data are presented as mean±SD.
Results were presented as numbers and percentages and compared using Chi-square test. If the results were significant multi-comparison were done between groups using Chi-square test.
Results were presented as mean ± SD and compared using one-way ANOVA test. If the results were significant the post hoc analysis was done using LSD test.
6MWD — 6-minute walk distance; FEV_1/FVC — forced expiratory volume in 1 second/forced vital capacity; mMRC — modified medical research council; SpO_2 — peripheral oxygen saturation

exacerbator and non-exacerbator phenotypes had a significant higher number of severe exacerbations that need hospitalization in comparison to ACO patients. While patients of ACO phenotype had a higher percent of moderate exacerbations than the other phenotypes.

Discussion

Some studies found that COPD patients with different phenotypes have variable disease characteristics [4], however, the fate of these phenotypes on morbidity and mortality is still elusive. So, this research was performed to assess the effect of different COPD phenotypes on disease outcome.

COPD severity indices that were measured in our study were (CAT score, GOLD categories, and BODE index).

We found that exacerbator and non-exacerbator groups had a higher CAT score than the ACO group (14.7 ± 1.5; 14.4 ± 1.4 *vs* 13.7 ± 1.7 respectively p = 0.04). Previous studies found that the exacerbator phenotype mainly exacerbator chronic bronchitis had the highest CAT score [5, 17]. A meta-analysis study found that in ten studies that included 4568 patients, the frequent exacerbator of chronic bronchitis phenotype was associated with a high CAT score than in the ACO phenotype [18].

Regarding COPD categories using A, B, C, D assessment, our study found that all exacerbators were in category class (C) and (D) (42.4% and 59% respectively) which represented the most severe categories, non-exacerbators and ACO patients had a lower degree of disease severity as more than 50% of the involved patients were in cate-

Table 2. Chronic obstructive pulmonary disease (COPD) severity classification among different phenotypes

Variable	Exacerbator (I)	Non- exacerbator (II)	ACO (III)	P-value		
	n = 45	n = 37	n = 18			
CAT score						
Range	12–20	10–18	12–18		0.040	
Mean ± SD	14.7 ± 1.5	14.4 ± 1.4	13.7 ± 1.7	I vs II	I vs III	II vs III
				0.356	0.024	0.111
BMI (kg/m^2)						
Range	20.4–44.9	20.6–37	20.4–50		0.267	
Mean ± SD	28.1 ± 6.9	25.6 ± 3.8	26.4 ± 6.1			
GOLD categories, n (%)						
A	0 (0%)	10 (26.3%)	1 (5.6%)		0.001	
B	0 (0%)	22 (57.8%)	9 (50%)			
C	19 (42.2%)	5 (13.5%)	7 (38.9%)	I vs II	I vs III	II vs III
D	26 (59%)	0 (0%)	1 (5.6%)	< 0.001	< 0.001	0.034
BODE index						
Range	4–9	4–7	4–8		0.11	
Mean ± SD	6.3 ± 1.2	5.9 ± 0.9	5.1 ± 0.8			

Results were presented as numbers and percentages and compared using Chi-square test. If the results were significant multi-comparison were done between groups using Chi-square test.
Results were presented as mean ± SD and compared using one- way ANOVA test. If the results were significant the post hoc analysis were done using LSD test.
CAT — COPD assessment test; BMI — body mass index; BODE = body mass index (B), degree of airflow obstruction by FEV_1% pred. (O) and functional dyspnea (D) measured by mMRC scale, and exercise capacity (E) as assessed by the 6-minute walk test

Table 3. Inflammatory biomarkers among different phenotypes

Variable	Exacerbator n = 45	Non- exacerbator n = 37	ACO n = 18	P-value
WBCs (/Cu.mm)				
Range	4000–13000	2000–12000	3000–11000	0.35
Mean ± SD	7947.7 ± 23.9	7221.1 ± 2328.7	7427.8 ± 2352	
CRP, n (%)				
Negative	22 (48.8%)	20 (54.1%)	11 (61.1%)	0.62
Positive	23 (51.1%)	17 (45.9%)	7 (38.9%)	
CRP titre [mg/L]				
Range	9–98	6–96	10–48	0.30
Mean ± SD	44.5 ± 35.1	33.3 ± 33.5	27.4 ± 19.5	
Serum fibrinogen [ng/mL]				
Range	15–735	25–685	30–670	0.66
Mean ± SD	155.3 ± 133.6	120.8 ± 139.3	130.6 ± 122.9	

ACO — asthma COPD overlap; CRP — C-reactive protein; WBCs — white blood cells

gory (B) (57.8% and 50% respectively). In another multicenter study, most of the COPD patients were in the GOLD (D) group (74.3%) and frequent exacerbators with chronic bronchitis were the higher prevalence than other phenotypes [6].

The BODE index is a multidimensional tool that integrate quantifications of nutritional position, airflow limitation, dyspnea, and functional status. It provides an integrated assessment of the respiratory and non- respiratory domains of the disease that better represent disease severity [12]. We figured out although the highest score of the BODE index was found in the exacerbator group, no substantial difference between phenotypes was found. In agreement with our findings, other study showed that there was no significant difference between the BODE index and different phenotypes [5]. In contrast to this finding, another study [19] found that frequent exacerbators have a significantly worse BODE scores and lung function than non-exacerbators and ACO patients.

Several studies have shown that COPD patients even in the stable state have higher levels of some inflammatory markers in the blood [20,

Table 4. Comorbidities among different phenotypes

Variable	Exacerbator (I)	Non- exacerbator(II)	ACO (III)	P-value		
	n = 45	n = 37	n = 18			
No comorbidity, n (%)	2 (4.4%)	6 (16.2%)	5 (27.7%)		0.038	
				I vs II	I vs III	II vs III
				0.073	0.007	0.314
1 comorbidity, n (%)	4 (8.8%)	15 (40.5%)	3 (16.6%)		0.003	
				I vs II	I vs III	II vs III
				0.001	0.374	0.076
≥ 2 comorbidities, n (%)	39 (86.6%)	16 (43.2%)	10 (55.5%)		0.002	
				I vs II	I vs III	II vs III
				0.000	0.007	0.390
Systemic HTN, n (%)	12 (27.3%)	13 (34.2%)	5 (27.8%)		0.800	
DM, n (%)	7 (15.9%)	4 (10.5%)	1 (5.6%)		0.460	
IHD, n (%)	5 (11.4%)	3 (7.9%)	3 (16.7%)		0.580	
Anxiety, n (%)	28 (62.2%)	13 (35.1%)	7 (38.9%)		0.020	
				I vs II	I vs III	II vs III
				0.014	0.092	0.092
Depression, n (%)	29 (64.4%)	16 (43.2%)	8 (44.4%)		0.070	

DM — diabetes mellitus; HTN — hypertension; IHD — ischemic heart disease

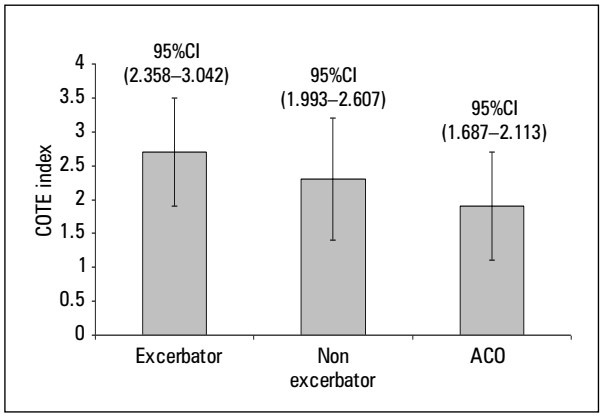

Figure 2. Mean value of COTE index among different phenotypes

21]. On assessment the systemic inflammatory markers in the current study, we found that in exacerbator phenotype, although, white cell counts, CRP, and serum fibrinogen were higher in that phenotype in comparison with the other phenotypes with no significant difference ($p > 0.05$). No previous studies have a comparison of systemic inflammatory markers to phenotype. Some studies showed that high plasma fibrinogen levels reflected severe symptomatic phenotypes and poor clinical outcomes [22], however, we did not perform a correlation analysis between it and outcomes.

The presence of significant comorbidities is one of the most important risk factors for severity in COPD, therefore, identifying and treating co-morbidities is an integral aspect of COPD's care plan.

Comorbidities can be related to any clinical phenotype [23] and should be included in a systemic therapy strategy. Some recent studies looked at the associations between comorbidities and unique COPD phenotypes [24] or identified novel phenotypes associated with comorbidities, but the findings of founding associations are still scarce or draw definite conclusions.

We found that 50% of the studied phenotypes had comorbidities with numbers of patients with anxiety and depression exceed those with the cardiovascular system affection and diabetes mellitus in all phenotypes. However, anxiety was the only significant one among the exacerbator phenotype ($p = 0.02$). Under these findings, a polish study [4], found also that depression and anxiety were significantly higher among exacerbator phonotype either chronic bronchitis or emphysema than other phenotypes ($p = 0.001$ and 0.04 respectively).

Table 5. Exacerbation characteristics among the studied phenotypes

Variable	Exacerbator (I)	Non- exacerbator (II)	ACO (III)	P -value		
	n = 45	n = 37	n = 18			
No exacerbation, n (%)	2 (5%)	14 (41.2%)	7 (43.7%)		0.0001	
				I vs II	I vs III	II vs III
				< 0.001	< 0.001	0.862
Frequency of exacerbation						
Range	3–4	0–1	0–3			
Mean ± SD	3.4 ± 0.5	0.8 ± 0.4	1.5 ± 1.2	I vs II	I vs III	II vs III
				< 0.001	< 0.001	0.003
Moderate exacerbation, n (%)	10 (25%)	4 (11.7%)	6 (66.6%)			
				I vs II	I vs III	II vs III
				0.147	0.349	0.033
Severe exacerbation, n, % Inward Admission	20 (71.4%)	14 (37.8%)	1 (11.1%)		0.02	
				I vs II	I vs III	II vs III
				0.447	0.002	0.011
ICU Admission	8 (28.6)	2 (5.4%)	2 (22.2%)		0.06	
Length of hospital stay [days], Mean ± SD	6.2 ± 1.8	6.1 ± 2.2	6.7 ± 1.4		0.78	
Hospitalization outcome						
Discharged alive, n (%)	26 (92.8%)	16 (100%)	2 66.7%)		0.30	
Death, n (%)	2 (7.2%)	0	1 (33.3%)		0.15	

COTE index that includes those comorbidities that impact on survival in COPD patients. It is the first specific COPD comorbidity index which predicts the risk of death associated with COPD accompanying co-morbidities [11], and more disease- specific than the Charlson comorbidity score, developed for patients with cancer. The scores range from 0–5. COTE Index was also described according to the mortality risk in < 4 points and ≥ 4 points. Our study is the first study to assess COTE index in different COPD phenotypes, we found that all COPD phenotypes had a mean index < 4 points with a higher significant score among exacerbators in comparison with the other phenotypes (COTE = 2.7; p = 0.01).

Exacerbations are an important occurrence, not just because they pose a major economic burden but more importantly because frequent exacerbations of COPD contribute to a worsening in health-related quality of life [25].

On follow up of the studied patients for assessment of frequency and severity of exacerbations, we found that frequency and severity of exacerbations were substantially more in exacerbator in comparison with other phenotypes. This is followed by ACO patients as 9 patients of ACO out of 16 (56%) had moderate to severe exacerbation during the time of the study with 2 patients (22 %) need intensive care unit (ICU) admission. Another study [26] found that the frequent exacerbator phenotype was closely associated with exacerbation-related hospitalizations, and exacerbation-related hospitalizations were associated with poorer survival. However, one study [27] suggested that the amount of exacerbation was similar in the three phenotypes, despite the evident differences in patient features.

In general, the frequency of exacerbation increases with the seriousness of the disease, as indicated by obstruction of the airflow [28], and some evidence suggests a possible role for extrapulmonary factors in exacerbation genesis like the BODE index, which is a better predictor of COPD hospitalization in a patient cohort than FEV_1 [29]. Based on these findings, we found that the frequent exacerbators with the higher frequency of exacerbation had also the lowest FEV_1 and a higher BODE index than other phenotypes. Another study [5] agreed with our findings as they found that the (frequent exacerbator chronic bronchitis) phenotype was the most symptomatic and had frequent exacerbation with higher BODE score and showed a trend to worse survival after one year.

This study has some shortcomings, one of them is the use of FEV1 and FVC in pulmonary function test in all phenotypes with no specification in specific phenotypes due to non-availability for measuring lung volumes as inspiratory capacity over total lung capacity ratio (IC/TLC) which is used as an index for assessing static lung hyperinflation which has a significant relationship to survival especially in COPD patients with emphysema phenotype [30].

Besides, 10% of the studied patients missed being followed which may influence the exacerbation history or the in hospital-mortality.

We have no data in this study on the timing of diagnosis of co-morbidities in different COPD phenotypes if they occur before or after diagnosis of COPD to understand if the pathophysiology of COPD and co-morbidity is common or they are considered as one of long term COPD complications.

Lastly, no follow up on 6MWD or BODE index was done during the follow- up visits to determine its change over time which may be one of the predictors for poor outcomes in some phenotypes.

Conclusion

Exacerbator phenotype is the most common phenotype encountered in this study followed by non- exacerbator then ACO patients. It is obvious that patients of exacerbator phenotype have a higher COPD severity index than the other phenotypes represented in CAT score and GOLD grade of categorization. COPD associated co-morbidities have a common denominator in all phenotypes with a predominance of psychological disorders than the other co-morbidities. Undoubtedly, exacerbators have a more frequency of exacerbations than the other phenotypes but also have a more severe exacerbations that require hospital admission.

Recommendations

Phenotypes classification should be done early in all COPD patients from the time of diagnosis as exacerbator phenotype has worse prognosis than other. More follow up visits to outpatients' clinics, educational training on diagnosis of exacerbations early and treatment options need to affordable especially for exacerbator phenotype.

Conflict of interest

None declared.

References:

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management and prevention of COPD. Eur Respir J. 2019; 53(5): 1900164.
2. Salzman SH. Which pulmonary function tests best differentiate between COPD phenotypes? Respir Care. 2012; 57(1): 50–60, doi: 10.4187/respcare.01585, indexed in Pubmed: 22222125.
3. Fragoso E, André S, Boleo-Tomé JP, et al. GI COPD — Interest Group on Chronic Obstructive Pulmonary Disease. Understanding COPD: a vision on phenotypes, comorbidities and treatment approach. Rev Port Pneumol (2006). 2016; 22(2): 101–111, doi: 10.1016/j.rppnen.2015.12.001, indexed in Pubmed: 26827246.
4. Kania A, Krenke R, Kuziemski K, et al. Distribution and characteristics of COPD phenotypes — results from the Polish subcohort of the POPE study. Int J Chron Obstruct Pulmon Dis. 2018; 13: 1613–1621, doi: 10.2147/COPD.S154716, indexed in Pubmed: 29844667.
5. Cosio BG, Soriano JB, López-Campos JL, et al. PLOS ONE Staff, CHAIN study. Distribution and outcomes of a phenotype-based approach to guide COPD management: results from the CHAIN cohort. PLoS One. 2016; 11(9): e0160770, doi: 10.1371/journal.pone.0160770, indexed in Pubmed: 27684372.
6. Arkhipov V, Arkhipova D, Miravitlles M, et al. Characteristics of COPD patients according to GOLD classification and clinical phenotypes in the Russian Federation: the SUPPORT trial. Int J Chron Obstruct Pulmon Dis. 2017; 12: 3255–3262, doi: 10.2147/COPD.S142997, indexed in Pubmed: 29138554.
7. Fletcher CM. Standardized questionnaire on respiratory symptoms: a statement prepared and approved by the MRC Committee on the Aetiology of Chronic Bronchitis (MRC breathlessness score). BMJ. 1960; 2: 1662.
8. Jones PW, Harding G, Berry P, et al. Development and first validation of the COPD Assessment Test. Eur Respir J. 2009; 34(3): 648–654, doi: 10.1183/09031936.00102509, indexed in Pubmed: 19720809.
9. Shear MK, Vander Bilt J, Rucci P, et al. Reliability and validity of a structured interview guide for the Hamilton Anxiety Rating Scale (SIGH-A). Depress Anxiety. 2001; 13(4): 166–178, indexed in Pubmed: 11413563.
10. Kroenke K, Spitzer R. The PHQ-9: a new depression diagnostic and severity measure. Psychiatric Annals. 2002; 32(9): 509–515, doi: 10.3928/0048-5713-20020901-06.
11. Divo M, Cote C, de Torres JP, et al. BODE Collaborative Group. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2012; 186(2): 155–161, doi: 10.1164/rccm.201201-0034OC, indexed in Pubmed: 22561964.
12. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004; 350(10): 1005–1012, doi: 10.1056/NEJMoa021322, indexed in Pubmed: 14999112.
13. Roberts W, Sedrick R, Moulton L, et al. Evaluation of four automated high-sensitivity C-reactive protein methods: implications for clinical and epidemiological applications. Clinical Chemistry. 2000; 46(4): 461–468, doi: 10.1093/clinchem/46.4.461.
14. Mackie IJ, Kitchen S, Machin SJ, et al. Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology. Guidelines on fibrinogen assays. Br J Haematol. 2003; 121(3): 396–404, doi: 10.1046/j.1365-2141.2003.04256.x, indexed in Pubmed: 12716361.
15. Miravitlles M, Calle M, Soler-Cataluña J. Clinical phenotypes of COPD: identification, definition and implications for guidelines. Archivos de Bronconeumología (English Edition). 2012; 48(3): 86–98, doi: 10.1016/j.arbr.2012.01.003.
16. Charlson M, Pompei P, Ales K, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of Chronic Diseases. 1987; 40(5): 373–383, doi: 10.1016/0021-9681(87)90171-8.
17. Chai CS, Liam CK, Pang YK, et al. Assessment test (CAT) score of patients with chronic obstructive pulmonary disease based on clinical phenotypes. Respirology. 2018; 23(S2): 246, doi: 10.1111/resp.13420_431.

18. Wu JJ, Xu HR, Zhang YX, et al. The characteristics of the frequent exacerbator with chronic bronchitis phenotype and non -exacerbator phenotype in patients with chronic obstructive pulmonary disease: a meta-analysis and system review. BMC Pulm Med. 2020; 20(1): 103, doi: 10.1186/s12890-020-1126-x, indexed in Pubmed: 32326924.
19. Corlateanu A, Botnaru V, Scutaru E, et al. Bode index in different phenotypes of COPD. Eur Resp J. 2017; 50(Suppl 61): PA 3621, doi: 10.1183/1393003.congress-2017.pa3621.
20. Dahl M, Tybjaerg-Hansen A, Vestbo J, et al. Elevated plasma fibrinogen associated with reduced pulmonary function and increased risk of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2001; 164(6): 1008–1011, doi: 10.1164/ajrccm.164.6.2010067, indexed in Pubmed: 11587987.
21. Broekhuizen R, Grimble RF, Howell WM, et al. Pulmonary cachexia, systemic inflammatory profile, and the interleukin 1beta -511 single nucleotide polymorphism. Am J Clin Nutr. 2005; 82(5): 1059–1064, doi: 10.1093/ajcn/82.5.1059, indexed in Pubmed: 16280439.
22. Kim TH, Oh DK, Oh YM, et al. Fibrinogen as a potential biomarker for clinical phenotype in patients with chronic obstructive pulmonary disease. J Thorac Dis. 2018; 10(9): 5260–5268, doi: 10.21037/jtd.2018.08.52, indexed in Pubmed: 30416773.
23. Miravitlles M, Soler-Cataluña JJ, Calle M, et al. Treatment of COPD by clinical phenotypes: putting old evidence into clinical practice. Eur Respir J. 2013; 41(6): 1252–1256, doi: 10.1183/09031936.00118912, indexed in Pubmed: 23060631.
24. Chubachi S, Nakamura H, Sasaki M, et al. Keio COPD Comorbidity Research (K-CCR) Group. Polymorphism of LRP5 gene and emphysema severity are associated with osteoporosis in Japanese patients with or at risk for COPD. Respirology. 2015; 20(2): 286–295, doi: 10.1111/resp.12429, indexed in Pubmed: 25392953.
25. Donaldson GC, Seemungal TAR, Bhowmik A, et al. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. Thorax. 2002; 57(10): 847–852, doi: 10.1136/thorax.57.10.847, indexed in Pubmed: 12324669.
26. Beeh KM, Glaab T, Stowasser S, et al. Characterisation of exacerbation risk and exacerbator phenotypes in the POET-COPD trial. Respir Res. 2013; 14(1): 116, doi: 10.1186/1465-9921-14-116, indexed in Pubmed: 24168767.
27. Izquierdo-Alonso JL, Rodriguez-Gonzálezmoro JM, de Lucas -Ramos P, et al. Prevalence and characteristics of three clinical phenotypes of chronic obstructive pulmonary disease (COPD). Respir Med. 2013; 107(5): 724–731, doi: 10.1016/j.rmed.2013.01.001, indexed in Pubmed: 23419828.
28. Dewan N, Rafique S, Kanwar B, et al. Acute exacerbation of COPD. Chest. 2000; 117(3): 662–671, doi: 10.1378/chest.117.3.662.
29. Ong KC, Earnest A, Lu SJ. A multidimensional grading system (BODE index) as predictor of hospitalization for COPD. Chest. 2005; 128(6): 3810–3816, doi: 10.1378/chest.128.6.3810, indexed in Pubmed: 16354849.
30. Marin JM, Carrizo SJ, Gascon M, et al. Inspiratory capacity, dynamic hyperinflation, breathlessness, and exercise performance during the 6-minute-walk test in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2001; 163(6): 1395–1399, doi: 10.1164/ajrccm.163.6.2003172, indexed in Pubmed: 11371407.