CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN CAN THO: CLINICAL CHARACTERISTICS AND FEATURES OF TREATMENT BY CLINICAL PHENOTYPES

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ABSTRACT

Background: *phenotypic approach in the treatment of COPD is lacking in general medical facilities, despite the importance of this data.* ***Objectives:*** *The study aimed to identify divergences in features, pharmacologic regimens of COPD by clinical phenotypes in the real-life context of care units in Can Tho City that manage outpatients with chronic respiratory diseases.* ***Materials and methods:*** *a prospective cohort study was carried out. We enrolled 158 patients who met the sampling criteria for this study. Data collected include (1) biometric characteristics, (2) medical history, (3) characteristics of COPD (including: symptoms, chest radiograph, peripheral blood eosinophil count, pulmonary ventilation parameters, bronchodilator test, and pharmacological regimen). COPD were classified into three phenotypic groups according to the criteria of the 2017 Spanish guideline (GesEPOC) and were also categorized into four groups (ABCD) according to the 2019 GOLD guideline.* ***Results:*** *the clinical AE phenotype was predominant at 41.8%, whereas the NON-AE and ACO was 38.6% and 19.6%. According to the GOLD, classifying as group A, B, C, D is 19%, 34.8%, 10.1%, and 36.1%, respectively. Between the different phenotypic groups, there were a variety of variances in the eosinophil count of the peripheral blood, but there were no changes in some kinds of chest radiograph images. Response-to-bronchodilator-test rate was higher in the ACO phenotype than in the NON-AE and the AE phenotypes. All ACO patients who received LABA/ICS. The proportion of using LABA/ICS accounted for most NON-AE and AE patients.* ***Conclusions:*** *among clinical phenotypes, the AE phenotype accounted for the highest percentage. There were differences in the clinical characteristics among phenotypes. ICS using is popular among COPD patients.*

Keywords: *Chronic; Obstructive; Pulmonary Disease; Clinical Phenotypes*

I. INTRODUCTION

COPD is a multi-component, heterogeneous disease with variable clinical manifestations that may respond discrepantly to therapeutic regimens [9]. The phenotypic approach is crucial in personalized medicine for each patient's setting. In 2012, the first Spanish guideline on COPD (GesEPOC) was released, and soon after, it was considered one of the first attempts to introduce a phenotypic COPD approach in clinical practice. In the updated version in 2017, GesEPOC retained the original of this phenotypic pattern, including non-exacerbator (NON-AE), asthma-COPD overlap (ACO), exacerbator with emphysema, and exacerbator with chronic bronchitis (AE-CB) [10]. In Vietnam, clinicians

have also gradually applied personalized therapeutic specific to each COPD phenotype, but implementation progress is inconsistent with its preeminence. Because of phenotypic classification's benefits, our study aimed to identify divergences in features and pharmacologic regimens of COPD by clinical phenotypes in the real-life context of care units in Can Tho City that manage outpatients with chronic respiratory diseases.

II. MATERIALS AND METHODS

2.1. Study subjects

Patients diagnosed with COPD according to GOLD 2019 criteria: (1) ≥ 40 years old; (2) have risk factors such as smoking, occupational or environmental exposure; (3) have chronic respiratory symptoms; (4) have been tested for pulmonary ventilation with a result of FEV1/FVC ≤ 0.7 after bronchodilator test. Excluded patients were those who had an exacerbation of COPD within eight weeks before the time of enrollment in the study. Patients diagnosed with other pulmonary diseases, such as newly acquired or recurrent tuberculosis and lung tumors, lung abscess, pneumonia, bronchiectasis were also excluded from the study.

2.2. Methods

- Study design: a prospective cohort study was conducted.

- Sample size, sampling method

The estimated sample size for the study was 124 based on the proportion of patients with the ACO phenotype of 8.8 % (ACO accounted for the lowest of the four phenotypes) in a 2016 study in Serbia by Zorica Lazic et al., with a class I error of 5% and an accuracy of 5% [8]. The attrition rate (dropout or loss to follow-up) was expected to be about 25%. Therefore, our estimated sample size was about 155 participants. COPD patients satisfying the selection criteria were randomly chosen.

- Research content

Patients with COPD at the time of participating in the study were collected information related to research variables, including: (1) biometric characteristics (including gender, age, body mass index), (2) medical history, including: a lifelong smoking history (defined as a person with a history of smoking is when he has consumed at least 100 cigarettes during his lifetime [2]), the pack-year, history of exacerbations in the previous 12 months, comorbidities (as determined by Charlson's score), a history of asthma before age 40, a history of any allergies, (3) characteristics of COPD, including: symptoms (cough, sputum production, dyspnea, rhonchus, decreased breath sounds, wheezing), severity of chronic dyspnea evaluated by mMRC questionnaire, severity of symptoms assessed by CAT scores (COPD Assessment Tool), emphysema, dirty lung and other abnormalities detected on the chest radiograph, peripheral blood eosinophil count, pulmonary ventilation parameters such as FVC%, FEV1%, FEV1/FVC, bronchodilator test, pharmacological regimen.

Based on the available data, participants were classified into three phenotypic groups according to the criteria of the 2017 Spanish guideline (GesEPOC) and related studies [10], [14].

- Asthma-COPD overlap (ACO) phenotype: meet two major criteria or one major criterion plus one minor criterion, including:
  - Major: (1) strong response after bronchodilator test; (2) history of asthma.
  - Minor: (1) history of any allergies; (2) bronchodilator test (+).

- Non-exacerbator (NON-AE) phenotype: history of no exacerbations in the past year.
- Exacerbator (AE) phenotype: having two or more exacerbations or at least one exacerbation requiring hospitalization in a year.

In addition, patients were also categorized into four groups (ABCD) according to the 2019 GOLD guideline based on two criteria, including a history of exacerbation and severity of symptoms (mMRC, CAT).

- Data collection: data were collected through studying medical records and taking medical history.

- Statistical analysis: data was analyzed by SPSS version 18.0 software (IBM Corporation, Armonk, NY, USA). Results are considered statistically significant when the probability of making a type I error is less than 5%.

III. RESULTS

Table 1. Clinical and demographic characteristics

	Patients (n=158)	**Phenotype**			**p**
		ACO (a)	**NON-AE (b)**	**AE (c)**	
Gender = male	155 (98.1%)	30 (96.8%)	60 (98.4%)	65 (98.5%)	0.797 (Fisher)
Age	65.98 ± 9.12	63.65± 9.87	66.02± 8.68	67.05± 9.08	0.232
History of smoking	156 (98.7%)	30 (96.8%)	60 (98.4%)	66 (100%)	0.337 (Fisher)
Number of pack-year	29.01± 11.65	27.77±11.45	26.69±10.72	31.72±12.16	**0.046**
BMI	20.85±3.28	21,97± 4.14	21± 2.84	20.2± 3.08	**0.040**
The frequency of exacerbations within 12 months					
≥2 exacerbations/year Exacerbation requiring hospitalization	43 (27.2%) 50 (31.6%)	2 [c] (6.5%) 5 [c] (16.1%)		41 [a] (62.1%) 45 [a] (68.2%)	0.000 0.000

[a, b, c] showed statistically significant difference between two phenotypes in pairwise comparisons

Comments: there was a difference in BMI between the phenotypes, specifically there was a significant difference between the group of AE phenotype and ACO phenotype (p = 0.034). The pack-year number was significantly higher in patients of the AE phenotype than ones of the NON-AE phenotype (p = 0.044).

Table 2. Proportional classifications of COPD phenotypes and groups

	Patients (n=158)	**Phenotype**			**p**
		ACO	**NON-AE**	**AE**	
GOLD classification					
A	30 (19%)	10 (32.3%)	20 (32.8%)	0	
B	55 (34.8%)	14 (45.2%)	41 (67.2%)	0	0.000
C	16 (10.1%)	3 (9.7%)	0	13 (19.7%)	
D	57 (36.1%)	4 (12.9%)	0	53 (80.3%)	

Comments: The AE phenotype predominated of the study population.

Table 3. Characteristics and the severity of symptoms in the stable phase

	Patients (n=158)	Phenotype			p
		ACO (a)	NON-AE (b)	AE (c)	
Respiratory symptoms					
Cough	128 (81.0%)	24 (77.4%)	46 (75.4%)	58 (87.9%)	0.171
Sputum production	100 (63.3%)	20 [c,d] (64.5%)	34 [c] (55.7%)	46 (69.7%)	0.261
Wheezes, bronchi, lung sound	23 (14.6%)	3 (9.7%)	11 (18.0%)	9 (13.6%)	0.540
reduction	42 (26.6%)	11 [d] (35.5%)	15 (24.6%)	16 (24.2%)	0.457
Wheezing (without a stethoscope)	152 (96.2%)	29 (93.5%)	59 (96.7%)	64 (97%)	0.746 (Fisher)
Dyspnea					
mMRC	2.01±0.9	1,74± 0.93	1,93±0.89	2,21±0.85	**0.036**
CAT	14.39±5.45	13.19±6.35	13.85±5,23	15.45±5.08	0.10

[a, b, c] showed statistically significant difference between two phenotypes in pairwise comparisons

Comments: dyspnea and cough were the two most common symptoms.

Table 4. Characteristics of pulmonary ventilation parameters

	Patients (n=158)	Phenotype			p
		ACO (a)	NON-AE (b)	AE (c)	
Pulmonary ventilation parameters after the bronchodilator test					
%FVC	83.38±17,47	82.43±18.42	86.03±17,91	81.30± 16.53	0.303
$\%FEV_1$	61.41±20,82	62.7±19,95	63.02±20,82	59.30±21,34	0.567
Gaensler index	53.54±11,69	55.87±10,15	53.49±11,67	52.50± 12.23	0.414
Response rate to	2	12 [b, c]	4 [a] (6.6%)	9 [a] (13.6%)	**0.001**
bronchodilator test	25 (15.8%)	(38.7%)			(Fisher)
GOLD classification of airflow limitation					
GOLD 1+GOLD 2	106 (67.1%)	23 (74.2%)	46 (75.4%)	37 (56.1%)	**0.044**
GOLD 3+GOLD 4	52 (32.9%)	8 (25.8%)	15 (24.6%)	29 (43.9%)	

[a, b, c] showed statistically significant difference between two phenotypes in pairwise comparisons

Comments: multiple pairwise comparisons of response-to-bronchodilator-test rate illustrated that it was higher in the ACO phenotype.

Table 5. Characteristics of eosinophils in peripheral blood

	Patients (n=158)	Phenotype			p
		ACO (a)	NON-AE (b)	AE (c)	
≥ 300 cells/mm^3	58 (40.8%)	18 [c] (64.3%)	23 (42.6%)	17 [a] (28.3%)	0.006
≥ 2%	88 (62%)	23 [c] (82.1%)	36 (66.7%)	29 (48.3%)	0.016

[a, b, c] showed statistically significant difference between two phenotypes in pairwise comparisons

Comments: patients in the ACO group had a higher percentage of eosinophils in peripheral blood (≥ 300, ≥ 2%) in AE group (p = 0.003).

Table 6. Characteristics of chest radiograph

	Patients (n=158)	Phenotype			p
		ACO (a)	NON-AE (b)	AE (c)	
Chest radiograph					
Emphysema	28 (20.6%)	1 (4.2%)	13 (23.6%)	14 (24.6%)	0.073
Dirty-lung	28 (20.6%)	6 (25.0%)	10 (18.2%)	12 (21.1%)	0.783
Others	59 (43.4%)	14 [c] (58.3%)	24 (43.6%)	21 (36.8%)	0.204

Comments: there were no differences in the proportion of emphysema and dirty lung images on straight chest X-rays of patients among the phenotypes.

Table 7. Medication therapy regimen for exacerbations prevention

	Patients (n=158)	Phenotype			p
		ACO (a)	NON-AE (b)	AE (c)	
Medication regimen for exacerbations prevention					
LAMA	18 (11.4%)	0 [c]	7 (11.5%)	11 [a] (16.7%)	0.001 (Fisher)
LAMA+LABA	22 (13.9%)	0 [c]	11 (18%)	11 [a] (16.7%)	
LABA+ICS	108 (68.4%)	31 [b, c] (100%)	39 [a] (63.9%)	38 [a] (57.6%)	
LAMA+LABA+ICS	10 (6.3%)	0 (0%)	4 (6.6%)	6 (9.1%)	
Use of ICS					
Non-using ICS	39 (24.7%)	0 [b,c]	17 [a] (27.9%)	22 [a] (33.3%)	0.001
Using ICS	119 (75.3%)	31 [b, c] (100%)	44 [a] (72.1%)	44 [a] (66.7%)	

[a, b, c] showed statistically significant difference between two phenotypes in pairwise comparisons

Comments: the proportion of using ICS accounted for most COPD patients. Combination of ICS in therapy in the ACO group was significantly higher than in the other groups.

IV. DISCUSSION

In our study, there were 41.78% of patients with AE phenotype, accounting for the largest proportion among groups. According to GOLD classification, GOLD B and GOLD D dominated with the rate of 34.8% and 36.1%, respectively; in which, GOLD D is mainly patients with exacerbator phenotype. When comparing between groups of patients by phenotype, there were differences in the number of pack-year, BMI, frequency of exacerbations and history of hospitalization for exacerbations within 12 months prior to the study, history of asthma before age of 40, severity of dyspnea according to mMRC scores, peripheral blood eosinophils, airway limitation, and management of medication regimen.

There have been many studies evaluating the prevalence of COPD phenotypes, most of these studies have a larger proportion of NON-AE phenotypes than the remaining phenotypes. Research by author Lazic in 2020 in Serbia [8] showed the proportion of ACO, NON-AE, AE-CB and AE-NON-CB phenotypes, respectively, 8.7%, 49.3%, 12.3%, and 29.7%. We found that patients with AE phenotypes accounted for a higher proportion than the remaining phenotypes. Author C. S. Chai also recorded similar results with the proportion of AE phenotype dominantly accounting for 58.2% (AE CB and AE NON-CB accounted for 39.7% and 18.5%, respectively) [3]. This could be explained because both our study and C. S. Chai's study were conducted with a small sample size, only focused on 1-2 central hospitals in big cities; therefore, there were inevitably a concentration of patients with multi-exacerbation COPD. By contrast, the studies of Lazic and author Bernardino were multi-center ones which had large sample size.

Regarding the exacerbator phenotype, our study noted some distinctive features of the AE patients compared with the ones in two remaining groups in terms of exacerbation history in the previous 12 months, BMI, number of pack-years, lung function and severity of symptom. Specifically, the AE phenotype had a higher proportion of patients with ≥ 2

moderate-severe exacerbations, a higher rate of hospitalization for exacerbations in the previous 12 months, and lower mean BMI than the ACO phenotype. AE patients also had bigger number of pack-year than the NON-AE ones. The frequency of moderate-severe exacerbations was also related to the degree of airway limitation [6]. This explained why in our study $\%FEV_1$ in AE patients was lower than that in other phenotypes, although this difference was not statistically significant. When dividing $\%FEV_1$ into two groups: < 50% and ≥ 50%, patients in the AE group had a significantly higher proportion of patients having $\%FEV_1$ < 50% after bronchodilator test, compared with the patients in the NON-AE group. G. Reiger et al. (2018) also showed that the AE CB phenotype had a significantly lower $\%FEV_1$ than AE phenotype and other phenotypes ($p = 0.001$) [11]. Not only prominent in the degree of airway limitation, the symptom burden of patients with multiple exacerbations, especially AE-CB was also quite prominent, this has been shown in many studies. A study in Malaysia in 2019 by C. S. Chai et al. showed that patients with AE phenotype had CAT scores and the rate of symptoms of cough, sputum production was significantly higher than patients with ACO or NON-AE phenotype [4]. H. Bao et al., in a study in China, showed that the group of AE-CB patients had mean scores of mMRC and CAT significantly higher than other groups [1]. In our study, patients with the AE - CB phenotype had a significantly greater mean mMRC score than patients in the ACO group. The mean CAT scores did not differ between groups, although when comparing the proportion of patients with cough and sputum production among phenotypes, the score in AE-CB phenotype was markedly higher than those of the other phenotypes. This could be explained by our small sample size, which did not clarify the difference in symptom burden between the phenotypic groups. Regarding medication treatment, the proportion of patients with AE CB and AE NON-CB treated with ICS accounted for a large proportion. This observation was like previous studies. Patients with exacerbator phenotype belonged to GOLD C and D groups, so the combination in ICS was understandable.

Some noteworthy points when referring to ACO phenotype included: history of asthma, blood eosinophil count, and response to bronchodilator test. Because of the overlapping features of asthma, the childhood history of asthma, the blood eosinophil value of these groups were relatively higher compared with the other phenotypes [3], [11]. Depending on the definition of ACO phenotype in each study, the rate of asthma before age of 40 in all phenotypes might vary slightly, but in general, this rate in the ACO group was significantly higher than in other remaining phenotypes. Our study also agreed with previous studies on this aspect. Specifically, the percentage of patients with asthma before age of 40 in the ACO group was 100% and the proportion of patients with blood eosinophils ≥ 2% in this group was significantly higher than in the AE group. Response to bronchodilator test was also an important feature of the ACO phenotype, patients in the ACO group had a significantly higher response-to-bronchodilator-test rate than patients with COPD alone [13]. In our study, patients with ACO phenotype had a response rate to bronchodilator test of 38.7%, higher than the group of NON-AE and AE ($p \leq 0.001$). Several studies have shown that patients with the ACO phenotype had significantly lower symptom severity and exacerbation frequency compared with the AE phenotype [7], [1]. The study of C. S. Chai in 2019 showed that patients with AE phenotype had a mean CAT score and a significantly higher proportion of patients with mMRC scores from 2-4, compared with ACO and NON-

AE groups. The frequency of exacerbations in the ACO group in this study was also significantly smaller than that in the AE group [4]. The results in our study were also similar, specifically, the frequency of exacerbations of the ACO phenotype is significantly lower than that of the AE group. In terms of symptom severity, the mMRC score of the ACO group was also lower than that of the AE group. Regarding the prevention of exacerbations with inhaled medications, we observed that 100% of ACO patients had ICS in their drug management, which was significantly different from the other phenotypes. Some studies also showed differences in this aspect, such as the study of G. Reiger et al. (89.4%) [11] and the study of A. Kania et al. (90.9%) [7]. This was consistent with the definition of ACO, which was the overlap of features of asthma and COPD as well as consistent with guidelines for the treatment of the ACO phenotype in the joint project of GINA and GOLD in 2017 [5].

Non-exacerbation phenotype accounted for the second highest percentage in the study. Regarding the phenotypic definition, NON-AE patients were at low risk of exacerbations, belonging to GOLD A and B. The symptom severity based on mMRC and CAT scores of the NON-AE group in our study was lower than that in AE group, however, this difference was not statistically significant. Many studies on COPD phenotypes have shown significant differences in mMRC and CAT scores in the NON-AE group compared with the remaining phenotypes as studied by the authors H. Bao, C. S. Chai, and G. Reiger [1], [4], [11]. This could be explained by the small sample size of our study, which has not yet highlighted this difference. Different from the ACO phenotype that required ICS in treatment, in COPD treatment guidelines, including GOLD, all prioritize bronchodilators as initial treatment for GOLD A and GOLD B patients, which in the context of our study were patients with NON-AE phenotype. However, in our study and some previous studies, the proportion of NON-AE patients managed with ICS was relatively high. Specifically, in our study, this proportion was 72.1%, in G. Reiger et al. was 84.3% [11]. It was difficult to explain this situation. Many explanations had been proposed such as the lack of updating new recommendations, lack of confidence in the therapeutic efficacy of bronchodilator agents and due to the popularity and cost of the drug which was suitable for most patients [12]. In the context of our research, the reason could be given that in Can Tho, as well as, in the southwestern provinces, access to ICS-coordinated preparations was easier and cheaper when compared with preparations containing only bronchodilator agents, especially long-acting ones. Another possible explanation was the effectiveness of ICS in preventing COPD exacerbations. The introduction of ICS into management was to bring a group of patients from AE phenotype transforming to NON-AE one after the treatment period.

V. CONCLUSIONS

Chronic obstructive pulmonary disease is a multi-component, heterogeneous disease with various clinical phenotypes. Among them, the AE phenotype accounted for the highest percentage. There were differences in the clinical characteristics among phenotypes. ICS using is popular in every group of COPD.

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