PATIENT CHARACTERISTICS AND SHORT-TERM EFFECTIVENESS OF SHORT-ACTING BRONCHODILATOR COMBINATION OF SALBUTAMOL/IPRATROPIUM IN PATIENTS WITH CHRONIC OBSTRUCTION PULMONARY DISEASE (COPD): A CROSS-SECTIONAL MULTICENTER STUDY IN VIET NAM

Nguyen Van Thanh[1], Dinh Ngoc Sy[2], Tran Van Ngoc[3], Nguyen Thanh Hoi[4], Cao Thi My Thuy[5], Nguyen Dinh Duy[6], Vu Van Thanh[7]

ABSTRACT

Background and objectives: Chronic obstructive pulmonary disease (COPD) is a common disease. There have been no studies evaluating patient characteristics, management and treatment status and short-term effectiveness of the short-acting bronchodilator combination of salbutamol/ipratropium in patients being managed by a respiratory facilities in Vietnam. This is the reason for this study. ***Patients and methods***: Prospective, descriptive, cross-sectional, multicenter study design. Patients are those who have been diagnosed with COPD (determined by FEV_1/FVC value <70%) and are being managed and treated at 5 medical facilities with representative respiratory operations across the country. Convenient, random, consecutive sampling of cases being managed and guided for treatment at participating facilities over a period of 30 days. All patients in the study were asked about treatment history and exacerbations in the previous 12 months, and assessed the level of current dyspnea compared to the best condition the patient had using the VAS scale (visual analogue scale) and performed chest X-ray, measured lung function by spirometry before and after nebulizing a dose of the short-acting bronchodilator of salbutamol/ipratropium combination. Data were recorded on a unified data collection sheet. ***Results and discussion***: There were 183 patients in the study. The rate of using LABDs is 98.4%, ICS is 58.5%. The number of patients with frequent exacerbations is 74 (40.40%). The number of patients with at least 1 severe exacerbation hospitalized is: 60 (32.78%). The number of patients who used medication (including at least one of short-acting bronchodilators, long-acting bronchodilators, and corticosteroids) within 4 hours before examination was: 176 (96.17%). The average VAS score before medication was 4.26. The proportion of chest X-rays containing old tuberculosis lesions is 26 (14.20%). There is a significant correlation between VAS scores before, after medication and FEV_1 values before, after medication and the change is ≥12% compared to predicted value. There is a high rate, 46.15% of patients with old tuberculosis lesions being treated with ICS. High rate of BMI <19 kg/m^2 (27.30%). There is a positive correlation between BMI and %FEV_1 pred. value, underweight (BMI <19kg/m^2) was significantly associated with reduced %FEV_1 pred. before medication (p<0.001). ***Conclusion:*** On 183 patients being managed and treated, it shows that there are characteristics that need to be paid attention to in terms of drug use indications, treatment effectiveness and physical characteristics expressed through BMI. With the above characteristics of symptoms, respiratory function and exacerbation, it shows that individualized management and treatment is not required to reduce symptoms. This shows that it is very necessary to add short-acting bronchodilators to treatment. The VAS scale, an intuitive, easy-to-use assessment tool that has a

[1, 2, 3, 4] *Vietnam Lung Association*
[5] *Can Tho national Hospital*
[6] *Pham Ngoc Thach Hospital, Ho Chi Minh City*
[7] *National Lung Hospital*
Responsible person: Nguyen Van Thanh
Email: drthanhbk@gmail.com
Date of receipt: 11/9/2023
Date of scientific judgment: 9/10/2023
Reviewed date: 16/10/2023

significant correlation with the FEV_1 value, can be helpful for quickly assessing the patient's symptom control status in daily practice.

Keywords: *COPD treatment, short-acting bronchodilator, body mass index*

I. INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common respiratory disease. Global prevalence is about 10% and is affecting the health of about 380 million people [1], this number in Vietnam is about 4 million people over the age of 40 [2].

Early diagnosis and treatment are necessary to slow the progression of symptoms and reduce exacerbations. In addition to non-pharmacological therapies (nutrition, rehabilitation therapy), the basic COPD treatment medications are bronchodilators and inhalers that are preferred over oral medications. COPD is a chronic disease that requires regular use of bronchodilators to maintain the best possible ventilation, and bronchodilators are the foundational treatment in COPD. To date, treatment recommendation documents agree that inhaled corticosteroids should only be considered for combination treatment in cases with multiple exacerbations and blood eosinophilia >300/mm^3. The therapeutic goals for a managed and treated case are to reduce exacerbations, minimize respiratory symptoms and increase the patient's quality of life.

This study was conducted with the goal of reviewing patient characteristics and COPD treatment in patients being managed and guided for treatment at respiratory facilities in Vietnam and evaluating the short-term effectiveness of the fast-acting bronchodilators of salbutamol/ipratropium combination.

II. PATIENTS AND METHODS

Study design:

- Descriptive, cross-sectional, multicenter.
- Sites participating in the study: Hai Phong International Hospital, National Lung Hospital, Pham Ngoc Thach hospital (Ho Chi Minh City), Ngoc Minh General Clinic (Ho Chi Minh City), Can Tho National General Hospital.

Patients:

- Diagnosis of COPD is based on COPD diagnostic criteria according to GOLD report 2023 [3].
- Select convenient, random, consecutive samples of cases being managed and treated for at facilities participating in the study over a period of 30 days (from August 1, 2023 to August 31/2023).
- All patients enrolled in the study were asked about treatment history and exacerbations in the previous 12 months, and assessed the current level of dyspnea compared to the best condition the patient using a visual analog scale (VAS) after being explained and evaluated together with the examining doctor, performed chest X-ray, measured lung function by spirometry before and after inhalation of 1 dose of short-acting bronchodilator of salbutamol/ipratropium, reassessed the level of VAS after 30 minutes inhaling the drug. Data were recorded on a unified data collection sheet.
- Statistic: Descriptive statistics for baseline data were presented as percentage or mean and SD. We tested for correlation with Pearson rho coefficient. A p-value of <0.05 was considered to be statistically significant. Data management and statistical analyses were performed using SPSS statistics software (version 20).
- Ethics statement:

All subjects signed a written informed consent, and ethical approval was provided by the Scientific and Ethical Council of the Vietnam Lung Association. The authors confirm that the study was conducted in accordance with the Declaration of Helsinki.

III. RESULTS AND DISCUSSION

3.1. Patients'characteristics: There were 183 cases from 5 sites included in the study. Patient characteristics are summarized in table 1.

Table 1. ***Patients'characteristics***

	N= 183
Gender, n (%)	
- Male	178 (97,30)
- Female	5 (2,70)
Age in years; mean value (SD)	68,19 (8,11)
Currently being treated, n (%)	
- Regimen with LABDs	180 (98,40)
- Regimen with ICS	107 (58,5)
History of exacerbations in the previous 12 months	
- Average number of exacerbations/patient, mean value (SD)	1,37 (2,01)
- Number of patients with at least 1 severe exacerbation hospitalized, n (%)	60 (32,78)
- Number of patients with frequent exacerbation, n (%)	74 (40,40)
Patients used medication at home before going to the doctor, n (%)	176 (96,17)
BMI, n (%)	
- Number of patients <19kg/m^2 (low)	45 (24,60)
- Number of patients 20-25kg/m^2 } (not low)	133 (72,70)
- Number of patients >25kg/m^2 } (not low)	5 (2,70)
Chest X-ray, n (%)	
- There are signs of emphysema	112 (61,20)
- There are signs of old tuberculosis	25 (14,20)
Spirometry	
- %FVC pred. before nebulizing bronchodilator, mean value (SD)	80,26 (18,08)
- %FVC pred. after nebulizing bronchodilator, mean value (SD)	107,97 (12,32)
- %FEV_1 pred. before nebulizing bronchodilator, mean value (SD)	55,22 (18,63)
- %FEV_1 pred. after nebulizing bronchodilator mean value (SD)	59,88 (19,29)

3.2. Analyze patient characteristics, treatment characteristics and short-term effectiveness of short-acting bronchodilator combination of salbutamol/ipratropium

Table 2 shows some analysis of patient characteristics: correlation between low BMI and respiratory function (FVC, FEV_1), treatment characteristics (having residual lesions of old tuberculosis and ICS treatment) and short-term effectiveness of short-acting bronchodilators on VAS score 30 minutes after nebulizing bronchodilators, change in %FVC pred. value. and %FEV_1 pred. 30 minutes after nebulizing bronchodilators.

Table 2. ***Analysis of patient characteristics, treatment characteristics and short-term effectiveness of short-acting bronchodilators***

Variables	Results	p-value
ICS treatment/patients with old tuberculosis sequelae, n (%)	12 (46,15)	-
Compare VAS scores before medication and after medication, mean value (SD)	4,25 (1,66) vs 3,18 (1,60)	0,0001
Correlation between BMI and %FEV_1 pred. before medication, pearson correlation coefficient	0,187	0,001
Compare the %FEV_1 pred. value before medication between low BMI and not low BMI groups (mean value, SD)	48,90 (15.30) vs 57,35 (18,68)	0,001
Compare the %FEV_1 pred. value after medication between low BMI and not low BMI groups (mean value, SD)	55,84 (16,13) vs 61,20 (20,10)	0,10
Compare %FVC values pred. before and after medication (mean value, SD)	80,26 (18,08) vs 107,97 (12,32)	0,0001
Compare %FEV_1 values pred. before and after medication (mean value, SD)	55,22 (18,63) vs 59,88 (19,29)	0,0001
Correlation between VAS score before medication and %FEV_1 pred. before medication (pearson correlation coefficient)	R= -0,169	0,01
Correlation between VAS score after medication and %FEV_1 pred. before medication (pearson correlation coefficient)	R= -0,135	0,03

Table 1 presents the characteristics of COPD patients being managed and treated with the following highlights: the great majority are men (97.30%). VAS score at an unacceptable level (≥ 5 points) is 25.70%. The number of patients being treated with inhaled corticosteroids (ICS) accounts for a high rate of 58.50%, however, compared to the 2018 ENHANCE study, also in these study facilities, 92.7% of patients were recorded. In patients receiving ICS-containing regimens [2], this rate has decreased significantly. The average number of exacerbations/patient/year in the study was 1.37. This number of exacerbations is higher than in a 2015 UK study, which was 0.89 [3]. According to the classification of more or less exacerbations in the GOLD document [3], the proportion of patients with frequent exacerbations in the study was 40.40%. Although this rate is still high compared to world medical literature [4], it has decreased much compared to that recorded from the ENHANCE study as cited above, which is 77.3% in records with a history of the attack [2]. Notably, the proportion of patients with at least 1 acute episode of exacerbation requiring hospitalization in the previous 12 months in this study was 32.78%. This rate is also higher than the UK study as cited above, which was 22.6% [3]. The number of patients with sequelae of old tuberculosis lesions on chest X-ray in the study was

14.2%. This rate is equivalent to a study in Turkey (2016) of 15.5% [5]. However, it should be noted that among 26 patients with old pulmonary tuberculosis sequelae on X-ray, 12 patients (46.15%) are receiving maintenance treatment with a regimen containing ICS.

This is probably the first study on the short-term effectiveness of the combination drug SAMA/SABA on COPD patients in Vietnam. Analysis of the use of short-acting drugs in COPD, Table 2 shows that short-acting bronchodilator combination have very good effects on VAS scores (significant improvement in VAS scores, p <0.0001) and lung function (significant improvement in %FVC pred. value and $\%FEV_1$ pred. value, p<0.0001) especially when this effect was seen in a study population that was being treated and had using at least one respiratory medication (bronchodilator and/or corticosteroid) at home before measuring lung function was 96.17%. A very interesting thing, in this study, is that the VAS score (a subjective variable based on questionnaire) has a significant correlation with the $\%FEV_1$ pred. (an objective measured value) both before and after using the bronchodilator nebulizing. Similarly, the VAS score had a significant negative correlation with the $\%FEV_1$ value pred. and before and after the drug. This shows that the VAS score (an easy-to-use visual scale) can be used to evaluate a patient's symptom control status in daily practice.

BMI is considered an indicator of nutritional status and has been studied extensively in COPD. Many studies have identified that BMI has a correlation with lung function and exacerbations [1]. In this study (table 2), it was shown that BMI has a significant positive correlation with the $\%FEV_1$ pred. value before bronchodilator bibulating. Besides, in this study, the rate of underweight (BMI < 19kg/mm^2) was 24.60% while the rate of overweight (BMI > 25kg/m^2) was only 2.70%. These rates are very different from those recorded from BMI studies on COPD patients from the world medical literature, the rate of underweight is lower and the rate of obesity is much higher. In the PLATINO study conducted in 5 Latin American countries [6], only 7% of patients were underweight, while 64% of patients were overweight and obese. A study in China [7] also showed similar results, the rate of underweight was 7.80% and the rate of overweight and obesity was 46.08%. In a meta-analysis, Yilan Sun et al found that low BMI is a risk factor for accelerated decline in lung function [8]. In this study, it was found that BMI had a significant negative correlation with $\%FEV_1$ pred. value (p=0.001) and patients in the low BMI group had $\%FEV_1$ pred. value before medication was significantly lower than the non-low BMI group (p=0.001). Some studies conducted in Vietnam have also made similar comments [9,10]. If the data in our study truly reflects the nutritional status of COPD patients in Vietnam, this is a very different point and requires research to evaluate and have the necessary nutritional impacts for the patient in the treatment approach.

In discussing the short-term effectiveness of combined short-acting bronchodilators in this study, in the spirit of achieving maximum control of respiratory symptoms with medication, the study's authors propose an initial regimen and maintain COPD treatment with a foundation of long-acting bronchodilator maintenance combined with short-acting bronchodilators when needed. Figure 1. describes the approach that we

propose and medication adjustments during the process of monitoring and evaluating effectiveness based on the recommendations of the GOLD report 2023 [3]. The approaches should be with motto "as simple as possible" in evaluating and optimizing the use of medication to relieve patients' symptoms [12]. The best short-term bronchodilator is the combination SABA/SAMA.

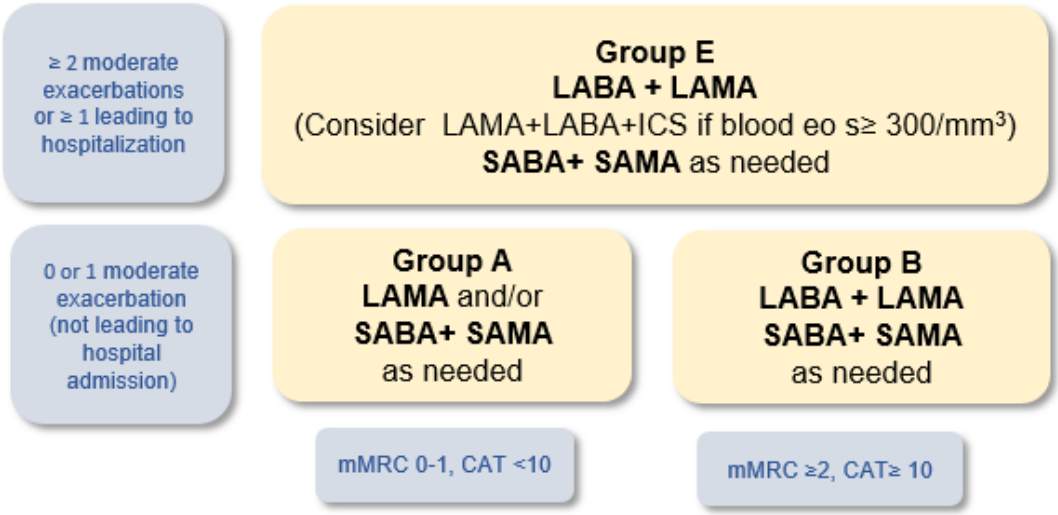

Figure 1. ***Initiation and maintenance of medication in COPD***
(drawn according to GOLD report 2023 [3] with modifications)

IV. CONCLUSION

On 183 patients being managed and treated, it has been shown that there are important characteristics that need to be noted in terms of drug use indications, treatment effectiveness and physical characteristics expressed through BMI.

The above characteristics of symptoms, lung function and exacerbation show that management and treatment are not maximally required to be individualized, especially to relieve symptoms. This shows that it is very necessary to add short-acting bronchodilators to treatment. The VAS scale, an intuitive, easy-to-use assessment tool that has a significant correlation with the FEV_1 value, can be helpful for quickly assessing the patient's symptom control status in daily practice. There is a need for better designed studies to evaluate exacerbations and treatment to reduce exacerbations, as well as to evaluate the level of malnutrition and the effectiveness of nutritional impact on COPD patients being managed in Vietnam.

REFERENCES

1. **Varmaghani M; Dehghani M; Heidari E; Sharifi F; Moghaddam SS; Farzadfar F.** Global prevalence of chronic obstructive pulmonary disease: systematic review and meta-analysis. East Mediterr Health J. 2019;25(1):47–57. https://doi.org/10.26719/emhj.18.014
2. **Vietnam Medical Association.** Guidelines for management and treatment of chronic obstructive pulmonary disease (COPD) Vietnam 2021. Medicine 2021.
3 **Global Initiative for Chronic Obstructive Lung Disease (GOLD) report 2023.** https://goldcopd.org/2023-gold 2023-2

3. **Lorcan McGarvey et al.** Characterisation of the frequent exacerbator phenotype in COPD patients in a large UK primary care population. Respiratory Medicine (2015) 109, 228-237
4. **Terence AR Seemungal et al.** Exacerbation rate, health status and mortality in COPD – a review of potential interventions. International Journal of COPD 2009:4 203–223
5. **Hakan Gunen et al.** The Role of TB in COPD. Poster (Chest annual meeting 2016). DOI: http://dx.doi.org/10.1016/j.chest.2016.08.956
6. **Maria Montes de Oca et al.** Chronic obstructive pulmonary disease and body mass index in five Latin America cities: The PLATINO study. Respiratory Medicine (2008) 102, 642–650
7. **Zhenchao Wu et al.** Body mass index of patients with chronic obstructive pulmonary disease is associated with pulmonary function and exacerbations: a retrospective real world research. J Thorac Dis 2018;10(8):5086-5099
8. **Yilan Sun et al.** BMI is associated with FEV1 decline in chronic obstructive pulmonary disease: a meta-analysis of clinical trials. Respiratory Research (2019) 20:236
9. **D. Hogan et al.** Nutritional status of Vietnamese outpatients with chronic obstructive pulmonary disease. Volume 30, Issue 1. February 2017. Pages 83-89.
10. **Uyen Phuong Truong et al.** Psychometric properties of Body Mass Index in screening malnutrition of COPD inpatients admitted at Nguyen Tri Phuong Hospital, Vietnam: a cross-sectional study. Med Pharm Res, 2021, Vol. 5, No. 3
11. **Ha Thanh nguyen et al.** Nutritional status, dietary intake, and health-related quality of life in outpatients with COPD. International Journal of COPD 2019:14 215–226
12. **Bartolome Celli, Jørgen Vestbo.** Simplifying pharmacotherapy for patients with COPD: a viewpoint. European Respiratory Journal 2023 62: 2300115; DOI: 10.1183/13993003.00115-2023.