

Original Research

EVALUATION TRIGGERS FOR EXACERBATION ACUTE CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS ADMITTED DEPARTMENT OF EMERGENCY MEDICINE THONG NHAT HOSPITAL

Le Bao Huy¹, Vu Dinh Chanh²

1. Thong Nhat Hospital, Ho Chi Minh City
2. Tam Anh General Hospital, Ho Chi Minh City

* Corresponding author: MSc. MD. Le Bao Huy; ✉ huylebao2005@gmail.com

ABSTRACT: Exacerbations of Chronic Obstructive Pulmonary Disease (COPD) lead to decline in lung function, quality of life, and increased costs and mortality. Identifying trigger factors for exacerbations, especially in elderly patients with comorbidities, is crucial due to limited research in Vietnam. To investigate trigger factors for COPD exacerbations in patients admitted to the Emergency Department of Thong Nhat Hospital, HCMC. A prospective, cross-sectional descriptive study was conducted on 95 patients admitted to the Emergency Department of Thong Nhat Hospital for COPD exacerbation from January 2020 to July 2020. The mean age was 75.39 years; 91.6% were male, and 60% of patients had ≥ 2 exacerbations per year. Common cardiovascular comorbidities included hypertension (85.3%) and coronary artery disease (41.1%). Multiple factors (cardiovascular disease, bronchiectasis, Asthma-COPD Overlap (ACO), smoking, non-compliance with treatment) were associated with more frequent and severe exacerbations. Importantly, infection and eosinophilia (≥ 300 cells/ μ L or $\geq 2\%$) were statistically significantly associated with exacerbations ($p < 0.05$). Patients with COPD exacerbation were predominantly elderly males, often with cardiovascular comorbidities. Infection and eosinophilia were factors statistically significantly associated with exacerbations.

Keywords: Acute dyspnea patients, EACOPD, Department of Emergency Medicine.

1. INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a serious public health problem, the fourth leading cause of death worldwide, with over 3 million deaths in 2012 [1]. A COPD exacerbation is defined as an acute worsening of respiratory symptoms requiring a change in treatment [2]. These are critical clinical events as they negatively impact health status, increase hospitalization and readmission rates, and accelerate disease progression.

Triggering factors for COPD exacerbations are diverse, primarily including respiratory viral infections, bacterial infections, and environmental factors such as air pollution [3]. Additionally, eosinophilic inflammatory responses [1], non-compliance with treatment, or even unknown causes can trigger exacerbations [3]. Patients with frequent COPD exacerbations experience faster lung function decline, lower quality of life, increased treatment costs, and higher mortality rates. Understanding, evaluating, and managing the triggering factors for COPD exacerbations is essential, especially in elderly patients with worsening conditions. In Vietnam, research on triggering factors for COPD exacerbations requiring emergency admission is limited. Recognizing this as a common condition in the Emergency Department of Thong Nhat Hospital, we conducted this study to investigate the triggering factors for COPD exacerbations, aiming to determine clinical and paraclinical characteristics, the prevalence of triggering factors, and their association with exacerbation severity. Therefore, we decided to conduct this study to investigate the triggering factors for COPD exacerbations in patients admitted to the Emergency Department of Thong Nhat Hospital with the following objectives:

- + Investigate the clinical and paraclinical characteristics of patients experiencing COPD exacerbations.

- + Determine the prevalence and combination of triggering factors in patients experiencing COPD exacerbations.

- + Investigate the association between triggering factors and the severity of COPD exacerbations

2. SUBJECTS AND RESEARCH

METHODS

2.1. Research Subjects

Patients diagnosed with COPD exacerbation admitted to the Emergency Department of Thong Nhat Hospital from January 2020 to July 2020.

Inclusion Criteria:

Acute dyspnea: Patients with acute dyspnea symptoms (respiratory rate >20 or <10 breaths/min, abnormal breathing pattern, use of accessory respiratory muscles, cyanosis, sweating, altered consciousness, SpO₂ < 90%)

And Anthonisen criteria for exacerbation (Increased dyspnea, increased sputum volume, purulent sputum; having 1 of these 3 symptoms plus 1 of the following signs: respiratory tract infection within the previous 5 days, fever without other cause, increased cough or wheezing, increased heart rate or respiratory rate by 20% compared to baseline). Patients were divided into 3 groups (mild, moderate, severe).

Exclusion Criteria: Patients who declined to participate or did not meet the sampling criteria.

2.2. Research Method

A descriptive cross-sectional study using convenience sampling was performed. Data were collected using a standardized medical record: age, gender, medical history, cough symptoms, dyspnea, sputum color change, peripheral edema, crackles, atrial fibrillation, lung consolidation, pleural effusion, pneumothorax, and triggering factors.

2.3. Data Processing

Data were analyzed using SPSS 20.0 software. Quantitative variables are presented as mean ± standard deviation (Mean ± SD), qualitative variables as frequency and percentage (%). Chi-square test (*) and T-test (#) were used to compare characteristics between groups, with P < 0.05 considered statistically significant.

3. RESULTS

From January 2020 to July 2020, 95 COPD patients admitted for exacerbation met the inclusion criteria.

3.1. General Characteristics of the Study Subjects

Table 1. General Characteristics of the Study Subjects

Characteristic	Overall N=95 (%) (Mean ± SD)	Group 1 (Mild) N=21 (%) (Mean ± SD)	Group 2 (Moderate) N=65 (%) (Mean ± SD)	Group 3 (Severe) N=9 (%) (Mean ± SD)	P-value
Age	75,39 ± 10,76	76,43 ± 12,75	75,43 ± 10,64	72,67 ± 6,08	0,684#
Gender, n (%)					
Male	87 (91,6)	19 (21,8)	61 (70,2)	7 (8,0)	0,261*
Female	8 (8,4)	2 (25,0)	4 (50,0)	2 (25,0)	
Exacerbations/year, n (%)					
0 – 1	38 (40,0)	10 (26,3)	26 (68,4)	2 (5,3)	0,429*
≥ 2	57 (60,0)	11 (19,3)	39 (68,4)	7 (12,3)	
Comorbidities, n (%)					
Hypertension	81 (85,3)	18 (22,2)	57 (70,4)	6 (7,4)	0,248
Heart Failure	15 (15,8)	3 (20,0)	10 (66,7)	2 (13,3)	0,851
Coronary Artery Disease	39 (41,1)	10 (25,6)	25 (64,1)	4 (10,3)	0,742
Diabetes Mellitus	20 (21,1)	3 (15,0)	15 (75,0)	2 (10,0)	0,689
Chronic Kidney Disease	4 (4,2)	2 (50,0)	2 (50,0)	0 (0,0)	0,355
Dyslipidemia	12 (12,6)	2 (16,7)	9 (75,0)	1 (8,3)	0,865
Osteoporosis	1 (1,1)	0 (0,0)	1 (100)	0 (0,0)	0,792
Alcoholism	1 (1,1)	0 (0,0)	0 (0,0)	1 (100)	0,008
Liver Cirrhosis	1 (1,1)	0 (0,0)	1 (100)	0 (0,0)	0,792
History of Pulmonary TB	12 (12,6)	2 (16,7)	6 (50,0)	4 (33,3)	0,01
IV Antibiotics in last 90 days	13 (13,7)	1 (7,7)	9 (69,2)	3 (23,1)	0,113

* Chi-square Test, # T-test

The mean age of patients was 75.39 ± 10.76 years. Males constituted the majority with 87 patients (91.6%), while females comprised only 8 patients (8.4%). Most patients (60%) had a history of ≥2 exacerbations/year. Hypertension was the most common comorbidity (85.3%), followed by coronary artery disease (41.1%) and heart failure (15.8%). History of previous pulmonary TB (12.6%) and alcoholism (1.1%) were also noted, with alcoholism showing a statistically significant association (p = 0.008) with exacerbation severity.

3.2. Clinical and Paraclinical Characteristics

All 95 patients had acute dyspnea symptoms (100%). Increased sputum volume was recorded in 75 patients

(78.9%), and sputum color change in 35 patients (36.8%). Vital signs such as temperature, heart rate, respiratory rate, and SpO2 showed statistically significant differences between severity groups. Specifically, the severe exacerbation group had significantly higher temperature (37.40 ± 0.67 °C), heart rate (115.44 ± 18.58 beats/min), and respiratory rate (30.00 ± 7.46 breaths/min), while SpO2 (83.44 ± 9.41%) was lower compared to other groups (p < 0.05).

Regarding paraclinical findings, mean white blood cell count and CRP were elevated in the severe exacerbation group (WBC: 13.31 K/μL, CRP: 46.15 mg/L), with statistical significance (p < 0.05). Elevated eosinophils (≥ 2%) were noted in 40% of the total patients, primarily concentrated in the moderate exacerbation group (71.1%), showing statistical significance

Bảng 2: Đặc điểm lâm sàng của đối tượng nghiên cứu

Clinical Feature	Overall N=95 (%) (Mean ± SD)	Group 1 (Mild) N=21 (%) (Mean ± SD)	Group 2 (Moderate) N=65 (%) (Mean ± SD)	Group 3 (Severe) N=9 (%) (Mean ± SD)	
Temperature (°C)	36,97±0,55	36,82±0,49	36,96±0,53	37,40±0,67	0,031
Heart Rate (beats/min)	100,25±18,92	96,67±16,56	99,31±18,96	115,44±18,58	0,033
Respiratory Rate (breaths/min)	26,19±5,69	23,76±5,38	26,45±5,24	30,00±7,46	0,017
Systolic BP (mmHg)	133,05±24,30	130,0±24,49	131,62±22,43	150,56±32,06	0,072
Diastolic BP (mmHg)	78,11±12,14	76,19±9,73	77,00±11,71	90,56±14,24	0,004
SpO2 (%)	89,85±6,79	93,38±2,80	89,60±6,66	83,44±9,41	0,001
Cough, n (%)	86 (90,5)	19 (22,1)	60 (69,8)	7 (8,1)	0,378
Increased Sputum, n (%)	75 (78,9)	16 (21,3)	53 (70,7)	6 (8,0)	0,556
Sputum Color Change, n (%)	35 (36,8)	7 (20,0)	24 (68,6)	4 (11,4)	0,952
Dyspnea, n (%)	95 (100,0)	21 (22,1)	65 (68,4)	9 (9,5)	0,367
Chest Pain, n (%)	15 (15,8)	2 (13,3)	10 (66,7)	3 (20,0)	0,258
Crackles, n (%)	30 (31,6)	4 (13,3)	22 (73,3)	4 (13,3)	0,306

* Chi-square Test, # T-test

Table 3. Paraclinical Characteristics of the Study Subjects

Clinical Feature	Overall N=95 (%) (Mean ± SD)	Group 1 (Mild) N=21 (%) (Mean ± SD)	Group 2 (Moderate) N=65 (%) (Mean ± SD)	Group 3 (Severe) N=9 (%) (Mean ± SD)	P-value
Chest X-ray, n(%)					
Pulmonary Infiltrate	36 (37,9)	4 (11,1)	27 (75,0)	5 (13,9)	0,094
Pneumothorax	2 (2,1)	0 (0,0)	1 (50,0)	1 (50,0)	0,129
Pleural Effusion	8 (8,4)	1 (12,5)	6 (75,0)	1 (12,5)	0,777
Atelectasis	3 (3,2)	0 (0,0)	3 (100,0)	0 (0,0)	0,489
Complete Blood Count					
WBC (K/uL)	9,72±3,71	9,14±2,67	9,41±3,03	13,31±7,39	0,008
Eosinophil (K/uL)	0,69±1,37	0,95±1,63	0,66±1,37	0,39±0,45	0,542
EOS < 2%	57 (60%)	10 (17,5%)	38 (66,7%)	9 (15,8%)	0,025
EOS ≥ 2%	38 (40%)	11 (28,9%)	27 (71,1%)	0 (0%)	
RBC (M/uL)	4,39±0,63	4,20±0,45	4,42±0,64	4,62±0,78	0,201
HGB (g/dL)	14,10±8,60	12,83±1,12	14,62±10,36	13,26±1,23	0,678
Biochemistry					
Glucose (mmol/L)	7,39±2,67	6,92±2,13	7,31±2,75	8,92±2,80	0,166
CRP (mg/dL)	19,57±30,91	15,80±25,31	16,96±29,63	46,15±41,54	0,035
Urea (mmol/L)	5,95±3,80	7,30±6,71	5,64±2,47	5,07±1,15	0,170
Creatinine (µmol/L)	94,80±40,5	101,10±73,8	92,22±24,71	98,79±25,29	0,656
Na+ (mmol/L)	136,22±4,15	135,81±4,47	136,29±3,82	136,67±5,94	0,851
K+ (mmol/L)	4,14±3,36	3,83±0,95	4,32±4,02	3,53±0,40	0,720
Arterial Blood Gas					
PaO2 (mmHg)	123,43±61,4	130,14±85,69	117,71±56,50	148,82±51,57	0,346
PaCO2 (mmHg)	47,74±16,74	46,47±12,62	45,54±15,22	54,26±27,63	0,356
PaO2/FiO2	385,62±177,3	519,22±274,3	356,52±143,7	382,10±134,0	0,014

Phép kiểm T-test, * Phép kiểm chi bình phương

(p = 0.025). PaO2/FiO2 also showed a significant difference between groups (p = 0.014), reflecting more severe respiratory failure in the severe exacerbation group.

Bảng 4. Mối liên quan giữa các yếu tố thúc đẩy với độ nặng ở bệnh nhân đợt cấp COPD

Triggering Factor	Overall N=95 (%) (Mean ± SD)	Group 1 (Mild) N=21 (%) (Mean ± SD)	Group 2 (Moderate) N=65 (%) (Mean ± SD)	Group 3 (Severe) N=9 (%) (Mean ± SD)	P-value
Smoking, n (%)	48 (50,5)	12 (25,0)	30 (62,5)	6 (12,5)	0,406
Non-compliance with treatment, n (%)	1 (1,1)	1 (1,1)	0 (0,0)	0 (0,0)	0,169
Infection, n (%)	65 (68,4)	10 (15,4)	46 (70,8)	9 (13,8)	0,014
EOS (≥ 300/uL or ≥ 2%)	38 (40,0)	11 (28,9)	27 (71,1)	0 (0,0)	0,025
Comorbidities, n (%)					
Hypertension	81 (85,3)	18 (22,2)	57 (70,4)	6 (7,4)	0,248
Heart Failure	15 (15,8)	3 (20,0)	10 (66,7)	2 (13,3)	0,851
Coronary Artery Disease	39 (41,1)	10 (25,6)	25 (64,1)	4 (10,3)	0,742
Arrhythmia (Atrial Fibrillation)	7 (7,4)	1 (14,3)	4 (57,1)	2 (28,6)	0,196
Bronchiectasis	3 (3,2)	0 (0,0)	2 (66,7)	1 (33,3)	0,287
ACO	8 (8,4)	3 (37,5)	4 (50,0)	1 (12,5)	0,483

ACO: Asthma COPD Overlap; EOS: Eosinophil

3.3. Association between Triggering Factors and Severity in COPD Exacerbation Patients

The study indicated that infection and elevated eosinophil count (≥ 300/μL or ≥ 2%) were statistically significantly associated with COPD exacerbation (p < 0.05). Infection was the most common triggering factor, accounting for 68.4% of exacerbation cases. Elevated eosinophils were detected in 40% of exacerbation cases. Other factors such as smoking, non-compliance with treatment, comorbidities (hypertension, heart failure, coronary artery disease, bronchiectasis, ACO) did not show a statistically significant association with exacerbation severity in this study.

4. DISCUSSION

4.1. General Characteristics

Our study showed the mean age of patients with COPD exacerbation was 75.39 years, higher than previous studies in Vietnam and internationally, such as author Nguyen Thanh Hoi (2013) with a mean age of 68 and the study by Alberto Papi with a mean patient age of 70.6. Regarding gender, males accounted for 91.6%, more than 11 times higher than

females; similar to studies by Nguyen Thanh Hoi and Alberto Papi [4,5]. Regarding history, 60% of COPD patients had a history of ≥2 exacerbations/year, similar to the study by author Nguyen Quang Doi (53.3%) [6]. Patients with COPD exacerbations had cardiovascular comorbidities such as hypertension in 81 cases (85.3%), coronary artery disease in 39 cases (41.1%); heart failure in 15 cases (15.8%), higher than the study by author Sumitra Shantakumar with a history of hypertension at 40.1% and the study by author Hasegawa with a history of chronic coronary artery disease at 16% [7,8]. The differences in general characteristics mentioned above may be because our study was conducted at Thong Nhat Hospital, which primarily treats elderly patients with multiple cardiovascular diseases, mainly hypertension and chronic coronary artery disease. The presence of cardiovascular comorbidities in COPD patients is associated with increased mortality, poor outcomes, higher hospitalization rates, and lower quality of life [9].

4.2. Clinical and Paraclinical Characteristics

Acute dyspnea was the most prominent symptom, present in 100% of patients.

Increased sputum volume (78.9%) and sputum color change (36.8%) were also common, consistent with Anthonisen's triad. In the severe exacerbation group, vital signs such as temperature, heart rate, and respiratory rate were significantly higher, and SpO₂ was significantly lower ($p < 0.05$), reflecting more severe respiratory failure. According to author Giang Cam Nhung, SpO₂ < 88% increases the risk of severe disease by 8.5 times within 72 hours of admission [10]. Chest pain or tightness is a common complaint in elderly patients with heart or chronic lung disease but is non-specific. We recorded the frequency of chest pain/tightness distributed evenly among COPD exacerbation severity groups, with 15 cases accounting for 15.8%.

Regarding paraclinical findings, elevated mean blood leukocyte count and CRP in the severe exacerbation group were statistically significant ($p < 0.05$), suggesting an infectious state. Elevated eosinophils ($\geq 2\%$) were noted in 40% of patients, similar to the study by Hasegawa K. [8] Although mean PaCO₂ was highest in the severe exacerbation group (54.2 mmHg), there was no statistical significance between groups in this study ($p = 0.356$). However, PaO₂/FiO₂ showed a statistically significant difference ($p = 0.014$), indicating more severe gas exchange impairment in the severe group. The AP chest X-ray showed pulmonary infiltrates in 36 cases (37.9%), pneumothorax in 2 cases (2.1%) mainly in the moderate COPD group (1 case) and severe group (1 case), pleural effusion mainly in the moderate exacerbation group with 6 cases (75%), and atelectasis in 3 cases (100%) in the moderate exacerbation group.

4.3. Causes of COPD Exacerbation Onset

Infection was the most common cause of exacerbation onset in our study (68.4%), similar to the study by Alberto Papi (78% of exacerbations had detected viral and/or bacterial infection) and Nguyen Quang Doi (88.6% had infection) [5, 6]. These authors also indicated that infectious exacerbations often prolong hospital stays and cause more severe lung function decline.

Smoking was a triggering factor in 50.5% of patients in the study. This is a

major risk factor for the development and progression of COPD, causing faster lung function decline and higher mortality. Other studies also emphasize the association between smoking and COPD exacerbation [2].

Elevated eosinophil count ($\geq 300/\mu\text{L}$ or $\geq 2\%$) was detected in 40% of COPD exacerbation cases in the study. This is similar to the finding by Hasegawa K. et al. that COPD patients with blood eosinophilia have a higher frequency of hospitalization for COPD exacerbation [8].

Non-compliance with treatment in our study was recorded at only 1.1%, lower than the study by author Nguyen Quang Doi at 42.9%, and similar to author Tran Van Ngoc (5.95%) [6][11]. The effectiveness of inhaled medications is affected by patient adherence. Good adherence reduces the risk of hospitalization and death due to AECOPD. [6] Author Koehorst-ter Huurne showed that patients with suboptimal or excessive use of tiotropium had an increased risk of severe AECOPD, pneumonia, and higher mortality compared to patients using the medication optimally.[12] Author Phung Thi Thanh noted that non-compliant patients increased the risk of exacerbation by 3.3 times [13].

Bronchiectasis in our study was detected in 3.2% of patients with exacerbation. Some studies show an association between bronchiectasis and COPD, noting more frequent and severe exacerbations, longer hospital stays, impaired quality of life, and reduced survival [14].

In our study, the number of ACO cases was 8, accounting for 8.4% of exacerbations, and no difference was seen compared to the non-ACO group. This may be due to the very small number of ACO cases in our study. Author Le Thi Tuyet Lan, studying 300 patients with Asthma-COPD Overlap, showed that 82 (27.3%) patients were diagnosed with Asthma-COPD Overlap. 28.3% of ACO patients had a history of exacerbations in the past year, with an average of 2 exacerbations/year, an average hospital stay of 6.06 days/year, and an average emergency admission of 2.41 days/year. ACO group patients had many symptoms (mean CAT score 14.82; mean mMRC score 2.09) and a mean blood eosinophil count of 462 cells/ μL [15].

Cardiovascular comorbidities were common in COPD patients in our study, with hypertension in 81 cases (85.3%), heart failure in 15 cases (15.8%), coronary artery disease in 39 cases (41.1%), and atrial fibrillation in 7 cases (7.4%). According to the literature, cardiovascular disease, especially hypertension, is a common comorbidity in COPD patients. The presence of cardiovascular comorbidity in COPD patients is associated with increased mortality, poor outcomes, higher hospitalization rates, and lower quality of life, increasing the risk of frequent exacerbations [10] [13]. Acute decompensated heart failure can overlap with COPD exacerbation, and the presence of this comorbidity is an independent predictor of mortality. Atrial fibrillation can be a consequence or a triggering factor for COPD exacerbation [9].

5. CONCLUSION

The study of 95 patients at the Emergency Department of Thong Nhat Hospital showed that COPD exacerbation patients were predominantly elderly (mean age 75.39), with a high proportion of males (91.6%). Prominent clinical symptoms were acute dyspnea (100%), increased sputum volume (78.9%), and sputum color change (36.8%). Cardiovascular comorbidities were very common in COPD patients, particularly hypertension (85.3%), coronary artery disease (41.1%), and heart failure (15.8%).

The main triggering factors statistically significantly associated with COPD exacerbation were infection and elevated eosinophil count ($\geq 300/\mu\text{L}$ or $\geq 2\%$). Identifying and effectively managing these factors is crucial to improving prognosis and quality of life for COPD patients.

REFERENCES

[1] Vedel-Krogh S, Nielsen SF, Lange P, Vestbo J, Nordestgaard BG. Blood eosinophils and exacerbations in chronic obstructive pulmonary disease: the Copenhagen general population study. *Am J Respir Crit Care Med.* 2016;193(9):965-974.

[2] Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease: 2020 report. Available from: <https://goldcopd.org>

[3] Sapey E, Stockley RA. COPD exacerbations.

2: Aetiology. *Thorax.* 2006;61(3):250-258.

[4] Nguyễn TH, Phan TH. Nghiên cứu đặc điểm lâm sàng, X-quang phổi và kết quả khí máu của bệnh nhân có đợt cấp bệnh phổi tắc nghẽn mạn tính điều trị tại Trung tâm Hô hấp – Bệnh viện Bạch Mai. *Tạp chí Lao và Bệnh phổi.* 2013;(15).

[5] Papi A, Bellettato CM, Braccioni F, et al. Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. *Am J Respir Crit Care Med.* 2006;173(10):1114-1121.

[6] Nguyễn QĐ. Đặc điểm lâm sàng, cận lâm sàng tắc động mạch phổi ở bệnh nhân đợt cấp bệnh phổi tắc nghẽn mạn tính, Trường Đại học Y Hà Nội; 2019.

[7] Shantakumar S, Pwu RF, D'Silva L, et al. Burden of asthma and COPD overlap (ACO) in Taiwan: a nationwide population-based study. *BMC Pulm Med.* 2018;18(1):1-12.

[8] Hasegawa K, Camargo CA Jr. Prevalence of blood eosinophilia in hospitalized patients with acute exacerbation of COPD. *Respirology.* 2016;21(4):761-764.

[9] Müllerová H, Shukla A, Hawkins A, Quint J. Risk factors for acute exacerbations of COPD in a primary care population: a retrospective observational cohort study. *BMJ Open.* 2014;4(12):e006171.

[10] Giang CN, Cao TMTh. Khảo sát một số yếu tố tiên lượng đợt cấp COPD tại Bệnh viện Đa khoa Trung ương Cần Thơ. *Tạp chí Y Dược học Cần Thơ.* 2023;56:94-100.

[11] Trần VN, Mã VĐ. Đặc điểm lâm sàng và yếu tố thúc đẩy vào đợt cấp bệnh phổi tắc nghẽn mạn tính nhập viện thường xuyên ở nhóm nguy cơ cao. *Tạp chí Y học TP. Hồ Chí Minh.* 2018;22(2):186-193.

[12] Koehorst-ter Huurne K, Groothuis-Oudshoorn CGM, Vandervalk PDLPM, Movig KLL, van der Palen J, Brusse-Keizer M. Association between poor therapy adherence to inhaled corticosteroids and tiotropium and morbidity and mortality in patients with COPD. *Int J Chron Obstruct Pulmon Dis.* 2018;13:1683-1690.

[13] Phùng TT. Yếu tố nguy cơ gây đợt cấp COPD ở Trung tâm Hô hấp, Bệnh viện Bạch Mai. *Tạp chí Y học Việt Nam.* 2022;(1):100-104.

[14] Martinez-Garcia MA, Miravittles M. Bronchiectasis in COPD patients: more than a comorbidity? *Int J Chron Obstruct Pulmon Dis.* 2017;12:1401-1411.

[15] Lê TTL, Ngô QC. Nghiên cứu về thực trạng bệnh phổi tắc nghẽn mạn tính chồng lấp hen tại Việt Nam. *Tạp chí Y học Lâm sàng.* 2017;(99):253-260.