

# FACTORS ASSOCIATED WITH FREQUENT HOSPITALIZATION IN PATIENTS WITH ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN VIET NAM

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*Acute exacerbations of chronic obstructive pulmonary disease (AE-COPD) increase hospitalization and death rates, impair quality of life, and increase the burden of morbidity and treatment costs. The prevention of AE-COPD is considered an important goal in the management of COPD. Identifying patients who are more likely to experience acute exacerbations and provide appropriate treatment not only avoid hospitalization but also slow the progression of the disease. Due to its importance, there is a special interest in understanding the factors associated with hospitalization. However, to date, in Vietnam, there have been few studies on risk factors for frequent hospitalization in patients with COPD exacerbations. Therefore, we conducted this study to determine the risk factors associated with frequent hospitalization due to COPD exacerbation. 109 patients, admitted to the hospital with AE-COPD, were enrolled in the study. Data on clinical and subclinical symptoms, history of smoking, and vaccinations were collected. Three factors: "hypertension", "high CAT score" and "high tobacco consumption" were all found to be significant risk factors for frequent hospitalization. Influenza vaccination is one factor that reduces the risk of hospitalization. Therefore, it is necessary to advise patients on smoking cessation, receive the influenza vaccine, and properly manage comorbidities such as hypertension to avoid hospitalization.*

**Keywords:** COPD, Acute exacerbation, Hospitalization, Risk factors

## I. INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide.<sup>1</sup> Currently, COPD is the fourth leading cause of death in the world,<sup>2</sup> but it is predicted to be the third leading cause of death by 2020.<sup>3</sup> COPD is complicated by frequent and recurrent acute exacerbations (AEs), which are associated with increased morbidity and mortality and significantly affect the socioeconomic status of patients. There is a correlation between frequent severity

and impaired quality of life (QoL) and a faster decline in lung function over time. In addition, severe exacerbation requiring admission is relevant to the direct cost of treating COPD.<sup>4</sup> The prevention of acute exacerbations of chronic obstructive pulmonary disease (AE - COPD) is considered an important goal in the management of COPD.<sup>5</sup> Identifying patients who are more likely to experience acute exacerbation and treat them appropriately not only avoid hospitalization but also slow the progression of the disease. The available studies have mostly focused on risk factors for admission of stable COPD patients,<sup>6,7</sup> external factors (such as air pollution)<sup>8</sup> and hospitalization or risk factors for hospital mortality.<sup>9</sup> Observational studies with different designs have evaluated risk factors

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for hospitalization due to COPD. Percentage of predicted FEV1,<sup>10</sup> previous hospital admission,<sup>11</sup> systemic corticosteroids,<sup>6,12</sup> co-morbidities,<sup>13</sup> low body mass index (BMI),<sup>7</sup> lack of influenza vaccination<sup>14</sup> were all associated with an increased risk of both admission and re-admission to the hospital. However, to date, we could not find any research on risk factors for frequent hospitalization in patients with acute exacerbations of COPD in Vietnam. The objectives of this study were to assess the risk factors that may be associated with frequent hospitalization in patients with COPD exacerbation at the Respiratory Center of Bach Mai Hospital in Hanoi, Vietnam.

## II. METHOD

### 1. Subject

A cross-sectional, observational study was conducted to identify factors associated with hospitalization in patients with AE - COPD. A total of 109 COPD patients admitted to the Respiratory Center of Bach Mai hospital due to acute exacerbations were recruited in this study.

#### *Inclusion criteria*

Patients diagnosed with AECOPD according to guidelines for diagnosis and treatment of chronic obstructive pulmonary disease of Vietnam Ministry of Health (2018):

- Symptoms: dyspnea (progressive over time; characteristically worse with exercise; persistent), chronic cough (may be intermittent and may be unproductive; recurrent wheeze), chronic sputum pattern production (any pattern of chronic sputum production may indicate COPD);

- Exposure to risk factors: Smoking tobacco, pipe tobacco, environmental pollution inside and outside the house, exposure to smoke, gas and dust.

- Measurement of ventilation function for definite diagnosis FEV1 / FVC <70% after bronchial recovery test.

- Symptoms of acute episodes according to Anthonisen (1987): Increased shortness of breath; increased sputum amount; changing the color of sputum, sputum changes into purulent sputum.

#### *Non-inclusion criteria*

Patients who were in an acute state of respiratory failure and/or have mental illnesses.

#### *Sampling method*

A convenient sampling method was adopted due to the time limit of the research. We have collected all hospitalized patients due to exacerbation COPD in 2 consecutive months.

#### *Research process*

We collected patient's data from medical records to determine the eligibility of participants for the research. The clinical and demographic characteristics of all the patients were recorded, including age, gender, years since diagnosis of COPD, treatments and vaccinations, smoking status, length of previous hospitalization and comorbidities. Face-to-face interviews were only carried out when patients overcame the acute stage of their exacerbation and their health condition was relatively stable. The questionnaires were administered with the support of a member of the research team.

#### *Research variables*

- Age
- Gender
- Body mass index: the weight in kilograms divided by the square of the height in meters, a measure of body fat that gives an indication of nutritional status. In Asia, commonly accepted BMI ranges are underweight (under 18.5 kg/m<sup>2</sup>), normal weight (18.5 to under 23), overweight ( $\geq 23$ )
- Smoking history: pack-years

- Vaccinations (influenza, pneumococcal)
- Co - morbidities.
- Number of follow - up per year.
- Duration of COPD (years)
- CAT score, mMRC grade: Clinical symptoms are assessed by one of the following scoring tools: the COPD Assessment Test (CAT) or the modified British Medical Research Council (mMRC).

When assessing the severity of symptoms according to CAT: 0 - 10 points: mild effect; 11 - 20 points: average effect; 21 - 30 points: severe effects; 31 - 40 points: very serious.

Severity of dyspnea can be assessed by the mMRC tool (Modified Medical Research Council Scale).

- Grade 0: Difficulty breathing upon exertion.
- Grade 1: Difficulty breathing when going fast or on the slope.
- Grade 2: Difficulty breathing, walking slower than people of the same age
- Grade 3: Difficulty breathing when walking 100m.
- Grade 4: Shortness of breath even without exertion (changing clothes)
- Type of exacerbation: According to Anthonisen:
  - Severe levels: difficulty breathing increases, the amount of sputum increases and phlegm changes into purulent sputum.
  - Average level: there are 2 out of 3 symptoms of severity.
  - Mild degree: there is one of the symptoms of severity and other symptoms: cough, unexplained fever, upper respiratory tract infection for 5 days, increased breathing rate, increased heart rate > 20% compared to the beginning.

● Total number of exacerbations in the last 12 months = hospitalized exacerbation + non - hospitalized exacerbation.

- GOLD 2018 classification: A, B, C, D:
  - Group A - Low risk, few symptoms: 0 to 1 exacerbation in the past 12 months (exacerbation and no use of antibiotics, corticosteroids) and mMRC 0 - 1 or CAT < 10.
  - Group B - Low risk, many symptoms: 0 to 1 exacerbation in the past 12 months (exacerbation, no antibiotics, corticosteroids) and mMRC ≥ 2 or CAT ≥ 10 points.
  - Group C - High risk, few symptoms: ≥ 2 exacerbations in the last 12 months (or 1 severe exacerbation or hospitalization) and mMRC 0 - 1 or CAT score <10.
  - Group D - High risk, many symptoms: ≥ 2 exacerbations in the past 12 months or 1 exacerbation and mMRC ≥ 2 or CAT ≥ 10 points..
- Clinical and subclinical characteristics: Purulent sputum, neutrophils, FEV1%,....

## 2. Statistical analysis

All patients were divided into 2 groups:

- + Group 1: 1 time of hospitalizations due to AE - COPD in the previous 12 months.
- + Group 2: more than 1 time.

We defined frequent hospitalization (frequent exacerbator phenotype) as more than 1 hospitalization in a year (including this exacerbation); we did so because this definition coincides with the current criteria for frequent exacerbations of GOLD 2018.

We assessed statistical differences between groups using the chi - square test, where appropriate, for categorical variables. We used the Student's t test for the continuous variables.

The alpha error was set at 0.05, and all p values were bilateral. We conducted all statistical analyses using IBM SPSS Statistics version 20.0.

## 3. Ethical considerations

The purpose of the study was clearly explained to the participants and the

questionnaires were given to those willing to participate; the nature of the study was entirely voluntary. The participants were informed that they had the right to withdraw at any time they wanted without any negative consequences of their current treatment. All information was encoded without revealing the name and personal information. The study protocol was approved by the Institutional Review Board of the Bach Mai Hospital and Hanoi Medical University.

### III. RESULTS

We collected data of 143 admitted patients from 9/2018 to 11/2018; one hundred and nine patients met the research criteria. The sample was comprised of 91.7% males and 8.3% females. The demographic baseline characteristics of patients are shown in Table 1.

**Table 1. Sociodemographic and COPD - related characteristics (n = 109)**

Variables	Mean	SD	Min	Max
Age (years)	69.44	9.04	51	93
Body mass index (BMI)(kg/m <sup>2</sup> )	19.26	3.91	10.9	30.1
Number of pack - year	23.04	18.91	0	80
Duration of COPD in year	5.94	6.58	1	49
Number of follow - up per year	3.07	4.51	0	15
The number of hospitalizations due to AE - COPD	3.10	2.22	1	15
Category			N = 109	Percent
Age Group	Non - elderly (< 65 years)		32	29.4%
	Elderly (≥ 65 years)		77	70.6%
Sex	Male		100	91.7%
	Female		9	8.3%
BMI Group (kg/m <sup>2</sup> )	<18.5		49	45%
	18.5 - < 23		43	39.4%
	≥ 23		17	15.6%
Smoking status	Current smoker		8	7.3%
	Past smoker		90	82.6%
	Never smoker		11	10.1
Duration of COPD (year)	≤ 1 year		19	17.4
	2 - 5 years		55	50.5
	6 - 10 years		25	22.9
	> 10 years		10	9.2
The number of hospitalizations due to AE - COPD (include this exacebation)	< 2		25	22.9
	≥ 2		84	77.1

Type of exacerbation	Type 1 (Severe)	84	77.1
	Type 2 (Average)	15	13.7
	Type 3 (Mild)	10	9.2
mMRC grade	0	4	3.7
	1	23	16.5
	2	32	33.9
	3	41	37.6
	4	9	8.3
CAT score	Low ( $\leq 10$ )	27	24.8
	Medium (11 - 20)	24	22.0
	Severe (21 - 30)	52	47.7
	Very severe ( $> 30$ )	6	5.5
GOLD 2018	GOLD C	27	20.2
	GOLD D	82	79.8
Influenza - vaccination		35	32.1
Comorbidities		76	69.7

Most study patients were at old age 89.9% of the admitted patients had current or past smoking habit. The majority of them were past smokers but had quit since the diagnosis of COPD (82.6%), 10.1% of subjects were “never - smokers.” About half of the participants (50.5%) had had COPD for 2 - 5 years, 77.1% of patients had at least one admission and 57.8% of patients had at least two admissions due to AE - COPD in the previous 12 months. The majority of the patients with severe (CAT 21 - 30) and intermediate (CAT 11 - 20) impact to quality of life was 47.7% and 22.0%, respectively. The rate of patients who had influenza vaccination was only 32.1%.

A univariate analysis of each variable was carried out to determine the variables independent statistically significant association with frequent hospitalization. The results are shown in Table 2, 3 and 4.

**Table 2. Relation between sociodemographic characteristic and frequent hospitalization**

Total n = 109	Group 1	Group 2	p - value*
	(1 hospitalization) (n = 25)	(> 1 hospitalization) (n = 84)	
Factors	Mean (SD)		
Age	70.2 (9.6)	69.2 (8.9)	0.652
BMI (kg/m <sup>2</sup> )	18.8 (3.9)	19.6 (3.8)	0.539
Pack - years (tobacco)	14.7 (14.5)	25.5 (19.4)	0.011
Pack - years (pipe tobacco)	14.2 (15.1)	13.7 (16.9)	0.906

*p - value\*: Independent sample t - test*

There were statistically significant differences in pack - years of smoking tobacco between Group 1 and Group 2 ( $p = 0.011$ ). No association was found between age, BMI and pack - years of smoking pipe tobacco and the risk of frequent hospitalization due to acute exacerbation.

**Table 3. Relation between clinical characteristics of COPD exacerbations and frequent hospitalization**

Hospitalization		Group 1 (n = 25)		Group 2 (n = 84)		OR (95%CI)
		n	%	n	%	
Hypertension	No	20	31.2	44	68.8	3.6 (1.2 - 10.6)
	Yes	5	11.1	40	88.9	
Diabetes	No	24	24.7	73	75.3	3.6 (0.4 - 29.5)
	Yes	1	8.3	11	91.7	
Heart failure	No	24	26.1	68	73.9	5.6 (0.7 - 44.9)
	Yes	1	5.9	16	94.1	
Chronic cor pulmonale	No	21	23.1	70	76.9	1.1 (0.3 - 3.5)
	Yes	44	22.2	14	77.8	
Pneumococcal vaccination	No	24	23.5	78	76.5	1.8 (0.2 - 16.1)
	Yes	1	14.3	6	85.7	
Influenza vaccination	No	10	13.5	64	86.5	0.2 (0.08 - 0.54)
	Yes	15	42.9	20	57.1	
Factors		Mean (SD)				p - value*
Duration of COPD (years)		5.1 (5.4)		6.2 (6.9)		0.456
Number of follow - up per year		2.4 (3.9)		3.3 (4.7)		0.369
Number of exacerbations non - hospitalization		2.0 (2.8)		1.3 (1.7)		0.117
CAT score		16.8 ( 7.4)		21.7 (8.2)		0.009

*p - value\*:* Independent sample *t - test*;, OR = Odds ratio, CI = Confidence interval.

Patients with hypertension and high CAT score were at risk of frequent hospitalization; OR = 3.6 (95%CI = 1.2 - 10.6), and  $p - value = 0.009$ , respectively. In addition, influenza vaccination seemed to be a protective factor, reducing the risk of hospitalization due to acute exacerbations (OR = 0.2, 95% CI = 0.08 - 0.54).

**Table 4. Relation between subclinical characteristics of COPD exacerbations and frequent hospitalization.**

Hospitalization		Group 1 (n = 25)		Group 2 (n = 84)		OR (95%CI)
		n	%	n	%	
Leukocytes (G/L)	< 10	11	19	47	81	0.62 (0.25 - 1.52)
	≥ 10	14	27.5	37	72.5	
PaCO <sub>2</sub> (mmHg) (n = 103)	< 45	18	26.1	51	73.9	2.05 (0.69 - 6.09)
	≥ 45	5	14.7	29	85.3	
ECG	Normal	13	20	52	80	0.67 (0.27 - 1.64)
	Abnormal	12	27.3	32	72.7	
Emphysema on chest X - ray	No	14	23.3	46	76.7	1.05 (0.43 - 2.58)
	Yes	11	22.9	38	77.1	

We found no relation between subclinical characteristics of COPD exacerbations and frequent hospitalization.

**Table 5. Risk factors associated with hospitalization due to AE - COPD**

Variables	*P - value	*OR	95%*CI
Hypertension	0.062	3.186	0.943 - 10.771
Influenza - vaccination	0.009	0.233	0.078 - 0.693
High tobacco consumption	0.022	1.042	1.006 - 1.078
High CAT score	0.025	1.076	1.009 - 1.147

\*P - value: Binary logistic regression, OR = Odds ratio, CI = Confidence interval.

From the results of Table 5, we found that factors associated with a high risk of frequent hospitalization due to COPD exacerbation were high tobacco consumption (p = 0.022, OR = 1.042), and high CAT score (p = 0.025, OR = 1.076).

Influenza vaccination is a protective factor, reducing the risk of hospitalization due to acute exacerbations (p = 0.009, OR = 0.233). There was no relationship between hypertension and the risk of frequent hospitalization due to COPD exacerbation in the binary logistic regression analysis.

#### IV. DISCUSSION

The purpose of this study was to determine the risk factors associated with hospitalization due to AE - COPD. In this study, three factors: “high CAT score”, “hypertension, and “high tobacco consumption” were all found to be significant risk factors of frequent hospitalization.

Co - morbidity was an important factor.<sup>15,16</sup> 69.7% of patients had at least one co - morbid disease, mainly hypertension (41.3%), chronic cor pulmonale (16.5%), heart failure (15.6%), and diabetes (11%).



Advanced age, smoking are risk factors for COPD as well as many other diseases. Therefore, patients with COPD often have co - morbidities. Common co - morbidities include cardiovascular, musculoskeletal dysfunction, hardened metabolic syndrome, osteoporosis, depression, and bronchial cancer. Cardiovascular comorbidity is common among COPD patients. In an Italian study of hospitalized AECOPD patients, 55% had arterial hypertension, 27% had chronic heart failure, and 17% had ischemic heart disease.<sup>17</sup> Our study also showed that 69.7% of patients had at least one co - morbid condition, of which the proportion of patients with hypertension accounted for the highest rate (41.3%). In our study, patients with a history of hypertension are at risk of frequent hospitalization. Patients with chronic hypercapnia, and hence raised actual bicarbonate, are probably more symptomatic than normocapnic patients because of their rapid and shallow breathing pattern,<sup>18</sup> resulting in an earlier and more frequent need for medical attention. Therefore, the treatment and management of co - morbidities, especially hypertension, are also one of the issues that need attention in the treatment and management of COPD patients to reduce the risk of hospitalization.<sup>19</sup>

High CAT scores are also a risk factor for hospitalization. A change of  $\leq 4$  points in the CAT score at discharge compared to that obtained at admission due to severe exacerbation of COPD, helps to predict therapeutic failure such as a new exacerbation, readmission or death in the subsequent three months.<sup>20</sup> High CAT score can be used to make the decision of hospitalization from the emergency department in acute exacerbations of COPD.<sup>21</sup>

The negative association between current smoking and hospital admission was explained

by Anthonisen<sup>22</sup> in that many patients with COPD spontaneously quit smoking in response to their symptoms and disability, and these patients do not do well afterward. For this reason, studies of patients with well - established disease have often not shown a reduction in admission with smoking cessation. Therefore, it is possible that the risk of hospitalization is more accurately reflected by the years spent smoking. Our results have shown an association between an increase in pack - years of smoking tobacco and the risk of frequent hospitalization ( $p = 0.005$ ,  $OR = 1.057$ ).

In addition, we found that Influenza vaccination is one factor that reduces the risk of hospitalization. Research by Nichol et al shows that the influenza vaccination was associated with fewer hospitalizations for pneumonia and influenza (adjusted risk ratio, 0.48 [95% CI, 0.28 to 0.82]) and with a lower risk for death (adjusted odds ratio, 0.30 [CI, 0.21 to 0.43]) during the influenza seasons.<sup>14</sup> Therefore influenza vaccination is essential for COPD patients.<sup>23</sup> No association was found between pneumococcal vaccination and the risk of frequent hospitalization due to exacerbation. It is possible that the number of patients with pneumococcal vaccination in our research sample was too small, with only 7 patients, accounting for 6.4%.

A major drawback of this study is the lack of pulmonary function data as an assessment of severity. The role of forced expiratory volume in 1 sec (FEV1) and in predicting hospital utilization is controversial.<sup>24,25</sup> Most previous studies on COPD hospitalization did not provide comprehensive information or analysis in lung function. Even in a well - designed prospective study like SUPPORT,<sup>26</sup> only 27% of patients had pulmonary function tests performed within 1 year of admission. In our study, 63.3% did



not have lung function performed during their inpatient stay. Apart from a research setting, lung function testing may not be practical for various reasons in patients admitted for exacerbations. This may include problems with the ability of a sick patient to perform the maneuver, the technique of the patients, the timing of the test in relation to the exacerbation and the need to initiate immediate treatment. However, we believe that lung function testing is an integral component in COPD management, both to monitor the trend of exacerbations and to allow severity categorization.

## V. CONCLUSION

Three factors: "hypertension, "high CAT score" and "high tobacco consumption" were all found to be significant risk factors for frequent hospitalization. Influenza vaccination is one factor that reduces the risk of hospitalization.

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