Risk Factors of Severe Acute Exacerbation of Chronic Obstructive Pulmonary Disease Among Patients Regularly Managed by Pulmonologists

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Objective: *The present study intended to determine the risk factors of severe exacerbation in chronic obstructive pulmonary disease patients even though managed by pulmonologists on a regular basis.*

Material and Method: *A retrospective case-controlled study was conducted at the chest clinic, Maharaj Nakorn Chiang Mai Hospital from 1st August 2009 to 31st July 2010. The clinical relevant data for acute exacerbation (age, sex, co-morbidity, severity of COPD, COPD medication, annual influenza vaccination, compliance with inhaled drug use, chest radiographic abnormality, and long-term oxygen therapy) were compared between severe AECOPD and stable COPD patients by logistic regression analysis.*

Results: *Out of 137 COPD patients, 17 (12.4%) had severe AECOPD with 29 episodes (21.2%). Six risk factors were identified, two modifiable and four non-modifiable. The two modifiable risk factors were annual influenza non-vaccination (odds ratio [OR] 27.79; 95% confidence interval [CI], 2.29-337.66, p-value = 0.01) and improper use of inhaled devices (OR 9.94, 95%CI 1.07-92.54, p-value = 0.04). The four non-modifiable risk factors were age <60 yrs (OR, 10.67; 95%CI, 1.92-59.31, p-value = 0.01), hypertension (OR, 4.03; 95%CI. 1.05-15.44, p-value = 0.04), enlarged pulmonary trunk as demonstrated by chest radiograph (OR, 8.61; 95%CI, 1.49-49.85, p-value = 0.02), and long-term oxygen therapy (OR, 7.09; 95%CI, 1.36-37.00, p-value = 0.02).*

Conclusion: *Six risk factors of severe AECOPD among patients whom were provided regularly managed by pulmonologists were identified; two of them, annual influenza non-vaccination and improper use of inhaled devices, could be potentially modified.*

Keywords: *Risk factor, Chronic obstructive pulmonary disease, Exacerbation*

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Acute exacerbation of chronic obstructive pulmonary disease (AECOPD), is an important phenomenon that has several unfavorable impacts on the long-term clinical course of patients with chronic obstructive pulmonary disease (COPD), besides high socioeconomic costs[1]. This condition is characterized by acute physiological changes and inflammation of the lower respiratory tract causing symptom deterioration more than the usual day–to–day variation[2]. The known major causes of AECOPD are acute lower respiratory tract infection of either viral or bacterial etiology, pollution and climate change; however, in about one-third of the patients the cause cannot be identified[1,3]. In addition to the causes of exacerbation, several predisposing risk factors were determined including age[4], body mass index (BMI)[5,6], walking distance within the 6 minutes (6–minute walk distance)[6,7], PaO2 ≤65 mmHg[6,7], $PaCO_2$>44 mmHg[5], long-term oxygen therapy (LTOT)[7,8], quality of life[7], forced ex-

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piratory volume in first second (FEV_1)[4,6,8], smoking[8], co-morbidities[7], and poor inhalation technique[5,6]. In Thailand, 28.7% of COPD patients were reported to have a history of severe acute exacerbation at least once within the past year in primary care practice, however, only 23.7% of them had received regular bronchodilator therapy and none received pulmonary rehabilitation or LTOT although they were indicated[9]. The present study intended to identify the risk factors for severe acute exacerbations among the COPD patients even though they were regularly managed by their pulmonologists at a medical academic center. Some identified risk factors could be potentially modified to further decrease the severity of AECOPD in the future.

Material and Method

A retrospective case-controlled study was conducted on COPD patients regularly managed by pulmonologists at the chest clinic of Maharaj Nakorn Chiang Mai Hospital from 1st August 2009 to 31st July 2010. The enrolled COPD patients were diagnosed according to GOLD criteria based on post-bronchodilator (BD) forced expiratory volume in first second (FEV_1)[1]. The patients were regularly managed by pulmonologists at least one year before enrolment. The severe acute exacerbation in the present study was defined as the presence of acute worsening of COPD symptoms (dyspnea, cough, secretion) that required hospitalization and treatment with systemic corticosteroids and/or antibiotics without radiographic confirmed pneumonia, left ventricular failure, or any other pulmonary diseases[2]. They were excluded from the study if they had acute exacerbation managed as outpatients and admitted due to other reasons (such as pneumonia, heart failure, worsening of their co-morbidities). The patients were categorized into 2 subgroups: severe AECOPD and stable COPD. The clinical relevant variables (age, sex, BMI, smoking status, smoking pack-years, co-morbidity, post– BD FEV_1, modified Medical Research Council (mMRC) score, six-minute walk distance (6–MWD), quality of life (St George's respiratory questionnaire; SGRQ), COPD medications, annual influenza vaccination, improper use of inhaled devices, chest radiographic abnormality, and LTOT were recorded and analysed. All observations of inhaler use were recorded in accordance with a standardized device checklist included a variable number of steps for each inhaler focusing the analysis on critical errors which are likely to make therapy useless. The study was approved by the Ethics Committee of the Faculty of Medicine, Chiang Mai University (Study code: MED–10–11–03A–11–X, Date approval: 27th January 2011).

Statistical analysis

The data were compared between stable COPD and severe AECOPD groups. Categorical variables were analyzed using the Fisher's exact test. Continuous variables were compared using Student t–test or Wilcoxon rank sum test as appropriate. Univariable and multivariable logistic regressions were performed to identify the prognostic factors of severe AECOPD patients. The potential risk factors from univariable test with p-value <0.25 were analyzed by using logistic multivariable analysis[10]. Results were displayed as adjusted odds ratio (OR) together with 95% confidence interval (CI) for OR. A p–value of less than 0.05 was considered as statistical significant.

Results

From 1st August 2009 to 31st July 2010, a total of 137 COPD patients were included, 77 males (56.2%) with mean age 71.9±8.6 years, and mean BMI 20.3±3.7 kg/m^2. Only 10 cases (7.3%) were current smokers. According to severity of the disease, 8 (5.8%), 52 (38%), 49 (35.8%), and 28 (20.4%) cases were classified to GOLD stage I, II, III, and IV, respectively. Most of baseline characteristics between groups were comparable except hypertension and chronic kidney disease (Table 1). Half of the cases showed hyperaeration on chest radiogram. The enlarged pulmonary trunk was more frequently found in severe AECOPD group (29.4% vs. 10.0%, p–value = 0.04) (Table 2). Almost all of the patients (99.3%) were treated with a combination of short–acting $beta_2$ agonist (SABA) and short–acting anticholinergic (SAAC) in the same device on as needed basis. Half of them (50.4%) were regularly treated by a combination of LABA and ICS in the same device, 40.9% of the patients were regularly treated with triple therapy of long-acting $beta_2$ agonist (LABA) and inhaled corticosteroid (ICS) with LABA and ICS plus long-acting anticholinergic (LAAC). Twenty cases (14.6%) received LTOT. The uses of pharmacological treatment were not different between the two groups. However, patients in severe AECOPD

Table 1. Clinical characteristic of patie nts

Variables	Severe AECOPD		*p*–value
	Yes, n = 17	No, n = 120	
Male gender	8 (47.1)	6.9 (57.5)	0.44
Age	69.1±10.7	72.4±8.2	0.14
Age ≤60 year	4 (23.5)	12 (10.0)	0.12
BMI (kg / m^2)	20.8±4.0	20.2±3.7	0.58
Current smoker	0	10 (8.3)	0.61
Duration of symptom (yrs)	8.5±6.8	8.9±6.8	0.86
Duration of diagnosis (yrs)	7.3±6.0	7.4±5.7	0.74
Co-morbidities			
Diabetes mellitus	1 (5.9)	9 (7.5)	0.64
Hypertension	11 (64.7)	43 (35.8)	0.03
Hyperlipidemia	5 (29.4)	17 (14.2)	0.15
Chronic kidney disease	1 (5.9)	8 (6.7)	0.69
Coronary artery disease	4 (23.5)	8 (6.7)	0.04
Post-bronchodilator FEV_1 (%)	45.8±17.8	47.7±17.6	0.68
Severity of the disease (GOLD stage)			
I	1 (5.9)	7 (5.8)	0.79
II	6 (35.3)	46 (38.3)	
III	5 (29.4)	44 (36.7)	
IV	5 (29.4)	23 (19.2)	
6-MWD (m)	330.4±73.5	312.2±99.3	0.87
mMRC (median, min-max)	2 (1-3)	2 (4-1)	0.45
SGRQ score	43.4±22.7	39.5±18.0	0.49

Data are n (%) or mean ± SD
AECOPD = Acute exacerbation of chronic obstructive pulmonary disease, BMI = Body mass Index, FEV_1 = forced expiratory volume in first second, 6-MWD = 6-minute walk distance, mMRC = modified medical research council dyspnea scale, SGRQ = St. George's respiratory questionnaire

Table 2. Chest radiographic findings of COPD patients

Chest radiographic findings	Severe AECOPD		*p*–value
	Yes, n = 17	No, n = 120	
Hyperaeration	10 (58.8)	59 (49.2)	0.60
Flattening diaphragm	8 (47.1)	38 (31.7)	0.27
Tubular heart shaped	3 (17.6)	16 (13.3)	0.71
Enlarged pulmonary trunk	5 (29.4)	12 (10.0)	0.04
Reticular infiltration at basal lungs	1 (5.9)	8 (6.7)	0.69

Data are n (%)

AECOPD = Acute exacerbation of chronic obstructive pulmonary disease

Table 3. Management of COPD patients

Management	Severe AECOPD		*p*–value
	Yes, n = 17	No, n = 120	
Pharmacological			
SABA+SAAC (as needed)	17 (100)	119 (99.2)	0.88
LAAC alone	1 (5.9)	6 (5.0)	0.79
LABA+ICS combination	10 (58.8)	59 (49.2)	0.54
Triple therapy (LABA+ICS +LAAC)	6 (35.3)	50 (41.6)	0.82
Methylxanthine	15 (88.2)	82 (68.3)	0.15
Non-pharmacological			
Long-term oxygen therapy	6 (35.3)	14 (11.7)	0.02
Influenza vaccination	1 (5.9)	42 (35.0)	0.02
Improper use of inhaled devices	3 (17.6)	5 (4.2)	0.06

Data are n (%)

AECOPD = Acute exacerbation of chronic obstructive pulmonary disease, SABA = short-acting beta$_2$ agonist, SAAC = short-acting anticholinergic, LABA = long-acting beta$_2$ agonist, LAAC = long-acting anticholinergic, ICS = inhaled corticosteroids

Table 4. Risk factors of severe AECOPD by univariable analysis

Variables	OR	95% CI	*p*-value
Age <60 yrs	2.8	0.8 to 9.8	0.11
Hypertension	3.3	1.1 to 9.5	0.03
Coronary artery disease	4.3	1.1 to 16.3	0.03
Influenza non-vaccination	8.6	1.1 to 67.3	0.04
Long-term oxygen therapy	4.1	1.3 to 12.9	0.02
Improper use of inhaled devices	4.9	1.1 to 22.9	0.04
Enlarged pulmonary trunk	3.8	1.1 to 12.5	0.03

AECOPD = Acute exacerbation of chronic obstructive pulmonary disease, OR = odd ratio, CI = confidence interval

Table 5. Risk factors of severe AECOPD by multivariable analysis

Variables	Adjusted OR	95% CI	*p*-value
Age <60 yrs	10.7	1.9 to 59.3	0.01
Hypertension.	4.0	1.1 to 15.4	0.04
Influenza non-vaccination	27.8	2.3 to 337.7	0.01
Use of long-term oxygen therapy	7.1	1.4 to 37.0	0.02
Improper use of inhaled devices	9.9	1.1 to 92.5	0.04
Enlarged pulmonary trunk	8.6	1.5 to 49.9	0.02

AECOPD = Acute exacerbation of chronic obstructive pulmonary disease, OR = odd ratio, CI = confidence interval

group had statistically received higher LTOT (*p*–value = 0.02) and lower rate of annual influenza vaccination (*p*–value = 0.02) (Table 3). All of them were in compliance with every scheduled visit for the entire study period, except when they were admitted to the hospital.

The study recorded 17 (12.4%) AECOPD patients with 29 (21.2%) episodes of hospitalization. Univariable analysis showed that risk factors of severe acute exacerbations were patients younger than 60 years (OR, 2.7; 95% CI, 0.8–9.8, *p*–value=0.11), hypertension "OR", 3.3; 95% CI, 1.1–9.5, *p*–value = 0.03), coronary artery disease (OR, 4.3; 95% CI, 1.1–16.3, *p*–value = 0.03), influenza non-vaccination within the past year (OR, 8.6; 95%CI, 1.1–67.3, *p*–value = 0.04), improper use of inhaled devices (OR, 4.9; 95% CI, 1.1–22.9, *p*–value = 0.04), using LTOT (OR, 4.1; 95% CI, 1.3–12.9, *p*–value = 0.02), and enlarged pulmonary trunk (OR, 3.8; 95%CI, 1.1–12.5, *p*–value = 0.03) (Table 4). Multivariable analysis revealed that risk factors affecting the occurrence severe AECOPD were patients younger than 60 year (adjusted OR, 10.7; 95% CI, 1.9–59.3, *p*–value = 0.01), hypertension (adjusted OR, 4.0; 95% CI, 1.1–15.4, *p*–value = 0.04), influenza non-vaccination within the past year (adjusted OR, 27.8; 95% CI, 2.3–337.7, *p*–value = 0.01), improper use of inhaled devices (adjusted OR, 9.9; 95% CI, 1.1–92.5, *p*–value = 0.04), using LTOT) adjusted OR, 7.1; 95% CI, 1.4–37.0, *p*–value 0.02), and enlarged pulmonary trunk (adjusted OR, 8.6; 95% CI, 1.5–49.9, *p*–value = 0.02) (Table 5).

Discussion

The patients in the present study were mostly of severe stage, however, almost all of them had received a regular combination of LABA and ICS in the same device (50.4%) or triple therapy (LABA and ICS plus LAAC) (40.9%) for at least one year before their enrollment and during the entire study period. Despite regularly use of inhaled COPD medication, there were still 17 (12.4%) severe AECOPD patients with 29 (21.2%) episodes. However, on contrary to a previous study where the patients were managed in primary care practice, the incidence of severe AECOPD in this study was 2.3 times lower although the disease severity was similar between the two studies[9]. There were six risk factors identified for severe AECOPD which could be classified into two groups, non-modifiable and modifiable risk factors. The non-modifiable risk factors were patients younger than 60 years, hypertension, use of LTOT, and enlarged pulmonary trunk. The modifiable risk factors were influenza non-vaccination within the past year and improper use of inhaled devices. Comparing the risk factors in this study with the recent systematic review showed only 3 matched risk factors; long-term oxygen therapy, influenza non-vaccination, and poor inhalation technique[11]. The present study differs from the previous ones which showed that older age had higher risk of AECOPD[12,13]. A possible explanation for the younger age as one of the non-modifiable factors may be that they are more exposed to higher risk working environments such as respiratory infection, air pollution and climate changes in their daily life than the retirees. Hypertensive patients, another risk factor, might cause diastolic dysfunction of the left ventricle[14] or acute exacerbation might be aggravated by the drugs used for controlling their blood pressure, such as a beta-blocker group. The remaining non-modifiable factors: long-term oxygen therapy and enlarged pulmonary trunk, associated with advance disease are already well-known risk factors of severe AECOPD[8,11]. The two modifiable risk factors, influenza non-vaccination and improper use of inhaled devices were the unexpected findings in the present study as a result of rigorous follow up one year prior to and throughout the entire study year. There were only 43 patients (31.4%) annually vaccinated with influenza vaccine. The unvaccinated patients had the greatest risk of severe AECOPD in this study. This risk could be modified easily by heeding the warning label on the outpatient medical record. The improper use of inhaled devices was revealed as one of the modifiable risk factors in the present study (Adjusted OR = 9.9, *p*–value =0.04). This finding highlights the importance of checking on inhaler use and adherence every visit, even though the patients compliant with the scheduled visits. Patients unable to use the devices correctly should be identified for optimum technique training for each device and practice at every visit. In addition, family members should be educated to encourage the patients on regular use of inhalers.

There were some limitations in the present study. Firstly, the study was conducted in a single academic center and the risks identified in the present study might not be generalized to other centers. However, every COPD clinic, whether supervised by a pulmonologist or general practitioner, should

be on the watch out to reduce the modifiable risks of severe AECOPD periodically among their patients to improve quality of care. Secondly, the numbers of the severe AECOPD in the study was rather low, which was probably due to the strict study inclusion criteria defined to enroll only complied patients with every scheduled visit at least a year prior to the enrollment. Thirdly, there could be other potential risk factors which were not explored in the present study such as air pollution exposure, arterial blood gas parameter, inflammatory biomarkers, and daily physical activity level. The present study was unable to demonstrate the effect of pulmonary rehabilitation on the risk of severe AECOPD because all of the patients did not receive any structural pulmonary rehabilitation program. Fourthly, the study was not designed to investigate the risks of severe AECOPD at the educational level, socioeconomic status and personal psychosocial factor.

Conclusion

Moderate to very severe COPD patients are susceptible to several insults that can rapidly lead to severe acute exacerbation even though they are regularly managed by their pulmonologists. Six risk factors were identified; two of them, annual influenza non-vaccination and improper use of inhaled devices, could be potentially modified.

What is already known on this topic?

There were well known several risk factors for acute exacerbation of COPD. In Thailand, 28.7% of COPD patients were reported to have a history of severe acute exacerbation at least once within the past year in primary care practice, however, only 23.7% of them had received regular bronchodilator therapy and none received pulmonary rehabilitation or long-term oxygen therapy although they were indicated[9].

What this study adds?

This study intended to identify the risk factors for severe acute exacerbations among the COPD patients even though they were regularly managed by their pulmonologists at a medical academic center. Some identified risk factors could be potentially modified to further decrease the severity of AECOPD in the future.

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Potential conflicts of interest

None.

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ปัจจัยเสี่ยงของภาวะการกำเริบรุนแรงของโรคปอดอุดกั้นเรื้อรังในผู้ป่วยที่ได้รับการรักษาอย่างสม่ำเสมอโดยอุรแพทย์

ชายชาญ โพธิรัตน์, ธัชตะวัน โพธิรัตน์, เฉลิม ลิ่วศรีสกุล, ชัยวัฒน์ บำรุงกิจ, อรรถวุฒิ ดีสมโชค, ธีรกร ธีรกิตติกุล, อติคุณ ลิ้มสุคนธ์

วัตถุประสงค์: *เพื่อศึกษาปัจจัยเสี่ยงที่ทำให้โรคปอดอุดกั้นเรื้อรังกำเริบเฉียบพลันแม้ได้รับการรักษาอย่างสม่ำเสมอจากอุรแพทย์*
วัสดุและวิธีการ: *ทำการศึกษาย้อนหลังในผู้ป่วยโรคปอดอุดกั้นเรื้อรังที่ได้รับการรักษาอย่างสม่ำเสมอจากอุรแพทย์ที่คลินิกโรคระบบการหายใจ โรงพยาบาลมหาราชนครเชียงใหม่ ระหว่างวันที่ 1 สิงหาคม พ.ศ. 2552 ถึง 31 กรกฎาคม พ.ศ. 2553 นำข้อมูลทางคลินิกที่มีความสัมพันธ์กับการกำเริบของโรคปอดอุดกั้นเรื้อรังขั้นรุนแรงได้แก่ อายุ เพศ โรคประจำตัว ระดับความรุนแรงของโรค ยาที่ใช้ในรักษา การได้รับการฉีดวัคซีนไข้หวัดใหญ่ภายในปีที่ผ่านมา ความร่วมมือในการใช้ยาสูด ภาพถ่ายรังสีทรวงอก และการใช้ออกซิเจนบำบัดระยะยาว มาวิเคราะห์ทางสถิติเปรียบเทียบระหว่างกลุ่มที่มีการกำเริบขั้นรุนแรงและกลุ่มที่ไม่มีการกำเริบด้วยวิธีการวิเคราะห์การถดถอยโลจิสติก*
ผลการศึกษา: *จากจำนวนผู้ป่วยทั้งสิ้น 137 ราย มี 17 ราย (ร้อยละ12.4) ที่มีภาวะโรคกำเริบขั้นรุนแรง จำนวน 29 ครั้ง (ร้อยละ 21.2) พบว่ามีปัจจัยเสี่ยง 6 ประการ ซึ่งแบ่งเป็นกลุ่มที่สามารถเปลี่ยนแปลงได้ 2 ประการคือ การไม่ได้รับการฉีดวัคซีนไข้หวัดใหญ่ประจำปีที่ผ่านมา (OR 27.79; 95% CI, 2.29-337.66, p = 0.01) และ เทคนิคการใช้ยาสูดไม่ดี (OR 9.94, 95%CI 1.07-92.54, p = 0.04) ส่วนอีก 4 ปัจจัยที่เปลี่ยนแปลงไม่ได้คือ อายุ <60 ปี (OR, 10.67; 95%CI, 1.92-59.31, p = 0.01) โรคความดันโลหิตสูง (OR, 4.03; 95%CI. 1.05-15.44, p = 0.04) หลอดเลือดแดงพุลโมนารีย์ขนาดใหญ่จากภาพรังสีทรวงอก (OR, 8.61; 95%CI, 1.49-49.85, p = 0.02) และการได้รับออกซิเจนบำบัดแบบระยะยาว (OR, 7.09; 95%CI, 1.36-37.00, p = 0.02)*
สรุป: *แม้ผู้ป่วยจะได้รับการรักษาอย่างสม่ำเสมอจากอุรแพทย์ ยังมีปัจจัยเสี่ยงต่อการกำเริบของโรคปอดอุดกั้นเรื้อรังขั้นรุนแรง 6 ประการ โดยปัจจัยเสี่ยง 2 ประการ เป็นปัจจัยที่สามารถเปลี่ยนแปลงได้คือ การไม่ได้รับการฉีดวัคซีนไข้หวัดใหญ่ในรอบปีที่ผ่านมาและเทคนิคการสูดยาไม่ดี*