ORIGINAL ARTICLE

Risk Factors Associated with Exacerbation Frequency in Chronic Obstructive Pulmonary Disease

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Background: By 2030, chronic obstructive pulmonary disease (COPD) will become the third leading cause of death globally according to the World Health Organization (WHO) prediction. COPD exacerbation, its flared symptoms causing economic and health burdens to the patients, especially those in lower-to-middle income countries, however, its aggravating factors are yet poorly clarified and under-acknowledged.

Objective: The present study aimed to detect patients at high risk of frequent exacerbations based on their individual risk factors, which may minimize cost and damage of the disease.

Materials and Methods: The study population was the 268 COPD-diagnosed patients coded with "J440" or "J441" of ICD10, with spirometry results, followed-up at the COPD clinic of Sanam Chai Khet Hospital in 2023, and visiting the clinic in January, 2023. The dependent variable was the number of acute exacerbations resulting in hospitalization in 2023, independence variables were gender, age, underlying diseases, baseline FEV1, BMI, smoking status, and forms of 1-year dust exposures. The associations among these variables were measured by multiple risk regression analysis.

Results: The incidences of infrequent and frequent exacerbations were 74.63% and 25.37%, respectively. After adjusting for the confounding factors, the factors, such as 30% to 49% of FEV1 (GOLD 3) (IRR 2.36, 95% CI 1.32 to 4.20), overweight and obesity (IRR 0.45, 95% CI 0.20 to 0.97), smoking status including both former (IRR 4.66, 95% CI: 1.45 to 14.94) and current smokers (including those who were less than 1-month ex-smoker) (IRR 6.88, 95% CI: 2.09 to 22.65), chronic exposure to organic (IRR 2.47, 95% CI 1.28 to 4.78), and coal dust (IRR 2.80, 95% CI 1.46 to 5.36) had shown significant associations with frequent exacerbations.

Conclusion: COPD exacerbation, a crisis in healthcare systems, flared up by multi-factors. Smoking, its most common cause, was strongly supported by the present study with significant associations in both current and ex-smokers. Baseline lung function and BMI are suggested to be considered for further investigations. Chronic exposure to dusts such as coal and organic dust, are preventable but under-acknowledged factor, especially in lower-to-middle income countries where agriculture and factory works are the main income of their rural populations.

Keywords: Chronic obstructive pulmonary disease (COPD); Chronic obstructive pulmonary disease exacerbation (COPD exacerbation); Risk factors; Frequent exacerbations

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According to the World Health Organization (WHO) prediction, by 2030, chronic obstructive pulmonary disease (COPD) will turn into the third leading cause of death globally, estimating 90% of the cases in lower-middle-income countries[1] where prevention, early diagnosis, and the availability of healthcare resources are limited[2].

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COPD exacerbation, an acute worsening of respiratory symptoms, which requires additional management[3], has an enormous impact on economic and health burden, severity, and mortality rate of the disease[4]. According to the study from Soler-Cataluña et al, patients with three or more exacerbations per year had only 30% of 5-year survival rate, which was 50% lower than those without exacerbation history[5], supported by another study that found a comparable result of forced expiratory volume in one second (FEV1) produced by frequent exacerbators to those moderate-to-severe COPD patients regardless of their lower exacerbation rates[6]. In addition to its negative impacts, a higher possibility of developing respiratory tract infections among COPD patients was also presented by one more study[7].

In 2023, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) had developed the

ABE scheme for COPD management based on level of symptoms accounted by either the COPD assessment test (CAT) or the modified Medical Research Council (mMRC) score, and the exacerbations[8]. However, many risk factors associated with acute exacerbations are poorly clarified[9].

Sanam Chai Khet is a 171500-hectare district in Chachoengsao province of Thailand with a population of 66,415 people. The district has huge polluting industries such as coal factories, metal factories, and agricultures[10]. As a result, the daily average Air Quality Index (AQI) mostly ranges between moderate to unhealthy, and PM 2.5, its main pollutant, normally exceeds 4 to 5 times of WHO annual air quality guideline value[11]. Moreover, agriculture and factory workers are the most common occupations in this area[10], thus dust exposures, the under-acknowledged factors of COPD[12], are unavoidable in some patients. As a result, the present study was aimed to minimize the damage and cost of exacerbations by exploring the individual factors aggravating COPD exacerbations, leading to an early detection of patients at high risk of developing frequent exacerbations. This might increase the level of awareness by the patients and healthcare professionals resulting in effective management and preventions in the future.

Materials and Methods

Study design and subjects

A retrospective cohort study was conducted, using electronic and paper-based medical records as secondary data from the COPD clinic of Sanam Chai Khet Hospital that is a primary-level hospital in Thailand.

The present study had followed the criteria for a waiver of informed consent, which involved no more than minimal risk to the subjects and would not be feasible or practicable to carry out without the waiver or modification[13]. The study was reviewed and approved by The Institutional Review Board, Royal Thai Army Medical Department (No. IRBRTA 0364/2024, Code: M006h/67_Exp).

Population

The study population was the 268 COPD-diagnosed patients coded "J440" or "J441" of ICD10, with spirometry results, followed up by the COPD clinic of Sanam Chai Khet Hospital in 2023 and that visited the clinic in January, 2023. The excluded populations were those who had exacerbated on the first visiting date and those without spirometry results, with the total number of 1 and 37 patients, respectively (Figure 1).

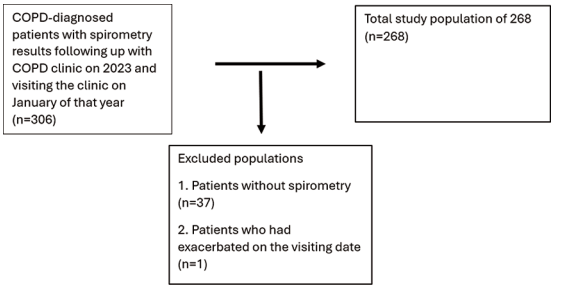

Figure 1. The study population.

The study population was calculated by the formula[14]:

$$n = \left(Z^2_{\frac{\alpha}{2}}\, p(1-p)\right) / d^2$$

where,

n=sample size

$Z^2_{\alpha/2}$=level of significance

p=expected proportion

d=desired precision

α=0.05, d=0.05, and p=0.22 according to the previous study, Germany[15]

Data collection and measurements

Baseline characteristics were divided into genders, ages with less than 60 and greater than or equal to 60 years old[16]; underlying diseases such as asthma-COPD overlap syndrome (ACOS)[17], cardiovascular disease[18], hypertension (HT)[19], diabetes mellitus type 2 (DM)[20], baselines FEV1 that were grouped for the severity of airflow obstruction by GOLD criteria 2023[21], and body mass index (BMI) classifications, which were grouped by WHO criteria[22].

Independent variables were baseline characteristics, smoking status which was divided into never-smoking, more than 1-month ex-smoking, and current or less than 1-month ex-smoking, and more than one year history of exposure to different types of dust including organic dust such as agriculture, textile, and wood industry works; coal dust such as coal miners and charcoal workers; silica dust such as mining, ceramic, and tiles industry works; and road such as road workers, street food vendors, and traffic polices, prior to the clinic visiting date.

The outcome was measured by the number of COPD exacerbations resulting in hospitalization in 2023 after the COPD visit date in January, 2023 when the patients were expected to have no exacerbation on that day[23]. Exacerbation frequencies

were categorized into infrequency as less than two exacerbating per year, and frequency as greater than or equal to two exacerbating per year, defined and analyzed by the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) investigators[24,25].

Data analyses

The secondary data were collected, then analyzed and adjusted for the confounding factors that were the baseline characteristics, smoking status, and history of long-term exposure to diverse types of dust by multiple risk regression analysis, where a p-value of less than 0.05 was considered as statistical significance. This was based on the fact that a one-year history of exacerbation frequency was observed after the first visiting date with an exacerbation-free baseline in January, 2023. Therefore, a closed cohort with short-term follow up was conducted. Although there were some missing data presented in less than 5% of the population in each independent variable, they were handled by a complete-case analysis. The process of data analysis was done using Stata Statistical Software, version 17 (StataCorp LLC, College Station, TX, USA) which contains a set of functions for automating and producing statistical results in text format.

Results

Two hundred sixty-eight patients were included in the present study, with a majority of male at 78.73% and over or equal to 60 years of age at 79.48%. Among the disease severity, GOLD1 with greater than or equal to 80% of measured FEV1[21], was the most diagnosed at 44.78%, followed by GOLD 2, representing 50% to 79% of measured FEV1[21], was diagnosed at 36.94%. The percentage of the underweight were similar to the overweight, at 19.03% and 18.66%, respectively. There was a varying proportion of the underlying diseases, which was mostly occupied by hypertension at 30.22%. The characteristics of the present study population are shown in Table 1.

For the dependent variable, the incidence of infrequent exacerbations was noticeably higher than of frequent exacerbations, with 74.63% and 25.37%, respectively (Table 2). Overall, the cumulative incidence of exacerbations was 38.06%.

According to the multiple risk regression analysis, after adjusting for the confounding factors, the factors found to be associated with exacerbation frequency were those with 30% to 49% of FEV1 (GOLD 3) (IRR 2.36, 95% CI 1.32 to 4.20), overweight and obesity (IRR 0.45, 95% CI 0.20 to 0.97) (Table 3), smoking status including both former (IRR 4.66, 95% CI 1.45 to 14.94) and current smokers (and those less than 1-month ex-smoking) (IRR 6.88, 95% CI 2.09 to 22.65), and chronic exposure to organic (IRR 2.47, 95% CI 1.28 to 4.78) and coal dust (IRR 2.80, 95% CI 1.46 to 5.36) (Table 3, 4).

Table 1. Characteristics of the study population (total n=268)

Characteristics	n (%)
Sex	
Female	57 (21.27)
Male	211 (78.73)
Age (years)	
<60	55 (20.52)
≥60	213 (79.48)
Mean±SD	68.81±11.28
Underlying disease	
ACOS	11 (4.1)
Cardiovascular	52 (19.40)
HT	96 (30.22)
DM	60 (22.39)
Others	30 (11.19)
Baseline FEV1	
≥80% (GOLD 1)	120 (44.78)
50% to 79% (GOLD 2)	99 (36.94)
30% to 49% (GOLD 3)	40 (14.93)
<30% (GOLD 4)	9 (3.36)
BMI (kg/m^2)	
Underweight	51 (19.03)
Normal weight	157 (58.58)
Overweight	50 (18.66)
Obesity	10 (3.73)

SD=standard deviation; ACOS=asthma-COPD overlap syndrome; HT=hypertension; DM=diabetes mellitus type 2; FEV1=forced expiratory volume in one second; BMI=body mass index

According to WHO criteria of nutritional status, underweight is defined by BMI <18.5 kg/m^2, normal weight is defined by BMI 18.5 to 24.9 kg/m^2, overweight is defined by BMI 25.0 to 29.9 kg/m^2, and obesity is defined by BMI ≥30 kg/m^2

Table 2. The incidences of acute exacerbations frequency

Characteristics	Incidence (%)
Infrequent (<2 times per year)	74.63
Frequent (≥2 times per year)	25.37

Discussion

According to this 1-year retrospective cohort study, the cumulative incidence of the exacerbations was 38.06%, higher than the 8-year study from Germany, which was 22%[15]. After adjusting for

Table 3. The multiple regression analysis of individual characteristic factors for COPD exacerbations

	Infrequent; n (%)	Frequent; n (%)	Crude RR	95% CI	p-value	Adjusted RR	95% CI	p-value
Sex								
Female	47 (82.46)	10 (17.54)	1			1		
Male	153 (72.51)	58 (27.49)	1.57	0.86 to 2.87	0.15	1.1	0.58 to 2.09	0.77
Age (years)								
<60	44 (80)	11 (20)	1			1		
≥60	156 (73.24)	57 (26.76)	1.34	0.75 to 2.38	0.32	1.03	0.55 to 1.92	0.94
Underlying disease								
ACOS								
• No	192 (74.71)	65 (25.29)	1			1		
• Yes	8 (72.73)	3 (27.27)	1.08	0.40 to 2.90	0.88	1.06	0.37 to 3.01	0.92
Cardiovascular								
• No	163 (75.46)	53 (24.54)	1			1		
• Yes	37 (71.15)	15 (28.85)	1.18	0.72 to 1.91	0.52	1.28	0.81 to 2.01	0.29
HT								
• No	145 (77.54)	42 (22.46)	1			1		
• Yes	55 (67.90)	26 (32.10)	0.86	0.55 to 1.33	0.49	0.91	0.59 to 1.39	0.66
DM								
• No	126 (73.26)	46 (26.74)	1			1		
• Yes	74 (77.08)	22 (22.92)	0.98	0.60 to 1.61	0.94	1.16	0.73 to 1.86	0.53
Baseline FEV1								
≥80% (GOLD 1)	100 (83.33)	20 (16.67)	1			1		
50% to 79% (GOLD 2)	72 (72.73)	27 (27.27)	1.64	0.98 to 2.74	0.06	1.38	0.84 to 2.26	0.2
30% to 49% (GOLD 3)	23 (57.50)	17 (42.50)	2.55	1.49 to 4.37	0.001	2.36	1.32 to 4.20	0.004
<30% (GOLD 4)	5 (55.56)	4 (44.44)	2.67	1.16 to 6.14	0.021	1.49	0.65 to 3.40	0.341
BMI (kg/m^2)								
Underweight	34 (66.67)	17 (33.33)	1.16	0.73 to 1.84	0.52	0.82	0.50 to 1.34	0.5
Normal weight	112 (71.34)	45 (28.66)	1			1		
Overweight and obesity	54 (90)	6 (10)	0.35	0.16 to 0.78	0.01	0.45	0.20 to 0.97	0.043

RR=relative risk; CI=confidence interval; ACOS=asthma-COPD overlap syndrome; HT=hypertension; DM=diabetes mellitus type 2; FEV1=forced expiratory volume in one second; BMI=body mass index

Table 4. The multiple regression analysis of individual predictive factors for COPD exacerbations

	Infrequent; n (%)	Frequent; n (%)	Crude RR	95% CI	p-value	Adjusted RR	95% CI	p-value
Smoking status								
Never-smoker	58 (95.08)	3 (4.92)	1			1		
Ex-smoker for more than 1 month	99 (72.26)	38 (27.74)	5.64	1.81 to 17.60	0.003	4.66	1.45 to 14.94	0.01
Current or less than 1-month ex-smoker	43 (61.43)	27 (38.57)	7.84	2.50 to 24.63	<0.001	6.88	2.09 to 22.65	0.002
Chronic dust exposure								
No history	57 (87.69)	8 (12.31)	1			1		
Coal dust	43 (67.19)	21 (32.81)	2.67	1.27 to 5.58	0.009	2.8	1.46 to 5.36	0.002
Silica dust	13 (86.67)	2 (13.33)	1.08	0.25 to 4.60	0.914	1.46	0.38 to 5.59	0.577
Organic dust	67 (67.00)	33 (33.00)	2.68	1.32 to 5.44	0.006	2.47	1.28 to 4.78	0.007
Road dust	20 (83.33)	4 (16.67)	1.35	0.45 to 4.10	0.591	1.19	0.43 to 3.32	0.741

RR=relative risk; CI=confidence interval

the confounding factors, some factors had shown interestingly significant associations with frequent exacerbations (Table 3, 4).

Lung function is well-known for its association with exacerbation frequency. Many studies had concluded that the more frequent the exacerbations became, the more lung function declined[26,27]. In addition, the ECLIPSE study found that 22%, 33%, and 47% of the patients diagnosed with GOLD 2, 3, 4 of COPD, respectively, had become frequent

exacerbators[25]. For the present study, the authors had only found the significant association among those with GOLD 3 stage, without further relationship developed between GOLD 4 and the frequency. However, this may be due to a limit to the number of severely stage (GOLD 4) patients in this setting of primary-level hospital where a total of 9 patients (3.36%) was found.

The impact of overweight and obesity on COPD is not yet clarified. The retrospective studies from the Taiwan Obstructive Lung Disease (TOLD) and the Zuyderland Medical Center in The Netherlands had agreed on its association with lower risks of exacerbations[28,29]. However, its negative effects on severity and frequency of exacerbations were also reported by others[30,31]. According to the present study, overweight and obese patients had about 0.45 times higher risk of developing frequent exacerbations than the normal-weight population (95% CI 0.20 to 0.97) (Table 3). However, as a total number of patients representing this factor were relatively low (Table 1), compared with the previous studies[28-31], a larger study population was suggested for further investigations.

Smoking, the most common cause of COPD, had led to 80% to 90% of COPD cases in the United States in 1980[32]. In addition, the present study found significant associations between patients with smoking history and their exacerbation frequency, especially for those who were current or less than 1-month ex-smokers.

Long-term exposure to dust, a preventable but under-acknowledged factor[12], was found associating with the exacerbations in the present study. Among those who had been exposed to organic and coal dust, were 2.47 times (95% CI 1.28 to 4.78) and 2.8 times (95% CI 1.46 to 5.36) greater risk of developing frequent exacerbations, respectively. According to related studies, animal farming where organic dusts had been exposed to the farmers, causing a decrease in their lung function, as a result, this type of particles was identified as one of the specific agents for COPD diagnosed[33]. Moreover, more than 30 years of evidence has been recorded that coal mining is a factor increasing the severity of COPD[34], thus, as an occupational disease, work injury compensation must be paid to COPD diagnosed workers in England and Germany[34].

The present research is a retrospective cohort study, which risk factors, magnitude on the associations, and temporal relationships can be identified. However, there might be some information biases as the exposure history could be uncertainly probed by the nurses who took some medical records for the physicians, and misinformation from patients could be given due to the fear of being inhibited from work. Apart from that, only the exposure history of more than one-year duration was taken, regardless of other factors such as air temperature, air pressure, and relative humidity, which could affect dust particle concentrations[35]. In addition, missing data, managed by a complete-case analysis, may yield a valid estimate of the outcome. Lastly, there were limits on the generalizability as the data was only collected from patients visiting COPD clinic in January, 2023 and some were excluded by the exclusion criteria.

Conclusion

COPD exacerbation, an acute worsening of respiratory symptoms causing an enormous impact on healthcare systems, is aggravated by multi-factors that are still controversial. Smoking, its most common cause, was strongly supported by the present study with significant associations in both current and ex-smokers. In addition, baseline lung function of 30% to 49% of measured FEV1, overweight, and obesity were found to associate with the exacerbation frequency. Thus, further investigations in larger study populations should be considered. Lastly, chronic exposure to dusts such as coal and organic dust, which are preventable but under-acknowledged factors, were found. As a result, more attention should be given to them, especially in lower-to-middle income countries where agriculture and factory works are the main income of their rural populations.

What is already known on this topic?

COPD exacerbations are aggravated by multi-factors including smoking, air quality, underlying diseases, and the exposure to various particles. However, a factor such as BMI is still controversial.

What does this study add?

Exacerbation frequencies of COPD can also be negatively affected by long-term exposure of more than one year to organic and coal dusts, overweight, and obesity.

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Conflicts of interest

The authors declare no conflict of interest.

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