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The Association between Using of corticosteroids and Pulmonary Tuberculosis in Patients with Chronic Obstructive Pulmonary Disease

หทัยชนน์ บุญหัตถ์ (Hathaichon Boonhat) [1] ดุสิต สุจิรารัตน์ (Dusit Sujirarat) [2]

มธุรส ทิพยมงคลกุล (Mathuros Tipayamongkholgul) [3]

Abstract

Tuberculosis is an infectious disease increases the burden of disease in developing countries. There are many factors associated with developing active TB. Some medications are the risk factor of TB. Using of inhaled corticosteroids (ICS) would increase the risk of TB activation. Especially, the areas with a high incidence of TB combined with a high dose of ICS. The aim of this study was to identify the association between using corticosteroids (type/dose) and TB in COPD patients. A case-control study design was conducted on patients who were diagnosed with COPD at Chiangrai Prachanukroh hospital between 1st January 2011 – 31st May 2015. The patients were identified, aged more than 40 years. The case must be registered following TB treatment procedure and also treated during the same period of the study. The control was COPD patient without TB. If the control who used to be TB, they must have been cured more than 2 years. The population in this study were matched 33 of the cases and 132 of control. ICS use was an associated 8.41-fold (95% CI, 1.98 to 35.58) increased risk for developing TB. Oral corticosteroid (OCS) use was 2.8 (95% CI, 1.26 to 24.12) at an increased risk for TB activation. Adjusted OR of ICS use was significantly increased risk of developing TB (AOR = 9.3;95% CI, 1.92 to 45.2). The association of cumulative dose tend to increase the risk of TB development (p = 0.011). The results showed use of high dose of ICS was an increased risk of developing TB.

Keywords: COPD, Tuberculosis, Corticosteroids, Smoking, BMI

1 Master of Department of Epidemiology and Infectious disease, Faculty of Public Health, Mahidol University

htc.boonhat@gmail.com

2 Associate Professor of Department of Epidemiology and Infectious disease, Faculty of Public Health, Mahidol University

3 Assistant Professor of Department of Epidemiology and Infectious disease, Faculty of Public Health, Mahidol University

Introduction

Tuberculosis is an infectious disease which severely affects a public health in many countries. Especially, TB is a second leading cause of death in the group of infectious diseases after AIDS. In 2013, WHO (World Health Organization) estimated new cases of pulmonary tuberculosis would be around 9.0 million a year (range, 8.6 million - 9.4 million) equivalent to 126 per 100,000 population. The death cases of tuberculosis was 1.5 million per year (WHO,2014). Moreover, WHO reported that there were 22 of countries which had a tuberculosis crisis. Thailand was one of these countries. In 2013, WHO reported the prevalence of tuberculosis in Thailand at 149 per 100,000 population. The incidence of tuberculosis in Thailand was 119 per 100,000 population and the number of deaths was 12 per 100,000 population (WHO, 2014). According to report of the 10th office of Disease Prevention and Control in Chiang Mai and Bureau of Epidemiology (2015) demonstrated, the incident rate of TB between 2009 – 2013 were 5,195 of new cases of pulmonary tuberculosis. The incident rate equivalent to 91.52 per 100,000 population. However, most of the TB cases were occurred in Chiang Rai province which morbidity rate was 116.05 per 100,000 population and there were 548 deaths. The highest incident rate of TB is Chiang Rai which equivalent to 128.63 (5 years median per 100,000 population). In 2013, The most number of TB new cases were Chiang Rai (1,449 cases). Moreover, The patients were registered at ChiangRai Prachanukroh hospital.

Furthermore, there is evidence to suggest that risk factors of tuberculosis infection including age, gender(mainly male), living conditions, contact with TB patients who had symptoms, drinking alcohol, smoking, liver disease, chronic kidney disease, silicosis, low socioeconomic status, HIV infection, cancer, diabetes, immigration status, low immunity, malnutrition, and corticosteroids use as (สำนักระบาดวิทยา, 2012; Benfield, Lange, Vestbo, 2008; Corbett et al, 2009; Dheda, 2007; Didilescu, Ibraim, Plopeanu 2000.). Moreover, there found the association between obstructive pulmonary disease (such as Chronic Obstructive Pulmonary Disease and Asthma) and pulmonary tuberculosis especially, when using of corticosteroids. (Drummond MB, 2008; Ni, Fu, Zhao, Liu, 2014)

Chronic Obstructive Pulmonary Disease (COPD) caused illness and death in developed and developing countries. It occurs in males more than females but a recent survey currently shows an increasing trend of commonly smoking habit in female also mostly in high income countries and low income countries with air pollution factors. At the present, COPD has been found in both males and females equally, 90% of the deaths occur in middle and low income countries. For the situation of COPD in 2002, WHO estimated COPD ranked as the 5th leading cause of death, predicted that it will increase up to 30% in next 10 years. In 2030, COPD will be the 3rd leading a cause of death worldwide.(WHO, 2013)

In 2012, the report of non-communicable disease (Bureau of Epidemiology, 2012) found 39,017 new cases of chronic lower respiratory tract disease classified as COPD 35,560 cases (91.14%) and 2,472 of chronic bronchitis cases (6.34%). 167,651 cases of cumulative chronic lower respiratory tract disease were found, including 150,549 cases of COPD (89.80%) and 12,523 chronic bronchitis cases (7.47%). The Annual report 2014 of Bureau of non-communicable disease reported mortality rate was 5.6 per 100,000 population (Bureau of non-communicable disease, 2014). Chiang Rai province was one of 5 provinces which had the highest rate of chronic lower respiratory tract disease, 279.63 per 100,000 population

Nowadays, there are not specific medicines to treat chronic obstructive pulmonary disease patients for decrease the death rate. However, there are some medications to relieve symptoms. The Global Initiative for Chronic Obstructive Lung Disease (GOLD guideline, 2011) was suggested that using main bronchodilators with inhaled corticosteroids (ICS) could reduce the exacerbation of low lung function patients (in case of exacerbation). Treatment with inhaled corticosteroids that was considered by the Model of Symptom/Risk of Evaluation of COPD. However, Thailand was followed the GOLD guideline for treatment. A previous study (Havlir et al 2008) which emphasized the result of treatment with inhaled corticosteroids in COPD patients found inhaled corticosteroids may reduce inflammation in bronchus that results in a decrease in systemic inflammation and myocardial infraction. Moreover, ICS have the ability to decrease exacerbation and the risk of all-causes of mortality up to 27% (Sin et al , 2005). Although, the treatment with ICS was an effective treatment but, the side effects of treatment regarding to immunity in lungs (Suissa et al, 2007).

There were also that indicated the treatment with ICS would increase the risk for developing pulmonary tuberculosis. The Burden of Lungs Disease (BOLD) study in South Africa was studied respiratory infections, pulmonary tuberculosis, and HIV infections. The results showed that the patients with COPD in stage 3 and 4 who were found a history of TB of 53%, and patients with COPD in stage 1 and 2 who had a history of TB of 25% (Jithoo and Buist, 2007). Pulmonary tuberculosis patients were infected with co-morbidities disease and COPD as a second rank followed by diabetes (Mannino DM and Buist AS, 2007). In the study of Lui et al (2005) pulmonary tuberculosis pleurisy patients with common co-morbid disease as COPD of 23%. Likewise, the study in Romania found recurrent TB patients with COPD of 10.6% (Didilescu et al, 2000). Especially, the areas with a high incidence of TB combined with a high dose of corticosteroid therapy were increased risk to TB activation (Benfield, Lange and Vestbo, 2008). Significantly, Thailand was a high endemic area of exposure to the risk of infection with pulmonary tuberculosis. In fact, several studies (Lee et al, 2012; Lee et al, 2013; Jick et al, 2006; Kim et al, 2013) have found increased risk for developing TB among COPD patients who use corticosteroids. Recently, an increased risk of TB development among ICS users was suggested in an analysis of a cohort based in Taiwan (Chung et al, 2014). In light of evidence from the 2010 - 2014 studies (Lee et al, 2012; Lee et al, 2013; Kim et al, 2013; Shu et al, 2010; Chung et al, 2014) , we have a better understanding of using of high dose corticosteroids increases the risk of developing TB.

Theoretically, corticosteroid is a risk factor for tuberculosis, whether ICS therapy is associated with increased risk of TB has not been investigated in Thailand. Therefore, this study aimed to explore the association between corticosteroids (types/doses) and the risk of TB development. It could be improved the management of TB in the future.

Objectives

1. To describe the association between using of corticosteroid (types/doses) and the risk of TB development in COPD patient.
2. To identify the association between personel characteristic factors including BMI, smoking, and TB history with the risk of TB development in COPD patient.
3. To determine the association between COPD treatment factors including receiving bronchodilators, exacerbation of COPD, severity of COPD, and treatment duration of COPD with the risk of TB development in COPD patient.
4. To examine the association between environmental factors including crowded household, and contact with TB patients with the risk of TB development in COPD patient.
5. To evaluate the association between co-morbidities disease factors including diabetes, chronic liver disease, and cirrhosis with the risk of TB development in COPD patient.

Research methodology

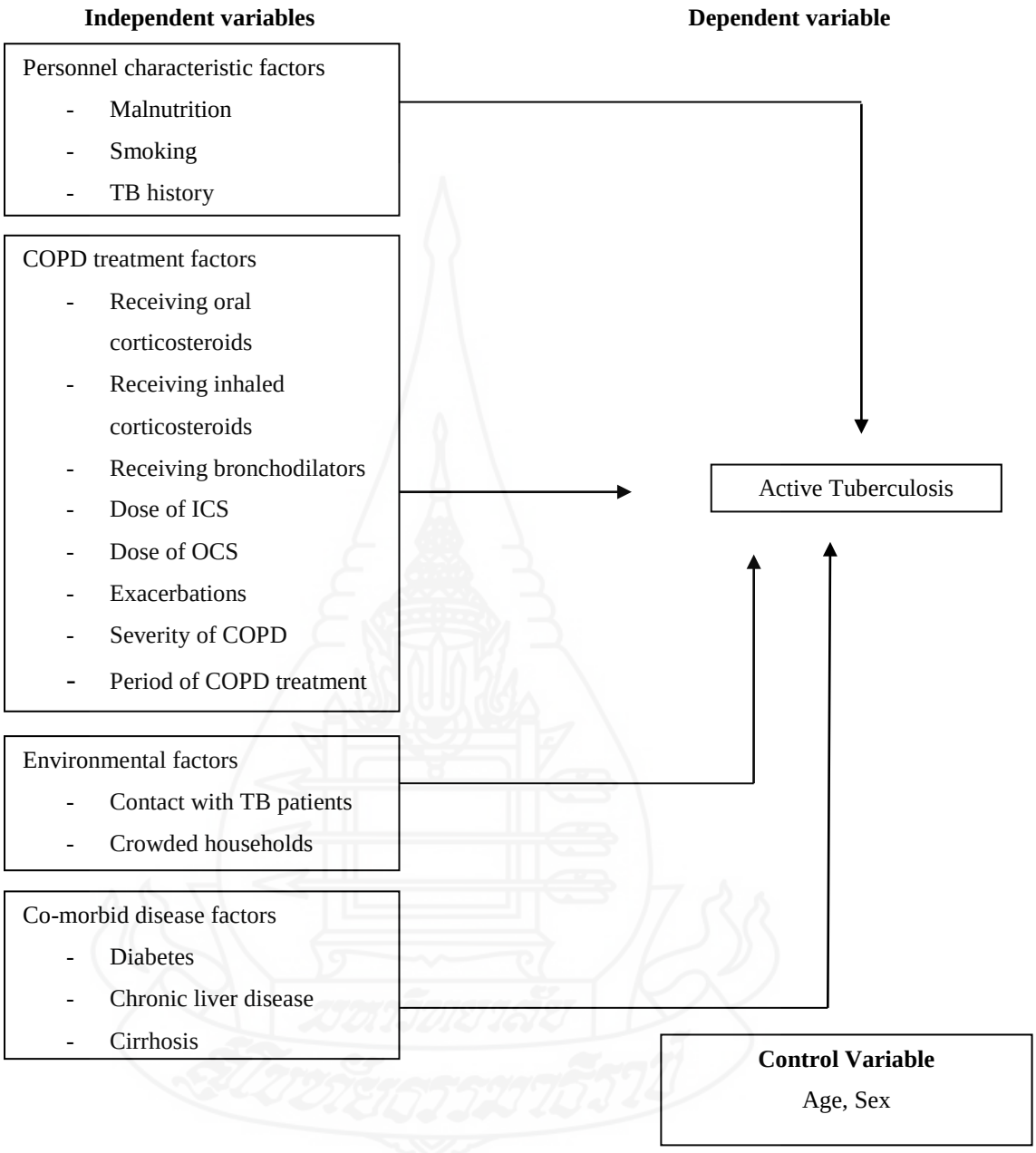
This research is a case-control study design by matching age and sex. The population in this study were patients who diagnosed with Chronic Obstructive Pulmonary Disease and registered at least 1 year before enrolled to the study. The study was conducted on Chiangrai Prachanukroh hospital since 1st January 2012 to 31st May 2015. The participants were patients aged more than 40 years and participated in the study. The case must be registered following TB treatment procedure and also treated in the same period of the study. The control was patients with COPD, which was diagnosed with no TB during the period of study. If the controls that ever had TB, there must have been cured more than 2 years. The patients who were TB since 1st January 2009 – 31st December 2011 and case who had a relapse in the period of study were excluded. This study has been reviewed and approved by the ethical committee for Human Research, Faculty of Public Health, Mahidol University and Chiangrai Prachanukroh hospital.

The data collection method in this study was divided into two parts. First, the questionnaire was used to interview the participants for personel and environmental factors. Second, the medical record was reviewed for the clinical factors of COPD include co-morbidities disease. The cases were enrolled to the study by inclusion criteria and the controls were randomly matched for age (+/- 2 years), sex same as cases. If the control who refused enroll to the study , they would be excluded. The quantities of corticosteroids was

calculated as cumulative dose, daily dose. ICSs was included budesonide and fluticasone, either dispensed alone or in a combination inhaler with an inhaled β_2 – agonist. ICS user was reviewed the previous prescriptions before the index date. The Equivalent was based on the potency according to the Global Strategy for Asthma Management and Prevention 2014 (GINA). The daily dose (mcg) was divided into 3 groups: 200 – 400 µg budesonide as low group, >400 – 800 µg as medium group, and >800µg as high group. These study was not convert the equivalent of budesonide to fluticasone. Oral corticosteroids (OCS) was prednisolone and dexamethasone there would be calculated as OCS used. OCS user was calculated the previous prescriptions before the index date. The cumulative dose of ICSs and OCS used also calculated from the previous prescriptions until the index date (include the history of use of corticosteroids at first of diagnosed with COPD). This study no classify the cumulative dose of OCS used because OCS did not frequently used, there would be used when the patient have an acute exacerbation.

The statistical analysis for general characteristics, medical conditions and clinical characteristics for cases and controls were analyzed by descriptive include proportion for categorical variables by using chi-square and mean, SD for continuous variables by using t-test. Conditional logistic regression was used to identify the association between use of inhaled respiratory medications and TB. It was matched age and sex for cases and controls. Variables for adjustment were selected at p-value <0.1 to the multivariate analysis model. Multivariate analysis was presented with 95% CI and p-value <0.05. To examine the cumulative dose-response relationship with TB, the cumulative ICS doses were divided into 3 groups based on the Global Strategy for Asthma Management and Prevention 2014 (GINA). The cumulative ICS dose defined as the previous prescriptions of ICS until index date. The units of cumulative ICS dose was compared the potency dose of ICS equivalent to years. The effect modification of corticosteroids and TB were tested at p-value < 0.05. The interaction all of variable were not significantly. The program of statistical analysis was using stata v. 12.0.

Conceptual framework



Results

A total of 33 TB cases in patients with COPD and 132 COPD patients were analyzed. The main participants of this studied were male 67%. The mean age of both groups were aged higher than 69 years. The majority of age between two groups ranged 60 – 79 years. The group of TB/COPD performed a higher prevalence of underweight than the group of patients with COPD. Education status of population mostly was primary school. There was unemployed 75% (control group) and 63% (case group). Smoking status of participants showed mainly ex-active smoker 86.36% (control group) and 75.76% (case group), the average number of smoking was 12.3 ± 9.8 (cigarettes/day) in cases and 9.17 ± 9.5 in COPD patients group. The means of smoking duration in each group were no different. It

was 33.64±17.36 of cases and 34.27±18.11 of COPD patients. However, there was no significant difference for TB history in both groups. Furthermore, the environmental management of participant has exhibited about the proportion of closing contact with TB that there was the people who lived in the same house but separated bedroom which was higher than the people who lived in the same house and used the same bedroom. The average of crowded household more than 5 people was 45.45% in cases. Moreover, there was a different between both of groups. The proportion of co-morbidities disease in cases was higher than COPD patients. The most common underlying co-morbidities in the case and control were chronic kidney disease (CKD). However, HIV/AIDS was excluded because the number of HIV/AIDS was small in both of groups. (Table 1).

Table.1 General Characteristics and medical conditions of cases and controls

Variables	Cases (N =33)	Controls (N=132)	P-value
Gender			0.934
Male	22(66.67)	89(67.42)	
Female	11(33.33)	43(32.58)	
Age, years			
Mean (SD)	69±65.3	69±67.3	0.961
40 – 59	8(24.24)	30(22.73)	0.982
60 – 79	20(60.61)	82(62.12)	
> 80	5(15.15)	20(15.15)	
Body Mass Index (Kg/m^2)			0.001
Underweight (<18.5)	29(87.88)	70(53.03)	
Normal weight (18.6 – 22.9)	2(6.06)	40(30.30)	
Overweight (> 23)	2(6.06)	22(16.7)	
Education status			0.002
Uneducated	7(21.21)	51(36.64)	
Primary School	22(66.67)	76(57.58)	
Secondary school	1(3.03)	5(3.79)	
Bachelor's degree or higher	3(9.09)	0	
Occupation			0.362
Unemployed	21(63.64)	100(75.76)	
Agriculture	3(9.09)	13(9.85)	
Employee	7(21.21)	14(10.61)	
Self business	2(6.06)	5(3.79)	
Smoking status			0.009
Non smoker	3(9.09)	15(11.36)	
Ex-active smoker	25(75.76)	114(86.36)	
Current active smoker	5(15.15)	3(2.27)	
No. of smoking (cigarettes/day)	12.3±9.822	9.17±9.502	1.685
Duration of smoking (years)	33.64±17.363	34.27±18.114	0.678
TB history			0.798
Yes	3(9.09)	14(10.61)	
No	30(90.91)	118(89.39)	
Environmental factor			
Contact with TB patient			
TB patient in the house	1(3.03)	4(3.03)	1.00

Never had TB patients in the house	32(96.97)	128(96.97)	
Close contact with TB			0.786
Live in same house, separate rooms	26(78.79)	107(81.06)	
Live in same house, used the same bedroom	7(21.21)	25(18.94)	
Crowded household			0.067
< 5	18(54.55)	94(71.21)	
>5	15(45.45)	38(28.79)	
Co-morbidities disease factor			
Diabetes			0.864
Yes	2(6.06)	7(5.3)	
No	31(93.94)	125(94.70)	
Duration of DM treatment	103.42±452.332	74.25±346.083	0.405
Chronic kidney disease			0.312
Yes	4(12.12)	9(6.82)	
No	29(87.88)	123(93.18)	
Duration of CKD treatment	80.52±243.9	67.99±271.449	0.242
Cirrhosis			0.041
Yes	2(6.06)	1(0.76)	
No	31(98.94)	131(99.24)	
Duration of cirrhosis treatment	22.52±120.34	0.61±6.96	1.045

The lung function including FEV_1, FVC, and FEV_1/FVC of case and control were not significantly different. During the period of study we identified the participants with prescriptions for oral corticosteroid (OCS) and inhaled corticosteroid (ICS) including respiratory medications. The duration for prescriptions must be longer than 30 days also including the previous prescriptions for any respiratory medications. Patients with COPD who had been diagnosed with TB during 2 years before enrolled to the study it would be excluded. The results of COPD treatment factor showed the significantly different between the OCS-users and Non-OCS users groups. Also ICS user and Non-ICS users there were significantly different between two groups. All of patients were received bronchodilators. The averages of dosages in any bronchodilators were not different. The dosage of Ipratrapium was different. The ICS use was separated into two inhaled. However, this study did not convert the dose into fluticasone equivalent because there were a few fluticasone users which obtained from the combination therapy. The cumulative dose of budesonide and daily doses used were significantly different. The daily doses of budesonide equivalent were significantly different. The patients were more likely to received medium doses. The cumulative dose of oral corticosteroid received in the previous years was, respectively, 41073.42 mg and 30925.11 mg. The exacerbation for both of groups was not different. The severity of COPD factor, results found more than half of the participants were C group based on GOLD guideline. The average duration of follow up was 6.6 years of case and 8.2 years of control. (Table.2)

Table.2 Clinical characteristic of COPD of cases and controls

Variables	Cases	Controls	P-value
Pulmonary function			
FEV_1,(L)	1.54±0.42	1.76±0.72	2.260
FVC,(L)	1.19±0.44	1.17±0.58	0.234
FEV_1/FVC (%)	56.06±8.45	57.61±12.38	0.888
COPD treatment factor			
Receiving OCS			<0.001
OCS users	32(96.97)	84(63.64)	
Non-OCS users	1(3.03)	48(36.36)	
Receiving ICS			0.006
ICS users	30(90.01)	44(33.33)	
Non-ICS users	3(9.09)	88(66.67)	
Receiving bronchodilator			
Yes	33(100)	132(100)	
No	0	0	
Dose of bronchodilators			
Dose of Salbutamol(Bottle)	27.27±62.61	68.18±89.37	3.05
Dose of Salbutamol(Pill)	2.3±2.69	3.03±2.58	1.43
Dose of Sameterol	0	36.11±69.19	< 0.001
Dose of Formeterol	0	1.44±4.11	<0.001
Dose of Tiotropium	5.45±20.36	85.23±895.62	0.51
Dose of Aminophylline	60.61±169.44	153.03±239.41	2.55
Dose of theophylline	266.67±119.02	269.7±196.12	0.085
Dose of Fenoterol	2.3±0.47	2.13±0.64	0.1603
Dose of Ipratrapium	0.96±0.13	0.86±0.27	0.048
ICS use*			
Cumulative dose(mcg)	1100416±741957.5	268159±528386.5	< 0.001
Total day of used(mcg/day)	687.93±223.26	303.61±311.08	<0.001
Never user	3(9.09)	77(58.33)	<0.001
Daily dose of ICS*			<0.001
None	3(9.09)	76(57.58)	
Low	2(6.06)	10(7.58)	
Medium	27(81.82)	46(34.85)	
High	1(3.03)	0	
OCS use€			
Cumulative dose(mg)	41073.42±37494.32	30925.11±45439.74	0.237
Total day of used(mg/day)	20.69±9.13	22.33±66.97	0.889
Never user	3(9.09)	50(57.88)	<0.001
Exacerbation			0.468
Yes	26(78.79)	21(15.91)	
No	7(21.21)	111(84.09)	
Severity of COPD			0.062
A group	1(3.03)	18(13.64)	
B group	6(18.18)	27(20.45)	
C group	26(78.79)	76(57.58	
D group	0	11(8.33)	
Time of COPD treatment (days)			
	2416.94±1198.905	3025.5±1249.841	2.522
Duration of treatment(yr)			0.093
< 6.8	22(66.67)	60(45.45)	
6.8 – 11.1	6(18.18)	40(30.30)	
> 11.1	5(15.15)	32(24.24)	

* Budesonide

€ Prednisolone

Table 3 shows the univariate analysis for potential factors influencing the risk of TB development. COPD patient with underweight was associated with TB development (P = 0.009). Likewise, the current active smoker was associated an increased risk of developing TB (P = 0.036). There was no significant association between TB history and risk for TB development. In addition, ICS users were a significantly higher risk for developing TB (OR = 8.41; 95% CI,1.98 to 35.58). Similarly, OCS users were associated with an increased risk for developing TB (OR = 5.52;95% CI, 1.26 to 24.12). Receiving the daily dose of ICS in low quantity was no significantly with TB (p = 0.125) but the patients who received medium dose of ICS could increase risk for developing TB (OR = 15.67;95% CI,3.5 – 69.6). The cumulative dose of ICS shows trend for using of ICS. The patients who received the ICS ≥ 584,000 mcg were at an increased the risk for developing TB (P < 0.001).

Multivariate analysis after adjusting the potential confounder, patients with BMI < 18.5 (kg/m^2) were at an increased the risk for developing TB (aOR = 18.68; 95% CI, 1.04 to 335.16). Smoking status was not associated with TB. Moreover, using of ICS was remained the risk for pulmonary tuberculosis. ICS use was statistically significant at an increased risk for developing TB (aOR = 9.3;95% CI, 1.92 to 45.29). However, OCS use was no significantly associated with developing TB in COPD patient. The variables were recruited at p <0.1 for univariate analysis including smoking status, daily dose of ICS, crowded household, and cirrhosis. There was no association after adjusting OR to increase the risk on TB. (Table.4)

Table.3 Univariate analysis of risk factors for pulmonary tuberculosis in patients with COPD

Variables	Odds ratio*	95% CI	P-value
Personel factor			
Body Mass Index (Kg/m^2)			
Underweight (< 18.5)	7.03	1.62 – 30.4	0.009
Normal weight (18.6 – 22.9)	1	1	
Overweight (> 23)	1.57	0.19 – 12.95	0.672
Education status			
Uneducated	0.23	0.009 – 6.08	0.383
Primary school	0.86	1.14 – 44.39	0.934
Secondary school or higher	1		
Smoking status			
Non smoker	1	1	
Ex-active smoker	1.07	0.29 – 3.92	0.91
Current active smoker	7.11	1.14 – 44.39	0.036
TB history	0.84	0.23 – 3.09	0.8
COPD treatment factor			
ICS use€			
Non – ICS users	1	1	
ICS users	8.41	1.98 – 35.58	0.004
Cumulative dose ICS (mcg)			
None	1	1	
Low (< 584,000 mcg)	0.96	0.1 – 8.5	0.402
Medium (≥ 584,000 - ≤ 1,168,000 mcg)	68.59	7.07 – 664.76	< 0.001
High (> 1,1168,000 mcg)	70.73	2.29 – 747.12	< 0.001
Daily dose of ICS			
None	1	1	

Low	2.44	0.28 – 20.9	0.125
Medium+High	15.67	2.5 – 69.6	< 0.001
OCS use£			
Non-OCS users	1	1	
OCS users	5.52	1.26 – 24.12	0.023
Exacerbations	0.89	0.32 – 2.45	0.835
Severity of COPD			
A group	1	1	
B group	3.81	0.42 – 33.87	1.2
C + D group	5.2	0.67 – 40.34	1.58
Environmental factor			
Contact with TB patient			
Never had TB patient in the house	1	1	
TB patient in the house	1	0.09 – 10.07	1.00
Close contact with TB			
Live in same house, separate rooms	1	1	
Live in same house, used the same bedroom	1.15	0.94 – 3.01	0.76
Crowded household			
< 5	1	1	
≥ 5	2.11	0.94 – 4.73	0.068
Co-morbidities disease factor			
Diabetes	1.14	0.237 – 5.501	0.869
Chronic kidney disease	2.1	0.531 – 8.36	0.299
Cirrhosis	8	0.725 – 88.22	0.08

*Matched gender and age
€Budesonide
£Prednisolone

Analysis according to the cumulative dose of inhaled corticosteroid received in the previous year (Table.5). There was a dose-response relation between cumulative dose and risk of developing TB among COPD patient. Overall, the COPD patients with cumulative dose of ICS higher than 584,000 µg were at an increased risk of TB development (aOR = 70.47; 95% CI, 2.55 to 1941.2). Among users of ICS, no significant relationship of TB development could be demonstrated with low, or medium and high daily dose.

Table.4 Multivariate analysis for adjusted OR of risk factors for pulmonary tuberculosis in patients with COPD

Variables	Odds ratio	95% CI	P-value
Body Mass Index (Kg/m^2)			
Underweight (< 18.5)	16.86	2.26 – 125.39	0.006
Normal weight (18.6 – 22.9)	1	1	
Overweight (> 23)	2.7	0.21 – 33.41	0.437
Smoking status			
Non smoker	1	1	
Ex-active smoker	1	0.19 – 5.15	0.996
Current active smoker	5.2	0.53 – 50.59	0.155
ICS use			
Non – ICS users	1	1	
ICS users	9.3	1.92 – 45.29	0.006
OCS use			
Non – OCS users	1	1	
OCS users	5.5	0.92 – 33.57	0.061
Crowded household			
<5	1	1	
≥5	2.42	0.65-8.97	0.184
Co-morbidities factor			
Cirrhosis	1.2	0.07 – 18.78	0.895

Table.5 Association between cumulative dose of ICS and the risk of TB development in patient with COPD.

Variable	Odds ratio	95% CI	P-value
Daily dose of ICS*			
None	1	1	
Low	4.81[a]	0.19 – 116.45	0.334
Medium + High	3.14[a]	0.21 – 54.73	0.385
Cumulative dose of ICS*(mcg)			
None	1	1	
< 584,000 mcg	0.65[b]	0.06 – 6.97	0.724
≥ 584,000 mcg	74.6[b]	2.66 – 2093.13	0.011

a Matched age and sex. Adjusted for BMI, smoking status, ICS use, OCS use, crowded household, co-morbidities disease, and cumulative dose of ICS

b Matched age and sex. Adjusted for BMI, smoking status, ICS use, OCS use, crowded household, co-morbidities disease, and daily dose of ICS

*Budesonide

Discussion

This study aimed to find out the risk factors was associated with TB in patients with COPD. After adjusting the covariates and also matching for age and gender. The result shows the COPD patient who was BMI < 18.5 or underweight remained as risk factor for developing TB (aOR = 16.86; 95% CI, 2.26 to125.39). Underweight is one of the risk factor for TB. The patient with malnutrition or underweight is more likely to changes in their metabolism of nutrients (i.e. protein, carbohydrate and fat). TB patients are protein breakdown that effects to fever and also worsen under nutrition which

effects to impair resistance against the infection. However, the relationship between TB and nutrition are not clear (Nutrition Information Centre University of Stellenbosch, 2007). Similarly, the previous study of Jick ss et al (2006) found the COPD patients who were BMI < 20 or underweight at an increased risk for TB developed. However, the smoking status variable in this study was not significantly associated with TB. Lin HH et al (2007) conducted a systemic review and mata-analysis to determine the association between smoking, pollution, and tuberculosis their found TB might be related with cigarettes smoked and people who were smoking in the period of study had an increased risk of pulmonary tuberculosis. Additionally, the study of Jick ss et al. (2006) adjusted OR was significantly increased the risk for developing TB in current smoker. In the other hand, Shu cc et al.(2010) was not found the association between smoking and TB after adjusting covariates. Crowded household in this study conducted on the patients with COPD. The association between crowded household of COPD patient and TB were not significantly association. The subjects in this study might be not enough to find the association. Moreover, the community of this people were located on the city. The most family structure was nuclear family. However, Hill PC et al(2006) results found the family member who lived in the house more than 3 people could increase risk of TB. Likewise, the study of Corbett E.L et al (2009) found the family member who lived in the house 2-4 people increased risk of TB. Moreover, the study of Tipayamongkholgul M et al(2005) conducted on Thailand found the household with an average family members 5 people or more per one room were significantly at an increased risk of TB. The co-morbidities disease including diabetes mellitus, cirrhosis, and chronic kidney disease were the most common underlying disease in COPD patient. However, the several studies (Jick et al, 2006; Lee et al, 2012; Shu et al, 2010;) showed that co-morbidities were associated with TB activation. Unfortunately, sample size in this study was small, the results was not exhibited the association between co-morbidities disease and TB developed.

Using of ICS was significantly at an increased risk for developing TB (aOR = 9.3; 95% CI, 1.92 to 45.29). COPD patients were prescribed by doctor with budesonide and bronchodilators either, dispensed alone or in a combination inhaler with an inhaled β_2 – agonist. The previous study of Jick SS et al. (2006) performed COPD patients with ICS more likely to increased risk of developing TB especially, patients who ever received corticosteroid recently. Similarly, the study of Brassard P et al.(2011) were identified the effect of ICS with patients who received ICS therapy during the study it could be increased risk of TB. Furthermore, there is evidence of Lee CH(2012) to suggest that the relationship between ICS and risk of TB were depended on dose dependent. OCS use nearly to significantly association with TB. The sample size was small, but the results were important despite this. In addition, this study was found the effect of ICS quantity on the risk of TB development. We stratified the cumulative dose of ICS for explore with a dose-dependent. Besides, this study showed that quantity of cumulative ICS higher than 584,000 mcg was significantly associated with an increased risk of TB development among inhaler users. Although, the biological of the association of ICS therapy with tuberculosis remains unclear. The potential explanation is that ICS therapy may increases tuberculosis risk in COPD patients by increasing local airway immunosuppression. The main immune protection mechanism of TB is cellular immunity and ICS could decline local immunity of lungs. Furthermore, ICS could easily provide the latent infection of mycobacterium TB for the patients with prior tuberculosis. This could decrease the ability of the innate immune system to defend against primary bacterial infections or post viral super infections. Glucocorticoids can invade with the division and proliferation of lymphoid tissue under the action of antigen, and blockage the accumulation of monocytes and macrophages induced by sensitized T lymphocyte, and then suppress the immunization. Accordingly, using of high dose of ICS can increase the opportunity to infect mycobacterium. (Drummond MB, 2008; Ni et al, 2014; Suissa et al, 2007)Consistent with this hypothesis, our results demonstrated that higher ICS doses are associated with increased tuberculosis risk in a dose-dependent. Nevertheless, there were some limitations in this study. Firstly, The sample size is not large enough to provide decisional clinical evidence, but the results were important despite this. Secondly, the studies were conducted in only one tertiary hospital; therefore the conclusions might not be generalized to Thailand population. Thirdly, this study lack of D groups of the severity of disease also lack of the highest dose of ICS category because the doctor unlikely to prescribed high dose of ICS. Fourthly, it might be recall bias for the patients by interviewed because some patients no concern of treatment. They cannot remember the first infected active TB (if they ever had TB history).

Suggestion

Considering the results, this data were obtained from tertiary hospital for study of 33 COPD/TB patients and 132 COPD patients determined the effect of use of corticosteroid in long-term. There shows the association of use of ICS and TB include dose-depended of ICS used. The ICS user was an associated 9.3-fold increased risk for developing TB. Also COPD patients with higher dose than 584,000 µg was significantly increased risk for developing TB (P = 0.011). More large scale, well designed, high quality studies are required to validate our findings. More sample size and different types of respiratory diseases should also be considered to study in future. The findings explore the effect of use of corticosteroids in long-term to the COPD patients for developing TB. The clinicians should be carefully and aware to prescribing the long-term use of corticosteroids to patients.

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