Original paper

Chronic Respiratory Disease

Chronic Respiratory Disease
Volume 16: 1–11

DOI: 10.1177/1479973118815694
journals.sagepub.com/home/crd

SAGE

Clinical outcomes of theophylline use as add-on therapy in patients with chronic obstructive pulmonary disease: A propensity score matching analysis

Preyanate Wilairat[1,2], Kirati Kengkla[1,2], Chaiyawat Thayawiwat[1], Phongsathorn Phlaisaithong[1], Supakorn Somboonmee[1] and Surasak Saokaew[1,2,3]

Abstract

To examine clinical outcomes of theophylline use in patients with chronic obstructive pulmonary disease (COPD) receiving inhaled corticosteroids (ICS) and long-acting beta-2 agonists (LABA). Electronic data from five hospitals located in Northern Thailand between January 2011 and December 2015 were retrospectively collected. Propensity score (PS) matching (2:1 ratio) technique was used to minimize confounding factors. The primary outcome was overall exacerbations. Secondary outcomes were exacerbation not leading to hospital admission, hospitalization for exacerbation, hospitalization for pneumonia, and all-cause hospitalizations. Cox's proportional hazards models were used to estimate adjusted hazard ratio (aHR) and 95% confidence interval (CI). After PS matching, of 711 patients with COPD (mean age: 70.1 years; 74.4% male; 60.8% severe airflow obstruction), 474 theophylline users and 237 non-theophylline users were included. Mean follow-up time was 2.26 years. Theophylline significantly increased the risk of overall exacerbation (aHR: 1.48, 95% CI: 1.11–1.96; $p = 0.008$) and exacerbation not leading to hospital admission (aHR: 1.47, 95% CI: 1.06–2.03; $p = 0.020$). Theophylline use did not significantly increase the risk of hospitalization for exacerbation (aHR: 1.11, 95% CI: 0.79–1.58; $p = 0.548$), hospitalization for pneumonia (aHR: 1.28, 95% CI: 0.89–1.84; $p = 0.185$), and all-cause hospitalizations (aHR: 1.03, 95% CI: 0.80–1.33; $p = 0.795$). Theophylline use as add-on therapy to ICS and LABA might be associated with an increased risk for overall exacerbation in patients with COPD. A large-scale prospective study of theophylline use investigating both safety and efficacy is warranted.

Keywords

Theophylline, exacerbation, hospitalization, pneumonia, chronic obstructive pulmonary disease

Date received: 21 June 2018; accepted: 6 October 2018

[1] School of Pharmaceutical Sciences, University of Phayao, Phayao, Thailand
[2] Center of Health Outcomes Research and Therapeutic Safety (Cohorts), School of Pharmaceutical Sciences, University of Phayao, Phayao, Thailand
[3] School of Pharmacy, Monash University Malaysia, Selangor, Malaysia

Corresponding author:
Surasak Saokaew, Center of Health Outcomes Research and Therapeutic Safety (Cohorts), School of Pharmaceutical Sciences, University of Phayao, Phayao, 56000 Thailand.
Emails: surasak.sa@up.ac.th; saokaew@gmail.com

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive complex lung disease, which is a leading cause of death and a significant burden on the healthcare system worldwide.[1–3] Current clinical practice guidelines for COPD management recommend short-acting bronchodilators or long-acting bronchodilators for patients with low-risk of exacerbations and step-up to inhaled corticosteroids (ICS) with long-acting beta-2 agonists (LABA) in moderate to severe airflow limitation with high risk of exacerbations.[4] Theophylline may be prescribed to control symptoms if other choices are unaffordable.[4]

Theophylline is a xanthine derivative that has been used as a conventional bronchodilator to control symptoms in patients with COPD for more than 80 years.[5] Theophylline was prescribed to 35% of patients with COPD in the past and up to 64% in Taiwan because theophylline is convenient to use and inexpensive.[5–7] Previous randomized controlled trials showed that theophylline monotherapy could decrease respiratory symptoms and exacerbation rate.[8,9] Theophylline might enhance the anti-inflammatory effects of ICS, lead to an increased ability to control symptoms, and improve lung function.[1] When theophylline is used as add-on therapy to the combination of ICS and LABA, theophylline also demonstrated high efficacy to reduce symptoms and improve lung function.[10] However, theophylline has lower efficacy to control symptoms and was associated with higher side effects than LABA monotherapy and in combination with ICS.[11–13]On the contrary, a previous retrospective cohort indicated that theophylline use was associated with a significantly increased risk of exacerbations and hospitalizations in patients receiving any COPD regimen.[14]

To the best of our knowledge, evidence to confirm clinical outcomes of theophylline use as add-on therapy to the combination of ICS and LABA in COPD patients in real-world practice remains unclear. Consequently, we aimed to perform a propensity score (PS) matching analysis to clarify the risk and benefit of theophylline use as add-on therapy to the combination of ICS and LABA in patients with COPD.

Methods

Study design and data source

A multicenter retrospective cohort study was performed. We collected data from the COPD Clinic Registry from five medical center hospitals in Northern of Thailand. Data consisted of COPD diagnosis date, lung function (forced expiratory volume in 1 second (FEV1) and forced vital capacity), COPD Assessment Test (CAT) score, modified Medical Research Council (mMRC) Dyspnea Scale score, and smoking status. Patient demographic, date of birth, comorbidity using the International Statistical Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM), and prescription records were collected from the electronic database from all five hospitals. All data were collected between January 2011 and December 2015. This study was approved by the Research Ethics Committee of the Division of Research Administration and Educational Quality Assurance, University of Phayao, Phayao, Thailand (No. 2/061/59).

Sample size estimation

We estimated the sample size based on the primary outcome (overall exacerbations). Based on an HR 1.41 in the theophylline group versus the non-theophylline group with a 3.5-year follow-up period reported in a previous study, a sample size of 160 patients per group would be required to have a statistical power of 80% and type-1 error of 5%.[14]

Study population

We included patients diagnosed with COPD (ICD-10 code J44x) and registered in the COPD Clinic National Registry. The definition of COPD was based on the Global Initiative on Obstructive Lung Disease, and the severity was classified by the combined COPD assessment tool.[4] Patients were excluded if they did not receive combination ICS and LABA therapy, received aminophylline or doxophylline, the duration of ICS and LABA use was less than 6 months, or had asthma with ICD-10 code of J45x, to exclude COPD overlap syndrome. Patients were divided into two groups, patients who received theophylline (exposure group) and patients who did not receive theophylline (non-exposure group). Patients were followed from index date (the beginning time of receiving theophylline with ICS+LABA or ICS+LABA without theophylline) until the end of the study (December 31, 2015), the regimen changed, lost to follow-up, or death, whichever occurred first.

Outcome measures

The primary outcome was overall exacerbations, defined as the occurrence of acute COPD exacerbation (ICD-10 code J441). Secondary outcomes were exacerbation not leading to hospital admission (outpatient exacerbation), hospitalization for exacerbation (inpatient exacerbation), hospitalization for pneumonia (ICD-10 code J12x-J18x and J440), and all-cause hospitalizations.

Statistical analyses

Baseline characteristics were measured before the patient's index date and presented as numbers with a percentage or mean, along with standard deviation (SD) or median with interquartile range as appropriate. Patient characteristics were compared using an exact probability test for categorical variables and an independent *t*-test or Wilcoxon rank sum test for continuous variables as appropriate. Since the amount of missing data varied from 0.7% to 22.6% for any single variables, we used multiple imputation by chained-equations to impute missing values of co-variables for eligible participants based on patients who provided observable data according to the method described by Royston.[15,16] The distributions of the variables did not differ substantially between participants with observed data and those with imputed data (see the Online Supplementary Appendix).

Because of the non-randomized study design, certain baseline characteristics between groups might be different. Thus, we used a PS matching method to minimize confounding factors.[17,18] We calculated PS using a multivariable logistic regression. The variables included in the PS calculation were age, gender, duration of COPD, severity of COPD, CAT score, smoking status, and baseline covariates with an inclusion criterion of p-value < 0.1.[19]

We used Cox's proportional hazard model to estimate the hazard ratio between theophylline use and clinical outcomes. The potential prognostic factors including, gender, age, duration of COPD, severity of COPD, smoking status, number of pack-years of smoking, reliever and controller medications, other concomitant drugs, percentage of compliance, and Charlson comorbidity index were adjusted in the model.[20,21] Additionally, we used generalized estimating equation analysis and Prentice–Williams–Peterson elapse time for recurrent event data.[22] We estimated the proportional hazards assumption with the Schoenfeld residuals test and complementary log–log plots.[23] We used time-varying covariates in the model to fit nonproportional hazard when nonproportional hazard variables were found.[24] Subgroup analyses were performed to examine the association between overall exacerbations and each factor of interest including: age (<60 and ≥60 years), gender (male and female), smoking status (never, ex-smoker, and smoker), the prescribed daily dose of theophylline (≤200 and >200 mg per day), and risk and symptom category to perform the treatment effects in each subcohort of COPD patients. To test the robustness of the results, analysis by excluding cases with missing smoking status, mMRC score, and post-predicted FEV1 was also conducted.

Cumulative incidence curves, adjusted hazard ratios (aHRs), and 95% confidence intervals (95% CIs) were reported. All analyses were performed using STATA version 14 (StataCorp, College Station, Texas, USA). All statistical tests were two-sided tests, where $p < 0.05$ indicated significance.

Results

Baseline characteristics

A total of 2485 COPD patients were identified. Of these, 1230 patients were excluded according to exclusion criteria (Figure 1). The major reasons for exclusion were no combination ICS and LABA therapy and a follow-up time of less than 6 months; 1255 COPD patients were included (Figure 1). Of the included patients, 1009 patients were theophylline users (exposed group) and 246 were non-theophylline users (nonexposed group). Demographic and clinical characteristics of the two groups are shown in Table 1.

In the unmatched cohort, patients between the two groups were imbalanced in some characteristics such as smoking history, duration of COPD, severity of COPD, and some comorbidities (Table 1).

After matching patients in a 2:1 ratio using PSs, 711 patients were included where 474 patients were assigned to the exposed group and 237 were assigned to the nonexposed group. The characteristics of the two groups were similar with a mean PS of 0.77 (SD: 0.76–0.78). The distribution of PS between groups before and after matching can be seen in Figure 2. Patient characteristics between the two groups (i.e. duration of COPD, severity of COPD, smoking status) were largely similar between two groups after propensity matching (Table 1). The majority of patients were

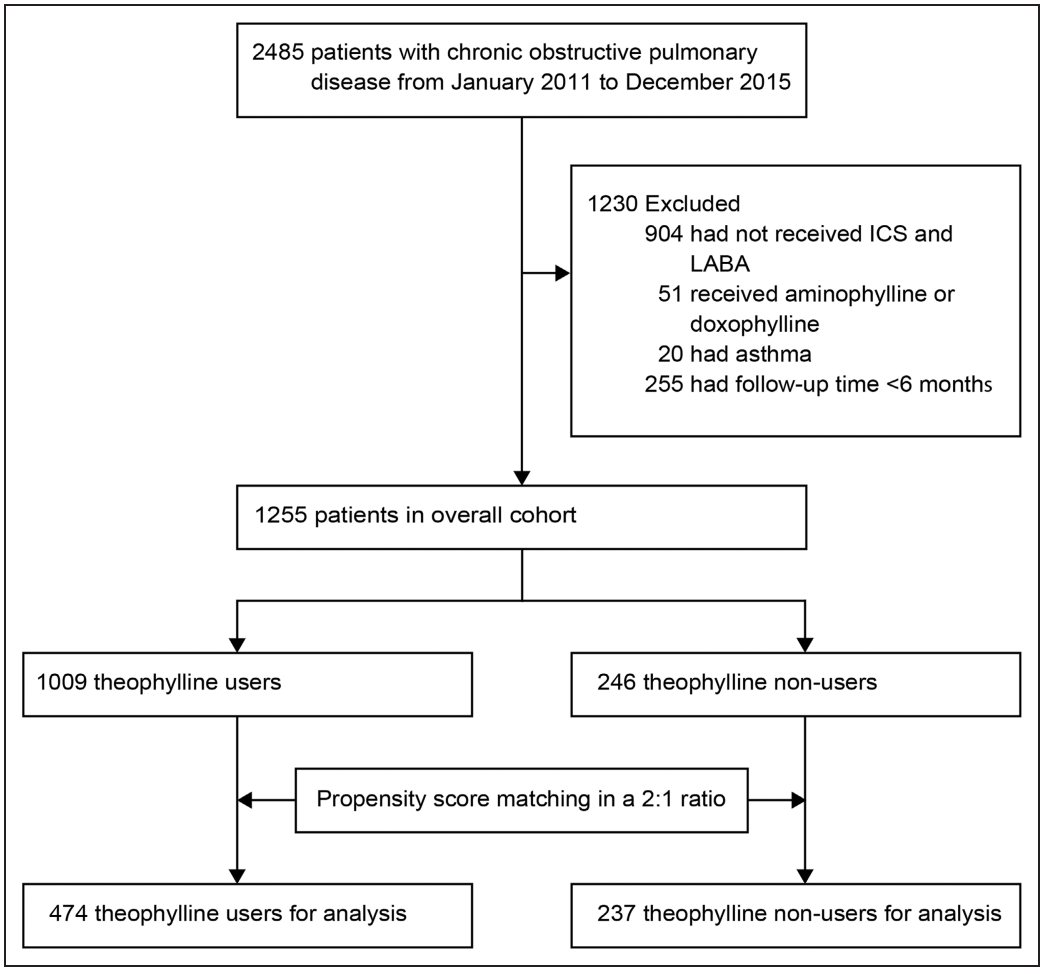

Figure 1. Cohort selection flow.

Table 1. Baseline characteristics.

	Unmatched cohort			Propensity-matched cohort (2:1)		
Characteristics	Theophylline ($n = 1009$)	Non-theophylline ($n = 246$)	*p*-Value	Theophylline ($n = 474$)	Non-theophylline ($n = 237$)	*p*-Value
Age (years)	69.93 (10.53)	70.53 (11.35)	0.432	70.02 (10.68)	70.29 (11.41)	0.755
Male	763 (75.62)	182 (73.98)	0.621	350 (73.84)	179 (75.53)	0.650
BMI (kg/m^2)	20.22 (4.23)	20.70 (4.69)	0.114	20.49 (4.25)	20.68 (4.70)	0.585
Smoking status						
Ex-smoker	832 (82.46)	179 (72.76)	0.040	380 (80.17)	176 (74.26)	0.161
Smoker	41 (4.06)	15 (6.10)		14 (2.95)	15 (6.33)	
Number of pack-years of smoking	13.50 (4.50–25.00)	11.50 (2.00–25.00)	0.225	12.00 (3.00–23.00)	12.50 (4.50–25.50)	0.391
Duration of COPD (years)	6.70 (8.01)	5.44 (7.23)	0.007	5.64 (6.72)	5.54 (7.32)	0.670
CAT score $\geq$ 10 points	344 (34.09)	37 (15.04)	<0.001	85 (17.93)	37 (15.61)	0.462
mMRC score $\geq$ 2 points	343 (33.99)	56 (22.76)	0.001	109 (23.00)	56 (23.63)	0.851
Post-predicted %FEV1	56.33 (14.68)	59.53 (13.69)	0.002	59.14 (14.70)	59.31 (13.77)	0.884

(continued)

Table 1. (continued)

Characteristics	Unmatched cohort			Propensity-matched cohort (2:1)		
	Theophylline ($n = 1009$)	Non-theophylline ($n = 246$)	p-Value	Theophylline ($n = 474$)	Non-theophylline ($n = 237$)	p-Value
Previous exacerbation (not leading to hospital admission) within 1 year						
1	111 (11.00)	24 (9.76)	0.025	55 (11.60)	23 (9.70)	0.522
2	56 (5.55)	5 (2.03)		18 (3.80)	5 (2.11)	
3+	101 (10.01)	17 (6.91)		38 (8.02)	17 (7.17)	
Previous OPD exacerbation leading to hospital admission within 1 year						
1	105 (10.41)	17 (6.91)	0.046	29 (6.12)	17 (7.17)	0.829
2	61 (6.05)	7 (2.85)		14 (2.95)	7 (2.95)	
3+	41 (4.06)	8 (3.25)		12 (2.53)	8 (3.38)	
Severity of COPD						
Low risk—low symptoms	225 (22.30)	54 (21.95)	<0.001	105 (22.15)	54 (22.78)	0.979
Low risk—high symptoms	182 (18.04)	40 (16.26)		80 (16.88)	40 (16.88)	
High risk—low symptoms	303 (30.03)	116 (47.15)		221 (46.62)	107 (45.15)	
High risk—high symptoms	299 (29.63)	36 (14.63)		68 (14.35)	36 (15.19)	
Comorbidity						
Chronic heart failure	110 (10.90)	34 (13.82)	0.219	49 (10.34)	32 (13.50)	0.213
Pulmonary disease	1009 (100.00)	246 (100.00)	1.000	474 (100.00)	237 (100.00)	1.000
Liver disease	20 (1.98)	8 (3.25)	0.230	8 (1.69)	8 (3.38)	0.181
Renal disease	172 (11.05)	43 (17.48)	0.851	75 (15.82)	42 (17.72)	0.521
Tuberculosis	106 (10.51)	26 (10.57)	1.000	37 (7.81)	25 (10.55)	0.259
CCI score, median (range)	2 (1–3)	2 (1–3)	0.057	2 (1–3)	2 (1–3)	0.570
Controller medications						
LABA and ICS	1009 (100.00)	246 (100.00)	1.000	474 (100)	237 (100)	1.000
LAMA	292 (28.94)	62 (25.20)	0.269	135 (28.48)	59 (24.89)	0.327
Reliever medications						
SABA	248 (24.58)	35 (14.23)	<0.001	76 (16.03)	34 (14.35)	0.364
SABA and SAMA	935 (92.67)	213 (86.59)	0.003	415 (87.55)	205 (86.50)	0.647
Concomitant drugs						
Statins	324 (32.11)	108 (43.90)	0.001	201 (42.41)	101 (42.62)	0.817
ACEI or ARB	358 (35.48)	113 (45.93)	0.003	179 (37.76)	89 (37.55)	0.643
Influenza vaccine	112 (11.10)	5 (2.03)	<0.001	12 (2.53)	5 (2.11)	0.625
Short-course oral corticosteroids used	463 (45.89)	76 (30.89)	<0.001	149 (31.43)	75 (31.65)	0.727
Mean percentage of compliance	92.49 (6.93)	90.39 (5.75)	<0.001	91.68 (6.63)	91.35 (5.75)	0.239
Propensity score	0.81 (0.81–0.82)	0.76 (0.75–0.77)	<0.001	0.77 (0.76–0.78)	0.77 (0.76–0.78)	0.591

BMI: body mass index; COPD: chronic obstructive pulmonary disease; CAT: COPD Assessment Test; mMRC: modified Medical Research Council; FEV1: forced expiratory volume in 1 second; CCI: Charlson comorbidity index; LABA, long acting beta2-agonists; ICS: inhaled corticosteroids; LAMA: long-acting muscarinic antagonists; ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blocker; SABA: short-acting beta-2 agonists; SAMA: short-acting muscarinic antagonists.

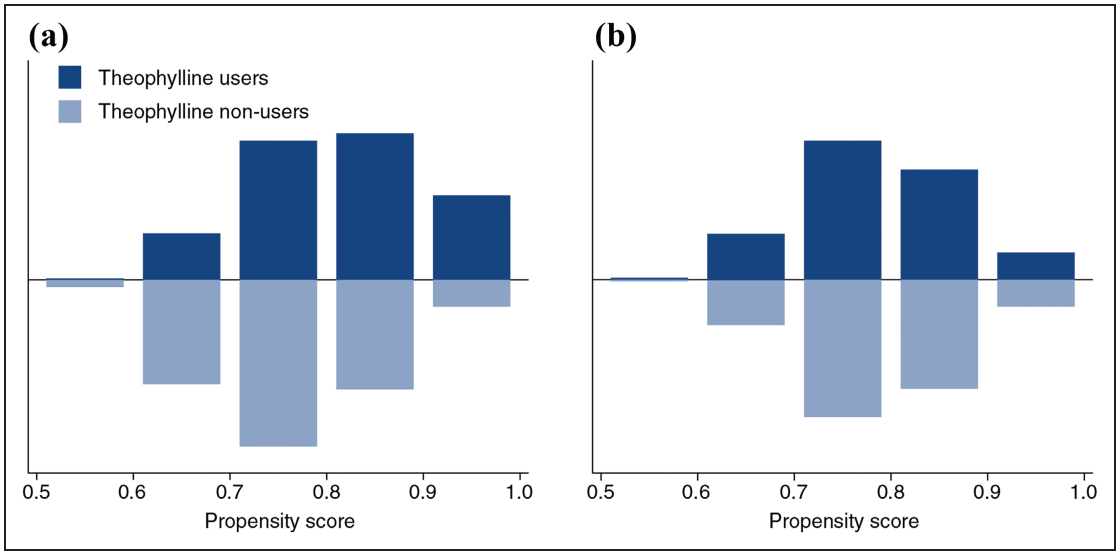

Figure 2. Distribution of propensity score. (a) Propensity score before matching and (b) propensity score after matching.

Table 2. Association between theophylline users and clinical outcomes.[a]

Outcomes	Cox proportional hazards regression	*p*-Value	Propensity score matched Cox proportional hazards regression	*p*-Value
Overall COPD exacerbations	1.72 (1.31–2.25)	<0.001	1.48 (1.11–1.96)	0.008
Inpatient COPD exacerbations	1.52 (1.09–2.14)	0.015	1.11 (0.79–1.58)	0.548
Outpatient COPD exacerbations	1.48 (1.01–2.18)	0.047	1.47 (1.06–2.03)	0.020
Pneumonia	1.27 (0.89–1.81)	0.184	1.28 (0.89–1.84)	0.185
All-cause hospitalizations	1.12 (0.90–1.39)	0.310	1.03 (0.80–1.33)	0.795

COPD: chronic obstructive pulmonary disease.
[a] Data are adjusted hazard ratios (aHR) by age, gender, duration of COPD, severity of COPD, smoking status, number of pack-years of smoking, reliever and controller medications, other concomitant drugs, percentage of compliance and Charlson comorbidity index with 95% confidence intervals (CI), unless otherwise specified.

male ($n = 529$, 74.40%) and the mean age of the matched cohort was 70.11 years (SD = 10.92). Mean duration of COPD was 5.61 years (SD = 6.92). Most cases ($n = 432$, 60.76%) were considered at high risk of a COPD exacerbation.

Unmatched cohort analyses

The multivariable regression analysis indicated that theophylline use significantly increased the risk of overall exacerbations (aHR: 1.72, 95% CI: 1.31–2.25; $p < 0.001$), outpatient exacerbations (aHR: 1.48, 95% CI: 1.01–2.18), and exacerbations requiring admission (aHR: 1.52, 95% CI: 1.09–2.14; $p = 0.015$). However, theophylline use did not significantly increase the risk of hospitalization for pneumonia (aHR: 1.27, 95% CI: 0.89–1.81; $p = 0.184$) and all-cause hospitalizations (aHR: 1.12, 95% CI: 0.90–1.89; $p = 0.310$) compared to non-theophylline users (Table 2).

Propensity-matched cohort analyses

Results from the PS matching analysis using Cox's proportional hazards model were similar to those from the unmatched analysis. Theophylline use significantly increased the risk of overall exacerbations (aHR: 1.48, 95% CI: 1.11–1.96; $p = 0.008$) and outpatient exacerbations (aHR: 1.47, 95% CI: 1.06-2.03; $p = 0.020$), but did not significantly increase the risk of exacerbation requiring hospital admission (aHR: 1.11, 95% CI: 0.79–1.58; $p = 0.548$; Table 2 and Figure 3), hospitalization for pneumonia (aHR: 1.28, 95% CI: 0.89–1.84; $p = 0.185$), and all-cause hospitalizations (aHR: 1.03, 95% CI: 0.80–1.33; $p = 0.795$) compared with non-theophylline users (Table 2 and Figure 4).

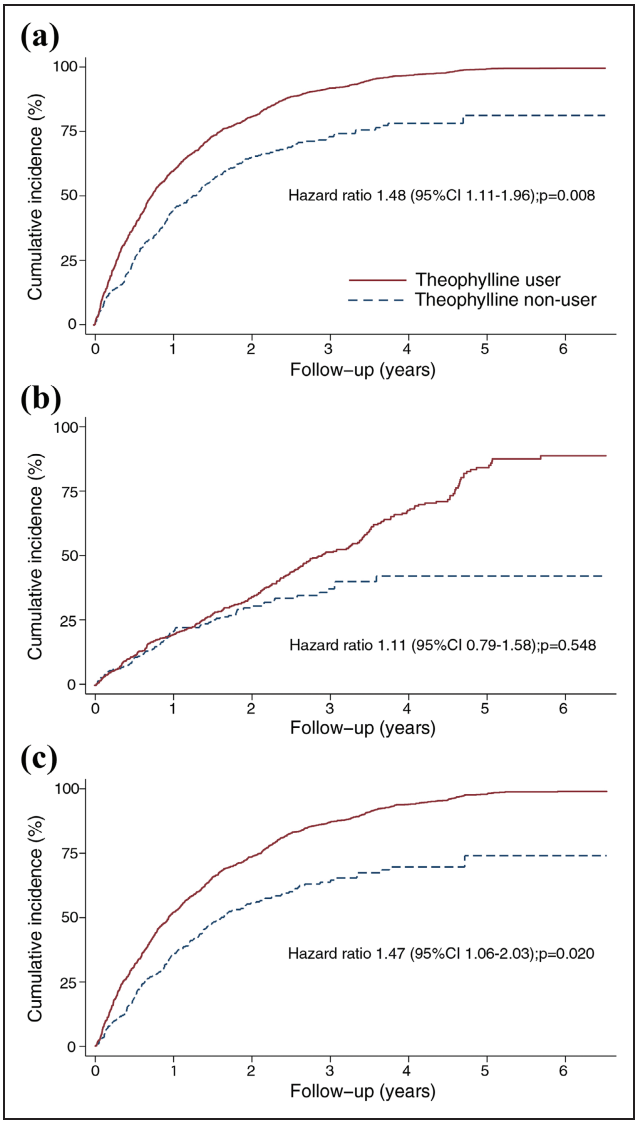

Figure 3. Cumulative incidence of (a) overall COPD exacerbations, (b) inpatient COPD exacerbations, and (c) outpatient COPD exacerbations, among matched patients with COPD receiving ICS and LABA, according to theophylline use. COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonists.

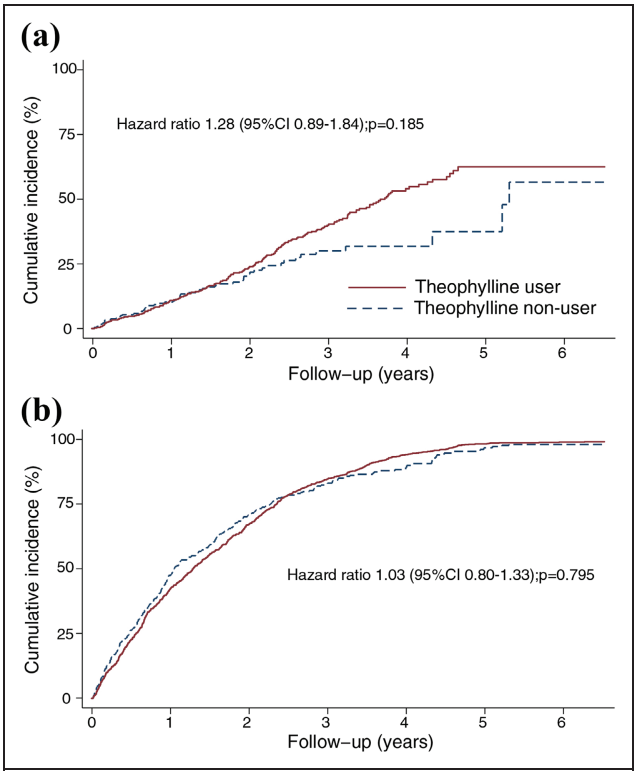

Figure 4. Cumulative incidence of (a) pneumonia and (b) all-cause hospitalizations, among matched patients with COPD receiving ICS and LABA, according to theophylline use. COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonists.

Subgroup analyses

In subgroup analyses of the matched cohort for overall exacerbation, theophylline use showed an increased risk of overall exacerbation in most subgroups. Exacerbations are significantly increased in patients aged >60 years (aHR: 1.23, 95% CI: 1.17–2.12), ex-smoker patients (aHR: 1.39, 95% CI: 1.02–1.90), patients at high risk for exacerbations (aHR: 1.44, 95% CI: 1.03–2.00), and patients with more symptoms (aHR: 2.16, 95% CI: 1.41–3.29), but were not significantly increased in patients aged <60 years and smoker patients. As predicted, high-dose theophylline (more than 200 mg per day) consumption displayed a significantly increased risk of overall exacerbations (aHR: 1.92, 95% CI: 1.41–3.29), whereas low-dose theophylline (less than or equal to 200 mg per day) intake was not associated with an increase in overall exacerbations (aHR: 0.93, 95% CI: 0.66–1.32; Figure 5).

Discussion

To the best of our knowledge, this is the first multicenter cohort study with propensity matching analysis that provides the clinical experiences of theophylline use as add-on therapy in patients with COPD receiving combination ICS and LABA therapy. We found theophylline use was associated with an increased risk of overall COPD exacerbations and outpatient exacerbations. A majority of patients in the cohort had severe airflow limitation with a high risk of exacerbation, particularly in the elderly patients. Although there was no statistically significant difference

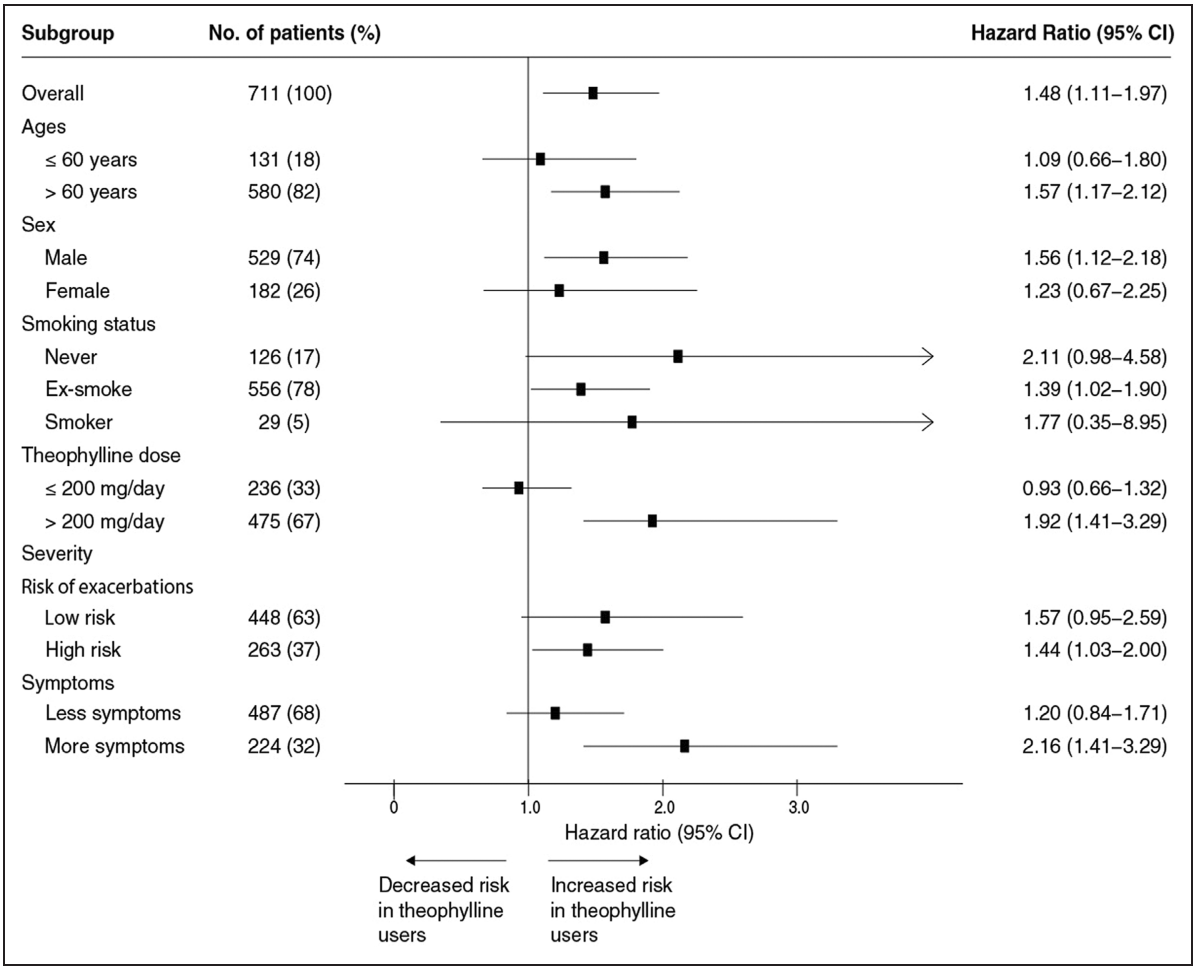

Figure 5. The risk of overall exacerbations with theophylline use in subgroups of matched patients with COPD receiving ICS and LABA. COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonists.

between the two groups in all-cause hospitalization and hospitalization for pneumonia, theophylline used trended to be associated with a higher risk of all-cause hospitalizations compared to the non-theophylline group. This study does not support the use of theophylline to control symptoms of COPD patients even when used as an add-on therapy to ICS+LABA since the results indicated no additional benefit in the management of COPD in routine clinical practice.

The current findings on theophylline use and clinical outcomes were similar to those of previous studies, which found that theophylline used as combination therapy with any COPD regimens significantly increased the risk of the first exacerbation (HR: 1.41, 95% CI: 1.24–1.60) compared with non-exposed group.[14] The finding from another pilot clinical trial found that the combination of low-dose oral theophylline and ICS was not associated with increased exacerbation rate compared with ICS monotherapy.[25] However, exacerbation rate was observed more frequently in the intervention group.

Regarding the risk of hospitalization, our findings were not similar to previous studies. Cyr et al. reported that theophylline used in combination with ICS may lower the likelihood of overall exacerbation (RR: 0.89, 95% CI: 0.87–0.92) compared with those receiving combination in LABA and ICS therapy.[26]

Based on current evidence, theophylline may enhance immunosuppressive effects of ICS by restoring corticosteroid sensitivity through increased histone deacetylases[27,28] and may increase the risk of pneumonia and COPD exacerbation.[1,29,30] However, other possible causes, which might affect the association between theophylline use and exacerbations, were drug interactions and adverse drug events. Additionally, results from subgroup analyses displayed

that an increase in overall COPD exacerbations were observed when using high-dose theophylline. This association may be considered as a dose–response effect (see the Online Supplementary Appendix). However, further studies needed to be conducted to understand the association and mechanism behind theophylline use with ICS.

This study indicates that there are no additional benefits from the use of theophylline to reduce exacerbations and hospitalization rates, even used as an add-on therapy to ICS plus LABA according to the recommendations from clinical practice guideline.[4] However, theophylline may be useful to reduce respiratory symptoms if the other choices are unavailable or unaffordable due to lack of clinical benefit, ineffectiveness, or poor tolerability even in additional to ICS or long-acting bronchodilators.[3] To date, evidences suggest that theophylline has limitations in terms of its efficacy[11,12] and has many adverse effects. Palpitation, tremor, and other arrhythmia were frequently reported.[5,9,31,32] Additionally, a previous meta-analysis of seven observational studies illustrated that theophylline use was associated with a significantly increased all-cause mortality risk in COPD patients.[33] Thus, prescribing of theophylline should be approached with caution due to the increased risk of exacerbation of concurrent conditions such as seizure disorders and cardiac arrhythmias.

The study has some limitations. There are a number of significant differences in baseline characteristics due to the retrospective nature of the study and unknown prescribing patterns. This was addressed using PS matching by disease severity and other factors, including smoking status, duration of COPD, lung function, respiratory symptoms, history of exacerbation, comorbidities, and concomitant drug use. We found that the results remained similar before and after PS matching (Table 2). However, conclusions of this study are limited as the study population may not be representative of the total population. The present study has no information on lifestyle parameters, primary health-care data, or socioeconomic data, and consequently, there may be remaining confounding factors. Although a PS-matching method was used to adjust for known baseline characteristics, the residual bias and confounders from unmeasured variables may have influenced the findings.[34] Further prospective cohort studies should be conducted to confirm these findings. This study has no data on serum concentrations of theophylline to confirm whether theophylline was associated with an increased risk of exacerbation from supratherapeutic or subtherapeutic level. Moreover, the effects of drug interactions cannot be ruled out. Data were collected from hospitals in rural communities with a higher prevalence and severity of COPD,[35] which might limit the generalizability in urban community or in country with low prevalence of COPD.

Several strengths of this study should be highlighted. First, this is an observational design which reflects the effect of theophylline use in real-world clinical practice. Thus, it provides a high external validity and can be generalized to other populations with similar circumstances. Second, the sample size in this study is large enough to allow us to examine the effect of theophylline as an add-on therapy to a combination of ICS and LABA. Sensitivity analyses can be done to ensure the robustness of the estimates effect size. Third, our propensity matching technique minimizes bias by comparing groups with similar observed characteristics, without specifying the relationships between confounders and outcomes.[36]

In conclusion, there is no additional benefit adding theophylline with a combination of ICS and LABA to control symptoms in patients with stable COPD. Theophylline use with a combination of ICS and LABA was associated with a significantly increased risk of overall exacerbation in patient with COPD. Although this study has some limitations, these findings reflect real-world practice. Prescribing of theophylline should be approached with caution. Well-designed, large-scale, prospective studies of theophylline use in COPD patients will help to provide more definitive evidence on this issue.

Authors' note

This study was partially presented as abstract form in ISPOR 20th Annual European Congress Conference on November 7, 2017 in Glasgow, Scotland, UK.

Acknowledgements

The authors would like to thank Eric Baehr (The University of Illinois at Chicago College of Pharmacy) for proofreading and English language review and Assist. Prof. Napawan Jeanpeerapong, Department of Pharmacy, Buddhachinaraj Regional Hospital, Phitsanulok, Thailand, for providing data.

Authors' contributions

PW, KK, and S. Saokaew conceived and designed the study. CT, PP, S. Sombunmee, and PW collected and

manipulated data. PW, KK, and PP conducted the statistical analysis and interpretation of data. PW, KK, CT, and S. Sombunmee wrote the manuscript. S. Saokaew contributed a critical revision of the manuscript and prepared final editing to the manuscript. All authors participated in the review and final approval of the manuscript to be published.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the School of Pharmaceutical Sciences, University of Phayao, Phayao, Thailand (grant number PHAR 001/2016).

ORCID iD

Surasak Saokaew https://orcid.org/0000-0002-1382-0660

Supplemental material

Supplemental material for this article is available online.

References

1. Ford PA, Durham AL, Russell RE, et al. Treatment effects of low-dose theophylline combined with an inhaled corticosteroid in COPD. *Chest* 2010; 137: 1338–1344.
2. Dhamane AD, Moretz C, Zhou Y, et al. COPD exacerbation frequency and its association with health care resource utilization and costs. *Int J Chron Obstruct Pulmon Dis* 2015; 10: 2609–2618.
3. Ko FW, Chan KP, Hui DS, et al. Acute exacerbation of COPD. *Respirology* 2016; 21: 1152–1165.
4. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management and prevention of COPD, https://goldcopd.org/global-strategy-diagnosis-management-prevention-copd-2016/ (2016).
5. Barnes PJ. Theophylline. *Am J Respir Crit Care Med* 2013; 188: 901–906.
6. Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008; 359: 1543–1554.
7. Devereux G, Cotton S, Barnes P, et al. Use of low-dose oral theophylline as an adjunct to inhaled corticosteroids in preventing exacerbations of chronic obstructive pulmonary disease: study protocol for a randomised controlled trial. *Trials* 2015; 16: 267.
8. Zhou Y, Wang X, Zeng X, et al. Positive benefits of theophylline in a randomized, double-blind, parallel-group, placebo-controlled study of low-dose, slow-release theophylline in the treatment of COPD for 1 year. *Respirology* 2006; 11: 603–610.
9. Ram FS, Jardin JR, Atallah A, et al. Efficacy of theophylline in people with stable chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Respir Med* 2005; 99: 135–144.
10. Subramanian, Ragulan, Jindal A, et al. The study of efficacy, tolerability and safety of theophylline given along with formoterol plus budesonide in COPD. *J Clin Diagn Res* 2015; 9: OC10–OC13.
11. Broseghini C, Testi R, Polese G, et al. A comparison between inhaled salmeterol and theophylline in the short-term treatment of stable chronic obstructive pulmonary disease. *Pulm Pharmacol Ther* 2005; 18: 103–108.
12. Rossi A, Kristufek P, Levine BE, et al. Comparison of the efficacy, tolerability, and safety of formoterol dry powder and oral, slow-release theophylline in the treatment of COPD. *Chest* 2002; 121: 1058–1069.
13. Cazzola M, Noschese P, Centanni S, et al. Salmeterol/fluticasone propionate in a single inhaler device versus theophylline+fluticasone propionate in patients with COPD. *Pulm Pharmacol Ther* 2004; 17: 141–145.
14. Fexer J, Donnachie E, Schneider A, et al. The effects of theophylline on hospital admissions and exacerbations in COPD patients: audit data from the Bavarian disease management program. *Dtsch Arztebl Int* 2014; 111: 293–300.
15. Rubin DB. Multiple imputation after 18+ years. *J Am Stat Assoc* 1996; 91: 473–489.
16. Royston P. Multiple imputation of missing values. *Stata J* 2004; 4: 227–241.
17. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res* 2011; 46: 399–424.
18. Guo S and Fraser MW. *Propensity score analysis: statistical ethods and Applications. Advanced quantitative techniques in the social sciences series*. Los Angeles: SAGE, 2010.
19. Patrick AR, Schneeweiss S, Brookhart MA, et al. The implications of propensity score variable selection strategies in pharmacoepidemiology: an empirical illustration. *Pharmacoepidemiol Drug Saf*. 2011; 20: 551–559.

20. Spruance SL, Reid JE, Grace M, et al. Hazard ratio in clinical trials. *Antimicrob Agents Chemother* 2004; 48: 2787–2792.
21. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 40: 373–383.
22. Sagara I, Giorgi R, Doumbo OK, et al. Modelling recurrent events: comparison of statistical models with continuous and discontinuous risk intervals on recurrent malaria episodes data. *Malar J* 2014; 13: 293.
23. Wileyto EP, Li Y, Chen J, et al. Assessing the fit of parametric cure models. *Biostatistics (Oxford, England)*. 2013; 14: 340–350.
24. Kleinbaum DG and Klein M. *Survival analysis*, 3rd ed. Berlin: Springer, 2012.
25. Cosio BG, Shafiek H, Iglesias A, et al. Oral low-dose theophylline on top of inhaled fluticasone-salmeterol does not reduce exacerbations in patients with severe COPD: a pilot clinical trial. *Chest* 2016; 150: 123–130.
26. Cyr MC, Beauchesne MF, Lemière C, et al. Effect of theophylline on the rate of moderate to severe exacerbations among patients with chronic obstructive pulmonary disease. *Br J Clin Pharmacol* 2008; 65: 40–50.
27. Cosio BG, Iglesias A, Rios A, et al. Low-dose theophylline enhances the anti-inflammatory effects of steroids during exacerbations of COPD. *Thorax* 2009; 64: 424–429.
28. Cosio BG, Tsaprouni L, Ito K, et al. Theophylline restores histone deacetylase activity and steroid responses in COPD macrophages. *J Exp Med* 2004; 200: 689–695.
29. Kew KM and Seniukovich A. Inhaled steroids and risk of pneumonia for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2014; 10(3): CD010115.
30. Crim C, Dransfield MT, Bourbeau J, et al. Pneumonia risk with inhaled fluticasone furoate and vilanterol compared with vilanterol alone in patients with COPD. *Ann Am Thorac Soc* 2015; 12: 27–34.
31. Barr RG, Rowe BH, and Camargo CA, Jr. Methylxanthines for exacerbations of chronic obstructive pulmonary disease: meta-analysis of randomised trials. *BMJ* 2003; 327: 643.
32. Rusinowicz T, Zielonka TM, and Zycinska K. Cardiac Arrhythmias in Patients with Exacerbation of COPD. *Adv Exp Med Biol* 2017; 1022: 53–62.
33. Horita N, Miyazawa N, Kojima R, et al. Chronic use of theophylline and mortality in chronic obstructive pulmonary disease: a meta-analysis. *Arch Bronconeumol* 2016; 52: 233–238.
34. Groenwold RH, de Groot MC, Ramamoorthy D, et al. Unmeasured confounding in pharmacoepidemiology. *Ann Epidemiol* 2016; 26: 85–86.
35. Pothirat C, Chaiwong W, Phetsuk N, et al. A comparative study of COPD burden between urban vs rural communities in northern Thailand. *Int J Chron Obstruct Pulmon Dis* 2015; 10: 1035–1042.
36. Austin PC. The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. *Stat Med* 2014; 33: 1242–1258.