Long-acting muscarinic antagonist versus long-acting β_2 agonist/corticosteroid for moderate to severe chronic obstructive pulmonary disease patients: Exacerbation risk assessment

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Abstract

Background: Whether the beneficial effects of long-acting muscarinic antagonists (LAMA) are better than those of long-acting β_2 agonist/corticosteroids (LABA/ICS) in preventing exacerbations in chronic obstructive pulmonary disease (COPD) remains unclear. This study aimed to assess the risk of exacerbations in moderate to severe COPD patients receiving LAMA versus LABA/ICS.

Methods: We retrospectively reviewed the medical records of patients diagnosed with COPD (2008-2010). The inclusion criteria were age ≥ 40 years, forced expiratory volume in 1 second (FEV_1) 30% to 80% of predicted value and at least three prescriptions for COPD medication, including LAMA or LABA/ICS.

Results: Of the 557 COPD patients screened, 90 patients were enrolled in the analysis. The demographic characteristics of patients receiving LABA/ICS or LAMA were similar. The all exacerbation rates was significantly higher in patients with global initiative for chronic obstructive lung disease stage II COPD treated with LABA/ICS than in those treated with LAMA (p = 0.001), regardless of previous exacerbation history. Patients with previous exacerbation history showed an independent increase in the risk of moderate or severe exacerbation compared with those without exacerbation history (hazard ratio 3.86, 95% CI 1.75-8.53, p = 0.001).

Conclusion: In comparison with LABA/ICS, LAMA is beneficial in reducing exacerbation risk for moderate COPD. Previous exacerbation history independently predicts the future risk of exacerbation regardless of treatment.

Keywords: Chronic obstructive pulmonary disease; Combined inhaled corticosteroid/long-acting β_2 agonist; Exacerbation; Long-acting muscarinic antagonist; Risk

1. INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized as persistent respiratory symptoms and airflow limitation[1] and a leading cause of morbidity and mortality worldwide.[2] Exacerbations become frequent and severe with increased severity of COPD. Hurst et al reported that each patient with the global initiative for chronic obstructive lung disease (GOLD) stage II COPD (forced expiratory volume in 1 second [FEV_1] between 50% and 80% of predicted value) experiences 0.85 exacerbations per year; the exacerbation rate is 1.34 for those with GOLD stage III COPD (FEV_1 30% to 50% of predicted value) and 2.0 for those with GOLD stage IV COPD (<30% of predicted value).[3] The exacerbations of COPD cause a rapid decline in lung function, which results in increased hospitalization, mortality, and healthcare resource utilization.[4–7] Pharmacological therapy is applied to reduce the symptoms and frequency of exacerbations and improve health and quality of life.[1]The prevention of exacerbation is now becoming an important treatment goal.[8]

To date, a reasonable number of clinical trials have shown that long-acting β_2 agonist (LABA), long-acting muscarinic antagonists (LAMA) or LABA/corticosteroids (ICS) can reduce the exacerbation rate of COPD. LABA/ICS significantly reduces exacerbation frequency in patients with moderate to severe

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COPD to a higher extent than that of monotherapy with LABA or ICS alone.[9–11] Tiotropium, a LAMA, can reduce exacerbation and improve quality of life and eventually mortality.[12–14] Karner et al conducted a systemic review and reported that compared with placebo, tiotropium can reduce COPD exacerbations by 22% (odds ratio [OR] 0.78; 95% CI 0.70-0.87).[15] Furthermore, in a prespecified subset analysis of patients from a four-year trial in COPD, tiotropium reduces the rate of decline of postbronchodilator FEV_1 in patients with GOLD stage II COPD.[16]The annual decline of FEV_1 in patients with GOLD stage I and II COPD treated with tiotropium was recently reported by Zhou et al.[17]

Although LAMA and LABA/ICS have been extensively used in the management of COPD patients, whether the beneficial effects of LAMA are better than those of LABA/ICS in preventing exacerbations in COPD patients remain unclear. To date, only one large study evaluated the effects of two different treatments on exacerbations of patients with severe to very severe COPD over a two-year period. They reported no significant difference in the annual exacerbation rates related to salmeterol/fluticasone propionate (LABA/ICS) and tiotropium (LAMA).[18] In the current study, we aimed to compare the relative efficacy of LAMA and LABA/ICS in reducing the exacerbation of COPD, especially for patients with GOLD stage II and III COPD. The influence of airflow limitation on exacerbation and previous history of exacerbation were also analyzed.

2. METHODS

2.1. Study design

We consulted with the institutional review board of Taipei Veterans General Hospital (approval number: IRB10-08-019IC) and waived informed consent for our retrospective observational cohort study. The enrolment period set in this study was between January 1, 2008 and January 1, 2010. Patients were eligible for inclusion if they were aged ≥ 40 years at the index date, diagnosed with COPD (International Classification of Diseases 9th Edition, Clinical Modification [ICD-9-CM] codes 491.xx, 496.xx) in any diagnosis field during the preindex period (12 months) or on the index date and an index event of receiving one of LAMA and ICS/LABA for COPD treatment during the study period (from January 1, 2007 to January 1, 2010). Patients were excluded from the study if (1) no baseline pulmonary function test was recorded during the preindex period and on the index date, (2) the ratio of FEV_1/FVC (forced vital capacity) > 0.7, (3) the duration of receiving index drugs was ≤3 months, and (4) with history of asthma, lung cancer, or previous lung reduction surgery. The enrolled patients were divided into one of the two groups: LAMA alone or LABA/ICS, according to their medication use at the index date. Patients were assigned to a drug therapy cohort and considered to be using that therapy during the entire follow-up period. The primary outcome measurement was the occurrence of moderate or severe COPD exacerbation during the follow-up period.

2.2. Data source

Data were obtained from the electronic medical records of the Taipei Veterans General Hospital. The data available for each patient comprised inpatient and outpatient diagnoses (by ICD-9-CM diagnosis code) and order prescription records, including the drug name and quantity dispensed. Additional data elements included demographic variables (eg, age, gender, and geographic region), smoking history, spirometric results, previous treatment, which includes maintenance medicine, blood eosinophil count, comorbidities, and history of acute exacerbation of COPD in the preindex period. A moderate or severe exacerbation of COPD, concurrent used medicine and medication possession ratio (MPR), the percentage of the sample switched to other maintenance therapy were all collected in the postindex period. MPR was calculated by dividing the total number of prescription days by the total number of follow-up days.

2.3. Definition

An index medication prescription for COPD was defined as the first chronologically occurring pharmacy claim for medications of COPD during the enrollment period. The date of the index medication prescription for COPD was denoted as the index date. The preindex period was the one-year period before the index date. The postindex period included a follow-up period of variable length, starting at one day to a maximum of one year, during which study outcomes were assessed. The length of the follow-up period was defined as the duration between the index date and the first occurrence of any of the following events: (1) a moderate or severe exacerbation of COPD, (2) end of the study period, or (3) end of the one-year follow-up period. The severity of COPD was based on the spirometric value of FEV_1% predicted in the GOLD guideline.[1]Moderate COPD exacerbation was defined to include a physician visit in any field with a diagnosis code for COPD and a prescription for an oral corticosteroid and/or an antibiotic. Severe COPD exacerbation was defined as an emergency room visit with a primary diagnosis code for COPD or hospitalization with a primary discharge diagnosis for COPD.

2.4. Statistical analysis

The baseline characteristics of study patients were summarized with descriptive statistics. χ^2 test for categorical variables and *t*-test/Mann–Whitney *U* test for continuous variables were used to quantify differences among cohorts. Cox proportional hazard regression analysis was used to calculate crude and adjusted hazard ratios (HRs) for moderate, severe, and all COPD exacerbation in comparison with the control group of LAMA alone. HRs were calculated from Cox regression models following a forced entry of all available covariates to reduce residual confounding. The covariates included age, sex, smoking status, COPD stage, cardiovascular and respiratory admissions, and diabetes. The exacerbation rate for moderate or severe COPD exacerbation for patients exposed to two treatments using LAMA alone as control with different lung functions were assessed by a two-sample test of proportion. Time to the first moderate or severe COPD exacerbation during the follow-up period was compared between study patients with and without history of COPD exacerbation by using the Kaplan–Meier method and the log-rank test.

The sample size was measured by G-Power analysis and parameter calculation based on setting the differences of two proportion was 30%, power =95%, $\alpha = 0.05$, sample size ratio in $N_2/N_1 = 2$. Hence, the total sample sizes was 75 ($N_1 = 25$, $N_2 = 50$). Considering that 10% missing data, total sample size was 90 finally. For all tests, $p < 0.05$ was considered significant. All analyses were performed using SPSS version 19.0 (SPSS, Inc) and STATA 12 (Stata Corp LP) statistical software. G-Power analysis was done by using GPower_3.1.9.2.

3. RESULTS

3.1. Patient characteristics

Of the 557 COPD patients screened, 90 patients who satisfied the inclusion criteria were enrolled in the analysis (Fig. 1). Of the 90 patients enrolled, 30 patients received LAMA treatment (tiotropium HandiHaler [Boehringer, Germany] 18 μg/cap once daily), and 60 patients received LABA/ICS treatment

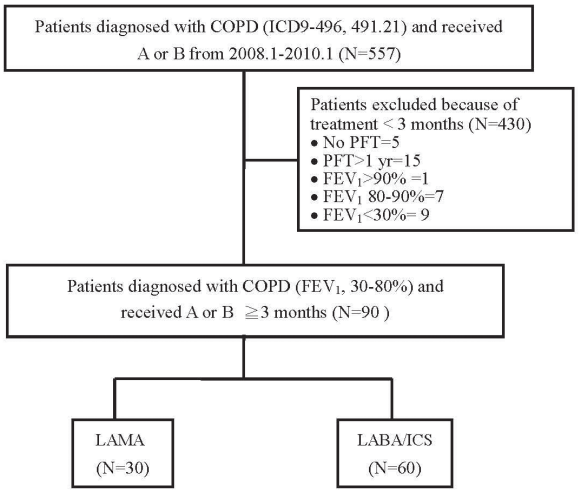

Fig. 1 Flow chart of patient inclusion. COPD, chronic obstructive pulmonary disease; PFT, pulmonary function test; FEV_1, forced expiratory volume in 1 s; A, Tiotropium; B, long-acting β_2 agonist/corticosteroids.

(formoterol/budesonide Turbuhaler [Astezenca, Sweden] 9 μg/320 μg twice daily, 20%; salmeterol/fluticasone Evohaler [Glaxowellcome/GSK, Spain] 50 μg/500 μg twice daily, 65%; Accuhaler [Glaxowellcome/GSK, France] 25 μg/250 μg twice daily, 11.7%; Evohaler [Glaxowellcome/GSK, Spain] 50 μg/250 μg twice daily, 3%). Baseline characteristics were similar in the two treatment groups in terms of age, sex, smoking history, comorbidities, previous treatment, concurrent medications, lung function, disease severity, and exacerbation during previous year, and concurrent medications used in postindex medication were similar between two groups (Table 1). Particularly, no difference was noted in the blood eosinophil counts and bronchial reversibility between treatment groups. The MPR was >85% in both group, no difference in two groups.

3.2. Airflow limitation and COPD exacerbations

The exacerbation rate based on airflow limitation, exacerbation history, and medications are shown in Table 2. For patients with GOLD stage II, the all exacerbation rate was significantly higher in COPD patients treated with LABA/ICS (0.51) than in those treated with LAMA (0.10; p = 0.001), regardless of previous history of exacerbation (Table 2). Nevertheless, the beneficial effects of treatment on the prevention of severe exacerbation in the LAMA group were not as significant as those in the LABA/ICS group (p = 0.088). In severe patients with FEV_1 30% to 50% of predicted value, no significant difference was detected in the prevention of exacerbation between two groups with or without previous history of exacerbation (Table 2). Overall, treatment with LAMA was associated with fewer exacerbations than that with LABA/ICS in patients with moderate COPD. The adjusted HR of an exacerbation of COPD in patients receiving LABA/ICS vs LAMA was 5.09 (95% CI 1.52-17.11, p = 0.008) (Table 3).

3.3. Independent factor associated with COPD exacerbation

We further analyzed the relation between the history of exacerbations in the preceding year and the risk of developing moderate and severe exacerbations in the follow-up period. In the multivariate Cox regression analysis, a history of exacerbation in the preceding year was associated with an increased risk of moderate, severe, and all exacerbations with statistically significant adjusted HRs of 4.03, 6.72, and 3.86, respectively (Table 4). The Kaplan–Meier estimates of the probability of time for the first moderate (Fig. 2b), severe (Fig. 2c), and all exacerbations (Fig. 2a) for patients with or without previous history of exacerbations are shown in Fig. 2.

Table 1

Patient characteristics

Variables	LAMA (n = 30)	LABA/ICS (n = 60)	*p*
Male	27 (90)	60 (100)	0.04
Age, y	79.3 ± 4.7	77.5 ± 6.7	0.20
Smoking history			0.40
Never smoke	0	2 (3.5)	
Ex-smoker	25 (83.3)	38 (65.5)	
Current smoker	5 (16.7)	18 (31)	
Comorbidities			
Cardiovascular disease	19 (63.3)	31 (51.7)	0.29
Diabetes mellitus	2 (6.7)	8 (31.3)	0.34
BMI, kg/m^2	19 ± 11.7	17.3 ± 10.3	0.48
Blood eosinophil, per μL	160.8 ± 162.9	167.2 ± 162.4	0.98
Pulmonary function test (postbronchodilator)			
FVC(L)	2.17±0.56	2.32±0.54	0.24
FVC % predicted	72 ± 17	73 ± 16	0.77
FEV_1(L)	1.20 ± 0.23	1.30 ± 0.31	0.13
FEV_1% predicted	57 ± 10	59 ± 11	0.43
FEV_1/FVC%	57 ± 13	57 ± 11	0.83
FEV_1 reversibility	7.2 ± 5.9	10.5 ± 9.9	0.34
Symptom			
Cough	13 (43.3)	22 (36.7)	0.647
Effort dyspnea	21 (70)	36 (60)	0.487
Previous treatment[a]			
Treatment naïve	20 (66.7)	45 (75)	0.407
LAMA	10 (33)	0	<0.001
LABA/ICS	0	15 (25)	0.002
Drug for symptom-no.			0.829
1	6 (20)	10 (16.7)	
≧2	7 (23.3)	12 (20)	
Concurrent used medicine			
Tiotropium[b]	30 (100)	0 (0)	
Formoterol/Budesonide[c]	0 (0)	12 (20)	
Salmeterol/Fluticasone[d]	0 (0)	48 (80)	
Acetylcysteine	12 (40)	32 (53.3)	0.24
Theophylline	27 (90)	52 (86.7)	0.65
MPR for Index drug, %	86.4 ± 22.9	87.6 ± 19.9	0.79
Switch to other maintenance drug, %	0(0)	3(5)	0.548
Severity of COPD			0.72
GOLD stage II[e]	23 (77)	48 (80)	
GOLD stage III[f]	7 (23)	12 (20)	
Exacerbation during previous year – no.			
≥2	2 (6.7)	3 (5)	0.74
1	6 (20)	11 (18.3)	0.85
0	22 (73.3)	46 (76.7)	0.726

Data are presented as mean ± SD (continuous variables) or no (%) (category variables).

FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; LABA/ICS = long-acting β_2-agonist/corticosteroid; LAMA = long-acting muscarinic antagonist; MPR = medication possession ratio; no = number.

[a]Study drug used in the 12 mo before study start.

[b]Tiotropium HandiHaler 18 μg/cap qd.

[c]Formoterol/Budesonide Turbuhaler 9 μg/320 μg bid.

[d]Salmeterol/Fluticasone Evohaler 50 μg/500 μg bid (39/60, 65%); Accuhaler 25 μg/250 μg bid (7/60, 11.7%); Evohaler 50 μg/250 μg bid (2/60, 3%).

[e]GOLD stage II: Moderate (FEV_1 50%-79%).

[f]GOLD stage III: Severe (FEV_1 30%-49%).

Table 2

The exacerbation rate by airflow limitation, exacerbation history, and COPD medication

	Moderate AE		Severe AE		All AE	
Treatment group	**Rate[a]**	***p***	**Rate[a]**	***p***	**Rate[a]**	***p***
A: FEV_1 50%-80% of predicted value (n = 68)						
Total patient (n = 68)						
LAMA	0.05	–	0.05	–	0.10	–
LABA/ICS	0.30	0.021b	0.21	0.088	0.51	0.001b
Without AE history (n = 51)						
LAMA	0	–	0.07	–	0.07	–
LABA/ICS	0.25	0.033b	0.11	0.662	0.36	0.032b
With AE history (n = 17)						
LAMA	0.17	–	0	–	0.17	–
LABA/ICS	0.45	0.235	0.55	0.027b	1.00	0.0003
B: FEV_1 30%-50% of predicted value (n = 22)						
Total patient (n = 22)						
LAMA	0.11	–	0.11	–	0.22	–
LABA/ICS	0.31	0.280	0.08	0.785	0.39	0.420
Without AE history (n = 17)						
LAMA	0	–	0	–	0	–
LABA/ICS	0.2	0.208	0	NA	0.20	0.208
With AE history (n = 5)						
LAMA	0.50	–	0.50	–	1.00	–
LABA/CS	0.67	0.709	0.33	0.709	1.00	>0.999

AE = acute exacerbation; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 s; ICS = corticosteroid; LAB = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist.
[a]Expressed as exacerbation rate per patient per year.
[b]Expressed as $p < 0.05$ from two-sample test of proportion, with LAMA as control group.

Table 3

HR of an exacerbation of COPD in patients receiving LABA/ICS vs LAMA

Treatment group	Crude HR (95% CI)	Adjusted HR (95% CI)	*p*
Moderate AE	4.30 (0.98-18.81)	4.03 (1.06-20.31)	0.042
Severe AE	3.40 (0.75-15.35)	3.99 (0.88-18.11)	0.073
All AE	4.49 (1.34-15.02)	5.09 (1.52-17.11)	0.008

AE = acute exacerbation; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; ICS = corticosteroid; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist.

Table 4

HR of an exacerbation of COPD in patients with previous history of exacerbation vs none

History of exacerbation	Crude HR (95% CI)	Adjusted HR (95% CI)	*p*
Moderate AE	3.71 (1.63-8.47)	4.03 (1.54-10.52)	0.004
Severe AE	7.06 (2.44-20.38)	6.72 (2.17-20.78)	0.001
All AE	3.87 (1.94-7.69)	3.86 (1.75-8.53)	0.001

AE = acute exacerbation; COPD = chronic obstructive pulmonary disease; HR = hazard ratio.

4. DISCUSSION

In this retrospective analysis, we observed that LAMA, mainly tiotropium, showed fewer exacerbations than LABA/ICS in the treatment of moderate COPD patients with FEV_1 50% to 80% of predicted value, regardless of previous history of exacerbations. The bronchial reversibility, blood eosinophil counts, and concurrent medications were similar in both treatment groups. However, the result was different for patients with severe COPD and FEV_1 30% to 50% of predicted value. In addition, LAMA demonstrated no superiority in preventing severe exacerbations over LABA/ICS in moderate and severe COPD. Previous exacerbation history is an independent factor for predicting the future risk of developing moderate and severe exacerbations.

Tiotropium is a potentially effective LAMA in the treatment of COPD. Tiotropium has been reported as more effective than salmeterol in preventing moderate and severe exacerbations in patients with moderate to very severe COPD.[19] In a randomized, double-blind, and parallel-group trials, tiotropium was as effective as indacaterol/glycopyrronium (LABA/LAMA) in preventing moderate and severe exacerbations. Tiotropium was also better than glycopyrronium in reducing severe exacerbations in this 64-week study.[20] The Investigating New Standards for Prophylaxis in Reducing Exacerbations (INSPIRE) study[18] was the first large-scale and randomized trial to compare the relative efficacy of LABA/ICS (salmeterol/fluticasone) with that of LAMA (tiotropium) in terms of the rate of moderate and severe exacerbations in severe and very severe COPD for a two-year treatment period. No difference was observed in the exacerbation rates of the two treatment groups at the end of the study. The INSPIRE study results were consistent with our findings that neither LABA/ICS nor LAMA demonstrated superiority in preventing exacerbations in severe COPD.

LAMA and LABA are the major treatments for COPD to improve airflow limitation, respiratory symptoms, and quality of life and reduce exacerbations.[21,22] We previously reported that the combination of inhaled salmeterol and fluticasone (LABA/ICS) caused a significant reduction in interleukin-8 and matrix metalloprotease in induced sputum from COPD patients compared with the levels in those who received treatment with tiotropium alone.[23]We also showed that glycopyrronium bromide, a LAMA, can inhibit lung inflammation and small airway remodeling induced by cigarette smoke exposure in mouse models.[24]Tiotropium can inhibit airway inflammation and remodeling[25] and attenuate neutrophilic inflammation; tiotropium is also associated with various mediators in animal models.[26] In clinical studies, the OR for tiotropium in reducing exacerbations compared with placebo was 0.74 (95% CI, 0.66-0.83) and that for hospitalizations was 0.69 (95% CI, 0.55-0.87).[27]

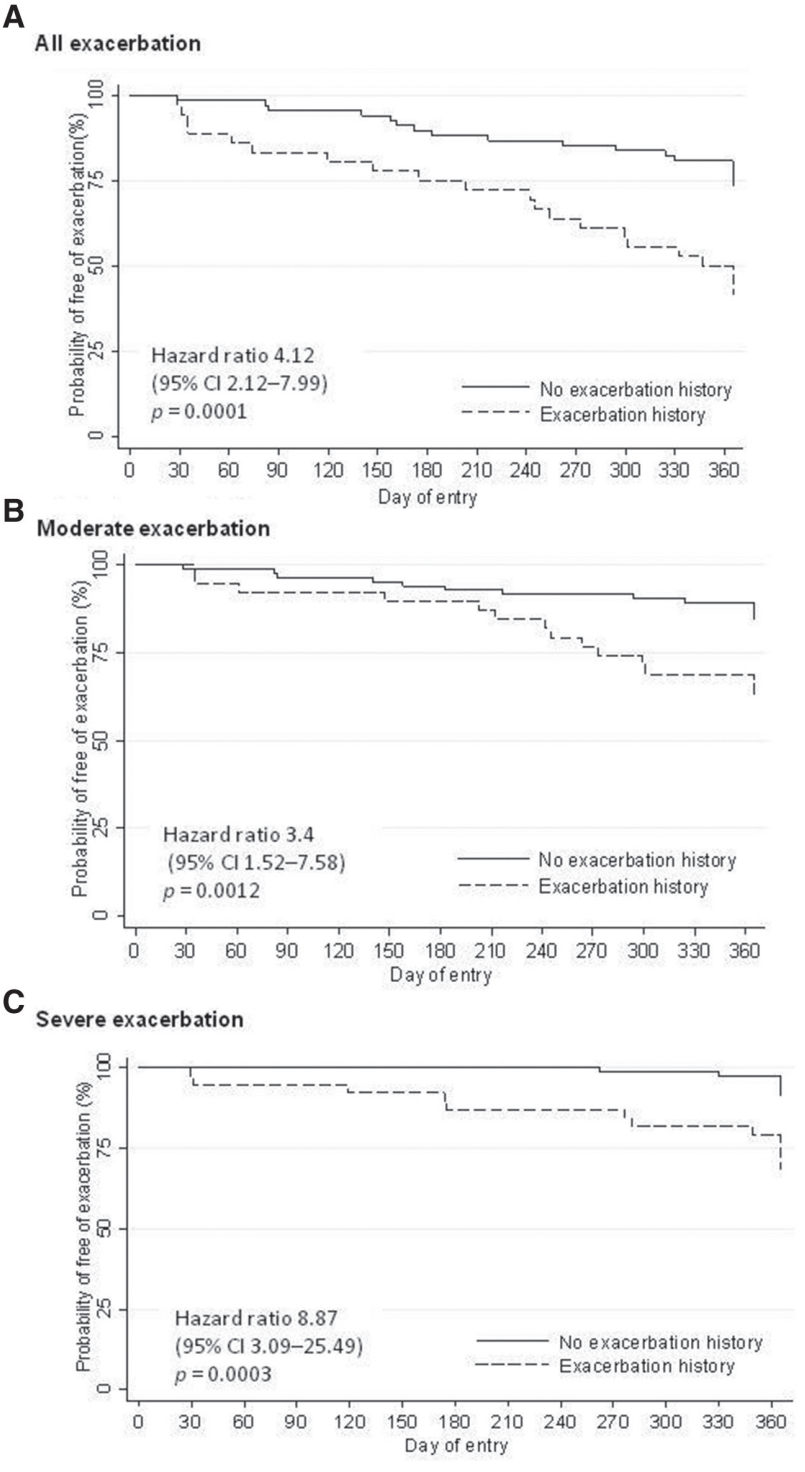

Fig. 2 Kaplan–Meier estimates of the probability of time to first exacerbation for patients with or without previous history of exacerbation.

In a recent systematic review, Halpin et al collected 29 randomized controlled trials that compared tiotropium with placebo and/or other therapies, including LABA, dual therapy (LABA/LAMA or LABA/ICS), and/or triple therapy. They concluded that tiotropium is beneficial in reducing exacerbation risk vs placebo or other maintenance treatments.[28] In our study, we found that tiotropium showed fewer exacerbations only for moderate COPD patients with FEV_1 50% to 80% of predicted value and not for severe COPD patients (FEV_1 30% to 50% of predicted value). In addition, LAMA demonstrated no superiority in preventing severe exacerbations compared with LABA/ICS in moderate and severe COPD. Hence, whether the anti-inflammatory effects of LABA/ICS or LAMA are sufficient to overcome the overwhelming exacerbations triggered by factors, such as severity-associated inflammation, bacteria, virus, temperature, or environmental pollutants, and the underlying mechanism that can explain the frequent exacerbation phenotype of COPD remain unknown. The breach of stability of airway inflammation leading to exacerbation may involve airway eosinophilia, bronchiectasis with bacterial colonization, and gastroesophageal reflux disease, which commonly exist in COPD patients.[29] These comorbidities may influence exacerbation rates, which cannot be intervened by long-acting bronchodilators alone with limited anti-inflammatory effects.

In the Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) study, frequent exacerbation phenotype is associated with prior exacerbations.[30] Our results in which previous exacerbation history is an independent factor for predicting the future risk of developing moderate and severe exacerbations were consistent with this phenomenon. In addition, the phenotype was independently associated with history of gastroesophageal reflux or heartburn, poor quality of life, and increased white cell count. Factors causing frequent exacerbations may need alternative strategies to reduce exacerbation, in addition to treatment with long-acting bronchodilators.

We acknowledge that our study has some limitations, given that it was a retrospective analysis. We used a Cox regression model by correcting all available covariates and performing a time-dependent analysis to validate results. We excluded the patients with very severe COPD to clarify the treatment effects on the exacerbation rates of the LABA/ICS and LAMA groups. Moderate COPD exacerbation was defined as a prescription of an oral corticosteroid and/or an antibiotic. All data were only obtained from the electronic medical records of the Taipei Veterans General Hospital. However, patients who suffered from acute exacerbation of COPD may seek help at local medical doctors or visit MER at local hospital, the real incidence of AE may be underestimated. Further study, for adequate exacerbation history, should be traced by national health insurance database or other methods.

Although this study showed the higher internal validity (power = 95%), but the data from one center, the external validity needed further is conducted in multicenter trial. The following are the strengths of the hospital-based data used in this work: all COPD diagnosis were performed according to the guidelines; medication, blood, and spirometric records were completed, more than 85% of MPR; and moderate and severe exacerbations were clearly defined and recorded.

In conclusion, in comparison with LABA/ICS, LAMA is beneficial in reducing the risk of moderate acute exacerbation for COPD patients with FEV_1 50% to 80%.

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