Heliyon 10 (2024) e35367

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Investigating effectiveness of adherence of long-acting bronchodilator in chronic obstructive pulmonary disease with influenza infection

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ARTICLE INFO

Keywords:
Chronic obstructive pulmonary disease
Influenza
Adherence

ABSTRACT

Objectives: Long-acting bronchodilators are important treatments for chronic obstructive pulmonary disease (COPD) and adequate medication adherence decreases COPD exacerbations, especially in reducing the hazard of influenza infection. Therefore, the study aim was to evaluate adherence of long-acting bronchodilator treatment and the risk of influenza in patients with COPD.

Methods: This retrospective nested case-control study included patients with newly diagnosed COPD from 2012 to 2018. Cases with influenza infection were defined and matched to 2 randomly selected controls. The influenza infection date was the index date. Conditional logistic regressions were used to estimate odds ratios of influenza from proportion of days covered (PDC) of long-acting bronchodilators measured in one year before the index date. Adherence was divided into high adherence (PDC $\geq$80 %) and low adherence (PDC <80 %).

Results: This population-based study included 6,073 patients in the case group and 12,146 in the control group. High PDC of long-acting bronchodilators in COPD was associated with a 0.811-fold (95 % confidence interval: 0.754–0.883, P < 0.001) decreased influenza risk, where 906 (14.92 %) high PDC in case and 2,130 (17.54 %) in control. Low PDC without influenza vaccination in COPD patients is associated with increased influenza risk, regardless of exposure period.

Conclusion: In Taiwan, COPD patients with high PDC were associate with lower COPD exacerbation. Different long-acting bronchodilator exposure or dose need to be further investigated in COPD patients.

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https://doi.org/10.1016/j.heliyon.2024.e35367
Received 5 May 2024; Received in revised form 25 July 2024; Accepted 26 July 2024
Available online 27 July 2024

1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by long term airway symptoms and irreversible airway obstruction [1]. COPD is a risk factor for influenza infection, and influenza infection accounts for 5%–28% of COPD exacerbations [2,3]. Patients with COPD experience acute exacerbations after influenza virus infection and deteriorated lung function, increased medical cost, worsening of quality of life, leading to hospital admission and increased morbidity and mortality [4,5].

The goal for treating COPD is to reduce exacerbations and improve symptoms. Inhaled bronchodilators are the important treatment for COPD. Adherence to bronchodilator treatment in COPD patients is generally low [6]. Moreover, patient adherence to bronchodilator treatment in COPD is essential to optimize disease management and improve disease symptoms. Poor adherence to COPD treatment may cause frequent exacerbations [7]. The exhaled alveolar fraction of nitric oxide is one of the biomarker of lung inflammation in COPD. A previous study demonstrated the efficacy of long-acting bronchodilators in reducing the levels of the alveolar fraction of nitric oxide [8]. The efficacy of adherence to bronchodilator treatment in COPD can slow the rate of lung function decline and may also reduce the risk of influenza virus infection [9]. Therefore, our study evaluated the association between adherence to long-acting bronchodilator treatment and influenza infection in COPD patients.

2. Methods

2.1. Study design and data source

A nested case-control study based on population data was conducted using COPD patient records from Taiwan National Health Insurance Research Database (NHIRD) spanning January 1, 2011, to December 31, 2019. This dataset encompassed claims information from the National Health Insurance (NHI) program, which was initiated in 1995. It includes details on outpatient visits, hospital admissions, emergency treatments, surgeries, and prescribed medications. The NHI program covers nearly 99.99 % of Taiwan's population, making the NHIRD a comprehensive reflection of the nation's health status [10]. The study adhered to the principles of the Declaration of Helsinki and received approval from the Institutional Review Boards of Kaohsiung Medical University Hospital (KMUHIRB-E(I)-20220055), which also waived the need for informed consent.

2.2. Definition of study cohort

Patients were selected based on the inclusion criteria, which required them to be aged between 40 and 90 years and to have had either more than three outpatient visits or at least one inpatient record of COPD from January 1, 2012, to December 31, 2018. The diagnosis needed to be coded according to the *International Classification of Diseases, Ninth Revision* (ICD-9) codes 490, 491, 492, or 496, or *Tenth Revision* (ICD-10) codes J40, J41, J43, or J44. Patients were excluded if they had lung cancer, had undergone lung transplantation within a year before the study period, or had been diagnosed with asthma. Additionally, COPD patients who had not been prescribed bronchodilator inhalers were also excluded. The follow-up period continued until the first occurrence of one of the following events: an influenza infection (which defined the case group), death, withdrawal from the NHIRD, or the end of the study on December 31, 2019.

2.3. Case and control identification

The case group was COPD patients with influenza infection (ICD-9 code 487 and ICD-10 code J09-J11) after COPD diagnosis. The first influenza infection date was the index date. Moreover, the first influenza infection was required to be after one year of use of long-acting bronchodilators.

COPD patients who had an influenza infection were matched with two randomly selected control patients who had COPD but no influenza infection. The matching criteria included age, sex, risk of COPD exacerbation, chronic liver disease, diabetes mellitus, stroke, chronic kidney disease, hypertension, coronary heart disease, hyperlipidemia, and malignancy [11].

2.4. Outcome measurement

The proportion of days covered (PDC) was employed to evaluate adherence to long-acting bronchodilators before the index date. The bronchodilators considered included long-acting beta-2 agonists (LABAs), long-acting muscarinic agonists (LAMAs), LABA + LAMA combinations, and LABA + inhaled corticosteroids (ICSs). Adherence was categorized as high if the PDC was 80 % or greater and low if the PDC was less than 80 %.

2.5. Covariate measurement

The characteristics of study patients encompassed age, sex, level of urbanization (categorized as urban, suburban, or rural), monthly insurance premium (less than New Taiwan Dollar (NTD) $20,000, NTD $20,000 to $40,000, and more than NTD $40,000), severity of COPD, medications for COPD, comorbidities, and co-medications (see Supplement Table 1). These details regarding medications and comorbidities were evaluated for the year preceding the index date.

To determine COPD exacerbation, we utilized proxy indicators such as the number of outpatient visits, hospital admissions, or

emergency room (ER) visits related to COPD, and the use of short-acting beta-agonists (SABAs), antibiotics, and oral corticosteroids. Acute COPD exacerbations were classified as either severe or moderate. Severe exacerbations were those requiring ER visits or hospitalization, while moderate exacerbations were managed with SABAs, antibiotics, or oral corticosteroids. Patients with more than two moderate exacerbations or more than one severe exacerbation were deemed at high risk for exacerbation. Those with no exacerbations or only one moderate exacerbation were considered at low risk for exacerbation (see Supplement Table 2).

2.6. Statistical analysis

Continuous variables are shown as means with standard deviations, and comparisons between two samples were made using Student's t-test. Categorical variables are expressed as counts and percentages, and comparisons between two groups were performed using the Chi-square test. Conditional logistic regression was applied to estimate the odds ratio (OR) for adherence to long-acting bronchodilators and the associated risk of influenza infection. This regression model was adjusted for covariates recorded one year before the index date, including urbanization level, income, comorbidities, and co-medications.

Further stratification of the population into four groups based on level of adherence to long-acting bronchodilators (high or low) and influenza vaccination status revealed distinct outcomes. Group 1 comprised patients with PDC ≥80 % who received influenza vaccination, while Group 2 included those with PDC ≥80 % without vaccination. Group 3 consisted of patients with PDC <80 % who received vaccination, and Group 4 encompassed those with PDC <80 % without vaccination. Influenza vaccination status was

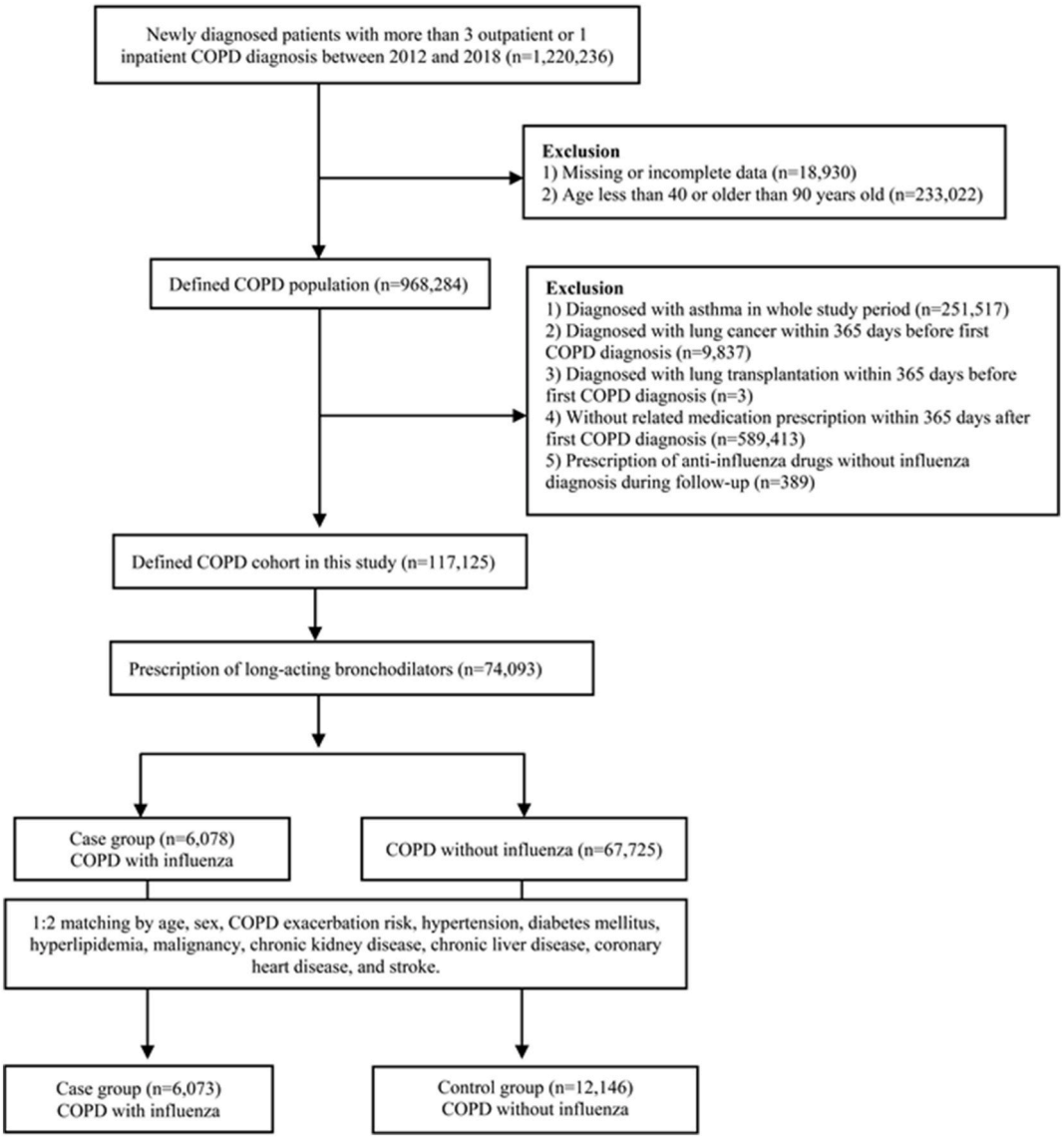

Fig. 1. Flow chart of study population.

determined using ICD-9 codes V04.7 and V04.8, as well as relevant drug codes.

In the subgroup analysis, the population was further categorized by age group, sex, and risk of COPD exacerbation to evaluate influence of factors on the likelihood of influenza infection. In the sensitivity analysis, we changed the PDC cutoff value to ≥80 %, ≥70 %, ≥60 %, ≥50 %, ≥40 %, ≥30 %, ≥20 %, and ≥10 % to test outcome.

All data processing and statistical analyses were conducted using SAS 9.4 software. Statistical significance was defined as a two-tailed P-value of less than 0.05. Given the large sample size, there is an increased risk of Type 1 error, thus a lower P-value threshold is necessary to minimize this risk.

Table 1
Baseline characteristic between cases and controls after matching.

Baseline characteristics N (%)	Case (N = 6073)	Control (N = 12,146)	*P-value*	
Age mean (SD)	66.15 (11.58)	66.05 (11.44)	0.5859	
Gender			1.000	
male	4679 (77.05)	9358 (77.05)		
Insurance premium (NT$)			<0.0001	
<20,000	1389 (22.87)	3109 (25.60)		
20,000–40,000	3637 (59.89)	6859 (56.47)		
>40,000	1047 (17.24)	2178 (17.93)		
Urbanization level			0.0107	
Urban	2675 (44.05)	5526 (45.50)		
Suburban	2719 (44.77)	5426 (44.67)		
Rural	679 (11.18)	1194 (9.83)		
COPD severity rowhead				
Severe exacerbations			<0.0001	
0	5015 (82.58)	10,643 (87.63)		
1	557 (9.17)	821 (6.76)		
≧2	501 (8.25)	682 (5.62)		
Moderate exacerbations rowhead				
0	4705 (77.47)	9213 (75.85)	<0.0001	
1	302 (4.97)	482 (3.97)		
≧2	1066 (17.55)	2451 (20.18)		
COPD exacerbation risk			0.4825	
High	1683 (27.71)	3304 (27.20)		
Low	4390 (72.29)	8842 (72.80)		
COPD medication rowhead				
LABA	309 (5.09)	587 (4.83)		0.4526
LAMA	997 (16.42)	2147 (17.68)		0.0339
LABA + LAMA	769 (12.66)	1957 (16.11)		<0.0001
LABA + ICS	931 (15.33)	1833 (15.09)		0.6719
SABA	1303 (21.46)	2246 (18.49)		<0.0001
SAMA	278 (4.58)	465 (3.83)		0.0159
SABA + SAMA	492 (8.10)	897 (7.39)		0.0859
Methylxanthines	3058 (50.35)	5211 (42.90)		<0.0001
ICS	115 (1.89)	222 (1.83)		0.7558
Comorbidity rowhead				
Hypertension	1541 (25.37)	3085 (25.40)		0.9712
Diabetes mellitus	1490 (24.53)	2951 (24.30)		0.7235
Hyperlipidemia	1418 (23.35)	2797 (23.03)		0.6280
Obesity	17 (0.28)	36 (0.30)		0.8458
Malignancy	924 (15.21)	1862 (15.33)		0.8385
Chronic kidney disease	478 (7.87)	928 (7.64)		0.5826
Chronic liver disease	491 (8.08)	1011 (8.32)		0.5807
Solid organ transplant	31 (0.51)	41 (0.34)		0.0795
Depression	258 (4.25)	478 (3.94)		0.3120
Dementia	282 (4.64)	448 (3.69)		0.0019
Insomnia	499 (8.22)	977 (8.04)		0.6868
Alcohol-related disease	72 (1.19)	129 (1.06)		0.4519
Coronary artery disease	1168 (19.23)	2290 (18.85)		0.5389
Peripheral vascular disease	87 (1.43)	161 (1.33)		0.5567
Stroke	602 (9.91)	1183 (9.74)		0.7113
Heart failure	501 (8.25)	951 (7.83)		0.3239
Atrial fibrillation	476 (7.84)	866 (7.13)		0.0846

LABA = long-acting beta-agonist; ICS = inhaled corticosteroids; LAMA = long-acting muscarinic antagonists; SABA = short-acting beta-agonist; SAMA = short-acting muscarinic antagonists. Comorbidities, COPD severity, medication for COPD, and comedication were measured within the one year before the index date.

3. Results

3.1. Study population

The study initially identified 1,220,236 COPD patients from study period. Applying study criteria, 117,125 patients were eligible for inclusion. After excluding those who did not meet the eligibility requirements, the final cohort comprised 74,093 COPD patients (see Fig. 1). Through 1:2 propensity score matching, the final analysis included 6,073 patients in the case group and 12,146 patients in the control group.

The average age of patients in both the case and control groups was similar, at 66.15 (±11.58) and 66.05 (±11.44) years, respectively, with 77.05 % of the patients being male. Variables such as age, gender, COPD exacerbation risk, comorbidities were matched across both groups (see Table 1).

3.2. Adherence to long-acting bronchodilators and influenza hazard

In the case group, 906 patients (14.92 %) had a PDC ≥80 %, compared to 2130 patients (17.54 %) in the control group. Within one year leading up to the index date, high adherence (PDC ≥80 %) was associated with a 0.811-fold decrease in the risk of influenza infection (95 % CI: 0.754–0.883, P < 0.001) (see Table 2).

Compared to Group 4, patients in Groups 1, 2, and 3 exhibited significantly reduced influenza risk, with adjusted odds ratios (aORs) of 0.719 (95 % CI: 0.630–0.820, P < 0.001), 0.811 (95 % CI: 0.729–0.903, P < 0.001), and 0.853 (95 % CI: 0.792–0.919, P < 0.001), respectively (see Table 3).

3.3. Subgroup analysis

Subgroup analysis by age group, sex, and COPD exacerbation risk demonstrated consistent findings. Among different age groups, high adherence was associated with significantly lower influenza risk in patients aged 60–69 years (aOR: 0.762, 95 % CI: 0.649–0.893, P = 0.0008) and 70–79 years (aOR: 0.795, 95 % CI: 0.678–0.933, P = 0.0048). Similar trends were observed for sex and COPD exacerbation risk. Thus, maintaining high adherence to bronchodilator treatment appears to mitigate the risk of influenza infection (see Table 4).

3.4. Sensitivity analysis

The odds ratios of influenza virus infection were 0.846 (cut-off: 80 %), 0.821 (cut-off: 70 %), 0.820 (cut-off: 60 %), 0.804 (cut-off: 50 %), 0.809 (cut-off: 40 %), 0.817 (cut-off: 30 %), 0.813 (cut-off: 20 %), and 0.825 (cut-off: 10 %), respectively. They were all significantly different at different PDC cutoff values (P < 00.0001). The results are presented in Supplemental Table 3.

4. Discussion

This study assessed the association between adherence to long-acting bronchodilator treatment and risk of influenza infection. Our results show that good medication adherence to bronchodilator treatment may decrease the risk of influenza infection.

High adherence has efficacy for symptom control in patients with COPD and reduces the risk of influenza infection. During the one-year follow-up period, COPD patients with high adherence to long-acting bronchodilator treatment had a reduced risk of influenza infection (adjusted OR: 0.811, 95 % CI: 0.754–0.883, P < 0.0001). According to a previous study, high adherence to treatment with COPD medications has several benefits, including a reduced risk of hospitalization, acute exacerbations, exacerbation-related medical costs, and improved pulmonary functions [12,13]. A previous study showed that women, higher Charlson Comorbidity Index score, and reduced frequency of specialist visits correlated with earlier cessation of COPD treatment [14]. There are limited data about medication adherence and influenza infection in patients with COPD. Some possible mechanisms of reduced influenza virus infection in patients with COPD with higher adherence have been noted. First, higher adherence to treatment with bronchodilator medications not only reduces COPD exacerbations but also reduces the risk of lung inflammatory responses triggered by virus infection [15]. The main mechanism of influenza pathophysiology is viral infection of the respiratory epithelium, and an increased immune response results in lung inflammation and virus spreading.

In laboratory settings, muscarinic receptor antagonists exhibit an anti-inflammatory effect by lowering cytokine levels (IL-1β, IL-6, and IL-8) after rhinovirus infection in human tracheal surface epithelial cells from patients with COPD [16]. LAMAs also decrease the translocation of nuclear inhibitor kappa kinase alpha and tumor growth factor-beta 1 by restraining the overexpression of

Table 2
Risk of influenza and long-acting bronchodilator adherence.

PDC, No (%)	Case (n = 6073)	Control (n = 12,146)	Crude OR (95 % CI)	*P-value*	Adjusted OR[a] (95 % CI)	*P-value*
≥80 %	906 (14.92)	2130 (17.54)	0.825 (0.758–0.897)	<0.0001	0.811 (0.754–0.883)	<0.0001
<80 %	5167 (85.08)	10,016 (82.46)	1 (ref.)		1 (ref.)	

[a] Adjusted for comorbidities and co-medications; ref. = reference group.

Table 3
Long-acting bronchodilator adherence with or without influenza, stratified by PDC value combined with influenza vaccination.

Group, No (%)	Case (n = 6073)	Control (n = 12,146)	Crude OR (95 % CI)	*P-value*	Adjusted OR[a] (95 % CI)	*P-value*
PDC≥80 % with vaccination	343 (5.65)	857 (7.06)	0.745 (0.654–0.850)	<0.0001	0.719 (0.630–0.820)	<0.0001
PDC≥80 % without vaccination	563 (9.27)	1273 (10.48)	0.824 (0.740–0.916)	0.0004	0.811 (0.729–0.903)	0.0001
PDC<80 % with vaccination	1419 (23.36)	3037 (25.00)	0.870 (0.808–0.937)	0.0002	0.853 (0.792–0.919)	<0.0001
PDC<80 % without vaccination	3748 (61.72)	6979 (57.46)	1 (ref.)	–	1 (ref.)	–

[a] Adjusted for comorbidities and co-medications; ref. = reference group.

Table 4
Subgroup analysis of risk of influenza and long-acting bronchodilator adherence.

	PDC	Case (n = 6073)	Control (n = 12,146)	cOR (95 % CI)	*P-value*	aOR[a] (95 % CI)	*P-value*
Classify by age group							
40 ≤ age<49	≥80 %	35 (0.58)	84 (0.69)	0.790 (0.524–1.190)	0.2598	0.837 (0.545–1.284)	0.4147
	<80 %	472 (7.77)	895 (7.37)	1 (ref.)		1 (ref.)	
50 ≤ age<59	≥80 %	158 (2.60)	363 (3.00)	0.879 (0.720–1.073)	0.2062	0.910 (0.738–1.122)	0.3791
	<80 %	1156 (19.03)	2335 (19.22)	1 (ref.)		1 (ref.)	
60 ≤ age<69	≥80 %	273 (4.50)	680 (5.60)	0.763 (0.654–0.889)	0.0005	0.762 (0.649–0.893)	0.0008
	<80 %	1517 (24.98)	2882 (23.73)	1 (ref.)		1 (ref.)	
70 ≤ age<79	≥80 %	290 (4.78)	677 (5.57)	0.825 (0.708–0.961)	0.0134	0.795 (0.678–0.933)	0.0048
	<80 %	1326 (21.83)	2553 (21.02)	1 (ref.)		1 (ref.)	
80 ≤ age≤90	≥80 %	150 (2.47)	326 (2.68)	0.893 (0.721–1.106)	0.3004	0.837 (0.669–1.046)	0.1179
	<80 %	696 (11.46)	1351 (11.12)	1 (ref.)		1 (ref.)	
Classify by gender							
Male	≥80 %	788 (12.98)	1814 (14.93)	0.842 (0.768–0.924)	0.0003	0.827 (0.753–0.907)	<0.0001
	<80 %	3891 (64.07)	7544 (62.11)	1 (ref.)		1 (ref.)	
Female	≥80 %	118 (1.94)	316 (2.60)	0.723 (0.579–0.903)	0.0043	0.729 (0.583–0.913)	0.0058
	<80 %	1276 (21.01)	2472 (20.36)	1 (ref.)		1 (ref.)	
Classify by COPD severity							
High risk	≥80 %	496 (8.17)	1125 (9.26)	0.826 (0.727–0.937)	0.0031	0.812 (0.714–0.923)	0.0014
	<80 %	1192 (19.63)	2232 (18.38)	1 (ref.)		1 (ref.)	
Low risk	≥80 %	410 (6.75)	1005 (8.27)	0.799 (0.708–0.902)	0.0003	0.816 (0.722–0.923)	0.0012
	<80 %	3975 (65.45)	7784 (64.09)	1 (ref.)		1 (ref.)	

macrophage-1 antigen and increase the activity and expression of histone deacetylase 2 and the inhibitory activity of nuclear factor-κB after induction of an inflammatory stimulus in vitro [17].

Second, inflammatory cytokines are negatively correlated with lung function, indicating a relationship between virus infection and airway obstruction. Good adherence improves lung function, reduces exacerbation and decreases cytokine levels and risk of influenza virus infection [18].

Our study found that 14.92% and 17.54% of patients with COPD had an adherence-related PDC value of ≥80% with respect to long-acting bronchodilators in the case and control groups, respectively. Several other studies have evaluated adherence to treatment with COPD medications; however, different results have been reported because of various enrollment criteria, assessment tools, observation periods, and different definitions of adherence and medication. For example, a cross-sectional study in Greece using structured interviews and self-report questionnaires reported that 25.9% of the patients had good adherence [19]. Another study utilized retrospective claims data in the United States from 2008 to 2012 and showed that 20.8% of patients adhered to treatment with COPD maintenance medications [20]. The study used ICD codes to define COPD, enrolled patients aged 40–89 years, required more than one prescription record of COPD bronchodilators, and assessed COPD medication adherence by PDC for one year. This study design was relatively similar to ours but only measured medication with LAMAs and LABAs/ICSs. Another study also retrieved data from the NHIRD to assess COPD medication adherence and the risk of dementia in Taiwan, indicating that 11.28 % of patients had a PDC of ≥80 % [21]. They included long-acting bronchodilators and a few short-acting medications with a longer observation period.

In the subgroup analysis, the different scenarios were presented for the effect of adherence on influenza risk, including age group, sex, and COPD exacerbation risk. In the age group analysis, the odds ratios of influenza risk also showed a significant difference in the 60–70-year and 70–80-year age groups. This result may contribute to a policy of influenza vaccination in Taiwan. The government-funded vaccination was available to all seniors over 65 years or those aged between 60 and 64 with high-risk chronic diseases. Patient received influenza vaccination against influenza virus infection and decrease the severity and complications of airway diseases. Our study found adherence to long-acting bronchodilators decreased the risk of influenza infection in the COPD population and influenza vaccine on the risk of influenza were additive. LABA/LAMA also did not have similar effects to reduce risk of influenza virus infection in patients younger than 60 after subgroup analysis of risk of influenza infection and long-acting bronchodilator adherence.

Regarding gender differences, female patients had lower PDC values than males, which was as suggested in previous studies showing that female patients were less likely to adhere to using medications [21–23]. When classified by COPD exacerbation risk, the odds ratios of virus infection revealed associations with COPD exacerbation risk in both sexes. This also showed that COPD

exacerbation risk was associated with the risk of influenza virus infection.

This is the first study investigating the association between adherence to long-acting bronchodilators and the influenza infection among individuals with COPD in Taiwan. There were some advantages to our study. First, the study was conducted using the NHIRD database in Taiwan. The NHI program enrolled 99.99 % of 23 million of Taiwan's population, and the NHIRD can be used to comprehensively register occurrence of the disease in the Taiwanese population. In addition, our study had a sufficient sample size and reflects the characteristics of the entire COPD population. Second, our study used data from COPD patients from 2011 to 2019 and had a long observation period to measure the outcome. Third, the study used a nested case−control study to reduce the misclassification of adherence to treatment with long-acting bronchodilators. All long-acting bronchodilators were comprehensively tracked for evaluation without focusing on any one type of specific long-acting bronchodilator.

There were also several limitations in our study. First, the definition of the study population and outcomes were defined by ICD-9 and ICD-10 codes, and we lacked data on pulmonary tests, smoking status, body mass index, and personal lifestyle.

Second, the laboratory data, self-pay healthcare and out-of-pocket payments, medical equipment, or costs of alternative medicine could not be retrieved from the NHIRD.

Third, medication adherence may have been overestimated in the study since patients' actual medication-taking behaviors differ and patients may not take medications after prescription. It is also a limitation of our study that we did not analyze the differences between LAMA and LABA in preventing influenza in patients with COPD. Our study focused on analyzing the association between adherence to all types of bronchodilators in COPD and the risk of influenza infection.

Our study tests the association between the prescription of long-acting bronchodilators and the risk of influenza virus infection. There may be confounders that were responsible for the association between prescription and influenza virus infection. There were factors other than LABA/LAMA responsible for the influenza virus infection since even a 10 % cutoff value is associated with decreased influenza virus infection risk.

Besides, there are some patients who received concurrent treatment with bronchodilators and inhaled corticosteroids and this treatment category is totally different from patients without inhaled corticosteroids. However, the number of these patients was small. There were 115 patients out of 6,023 in the case group and 222 out of 12,146 in the controls. There was no significant impact on the statistic evaluation.

Nevertheless, we assumed that prescription refilling patterns represented patients' adherence to medical service; in this context, high adherence to treatment with long-acting bronchodilators was associated with a reduced risk of influenza.

5. Conclusion

Good adherence to treatment with long-acting bronchodilators (PDC$\geq$80%) could decrease the risk of influenza infection. Using long-acting bronchodilators not only improves the symptoms of COPD and reduces COPD exacerbation but also prevents influenza virus infection.

Data availability statement

The corresponding author (Prof. Chung-Yu Chen) had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Data are available from the National Health Insurance Research Database (NHIRD) published by the Bureau of National Health Insurance (BNHI) of the Ministry of Health and Welfare in Taiwan. Owing to the legal restrictions imposed by the Government of Taiwan related to the Personal Information Protection Act, the database cannot be made publicly available. Data are however available from the corresponding author upon reasonable request and with permission of NHIRD.

Consent for publication

NA.

Ethics statement

This study was carried out in accordance with the Declaration of Helsinki and was approved by the Institutional Review Boards of Kaohsiung Medical University Hospital (KMUHIRB-E(I)-20220055), which waived the requirement for informed consent.

Funding

The research reported in this publication was supported by a grant from the Chi-Mei Medical Center and Kaohsiung Medical University Research Foundation (111CM-KMU-006).

CRediT authorship contribution statement

Kuang-Ming Liao: Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Hsiao-Feng Huang:** Resources, Investigation, Conceptualization. **Yi-Ju Chen:** Methodology, Investigation, Formal analysis, Data curation. **Chuan-Wei Shen:** Resources, Project administration, Methodology, Investigation. **Chung-Yu Chen:** Writing – review & editing, Writing – original

draft, Validation, Supervision, Software. **Yaw-Bin Huang:** Writing – review & editing, Visualization, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

This study was based in part on data from the NHIRD provided by the BNHI of the Department of Health and managed by the National Health Research Institute. The conclusions presented in this study are those of the authors and do not necessarily reflect the views of the BNHI of the Ministry of Health and Welfare. This work was supported by the Chi-Mei Medical Center and Kaohsiung Medical University Research Foundation (111CM-KMU-006).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e35367.

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