

The Influence of Influenza Virus Infections in Patients with Chronic Obstructive Pulmonary Disease

Kuang-Ming Liao¹, Yi-Ju Chen², Chuan-Wei Shen², Shao-Kai Ou², Chung-Yu Chen²⁻⁴

¹Department of Internal Medicine, Chi Mei Medical Center, Chiali, Taiwan; ²School of Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan; ³Department of Pharmacy, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan; ⁴Department of Medical Research, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan

Correspondence: Chung-Yu Chen, School of Pharmacy, Kaohsiung Medical University, No. 100, Shihcyuan 1st Road, Sanmin District, Kaohsiung City, 80708, Taiwan, Tel +886-7-3121101 ext 2375, Fax +886-7-3210683, Email jk2975525@hotmail.com

Introduction: Chronic obstructive pulmonary disease (COPD) is a common disease and is preventable and treatable. A previous study showed that influenza virus infections were also associated with the risk of acute exacerbation in patients with COPD, and other studies showed that the influenza virus might increase the risk of stroke. However, studies on the influence of influenza infection among COPD patients are limited. In this study, we review the role of influenza infection in contributing to mortality, pneumonia, respiratory failure, COPD acute exacerbation, and ischemic stroke among COPD patients.

Materials and Methods: We performed a population-based cohort study of COPD patients using data from Taiwan between January 1, 2011, and December 31, 2019. We excluded patients with lung cancer, lung transplantation and asthma. We also excluded patients who lacked COPD medication prescriptions and those treated with anti-influenza drugs without flu diagnosis records. Patients with missing or incomplete data were also excluded from the study cohort.

Results: After 1:1 matching by age, sex, COPD duration, diagnosed years and comorbidities, we enrolled 10,855 cases and controls for further analysis. The risks of pneumonia, respiratory failure, COPD acute exacerbation, and ischemic stroke were 1.770 (95% CI=1.638–1.860; $P<0.0001$), 1.097 (95% CI=1.008–1.194; $P=0.0319$), 1.338 (95% CI=1.248–1.435; $P<0.0001$), and 1.134 (95% CI=1.039–1.239; $P=0.0051$), respectively, in the influenza infection group compared with COPD patients without influenza infection.

Conclusion: Influenza infections are linked to an increased risk of ischemic stroke, pneumonia, respiratory failure, and COPD acute exacerbation among COPD patients. In conclusion, patients with COPD need to be closely monitored after having an influenza infection.

Keywords: acute exacerbation, chronic obstructive pulmonary disease, influenza virus, pneumonia, stroke, respiratory failure

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic and systemic inflammatory disease associated with airflow obstruction. Patients with COPD may experience an acute exacerbation, which is characterized by worsening symptoms of cough, sputum production, and dyspnea¹ and results in lung function decline,² increased hospital admission, morbidity, mortality,³ deteriorating quality of life,⁴ significant economic burden and medical expenditure.⁵ Most exacerbations are caused by infection with either bacteria or viruses,⁶ in which the primary pathogen is the rhinovirus, and one of the most common viruses is the influenza virus.⁷ Patients with superimposed bacterial infection or virus and bacteria coinfections may also occur after virus infections⁸ and progression in the disease process resulting in severe pneumonia or respiratory failure. A previous study also showed that influenza virus infections were also associated with the risk of stroke.⁹ However, studies on whether influenza infection is associated with an increased risk of stroke among COPD patients are limited. Thus, in this study, we examined the risk of ischemic stroke after influenza infection among patients with COPD in Taiwan. We also review the role of influenza infection in contributing to mortality, pneumonia, respiratory failure, and COPD acute exacerbation among COPD patients.

Methods

Study Design and Data Source

We performed a population-based cohort study of COPD patients using data from the Taiwan National Health Insurance Research Database (NHIRD) between January 1, 2011, and December 31, 2019. The NHIRD was retrieved from claims data of the National Health Insurance (NHI) program, which was launched in 1995 and contained comprehensive pharmacy and medical records. The NHI program covers up to 99.99% of Taiwan's population, and the database can represent the health condition of the entire Taiwanese population. The study was conducted according to the Declaration of Helsinki and was approved by the Institutional Review Boards of Kaohsiung Medical University Hospital (Research Ethics Committee No. KMHIRB-E(II)-20200044), which waived the requirement for written informed consent.

Definition of Study Cohort

The eligible subjects of the study included patients who were between 40 and 90 years of age and had more than three outpatient diagnoses or more than one inpatient diagnosis of COPD (ICD-9CM: 490–492, 496; ICD-10CM: J40–J44) from January 1, 2012, to December 31, 2018. The exclusion criteria were patients with lung cancer (ICD-9CM: 162; ICD-10CM: C33, C34, C78.00, C78.01, C78.02, C7A.090, Z85.118) or lung transplantation (ICD-9CM: 996.84, V42.6; ICD-10CM: T86.81, Z94.2) one year before cohort entry and patients with asthma (ICD-9CM: 493; ICD-10CM: J45) in the whole study period. We also excluded patients who lacked COPD medication prescriptions and those treated with anti-influenza drugs without a recorded flu diagnosis. Furthermore, patients with missing or incomplete data were also excluded from the study cohort.

Patients diagnosed with influenza (ICD-9CM: 487; ICD-10CM: J09–J11) after COPD from 2012 to 2018 were included in the influenza group, while others without an influenza diagnosis were included in the non-influenza group. We performed propensity-score matching of each influenza case matching to one randomly selected non-influenza case by age, gender, insurance premium, urbanization level, COPD duration, COPD severity, and comorbidities (including pneumonia, hypertension, respiratory failure, diabetes mellitus, hyperlipidemia, malignancy, chronic kidney disease, chronic liver disease, and anemia). The matching comorbidities were potential risk factors of influenza and related complications according to the Centers for Disease Control and Prevention. The index date was defined as the date of the first influenza diagnosis and was assigned to the non-influenza groups by matched grouping.

Outcome Measurement

The influenza and non-influenza groups were followed until the earliest outcomes of interest, including death, NHI program withdrawal, or one year after the index date. The primary outcome measurements included all-cause mortality, pneumonia (ICD-9CM: 480–486; ICD-10CM: J12–J18, B25, B44, A22.1, A37.91), respiratory failure (ICD-9CM: 518.81–518.84; ICD-10CM: J96), acute COPD exacerbation (ICD-9CM: 491.21; ICD-10CM: J44.1), and ischemic stroke (ICD-9CM: 433, 434; ICD-10CM: I63–I66).

Covariate Measurement

The demographic characteristics of COPD patients included age, age group (stratified by ten years), sex, urbanization level (urban, suburban, and rural), and monthly insurance premium rates. Comorbidities, concomitant medications, and COPD-related medications were measured one year before index date. The severity of COPD was divided into severe exacerbations and moderate exacerbations. Severe exacerbations were defined as exacerbations resulting in visiting the emergency room or hospitalization. In contrast, moderate exacerbations were defined as exacerbations not leading to hospital admission, but patients were treated with short-acting β_2 -agonists (SABA) plus antibiotics or oral corticosteroids. If patients had more than two moderate exacerbations or more than one severe exacerbation within one year, they were classified as having a high exacerbation risk. Instead, others with no exacerbation or one moderate exacerbation were considered low exacerbation risk.

Statistical Analysis

For the characteristics listed at baseline, continuous variables were presented as the means (standard deviation) and were analyzed by Student's *t*-test. Categorical variables were shown as the number (percentage) and were analyzed by the chi-square test. We performed a time-to-event analysis by applying the Cox proportional hazard regression model with adjusted potential confounders to assess the risk of one-year outcomes of influenza and non-influenza groups. The potential confounders included age, sex, COPD severity, urbanization, monthly income, comedications, and comorbidities. Kaplan–Meier analysis was also used to compare the incidence of outcomes of interest. Data processing and analysis were conducted with Statistical Analysis Software (SAS), version 9.4 (SAS Institute Inc., Cary, NC). Statistical significance was defined as a *P* value of <0.05.

Results

Between January 1, 2012, and December 31, 2018, we identified 1,220,236 COPD patients who were followed until the end of 2019 or until death or withdrawal from the national health insurance system. The final cohort consisted of 117,125 COPD patients (Figure 1) after excluding exclusion criteria. There were 13,221 COPD patients with an influenza diagnosis and 103,904 COPD patients without an influenza diagnosis. After 1:1 matching by age, sex, COPD duration, diagnosed years and comorbidities, we enrolled 10,855 cases and controls for further analysis.

Demographic characteristics and comorbidities in COPD patients with and without influenza after matching are presented in Table 1. Most patients' ages were between 70 and 80 years, followed by between 60 and 70 years. There was a higher proportion of males in the study population, accounting for 73.53%. The three most common comorbidities in the COPD group were hypertension (42.86%), diabetes (24.04%), and hyperlipidemia (19.83%) in influenza group.

In Figure 2, there were higher incident rate observed in pneumonia ($p<0.001$), respiratory failure ($p<0.001$) and ischemic stroke ($p=0.0327$). However, there was no significantly difference between case and control group, including all-cause mortality ($p=0.0707$) and acute exacerbation ($p=0.0581$). We compared the outcomes, including death, pneumonia, respiratory failure, COPD acute exacerbation, ischemic stroke between COPD patients with and without influenza infection 1 year after the index date. (Table 2). In addition to mortality, the risk of outcome in the influenza infection group cohort was significantly higher than that without influenza infection. The aHRs of pneumonia, respiratory failure, COPD acute exacerbation, and ischemic stroke were 1.770 (95% CI=1.638–1.860; $P<0.0001$), 1.097 (95% CI=1.008–1.194; $P=0.0319$), 1.338 (95% CI=1.248–1.435; $P<0.0001$), and 1.134 (95% CI=1.039–1.239, $P=0.0051$), respectively.

Discussion

This nationwide population-based study showed that compared without influenza infection, patients with COPD and influenza infection had a significantly higher risk of pneumonia, respiratory failure, COPD acute exacerbation, and ischemic stroke incidence after adjusting for age, sex, urbanization level, income, COPD severity, comorbidities, and comedications listed in baseline characteristics.

Influenza Infection and COPD Acute Exacerbation

Studies have demonstrated that bacteria are responsible for most acute exacerbations in COPD; however, the prevalence of respiratory virus increased after using PCR testing.¹⁰ Serological and viral culture techniques can only detect viruses in approximately 30% of patients with COPD acute exacerbation.¹¹ After applying PCR, it was found that viruses are associated with more than half of COPD exacerbations.¹² There is growing evidence that host inflammation dysregulates the immune response against viral infection and increases plasma fibrinogen and serum IL-6 levels and associated lung functions.¹³ Respiratory virus infections are correlated with more severe and frequent exacerbations and may also lead to chronic infection in COPD.¹⁴ The mechanism of respiratory viral infections in COPD includes desquamation of epithelial cells in the airway, microvascular dilatation and edema, recruitment of inflammatory cell infiltrate, followed by decreased mucociliary clearance function and bacterial killing by macrophages, leading to bacterial infections and dysregulation of hyperinflammation that leads to disease progression.¹⁵ A systematic review combined nineteen studies with 1728 patients

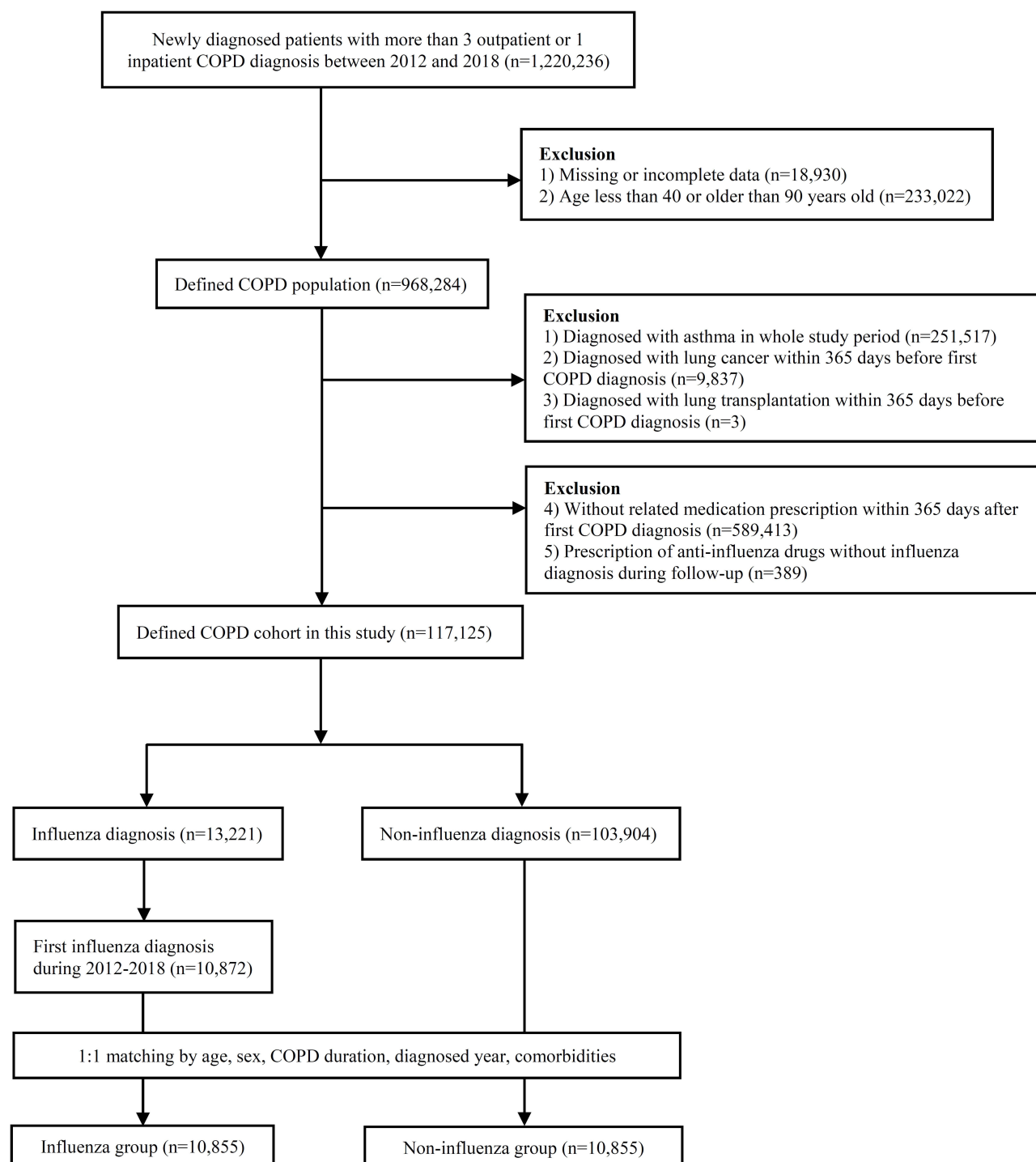


Figure I Flow diagram of patient selection.

and evaluated the literature of the prevalence of respiratory viruses in patients with COPD acute exacerbation detected by PCR and found that rhino/enteroviruses (16.39%), respiratory syncytial virus (9.90%), and influenza (7.83%) were the most common viruses.¹⁶ These data present viruses in a meaningful proportion of COPD exacerbations; however, these studies do not demonstrate causality, and respiratory viruses appearing in stable COPD have also been shown.^{17,18} There are limited data to show the incidence of acute exacerbation after influenza virus infection. According to our findings, patients with COPD after influenza infection are 1.338 times more vulnerable to acute exacerbation.

Table I Demographic Characteristics and Comorbidities in COPD Patients with and without Influenza After Matching

Baseline Characteristics N (%)	Influenza (N=10,855)	Non-Influenza (N=10,855)	P-value
Age mean (SD)	68.73 (12.30)	68.91 (12.14)	0.2890
Age group			0.1821
40≤age<49	783 (7.21)	733 (6.75)	I
50≤age<59	1918 (17.67)	1970 (18.15)	
60≤age<69	2707 (24.94)	2605 (24.00)	
70≤age<79	2913 (26.84)	2913 (26.84)	
80≤age≤90	2534 (23.34)	2634 (24.27)	
Gender			0.3177
Male	7982 (73.53)	7982 (73.53)	
Female	2873 (26.47)	2873 (26.47)	
Insurance premium (NT\$) ^a			0.9272
≥monthly minimum wage	7865 (72.46)	7799 (71.85)	
<monthly minimum wage	2990 (27.54)	3056 (28.15)	
Urbanization level			0.9272
Urban	4740 (43.67)	4719 (43.47)	
Suburban	4869 (44.85)	4874 (44.90)	
Rural	1246 (11.48)	1262 (11.63)	
COPD severity			
Severe exacerbations			<0.0001
0	7359 (67.79)	7770 (71.58)	
I	2050 (18.89)	1871 (17.24)	
≥2	1446 (13.32)	1214 (11.18)	<0.0001
Moderate exacerbations			
0	7763 (71.52)	7661 (70.58)	
I	852 (7.85)	676 (6.23)	
≥2	2240 (20.63)	2518 (23.19)	
COPD exacerbation risk			I
High	4836 (44.55)	4836 (44.55)	
Low	6019 (55.45)	6019 (55.45)	
COPD duration mean (days, std)	564.7 (542.04)	615.3 (535.5)	0.1466
COPD medication			
LABA	573 (5.28)	668 (6.15)	0.0055
LAMA	1592 (14.67)	1868 (17.21)	<0.0001
LABA+LAMA	795 (7.32)	1005 (9.26)	<0.0001
LABA+ICS	1807 (16.65)	1916 (17.65)	0.0497
SABA	3513 (32.36)	2850 (26.26)	<0.0001
SAMA	1193 (10.99)	853 (7.86)	<0.0001
SABA+SAMA	1501 (13.83)	1275 (11.75)	<0.0001
Methylxanthines	6810 (62.74)	6019 (55.45)	<0.0001
Co-medication			
Chemotherapy	399 (3.68)	388 (3.57)	0.6896
Immunosuppressant	48 (0.44)	37 (0.34)	0.2319
Corticosteroid	6637 (61.14)	5785 (53.29)	<0.0001

(Continued)

Table 1 (Continued).

Baseline Characteristics N (%)	Influenza (N=10,855)	Non-Influenza (N=10,855)	P-value
Comorbidity			
Pneumonia	1715 (15.80)	1789 (16.48)	0.1722
Respiratory failure	499 (4.60)	519 (4.78)	0.5208
Pulmonary embolism	22 (0.20)	21 (0.19)	0.8787
Hypertension	4652 (42.86)	4642 (42.76)	0.8909
Diabetes mellitus	2610 (24.04)	2629 (24.22)	0.7631
Hyperlipidemia	2153 (19.83)	2084 (19.20)	0.2374
Obesity	25 (0.23)	28 (0.26)	0.6799
Malignancy	1221 (11.25)	1241 (11.43)	0.6686
Chronic kidney disease	712 (6.56)	725 (6.68)	0.7227
Chronic liver disease	997 (9.18)	984 (9.06)	0.7593
Solid organ transplant	39 (0.36)	25 (0.23)	0.0797
Depression	441 (4.06)	432 (3.98)	0.7559
Dementia	594 (5.47)	601 (5.54)	0.8350
Insomnia	704 (6.49)	672 (6.19)	0.3727
Nervous system diseases	1621 (14.93)	1678 (15.46)	0.2812
Anemia	554 (5.10)	539 (4.97)	0.6415
Autoimmune disease	254 (2.34)	231 (2.13)	0.2909
ASCVD			
Coronary artery disease	1865 (17.18)	1874 (17.26)	0.8715
Peripheral vascular disease	289 (2.66)	288 (2.65)	0.9663
Ischemic stroke/ Transient ischemic stroke	1292 (11.90)	1322 (12.18)	0.5315
Hemorrhagic stroke	251 (2.31)	266 (2.45)	0.5043
Heart failure	975 (8.98)	998 (9.19)	0.5871
Left ventricular hypertrophy	39 (0.36)	42 (0.39)	0.7384
Atrial fibrillation	936 (8.62)	954 (8.79)	0.6648

Notes: *The range of minimum incomes from government announcements. Comorbidities, COPD severity, medication for COPD, and comedication were measured within one year before the index date.

Abbreviations: LABA, long-acting beta-agonist; ICS, inhaled corticosteroids; LAMA, long-acting muscarinic antagonists; SABA, short-acting beta-agonist; SAMA, short-acting muscarinic antagonists, NA, not applicable.

Pneumonia and Respiratory Failure

There is a small number of clinical studies that delineate the association between influenza infection and COPD. Most studies focus on influenza vaccination reducing COPD exacerbations.^{19–22} Yap et al²³ reported that influenza activity is associated with significant excess hospitalization among elderly individuals aged 65 or above with COPD in Hong Kong, comparable to Western countries. Influenza infection superimposed on secondary bacterial pneumonia was a common and severe complication. It is also the leading cause of morbidity and mortality during influenza pandemics.^{24–26} After an influenza infection, airway epithelial barrier disruption increases bacterial proliferation and enhances bacterial adherence. In addition, influenza downregulates the host immune response, induces neutrophil apoptosis and dysfunction, and suppresses macrophage phagocytosis to increase bacterial infection.^{27–30} The study showed that the influenza virus increased pneumonia risk but did not focus on the COPD population, and the risk of respiratory failure was also lacking. From our study, we found that COPD patients had a 1.770- and 1.097-fold increased risk of pneumonia and respiratory failure after influenza infection, respectively, compared with those without influenza infection.

Influenza Infection and Stroke

Influenza infections are linked to an increased risk of ischemic stroke and have been reported in previous research studies. Influenza virus may induce nonspecific proinflammatory and procoagulant changes and worsen underlying atherosclerotic disease.³¹ Toschke et al³² reported an association between influenza infections and subsequent first-ever

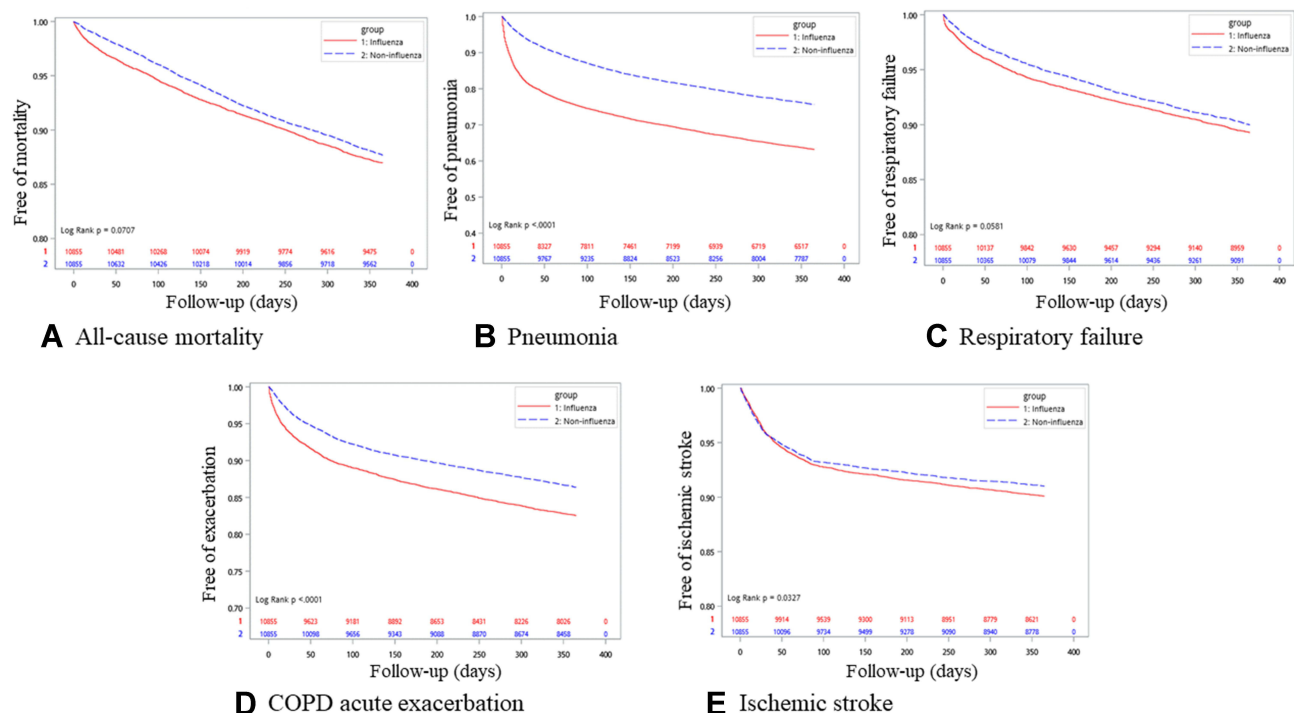


Figure 2 Kaplan–Meier curves demonstrate the outcomes of the influenza and non-influenza groups in the COPD population. Outcome measurement: (A) All-cause mortality, (B) Pneumonia, (C) Respiratory failure, (D) COPD acute exacerbation, (E) Ischemic stroke.

stroke. Smeeth et al³³ also reported that influenza infection is associated with a risk of stroke. Inflammation can induce atherosclerotic disease and result in a stroke. Kulick et al³⁴ used the New York Statewide Planning and Research Cooperative System (SPARCS) to estimate the risk of ischemic stroke after an influenza-like illness from 2012 to 2014. They found that influenza-like illnesses in the 15 days prior increased the odds of ischemic stroke by 39% (95% CI 1.09–1.77) and increased the odds to approximately 70% when looking at influenza-like illness events over the last year. Our study found that influenza infection significantly increased the risk of ischemic stroke in COPD. COPD itself is a risk factor for ischemic stroke. Compared with patients with COPD without an influenza infection, patients with COPD with an influenza infection were more vulnerable to ischemic stroke. To sum up, due to relative poor outcomes in COPD patients with influenza, annual influenza vaccination is important for this population.

Strengths and Limitations

The strengths of our study include the use of nationwide, large amounts of data regarding the generalized COPD population for 8 years. We also controlled for multiple comorbidities, age, sex and COPD severity. In the cohort study, we showed outcomes after influenza infection, which is likely to indicate a causal relationship. The use of medication-

Table 2 Comparison of Risks of One-Year Outcomes of Interest Between the Influenza and Non-Influenza Groups

Variables ^a	Influenza (n=10,855)	Non-Influenza (n=10,855)	Influenza vs Non-Influenza (Ref.)			
	Event (%)	Event (%)	Crude HR (95% CI)	P-value	Adjusted HR ^b (95% CI)	P-value
All-cause mortality	1416 (13.04)	1337 (12.32)	1.071 (0.994–1.154)	0.0709	1.077 (0.999–1.161)	0.0524
Pneumonia	3898 (35.91)	2583 (23.80)	1.724 (1.640–1.812)	<0.0001	1.770 (1.638–1.860)	<0.0001
Respiratory failure	1118 (10.30)	1049 (9.66)	1.085 (0.997–1.18)	0.0582	1.097 (1.008–1.194)	0.0319
COPD acute exacerbation	1817 (16.74)	1422 (13.10)	1.333 (1.244–1.429)	<0.0001	1.338 (1.248–1.435)	<0.0001
Ischemic stroke	1031 (9.50)	949 (8.74)	1.101 (1.008–1.202)	0.0329	1.134 (1.039–1.239)	0.0051

Notes: ^aAll variables were followed one year after the index date. ^bCox proportional hazard model adjusted for age, sex, urbanization level, income premium, COPD severity, comorbidities and comedication.

Abbreviations: ref., reference group; cHR, crude hazard ratio; aHR, adjusted hazard ratio; CI, confidence interval.

confirmed measures improved COPD and influenza diagnostic specificity. Our population-based approach means that these results may be generalizable to COPD patients in similar conditions.

Our study nevertheless had some limitations. Although analyses used medication-confirmed measures to improve COPD and influenza diagnosis, pulmonary function test data were lacking in our database, and the COPD stage could not be obtained. It was not possible to investigate the dyspnea score of COPD patients. Despite indirect measurements of COPD severity in database analysis, COPD exacerbation frequency was considered because it was an alternative indicator of COPD disease severity.

We were also unable to investigate the pneumonia pathogen. The pneumonia pathogen also could not be identified in our patients. Therefore, we cannot discriminate between different causative organisms in this study. Moreover, nasopharyngeal swab or other reconfirmed tests were lack in database; therefore, influenza diagnosis was evaluated based on ICD codes. Last, smoking condition, personal lifestyle, or environmental effect could not be completely evaluated in NHIRD database. In hence, adjustments could not be made for these risk factors or potential confounders, which may influence the outcomes.

In conclusion, in our nationwide population-based cohort study, influenza infection was positively associated with the risk of pneumonia, respiratory failure, acute exacerbation and stroke. Patients with COPD need to be closely monitored after having an influenza infection. Influenza vaccination is also encouraged among this certain risk group.

Data Sharing Statement

The data supporting the present research findings were sourced from NHIRD 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.

Ethics Statement

This study was approved by the IRB of Kaohsiung Medical University Hospital (KMUHIRB-E(I)-20220055). Because patients' data could not be identified, the requirement for informed consent was waived.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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