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Original Article

Influenza vaccination and risk of respiratory failure in patients with chronic obstructive pulmonary disease: A nationwide population-based case-cohort study



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KEYWORDS

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Abstract *Background:* Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease which causes a considerable disease burden. Patients with COPD are at a higher risk for influenza infection and influenza vaccination are recommended at this high risk patient group. In the current study, we aimed to evaluate the association between influenza vaccination and the risk of respiratory failure (RF) in COPD patients.

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Chronic obstructive pulmonary disease; Taiwan National Health Insurance Research Database

Methods: From 2001 to 2005, patients with newly diagnosed COPD were identified from the NHIRD, and were followed until 2010. We explored the influenza vaccination rate among this COPD cohort. Furthermore, patients who experienced RF were defined as case group, whereas the others were defined as control group. Baseline characteristic were compared and association between influenza vaccination and RF were evaluated.

Results: The rate of influenza vaccination was significantly higher in patients age ≥ 65 years than those age < 65 years (54.8% vs. 4%, $p < 0.001$). The vaccine cohort had more comorbidities, more health care utilization and more frequent acute exacerbations as compared with nonvaccine cohort. In multivariable logistic regression, influenza vaccination was associated with a reduced risk of respiratory failure (adjusted odds ratio [aOR] 0.87, 95% confidence interval [CI] 0.79–0.96). In subgroup analysis, we found that the association was insignificant in patients age < 65 years, patients with relatively unstable disease status and patient did not receive influenza vaccination annually.

Conclusions: Influenza vaccination was associated with a decreased risk of RF in patients with COPD. Recommendation of annual influenza vaccination should be made when managing this high-risk patient group.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease, which is characterized by irreversible airflow limitation and decline in pulmonary function.^{1,2} As the disease progresses, exacerbation can occur several times per year, and it causes a considerable burden on the global health care system.²

Patients with COPD are at an increased risk for respiratory tract infection,^{3,4} resulting in increased mortality and morbidity.^{5,6} Historically, bacteria have been considered the main infectious cause of COPD exacerbations.⁷ However, a growing body of evidence implicates viral infections in the pathogenesis of COPD and as a major trigger of acute exacerbations.^{8,9} Among various viral pathogens, influenza is one of the most frequently detected.¹⁰ Several studies reported the presence of influenza virus in up to 28% of COPD patients with exacerbation,^{11,12} and it resulted in severe complications, such as respiratory failure (RF) and death.⁵

Previously, only a small proportion of exacerbations in COPD patients were attributed to viral infection, but through polymerase chain reaction techniques, it is now acknowledged that viral infection could account for up to 50% of exacerbations, with the influenza virus being detected in up to 28% of COPD patients with exacerbation.^{11,12} While rhinovirus is the most common cause of exacerbations, influenza is also a common causative organism in exacerbation of COPD that is severe enough to require hospital admission, and is thus a major contributor of mortality and morbidity in COPD.^{12–14}

A 2006 Cochrane review evaluated the results of 11 randomized controlled trials to determine the efficacy of the influenza vaccine in patients with COPD (Table 1). Patients with COPD who were administered the inactivated influenza vaccine experienced significantly fewer exacerbations per year than patients with COPD who were administered a placebo. The review thus concluded that the influenza vaccine reduced the incidence of influenza-related respiratory infections.¹⁵

Currently, therefore, patients with COPD are a high priority for influenza vaccination, and annual vaccination is universally recommended in almost all COPD guidelines.^{16–18} However, evidence on whether influenza vaccination is associated with a decreased risk of respiratory failure (RF) among COPD patients is limited. Thus, in this study, we explored the rate of influenza vaccination among COPD patients in Taiwan. We also evaluated whether influenza vaccination was associated with a decreased risk of RF among COPD patients and clarified whether vaccination had a different protective effect against RF using subgroup analysis.

Methods

Overview of the health care system in Taiwan

Taiwan's National Health Insurance (NHI) program is a single-payer, mandatory unanimous social insurance, which was established in 1995. It provides comprehensive coverage to all Taiwan's residents, and includes outpatient,

Table 1 The proportion of individuals who had received influenza vaccination within a 1-year period after COPD diagnosis (stratified by different age groups).

| Age group (y) | n | Influenza vaccination | | Proportion of vaccination (%) |
|---------------|---------------|-----------------------|-------------|-------------------------------|
| | | Yes | No | |
| 45–64 | 8639 | 344 | 8295 | 3.98 |
| 45–54 | 4250 | 55 | 4195 | 1.29 |
| 55–64 | 4389 | 289 | 4100 | 6.58 |
| >65 | 11,149 | 5779 | 5370 | 51.83 |
| 65–74 | 5816 | 3231 | 2585 | 55.55 |
| 75–84 | 4306 | 2133 | 2173 | 49.54 |
| ≥ 85 | 1027 | 415 | 612 | 40.41 |

inpatient, emergency, dental, and traditional Chinese medical services, as well as surgical procedures and prescription medicine.

Data sources

We conducted a retrospective nationwide study, based on information from the National Health Insurance Research Database (NHIRD) released by the Taiwan National Health Research Institutes (NHRI). The National Health Insurance (NHI) system is a mandatory universal health insurance program, which offers comprehensive medical care coverage to nearly all Taiwanese residents (with a coverage rate of 99.6% by the end of 2010) (<http://www.nhi.gov.tw/english/index.aspx>). The NHIRD is a cohort dataset containing all the medical claims data for 1,000,000 beneficiaries, who were randomly sampled from the 25.68 million enrollees under the NHI program. This random sample has been confirmed by the NHRI to be representative of the Taiwanese population. In this cohort dataset, the patients' original identification numbers have been encrypted to protect their privacy, but the encryption procedure was consistent, so that it is possible to link the claims belonging to the same patient within the NHI database, and patients can be followed continuously. This database, with its large sample size, provides an excellent opportunity to study the association between the influenza vaccination and the risk of RF among COPD patients.

Identification of COPD cohort

From January 1, 2001, to December 31, 2005, a total of 19,788 patients (age ≥ 45 years) with newly diagnosed COPD were identified in the NHIRD. The diagnosis of COPD was based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes (491, 492, or 496). To ensure the accuracy of diagnosis, we included patients with COPD only when it was a primary discharge diagnosis or was repeatedly confirmed more than twice in an outpatient department within 12 months. Patients had to have received respiratory medication to be included in the study, and patients with a combined diagnosis of asthma were excluded.¹⁹ The COPD cohort was followed until the end of 2010 or censure because of death or withdrawal from the insurance system.

Case and control groups

Among the COPD cohort, patients who experienced RF necessitating mechanical ventilation were identified as the case group. The remaining patients in this cohort who did not experience RF were defined as the control group. The index date was the date on which RF occurred or the date that participants were censored among the case and control groups, respectively. Exposure to influenza vaccine during the 365 days preceding the index date was analyzed and compared in the case and control groups.

Exposure to influenza vaccine

We defined patients who had received seasonal influenza vaccine within the 365 days preceding the index date, based on diagnosis (ICD-9-CM V04.7, V04.8) or drug code.²⁰

Covariate assessment

We used inpatient and outpatient diagnosis to identify comorbidities. As relevant comorbidities, we included hypertension, diabetes mellitus, congestive heart failure, coronary artery disease, chronic kidney disease, ischemic stroke, intracranial hemorrhage, malignancy, liver cirrhosis, anxiety, mood disorder, and insomnia. Health care utilization was estimated by measuring the annual number of outpatient physician visits, hospitalizations, and use of computed tomography (CT)/magnetic resonance imaging (MRI). We used acute exacerbation of COPD (ICD-9 codes 491.21) necessitating emergency room (ER) visits as a proxy measure of disease severity.

Statistical analysis

The SAS (version 9.2; SAS Institute, Inc., Gary, NC, USA) and SPSS (version 15, SPSS Inc., Chicago, IL, USA) statistical packages were used to analyze the data. Differences between categorical variables were compared using the McNemar test. Continuous variables were assessed using the two-sample t-test for normally distributed continuous variables, and the Mann–Whitney rank-sum test for skewed variables.

Baseline characteristics, including age, sex, comorbidities (i.e., hypertension, diabetes mellitus, congestive heart failure, coronary artery disease, chronic kidney disease, ischemic stroke, intracranial hemorrhage, malignancy, liver cirrhosis, anxiety, mood disorder, insomnia), health care utilization (i.e., the annual number of outpatient physician visits, hospitalizations, and use of CT/MRI), and acute exacerbation were compared between case and control groups. The differences were examined using the χ^2 test for categorical variables and the t-test for continuous variables. To estimate the risk of RF associated with influenza vaccine, we performed logistic regression to derive odds ratios (ORs) and 95% confidence intervals (CIs). We examined the variance inflation factors to establish whether the model exhibited multicollinearity; a value above 10 was deemed indicative of marked multicollinearity problem. A two-sided p value < 0.05 was considered statistically significant for all statistical analyses.

Results

Proportion of influenza vaccination within 1-year period after the diagnosis of COPD

Between January 1, 2001, and December 31, 2005, we identified 27,363 newly diagnosed COPD patients who were followed until the end of 2010 or until censored because of death or withdrawal from the insurance system. Of these,

7575 patients (27.7%) aged < 45 years or with a combined diagnosis of asthma were excluded. Therefore, the final cohort consisted of 19,788 COPD patients (Fig. 1). The proportion of individuals who had received influenza vaccination within a 1-year period after COPD diagnosis is presented in Table 1. Significantly more patients aged ≥65 years had been vaccinated than those aged <65 years (proportion of vaccination: 51.83% vs. 3.98%, respectively). The annual trend for influenza vaccination is shown in Figs. 2 and 3.

Baseline characteristics of COPD patients with and without vaccination within 1 year prior to RF

The nonvaccine and vaccine cohorts comprised 13,562 (68.5%) and 6226 (31.5%) of the COPD patient cohort. We compared the differences in the baseline characteristics between these two groups (Table 2). The mean age in the vaccine cohort was significantly higher than that in the

nonvaccine cohort (70.75 ± 9.03 vs. 63.95 ± 12.27 years, respectively). Elderly patients (≥65 years) constituted most of the vaccinated patients (n = 4698, 75.5%). As compared with the nonvaccine cohort, the vaccine cohort included a higher proportion of male sex, more comorbidities, more outpatient department visits and hospitalizations, and a higher annual rate of influenza vaccination during the follow-up period.

Comparison of COPD patients with and without RF

The baseline characteristics of patients with and without RF are shown in Table 3. Patients with RF were older, had a higher proportion of male sex, presented with more comorbidities, more health care utilization, and more acute exacerbations than those without RF. During the 1-year period before the index date, patients with RF also had a higher rate of influenza vaccination.

Association between influenza vaccination and risk of RF in COPD patients

The association between influenza vaccination and risk of RF, as represented by ORs, is shown in Table 4. Patient with influenza vaccination had a decreased risk of RF in comparison to those without vaccination (aOR 0.87, 95% CI 0.79–0.96) after adjustment for differences in comorbidities, annual health care utilization, and acute exacerbation.

Subgroup analysis

In subgroup analysis (Fig. 4), influenza vaccination was associated with a decreased risk of RF among patients aged ≥ 65 years (aOR 0.89, 95% CI 0.80–0.98), patients without acute exacerbation in the previous year (aOR 0.87, 95% CI 0.78–0.97), and patients who received influenza vaccine annually (aOR 0.74, 95% CI 0.57–0.96).

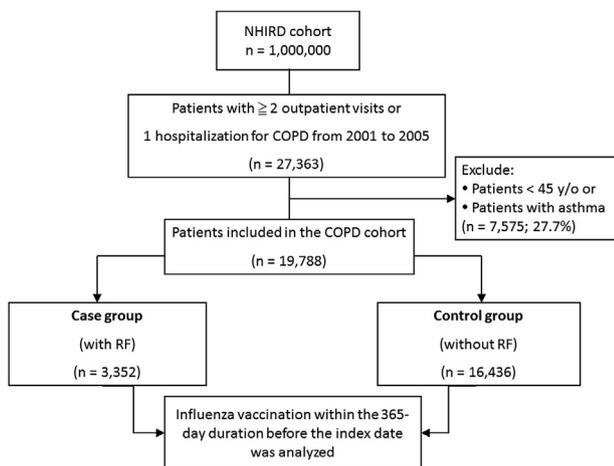


Figure 1. The flow chart of the enrollment of the COPD cohort.

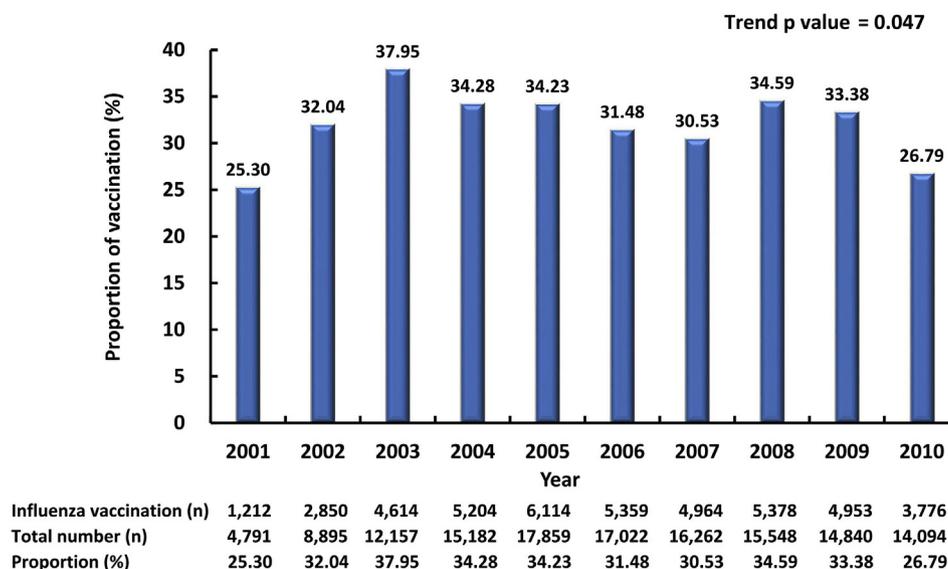


Figure 2. Annual trend of influenza vaccination among COPD patients.

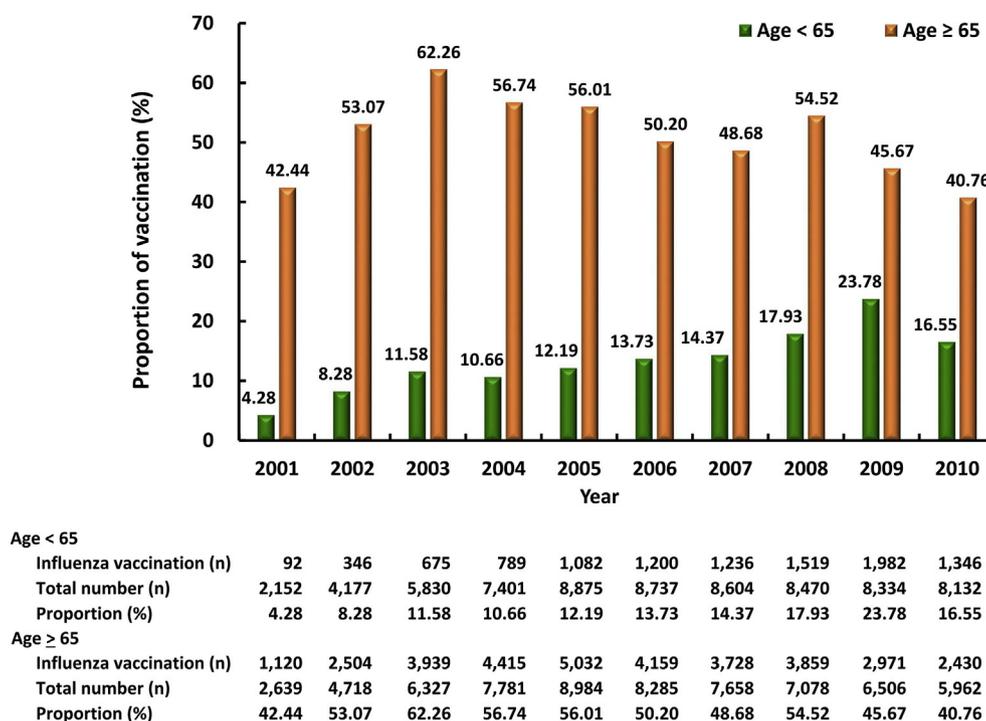


Figure 3. Annual trend of influenza vaccination among COPD patients.

Discussion

Main findings

This nationwide population-based observational study, which enrolled a total of 19,788 COPD patients aged ≥ 45 years, demonstrated the association between influenza vaccination and risk of RF. The main findings were as follows. (1) About 30.9% newly diagnosed COPD patients received influenza vaccination within 1 year after COPD diagnosis. The group of patients aged ≥ 65 years included a significantly higher proportion of vaccinated individuals than those aged < 65 years. (2) The vaccinated cohort had a higher mean age, more male patients, and presented with more comorbidities, more OPD visits, and more hospitalizations. (3) Patient who had received influenza vaccination had a lower risk of RF than those who had not been vaccinated, after adjustment for differences in baseline characteristics. (4) In subgroup analysis, influenza vaccination was associated with a decreased risk of RF among patients whose age ≥ 65 years, patients without acute exacerbation in the previous year, and patients who regularly received annual influenza vaccinations. The association was insignificant in patients aged < 65 years, patients with relatively unstable disease status (i.e., patients who experienced an acute exacerbation in the previous year), and patients who did not receive annual influenza vaccinations.

Influenza vaccination among COPD patients in Taiwan

The Taiwanese NHI Administration, of the Ministry of Health and Welfare, recommends annual influenza vaccination for

all people over 65 years of age, for patients of any age with chronic illnesses, for care givers of people at higher risk of complications, and for health care workers. Since 1998, influenza vaccines are offered free of charge for these at-risk groups.

In our study, the influenza vaccination rate among Taiwanese COPD patients aged over 65 years was 51.8%, which is below the 75% level set by the WHO. However, similar conditions were found in other countries. UK primary care consultation databases indicate that, in patients with lung disease, the influenza vaccination coverage rate was 36.1% among patients over 65 years of age.^{21,22} In other Mediterranean European countries, such as France, the 2009 annual vaccination coverage among asthma/COPD patients aged over 65 years was 63.3%.²³ The Spanish primary care database demonstrated that the influenza vaccination coverage rate among COPD patients aged over 65 y was 66.8%.²⁴

The relatively low vaccination rate in the elderly Taiwanese COPD patients is an important public health issue, and requires urgent action. The possible explanations for the low vaccination rate include a lack of awareness, doubt about the effectiveness of and fear of adverse reactions to the vaccination, and a lack of physician recommendation. The significance of medical advice in ensuring influenza vaccination has been highlighted in several previous studies.²⁵ Therefore, the role of health care workers in increasing vaccination uptake in high-risk populations is essential. Improving the knowledge of health care workers regarding the effectiveness, safety, and importance of influenza vaccination is an important strategy for increasing vaccination coverage. Campaigns directed at patients should be designed to increase their knowledge about the safety, effectiveness, and benefits of vaccination.^{26–28}

Table 2 Baseline characteristics of the COPD patients with and without vaccination within 1-year duration before RF.

| Variables | Nonvaccine cohort (n = 13,562) | Vaccine cohort (n = 6226) | p value |
|---|-----------------------------------|------------------------------|---------|
| Age, years (mean ± SD) | 63.95 ± 12.27 | 70.75 ± 9.03 | <0.001 |
| Age group, n (%) | | | <0.001 |
| 45–54 | 4015 (29.6) | 235 (3.8) | |
| 55–64 | 3096 (22.8) | 1293 (20.8) | |
| 65–74 | 3257 (24.0) | 2559 (41.1) | |
| 75–84 | 2563 (18.9) | 1743 (28.0) | |
| ≥85 | 631 (4.7) | 396 (6.4) | |
| Gender (male), n (%) | 7775 (57.3) | 3799 (61.0) | <0.001 |
| Comorbidity, n (%) | | | |
| Hypertension | 6204 (45.7) | 3751 (60.2) | <0.001 |
| Diabetes mellitus | 2513 (18.5) | 1401 (22.5) | <0.001 |
| Congestive heart failure | 1103 (8.1) | 744 (11.9) | <0.001 |
| Coronary artery disease | 3568 (26.3) | 2223 (35.7) | <0.001 |
| Chronic kidney disease | 1288 (9.5) | 730 (11.7) | <0.001 |
| Ischemic stroke | 1393 (10.3) | 990 (15.9) | <0.001 |
| Hemorrhagic stroke | 321 (2.4) | 241 (3.9) | <0.001 |
| Malignancy | 2978 (22.0) | 1400 (22.5) | 0.406 |
| Liver cirrhosis | 311 (2.3) | 149 (2.4) | 0.665 |
| Anxiety | 1013 (7.5) | 469 (7.5) | 0.875 |
| Mood disorder | 863 (6.4) | 476 (7.6) | 0.001 |
| Insomnia | 2185 (16.1) | 1163 (18.7) | <0.001 |
| Annual health care utilization (mean ± SD) | | | |
| OPD visits | 8.22 ± 7.10 | 10.64 ± 7.49 | <0.001 |
| Hospitalizations | 0.54 ± 1.08 | 0.62 ± 1.10 | <0.001 |
| ER visits | 0.28 ± 0.78 | 0.27 ± 0.72 | 0.268 |
| CT | 0.20 ± 0.56 | 0.21 ± 0.57 | 0.037 |
| MRI | 0.03 ± 0.18 | 0.03 ± 0.18 | 0.758 |
| Acute exacerbation, n (%) | 1318 (9.7) | 618 (9.9) | 0.648 |
| Pneumonia, n (%) | 2291 (16.9) | 1240 (19.9) | <0.001 |
| Mortality, n (%) | 3898 (28.7) | 2107 (32.4) | <0.001 |
| Annual rate of influenza vaccination (mean ± SD) | 0.19 ± 0.30 | 0.80 ± 0.48 | <0.001 |

COPD = chronic obstructive pulmonary disease; RF = respiratory failure; SD = standard deviation; OPD = out-patient department; ER = emergency room; CT = computed tomography; MRI = magnetic resonance imaging.

Table 3 Baseline characteristics of the COPD patients with and without RF.

| Variables | Control group (without RF) (n = 16,436) | Case group (with RF) (n = 3352) | p value |
|--|---|---------------------------------------|---------|
| Age, years (mean ± SD) | 64.33 ± 11.34 | 74.73 ± 9.97 | <0.001 |
| Gender (male), n (%) | 9333 (56.8) | 2241 (66.9) | <0.001 |
| Comorbidity, n (%) | | | |
| Hypertension | 7765 (47.2) | 2190 (65.3) | <0.001 |
| Diabetes mellitus | 2964 (18.0) | 950 (28.3) | <0.001 |
| Congestive heart failure | 1216 (7.4) | 631 (18.8) | <0.001 |
| Coronary artery disease | 4432 (27.0) | 1359 (40.5) | <0.001 |
| Chronic kidney disease | 1445 (8.8) | 573 (17.1) | <0.001 |
| Ischemic stroke | 1485 (9.0) | 898 (26.8) | <0.001 |
| Hemorrhagic stroke | 370 (2.3) | 192 (5.7) | <0.001 |
| Malignancy | 3616 (22.0) | 762 (22.7) | 0.352 |
| Liver cirrhosis | 346 (2.1) | 114 (3.4) | <0.001 |
| Anxiety | 1227 (7.5) | 255 (7.6) | 0.776 |
| Mood disorder | 1086 (6.6) | 253 (7.5) | 0.048 |
| Insomnia | 2681 (16.3) | 667 (19.9) | <0.001 |
| COPD medications, n (%) | | | <0.001 |
| Bronchodilator only | 5597 (34.1) | 705 (21.0) | |
| Combined steroid or other immune modifying agents | 10,839 (65.9) | 2647 (79.0) | |
| Annual health care utilization (mean ± SD) | | | |
| OPD visits | 9.10 ± 7.25 | 8.39 ± 7.57 | <0.001 |
| Hospitalizations | 0.31 ± 0.79 | 1.81 ± 1.42 | <0.001 |
| ER visits | 0.21 ± 0.68 | 0.64 ± 1.01 | <0.001 |
| CT | 0.13 ± 0.44 | 0.57 ± 0.86 | <0.001 |
| MRI | 0.02 ± 0.17 | 0.05 ± 0.24 | <0.001 |
| Acute exacerbation, n (%) | 1264 (7.7) | 672 (20.0) | <0.001 |
| Pneumococcal vaccination within 5-year before index date, n (%) | 1518 (9.2) | 194 (5.8) | <0.001 |
| Influenza vaccination within 1-year before index date, n (%) | 5060 (30.8) | 1166 (34.8) | <0.001 |

COPD = chronic obstructive pulmonary disease; RF = respiratory failure; SD = standard deviation; OPD = out-patient department; ER = emergency room; CT = computed.

The association between influenza vaccination and risk of RF among COPD patients

In our study, we found that influenza vaccine administration was associated with a reduced risk of RF. In subgroup analysis, only patients older than 65 years benefited from

the vaccination, whereas the risk reduction in younger adults was not significant. This finding coincides with the results of previous studies and current vaccination policies.

Furthermore, the association between influenza vaccination and risk of RF was insignificant among patients who

Table 4 Association between influenza vaccination and RF among COPD patients (n = 19,788).

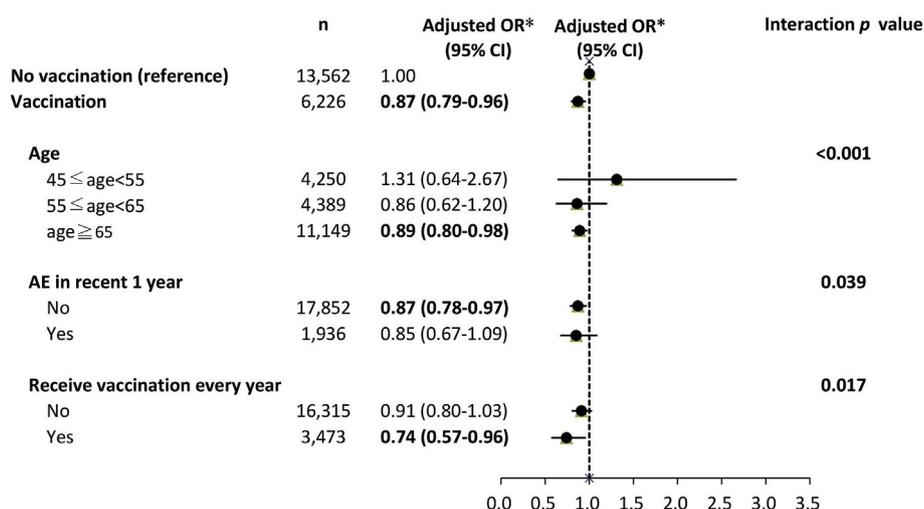
| Variable | All (n = 19,788) | RF | |
|--|------------------|-----------------------------------|---------------------------|
| | | No (n = 16,436) | Yes (n = 3352) |
| Influenza vaccination within 1-year prior to RF | n (%) | n (%) | n (%) |
| No | 13,562 (68.5%) | 11,376 (69.2%) ⁺ | 2186 (65.2%) |
| Yes | 6226 (31.5%) | 5060 (30.8%) | 1166 (34.8%) ⁺ |
| Crude odds ratio (95% CI) | | 1.20 (1.11–1.30); p value < 0.001 | |
| Adjusted model 1: odds ratio (95% CI) ^a | | 0.77 (0.71–0.83); p value < 0.001 | |
| Adjusted model 2: odds ratio (95% CI) ^b | | 0.84 (0.76–0.93); p value = 0.005 | |
| Adjusted model 3: odds ratio (95% CI) ^c | | 0.87 (0.79–0.96); p value = 0.006 | |

^a **Model 1:** adjustment for age, gender, comorbidities (including hypertension, diabetes mellitus, congestive heart failure, coronary artery disease, chronic kidney disease, ischemic stroke, hemorrhagic stroke, liver cirrhosis, mood disorder, and insomnia), and COPD medications.

^b **Model 2:** adjustment for variables in model 1, and annual health care utilization (including OPD visits, hospitalizations, ER visits, CT, MRI).

^c **Model 3:** adjustment for variables in model 2, acute exacerbation, and pneumococcal vaccination within 1-year before index date. RF = respiratory failure; COPD = chronic obstructive pulmonary disease; CI = confidence interval; OPD = out-patient department; ER = emergency room; CT = computed tomography; MRI = magnetic resonance imaging.

⁺ p value < 0.001 in comparison with patients without RF.

**Figure 4.** Association between influenza vaccination and risk of RF.

had experienced acute exacerbation in the previous year. A possible explanation for this phenomenon is that influenza infection is only one of the risk factors for RF among COPD patients; for instance, disease severity also plays an important role in RF.

Clinical implications

Our findings indicate that influenza vaccination is associated with a decreased risk of RF among COPD patients, especially those aged ≥65 years. Annual influenza vaccination should be recommended to COPD patients.

Limitations and strengths

This study had several limitations. First, sociodemographic variables, such as marital status, educational level, smoking, alcohol use, body mass index, and physical activity were not available in the database used. Therefore, we

were not able to explore these personal characteristics among the COPD cohort; this is a common limitation of secondary data analyses. Second, we could only imply the association between influenza vaccination and the risk of RF, but not a causal relationship. Third, data of pulmonary function test (PFT) was not available in this study and we used “acute exacerbation” as a proxy measure of disease severity. Comparing to PFT, “acute exacerbation” and other obtainable clinical variables were considered better parameters in predicting adverse outcomes among COPD patients according to various studies.^{29–31} Furthermore, we put the parameter “COPD medications, i.e. “bronchodilator only” or “bronchodilator combined with steroid or other immune modifying agents”, into the regression model, which may partially resolve the imbalance of disease severity among these two groups of patients.

Despite these limitations, the study also had important strengths. The association between influenza vaccination and risk of RF by using a nationwide representative cohort of COPD patients in Taiwan has not been reported to date.

The NHIRD includes all hospital admissions, outpatient visits, and prescription claims data in Taiwan, and was therefore not affected by selection bias from selective inclusion of specific hospitals or health insurance systems.

Conclusion

The influenza vaccination rate is low among Taiwanese COPD patients. Further efforts should be made to address this important public health issue. Influenza vaccination is associated with a reduced risk of RF among COPD patients, particularly those aged ≥ 65 years. Therefore, annual influenza vaccination should be recommended when managing these high-risk patients. Further large-scale prospective studies are warranted to investigate the efficacy of influenza vaccination in adults with COPD.

Conflict of interest

The authors declare that there is no conflict of interest.

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