Influenza vaccination reduces hospitalization for acute coronary syndrome in elderly patients with chronic obstructive pulmonary disease: A population-based cohort study

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A R T I C L E   I N F O

A B S T R A C T

Background: Elderly patients with chronic obstructive pulmonary disease (COPD) are at a higher risk of hospitalization for cardiovascular complications, especially during respiratory infections. Previous studies showed that vaccination for influenza may reduce the risk of recurrent major cardiovascular events in patients with acute coronary syndrome (ACS). The purpose of this study was to evaluate the hypothesis that influenza vaccination could reduce hospitalizations for ACS in elderly patients with COPD.
Method: Using the Taiwan Longitudinal Health Insurance Database 1996–2008, this cohort study comprised elderly patients ($\geq$55 years old) with a recorded diagnosis of COPD ($n = 7722$) between January 1, 2000 and December 31, 2007. Each patient was followed until the end of 2007. A propensity score was derived by using a logistic regression model to reduce vaccine therapy selection bias. The hazard ratio (HR) and 95% confidence interval (CI) for the association between the influenza vaccination and the occurrence of first hospitalization for ACS in elderly COPD patients was examined by Cox proportional hazards regression analysis. In addition, we categorized the patients into four groups according to vaccination status (unvaccinated, total number of vaccinations: 1, 2–3, and $\geq$4).
Results: We found that elderly patients with COPD receiving influenza vaccination had a lower risk of hospitalization for ACS (adjusted HR = 0.46, 95% CI (0.39–0.55), $p < 0.001$). We observed similar protective effects in both sexes and all age groups (55–64, 65–74, $\geq$75) regardless of influenza seasonality. When the patients were stratified according to the total number of vaccinations, the adjusted HRs for hospitalization because of ACS were 0.48 (0.38–0.62) and 0.20 (0.14–0.28) for patients who received 2–3 and $\geq$4 vaccinations during the follow-up period.
Conclusion: Our data showed that there was a lower risk of ACS hospitalization in elderly patients with COPD receiving annual influenza vaccination.

1. Introduction

Chronic obstructive pulmonary disease (COPD), a chronic inflammatory disease, affects more than 200 million people every year. It is the third leading cause of death in the United States [1,2] and is predicted to become the third most common cause of death worldwide by 2030 [3]. The incidence of COPD increases rapidly with age and the development of COPD is higher in men

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than in women at age 55 years or older [4]. Among elderly individuals, those with COPD are at a higher risk for developing serious influenza-related complications [5,6]. Their hospitalization rates for pneumonia are two to seven times that of those at the same age but without chronic lung conditions [7,8]. The serious complications of influenza, pneumonia and acute exacerbations of coexisting conditions, can cause hospitalization or even death in this group of patients [9,10]. Previous studies suggest that patients with COPD are two to three times more at risk for cardiovascular mortality compared to the general population [11]. During influenza epidemics, upper respiratory tract infections may trigger of acute cardiovascular events in these patients [12,13]. Thus, influenza-related complications can be reduced with influenza vaccination [14–19].

Infectious agents are thought to play a role in the pathophysiology of atherosclerosis progression and its clinical events. Because COPD is associated with chronic inflammation and/or recurrent infection, it is a reasonable hypothesis that influenza vaccination is beneficial in this group of patients. Previous studies have shown that influenza vaccination reduces the risk of further major cardiovascular events in patients with acute coronary syndrome (ACS) or coronary artery disease (CAD) [16,19]; however, the protective effect of influenza vaccination for developing ACS in elderly patients with COPD was not demonstrated in these studies. To clarify the potential protective benefit of influenza vaccination on hospitalization for ACS in a group of the elderly Taiwanese patients with COPD, we conducted a population-based cohort study using reimbursement claims from Taiwan's National Health Insurance Research Database (NHIRD).

2. Methods

The National Health Insurance (NHI) program has existed since 1995 to provide comprehensive health insurance coverage for all of Taiwan residents. Currently, 98% of the more than 23 million enrollees are covered under the NHI. This study used data from the Taiwan NHIRD 1996–2008. There were no statistically significant differences in age, sex, or healthcare costs between the sample group and all enrollees. The Taiwan Center of Disease Control generally defines the influenza season as the interval from October to March. The information obtained from the database was entirely anonymous, and the study was approved by the Joint Institutional Review Board of Taipei Medical University (TMU-JIRB No. 201311001).

The study cohort comprised all patients who visited healthcare facilities in Taiwan with diagnosis of COPD (International Classification of Disease, the 9th Revision, Clinical Modification Code) over a 8-year period ($n = 80,007$) from January 1, 2000 to December 31, 2007. All subjects without a subsequent outpatient visit, emergency department visit or inpatient hospitalization for COPD within 12 months of first presentation were excluded ($n = 45,009$) because they were considered not to have chronic pulmonary disease (see Fig. 1). We excluded 27,276 individuals who are younger than 55 years old ($n = 17,887$) and had a history of myocardial infarction (MI) ($n = 1064$), angina pectoris ($n = 2292$), stroke ($n = 4015$) or heart failure ($n = 2016$) before the diagnosis of COPD was established. We also excluded one patient with an unclear gender (Fig. 1). In Taiwan, influenza vaccination has been free of charge and recommended for the high-risk elderly population (people aged ≥50 with type 2 diabetes, chronic liver infection or liver cirrhosis, cardiovascular diseases, or chronic pulmonary diseases) since 1998, and for all adults older than 65 years since 2001 [18]. The vaccination status was identified by code V048 and/or the use of vaccine (confirmed by drug codes). Our final study cohort consisted of 7722 cases of COPD between 2000 and 2007 in Taiwan; 3027 were vaccinated against
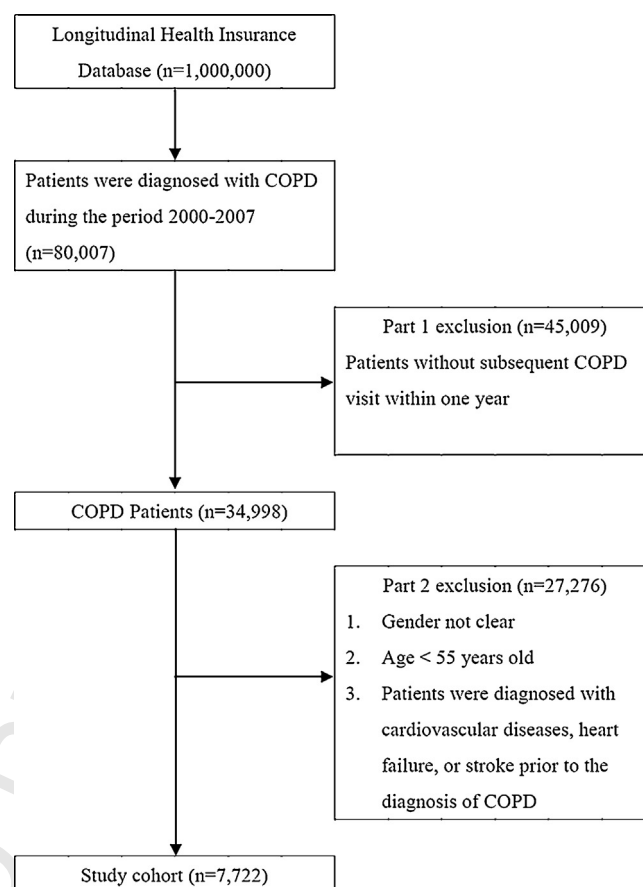

Longitudinal Health Insurance Database (n=1,000,000)

Patients were diagnosed with COPD during the period 2000-2007 (n=80,007)

Part 1 exclusion (n=45,009)
Patients without subsequent COPD visit within one year

COPD Patients (n=34,998)

Part 2 exclusion (n=27,276)
1. Gender not clear
2. Age < 55 years old
3. Patients were diagnosed with cardiovascular diseases, heart failure, or stroke prior to the diagnosis of COPD

Study cohort (n=7,722)

Fig. 1. The process of patient selection.

influenza and 4695 were not vaccinated during the 8-year follow-up period. Each patient was tracked for the Charlson Comorbidity Index (CCI) and the CAD risk factors: hypertension, diabetes mellitus, and dyslipidemia. A propensity score (PS) was derived using a logistic regression model to estimate the effect of vaccination by accounting for the covariates that predict receiving the intervention (vaccine). This method is used in observational studies to reduce selection bias [20]. The covariates used to calculate the PS were age, gender, comorbidity condition (CCI; pneumonia; sepsis), cardiac arrhythmia, monthly income (0, NT\$1 to NT\$15840, NT\$15841 to NT\$25000, NT\$25001; NT\$ represents new Taiwan dollar), urbanization level (urban, suburban, and rural), and geographic location of residency (Northern, Central, Eastern, and Southern Taiwan) [21,22]. The primary endpoints of our study were hospitalization for acute MI (ICD-9-CM codes 410.xx and 411.xx) or angina pectoris (ICD-9-CM codes 413.xx and 414.xx) with percutaneous transluminal coronary intervention (PCI) or coronary artery bypass grafting (CABG) procedures in COPD patients during the influenza season, noninfluenza season (April–September), and all seasons during the following years. Because the vaccine does not take effect for approximately 2 weeks, we excluded patients for whom the duration between vaccination and ACS hospitalization was shorter than 2 weeks [23]. Data were collected from the claims records of discharged patients and analyzed.

2.1. Statistical analysis

A logistic regression was applied to calculate the PS. Chi-square analyses were conducted to examine the differences between the vaccinated and unvaccinated groups in the relationships among demographic variables, socioeconomic status, and comorbidities.