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Original Article

Association between influenza vaccination and the reduced risk of acute kidney injury among older people: A nested case-control study☆

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ABSTRACT

Objective: The objective of this study is to determine whether vaccination against influenza is associated with a reduced risk of acute kidney injury (AKI) in a nationwide cohort of adults aged ≥65 years.
Methods: We investigated a total of 13,270 patients aged ≥65 years who were hospitalized for AKI between 2000 and 2013 from Taiwan's National Health Insurance Research Database. Each AKI case was matched with one control subject according to duration of follow-up, age, sex, monthly income, urbanization level, and baseline comorbidities. Odds ratios (ORs) for AKI associated with exposure to the influenza vaccine in the previous year were calculated in a nested case-control analysis.
Results: Influenza vaccination in the previous year was associated with a lower risk of AKI (adjusted OR 0.67, 95% confidence interval [CI] 0.63–0.72). Compared with a reference group of unvaccinated individuals with no influenza infection, vaccination with no influenza infection was associated with a lower risk of AKI (adjusted OR 0.68, 95% CI 0.64–0.73). Lack of vaccination and presence of influenza infection was associated with a higher risk of AKI (adjusted OR 1.78, 95% CI 1.57–2.01), whereas the risk of AKI was insignificant in vaccinated patients who developed influenza (adjusted OR 1.01, 95% CI 0.69–1.18).
Conclusions: The risk of AKI was 37% lower among older people who received vaccination against influenza in a real-world setting. Further work is required to clarify causality.

1. Introduction

The incidence rate of influenza in adults aged 65 years and older is increasing in the US [1]. The older population is particularly susceptible to the development of influenza complications as a result of associated hospitalizations and deaths [2,3]. Although previous studies have found that vaccination against influenza is associated with decreased risks of influenza-related morbidity and mortality, including pneumonia and cardiovascular events [4,5], little is known about the associations of influenza vaccines with future renal complications.

Acute kidney injury (AKI) following influenza infection is not uncommon in the older population, but this important renal complication is often overlooked. It has been documented primarily as single cases or case series of patients infected with the influenza virus, hypothesized to

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be associated with rhabdomyolysis, hemolytic-uremic syndrome, disseminated intravascular coagulation, or complicated critical illness [6]. However, data regarding the renal effects of influenza vaccination remain insufficient at a population level. Meanwhile, the influenza vaccination rate remains below the recommended goal worldwide, especially in Asian countries [7]. Thus, we studied a nationwide cohort of adults aged ≥65 years in Taiwan during 2000–2013 to evaluate whether influenza vaccination was associated with a reduced risk of AKI.

2. Methods

2.1. Data source

This nested case-control study employed data from Taiwan's National Health Insurance Research Database (NHIRD), which has been described in detail elsewhere [8–10]. We extracted data from an NHIRD dataset of people aged ≥65 years, with a sampling fraction (3:1 ratio) based on a regulation that prohibits use of the maximal amount of claims data for research purposes. Thus, the dataset contained information on all hospital admissions, outpatient visits, diagnoses, prescriptions, and procedures for one-third of the whole Taiwanese population aged ≥65 years. Details associated with inpatient and outpatient encounters were ascertained by International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnostic and procedural codes. As patient information in the NHIRD is secondary, de-identified, and encrypted, this study was exempted from a full ethics review by the institutional review board of Taipei City Hospital (TCHIRB-1030407-W).

2.2. Subjects

We identified all study subjects who were hospitalized with a principal diagnosis of AKI (ICD-9-CM code 584.9) between 1 January 2000 and 31 December 2013 as the case group. The accuracy of diagnostic coding for AKI cases in this database has been validated [11,12]. Cohort entry was defined by the date of study subjects aged 65 or older since 1 January 2000. The date of hospitalization for AKI was defined as the index date. Patients with histories of dialysis, kidney transplant recipients, and those hospitalized within 365 days before the index date were excluded. Other subjects with the same follow-up periods as cases, but without previous registry of an ICD-9 code for AKI, were extracted as a pool of potentially eligible controls. One eligible control was selected randomly and matched to each case by age (±1 year), sex, month and year of index date, urbanization level, monthly income, Charlson Comorbidity Index (CCI) score [1] (±2), and comorbidities (hypertension, peripheral vascular disease, heart failure, liver disease, dyslipidemia, chronic kidney disease). We also took into account concomitant use of drugs, including anti-platelet agents, insulin or oral anti-hyperglycemic drugs, diuretics, calcium channel blockers, beta blockers, alpha blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, statins, proton-pump inhibitors, nonsteroidal anti-inflammatory drugs, steroids, antidepressants, and warfarin.

2.3. Statistical analysis

We used the chi-squared test to compare categorical demographic variables between cases and controls, and the independent *t*-test to compare continuous variables. Then, we analyzed all episodes of influenza infection and all prescriptions of influenza vaccine within 1 year before the index date in cases and controls. In this study, vaccination was provided at no cost to study subjects by Taiwan's National health insurance, and all were nonadjuvant, trivalent, inactivated split-virus influenza vaccines. We calculated odds ratios (ORs) for vaccination in patients with AKI and controls. Conditional logistic regression was used to adjust for confounding. The likelihood ratio test was used to identify any interaction between vaccination and the following factors: sex, age, CCI score, hypertension, diabetes mellitus, peripheral vascular disease, dyslipidemia, chronic kidney disease, influenza season (1 October to 31 March of the following year) [13], and previous vaccination (>1 year before the index date). Based on the results of these tests subgroup analyses were performed accordingly. The Microsoft SQL Server 2012 (Microsoft Corporation, Redmond, WA, USA) was used for data linkage, processing, and sampling. All analyses were performed using STATA statistical software (version 12.0; StataCorp, College Station, TX, USA), with two-sided tests at a significance level of $P < .05$.

Table 1
Characteristics of the cases and controls.

	Cases (n = 13,270)	Control (n = 13,270)	P-value
Age, mean (SD), year	79.8 (7.7)	79.8 (7.6)	0.317
Male sex, n (%)	7180 (54.1)	7180 (54.1)	> 0.99
Monthly income, n (%)			
Dependent	5433 (40.9)	5433 (40.9)	> 0.99
0–19,100 NT dollars	3382 (25.5)	3382 (25.5)	
19,100–42,000 NT dollars	4398 (33.1)	4398 (33.1)	
> 42,000NT dollars	57 (0.4)	57 (0.4)	
Urbanization[a], n (%)			
Level 1	2995 (22.6)	2995 (22.6)	> 0.99
Level 2	9562 (72.1)	9562 (72.1)	
Level 3	603 (4.5)	603 (4.5)	
Level 4	110 (0.8)	110 (0.8)	
Charlson comorbidity index score[b], median (IQR)	10 (8–12)	9 (8–12)	0.711
Previous vaccination, n (%)	9816 (74.0)	10,430 (78.6)	< 0.001
Other comorbidity, n (%)			
Hypertension	12,004 (90.5)	12,004 (90.5)	> 0.99
Peripheral vascular disease	1599 (12.0)	1599 (12.0)	> 0.99
Heart failure	4249 (32.0)	4249 (32.0)	> 0.99
Dyslipidemia	7725 (58.2)	7725 (58.2)	> 0.99
Chronic liver disease	4560 (34.4)	4560 (34.4)	> 0.99
Chronic kidney disease	5869 (44.2)	5869 (44.2)	> 0.99
Medication, n (%)			
Anti-platelet agent	3045 (22.9)	2255 (17.0)	< 0.001
Insulin	1063 (8.0)	270 (2.0)	< 0.001
Oral anti-hypergylcemic drug	2286 (17.2)	1755 (13.2)	< 0.001
Diuretics	3471 (26.2)	1183 (8.9)	< 0.001
Calcium channel blocker	3218 (24.3)	2645 (19.9)	< 0.001
Beta-blocker	2135 (16.1)	1579 (11.9)	< 0.001
Alpha-blocker	614 (4.6)	407 (3.1)	< 0.001
Angiotensin-converting-enzyme inhibitor/ angiotensin II receptor blocker	3329 (25.1)	2624 (19.8)	< 0.001
Statin	1146 (8.6)	1061 (8.0)	0.059
Proton pump inhibitor	623 (4.7)	202 (1.5)	< 0.001
Nonsteroidal anti-inflammatory drug	4624 (34.8)	2865 (21.6)	< 0.001
Steroid	1487 (11.2)	649 (4.9)	< 0.001
Antidepressants	792 (6.0)	543 (4.1)	< 0.001
Warfarin	166 (1.3)	102 (0.8)	< 0.001

[a] Urbanization levels in Taiwan are divided into four strata according to the Taiwan National Health Research Institute publications. Level 1 designates the most urbanized areas, and level 4 designates the least urbanized areas.

[b] Charlson Comorbidity Index (CCI) score is used to determine overall systemic health. With each increased level of CCI score, there are stepwise increases in the cumulative mortality.

3. Results

A total of 13,270 cases with AKI and 13,270 matched controls were identified. The mean follow-up period was 10.0 years (SD, 3.4 years). Their demographic characteristics and baseline comorbidities are shown in Table 1. The mean age was 79.8 years (range: 65–105 years) and the sample was predominantly male (54.1%). The incidence of