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Original article

Association between influenza vaccination and mortality due to COVID-19☆

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ABSTRACT

Background: It has recently been suggested that influenza vaccination may be a factor associated with decreased COVID-19 mortality.

Methods: An age-matched case–control study based on hospital cases. We included subjects aged 18 years and older with a diagnosis of moderate to severe COVID-19. Infection was corroborated by RT-PCR test for SARS-COV-2. Deceased subjects were considered cases, controls were patients discharged due to improvement of acute symptoms. We used bivariate analysis to determine factors associated with death from COVID-19, and calculated odds ratios and 95% confidence intervals.

Results: A total of 560 patients were included in the study, 214 (38.2%) were considered cases and 346 (61.7%) controls. A significant difference was observed with the presence of type 2 diabetes mellitus [54% vs. 39.3% between cases and controls, respectively (P = 0.04)] and having received influenza vaccination (P = 0.02). Type 2 diabetes mellitus was associated with higher COVID-19 mortality [OR 1.8 (95% CI 1.2–2.5) P = 0.01], whereas having been immunised against influenza in 2019 was associated with lower mortality in this group of patients [OR 0.6 (95% CI 0.4–0.9) P = 0.02].

Conclusions: Influenza vaccination in the previous year appears to be associated with lower mortality from COVID-19; whereas type 2 diabetes mellitus is confirmed as a condition associated with higher mortality.

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Asociación entre la vacunación contra influenza y la mortalidad por COVID-19

Palabras Clave:
Influenza
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Mortalidad

RESUMEN

Antecedentes: Recientemente se ha sugerido que la vacunación contra la influenza puede ser un factor asociado con la disminución de la mortalidad por la *Coronavirus Disease* 2019 (COVID-19).

Métodos: Mediante un estudio de casos y controles pareado por edad, basado en casos hospitalarios incluimos sujetos de 18 años en adelante con diagnóstico de COVID-19 moderado a grave. La infección se corroboró por RT-PCR para SARS-CoV-2. Los sujetos fallecidos fueron considerados casos, los controles fueron los pacientes que egresaron por mejoría del cuadro agudo. Se utilizó análisis bivariado, para determinar los factores asociados con la muerte por COVID-19, con cálculo de razón de momios e intervalos de confianza del 95%.

Resultados: Un total de 560 pacientes fueron incluidos en el estudio, 214 (38,2%) fueron considerados casos y 346 (61,7%) controles. Se observó diferencia significativa con la presencia de diabetes mellitus tipo 2 [54% vs. 39,3% entre casos y controles, respectivamente (p = 0,04)] y haber recibido la vacuna contra la influenza (p = 0,02). La diabetes mellitus tipo 2 se asoció con mayor mortalidad por COVID-19 [OR 1,8 (IC 95% 1,2-2,5) p = 0,01], mientras que el haberse inmunizado contra influenza en 2019 se asoció con menor mortalidad en este grupo de pacientes [OR 0,6 (IC 95% 0,4-0,9) p = 0,02].

Conclusiones: La vacunación contra influenza en el año previo parece asociarse con una menor mortalidad por COVID-19, mientras que se confirma a la diabetes mellitus tipo 2 como una condición asociada con mayor mortalidad.

Introduction

In December 2019, an outbreak of pneumonia of unknown aetiology emerged in the city of Wuhan, China, which was subsequently denominated, 'Coronavirus Disease 2019' (COVID-19).[1] By March 2020, it had been declared a pandemic by the World Health Organization.[2,3] Epidemiological data as of September indicated that COVID-19 was responsible for nearly 1 million deaths (3.2%) out of a total of 31 million confirmed cases.[4]

In early approaches to the disease, the recognition of populational risk factors for developing severe disease and even fatal outcomes were used to inform government policies, identify populations at risk, guide clinical decision-making, and prioritise future research.[5] Thus, it was established that predictors of severity for COVID-19 include age, smoking, and having diabetes mellitus, arterial hypertension, chronic obstructive pulmonary disease, or cardiovascular disease, as well as obesity and low degrees of physical fitness.[6,7] More recently and as part of this search, it has been suggested that vaccination against the flu could be deemed to be a factor related to mortality due to COVID-19; population-based studies have even found fewer cases of patients infected by SARS-CoV-2 when they had been previously immunised against influenza.[8–12]

On the other hand, clinical evaluations have shown that complications due to COVID-19 affect the cardiovascular system to a lesser extent, especially in subjects immunised for influenza,[13] and there is evidence that vaccination against influenza confers a better immune response,[14] which may, in time, reduce the risk of immunosenescence, decrease the risk of immunosenescence (progressive deterioration of the immune system with aging), preventing the disturbance in the generation of protective B- and T-cell mediated adaptive immunity in response to various pathogens, reducing the susceptibility and severity of the disease among the elderly.[15] Humoral immunity (hemagglutinin inhibition antibody [HAI]) and cell-mediated immunity are activated to varying degrees by the influenza vaccine, and the balance between both types of immunity are critical to controlling infection.[16] COVID-19 resolves when antiviral neutralising T cells and antibody immunity develop. Cross-immunity with other coronaviruses is currently under study.[17]

At present, clinical studies looking for an association between influenza immunisation and COVID-19 outcome are virtually non-existent. While there are indications that point toward an association in ecological studies, hospital-based studies are needed to establish the specific weight of this factor with the rest of the known risk determinants in the SARS-CoV-2 pandemic. Based on the above, we hypothesised that influenza immunisation in the 2019 cycle (1 year prior to the pandemic) is associated with fewer deaths from COVID-19 compared to subjects who were not immunised.

Methods

Design

An age-matched, case–control study based on hospital cases was carried out. Individuals aged 18 years and older with a diagnosis of COVID-19 identified through the Hospital Care

Information System of the Hospital Central Sur de Alta Especialidad de Petróleos Mexicanos (Mexico) were included. This is a third-level hospital belonging to the Health Services of Petróleos Mexicanos which was converted to provide care to patients with COVID-19 beginning in April 2020.

Individual electronic clinical records were reviewed to collect demographic information, clinical and laboratory data, and to establish the outcome of the disease at the time of hospital discharge.

Selection of participants (cases and controls)

Inclusion criteria

Patients hospitalised with moderate to severe COVID-19 who had RT-PCR for SARS-CoV-2 were included. Those who were discharged from the hospital due to death were classified as cases; controls comprised subjects over 18 years of age with moderate to severe COVID-19 who were discharged due to improvement of the acute condition.

Strategy to determine participants' vaccination status and risk factors

Given that the population using the hospital's services is largely stable and that all health care, at any level of care, is received at the same hospital, vaccination history is part of each patient's file. In the section regarding vaccination records, the authors determined whether the participants had received the flu vaccine in 2019. The same record was examined for the presence of other confounding factors, such as obesity, diabetes mellitus, arterial hypertension, immunodeficiencies, asthma, age over 60 years, use of immunosuppressants or steroids, and immunisation in 2019 against pneumococcus.

We attempted to decrease temporality bias by matching by age, which ensured that both cases and controls were exposed to the same vaccination schedule, the same epidemiologic conditions, and the same hospital management, including care by nurses and physicians, as well as existing standard treatments; all of this amounted to exposure to the same known risk factors for COVID-19.

Statistical analysis

Qualitative variables were compared using a chi-squared test. In addition, a bivariate analysis was performed to determine the factors associated with death due to COVID-19; the odds ratio was calculated based on odds ratios with 95% confidence intervals. The percentage of attributable risk was calculated for each variable. The EPI Info (version 3.5.3) and SPSS (version 10) programs were used for statistical analysis.

Ethics

The study was approved by the institutional research committee and the research ethics committee, with registration number CONBIOETICA 09-CEI-007-211-80-529.

Results

Population characteristics

A total of 560 patients were included in the study; 214 (38.2%) were defined as cases and 346 (61.7%) as controls. The mean age was 61.5 years, with a standard deviation (SD) of 12.6; 168 persons (30%) were female and 392 (70%) were male. The average interval between the onset of the suspected clinical symptoms of COVID-19 and when the patients sought medical care was 5.8 days (SD = 4).

With regard to non-infectious chronic diseases, 253 (45.1%) subjects had diabetes mellitus, of whom 215 (84.9%) were type 2, with an average duration of disease duration of 4.3 years. Seventy-five of the diabetic patients were considered to have adequate metabolic control (29.6%); 291 subjects had systemic arterial hypertension (51.9%) with an average evolution of 10 years; 101 subjects (34.7%) of those who had arterial hypertension were deemed to have good control of the disease at the time of infection. Other factors, such as smoking, were detected in 163 (29.1%) of the population, although the duration of smoking could not be evaluated because this information was not available in the clinical records. Overweight and obesity were present in 459 of the participants included in the study (81.9%).

The distribution of the characteristics found in our population is depicted in Table 1, with significant differences in the prevalence of type 2 diabetes mellitus [54% in cases vs. 39.3% in controls (P = 0.04)] and having received influenza vaccination in the previous year [27.1% in cases vs. 37.2% in controls (P = 0.02)].

Distribution of mortality in relation to flu vaccination and age

Influenza vaccination coverage in the study group in 2019 was 33.3% (187 subjects); 58/560 (10.3%) in the case group vs. 129/560 (23%) in the control group (P = 0.02). Of the 214 deaths, 27.1% were immunised against influenza vs. 37.2% of the controls (P < 0.05). Coverage against pneumococcus was 13% with no differences between groups (Table 1).

The highest percentage of mortality with respect to the group immunised against influenza was in the 70–79 years age group with 8.3% vs. 12.7% of non-immunised patients (difference of 4.4 percentage points) P < 0.05. The group between 80 and 89 years of age came next with 6.8% vs. 9.4%, respectively (percentage difference of 2.6%, P < 0.05). The greatest difference was found in the age group 50–59 years with 4.6 percentage points in the number of deaths in the non-immunised group. The remaining groups and the curve in relation to age are shown in graph 1. Among

Table 1 – Distribution of factors among the study groups of patients with COVID-19.

Risk factors	Cases n = 214 (%)	Controls n = 346 (%)	P
Age > 60 years	164 (76.6)	239 (69)	0.3
Mean age (SD)	65.6 (12.3)	65.5 (12.4)	1.0
Sex			
Male	155 (72.4)	237 (68.4)	0.6
Time elapsed between symptoms & consultation >5 days	105 (49)	201 (58)	0.2
Average number of days consultation	4.2 (2)	5.4 (4)	0.9
Influenza vaccination	58 (27.1)	129 (37.2)	0.02
Pneumococcal vaccination	31 (14.4)	42 (12.1)	0.8
Positive smoking	60 (28)	103 (29.7)	1
Diabetes mellitus	117 (54.6)	136 (39.3)	0.02
Average duration of diabetes	5 (3)	3.8 (2)	0.9
Arterial hypertension	121 (56.5)	170 (49.1)	0.3
Average duration of hypertension	4.4 (2.6)	4.5 (2.3)	1
Overweight/obesity	175(81.7)	284 (82.0)	1
Asthma	4 (1.8)	9 (2.6)	0.9
Chronic obstructive pulmonary disease	9 (4.2)	13 (3.7)	0.9
Rheumatologic disease	9 (4.2)	11 (3.1)	0.9
Cardiovascular disease	26 (12.1)	36 (10.4)	0.7
Cancer	8 (3.7)	12 (3.4)	0.9
Steroids	8 (3.7)	10 (2.8)	0.9
Immunosuppressants or anti-neoplastic drugs	2 (0.9)	2 (0.5)	0.9

the subjects considered as cases, 35 (63%) had not received even a single dose of the flu in the last 5 years.

Through bivariate analysis, having diabetes mellitus was associated with higher mortality due to COVID-19 [OR 1.8 (95% CI 1.2–2.5) P = 0.01], while having been immunised against influenza in 2019 can be considered a protective factor for death in hospitalised patients with COVID-19 [OR 0.6 (95% CI 0.4–0.9) P = 0.02] (Table 2). Multivariate analysis was not deemed necessary in light of the limited number of variables with significance.

Proportion of attributable risk

The calculation of the attributable risk ratio (i.e., the percentage of disease incidence that would be avoided among those exposed if exposure to the risk factor had been avoided) established that, among the factors studied, 82% of the deaths from COVID-19 of the overweight or obese persons are attributable to being exposed to this factor; while 67% of the deaths can be attributed to not being vaccinated against influenza in 2019. The attributable risks of the other factors analysed are outlined in Table 2.

Discussion

Vaccination is one of the most efficacious strategies in public health and can be regarded as the most successful medical action in the history of mankind, in addition to being a decisive element in terms of the epidemiological change that has occurred in recent decades.[18] However, for a variety of reasons, vaccination schedules that aim to prevent infections in adults tend to be incomplete and, in general, seriously deficient,[19]

Table 2 – Risk factors for mortality in subjects hospitalised for severe COVID-19 disease.

Risk factors	OR	CI (95%)	P	Attributable risk
Age > 60 years	1.4	0.9–2.1	0.06	60
Male sex	1.2	0.8–1.7	0.3	70
Time elapsed between symptoms & consultation >5 days	1.3	0.9–2	0.1	55
Influenza vaccination	0.6	0.4–0.9	0.02	67
Pneumococcal vaccination	1.2	0.7–2	0.4	13
Positive smoking	0.9	0.6–1.3	0.8	29
Diabetes mellitus	1.8	1.2–2.5	0.01	45
High blood pressure	1.3	0.9–1	0.1	49
Overweight/obesity	0.7	0.4–0.9	0.1	82
Asthma	0.7	0.2–2.3	0.7	39
Chronic obstructive pulmonary disease	1.1	0.4–2.6	0.9	4
Rheumatologic disease	1.3	0.5–3.2	0.6	4
Cardiovascular disease	1.1	0.6–2	0.6	11
Cancer	1	0.4–2.6	1	4
Steroids	1.3	0.5–3.3	1	4

which contributes to a poor immune response, even in infectious diseases for which they are not designed[20–22] and an incomplete vaccination schedule can be considered a risk factor that is partially responsible for a fatal outcome in groups considered to be vulnerable.[23–25]

The present study demonstrates that this preventive action could represent an opportunity for a favourable clinical outcome in subjects infected with SARS-CoV-2. In contrast to other factors identified in COVID-19 mortality, vaccination against influenza can be viewed as the one that could be accomplished in a higher proportion [of the population] compared to the remaining factors that require long-term treatment, which fosters lack of compliance. However, the percentage of coverage of the universal vaccination schedule must be constantly monitored for this to be achieved.[26–28]

In the adult population, it is not uncommon for vaccination schedules not to be complied with or to be interrupted by mistake due to chronic illness or medication, although the recommendations issued by the Centres for Disease Control and Prevention (CDC) state that the influenza vaccine can be administered even if the patient has a chronic illness or is undergoing pharmacological treatment.

Essentially, the immune status of the host who does not receive or does not complete the vaccination schedule is a factor that has been acknowledged as contributing to the development of serious infections, due to the fact that these patients, especially adults, manifest suppressed adaptive immunity and an excessively dysfunctional innate immune response. Co-infection of SARS-CoV-2 with other respiratory pathogens, including influenza, has been observed in more than 20% of patients, coinciding with low anti-influenza vaccination coverage in adults (45% in the United States).[29] Other authors in Italy report coverage rates for the anti-influenza vaccine ranging from 37% to 67% depending on the region. Both countries (United States and Italy), as well as the data obtained in our sample (Mexico), are consistent in terms of low vaccination coverage rates against influenza and are considered to be among the areas showing the highest mortality rates due to COVID-19.

This study is a purely associative, not causal, approach, whose findings suggest that a percentage of the mortality cases in our study population are associated with the lack of vaccination against influenza before the beginning of the COVID-19 pandemic (66% according to the risk rate), figures very similar to those obtained with diabetes mellitus and lower than those of obesity. Our results are consistent with studies that mention higher mortality rates at ages above 65 years and, more importantly, between 70 and 80 years. In all age groups, the lowest percentage of immunisation against influenza occurred in subjects who died.[30,31]

Some studies have focused their analyses on defining whether vaccination against influenza plays a protective role for severe disease and mortality due to COVID-19. Authors such as Marín-Hernández et al.,[9] Amato et al.,[10] and Ragni et al.[11] agree that influenza vaccination coverage in the population over 65 years of age can be considered a possible protective effect for COVID-19 mortality, in addition to finding an association with reduced spread and less severe clinical expression of COVID-19. These results were similar in the study conducted in the United States by Zanettini et al.[12]

Another argument that may support this association is presented in the paediatric age, a population in which fewer children are observed to contract COVID-19 and among those infected, they present less severe pictures. The theory based on pathophysiology establishes that children have a strong immune response due to acquired immunity, secondary to live vaccines and frequent viral respiratory infections, which probably leads to early control of the infection at the site of entry.[32] In adults, and under this premise, some studies have found a significantly low probability of having a positive SARS-CoV-2 test in young people immunised against influenza, and even in those vaccinated against pneumococcus.[33] The comparative is so important that the percentage of SARS-CoV-2 uninfected subjects immunised against influenza has been reported to be 93% vs. 6.1% of infected and immunised subjects.[34] A 10% increase in influenza vaccination coverage is associated with a 28% reduction in COVID-19 mortality rate in the elderly.[34,35]

The main limitations of our study include the fact that the population studied will most likely need to be increased. In addition, the way in which the information was obtained, by referring to clinical records, leaves open the possibility of information that cannot be corroborated. Our results point to the fact that, although we were dealing with a captive population, vaccination compliance in adulthood is low.

Evaluations of the association with vaccination and death from COVID-19 have been performed in ecological population-based cohorts; this study is set in a hospital-based group, so the result has value from a clinical and preventive point of view.

Conclusions

Approximately 65% of COVID-19 deaths could be associated with an incomplete influenza vaccination schedule. Strategies should be designed to improve the vaccination status of the population before individuals become ill with COVID-19. On the basis of our results and those obtained in other studies, influenza vaccination coverage should be expanded, for the simple reason that it appears to improve the immune status of older adult patients and indirectly to favour a better clinical course in patients with COVID-19.

Conflict of Interests

The authors have no conflict of interests to declare.

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