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Brief report

Influence of influenza vaccine and comorbidity on the evolution of hospitalized COVID-19 patients★☆



José Manuel Fernández Ibáñez^{a,*}, María del Carmen Morales Ballesteros^a,
Manuel José Fernández Anguita^b, María Ángeles Galindo Andúgar^d, Ángel Arias Arias^c,
José Ramón Barberá-Farré^d

^a Servicio de Medicina Interna, Sección Geriátrica, Hospital General Mancha Centro, Alcázar de San Juan, Spain

^b Servicio de Cardiología, Hospital General Mancha Centro, Alcázar de San Juan, Spain

^c Unidad de Investigación, Hospital General Mancha Centro, Alcázar de San Juan, Spain

^d Servicio de Medicina Interna, Hospital General Mancha Centro, Alcázar de San Juan, Spain

ARTICLE INFO

Article history:

Received 25 February 2021

Accepted 2 June 2021

Available online 26 May 2022

Keywords:

Influenza vaccine

COVID-19

Hospitalized patients

Age

Comorbidity

Mortality

ABSTRACT

Background and objective: The COVID-19 coronavirus disease outbreak is evolving around the world. Objective: To evaluate the associations between influenza vaccination and other factors and the risk of mortality in hospitalized COVID-19 patients.

Materials and methods: Retrospective observational study. This study was conducted among hospitalized patients with COVID-19 at Hospital La Mancha Centro between March 5 and 25, 2020. Information on influenza vaccination was extracted from electronic medical records. We used a multivariate logistic regression to explore the association between influenza vaccination and mortality from COVID and other risk factors.

Results: 410 patients were included. Influenza vaccine had no effect among COVID-19 hospitalized patients [OR: 1.55 (95%CI: 0.96–2.48; p = 0.071)]. Increasing hospital mortality was associated with older age [OR: 1.05 (95% CI 1.02–1.07), per year increase; p < 0.001], Charlson ≥ 3 [OR: 1.84 (95%CI: 1.07–3.15, p = 0.027)] and heart failure on admission [OR: 6 (IC95%: 1.6–21.7; p = 0.007)].

Conclusions: Influenza vaccine had no effect among COVID-19 hospitalized patients. The risk factors identified were older age, higher comorbidity and heart failure on admission.

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Influencia de la vacunación antigripal y la comorbilidad en la evolución de los pacientes hospitalizados por COVID-19

RESUMEN

Antecedentes y objetivo: El brote de la enfermedad COVID-19 está evolucionando en todo el mundo. Objetivo: Evaluar la asociación de la vacunación antigripal y otros factores y el riesgo de mortalidad en pacientes con COVID-19 hospitalizados.

Materiales y métodos: Estudio observacional retrospectivo. Se realizó entre pacientes hospitalizados con COVID-19 del Hospital La Mancha Centro entre el 5 y el 25 de marzo de 2020. Utilizamos una regresión logística multivariable para explorar la asociación entre la vacunación antigripal y la mortalidad por COVID y otros factores de riesgo.

Resultados: Se incluyeron 410 pacientes. La vacunación antigripal no tuvo efecto entre los pacientes hospitalizados por COVID-19 [OR: 1,55 (IC95%: 0,96–2,48; p = 0,071)]. El aumento de la mortalidad intrahospitalaria se asoció con edad avanzada [OR: 1,05, (IC95%: 1,02–1,07), por cada aumento de año; p < 0,001], Charlson ≥ 3 [OR: 1,84 (IC95%: 1,07–3,15, p = 0,027)] e insuficiencia cardíaca al ingreso [OR: 6 (IC95%: 1,6–21,7; p = 0,007)].

Palabras clave:

Vacuna antigripal

COVID-19

Pacientes hospitalizados

Edad

Comorbilidad

Mortalidad

★ Please cite this article as: Fernández Ibáñez JM, Morales Ballesteros MC, Fernández Anguita MJ, Galindo Andúgar MÁ, Arias Arias Á, Barberá-Farré JR. Influencia de la vacunación antigripal y la comorbilidad en la evolución de los pacientes hospitalizados por COVID-19. Med Clin (Barc). 2022;158:603–607.

* Corresponding author.

E-mail address: jmfernandez@sescam.jccm.es (J.M. Fernández Ibáñez).

Conclusiones: La vacuna antigripal no tuvo efecto en la evolución de pacientes hospitalizados por COVID-19. Los factores de riesgo identificados fueron la edad avanzada, mayor comorbilidad e insuficiencia cardíaca al ingreso.

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Introduction

COVID-19 is a disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has given rise to a pandemic that began in Wuhan (China) in December 2019. By February 2021, the number of cases worldwide had exceeded 103 million with more than 2.2 million deaths.¹

There are currently no treatments with a sufficient level of evidence. Most countries have resorted to public health measures such as isolation, quarantine, and social distancing to prevent the spread of the disease.

Until vaccination for SARS-CoV-2 becomes universally available, several authors suggest that influenza vaccination may offer cross-protection against respiratory viruses other than influenza and minimise the severity of COVID-19² disease.

Other authors propose increasing influenza vaccination rates to avoid co-infection of influenza with SARS-CoV-2.³ However, others suggest that vaccination may increase susceptibility to SARS-CoV-2 infection.⁴

This article analyses the influence of influenza vaccination and other prognostic factors on the mortality of COVID-19 patients admitted to the Mancha Centro hospital during the first wave of the pandemic.

Material and methods

Design and participants

Retrospective observational cohort study. A total of 410 patients admitted with a diagnosis of COVID-19 at the Hospital Mancha Centro from 5 to 25 March 2020 were consecutively included. Information on influenza vaccination in the fall of 2019 was obtained from Primary Care records.

The diagnosis of COVID-19 was confirmed by polymerase chain reaction (PCR) testing. Patients with negative PCR, inconclusive PCR or no PCR but with high clinical suspicion of disease were also included.

Variables studied

The main outcome variable was mortality. Influenza vaccination was the main independent variable. Control covariates were age, sex, residence (community or institution), functionality (Barthel scale), comorbidity (Charlson index), and underlying comorbidities on admission: Obesity, chronic respiratory diseases, ischemic heart disease and/or heart failure, kidney failure, chronic liver disease, hematologic malignancies, other neoplasms, receiving immunosuppressive treatment, diabetes, high blood pressure (HBP), cognitive impairment and other neurological diseases and depression. Heart failure and cardiovascular events during admission were also included.

Statistical analysis

Quantitative variables were described by mean and standard deviation (SD) and qualitative variables by absolute and relative frequencies.

By means of a bivariate analysis we identified the factors involved in mortality, using Student's *t* test for quantitative vari-

ables and the χ^2 test (or Fisher's exact test) for qualitative variables.

A multivariate analysis (binary logistic regression) was performed to independently identify possible risk factors and the role of influenza vaccination in the mortality of admitted COVID-19 patients.

All analyses were performed using the SPSS v18 statistical software and a *p*-value < 0.05 was considered statistically significant.

Results

410 patients admitted for COVID-19 were included. The mean age was 70.7 years (SD: 13.9; range 28–100). 49.3% were men and 50.7% women; 209 (51%) were vaccinated against influenza (101 men and 108 women) and 201 (49%) were not. The Barthel scale was >60 in 84.4% of cases and ≤60 in 15.6%. The Charlson index was < 3 in 78.8% and ≥ 3 in 21.2% of cases. The most common chronic diseases were hypertension (62.4% of patients), chronic respiratory diseases (35.4%), neurological diseases (35.4% including cognitive impairment), diabetes (26.6%) and obesity (21.5%). The PCR test was positive in 354 patients (86.3%), negative in 35 (8.5%), inconclusive in 6 (1.5%) and not performed in 15 (3.7%). 5.9% of patients (24) were admitted to the intensive care unit (ICU) and hospital mortality was 34.6% (142) (Table 1).

Vaccinated patients had a higher percentage of over 65 year olds (86.2%), higher level of dependency (Barthel < 60 20.8 vs. 10.2%; *p* = 0.004 vs. non-vaccinated), had a higher comorbidity (Charlson > 3 29.7 vs. 12.4%; *p* < 0.001), a higher percentage of chronic respiratory diseases (45.9 vs. 24.4%; *p* < 0.001), ischaemic heart disease (17.2 vs. 7%; *p* = 0.002), diabetes (34.4 vs. 18.4%; *p* < 0.001), HBP (71.8 vs. 52.7%; *p* < 0.001), cognitive impairment (15.8 vs. 8%; *p* = 0.015) and institutionalised patients (10.5 vs. 5%; *p* = 0.036). Vaccinated patients were admitted to the ICU less often (2.9 vs. 9%; *p* = 0.009) (Table 1).

Factors associated with mortality were: age, being more significant with increasing age (61.3% of patients over 85 years of age died), Barthel scale (patients with Barthel ≤ 60 [54.2 vs. 29.5%; *p* < 0.001]), Charlson index ≥ 3 (56.3 vs. 28.8%; *p* < 0.001), history of ischaemic heart disease/heart failure (56 vs. 31.7%; *p* < 0.001), having non-haematological malignancies (63.3 vs. 32.4%; *p* = 0.001), AHT (42.2 vs. 22.1%; *p* < 0.001), renal failure (53.1 vs. 32.1%; *p* = 0.004), being institutionalised (53.1 vs. 33.1%; *p* = 0.022) and influenza vaccination (44.5 vs. 24.4%; *p* < 0.001). Another risk factor for mortality is the presence of heart failure during admission (85 vs. 32.1%; *p* < 0.001) (Table 2).

The multivariate analysis finally identified age (OR: 1.05 [95% CI: 1.02–1.07 per year increase; *p* < 0.001]), Charlson index > 3 (OR: 1.84 [95% CI: 1.07–3.15; *p* = 0.027]) and having heart failure during admission (OR: 6 [95% CI: 1.6–21.7; *p* = 0.007]) as independent risk factors for in-hospital mortality. Influenza vaccination had no association with mortality (OR: 1.55 [0.96–2.48; *p* = 0.071]) (Table 3).

Discussion

This study shows that influenza vaccination has no effect on mortality in patients admitted for COVID-19 in agreement with other authors.^{5,6}

Table 1
Main characteristics of the patients included in the study and differences between vaccinated and unvaccinated patients.

| | Overall (n = 410) | Unvaccinated (n = 201) | Vaccinated (n = 209) | p |
|--|---------------------|------------------------|----------------------|--------|
| Mean age in years (SD; range) | 70.7 (13.9; 28–100) | 65.6 (14.3) | 75.6 (11.6) | <0.001 |
| <i>Age by groups</i> | | | | |
| Under 65 | 132 (32.2%) | 103 (51.2%) | 29 (13.9%) | <0.001 |
| Between 65 and 75 years | 103 (25.1%) | 45 (22.4%) | 58 (27.8%) | |
| Between 75 and 85 years | 113 (27.6%) | 30 (14.9%) | 83 (39.7%) | |
| More than 85 years | 62 (15.1%) | 23 (11.4%) | 39 (18.7%) | |
| <i>Sex</i> | | | | |
| Male | 202 (49.3%) | 101 (50.2%) | 101 (48.3%) | 0.697 |
| Female | 208 (50.7%) | 100 (49.8%) | 108 (51.7%) | |
| <i>Barthel</i> | | | | |
| > 60 | 319 (77.8%) | 167 (89.8%) | 152 (79.2%) | 0.004 |
| ≤ 60 | 59 (14.4%) | 19 (10.2%) | 40 (20.8%) | |
| Not available | 32 (7.8%) | – | – | |
| <i>Charlson</i> | | | | |
| <3 | 232 (78.8%) | 176 (87.6%) | 147 (70.3%) | <0.001 |
| ≥ | 87 (21.2%) | 25 (12.4%) | 62 (29.7%) | |
| <i>Comorbidities</i> | | | | |
| Obesity | 88 (21.5%) | 40 (19.9%) | 48 (23%) | 0.450 |
| Chronic Respiratory Disease | 145 (35.4%) | 49 (24.4%) | 96 (45.9%) | <0.001 |
| Ischemic heart disease / Heart failure | 50 (12.2%) | 14 (7%) | 36 (17.2%) | 0.002 |
| Renal failure | 49 (12%) | 20 (10%) | 29 (13.9%) | 0.221 |
| Chronic liver disease | 7 (1.7%) | 4 (2%) | 3 (1.4%) | 0.719 |
| Hematologic malignancy | 9 (2.2%) | 4 (2%) | 5 (2.4%) | 0.999 |
| Other neoplasms | 60 (7.3%) | 12 (6%) | 18 (8.6%) | 0.304 |
| Diabetes | 109 (26.6%) | 37 (18.4%) | 72 (34.4%) | <0.001 |
| HBP | 256 (62.4%) | 106 (52.7%) | 150 (71.8%) | <0.001 |
| Cognitive impairment | 49 (12%) | 16 (8%) | 33 (15.8%) | 0.015 |
| Other neurological diseases | 96 (23.4%) | 41 (20.4%) | 55 (26.3%) | 0.157 |
| Depressive syndrome | 61 (14.9%) | 27 (13.4%) | 34 (16.3%) | 0.420 |
| Heart failure on admission | 20 (4.9%) | 6 (3%) | 14 (6.7%) | 0.081 |
| Cardiovascular event during admission | 6 (1.5%) | Twenty-one% | 4 (1.9%) | 0.686 |
| Immunosuppressive treatment | 14 (3.4%) | 6 (3%) | 8 (3.8%) | 0.639 |
| Institutionalized | 32 (7.8%) | 10 (5%) | 22 (10.5%) | 0.036 |
| ICU admission | 24 (5.9%) | 18 (9%) | 6 (2.9%) | 0.009 |
| In-hospital death | 142 (34.6%) | 49 (24.4%) | 93 (44.5%) | <0.001 |

Table 2
Factors associated with hospital mortality according to bivariate analysis.

| | No death (n = 268) | Death (n = 142) | p |
|---|--------------------|-----------------|--------|
| Mean age in years (SD) | 67.4 (13.8) | 77 (12) | <0.001 |
| <i>Age groups</i> | | | |
| Under 65 | 113 (85.6%) | 19 (14.4%) | <0.001 |
| Between 65 and 75 years | 67 (65%) | 36 (35%) | |
| Between 75 and 85 years | 64 (56.6%) | 49 (43.4%) | |
| More than 85 years | 24 (38.7%) | 38 (61.3%) | |
| <i>Sex</i> | | | |
| Male | 131 (64.9%) | 71 (35.1%) | 0.829 |
| Female | 137 (65.9%) | 71 (34.1%) | |
| <i>Barthel</i> | | | |
| > 60 | 225 (70.5%) | 94 (29.5%) | <0.001 |
| ≤ 60 | 27 (45.8%) | 32 (54.2%) | |
| Not available | – | – | |
| <i>Charlson</i> | | | |
| < 3 | 230 (71.2%) | 93 (28.8%) | <0.001 |
| = > | 38 (43.7%) | 49 (56.3%) | |
| <i>Obesity</i> | | | |
| Yes | 51 (58%) | 37 (42%) | 0.099 |
| No | 217 (67.4%) | 105 (32.6%) | |
| <i>Respiratory disease</i> | | | |
| Chronic | | | |
| Yes | 86 (59.3%) | 59 (40.7%) | 0.057 |
| No | 182 (68.7%) | 83 (31.3%) | |
| <i>Ischemic Heart Disease / Heart Failure</i> | | | |
| Yes | 22 (44%) | 28 (56%) | <0.001 |
| No | 246 (68.3%) | 114 (31.7%) | |
| <i>Renal failure</i> | | | |
| Yes | 23 (46.9%) | 26 (53.1%) | 0.004 |
| No | 245 (67.9%) | 116 (32.1%) | |
| <i>Chronic liver disease</i> | | | |
| Yes | 5 (71.4%) | 2 (28.6%) | 0.999 |
| No | 263 (65.3%) | 140 (34.7%) | |

Table 2 (Continued)

| | No death (n = 268) | Death (n = 142) | p |
|--|--------------------|-----------------|--------|
| <i>Hematologic malignancy</i> | | | |
| Yes | 4 (44.4%) | 5 (55.6%) | 0.286 |
| No | 264 (65.8%) | 137 (34.2%) | |
| <i>Other neoplasms</i> | | | |
| Yes | 11 (36.7%) | 189 (63.3%) | 0.001 |
| No | 257 (67.6%) | 123 (32.4%) | |
| <i>Diabetes</i> | | | |
| Yes | 68 (62.4%) | 41 (37.6%) | 0.445 |
| No | 200 (66.4%) | 101 (33.6%) | |
| <i>HBP</i> | | | |
| Yes | 148 (57.8%) | 108 (42.2%) | <0.001 |
| No | 120 (77.9%) | 34 (22.1%) | |
| <i>Cognitive impairment</i> | | | |
| Yes | 29 (59.2%) | 20 (40.8%) | 0.332 |
| No | 239 (66.2%) | 122 (33.8%) | |
| <i>Other neurological diseases</i> | | | |
| Yes | 58 (60.4%) | 38 (39.6%) | 0.244 |
| No | 210 (66.9%) | 104 (33.1%) | |
| <i>Depressive syndrome</i> | | | |
| Yes | 35 (57.4%) | 26 (42.6%) | 0.155 |
| No | 233 (66.8%) | 116 (33.2%) | |
| <i>Heart failure during admission</i> | | | |
| Yes | 3 (15%) | 17 (85%) | <0.001 |
| No | 265 (67.9%) | 125 (32.1%) | |
| <i>Cardiovascular event during admission</i> | | | |
| Yes | 2 (33.3%) | 4 (66.7%) | 0.190 |
| No | 262 (65.5%) | 138 (34.5%) | |
| <i>Immunosuppressive treatment</i> | | | |
| Yes | 9 (64.3%) | 5 (35.7%) | 0.999 |
| No | 259 (65.4%) | 137 (34.6%) | |
| <i>Institutionalized</i> | | | |
| Yes | 15 (46.9%) | 17 (53.1%) | 0.022 |
| No | 253 (66.9%) | 125 (33.1%) | |
| <i>Influenza vaccine</i> | | | |
| Yes | 116 (55.5%) | 93 (44.5%) | <0.001 |
| No | 152 (75.6%) | 49 (24.4%) | |
| <i>ICU admission</i> | | | |
| Yes | 14 (58.3%) | 10 (41.7%) | 0.456 |
| No | 254 (65.8%) | 132 (34.2%) | |

Table 3
Multivariate analysis of factors associated with mortality.

| Variables | OR (95% CI) | p |
|-------------------------------|----------------------|--------|
| Age | 1.045 (1.024–1.066) | <0.001 |
| Charlson (≥ 3 vs <3) | 1.835 (1.07–3.148) | 0.027 |
| Heart failure on admission | 5.993 (1.625–21.659) | 0.007 |
| Influenza vaccine | 1.545 (0.963–2.477) | 0.071 |

Vaccinated patients are older and have higher comorbidity, which are the factors associated with higher mortality in COVID-19 patients with no influence from influenza vaccination.

Age, a high number of comorbidities prior to admission, and the presence of heart failure at admission were the risk factors independently associated with higher hospital mortality in COVID-19 patients.

The vast majority of studies find age as an independent risk factor for mortality in COVID-19 patients which could be explained in relation to immunosenescence.⁷

Our high comorbidity patients have a significantly higher mortality compared to those with low comorbidity⁸, in line with other studies.⁸

The presence of heart failure at admission was shown to be an important independent predictor of mortality in our study. According to some studies, left ventricular diastolic dysfunction is reported to be common in acute SARS infection, even among those without underlying heart disease.⁹

Our study has some limitations. We have not included analytical data that may be associated with increased mortality in various studies,⁸ but our aim was to assess influenza vaccination

and other comorbidities on the risk of in-hospital mortality. Nor have the treatments administered during admission been taken into account, due to their heterogeneity and the low level of evidence in the published studies.¹⁰ Additionally, the epidemiological situation may have determined the criteria for admission and bed availability and influenced mortality outcomes.

The strengths of our study were that the vast majority of COVID-19 cases were laboratory confirmed and all patient data were systematically collected, so we believe that the sample is representative of COVID-19 cases managed in our area.

Conclusions

Influenza vaccination does not seem to have an effect on hospital mortality in COVID-19 patients admitted to our hospital. Age, high comorbidity, and the presence of heart failure at admission are independent prognostic factors for mortality, which could help physicians identify patients with a poor prognosis for their management and treatment

Funding

This paper has not received any type of funding.

Conflict of interests

The authors declare that they have no conflict of interest.

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