MEDICINA CLINICA

Brief report

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

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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

Palabras clave:
Vacuna antigripal
COVID-19
Pacientes hospitalizados
Edad
Comorbilidad
Mortalidad

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)].

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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.

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-19[2] 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 variables 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]

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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
Age by groups				
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%)	
Sex				
Male	202 (49.3%)	101 (50.2%)	101 (48.3%)	0.697
Female	208 (50.7%)	100 (49.8%)	108 (51.7%)	
Barthel				
> 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%)	–	–	
Charlson				
<3	232 (78.8%)	176 (87.6%)	147 (70.3%)	<0.001
≥	87 (21.2%)	25 (12.4%)	62 (29.7%)	
Comorbidities				
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
Age groups			
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%)	
Sex			
Male	131 (64.9%)	71 (35.1%)	0.829
Female	137 (65.9%)	71 (34.1%)	
Barthel			
> 60	225 (70.5%)	94 (29.5%)	<0.001
≤ 60	27 (45.8%)	32 (54.2%)	
Not available	–	–	
Charlson			
< 3	230 (71.2%)	93 (28.8%)	<0.001
= >	38 (43.7%)	49 (56.3%)	
Obesity			
Yes	51 (58%)	37 (42%)	0.099
No	217 (67.4%)	105 (32.6%)	
Respiratory disease			
Chronic			
Yes	86 (59.3%)	59 (40.7%)	0.057
No	182 (68.7%)	83 (31.3%)	
Ischemic Heart Disease / Heart Failure			
Yes	22 (44%)	28 (56%)	<0.001
No	246 (68.3%)	114 (31.7%)	
Renal failure			
Yes	23 (46.9%)	26 (53.1%)	0.004
No	245 (67.9%)	116 (32.1%)	
Chronic liver disease			
Yes	5 (71.4%)	2 (28.6%)	0.999
No	263 (65.3%)	140 (34.7%)	

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Table 2 (*Continued*)

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

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Conflict of interests

The authors declare that they have no conflict of interest.

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References

1. COVID-19 Map - Johns Hopkins Coronavirus Resource Center. [Accessed 4 January 2021]. Available from: https://coronavirus.jhu.edu/map.html.
2. Zheng J, Perlman S. Immune responses in influenza A virus and human coronavirus infections: an ongoing battle between the virus and host. Curr Opin Virol. 2018;28:43–52, http://dx.doi.org/10.1016/j.coviro.2017.11.002.
3. Zanettini C, Omar M, Dinalankara W, Luidy E, Colantuoni E, Luidy Imada E, et al. Influenza vaccination and COVID-19 mortality in the USA: an ecological study. Vaccines (Basel). 2021;9:427, http://dx.doi.org/10.3390/vaccines9050427.
4. Tetro JA. Is COVID-19 receiving ADE from other coronaviruses? Microbes Infect. 2020;22:72–3, http://dx.doi.org/10.1016/j.micinf.2020.02.006.
5. Skowronski DM, Zou M, Clarke Q, Chambers C, Dickinson JA, Sabaiduc S, et al. Influenza vaccine does not increase the risk of coronavirus or other noninfluenza respiratory viruses: retrospective analysis from Canada, 2010–2011 to 2016–2017. Clin Infect Dis. 2020;71:2285–8, http://dx.doi.org/10.1093/cid/ciaa626.
6. Del Riccio M, Lorini C, Bonaccorsi G, Paget J, Caini S. The association between influenza vaccination and the risk of SARS-COV-2 infection, severe illness, and death: a systematic review of the literature. Int J Environ Res Public Health. 2020;17:1–9, http://dx.doi.org/10.3390/ijerph17217870.
7. Sun H, Ning R, Tao Y, Yu C, Deng X, Zhao C, et al. Risk factors for mortality in 244 older adults with covid-19 in Wuhan, China: a retrospective study. J Am Geriatr Soc. 2020;68:E19–23, http://dx.doi.org/10.1111/jgs.16533.
8. Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J. 2020;55:2000547, http://dx.doi.org/10.1183/13993003.00547-2020.
9. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol. 2020;5:802–10, http://dx.doi.org/10.1001/jamacardio.2020.0950.
10. Song Y, Zhang M, Yin L, Wang K, Zhou Y, Zhou M, et al. COVID-19 treatment: close to a cure? A rapid review of pharmacotherapies for the novel coronavirus (SARS-CoV-2). Int J Antimicrob Agents. 2020;56:106080, http://dx.doi.org/10.1016/j.ijantimicag.2020.106080.