Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Vacunas

www.elsevier.es/vac

Special article

Is there any effect of flu vaccine on the SARS-CoV-2 infected patients?

D. El-Qutob[a,*], M. Nieto[a], L. Alvarez-Arroyo[b], F.J. Carrera-Hueso[b]

[a] Unit of Allergy, Universitary Hospital of La Plana in Vila-Real, Spain
[b] Service of Pharmacy, Universitary Hospital of La Plana in Vila-Real, Spain

ARTICLE INFO

Article history:
Received 25 May 2021
Accepted 1 September 2021

Keywords:
Coronavirus
COVID-19
Severe Acute Respiratory Syndrome Coronavirus 2
Vaccination
Influenza
Human

ABSTRACT

Objectives: On 11 March, WHO declared a global pandemic caused by a new virus of the family *Coronaviridae* that has since been called SARS-CoV-2. COVID-19 does not have specific antiviral drug treatment currently. There are currently more than one hundred research projects into vaccines against SARS-CoV-2 worldwide, and 17 of them are already being tested on humans, according to the WHO. Until we have an effective vaccine, the possible preventive effect of flu vaccine for SARS-CoV-2 infection based on cross-reactivity has been postulated.

Our objective was to analyse the effect of vaccination against flu virus in the season prior to the COVID-19 pandemic in our hospitalized SARS-CoV-2 infected patients.

Methods: We performed a retrospective observational cohort study of patients admitted to hospital with SARS-CoV2 infection. We analysed the differences between patients who had received or had not the flu vaccination for the 2019–2020 season.

Results: We found no significant differences ($p = 0.09$) in patients who died (43 in total), of whom 23 (21.5%) were vaccinated against the flu and 20 (13.5%) were not. In mortality, we obtained an adjusted OR = 0.873 (95% CI: 0.294–2.083), and about the success of health care the adjusted OR was 1.447 (95% CI: 0.610–3.430).

Conclusions: Flu vaccination in patients admitted for SARS-CoV-2 infection had neither a beneficial nor a harmful effect on the clinical courses or outcomes of patients admitted to an European hospital.

* *Corresponding author.*
E-mail address: elqutob@comv.es (D. El-Qutob).
https://doi.org/ 10.1016/j.vacune.2022.07.003

¿Tiene algún efecto la vacuna frente a la gripe en los pacientes infectados por SARS-CoV-2?

Palabras clave:
Coronavirus
COVID-19
Síndrome respiratorio agudo severo por coronavirus 2
Vacunación
Gripe, Humanos

RESUMEN

Objetivos: El 11 de marzo, la OMS declaró una pandemia global causada por un nuevo virus de la familia *Coronaviridae* que desde entonces ha sido denominado SARS-CoV-2. Actualmente no existe ningún tratamiento frente a la COVID-19 con fármacos antivirales específicos. A día de hoy existen más de 100 proyectos de investigación sobre vacunas frente a SARS-CoV-2 a nivel mundial, habiendo sido ya probados 17 de ellas en humanos, según la OMS. Hasta que no se disponga de una vacuna efectiva se ha postulado el posible efecto preventivo de la vacuna frente a la gripe para la infección por SARS-CoV-2, basado en la reactividad cruzada. Nuestro objetivo fue analizar el efecto de la vacuna frente a la gripe en la temporada previa a la pandemia de COVID-19 en nuestros pacientes hospitalizados infectados por SARS-CoV-2.
Métodos: Realizamos un estudio retrospectivo observacional de cohorte de pacientes hospitalizados por SARS-CoV-2. Analizamos las diferencias entre los pacientes que habían recibido y los que no habían recibido aún la vacuna para la temporada 2019-2020.
Resultados: No encontramos diferencias significativas (p = 0,09) en cuanto a los pacientes fallecidos (43 en total), de los cuales 23 (21,5%) habían sido vacunados frente a la gripe y 20 (13,5%) no habían sido vacunados. En términos de mortalidad, obtuvimos un OR: 0,873 (IC 95%: 0,294-2,083), y en lo referente al éxito de los cuidados sanitarios el OR ajustado fue de 1,447 (IC 95%: 0,610-3,430).
Conclusiones: La vacunación frente a la gripe en los pacientes ingresados por SARS-CoV-2 no tuvo un efecto beneficioso ni perjudicial en los cursos clínicos o resultados de los pacientes ingresados en un hospital europeo.

Introduction

On 11 March, WHO declared a global pandemic caused by a new virus of the family *Coronaviridae* that has since been called SARS-CoV-2.[1]

COVID-19 does not have specific antiviral drug treatment currently, so the treatment of the disease is mainly focused on symptomatic treatment and oxygen therapy, although hundreds of clinical trials are being conducted (www.clinicaltrials.org). Therefore, the therapeutic attitude is empirical. Until we have an effective vaccine, the possible preventive effect of flu vaccine for SARS-CoV-2 infection based on cross-reactivity has been postulated.[2]

Our objective was to analyse the effect of vaccination against flu virus in the season prior to the COVID-19 pandemic in our hospitalized SARS-CoV-2 infected patients.

Materials and methods

A retrospective observational cohort study enrolled patients 18 years of age or older admitted to hospital consecutively between 26 February and 20 May 2020, inclusive, with SARS-CoV2 infection confirmed by a real-time reverse transcription polymerase chain reaction (RT-PCR) diagnostic test on a nasopharyngeal aspirate or sputum sample.

Due to false negatives in RT-PCR testing, a second diagnostic test was performed if infection was strongly suspected in view of patients' signs and symptoms and radiological examinations. With the result of the second test, the diagnosis was either confirmed or not confirmed. Patients with SARS-CoV-2 infection who visited the accident and emergency department and were discharged home were not included in the study.

Patients who declined to grant their informed consent to the SARS-CoV-2 infection treatments included in the protocol at our hospital were excluded from the study. Re-admitted patients were also excluded; only initial hospital admissions were included. Pregnant and breast-feeding women were excluded as well.

The data collected from each patient, obtained from each patient's hospital electronic medical record, were demographic data, main comorbidities, clinical symptoms on admission, laboratory results, radiological tests and drug treatment.

Patients' electronic records were consulted to confirm which of those patients admitted to our hospital during the COVID-19 pandemic had received the flu vaccination for the 2019–2020 season.

Personal data were dissociated and pseudoanonymised in the database for subsequent statistical analysis by an independent expert. To obtain patients' survival data, patients were followed up until their discharge from hospital, transfer to another hospital or death.

Patients' oxygen saturation on admission was measured using oxygen saturation measured by pulse oximetry/fraction of inspired oxygen (S/F) ratio. For proper interpretation, some variables were calculated categorised by CURB-65 score or short-form Charlson Comorbidity Index. Hospital care

failure was considered to be patient death or ICU admission.

Quantitative variables were expressed in terms of medians and interquartile ranges (IQRs); categorical variables were expressed in terms of absolute frequencies and percentages. To compare categorical variables, Pearson's χ^2 test, Fisher's exact test or, if necessary, the Mantel–Haenszel test for trend was used. In the analysis of mean differences, Student's *t* test was used for variables with a normal distribution, and the Mann–Whitney *U* test was used for variables with a non-normal distribution. To confirm the influence of flu vaccination, the odds ratio (OR) for death and success (discharge) were calculated using logistic regression, and the best model according to vaccination status was taken and further adjusted by sex, age, oxygen saturation/fraction of inspired oxygen ratio, and the main comorbidities with significance (HTA, diabetes, hyperlipidaemia, cardiovascular disease, COPD, dementia). To select the final model, we performed a step exclusion system (backstep LV) with a Pout > 0.20. No model with an explanatory or predictive purpose was prepared. The level of statistical significance adopted for all comparative tests was $p < 0.05$. Statistical analysis and processing of data was performed with the SPSS statistics software package (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp.).

Results

A total of 255 patients were admitted to our hospital with a positive RT-PCR test during the study period. The characteristics of all our cohort has been published in other publication.[3] Of them, 42% (N = 107) received the flu vaccination in the prophylactic vaccine campaign for the 2019–2020 season in our country, and 40 patients did not receive any type of vaccine. There was a preponderance of males (54.9%); this distribution was maintained in both study groups (Table 1). The mean age of the patients was 68.4 (SD = 15.9) years, and was older in the group of vaccinated patients, who had a mean age of 79.5 years, than in the group of non-vaccinated patients, whose mean age was 60.7 years. As Table 1 shows, the comorbidities that were statistically significant between the two groups were: hypertension, diabetes, chronic obstructive pulmonary disease (COPD), dyslipidaemia, dementia, kidney disease and cardiovascular disease, as well as home anticoagulant treatment and chronic NSAID treatment. The overall median number of comorbidities was 3; vaccinated patients had significantly more comorbidities than patients who did not receive prophylaxis (4 versus 2 [$p < 0.01$]). The same trend surfaced when the short-form Charlson Comorbidity Index was examined, as there were no comorbidities in 80.4% of non-vaccinated patients versus 58.9% of patients vaccinated against the flu ($p < 0.01$).

Among symptoms presented by patients on admission, statistically significant differences were found between vaccinated and non-vaccinated patients: dry cough (49.5% versus 69.6%; $p < 0.01$), muscle pain (12.1% versus 27.0%; $p < 0.01$), headache (5.6% versus 14.9%; $p = 0.02$) and diarrhoea (15.9% versus 27.7%; $p = 0.03$). Regarding chest X-ray patterns, there were no significant differences between the two groups ($p = 0.80$). Vaccinated patients presented significantly ($p < 0.01$) more confusion on admission (17.9%) than non-vaccinated patients (4.8%).

Table 2 shows the results of the patients' laboratory tests on admission. The differences found were consistent with both groups' clinical conditions and comorbidities.

Median respiratory function on admission, measured in terms of S/F ratio, was statistically better in non-vaccinated patients (383.72; IQR: 303.13–457.14) than in vaccinated patients (328.57; IQR: 230.00–447.62), although it had few clinical repercussions, since there were no differences with regard to need for non-invasive mechanical ventilation ($p = 0.07$).

Patients' mean duration of admission was 12.1 (SD = 10.8) days, with no statistically significant differences between the two groups ($p = 0.91$); mean length of stay was 9 (5–15) days for vaccinated patients and 8 (5–16) days for non-vaccinated patients. There were also no differences between the two groups with regard to duration of ICU admission ($p = 0.93$).

We found no significant differences ($p = 0.09$) with regard to patients who died (43 in total), of whom 23 (21.5%) were vaccinated against the flu and 20 (13.5%) were not. There were also no differences between the two groups when healthcare success was analysed ($p = 0.21$). Table 3 shows the odds ratios adjusted for the multivariate logistical analysis by the different covariates considered. It confirms that there were no significant differences on adjusting for said covariates in any of the endpoints considered.

Discussion

The median age of the vaccinated patients was much older (79.5 [71.5–85.0]) than the median age of the non-vaccinated patients (60.7 [49.1–75.1]), as Table 1 shows. This was because patients over 65 constitute a risk population for flu virus infection and, as a result, get the flu vaccine more often. In addition, the group of non-vaccinated patients had fewer comorbidities (80% with no comorbidities); this was probably linked to age. Nevertheless, despite this age difference, we did not observe any differences in outcomes for both patient groups in terms of either mortality rates or ICU admissions.

We did, however, detect significant differences in initial symptoms presented by patients. Patients not vaccinated against the flu more often had dry cough, muscle pain, diarrhoea and headache; this difference was significant. Strikingly, non-vaccinated patients presented higher S/F ratio values, but showed no differences compared to vaccinated patients with regard to duration of ICU admission.

These results could have been because SARS-CoV-2 may not have epitopes on the spike protein which are extremely similar to those of the influenza virus. Also, there are significant structural differences on the whole with regard to protein content. Indeed, influenza vaccines contain haemagglutinin (HA) antigen, which does not have any cross-reactivity with SARS-CoV-2 antigens. The flu vaccine does not cause people to test positive for SARS-CoV-2, and, of course, does not contain coronavirus particles and does not cause coronavirus infections.

Our study did not detect any influence on the part of the flu vaccine on the clinical course of patients admitted to

Table 1 – Demographic characteristics and significant comorbidities on admission of patients who had received the flu vaccine and patients who had not received the flu vaccine.

	Total N (%) (*n* = 255)	No flu vaccine (*n* = 148)	Flu vaccine (*n* = 107)	*p*
Median age (years) (IQR)	70.0 (55.9–82.1)	60.7 (49.1–75.1)	79.5 (71.5–85.0)	
Sex				
Male	140 (54.9)	81 (54.7)	59 (55.1)	
Female	115 (45.1)	67 (45.3)	48 (44.9)	0.95
Hypertension	148 (58.0)	67 (45.3)	81 (75.7)	<0.01
Diabetes	65 (25.5)	28 (18.9)	37 (34.6)	<0.01
Ischaemic cardiomyopathy	23 (9.0)	9 (6.1)	14 (13.1)	0.05
Chronic kidney disease	49 (19.2)	22 (14.9)	27 (25.2)	0.04
COPD	21 (8.2)	6 (4.1)	15 (14.0)	<0.01
Asthma	19 (7.5)	12 (8.1)	7 (6.5)	0.64
Chronic pulmonary diseases (neither ASTHMA nor COPD)	24 (9.4)	10 (6.8)	14 (13.1)	0.09
Heart failure	21 (8.2)	10 (6.8)	11 (10.3)	0.31
Neoplasm	31 (12.2)	15 (10.1)	16 (15.0)	0.25
Cardiovascular disease	71 (27.8)	31 (20.9)	40 (37.4)	<0.01
Cerebrovascular disease	18 (7.1)	9 (6.1)	9 (8.4)	0.47
Dyslipidaemia	108 (42.4)	52 (35.1)	56 (52.3)	<0.01
Obesity	62 (24.3)	35 (23.6)	27 (25.2)	0.77
Autoimmune diseases	15 (5.9)	5 (3.4)	10 (9.3)	0.05
Dementia	27 (10.6)	7 (4.7)	20 (18.7)	<0.01
Rheumatoid arthritis	6 (2.4)	1 (0.7)	5 (4.7)	0.09
Anticoagulant treatment	30 (11.8)	11 (7.4)	19 (17.8)	0.01
ACE inhibitor or ARB treatment	115 (45.1)	55 (37.2)	60 (56.1)	<0.01

Table 2 – Laboratory results for vaccinated and non-vaccinated patients on hospital admission.

Test	Cases (*N*)	Median (IQR)	No flu vaccine	Flu vaccine	*p*	Reference range
Absolute leucocyte count × 10^9/l	255	6.05 (4.85–7.95)	5.85 (4.68–7.23)	6.50 (5.23–8.73)	0.03	4.8–11
Absolute neutrophil count × 10^9/l	255	4.5 (3.2–6.3)	4.2 (2.9–6.0)	4.9 (3.4–7.0)	0.03	1.9–8
Lymphocyte count × 10^9/l	255	1.0 (0.8–1.4)	1.0 (0.8–1.4)	1.1 (0.8–1.4)	0.79	0.9–4.5
Haemoglobin (g/dl)	255	13.4 (12.5–14.5)	13.7 (12.7–14.8)	13.1 (11.9–14.2)	0.01	12–18
Platelet count × 10^9/l	255	191.5 (143.8–244.8)	192.3 (141.8–242.0)	190.0 (146.3–254.0)	0.93	130–400
D-dimer μ(g/ml)	240	760.5 (503.5–1341.0)	760.5 (475.0–1202.0)	760.8 (574.0–1423.5)	0.29	0–500
Prothrombin time (s)	255	13.1 (12.2–14.3)	13.0 (12.1–13.9)	13.4 (12.2–14.8)	0.25	9–13
Activated partial prothrombin time (s)	251	30.3 (25.2–32.8)	30.0 (28.3–32.8)	30.4 (28.0–32.8)	0.58	
Glycaemia (mg/dl)	255	115.0 (102.5–137.3)	112.3 (100.3–130.3)	123.5 (104.2–149.0)	0.01	82–115
Creatinine (mg/dl)	255	0.92 (0.73–1.19)	0.84 (0.70–1.12)	1.00 (0.78–1.26)	0.01	0.7–1.2
Urea (mg/dl)	255	37.0 (27.5–56.3)	32.5 (25.5–47.5)	44.0 (34.5–64.3)	<0.01	
Glomerular filtration rate (CKD-EPI: ml/min/1.73 m^2)	254	81.14 (54.33–95.96)	88.97 (64.25–100.97)	67.72 (44.71–82.95)	<0.01	
Sodium (mmol/l)	255	139.2 (136.8–141.1)	139.2 (136.8–141.0)	139.4 (136.8–141.3)	0.05	136–146
Potassium (mmol/l)	250	4.18 (3.93–4.47)	4.17 (3.92–4.44)	4.18 (3.93–4.63)	0.36	3.5–5.1
Phosphate (mg/dl)	177	3.08 (2.69–3.47)	3.16 (2.88–3.47)	2.89 (2.55–3.35)	0.27	
Total calcium (mg/dl)	195	9.0 (8.7–9.3)	8.9 (8.7–9.3)	9.1 (8.8–9.4)	0.03	
Albumin (g/dl)	199	3.65 (3.32–3.93)	3.71 (3.45–4.03)	3.54 (3.22–3.87)	<0.01	
Total bilirubin (mg/dl)	215	0.45 (0.33–0.60)	0.43 (0.31–0.59)	0.50 (0.35–0.64)	0.12	0.1–1.2
Aspartate aminotransferase (glutamic oxaloacetic transaminase [GOT]) (U/l)	100	51.1 (36.0–70.0)	52.3 (38.2–77.5)	47.4 (33.9–61.0)	0.94	5–40
Alanine aminotransferase (glutamic pyruvic transaminase [GPT]) (U/l)	250	24.9 (16.3–40.7)	29.4 (17.8–49.2)	20.4 (14.5–29.3)	0.05	5–41
Gamma-glutamyl transferase (GGT) (U/l)	152	40 (24–113)	48 (24–123)	32 (24–63)	0.09	5–61
Lactate dehydrogenase (LDH) (U/l)	243	275.0 (205.3–377.3)	273.0 (207.5–359.5)	281.3 (203.0–386.5)	0.62	135–225
Total creatine kinase (CK) (U/l)	213	88.5 (50.0–171.5)	83.0 (49.0–151.5)	93.5 (53.5–182.8)	0.41	24–192
C-reactive protein (mg/dl)	255	7.34 (3.31–14.11)	6.88 (2.28–13.92)	7.85 (4.33–14.25)	0.70	0.1–1.0
Procalcitonin (ng/ml)	182	0.131 (0.073–0.321)	0.116 (0.063–0.237)	0.148 (0.087–0.402)	0.43	0–0.5
Ferritin (ng/ml)	175	663.7 (323.6–1358.3)	693.9 (323.2–1371.9)	662.4 (331.1–1242.5)	0.65	30–400
Troponin T (pg/ml)	176	11.835 (6.443–27.468)	7.490 (5.245–18.245)	20.340 (11.835–33.665)	0.16	<14

Table 3 – Models for vaccinated and non-vaccinated patients adjusted for covariates and comorbidities considered.

Endpoint and covariates[a]	Vaccinated/non-vaccinated OR	95% CI		Adjusted OR VAC/non-VAC	Adjusted OR 95% CI		p
DEATH model	1.752	0.906	3.389	0.873	0.294	2.083	0.241
Age				1.074	1.013	1.140	0.017
Sex				0.431	0.166	1.117	0.083
S/F ratio				0.991	0.987	0.996	<0.001
HTA				3.502	0.823	14.892	0.090
Renal insufficiency				2.384	0.738	7.706	0.147
Cardiovascular disease				0.352	0.101	1.221	0.100
Dementia				2.730	0.675	11.033	0.159
Success model	0.688	0.380	1.243	1.447	0.610	3.430	0.402
Age				0.953	0.917	0.990	0.013
Sex				1.091	0.486	2.447	0.833
S/F ratio				1.009	1.006	1.013	<0.001
INSUF RENAL				0.386	0.128	1.162	0.090
ENF CVC				3.794	1.178	12.214	0.025

OR = odds ratio; S/F = oxygen saturation/fraction of inspired oxygen.

[a] Death model without diabetes, COPD and dyslipidemia. Successful model without diabetes, dyslipidemia, COPD, HTA, and dementia.

hospital or on their morbidity or mortality rates. Possible biases that could act as confounding factors such as age and respiratory function status were controlled for by logistic regression, which found no relationship between flu vaccination and clinical course of SARS-CoV-2 infection (Table 3). However, Fink *et al*. reported that patients vaccinated against the flu had significantly better clinical courses as well as significantly lower mortality rates than non-vaccinated patients: 17% lower odds of death (95% CI: 0.75, 0.89).[4] This study conducted in Brazil during the COVID-19 pandemic and during the seasonal flu period was population-based, unlike our study, which was hospital-based. Therefore, the two populations could be different as our study enrolled patients with more advanced and more serious cases of SARS-CoV-2 infection which required hospital admission and furthermore did not coincide with the flu season in our country. Reduced hospitalisation risk (72.5% vs. 27.5%) with prior flu vaccination was observed by other authors.[5] However, in this study all Covid positive patients, whether they were hospitalized or not, from across the Cleveland clinic health system were included, and this could be the reason of a different outcome about protective effect of flu vaccination. The same occurred in other multicenter, retrospective cohort study carried out in Ferrara with 952 adult patients (≥ 18 years old) with a laboratory diagnosis of SARS-CoV-2 infection.[6] Differences were found also in the need for hospitalisation between the two groups (255 vaccinated (VP) vs. 193 no-vaccinated (NV); $p < 0.001$), in the 30-days mortality rates (53 VP vs. 25 NV; $p < 0.001$) and in the time until negativity of swabs (33 ± 11 days for VP vs. 30 ± 10 for NV; $p = 0.001$). Vaccinated patients were on average older than unvaccinated patients (79 ± 13 vs. 64 ± 18), as in our study [79.5 (71.5–85.0) vs 60.7 (49.1–75.1)], and this made age a true predictive factor, and probably a confounding factor in these studies, for a worse prognosis and for the need of hospitalisation in patients with SARS-CoV-2 infection. Another study observed no difference in the number of patients deceased at 60 days from diagnosis (8/150, 5.3% vs 36/416, 8%; $p = 0.28$) between vaccinated and not vaccinated SARS-CoV-2 infected patients with univariate analysis.[7] However, after correction for gender, age, and comorbidities (cardiovascular diseases, COPD, neoplasms), we found that flu vaccination was independently associated with a lower risk of death at 60 days ($p < 0.001$; OR 0.2; IC 95% 0.082–0.510), but not to the need for endotracheal intubation in COVID-19 patients. In this study, authors enrolled only patients who need admission to Emergency Department and does not include patients with mild or absent symptoms. The death rate was reduced by flu vaccination only in a small group of patients who received the vaccine in the period immediately preceding the onset of the outbreak in an Italian epidemiological study.[8]

Our study was not free from limitations, which should be borne in mind in evaluating it. First, its sample size and single-site nature, as well as its conduct within a specific healthcare system, may have induced a sample selection bias which would preclude translation to other situations and generalisation of its results. In addition, the data were collected and analysed retrospectively; a prospective study with a pre-data collection design should be conducted to determine causality relationships. Another limitation of the study was that it only enrolled patients in advanced stages of COVID-19 who required hospital admission and therefore excluded cases of milder and asymptomatic disease states. Finally, bias may have been introduced into our study, as in population-based studies, as data on patient vaccination was collected from centralised official registries.

In conclusion, flu vaccination in patients admitted for SARS-CoV-2 infection had neither a beneficial nor a harmful effect on the clinical courses or outcomes of patients admitted to a European hospital. But taking in account other studies carried out in general population it seems that there is a flu vaccination protective effect for hospitalisation.

Ethics approval

The study protocol was approved by the Independent Ethics Committee for research involving medicinal products (mIEC) on 25 May 2020.

Informed consent

Exemption from requesting written informed consent from patients to take part in the study was obtained, given the study's retrospective observational design, under which the difficulty of obtaining patients' consent would have compromised the conduct thereof. Study participants' personal data were processed in compliance with current European legislation.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Acknowledgements

We acknowledge colleagues from our hospital who were on the front line of treatment of patients during the COVID-19 pandemic. They also contributed to the collection of necessary data to perform this study. We also want to thank the collaboration of Dr. Pilar Mañes from the Preventive Service of our hospital.

REFERENCES

1. WHO WHOJB. WHO statement regarding cluster of pneumonia cases in Wuhan, China. 2020;9.
2. Salem ML, El-Hennawy D. The possible beneficial adjuvant effect of influenza vaccine to minimize the severity of COVID-19. Med Hypotheses. 2020;140:109752.
3. Álvarez-Arroyo L, Carrera-Hueso FJ, El-Qutob D, Robustillo-Villarino M, Girona-Sanz AM, Pin-Godos MT, et al. Descriptive study of a cohort of COVID-19 hospitalized patients in Spain. Gac Med Mex. 2021;157:76–83.
4. Fink G, Orlova-Fink N, Schindler T, Grisi S, Ferrer AP, Daubenberger C, et al. Inactivated trivalent influenza vaccine is associated with lower mortality among Covid-19 patients in Brazil. medRxiv. 2020, 2020.06.29.20142505.
5. Jehi L, Ji X, Milinovich A, Erzurum S, Merlino A, Gordon S, et al. Development and validation of a model for individualized prediction of hospitalization risk in 4536 patients with COVID-19. PLOS ONE. 2020;15:e0237419–237420.
6. Greco S, Bella A, Bonsi B, Fabbri N, Califano A, Morrone S, et al. SARS-CoV-2 infection and H1N1 vaccination: does a relationship between the two factors really exist? A retrospective analysis of a territorial cohort in Ferrara, Italy. Eur Rev Med Pharmacol Sci. 2021;25:2795–801.
7. Candelli M, Pignataro G, Torelli E, Gulli A, Nista EC, Petrucci M, et al. Effect of influenza vaccine on COVID-19 mortality: a retrospective study. Intern Emerg Med. 2021.
8. Ragni P, Marino M, Formisano D, Bisaccia E, Scaltriti S, Bedeschi E, et al. Association between exposure to influenza vaccination and COVID-19 diagnosis and outcomes. Vaccines. 2020;8.