


## The effect of influenza vaccine on severity of COVID-19 infection: An original study from Iran

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### Abstract

**Background:** The COVID-19 infection is a novel virus that mainly targets the respiratory system via specific receptors without any coronavirus-targeted therapies. Many efforts have been made to prepare specific vaccines for COVID-19 or use of prefabricated vaccines of other similar viruses, especially severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and influenza (flu). We aimed to evaluate the effects of previous flu vaccine injection on severity of incoming COVID-19 infection.

**Methods:** We conducted a large cross-sectional study of 529 hospitalized Iranian COVID patients to evaluate the severity of disease courses in patients with or without previous flu vaccination history using some main factors like length of hospitalization, need for the intensive care unit (ICU) admission and length of stay in the ICU for comparison between COVID-19 infected patients with or without flu vaccination history. For the quantitative data, we used independent-samples t and Mann-Whitney tests. The qualitative data were calculated using the Fisher exact and chi-square tests in IBM SPSS Statistics version 22 (SPSS Inc) and P value <0.05 was considered statistically significant.

**Results:** There were no significant differences in the demographic data of patients, disease, and severity-related parameters between the 2 groups. It means that there were not any significant differences between patients with and without history of flu vaccination regarding mean days of hospitalization, percentage of needing to be admitted to the ICU, days being admitted to the ICU ( $8.44 \pm 6.36$  vs  $7.94 \pm 8.57$ ; 17% vs 11.5%; and  $1.17 \pm 3.09$  vs  $0.92 \pm 3.04$ , retrospectively) ( $p=0.883$ ,  $0.235$ , and  $0.809$ , respectively).

In the laboratory tests, in comparison between patients with and without history of previous flu vaccination, only lymphocytes count in the vaccine positive group was higher than the vaccine negative group ( $20.82 \pm 11.23$  vs  $18.04 \pm 9.71$ ) ( $p=0.067$ ) and creatine phosphokinase (CPK) levels were higher in the vaccine negative group ( $146.57 \pm 109.72$  vs  $214.15 \pm 332.06$ ) ( $p=0.006$ ).

**Conclusion:** We did not find any association between flu vaccination and decrease in disease severity in our patients. It seems that patients with previous history of flu vaccination may experience less laboratory abnormalities in some parameters that could be interpreted in favor of lower overall inflammation; however, this study cannot answer this definitely because of its design. As we collected retrospective data from only alive discharged patients and had no healthy control group, we could not discuss the probable effect of the vaccine on the mortality rate or its probable protective role against the infection. We need more well-designed controlled studies with different populations in different geographic areas to address the controversies.

**Keywords:** Corona, COVID-19, SARS-CoV-2, Influenza Vaccine, Flu, Vaccine, Vaccination, Severity, Outcome

**Conflicts of Interest:** None declared

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### ↑What is “already known” in this topic:

Many efforts have been made to prepare specific vaccines for COVID-19 or use of prefabricated vaccines of other similar viruses, especially severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and influenza (flu), since they may decrease infection rate and disease severity or improve final outcomes while being infected.

### →What this article adds:

There is no association between influenza vaccination and decrease in disease severity in our patients. However, we collected retrospective data from only alive discharged patients and had no healthy control group. More well-designed controlled studies with different populations in different geographic areas are needed to address the controversies.

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## Introduction

The COVID-19 infection is a novel virus that mainly targets respiratory system via specific receptors without any corona virus-targeted therapies; there are many other respiratory-associated viruses (like the influenza virus), which result in some similar clinical features (1) and there are some experiences about their vaccination, such as vaccine efficacy and its protective and therapeutic roles (eg, reduction of disease severity) (2). In addition to lack of virus-specific therapies, nowadays, COVID-19 vaccination is limited to some clinical trials and there is not any standard vaccination product and protocol yet, so one of management strategies in this pandemic is focusing on protective, therapeutic, and immune enhancing potentials of available vaccines of other respiratory-associated virus that may be beneficial for COVID-19 and may reduce severity of infection (3-5).

Based on the current literature review, it is found that there are many studies about COVID-19 vaccination also about the effects of the flu vaccine on various aspects of COVID-19; and logically there may be some controversies in these entities that need more evaluations in different populations in different geographic areas. In a systematic review about therapy and vaccination of COVID-19, the authors found that there were 5 vaccines under investigation in phase 1 trials for the corona virus and other similar viruses also there were 2 other phase 3 trials on BCG (Bacillus Calmette-Guérin) vaccine, so it seems we need an approved vaccination for breaking the chain of COVID-19 spreading (6). In another systematic review, it has been discussed that although phase 1 trials on DNA-based virus vaccines are available, vaccines which target other similar viruses like MERS-CoV-SARS-CoV could be effective options in this pandemic (pang). In May 2020, 1 other systematic review reported 10 human clinical trials on vaccination for COVID-19, 5 in phase 1, 2 in phase 2, and 3 in phase 3 (7). In a study that evaluated the effects of previous flu vaccine on COVID-19-associated outcome, means mortality, the authors found some positive protective effects of vaccine on COVID-19, especially in elderly population (8). In another study no effect of the flu vaccine was found on other respiratory-associated viruses like corona-viruses also the vaccine does not increase the risk of latter mentioned viruses (9).

We supposed that the flu vaccine may decrease the severity of COVID-19 infection in hospitalized patients with respect to duration of hospitalization and their need to treatment change or ICU admission, as it seems that the flu vaccine by increasing immunogenicity toward respiratory-associated viruses, may decrease the severity of disorder. Also, for a more complete discussion about this hypothesis, we need more well-designed case-controlled studies to find the protective effect of the flu vaccine as well. In this large cross-sectional study from Iran, we tried to evaluate the effects of previous flu vaccine injection on the severity of incoming COVID-19 in-

fection.

## Methods

This analytical cross-sectional study was conducted on 529 Iranian patients affected by COVID-19, between March to May, 2020, who were hospitalized in RasoolAkram Medical Complex affiliated to Iran University of Medical Sciences, Tehran, Iran. Their diagnoses were approved by a positive nasopharynx reverse transcription polymerase chain reaction (RT-PCR) test or in the case of negative PCR; based on very suggestive computed tomography imaging for COVID-19 scored by the CO-RADS classification system (10). From 529 patients, 59 cases (11.15%) had a positive history of the flu vaccine injection. We tried to compare the COVID-19 diseases severity in patients with or without vaccine history. The main outcomes of this study for comparison between 2 groups (which were considered indirectly to be associated with the overall severity score of the disease) were the mean days of hospitalization, the necessity for ICU admission, the mean days of staying in the ICU and the need to take second-line therapeutic options. For both groups we assessed demographic data of the disease and the patients, laboratory tests, and treatment protocols completely. The continuous variables were presented as mean and SD and for quantitative data we used independent-samples t test and Mann-Whitney test. The qualitative data were calculated using the Fisher exact and chi-square tests in IBM SPSS Statistics version 22 (IBM), and P value < .05 was considered statistically significant. The ethical code of the large cohort study of RasoolAkram Medical Complex from which these data were extracted was IR.IUMS.REC.1399.759.

## Results

Demographic data of the study participants are presented in Table 1. There were no significant differences in the demographic data of patients, disease, and severity-related parameters between the 2 groups and only the chest discomfort was significantly more prevalent in the influenza-negative vaccine group (42.4% vs 30%) ( $p=0.041$ ) (Table 1). In the laboratory tests, only the lymphocytes count in the vaccine positive group was higher than the vaccine negative group ( $p=0.067$ ) and CPK levels were higher in the vaccine negative group ( $p=0.006$ ) (Table 2). The length of hospital stay for the influenza-positive vaccine group was  $8.44 \pm 6.36$  days and for the influenza negative vaccine group was  $7.94 \pm 8.57$  days ( $p=0.924$ ). The need to ICU admission in the influenza-positive vaccine group was 16.9%, and in the influenza-negative vaccine group was 11.5% ( $p=0.235$ ), and the length of ICU admission for the influenza-positive vaccine group was  $1.17 \pm 3.09$  days, and for the influenza negative vaccine group was  $0.92 \pm 3.04$  days ( $p=0.809$ ). The need to second-line thera-

Table 1. Disease and patients' characteristics in patients with positive and negative history of influenza vaccination

Patient or disease characteristics	Influanza-Vaccine (positive) (n=59)	Influanza-Vaccine (negative) (n=470)	p
Gender (male) n%	32 (54.2)	196 (41.7)	0.578
Age (year) (Mean $\pm$ SD)	57.78 $\pm$ 6.36	59.11 $\pm$ 16.21	0.883
Hospitalization Days	8.44 $\pm$ 6.36	7.94 $\pm$ 8.57	0.924
ICU Days	1.17 $\pm$ 3.09	0.92 $\pm$ 3.04	0.809
IVIg (positive)	7 (11.9)	40 (8.5)	0.463
ICU Admission	10 (16.9)	54 (11.5)	0.235
PCR (positive)	6 (10.2)	47 (10.0)	1.000
chills (yes)	35 (59.3)	307 (65.3)	0.560
Fever (positive)	38 (64.4)	295 (62.80)	0.887
Fever length	2.53 $\pm$ 3.36	2.37 $\pm$ 3.40	0.746
Dyspnea (positive)	43 (72.9)	309 (65.7)	0.180
Fatigue (positive)	48 (72.9)	335 (71.3)	0.850
Anorexia (positive)	44 (74.6)	279 (59.4)	0.120
Body pain (positive)	35 (59.3)	279 (59.4)	0.886
Diarrhea history (positive)	16 (27.1)	80 (17)	0.420
New Diarrhea (positive)	5 (8.5)	47 (10)	1.000
Sore through (positive)	16 (27.1)	99 (21.1)	0.230
Nausea and Vomiting (positive)	22 (37.3)	164 (34.9)	0.773
Sputum (positive)	22 (37.3)	121 (25.7)	0.570
Chest discomfort (positive)	25 (42.4)	141 (30)	0.041
Headache (positive)	18 (30.5)	161 (30)	0.881
Vertigo (positive)	16 (27.1)	109 (23.2)	0.321
Delusion (positive)	5 (8.5)	50 (10.6)	1.000
Seizure (positive)	2 (3.4)	8 (1.7)	0.285
LOC (positive)	8 (13.6)	80 (17)	0.706
Anosmia/hyposmia(positive)	17 (28.8)	93 (19.8)	0.780
Dysgeusia (negative)	11 (18.6)	92 (19.6)	1.000
Heart Disease (positive)	15 (25.4)	116 (24.7)	0.748
Lung Disease (positive)	10 (16.9)	46 (9.8)	0.113
Kidney Disease (positive)	8 (13.6)	44 (9.4)	0.233
Dialyzed (positive)	1 (1.7)	15 (3.2)	1.000
Immunodeficiency (positive)	4 (6.8)	4 (0.9)	1.000
Diabetes Mellitus (positive)	19 (32.2)	145 (30.9)	0.762
Hypertension (positive)	21 (35.6)	132 (28.1)	0.217
Malignancy (positive)	5 (8.5)	21 (4.5)	0.181
Tuberculosis (negative)	1 (1.7)	7 (1.5)	1.000

Table 2. Laboratory test results in patients with positive and negative history of influenza vaccination

Laboratory tests	Influanza-Vaccine (positive) (n=59)	Influanza-Vaccine (negative) (n=470)	p
WBC	8.48 $\pm$ 5.20	7.47 $\pm$ 4.39	0.111
Diff _segment	57.34 $\pm$ 30	57.61 $\pm$ 32.40	0.951
Diff _lymphocyte	20.82 $\pm$ 11.23	18.04 $\pm$ 9.71	0.067
ESR	45.29 $\pm$ 23.56	48.86 $\pm$ 26.65	0.367
CRP	10.98 $\pm$ 17.72	8.05 $\pm$ 15.28	0.229
Cr	1.18 $\pm$ 0.66	1.14 $\pm$ 0.61	0.697
AST	34.70 $\pm$ 16.93	39.74 $\pm$ 28.85	0.223
ALT	24.20 $\pm$ 18.77	27.01 $\pm$ 32.13	0.512
LDH	571 $\pm$ 241.93	615 $\pm$ 258	0.248
CPK	146.57 $\pm$ 109.72	214.15 $\pm$ 332.06	0.006

Table 3. Initial therapies during hospitalization in patients with positive and negative history of influenza vaccination

supplementary treatments	Influanza-Vaccine (positive) (n=59)	Influanza-Vaccine (negative) (n=470)	p
Azithromycin	22 (37.3%)	158 (33.6%)	0.576
Heparin (I=yes)	44 (74.6%)	348 (74%)	0.930
Lopinavir _and ritonavir	40 (67.8%)	326 (69.4%)	0.807
Linezolid	18 (30.5%)	97 (20.6%)	0.123
Hydroxyl chloroquin	53 (89.8%)	413 (87.9%)	0.662

py means intravenous immunoglobulin (IVIg) therapy in influenza-positive vaccine group was 11.9% and in the influenza-negative vaccine group was 8.5% ( $p=0.235$ ) (Table 1). In Table 3, you can see the initial therapies of both groups that were not statistically different.

## Discussion

COVID-19 vaccination encompasses DNA-recombinant, mRNA-based, inactivated whole virus, and

live attenuated virus vaccines. There are only few vaccines that progressed to release the initial results, including MERS-CoV and SARS-CoV vaccine, which have shown positive outcomes that resulted in entrance to trial phase 2. As the SARS virus has genetic similarity of about 79% to the novel corona virus, it is expected that this vaccine has a promising effect on COVID-19 (7). It is proposed that in COVID-19 pandemic, especially in elderly people, one of main pathologic events is the downregula-

tion of the innate immune system, and as the live attenuated virus vaccines have proved to have positive effects on activity of this system, the vaccines (like influenza vaccine) could enhance the immune system function, and logically result in favorable achievements in final outcomes of the new corona virus (8).

With respect to COVID-19 vaccination, there are many clinical trials in different phases, some of which showed promising outcomes, although more evaluations and phase progression of clinical trials are necessary for more definite results (3, 6, 7). In a recent systematic review published May, 2020, a total of 10 human clinical trials were conducted on COVID vaccination, from which 7 studies focused on SARS-CoV-2 S-protein and 3 on the protective effects of the BCG vaccine based on lymphocyte activation theory. Immune-mediated preventive and therapeutic strategies are the hot topics in this pandemic area, especially via nanotechnology, which may enhance the efficacy and reduce the side effects of different modalities like vaccines (11).

With respect to influenza vaccination in COVID pandemic, there are some articles with various designs and purposes. In a study written by Grech V and Borg M, the authors said that although coinfection of COVID-19 and influenza does not seem to worsen patients' outcome in ongoing cold seasons, if we have a world-based vaccination we may expect to decrease the burden of the flu and more capacity to manage COVID patients (12). Grohskopf et al study also confirmed this theory (13).

In their study, Skowronski et al found no protective effect of influenza vaccine on respiratory associated viruses like corona viruses; also, they found that the vaccine did not increase the risk of latter mentioned viruses (9).

In a study on previous influenza vaccine effect on COVID-19-associated outcome, the authors found some positive protective effects of vaccine on COVID patients, especially on mortality rates of the elderly (8). However, in the present study, as we did not have a control group, we could not compare our results with the mentioned study due to not assessing the protective effect of vaccine. Although in our population, we did not find any severity reduction by previous influenza vaccine injection.

In Fink et al study from Brazil on 92,664 COVID patients, the authors evaluated the effect of influenza vaccine on the severity of the disease. They found about 8% lower odds of needing ICU admission, an 18% decrease in need for invasive respiratory support and a 17% decrease in mortality rate. Although these difference percentages are not high, considering the pandemic encountered, these differences are responsible for a large number of human beings, which is of great importance in life saving and financial issues (14). Unlike Fink et al study, we did not see any decrease of disease severity in our study, which could be because of our smaller sample size, lack of control group, various intervals of vaccine injection, and COVID-19 infection, and lack of assessment of mortality rate due to the retrospective design of our study. We only assessed duration of hospital stay, necessity to ICU admission, mean days of ICU admission, and need to IVIG therapy as severity-related parameters of this study.

The authors of this study have worked on various aspects of COVID-19 (15-28), and have tried to report the results of this study to evaluate the theory of beneficial effects of influenza vaccine-induced immunogenicity toward COVID-19; however, they did not find any significant association in this study.

### Study Limitations

In this study, we did not have a control group to evaluate the protective effect of the vaccine. Also, we did not consider mortality in our outcomes, as we retrospectively collected the data of vaccination of our discharged alive patients and we did not gather the data of patients who died during hospitalization. We did not ask about type of the flu vaccine (such as trivalent or quadrivalent), which we suggest asking in future studies so that researchers may find any association between type of vaccine and its protective or immune-enhancing effect against COVID-19. In our study, the clinical and imaging severity scores of patients were not calculated based on predefined scores, as during the data gathering of this study, these scores were not as popular as they are now, and the main outcomes of this study for comparison between the 2 groups (which were considered indirectly to be associated with the overall severity score of the disease) were the mean days of hospitalization, the necessity for ICU admission, the mean days of staying in ICU, and the need to take second-line therapeutic options.

### Conclusion

Although we did not find any association between the influenza vaccination and decrease of disease severity in our patients, for more definite comments about the protective and immune enhancing roles of the influenza vaccine in COVID-19 pandemic, we need more well-designed controlled studies of different populations in different geographic areas to address the controversies.

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### Conflict of Interests

The authors declare that they have no competing interests.

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