Evaluation of the Possible Effect of the Influenza Vaccine on the Severity, Mortality, and Length of Hospitalization among Unvaccinated COVID-19 Patients; An Observational, Cross-Sectional Study

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A R T I C L E   I N F O

A B S T R A C T

Background: Based upon WHO (World Health Organization) Coronavirus Dashboard more than 5 million deaths worldwide have been attributed to the COVID-19 (Coronavirus Disease 2019) caused by the SARS-Cov-2 virus (Severe Acute Respiratory Syndrome Coronavirus) till November 2021. The annual flu vaccination has raised many questions about the vaccine's effects on Covid-19 outcomes. Several possible mechanisms including cross-reactivity and cross-protection have been reported to be responsible for the potential protective effect of the flu vaccine on the COVID-19 infection. This study was performed to evaluate the possible effect of the influenza vaccine on the disease severity, the mortality rate, and the length of hospitalization in COVID-19 patients.

Methods: The data of 1300 patients were recorded from May 2020 to October 2020. Patients with a previous history of COVID-19, patients under 18 years old, and patients who did not have accurate information about their influenza vaccination history were excluded. 498 hospitalized unvaccinated COVID-19 patients with typical clinical manifestations and a positive PCR (Polymerase Chain Reaction) test for COVID-19 were included in this observational, cross-sectional study. The participants were divided into two groups (vaccinated and unvaccinated) based on the history of influenza vaccination at the time of admission.

Results: The length of hospital stay was lower in the vaccinated compared to the unvaccinated group (p < 0.05). However, there was no significant difference between the mortality rate, the need for ICU (Intensive Care Unit) admission, and the severity of the disease between the two groups (p> 0.05).
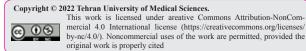
Conclusion: Since the patients studied in this article did not receive any of the Covid-19 vaccines; Therefore, the effect of influenza vaccination on the clinical course of Covid-19 can be evaluated using the results of this study. A longer length of hospital stay was observed in the unvaccinated patients in our study, which may suggest the possible protective effect of the influenza vaccine against COVID-19.

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Introduction

There are more than 5 million reports of death due to COVID-19 (Coronavirus Disease 2019) caused by the SARS-CoV-2 virus (Severe Acute Respiratory Syndrome Coronavirus) till November 2021. To this date, more than 7 billion doses of the COVID-19 vaccine are administered globally (1). Besides COVID-19, the international community was also affected by the influenza pandemic, several times in 1957, 1968, and 2009. Moreover, WHO (World Health Organization) warned about the next flu pandemic and suggest preparing for the next one (2). According to COVID-19 and the annual flu rate, these two viral infections are likely to occur at the same time. The possibility of co-infection with COVID-19 and the flu has been reported by several studies (3,4). The co-infection of influenza and COVID-19 is associated with the enhancement of SARS-CoV-2 infectivity (5). Some studies have investigated the effects of the influenza vaccine on the risk of COVID-19 infection and showed significantly lower rates of influenza vaccination in COVID-19 patients. Several possible mechanisms including cross-reactivity and cross-protection have been reported to be responsible for the protective effect of the influenza vaccine on the COVID-19 infection (6,7).

The question is whether the annual influenza vaccination, aside from preventing COVID-19 infection, has any effects on the COVID-19 course of illness. Due to the increasing coverage of COVID-19 vaccination worldwide, the possibility of examining the effect of other interventions on the clinical course of COVID-19 is reduced. This retrospective study is related to the period when COVID-19 vaccination was not started in Iran, so it made it possible to investigate the net effect of influenza vaccination on the clinical course of COVID-19. This study was performed to evaluate the possible effect of the influenza vaccination on the disease severity, the mortality rate, and the length of hospitalization among unvaccinated COVID-19 patients

Methods

This observational, cross-sectional study was performed at Baharloo Hospital affiliated with Tehran University of medical sciences from May 2020 to October 2020. The Inclusion criteria were patients with clinical manifestation of COVID-19, who were tested positive for COVID-19 polymerase chain reaction (PCR), and were hospitalized in Baharloo hospital. The data of 1300 patients were recorded from May 2020 to October 2020 The Exclusion Criteria of the study were patients under 18 years old and patients with a history of the previous COVID-19. The patients' history of vaccination against influenza was asked at the time of admission. Patients who did not have accurate information about their influenza vaccination history were excluded from the study and then a total number of 498 patients were included in this observational, cross-sectional study. Since the data bank was used in this study, the sample size was not calculated. Participants were divided into two groups (vaccinated and unvaccinated). 31 patients had received the flu vaccine and 467 patients had not. None of the patients were vaccinated against covid-19. The primary outcomes were the mortality rate and the length of hospitalization. Secondary outcomes were severity at hospitalization time, ICU admission, ventilation, and invasive ventilation need.

Patients' information such as demographics data, medication list, initial presentation, comorbidities, lab data, and patient outcomes were extracted from their hospital records.

All patients received nursing care, nutritional support, respiratory support, and medication including, Hydroxychloroquine, Corticosteroids, oral antiviral drugs, and vitamin D according to the COVID-19 protocol designed by the Iran Ministry of Health at the time of the study.

Patients who required intensive care unit (ICU) admission at the time of hospitalization were defined as severe. The disease severity at the time of hospitalization, the mortality rate, the need for ICU admission, the need for mechanical ventilation, and the length of hospitalization were compared between two groups using odds ratio. T-test and chi-square test were used to compare quantitative and qualitative variables, respectively. Stata version 4 was used for statistical analysis of the data and a P-value of less than 0.05 was considered significant.

Results

There was no significant difference between groups regarding age and sex. Hypertension and diabetes mellitus were the most common comorbidities in both groups.

The most common initial manifestations were dyspnea (57.6%), cough (57.6%), fever (57.2%), shivering (36.7%), malaise (36.3%), anorexia (19.9%), nausea (19.2%), vomiting (13.1%), anosmia (28%), and diarrhea (8.6 %), respectively. There was no significant difference between the two groups with regards to the initial clinical manifestation. The details of patients' demographics, comorbidities, and initial manifestations are displayed in Table 1.

Table 1. Demographic and baseline characteristics of COVID-19 Patients Admitted to Baharloo hospital in Tehran-Iran based on influenza vaccine.

	Total (n=498)	With influenza vaccine (n=31)	Without influenza vaccine (n=467)	*P-value*
Demographic				
Age (years)	57.39(± 18.24)	57.38 (±17.66)	57.37 (±18.25)	0.997
Male sex	282 (56.6)	19 (61.3)	263 (56.3)	0.588
Comorbidity				
Hypertension	167 (33.5)	18 (58.1)	149 (31.9)	0.003
Diabetes mellitus	150 (30.1)	12 (38.7)	138 (29.6)	0.282
CHD (coronary heart disease)	63 (12.7)	6 (19.4)	57 (12.2)	0.246
Previous Stroke	35 (7)	2 (6.5)	33 (7.1)	0.897
COPD (chronic obstructive pulmonary disease)	33 (6.6)	3 (9.7)	30 (6.4)	0.481
Hyper/HypoThyroidism	30 (6)	5 (16.1)	25 (5.4)	0.015
Chronic renal/kidney disease	17 (3.4)	1 (3.2)	16 (3.4)	0.953
Rheumatoid disease	13 (2.6)	4 (12.9)	9 (1.9)	<0.0001
Anemia	10 (2)	0	10 (2.1)	0.410
Previous Cancer	6 (1.2)	0	6 (1.3)	0.525
Initial symptoms				
Dyspnea	287 (57.6)	21 (67.7)	266 (57)	0.239
Cough	287 (57.6)	21 (67.7)	266 (57)	0.239
Fever	285 (57.2)	21 (67.7)	264 (56.5)	0.222
Chills	183 (36.7)	11 (35.5)	172 (36.8)	0.880
Myalgia	182 (36.5)	10 (32.3)	172 (36.8)	0.609
Anorexia	99 (19.9)	6 (19.4)	93 (19.9)	0.940
Nausea	99 (19.9)	7 (22.6)	92 (19.7)	0.697
Vomiting	65 (13.1)	4 (12.9)	61 (13.1)	0.980
Diarrhea	43 (8.6)	3 (9.7)	40 (8.6)	0.831
Anosmia	28 (5.6)	1 (3.2)	27 (5.8)	0.550

All data are reported as frequency and percent (in parenthesis), except for age that is reported as mean ± SD

All patients received nursing care, nutritional support, and respiratory support. Patients were treated according to the COVID-19 protocol designed by the Iran Ministry of Health at the time of the study. It should be noted that the treatment of patients has been different according to the patients' clinical condition. The frequency of types of medications is reported in all patients, vaccinated, and unvaccinated groups respectively in detail in Table 2.

Table 2. Type of medication in COVID-19 Patients Admitted to Baharloo hospital in Tehran-Iran based on influenza vaccine.

	Total (n=498)	With influenza vaccine (n=31)	Without influenza vaccine (n=467)	P-value
Chloroquine and Hydroxychloroquine	391 (78.5)	28 (90.3)	363 (77.7)	0.098
NSAIDs	245 (49.2)	20 (64.5)	225 (48.2)	0.078
IV Antibiotics	233 (46.8)	18 (58.1)	215 (46)	0.194
PPIs	202 (40.6)	16 (51.6)	186 (39.8)	0.196
Azithromycin	196 (39.4)	10 (32.3)	186 (39.8)	0.403
Oral antiviral	192 (38.6)	9 (29)	183 (39.2)	0.261
IV Corticosteroids	123 (24.6)	10 (32.3)	113 (24.1)	0.074
Enoxaparin	91 (18.2)	5 (16.1)	86 (18.4)	0.13

All data are reported as frequency and percent (in parenthesis). NSAIDs: Non-steroidal anti-inflammatory drugs; PPIs: Proton pump inhibitors; IV: intravenous

There was no significant difference between the two groups with regards to lab data, except for the blood sugar (BS) levels, which were higher in the vaccinated group (p-value = 0.017). Detailed data on lab data are provided in Table 3. The length of hospital stay was significantly lower in the vaccinated group compared to the other one (p = 0.010). However, there was no significant difference between the mortality rate, the need for ICU admission, the severity of the disease, and the need for invasive ventilation between the two groups (p> 0.05) (Table 4).

Table3. Results of post-admission lab data in COVID-19 Patients Admitted to Baharloo hospital in Tehran-Iran based on influenza vaccine.

	Total (n=498)	With influenza vaccine (n=31)	Without influenza vaccine (n=467)	*P-value*
White Blood Cell count (WBC) (10^9/L)	7.48 ± 5.92	8.05 ±3.44	7.44 ±6.05	0.584
Neutrophil (percentage)	74.36 ± 11.33	74.63 ±9.17	74.35 ±11.47	0.894
Lymphocyte (percentage)	22.59 ± 48.92	19.93 ±9.24	22.77 ±50.46	0.755
Neutrophil to lymphocyte ratio (NLR)	5.26 ± 4.09	4.66 ±2.24	5.31 ±4.18	0.394
Hemoglobin (g/dL)	13.36 ± 10.12	13.19 ±1.93	13.38 ±10.44	0.920
Platelet Count (10^9/L)	199.11 ± 78.89	204.51 ±65.01	198.75 ±79.77	0.694
C-Reactive Protein(CRP) (mg/L)	47.20 ± 48.63	57.68 ±39.85	46.50 ±49.12	0.216
Erythrocyte Sedimentation Rate(ESR) (mm/hour)	55.17 ± 29.71	57.21 ±27.34	55.03 ±29.88	0.692
Blood Sugar (mg/dL)	155.16± 67.40	181.80 ±76.40	153.400 ±66.47	0.023
Blood Oxygen Saturation (%)	90.75 ± 6.49	88.67 ±10.03	90.89 ±6.17	0.066
Blood Urea Nitrogen(BUN) (mg/dL)	47.27± 30.96	44.36 ±19.02	47.46 ±31.60	0.590
Serum Creatinine (mg/dL)	1.32± 0.93	1.36 ±1.12	±0.91 1.32	0.808
Lactate Dehydrogenase(LDH) (unit/L)	590.76± 314.90	687.43 ±375.99	±309.83 584.34	0.078

Table 4. Different outcome in COVID-19 Patients Admitted to Baharloo hospital in Tehran-Iran based on influenza vaccine.

	Total (n=498)	With influenza vaccine (n=31)	Without influenza vaccine (n=467)	*P-value*
Severity at time of hospitalization[1]	86 (17.26)	6 (19.35)	80 (17.13)	0.218
Mortality	103 (20.7)	7 (22.6)	96 (20.6)	0.388
ICU admission	158 (31.7)	12 (38.7)	146 (31.3)	0.788
Ventilation	143 (28.7)	12 (38.7)	131 (28.1)	0.204
Invasive ventilation	73 (14.7)	6 (19.4)	67 (14.3)	0.445
The average(mean) number of days that patients spend in hospital (the median of hospital stay days)	6 (7)	6 (6)	9 (13)	0.010

[1]Patinets who need ICU admission at time of hospitalization were defined as severe.
All data are reported as frequency and percent (in parenthesis), except for length of hospitalization which is reported as mean and as median (in parenthesis)

Discussion

Many studies have shown that using the flu vaccine can reduce the risk of COVID-19 infection (6-8), as well as reduce mortality and adverse outcomes in COVID-19 patients (8-10). A study with a sample size of 92,000 cases in Brazil showed that patients with COVID-19 who had received the influenza vaccine even after the onset of COVID-19 symptoms had lower mortality and less need for intensive care (11). Additionally, an Italian study has shown an inverse relationship between the coverage rates of the influenza vaccination and the severity of clinical expression of COVID-19 (12). Also, another research which was operated by Zanettini and his colleagues, demonstrated that vaccinating the elderly was associated with a reduction in COVID-19 mortality by 28 percent (13). A case-control study established by Massoudi et al., has also shown the possible protective effect of the influenza vaccine against COVID-19 (6). Additionally, a study based on the EPICOVID19 survey demonstrated that influenza and pneumococcal vaccination might promote the immune response in the elderly and therefore potentially reduce the risk and severity of other infections, including COVID-19 (7). By contrast, a study which was operated by Cowling and his colleagues demonstrated that patients who had received the influenza vaccine had a higher risk of getting infected by non-influenza respiratory viruses (NIRV) (14). Moreover, studies by Sundaram et al., showed that there is no association between influenza vaccination and the risk of RSV, adenovirus, human Metapenoma virus, human rhinovirus, or coronavirus (15).

Influenza vaccine can reduce the severity of COVID-19 infection in various ways. Co-infections in COVID-19 patients are associated with higher rates of unfavorable outcomes and death (16-18). Thus, preventing the occurrence of influenza and COVID-19 co-infection has been suggested as a possible mechanism for influenza vaccination (18).

Furthermore, cross-reactivity and cross-protection are also two possible hypotheses for the protective effects of the influenza vaccine against the COVID-19 virus (7). Both viruses are enveloped RNA-virus and have the same cell entrance and transmission pathway (19). The influenza vaccine may have a potential protective effect via boosting the innate immunity and increasing the production of TNF-α and IL-6 (11,20,21).

The main purpose of this study was to evaluate the prevalence of influenza vaccination in patients with COVID-19 and to compare the length of hospitalization, the mortality, and the severity of disease in COVID-19 patients who had received influenza vaccine versus unvaccinated ones. In this study, results showed that length of hospital stay was lower in the vaccinated group, although no between-group difference was detected in mortality rate, the need for ICU admission and invasive ventilation, and disease severity.

A longer length of hospital stay was observed in the unvaccinated patients in our study. However, we are aware that this study has certain limitations that have to be taken into consideration. One of the most important limitations is the low number of vaccinated patients against influenza compared to the unvaccinated group (31 versus 469), which might lower the accuracy of this study to detect the other significant outcomes such as mortality and the need for ICU admission. These findings may also imply the low coverage of influenza vaccination in Iran and the lack of national vaccination program for annual influenza vaccination. Therefore, the results should be interpreted with caution.

 In addition, influenza vaccination, on the community level, has an impact on the severity of COVID-19 infection even in unvaccinated patients, although the effects of influenza vaccination may differ depending on the population characteristics and the vaccination coverage (19). Thus, because coverage of influenza vaccination is quite low in Iran, the effects of influenza vaccination may be less prominent.

Furthermore, in this study, we investigated the outcomes of COVID-19 infection in an inpatient setting, without considering outpatient data. As influenza vaccination may attenuate COVID-19 disease course, fewer patients might require hospitalization. Thus, a more detailed investigation

in both outpatient and inpatient settings is needed to confirm the effects of influenza vaccination.

One of the other limitations of our study was that the groups were not matched regarding rates of comorbidities like hypertension and rheumatic diseases, which may affect the clinical outcome and also hospital stay.

In summary, our study provides evidence that the influenza vaccination may reduce the length of hospitalization in COVID-19 patients. These results indicate that more investigations are needed to confirm the possible effects of influenza vaccination.

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