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Relationship Between Influenza Vaccination and COVID-19 Infection among Personnel of Shahid Beheshti Hospital in Kashan, Iran

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ABSTRACT

Backgrounds: Reports show that vaccination against influenza could elicit nonspecific immune reactions against coronavirus disease-19 (COVID-19). The present research aimed to evaluate the prevalence of COVID-19 disease among the staff of Shahid Beheshti hospital in Kashan despite vaccination against influenza.

Materials & Methods: This study was performed on 1400 employees of Shahid Beheshti hospital in Kashan from February to August 2020. Personnel whose disease was confirmed by PCR test or CT scan were considered to have COVID19-. In the present research, the relationship between influenza vaccination and the incidence of COVID19- infection was evaluated. The collected data were analyzed by SPSS software Version 26.

Findings: Out of a total of 1400 hospital personnel participating in this study, 272 people were diagnosed as COVID-19. Among 272 patients, 23 (8.45%) cases were vaccinated. The average age of vaccinated patients was 33.48 ± 12.72 years, of whom 14 (60.87%) patients were female. Vaccination was significantly associated with prevention of COVID-19 infection (p< .05). The study of odds ratio (OR) to evaluate the effect of vaccination showed that the OR was 0.61 (95% CI: 0.39- 0.97). There was a significant difference in SpO2, type of treatment, and lung involvement based on CT between the two groups of vaccinated and unvaccinated COVID-19 patients (p< .05).

Conclusion: In vaccinated group, COVID19- was lower than of the no influenza vaccinated group. According to the results, the use of influenza vaccine as an effective vaccine against the new coronavirus strains could be helpful in controlling the disease.

Keywords: Influenza vaccine, COVID-19, Vaccine efficacy, COVID-19 disease severity

CITATION LINKS

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Introduction

In December 2019, a new viral infection was recorded in Wuhan city in Hubei province, central China. The causative agent was later called SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) and found to be a member of the *Coronaviridae* family, and the disease causing an ongoing pandemic was named coronaviridae disease 2019 (COVID-19). So far, COVID-19 has caused a large number of deaths and more than 90 000 confirmed cases. Accordingly, The World Health Organization (WHO) has declared COVID-19 as a public health emergency of international concern (PHEIC) [1]. COVID-19 co-infections with other respiratory pathogens are a new concern which might increase the disease symptoms and mortality. Both influenza virus A/B and SARS-CoV-2 are airborne pathogens that cause a wide range of asymptomatic/ mild to severe diseases and even death. Several studies have shown that co-infection of SARS-CoV-2 with influenza virus (type A/B) increases the severity of SARS-CoV-2 infection [2, 3].

Unfortunately, studies have reported the overlap of clinical signs of influenza virus A/B and SARS-CoV-2 infections during the COVID-19 pandemic. Coinfection with COVID-19 and flu in large populations is of great concern. Up to now, there are no COVID-19-specific strategies to improve vaccination and prevent the disease incidence. Therefore, policies to improve COVID-19 vaccination are vital to prevent the spread of SARS-CoV-2, especially among healthcare personnel who are at higher risk of SARS-CoV-2 infection. These strategies might help reduce the risk or severity of COVID-19 disease, especially among cases co-infected with influenza virus A/B and COVID-19, who are at higher risk of the disease exacerbation.

Huang et al. (2021) proposed that although the flu vaccine might confer only modest protection against SARS-CoV-2, influenza vaccine could be effective in reducing the incidence of COVID-19 co-infection with influenza [4]. In a study by Taghioff et al. (2021) on the impact of the flu vaccine on patients with COVID-19, patients vaccinated against influenza were shown to have significantly fewer signs, such as sepsis, acute myocardial infarction, dehiscence, thrombosis, etc [5]. In another study in Brazil in 2020, the results showed that the flu vaccine could be used as an adjuvant during the COVID-19 pandemic in Brazil. They reported that invasive ventilation, chance of ICU admission, and death were significantly lower in vaccinated COVID-19 patients [6]. The results of various studies confirm the effectiveness of influenza vaccination in reducing the severity of COVID-19 infection [6-10]. On the contrary, studies by Martínez-Baz et al. (2020) and Kissling et al. (2021) have indicated that the flu vaccine could not induce a significant protection against SARS-CoV-2 infection [11, 12].

Previous studies suggest that the flu vaccine might decrease the risk of developing COVID-19 disease. Furthermore, considering that influenza vaccines are now accessible in developing countries, vaccination might be a safe and rapid choice to reduce the prevalence of COVID-19 infection. Given that few studied have investigated the effect of the flu vaccine on COVID-19 patients in Kashan, Iran, evaluating the association between influenza vaccination and the incidence of COVID-19 infection in this region seems to be of great importance.

Objectives: This study aimed to analyze COVID-19 cases in Kashan, Iran in 2020 and to compare vaccinated and unvaccinated patients against influenza in terms of duration of hospitalization, duration of absence from work, severity of the disease, percentage of blood oxygen saturation, and

presence of underlying diseases.

Materials and Methods

Patients and study design: This analytical cross-sectional research was carried out on 1400 personnel of Shahid Beheshti hospital in Kashan, Iran (including nurses, paramedics, maids, interns, assistants, and doctors) from February to August 2020. These personnel had contact with COVID-19 infected patients. This study was approved by the Ethics Committee of Kashan University of Medical Sciences (approval number: IR.KAUMS.MEDNT.REC.1400.150).

Study protocol: The list of the hospital personal infected with COVID-19 as well as the names of those who received the Netherlands-made flu vaccine by the hospital's vaccination unit in 2018 were obtained from the nursing and management office. Detailed information was obtained from patients' hospitalization files archived in the hospital's medical records center. Data extracted from electronic medical records included demographic and clinical variables. The exclusion criterion was the incompleteness of people's files. Participants' COVID-19 disease was proven and considered positive based on throat swab test, real-time PCR method, or lung involvement (by CT scan). The required information was obtained through phone calls and medical files in case of hospitalization. Vaccinated and unvaccinated COVID-19 patients were examined in terms of type of treatment, length of hospitalization, length of absence from work, severity of the disease, percentage of blood oxygen saturation (SpO_2), and presence of underlying diseases. The information was checked for accuracy. The vaccination and disease statuses of the study participants are shown in Figure1.

Statistical analysis: Descriptive statistics and inferential statistics were analyzed

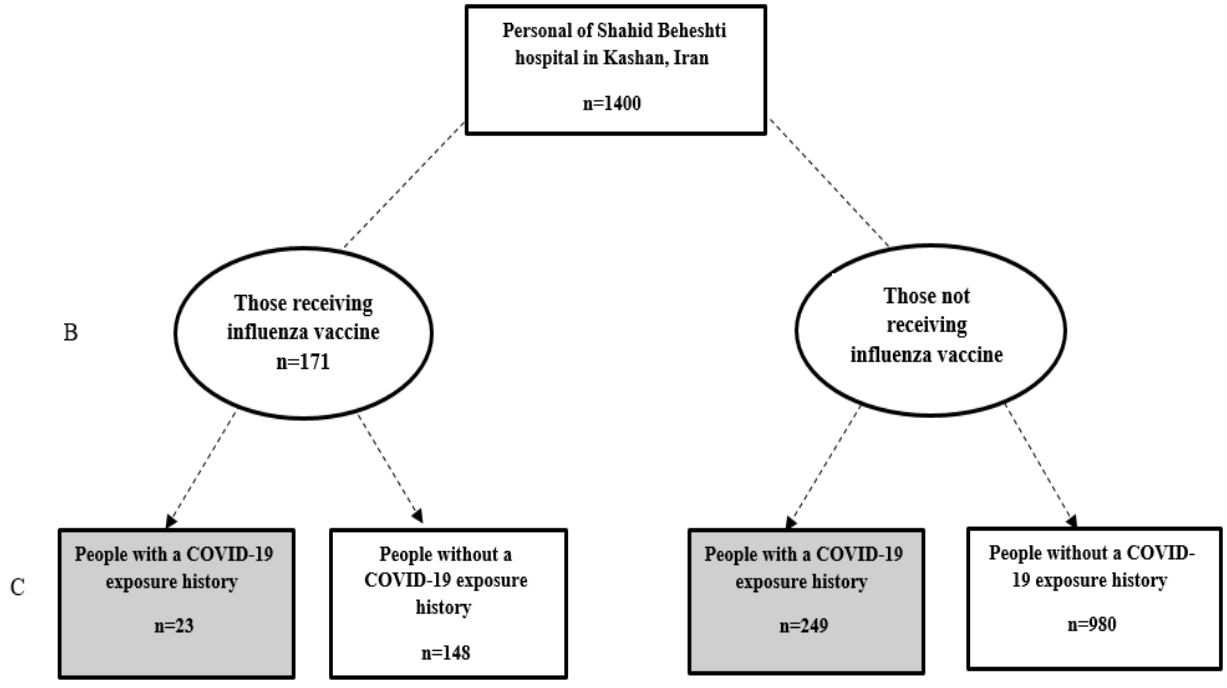

Figure 1) Patient selection among 1400 personal of Shahid Beheshti hospital in Kashan, Iran: 171 personnel received influenza vaccine, and 1229 personnel did not receive influenza vaccine. In the vaccinated group, 23 people were with a COVID19- exposure history, and 148 people were without a COVID19- exposure history. In the unvaccinated group, 249 people were with a COVID19- history, and 980 people were without a COVID19- exposure history.

by SPSS software Version 26. Qualitative variables were compared by Chi-square test, and quantitative variables were compared using student's t-test. The significance level was considered at *p*-value < .05.

Findings

Demographic and epidemiological characteristics: This study was conducted on 1400 hospital personal, of whom 272 (19.43%) cases were infected with COVID-19. Among 1400 personal, 12.21% (n=171) were vaccinated, and 87.78% (1229) were unvaccinated. The COVID-19 patients participating in the study had a positive PCR test or a positive chest CT scan. About 8.45% (23 of 272) of the participants with COVID-19 received an influenza vaccine between February to August 2020, while 91.55% (249 of 272) of the COVID-19 infected participants were not vaccinated against influenza, they were selected as a comparison group in this investigation. The odds ratio (OR) of developing COVID-19 for vaccinated personnel was 0.61 times that of unvaccinated personnel (95% CI: 0.39–0.97). Unvaccinated personnel were significantly more infected with COVID-19 (*p*-value< .05) compared to vaccinated personnel. The study participants' demographic information is shown in Table 1. The range age was 33.48±12.72 years for vaccinated COVID-19 patients (n=23) and 34.77±10.38 years for unvaccinated patients (n=249). The majority of vaccinated COVID-19 patients (14 of 23, 60.87%) were female, while the majority of unvaccinated patients (128 of 249, 51.4%) were male. There was no significant difference in gender between the two groups of vaccinated and unvaccinated COVID-19 patients (*p*= .06). **Characteristics of underlying diseases**: The underlying diseases of COVID-19 patients in both groups were analyzed. No significant difference was found between the two groups in terms of underlying

Table 1) Clinical and demographic characteristics of COVID-19 in the study population

Variable		Vaccinated Mean±SD/N(%)	Unvaccinated Mean±SD/N(%)	*P*-Value*
Total		23(8.45)	249 (91.55)	--
Age		33.48±12.72	34.77±10.38	.76
Gender	Male	9 (39.13)	128 (51.4)	.06
	Female	14 (60.87)	118 (47.39)	
Underlying diseases		2 (8.69)	12 (4.82)	.35
Length of hospital stay		8±2.6	8.47±3.31	.81
Patients group	Outpatient	22 (95.65)	219 (87.95)	.001
	Inpatient	1 (4.35)	30 (12.05)	
SpO_2	93%>	21 (91.31)	199 (79.92)	.04
	93%<	2 (8.69)	50 (20.08)	
Lung involvement based on CT		8 (34.78)	128 (51.4)	.01
Duration of absence from work (days)		10.88±5.3	14±4.56	0.06

diseases (Table 1). Among vaccinated and unvaccinated patients, 2 (8.69%) and 12 (4.82%) patients had underlying diseases, respectively. Among the vaccinated patients, 2 patients had hypertension and asthma disease, and the remaining 21 patients had no underlying diseases. Among patients not receiving the flu vaccine, 1.2% had asthma disease, 1.2% used immunosuppressive drugs, 0.8% suffered from diabetes mellitus and ischemic heart disease, and 0.4% had hypertension.

Patients groups: There was a significant difference in the type of treatment (outpatient or inpatient) between vaccinated and unvaccinated COVID-19 patients (p< .001) (Table 1). Inpatient treatment was more common among unvaccinated patients (n=30, 12.05%) compared to vaccinated patients (n=1, 4.35%).

Determining the average blood oxygen saturation (SpO_2): Among vaccinated and unvaccinated patients, 8.6% (n = 2) and 20.08% (n = 50) had SpO_2< 93%, respectively. The results showed that SpO_2< 93% was significantly more prevalent among unvaccinated individuals in comparison with participants that received influenza vaccine (p-value = .04).

Determining the lung involvement: In the vaccinated group, only 8 out of 23 (34.78%) patients were positive for lung involvement based on CT scan results, while in the unvaccinated group, 128 out of 249 (51.4%) patients were positive for lung involvement (Table 1). Lung involvement based on CT scan results was significantly more common among unvaccinated COVID-19 patients (p-value = .01).

Determining the average length of hospitalization: The length of hospital stay was 8 days for vaccinated patients and 8.47±3.31 days for unvaccinated patients. There was no statistically significant difference in the length of hospital stay between vaccinated and unvaccinated COVID-19 patients.

Determining the duration of absence from work: The duration of absence from work due to COVID-19 disease was lower for vaccinated patients compared to unvaccinated individuals (10.88±5.3 days vs. 14±4.56 days).

Discussion

Today, prevention and treatment strategies are hot topics during the COVID-19 pandemic. According to the findings of various studies, co-infection of COVID-19 with influenza could aggravate the patient's condition and in some cases even cause death [13]. Considering the emerging COVID-19 pandemic, it is necessary to manage COVID patients. There are some challenges to vaccination against SARS-CoV-2 infection. The main challenges to vaccination among different segments of the population are diverse and include vaccine hesitancy, safety concerns, and lack of access. It has been reported that those who have previously received influenza vaccine experience milder COVID-19 infection. This is because the flu vaccine, which is both available and safe, induces immune responses which cross-react with SARS-CoV-2 [14].

Some articles have confirmed that influenza vaccination could improve outcomes of COVID patients and reduce the burden of the flu [15, 16]. Furthermore, the WHO recommends influenza vaccination for different groups. As a result, the use of this vaccine as a bystander adjuvant is recommended to reduce the seriousness of COVID-19 disease. Thus, in this study, the relationship between influenza vaccination and the incidence of COVID-19 infection was investigated among the personnel of Shahid Beheshti hospital in Kashan.

The results propose that influenza vaccination is associated with better

outcomes in vaccinated patients compared with unvaccinated patients. This study results showed an association between influenza vaccination and the prevalence of COVID-19 infection, which was significantly higher among unvaccinated personnel. By comparing personnel receiving the flu vaccine with those not receiving the flu vaccine, it was found that the incidence rate of COVID-19 disease was significantly lower in the vaccinated group. Influenza vaccination decreased the odds of developing COVID-19 disease in the vaccinated group compared to the unvaccinated group.

According to the findings, the flu vaccine appears to confer protection against SARS-CoV-2 infection. These results suggest that the flu vaccine might prompt nonspecific immune reactions in vaccinated people, which could protect them against SARS-CoV-2 infection. These findings are in agreement with the results of an American study by Huang et al. (2021), reporting the lowest incidence rate and severity of SARS-CoV-2 infection among older adults receiving the flu vaccine [4].

These results are also in line with previous data indicating that influenza vaccination might decrease the incidence rate of COVID-19 infection [17]. Lung involvement was observed in 34.87% of vaccinated COVID-19 patients and 51.4% of unvaccinated patients in this study. Therefore, the prevalence of lung involvement was higher among unvaccinated COVID-19 patients, and this difference was statistically significant (p= .01). In their study, Kalantari et al. (2021) found no significant difference in lung involvement between vaccinated and unvaccinated patients; but they found that the disease symptoms were less in the vaccinated group [18].

According to the obtained data, the prevalence of SpO_2 <93% was significantly higher among unvaccinated COVID-19 patients; thus, receiving influenza vaccination was related to a significant increase in SpO_2 (p= .04). These data are in line with the findings of another study reporting a significant difference in SpO_2 levels between the vaccinated and unvaccinated groups [19]. In this study, inpatient treatment was more common among unvaccinated patients (12.05%) compared to vaccinated patients (4.35%), and this difference was statistically significant (p= .001).

A study by Skowronski et al. (2020) found no protective effect for influenza vaccine against COVID-19 disease [20].

In this study, there was no significant difference between the two groups of COVID-19 patients in terms of age, gender, underlying diseases, length of hospital stay, and duration of absence from work. Differences in the results of various studies could be attributed to differences in vaccine types, health status, heterogeneous populations, the onset of breakthrough infections, and the proactive attitude of individuals towards COVID-19 infection [21]. Influenza vaccine could benefit immune system function and play a logically positive role in preventing the incidence of COVID-19. Hypothetically, different mechanisms might describe the protective effects of the flu vaccine against COVID-19. The first mechanism is that influenza vaccination induces nonspecific immune responses that contribute to protection against SARS-CoV-2. The second mechanism is the generation of an enhanced cytokine response after the stimulation of the immune system with SARS-CoV-2. Additionally, a robust association has been reported between influenza H1N1-specific CD4 T-cell responses and SARS-CoV-2. Another reason is the possible similarities in binding receptors and structure of influenza and coronaviruses [21]. Although there are different studies, there is still much incredulity regarding the impact of

the flu vaccine on the outcomes of COVID-19 patients.

Thus, in this study, the relationship between influenza vaccination and the incidence of COVID-19 infection was investigated among the personnel of Shahid Beheshti hospital in Kashan during 2020. Although some significant associations were found in this study, more studies are needed to accurately evaluate the relationship between COVID-19 and influenza vaccination. To make a more definitive opinion about the protective role of the flu vaccine, more studies with larger sample sizes are needed. It is also recommended to conduct more studies in different geographical areas to obtain more accurate results.

Limitations: Conducting this study in Kashan was the strong of this research. The limitations of this study were as follows: this study was a single-center research conducted with a small sample size; in addition, the need for ICU admission, mortality, and laboratory findings were not evaluated.

Conclusion

According to the findings, people receiving the flu vaccine were significantly less likely to test positive for SARS-CoV-2 than people not receiving the flu vaccine.

Meanwhile, the findings showed significantly better clinical outcomes (oxygen saturation, length of hospitalization, and lung involvement based on CT) in patients who received the flu vaccine.

Overall, these findings suggest that influenza vaccination might lessen the burden of COVID-19 disease during the pandemic. Further clinical and epidemiological studies are essential to investigate how influenza vaccination affects COVID-19 in order to plan for influenza vaccination in the future. Also, due to people's fear of the unknown side effects of COVID-19 vaccines, which has become an excuse for not using COVID-19 vaccines, the influenza vaccine which has long been known to be effective could be suggested.

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Ethical permissions: The present research was approved by the Ethics Committee of Kashan University of Medical Sciences (IR.KAUMS.MEDNT.REC.1400.150).

Consent to participate: All experiments that involved human participants were performed according to the ethical standards of the Institutional and National Research Committee.

Availability of data and materials: The obtained results in the present research are available upon direct request from the authors.

Conflicts of interests: The authors have no competing interest to declare.

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Authors' contributions: All authors contributed equally.

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