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Influenza Vaccine and COVID-19 Pandemic: Could This Vaccine Help Limit the Potential Adverse Consequences of SARS-CoV-2?

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Abstract

The COVID-19 pandemic has prompted researchers to find treatments and vaccines to control SARS-CoV-2. There are some hypotheses about the benefit of respiratory virus vaccines, like MMR, for COVID-19 pneumonia severity, morbidity, and mortality. The influenza vaccine is one of the most frequently used respiratory virus vaccines covered by one of the Iranian insurance institutes. We have a symmetrical group of participants that have received this vaccine that could be compared with each other. We compared 3,379 persons aged 20 - 75 years for the effect of the influenza vaccine on COVID-19 mortality. We ultimately found that it does not affect mortality caused by COVID-19 pneumonia, but it can decrease the hospitalization cost in people over 65 years with a history of chronic disease.

Keywords: COVID-19, Influenza, Vaccine, Pneumonia, Mortality

1. Background

A novel coronavirus named Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), first reported in December 2019, has spread worldwide (1). Almost five million deaths have been reported from over 250 million positive cases by November 6, 2021. Coronaviruses (CoVs) mainly spread through respiratory droplets released from the saliva and mucus secretions from the mouth and nose during coughing, laughing, talking, breathing, sneezing, and singing (2). These virus droplets may have access to the body mainly via the nose, mouth, and eyes but not via the intact skin (3). Although SARS-CoV-2 is less lethal than the two earlier coronaviruses, SARS and MERS, it is more contagious (4).

The COVID-19 deaths are primarily attributed to respiratory failure caused by the cytokine storm, possibly due to the over-stimulation of the immune system (5). Many patients who die from SARS-CoV-2 respiratory infection have had concomitant infections or comorbidities (6). There is no effective and approved treatment for this respiratory infection. Prevention of other respiratory pathogen infections would help decrease COVID-19 infection mortality (7, 8).

Various COVID-19 resistance rates have been reported among different age groups. Infection rates were lower among children than among adults and elders. Though the mechanism for different severities and infection susceptibilities is unknown, this could be due to different quantities and qualities of the immune efficiency due to recent or previous vaccinations and infections.

2. Objectives

It appears that people in geographical locations with a high MMR vaccination rate have a lower COVID-19 death rate (9). There is also evidence that 955 sailors from the USS Roosevelt tested positive for the Coronavirus. The sailors exhibited milder symptoms, which may have been because all US Navy recruits must receive the MMR vaccine (10). Similarly, influenza vaccination may play a role in decreasing SARS-CoV-2 infection mortality. Our study tests this hypothesis.

3. Methods

The study population consisted of all insured individuals by one of the basic national health insurance organizations of the Islamic Republic of Iran, which covers flu vaccine administration for the insured according to eligibility criteria. This prospective study was conducted between August 2020 and February 2020. First, information about the people covered by this organization was extracted from relevant and reputable databases. In total, 21,071 persons aged 20 - 75 years were randomly selected from the list of insured persons covered by the mentioned insurance organization. Among them, 19,293 persons formed the study sample. Via three phases of short message service (SMS) notification, all of the individuals were asked to answer the questions by referring to the electronic portal of the insurance organization. During 30 days of the data collection phase, 3,435 persons referred to the announced electronic portal and completed the questionnaire. The accuracy of the answers was checked by calling the respondents. Therefore, individuals were divided into two general groups in this study: Vaccinated and non-vaccinated. This research utilized a researcher-made questionnaire of multiple-choice questions.

The questionnaires were reviewed and refined. Extra information on demographic data and costs of 3,379 people were also extracted from the organization's databases, including gender, age, geographical area of residence, the total number of visits to medical centers, the total cost of treatment, frequency of inpatient services use, and the total cost of inpatient services during the study period.

4. Results

In this study, 1,172 people who had been vaccinated against the flu were compared with 2,207 people who had not been vaccinated. The two groups were matched for age and gender. However, the vaccinated people were older on average and had more frequent comorbidities (Table 1).

Comparing the two groups in terms of COVID-19 diagnosis and mortality rates did not show any statistically significant difference (Table 2).

A comparison of the dead and living groups showed that studied population were older and, unexpectedly, the percentage of females was higher in the dead group. People with malignancy treated with immunosuppressants and chemotherapy, asthma, and chronic respiratory disease were more likely to die. There were fewer cases in the group of dead people with a history of exposure to chemical gases (Table 3).

In terms of COVID-19 infection, the history of chronic respiratory diseases, in particular asthma, history of exposure to chemical gases, and history of cardiovascular diseases were significantly correlated to the greater risk of COVID-19 infection, as noted in Table 4. Diabetes was marginally higher in the infected group.

More extensive analyses demonstrated that a history of cardiovascular disease increased the risk of COVID-19 infection by about 1.5 times [OR = 1.48 (1.02 - 2.15), P = 0.04]. A history of diabetes also increased the COVID-19 infection by 40% [OR = 1.38 (0.96 - 1.99), P = 0.08]. Also, a history of bronchiectasis and COPD increased the risk of COVID-19 by 2.9 and 2.1 times, respectively. A separate analysis of vaccinated and non-vaccinated groups did not yield new results.

An analysis was done separately in groups with and without underlying chronic disease. Out of 1,476 people who did not have a chronic disease, 47 (3.2%) had COVID-19, while it was 86 out of 1787 (4.5%) in people who had at least one chronic disease (P = 0.02). Multivariate analysis showed that only gender and age had independent effects on mortality, and interestingly, women were more likely to die. A history of influenza vaccine showed no impact on mortality.

Multivariate analysis of factors affecting COVID-19 showed that these factors did not significantly impact the disease, except for chronic respiratory diseases, which showed a partially independent effect.

Analysis of factors affecting health costs showed that total costs were higher in the vaccinated group because these people were at high risk, were older, and needed greater demands. However, hospitalization and imaging costs were non-significantly lower in the vaccinated group.

A separate analysis of hospitalization and imaging costs (type 1 cost) and the costs of visits, tests, and drugs (type 2 cost) in the group with a history of special disease showed the following results in Table 8.

In other words, influenza vaccination in people with a history of at least one chronic disease significantly reduced the costs of hospitalization and radiology by 110 million Rials per patient per year. However, it increased the outpatient costs by an average of five million Tomans per patient per year. Altogether, vaccination would save 60 million Rials per patient per year.

5. Discussion

Contrary to current information on sex differences in COVID-19 hospitalization and mortality, the percentage of female mortality was higher in our study, possibly because of men's health status (11). Mortality and morbidity from COVID-19 are higher among cancer patients because of the clinical challenges of cancer management, including immunosuppression, aging, and comorbidities (12). This agrees with our report and national studies in the UK (13)

Table 1. Specifications of Vaccinated and Non-vaccinated Groups [a]

Variables	Vaccinated (N = 1172)	Non-vaccinated (N = 2207)	P-Value
Age (mean ± SD)	58.2 ± 9.8	57.1 ± 10.7	0.004
Male gender	1082 (92.3)	1910 (86.5)	0.0001
Diabetes	385 (32.8)	578 (26.2)	0.0001
CV events history	374 (31.9)	461 (20.9)	0.0001
Hypertension	434 (37.0)	608 (27.5)	0.0001
Malignancies	53 (4.5)	48 (2.2)	0.0001
Organ transplantation	30 (2.6)	18 (0.8)	0.0001
Immunosuppressive therapy	127 (10.8)	113 (5.1)	0.0001
Current chemotherapy	48 (4.1)	41 (1.9)	0.0001
Asthma	67 (5.7)	55 (2.5)	0.0001
COPD	53 (4.5)	25 (1.1)	0.0001
Chemical gas exposure	439 (37.5)	493 (22.3)	0.0001
Morbid obesity	42 (3.6)	63 (2.9)	0.24

[a] Values are expressed as No. (%) unless otherwise indicated.

Table 2. Comparison of Outcomes in Vaccinated and Non-vaccinated Groups [a]

Variables	Vaccinated (N = 1172)	Non-vaccinated (N = 2207)	P-Value
Mortality	7 (0.6)	17 (0.8)	0.67
COVID-19 diagnosis	51 (4.5)	82 (3.8)	0.35

[a] Values are expressed as No. (%).

Table 3. Analysis of Variables in Dead and Living Groups [a]

Variables	Dead (N = 24)	Living (N = 3354)	P-Value
Age (mean ± SD)	62.9 ± 15.8	57.4 ± 10.4	0.01
Male gender	17 (70.8)	2974 (88.7)	0.01
Diabetes	8 (33.3)	955 (23.5)	0.65
CV events history	7 (29.2)	827 (24.7)	0.61
Hypertension	7 (29.2)	1034 (30.8)	0.86
Malignancies	2 (8.3)	99 (3.0)	0.12
Organ transplantation	0	48 (1.4)	-
Immunosuppressive therapy	4 (16.7)	236 (7.0)	0.07
Current chemotherapy	2 (8.3)	87 (2.6)	0.08
Asthma	3 (12.5)	119 (3.5)	0.05
COPD	2 (8.3)	76 (2.3)	0.05
Chemical gas exposure	2 (8.3)	930 (27.7)	0.03
Morbid obesity	1 (4.2)	104 (3.1)	0.76
Recent influenza vaccination	7 (29.2)	1164 (34.7)	0.67
COVID-19 diagnosis	2 (8.3)	131 (3.9)	0.43

[a] Values are expressed as No. (%) unless otherwise indicated.

and Sweden (14). Asthma and chronic respiratory disease are associated with a risk of severe disease and mortality in COVID-19 infection.

Contrary to expectations, a history of exposure to chemical gases had the opposite effect on mortality. Several reasons can explain this. First, these people in the country are under the constant support of treatment and examination throughout their lives and are treated with the slightest change in their condition. Second, these fragile individuals may have been more careful and taken more stringent preventive measures, as previously reported (15). Third, general quarantine applied for most of the study period resulted in a significant reduction in air pollution (16), which is known to promote the exacerbation of lung disease (17), including COVID-19 exacerbation (18).

A further examination showed that a history of cardio-

Table 4. Analysis of Univariate Factors Associated With COVID-19 [a]

Variables	COVID-19 diagnosis (N = 133)	No COVID-19 diagnosis (N = 3180)	P-Value
Age (mean ± SD)	57.5 ± 10.4	57.5 ± 10.8	0.95
Male gender	115 (86.5)	2820 (88.7)	0.43
Diabetes	47 (35.3)	902 (28.4)	0.08
CV events history	43 (32.3)	775 (24.4)	0.04
Hypertension	44 (33.1)	987 (31.0)	0.62
Malignancies	2 (1.5)	98 (3.1)	0.30
Organ transplantation	2 (1.5)	44 (1.4)	0.91
Immunosuppressive therapy	13 (9.8)	221 (6.9)	0.21
Current chemotherapy	5 (3.8)	84 (2.6)	0.43
Asthma	10 (7.5)	108 (3.4)	0.01
COPD	6 (4.5)	70 (2.2)	0.08
Chemical gas exposure	62 (46.6)	846 (26.6)	0.0001
Morbid obesity	4 (3.0)	100 (3.1)	0.93
Recent influenza vaccination	51 (38.3)	1094 (34.4)	0.35

[a] Values are expressed as No. (%) unless otherwise indicated.

Table 5. Multivariate Analysis

Variables	B	S.E.	Wald	df	Sig.	Exp(B)
Gender Code	0.962	0.481	4.001	1	0.045	2.618
Age	-0.045	0.020	5.092	1	0.024	0.956
COVID-19	0.030	0.614	0.002	1	0.961	1.030
Diabetes	-0.151	0.477	0.100	1	0.752	0.860
CV events history	0.015	0.253	0.003	1	0.953	1.015
Hypertension	0.139	0.170	0.672	1	0.412	1.149
Malignancies	-0.104	0.226	0.212	1	0.645	0.901
Immunosuppressive therapy	-0.174	0.122	2.031	1	0.154	0.840
Morbid obesity	-0.025	0.158	0.026	1	0.872	0.975
Current chemotherapy	-0.093	0.114	0.660	1	0.416	0.911
Asthma	-10.130	0.697	2.629	1	0.105	0.323
COPD	-0.441	0.457	0.932	1	0.334	0.643
Bronchiectasis	-0.066	0.238	0.076	1	0.782	0.936
Recent influenza vaccination	0.472	0.481	0.9 65	1	0.326	1.604
Constant	5.422	1.884	8.280	1	0.004	226.222

Table 6. Multivariate Analysis of Factors Affecting COVID 19

Variables	B	S.E.	Wald	df	Sig.	Exp(B)
Gender Code	-0.236	0.264	0.800	1	0.371	0.790
Age	-0.003	0.009	0.093	1	0.761	0.997
Diabetes	0.274	0.199	1.895	1	0.169	1.315
CV events history	0.157	0.103	2.303	1	0.129	1.170
Hypertension	-0.032	0.069	0.210	1	0.647	0.969
Malignancies	-0.272	0.190	2.039	1	0.153	0.762
Immunosuppressive therapy	0.048	0.063	0.585	1	0.444	1.049
Morbid obesity	-0.040	0.076	0.279	1	0.598	0.961
Current chemotherapy	0.065	0.064	1.054	1	0.305	1.067
Asthma	0.651	0.372	3.068	1	0.080	1.918
COPD	0.109	0.247	0.194	1	0.659	1.115
Bronchiectasis	0.139	0.105	1.743	1	0.187	1.149
Recent influenza vaccination	0.076	0.189	0.160	1	0.689	1.079
Constant	-2.889	.744	15.094	1	0.000	0.056

Table 7. Analysis of Factors Affecting Health Costs

Variables and History of Influenza Vaccination	N	Mean	Std. Deviation	Std. Error Mean	P-Value
Hospitalization cost (2018) (IRR)					0.65
No	399	63018760.95	86640905.370	4337470.499	
Yes	266	59963221.65	85304220.930	5230337.368	
Radiography cost (2018) (IRR)					0.59
No	1376	3382072.71	18886186.190	509137.458	
Yes	833	2977903.70	13162817.280	456064.588	
Visit cost (2018) (IRR)					0.000
No	2107	2795952.34	2587397.137	56367.766	
Yes	1146	3920477.52	3094557.972	91412.653	
Drug cost (2018) (IRR)					0.000
No	2109	12990007.85	39511805.730	860376.596	
Yes	1160	18511311.80	30730340.820	902273.874	
Test cost (2018) (IRR)					0.000
No	1674	2688451.36	3433791.621	83925.939	
Yes	1006	3323310.68	3814911.935	120277.814	
Total cost (2018) (IRR)					0.000
No	2152	37354303.48	76796865.440	1655473.986	
Yes	1160	47597349.75	68692286.050	2016874.965	
Hospitalization cost (2019) (IRR)					0.57
No	409	73205548.95	103935971.800	5139303.045	
Yes	259	68820241.44	85692080.710	5324646.814	
Radiography cost (2019) (IRR)					0.92
No	1376	3653143.92	17321328.270	466951.716	
Yes	822	3579883.44	13020608.450	454145.871	
Visit cost (2019) (IRR)					0.000
No	1621	3053668.89	3601901.951	89462.366	
Yes	974	3600435.67	3492060.379	111892.832	
Drug cost (2019) (IRR)					0.000
No	2109	3105911.54	3014019.966	65630.821	
Yes	1151	4392823.41	3735317.527	110100.645	
Test cost (2019) (IRR)					0.000
No	2131	17022517.77	45322908.140	981806.818	
Yes	1165	23054263.10	43907170.020	1286389.491	
Total cost (2019) (IRR)					0.001
No	2167	44843601.72	92737312.830	1992163.835	
Yes	1166	56165027.27	83170966.850	2435692.590	

Table 8. Comparison of Cost of Vaccinated and Non-vaccinated Groups

Variables	Vaccinated	Non-vaccinated	P-Value
Type 1 cost for disease group (IRR)	78'953'947	99'928'242	0.08
Type 2 cost in disease group (IRR)	36'972'762	31'558'206	0.01
Type 1 cost in disease-free group (IRR)	70'946'484	65'529'560	0.69
Type 2 cost in disease-free group (IRR)	25'822'055	21'886'501	0.40

vascular disease increased the risk of COVID-19 infection by 1.5 times because of the COVID-19 effect on the cardiovascular system, which increased the risk of cardiovascular events (19).

5.1. Conclusion

A history of influenza vaccine showed no effect on mortality caused by COVID-19 pneumonia. However, it decreased hospitalization costs in people over 65 years with a history of at least one chronic disease.

Footnotes

Authors' Contribution: Study concept and design, R. M., and A. K.; Analysis and interpretation of data, A. K., and H. F.; Drafting of the manuscript, H. F.; Critical revision of the

manuscript for important intellectual content, R. M., F. A., and M. A.; Statistical analysis, A. N. and V.A.

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