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The Relationship of COVID-19 Morbidity and Mortality with the History of Influenza Vaccination

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Abstract

Background: COVID-19 is currently the leading global health issue. Low- and middle-income countries (LMICs) face challenges in supplying COVID-19 vaccines. To assess an adjunctive preventive measure for COVID-19 burden, we aimed to evaluate the relationship of influenza vaccination in the previous year with outcomes of COVID-19 in affirmed cases after adjustment for relevant factors.

Methods: This prospective study was conducted using the provincial registry of confirmed COVID-19 cases in East-Azerbaijan province in North-West of Iran. The main outcomes were COVID-19 mortality and hospitalization. The influenza vaccination history in 2019 was collected by phone calls. Data analysis was done by SPSS software version 16, separately for healthcare workers and the general population. The logistic regression model was applied to compare the covariates in influenza vaccinated versus unvaccinated patients.

Results: From 1 March to 10 October 2020, 17,213 positive COVID-19 cases were registered, of which 916 patients were included. A total of 88 patients (9.6%) deceased due to COVID-19. Two hundred subjects (21.8%) reported receiving the influenza vaccine during the past year. Healthcare workers had a significantly higher vaccination rate than the general population (28.9% vs. 7.1%; $p<0.001$). After adjustment for socioeconomic and health covariates, the vaccinated cases in the general population had 84% lower odds of death (OR: 0.16; 95%CI: 0.05-0.60; $p=0.017$). In multivariate analysis, the influenza vaccination history in the previous year was not significantly related to the lower COVID-19 hospitalization rate.

Conclusion: The flu vaccination rate was not optimal in our community. The flu vaccination can be an independent preventing factor for COVID-19 mortality in the general population. The influenza vaccine can be considered as an effective adjutant preventive countermeasure for the COVID-19 burden.

Keywords: COVID-19, Vaccines, Influenza, SARS-CoV-2, Mortality

Conflicts of Interest: None declared
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Introduction

In December 2019, the emergence of COVID-19 (Corona Virus Disease 2019), a disease by a novel coronavirus termed SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), was detected in Wuhan, China, and has

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↑What is "already known" in this topic:
Currently, less than one-third of the world population is fully vaccinated against COVID-19. Developing countries have lower COVID-19 vaccination rates and the vaccine supply is a challenge for them.

→What this article adds:
Past-year influenza vaccine can be an effective adjutant countermeasure for COVID-19 mortality in the general population, with 84 percent lower odds of COVID-19 death in flu vaccinated versus unvaccinated cases. The flu vaccine can be a more available preventive measure for less developed countries.

spread out throughout the world (1). The COVID-19 pandemic is currently the leading global health issue due to high infectivity and mortality (2-4). By 20 September 2021, more than 228 million confirmed cases of COVID-19, including 4,679,099 deaths, were reported worldwide and are still increasing (5). COVID-19 cases vary in clinical presentation from asymptomatic to life-threatening lung injury (2), and mainly affect the elderly and patients with comorbidities, such as diabetes, obesity, cardiovascular, respiratory, renal, and lung diseases (1).

Currently, several vaccines against COVID-19 are developed, and mass vaccination is delivered in many countries. Up to 20 September 2021, globally 31.9% and 11.7% of the population are fully and partially vaccinated against COVID-19, respectively (5). In the USA, 54% of the population is fully vaccinated against COVID-19. However, according to the data from Iran's ministry of health, by the same date, only 14.4 million people (16.9% of the population) were fully vaccinated with two doses of COVID-19 vaccines and 17 million subjects received only the first shot. In low- and middle-income countries (LMICs), the problems of vaccine shortage, fiscal limitations, vaccine acceptance issues, and implementation difficulties result in lower vaccination rates. On the other hand, the long-term efficacy of vaccines is not established. The emerging variants of SARS-CoV-2 with increased infectivity surge a new problem. Moreover, post-vaccination transmission and positive tests for COVID-19 have been reported (6). Therefore, other countermeasures are still recommended like behavioral interventions for source control and reducing the transmission chain including the use of masks, social distancing, and quarantine.

Some researchers assessed the alternate preventing factors for this pandemic, such as the existing vaccines to step up in controlling the pandemic (7). Many studies attempted to analyze the relationship of the influenza vaccine with COVID-19 severity, but most of them were of ecologic design and are exposed to ecologic fallacy (8-13). In three patient-level studies, the authors concluded that the influenza vaccination can reduce the risk of COVID-19 severity (14-16). However, Zein et al. reported that after controlling for possible confounding factors, the influenza vaccination was not significantly associated with lower admission or mortality of COVID-19 (17). Therefore, considering this inconsistency, and to evaluate a more available preventive strategy for COVID-19 burden, especially for LMICs, we aimed to evaluate the relationship of influenza vaccination in the previous year with outcomes of COVID-19 in affirmed cases after adjustment for confounding factors.

Methods

Study Setting and Design

This study was conducted in the East-Azerbaijan province in North-West of Iran. A prospective provincial offline registry was developed for all confirmed cases of COVID-19 from March 2020. All hospitals, clinics, primary care centers, and laboratories throughout the province were mandated to send daily reports of the cases who were diagnosed with COVID-19 to the registry leadership team. Cases from both healthcare workers and the general population were included in the registry. The diagnosis was made by Reverse transcription-polymerase chain reaction (RT-PCR) or chest CT scan indicating COVID-19 pneumonia to assure consistency. We performed a systematic random sampling method to include the cases from the registry list. For the cases whose contact information was missing, the next person on the list was included.

Data Collection

A trained interviewer made phone calls to ask about the influenza vaccination history in 2019 and the COVID-19 mortality and hospitalization. The information on mortality and admission was obtained from the patients or their relatives and was checked with the data of the registry. The subjects who died of causes unrelated to COVID-19 were excluded. The available influenza vaccines in this period were trivalent inactivated influenza vaccine (IIV3 or TIV) and quadrivalent inactivated influenza vaccine (IIV4 or QIV), which are routinely administered from August to November in Iran.

The educational level based on the Iranian educational system was adjusted to the International Standard Classification of Education 2011 (ISCED-2011), which is an updated framework for organizing information on education developed by the United Nations Educational, Scientific and Cultural Organization (UNESCO) (18). The level of education was categorized into 5 groups including illiterate (ISCED level 0); primary (ISCED level 1 & 2); secondary (ISCED level 3 & 4); tertiary (ISCED level 5 & 6); and Master's or higher (ISCED level 7 & 8). The International Standard Classification of Occupations (ISCO), developed by the International Labor Organization, was used for grading occupations (19). The job state of the participants was grouped into 7 categories of unemployed/housewife; student; retired; manual worker (drivers, sellers, mechanics, farmers, etc.); clerical (including teachers, employees, and secretaries); technician (including nurses, health care workers, engineers, etc.); and professional (including physicians, managers, and faculty members). There were only 5 students among the participants that were excluded from job analyzes. Moreover, we assessed the BMI (body mass index), use of antibiotics during their symptomatic period, history of chronic diseases, using corticosteroids, and current smoking state.

Statistical Analysis

SPSS software version 16 was used for data analysis. To analyze the basic characteristics of flu vaccinated compared to the unvaccinated group, the chi-squared test was used for qualitative data and a t-test was done for quantitative variables. To compare the covariates in influenza vaccinated versus unvaccinated patients the logistic regression test was applied. The data for healthcare workers and the general population were analyzed separately to control the sampling bias. To mitigate the confounding bias, we used the multivariate logistic regression model. The significant variables in univariate analysis were entered into the multivariate model. The *P*-value <0.05 was considered to be statistically significant.

Results

From 1 March to 10 October 2020, a total of 17,213 positive cases were registered throughout the East-Azerbaijan province. In total, 916 patients participated in this study, of which 620 (67.7%) and 296 (32.3%) cases were healthcare workers and the general population, respectively. A total of 88 patients (9.6%) deceased due to COVID-19. Participants were from 8 to 99 years old with a mean (standard deviation) of 44.4 (15.98) years. Among the study population, 365 patients (39.8%) were male, and 551 subjects (60.2%) were female. Two hundred subjects (21.8%) reported receiving the influenza vaccine during the past year.

The characteristics of the study participants are presented in Table 1. Healthcare workers had a significantly higher flu vaccination rate than the general population ($p<0.001$). The unvaccinated group was significantly older than the vaccinated subjects ($p=0.001$). The occupation and education levels were significantly higher in the vaccinated versus unvaccinated population.

The logistic regression analysis showed that after adjustment for socioeconomic and health covariates, the vaccinated patients in the general population had significantly lower odds of death ($p=0.017$) (Table 2). Age, hypertension, diabetes mellitus, and heart disease were independent predictors of COVID-19 mortality in the general population.

In univariate analysis. the influenza vaccination history in the previous year was significantly related to a lower hospitalization rate in affirmed COVID-19 cases in the general population. But this association was non-significant after controlling for other variables (Table 3). However, the patient's education level was independently related to hospital admission.

After controlling the covariates, only patients' age was significantly related to the COVID-19 mortality in healthcare workers (Table 4). Multivariate analysis revealed that education level and hypertension were significantly related to COVID-19 hospitalization in healthcare workers (Table 5).

Discussion

This prospective study was conducted to analyze the relationship of the influenza vaccine history with the mortality and hospitalization rate of COVID-19. Because of using the data of the registry, the inclusion of both the general population and health care workers, performing subgroup analysis, and controlling the potential confounding variables in the multivariate analysis, our results can be generalizable to the general populations. The total past-year flu vaccination rate was 21.8% and was significantly higher for healthcare workers than the general population (28.9 vs. 7.1%). The flu vaccination rate was lower than in other countries (17). Evidence showed that despite 70-91% efficacy for influenza vaccines, the acceptance rate is not ideal. The general acceptance rate for flu vaccines was reported to be below 30% worldwide (20). The global flu vaccine coverage is moderate with much lower achieve-

Table 1. Patients characteristics in influenza vaccinated versus unvaccinated patients

Variable	Vaccinated N=200	Unvaccinated N=716	*P*-value
	N (%) / Mean (SD)		
Age	41.4 (13.84)	45.3 (16.44)	0.001
BMI	26.7 (3.93)	27.1 (4.28)	0.174
Sex			0.092
Male	90 (45.0)	275 (38.4)	
Female	110 (55.0)	441 (61.6)	
Healthcare worker			<0.001
Yes	179 (89.5)	441 (61.6)	
General population	21 (10.5)	275 (38.4)	
Job			<0.001
Unemployed/Housewife	13 (6.5)	149 (20.8)	
Retired	6 (3.0)	31 (4.3)	
Manual	1 (0.5)	62 (8.7)	
Clerical	52 (26.0)	82 (11.5)	
Technicians	91 (45.5)	334 (46.6)	
Professional	37 (18.5)	53 (7.4)	
Education			<0.001
Illiterate	5 (2.5)	72 (10.1)	
Primary	15 (7.5)	97 (13.5)	
Secondary	38 (19.0)	129 (18.0)	
Tertiary	90 (45.0)	304 (42.5)	
Master's & higher	52 (26.0)	114 (15.9)	
Hypertension	23 (11.5)	161 (22.5)	<0.001
Diabetes	20 (10.0)	117 (16.3)	0.026
Smoking	15 (7.5)	63 (8.8)	0.561
Heart disease	11 (5.5)	43 (6.0)	0.788
Renal disease	1 (0.5)	7 (1.0)	0.521
Asthma	10 (5.0)	51 (7.1)	0.287
Cancer history	3 (1.5)	6 (0.8)	0.401
Organ graft history	0 (0)	3 (0.4)	0.359

P-values were based on Chi-square test, except for age and BMI that were based on T-test.

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Table 2. The logistic regression analysis for the relationship between influenza vaccination and COVID-19 death in the general population

Predictor	Deceased	Alive	Univariate		Multivariate	
	N (%) / Mean (SD)		OR(95% CI)	*P*-value	OR(95% CI)	*P*-value
Age	74.4 (11.78)	51.7 (16.96)	1.10 (1.08-1.13)	<0.001	1.11 (1.07-1.15)	<0.001
BMI	29.7 (3.47)	28.5 (4.42)	1.07 (1.01-1.14)	0.032	1.04 (0.95-1.15)	0.401
Flu vaccination						
Yes	1 (1.3)	20 (9.1)	0.13 (0.017-0.99)	0.049	0.16 (0.05-0.60)	0.017
No	76 (98.7)	199 (90.9)	Referent		Referent	
Sex						
Male	39 (50.6)	104 (47.5)	Referent			
Female	38 (49.4)	115 (52.5)	0.88 (0.52-1.48)	0.633		
Education						
Illiterate	35 (45.5)	42 (19.2)	Referent		Referent	
Primary	25 (32.5)	71 (32.4)	0.42 (0.22-0.80)	0.008	1.55 (0.60-3.98)	0.367
Secondary	16 (20.8)	68 (31.1)	0.28 (0.14-0.57)	<0.001	3.93 (0.95-6.35)	0.060
Tertiary	0 (0)	29 (13.2)	-	0.998	-	0.998
Master's +	1 (1.3)	9 (4.1)	0.13 (0.016-1.10)	0.062	2.65 (0.12-6.30)	0.547
Job						
Unemployed/ Housewife	54 (70.1)	107 (48.9)	Referent		Referent	
Retired	14 (18.2)	22 (10.0)	1.26 (0.59-2.66)	0.542	1.18 (0.30-4.23)	0.818
Manual	9 (11.7)	52 (23.7)	0.34 (0.16-0.45)	0.007	1.18 (0.37-3.82)	0.780
Clerical	0 (0)	0 (0)	-	-	-	-
Technicians	0 (0)	30 (1.4)	-	-	-	-
Professional	0 (0)	3 (1.4)	-	-	-	-
Hypertension						
Yes	64 (83.1)	75 (34.2)	Referent		Referent	
No	13 (16.9)	144 (65.8)	0.11 (0.06-0.20)	<0.001	0.39 (0.16-0.96)	0.043
Diabetes						
Yes	50 (64.9)	51 (23.3)	Referent		Referent	
No	27 (35.1)	168 (76.7)	0.16 (0.09-0.29)	<0.001	0.37 (0.17-0.78)	0.009
Smoking						
Yes	10 (13.0)	32 (14.6)	Referent			
No	67 (87.0)	187 (85.4)	1.15 (0.54-2.46)	0.725		
Heart disease						
Yes	25 (32.5)	22 (10.0)	Referent		Referent	
No	52 (67.5)	197 (90.0)	0.23 (0.12-0.45)	<0.001	0.30 (0.13-0.73)	0.008
Renal disease						
Yes	2 (2.6)	5 (2.3)	Referent			
No	75 (97.4)	217 (97.7)	0.88 (0.17-4.61)	0.876		
Asthma						
Yes	18 (23.4)	26 (11.9)	Referent		Referent	
No	59 (76.6)	193 (88.1)	0.44 (0.23-0.86)	0.016	1.08 (0.43-2.69)	0.875
Cancer history						
Yes	3 (3.9)	3 (1.4)	Referent			
No	74 (96.1)	216 (98.6)	0.34 (0.07-1.74)	0.196		
Cortone therapy						
Yes	4 (5.2)	5 (2.3)	Referent			
No	73 (94.8)	2.4 (97.7)	0.43 (0.11-1.63)	0.213		

SD: standard deviation, OR: odds ratio, CI: confidence interval.

ment in low and middle-income countries (LMICs) (21). The higher education and occupation level groups had significantly higher flu vaccine uptake. This finding was congruent with other studies (10).

Our results showed that past-year flu vaccination can be an independent preventing factor for COVID-19 mortality in the general population. The flu-vaccinated group had 84% lower odds of COVID-19 death in comparison with unvaccinated subjects. Similarly, Fink et al. showed that the flu-vaccinated group had 18% lower invasive ventilation, 17% lower mortality, and 8% lower ICU admission after adjustment for comorbidities (14). Pawlowski et al. concluded that geriatric influenza vaccination can reduce COVID-19 infection even after controlling other relevant covariates (15), and Jehi et al. showed that flu vaccination was related to lower COVID-19 infection (16). On the contrary, Zein et al. indicated that flu vaccination was not significantly related to COVID-19 mortality and hospitalization after multivariate adjustment (17), and Wehenkel et al. showed that the flu vaccination was not related to the case fatality of COVID-19 after controlling the possible confounding covariates (12).

One possible reason for the observed preventive effect of influenza vaccination is that the vaccinated cases may have better health and healthier attitudes (13). However, the consideration of confounding factors like chronic diseases in the analysis devalued this explanation. It is proposed that the flu vaccine may induce the production of specific T-cell responses and specific neutralizing antibodies (14). Another plausible mechanism for this preventive effect is the development of a non-specific immune response or innate immunity that can activate an early response to immediate virus detection and on-time protection before organ invasion (10, 22-24). Another justifica-

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Table 3. The relationship of patient characteristics and influenza vaccination history with COVID-19 hospitalization in the general population

Predictor	Hospitalized	Non- Hospitalized	Univariate		Multivariate	
	N (%) / Mean (SD)		OR(95% CI)	*P*-value	OR(95% CI)	*P*-value
Age	58.4 (18.63)	49.6 (17.16)	1.03 (0.004-1.05)	0.019	1.02 (0.98-1.06)	0.219
BMI	28.7 (4.11)	29.6 (5.24)	0.95 (0.87-1.04)	0.297		
Flu vaccination						
Yes	18 (6.7)	3 (10.7)	0.60 (0.17-2.18)	0.438		
No	250 (93.3)	25 (89.3)	Referent			
Sex						
Male	129 (48.1)	14 (50.0)	Referent			
Female	139 (51.9)	14 (50.0)	1.08 (0.49-2.35)	0.851		
Education						
Illiterate	69 (25.7)	8 (28.6)	Referent		Referent	
Primary	89 (33.2)	7 (25.0)	1.47 (0.51-4.26)	0.474	4.61 (1.08-19.77)	0.040
Secondary	81 (30.2)	3 (10.7)	3.13 (0.80-12.26)	0.101	19.26 (2.99-23.92)	0.002
Tertiary	19 (7.1)	10 (35.7)	0.22 (0.08-0.64)	0.005	0.83 (0.16-4.27)	0.822
Master's +	10 (3.7)	0 (0)	-	0.999	-	0.999
Job						
Unemployed/ Housewife	148 (55.2)	13 (46.4)	Referent		Referent	
Retired	35 (13.1)	1 (3.6)	3.07 (0.39-4.29)	0.287	1.99 (0.20-9.75)	0.553
Manual	54 (20.1)	7 (25.0)	0.68 (0.26-1.79)	0.432	0.60 (0.17-2.11)	0.426
Clerical	0 (0)	0 (0)	-	-	-	-
Technicians	26 (9.7)	4 (14.3)	0.57 (0.17-1.89)	0.358	1.85 (0.34-10.11)	0.477
Professional	1 (0.4)	2 (7.1)	0.04 (0.004-0.52)	0.013	0.60 (0.01-1.16)	0.062
Hypertension						
Yes	133 (49.6)	6 (21.4)	Referent		Referent	
No	135 (50.4)	22 (78.6)	0.28 (0.11-0.70)	0.007	0.36 (0.11-1.28)	0.116
Diabetes						
Yes	98 (36.6)	3 (10.7)	Referent		Referent	
No	170 (63.4)	25 (89.3)	0.21 (0.06-0.71)	0.012	0.34 (0.09-1.32)	0.119
Smoking						
Yes	37 (13.8)	5 (17.9)	Referent			
No	231 (86.2)	23 (82.1)	1.36 (0.49-3.79)	0.560		
Heart disease						
Yes	46 (17.2)	1 (3.6)	Referent			
No	222 (82.8)	27 (96.4)	0.18 (0.03-1.35)	0.095		
Renal disease						
Yes	7 (2.6)	0 (0)	Referent			
No	261 (97.4)	28 (100)	-	0.999		
Asthma						
Yes	41 (15.3)	3 (10.7)	Referent			
No	227 (84.7)	25 (89.3)	0.66 (0.19-2.30)	0.519		
Cancer history						
Yes	6 (2.2)	0 (0)	Referent			
No	262 (97.8)	28 (100)	-	0.999		
Cortone therapy						
Yes	8 (3.0)	1 (3.6)	Referent			
No	260 (97.0)	27 (96.4)	1.20 (0.15-9.99)	0.864		

SD: standard deviation, OR: odds ratio, CI: confidence interval.

tion is that flu-vaccinated patients have reduced uncontrolled destructive pro-inflammatory responses, which results in lethal stages of COVID-19 (14).

The influenza vaccination history of the general population in the previous year was not related to a lower hospital admission rate in the general population. This can be attributable to the fact that at the beginning of the pandemic, the diagnostic test was prioritized for severe or hospitalized cases. That is why the majority of the cases from the general population that were included in this study (90.5%) had hospital admission, yielding a smaller sample size in the non-hospitalized patients. The multivariate analysis showed that in the general population, subjects with secondary and primary education had significantly higher odds of hospital admission than illiterate cases. This finding may be related to the lower affordability of hospitalization by illiterate groups.

Our results indicated that the history of flu vaccination was not related to COVID-19 mortality or hospitalization in healthcare workers. This finding can be a result of low mortality and hospitalization rate among healthcare workers. Similar to other studies, our analysis of both healthcare workers and the general population revealed that advancing age is an independent predictor of COVID-19 mortality (12, 14-16). Moreover, in this study, the advancing age, hypertension, diabetes mellitus, and previous heart disease independently increased the odds of COVID-19 death in the general population. On the other hand, healthcare workers with hypertension and diabetes mellitus had significantly higher odds of hospital admission.

Currently, the vaccination scale against COVID-19 may be limited in LMICs. Simultaneously, some mutations for

Table 4. The logistic regression analysis for the relationship between influenza vaccination and COVID-19 death in healthcare workers

Predictor	Deceased	Alive	Univariate		Multivariate	
	N (%) / Mean (SD)		OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age	58.4 (11.10)	37.9 (8.95)	1.24 (1.14-1.35)	<0.001	1.25 (1.11-1.41)	<0.001
BMI	29.6 (3.34)	26.3 (3.79)	1.19 (1.05-1.36)	0.006	1.24 (0.93-1.64)	0.143
Flu vaccination						
Yes	5 (45.5)	174 (28.6)	2.08 (0.63-6.91)	0.231		
No	6 (54.5)	435 (71.4)	Referent			
Sex						
Male	6 (54.5)	216 (35.5)	Referent			
Female	5 (45.5)	393 (64.5)	0.46 (0.14-1.52)	0.202		
Education						
Illiterate	0 (0)	0 (0)				
Primary	1 (9.1)	15 (2.5)	Referent		Referent	
Secondary	2 (18.2)	81 (13.3)	0.37 (0.03-4.35)	0.429	-	0.999
Tertiary	1 (9.1)	364 (59.8)	0.04 (0.01-0.70)	0.027	-	0.999
Master's +	7 (63.6)	149 (24.5)	0.71 (0.08-6.12)	0.751	-	0.999
Job						
Unemployed/ Housewife	0 (0)	0 (0)				
Retired	0 (0)	0 (0)				
Manual	1 (9.1)	1 (0.2)	Referent		Referent	
Clerical	1 (9.1)	134 (22.0)	0.01 (0.001-0.22)	0.005	-	0.999
Technicians	5 (45.5)	391 (64.2)	0.01 (0.001-0.23)	0.003	-	0.999
Professional	4 (36.4)	83 (13.6)	0.05 (0.01-0.91)	0.044	-	0.999
Hypertension						
Yes	5 (45.5)	40 (6.6)	Referent		Referent	
No	6 (54.5)	569 (93.4)	0.08 (0.03-0.29)	<0.001	0.35 (0.06-2.05)	0.245
Diabetes						
Yes	2 (18.2)	34 (5.6)	Referent			
No	9 (81.8)	575 (94.4)	0.27 (0.06-1.28)	0.099		
Smoking						
Yes	2 (18.2)	34 (5.6)	Referent			
No	9 (81.8)	575 (94.4)	0.27 (0.06-1.28)	0.099		
Heart disease						
Yes	1 (9.1)	6 (1.0)	Referent		Referent	
No	10 (90.9)	603 (99.0)	0.10 (0.01-0.91)	0.040	2.36 (0.07-8.03)	0.633
Renal disease						
Yes	1 (9.1)	0 (0)	Referent			
No	10 (90.9)	609 (100)	-	0.999		
Asthma						
Yes	0 (0)	17 (2.8)	Referent			
No	11 (100)	592 (97.2)	-	0.999		
Cancer history						
Yes	1 (9.1)	2 (0.3)	Referent		Referent	
No	10 (90.9)	607 (99.7)	0.03 (0.003-0.39)	0.007	0.02 (0.01-3.50)	0.198
Cortone therapy						
Yes	0 (0)	16 (2.6)	Referent			
No	11 (100)	593 (97.4)	-	0.999		

SD: standard deviation, OR: odds ratio, CI: confidence interval.

SARS-CoV-2 are emerging that raise concerns for this pandemic. In this period, the influenza vaccination can be considered an effective adjutant preventive countermeasure for COVID-19 in less developed countries, especially for elders, patients with comorbidities, pregnant women, and healthcare workers.

Study Limitations

Some limitations should be considered in interpreting the results of this study. Our data about the flu vaccination history were self-reported and exposed to recall bias. The data for some dead patients were missing because of their relative's non-response. The rate of mortality was low among the healthcare workers to ensure a robust statistical analysis.

Conclusion

The overall flu vaccination rate was low in our community, even among the healthcare workers. The influenza vaccine can be considered an effective adjutant preventive countermeasure for COVID-19 mortality and burden, especially for the general population. the advancing age, hypertension, diabetes mellitus, and previous heart disease were risk factors for COVID-19 death.

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Ethical Considerations

The study protocol was approved by the Ethical Committee of Tabriz University of Medical Sciences (No. IR.TBZMED.REC.1399.680). The study objectives were explained to the participants before data collection. The participants were assured of the confidentiality of the in-

Table 5. The relationship of patient characteristics and influenza vaccination history with COVID-19 hospitalization in healthcare workers

Predictor	Hospitalized	Non- Hospitalized	Univariate		Multivariate	
	N (%) / Mean (SD)		OR (95% CI)	P-value	OR (95% CI)	P-value
Age	41.1 (10.09)	38.1 (9.32)	1.03 (0.99-1.07)	0.058		
BMI	27.7 (4.57)	26.3 (3.72)	1.09 (1.01-1.18)	0.028	1.01 (0.92-1.11)	0.864
Flu vaccination						
Yes	17 (45.9)	162 (27.8)	2.21 (1.13-4.32)	0.021	1.94 (0.95-3.95)	0.069
No	20 (54.1)	421 (72.2)	Referent		Referent	
Sex						
Male	18 (48.6)	204 (35.0)	Referent			
Female	19 (51.4)	379 (65.0)	0.57 (0.29-1.11)	0.097		
Education						
Illiterate	0 (0)	0 (0)				
Primary	3 (8.1)	13 (2.2)	Referent		Referent	
Secondary	8 (21.6)	75 (12.9)	0.46 (0.11-1.97)	0.297	0.47 (0.09-2.32)	0.351
Tertiary	13 (35.1)	352 (60.4)	0.16 (0.04-0.63)	0.009	0.20 (0.04-0.95)	0.043
Master's +	13 (35.1)	143 (24.5)	0.39 (0.09-1.56)	0.185	0.38 (0.08-1.79)	0.221
Job						
Unemployed/ Housewife	0 (0)	0 (0)				
Retired	0 (0)	0 (0)				
Manual	0 (0)	2 (0.3)	Referent			
Clerical	14 (37.8)	121 (20.8)	-	0.999		
Technicians	15 (40.5)	381 (65.4)	-	0.999		
Professional	8 (21.6)	79 (13.6)	-	0.999		
Hypertension						
Yes	12 (32.4)	33 (5.7)	Referent		Referent	
No	25 (67.6)	550 (94.3)	0.13 (0.06-0.27)	<0.001	0.15 (0.06-0.36)	<0.001
Diabetes						
Yes	5 (13.5)	31 (5.3)	Referent		Referent	
No	32 (86.5)	552 (94.7)	0.36 (0.13-0.98)	0.047	0.93 (0.29-2.96)	0.911
Smoking						
Yes	3 (8.1)	33 (5.7)	Referent			
No	34 (91.9)	550 (94.3)	0.68 (0.20-2.33)	0.539		
Heart disease						
Yes	1 (2.7)	6 (1.0)	Referent			
No	36 (97.3)	557 (99.0)	0.37 (0.04-3.19)	0.369		
Renal disease						
Yes	1 (2.7)	0 (0)	Referent			
No	36 (97.3)	583 (100)	-	0.999		
Asthma						
Yes	3 (8.1)	14 (2.4)	Referent			
No	34 (91.9)	569 (97.6)	0.28 (0.08-1.02)	0.053		
Cancer history						
Yes	1 (2.7)	2 (0.3)	Referent			
No	36 (97.3)	581 (99.7)	0.13 (0.01-1.39)	0.091		
Cortone therapy						
Yes	1 (2.7)	15 (2.6)	Referent			
No	36 (97.3)	568 (97.4)	0.95 (0.12-7.4)	0.961		

SD: standard deviation, OR: odds ratio, CI: confidence interval.

formation. Participation in this research was voluntary.

Conflict of Interests

The authors declare that they have no competing interests.

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