

## Coronavirus Pandemic

# Side effects of COVID-19 vaccines among Iranian healthcare workers: a retrospective cohort study

Hassan Roudgari<sup>1</sup>, Koorosh Etemad<sup>2</sup>, Manoochehr Karami<sup>2</sup>, Farideh Mostafavi<sup>2</sup>, Sahar Sotoodeh Ghorbani<sup>2</sup>, Kosar Farhadi Babadi<sup>2</sup>, Elham Rahimi<sup>2</sup>, Niloufar Taherpour<sup>2,3</sup>, Seyed Mahmood Fattahi Masoom<sup>4</sup>, Masoud Habibi<sup>5</sup>, Hossein Kermanpour<sup>6</sup>, Reza Laripour<sup>7</sup>, Omid Manoochehri<sup>8</sup>, Mohammad Raeeszadeh<sup>9</sup>, Alireza Salimi<sup>10</sup>, Babak Shekarchi<sup>11</sup>, Ali Tajernia<sup>12</sup>, Mohammad Reza Zafarghandi<sup>13</sup>, Alireza Zali<sup>14</sup>, Afshin Zarghi<sup>15</sup>, Seyed Saeed Hashemi Nazari<sup>16</sup>

<sup>1</sup> Department of Research, IR Iran Medical Council, Genomic Research Center, National Center for Genomic Excellence, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>2</sup> Department of Epidemiology, School of Public Health and Safety, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>3</sup> Prevention of Cardiovascular Disease Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>4</sup> Chief Executive Officer, NOBAAN Private Corporation, Tehran, Iran

<sup>5</sup> Department of Photo Healing and Regeneration, Medical Laser Research Center, Yara Institute, ACECR, Tehran, Iran

<sup>6</sup> Emergency Department, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran

<sup>7</sup> Department of Education, Aja University of Medical Sciences, Tehran, Iran

<sup>8</sup> Chairman of the Board, NOBAAN Private Corporation, Tehran, Iran

<sup>9</sup> Faculty of Medicine, Baqiyatallah University of Medical Sciences, Tehran, Iran

<sup>10</sup> Chronic Respiratory Diseases Research Center, Anesthesia and Critical Care Department, Masih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>11</sup> Department of Radiology, School of Medicine, AJA University of Medical Sciences, Tehran, Iran

<sup>12</sup> Iranian Dental Association, Tehran, Iran

<sup>13</sup> Department of Vascular Surgery and Traumatology, Sina General Hospital, Tehran University of Medical Sciences, Tehran, Iran

<sup>14</sup> Functional Neurosurgery Research Center, Shohada Tajrish Neurosurgical Center of Excellence, Shohada Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>15</sup> Department of Medicinal and Pharmaceutical Chemistry, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>16</sup> Prevention of Cardiovascular Disease Research Center, Department of Epidemiology, School of Public Health and Safety, Shahid Beheshti University of Medical Sciences, Tehran, Iran

## Abstract

**Introduction:** This study assessed the incidence and severity of side effects associated with coronavirus disease 2019 (COVID-19) vaccination among healthcare workers registered with the Medical Council of the Islamic Republic of Iran.

**Methodology:** A retrospective cohort study was conducted on the healthcare workers focusing on the side-effects of COVID-19 vaccines from March to June 2021. Data were collected using online questionnaires. Multivariable logistic regression was used to assess the association between side effects of the vaccines and demographic variables, comorbidities, vaccine type, and history of COVID-19.

**Results:** Out of 42,018 people who were included, 55.85% reported at least one side effect after receiving the first vaccine dose. 4.59% of those with side effects sought diagnostic intervention or were referred to treatment centers. Multivariable logistic regression indicated that being a woman, higher education, having a history of COVID-19 infection, and having comorbidities increased the risk of side effects. The AstraZeneca vaccine significantly increased the risk of side effects compared to the Sputnik vaccine, while the Sinopharm vaccine decreased this risk. The risk of developing a side effect decreased with age. The risk of moderate and severe side effects was significantly associated with gender, younger age, comorbidities, and a history of COVID-19 infection. Moderate and severe side effects were less reported by those who received the Sinopharm vaccine.

**Conclusions:** Clinical complications after COVID-19 vaccination, directly or indirectly caused by the vaccines, are common. However, the benefits of COVID-19 vaccines greatly outweigh the risk of reversible side effects, especially among the high-risk population.

**Key words:** side effects; vaccine; COVID-19; healthcare workers.

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## Introduction

The coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome

coronavirus-2 (SARS CoV-2) and first appeared in Wuhan (China) in December 2019. Since then, it spread quickly. On 30 January 2020, the World Health

Organization (WHO) announced that the COVID-19 outbreak was a public health emergency of international concern (PHIC) [1]. Most COVID-19 patients experienced mild to moderate symptoms and recuperated without requiring special treatment; however, 20% of the infected patients were prone to develop severe to serious diseases with fatal consequences [2].

The development of safe and effective vaccines played a crucial role in controlling the SARS-CoV-2 pandemic by stimulating the human immune system to produce antibodies. Most COVID-19 vaccines target the S protein of the virus, a tool that helps the virus enter cells and initiate the infection [3-5]. Despite the fact that a significant number of people have been vaccinated around the world, many are still hesitant to receive the COVID-19 vaccines. Possible reasons for this are the rumors about the side effects of the vaccines that build distrust about the COVID-19 vaccines [6-7]. According to the WHO's Vaccine Safety Monitoring Guide, it is fundamental to constantly assess the safety of vaccines and demonstrate their safety to encourage the public to take vaccines. This means that passive reporting systems may not be sufficient for rapid assessment and appropriate public health response during COVID-19 vaccination drives [8].

Many mild to moderate, and reversible side effects of vaccines have been recorded and reported during clinical trials. These include lump formation, redness, and tenderness at the injection site; headache; high temperature; tiredness; malaise; body ache; muscle ache; nausea; vomiting; diarrhea; dizziness and fainting; herpes simplex infection or reactivation of varicella-zoster; nephrotic syndrome; acute kidney damage and so on [9-13].

An active surveillance study was conducted in San Marino between 4 March and 8 April 2021 to evaluate the safety of the Sputnik vaccine. Most of the side effects were mild to moderate, with only 0.8% reporting severe symptoms. No hospitalization or death was reported. Most of the side effects occurred within two days of injection and lasted less than two days. In general, the incidence of side effects after the second dose was 66.8% and after the first dose was 53.3% (seven days after injection) [14]. Severe reactions, including intravascular thrombosis and thrombocytopenia, have been associated with the ChAdOx1 (AZD1222) vaccine. This is because the ChAdOx1 vaccine increases the production of anti-platelet factor 4 antibodies [15-16]. Studies showed that the most common side effects after the first dose of the Sinopharm vaccine were pain at the injection site,

fatigue, and headache among participants younger than 50 years of age; however, after the second dose, pain at the injection site, fatigue, lethargy, headache, and tenderness were the more common side effects in all age groups. Generally, side effects following both doses were more common among younger participants and females. This study concluded that the most common reason people were unwilling to take the vaccine was their concerns about its effectiveness. [17].

The current study aimed to identify the side effects of the SARS-CoV-2 vaccines among the healthcare workers registered with the Medical Council of the Islamic Republic of Iran. We also evaluated the possible factors associated with the incidence and severity of the side effects. The results of our study can help address public concerns and reassure those who refuse to participate in national COVID-19 vaccination drive.

## Methodology

A retrospective cohort study was conducted on the members of the Islamic Republic of Iran Medical Council (IRIMC) to evaluate the side effects of the COVID-19 vaccines.

### *Study population*

The study participants were members of the IRIMC who were eligible to receive the vaccines. IRIMC is an independent professional organization that included, at the time of this study, 325,933 members from the medical professions, of which 194,185 were men and 131,748 were women.

Among the participants, 48.4% had a professional doctorate, 29.6% had a bachelor's degree, 16.9% were trained in a clinical/surgical specialty, 1.2% had a fellowship in clinical/surgical fields, 1.4% had a master's degree, 1.4% were trained in a subspecialty, and 1.1 % had a PhD degree in a medical sciences field.

### *Data collection*

The study was conducted between March and June 2021. Data collection was performed using online questionnaires. The participants received a message prompting them to use a link to access the questionnaire on the side effects of vaccines. A trained interviewer interviewed the participants who were hospitalized due to possible complications via phone. All the data collected were based on self-reporting by participants. The questionnaires collected participants' demographic data and data on the side effects of the vaccine. The side effects were recorded in separate categories: 1) side effects after the first, second, third, and fourth day after

vaccination; 2) side effects after the fourth to seventh day after vaccination; 3) side effects after eighth to 14<sup>th</sup> day after vaccination; and 4) side effects after 15<sup>th</sup> to

31<sup>st</sup> days after the first dose vaccination. The study evaluated the side effects of the AstraZeneca, Sputnik, and Sinopharm vaccines that were available in the

**Table 1.** Demographic characteristics of the cohort and COVID-19 vaccine side effects.

Characteristic	With side effect n = 23468 (55.85%), n (%)	Without side effect n = 18550 (44.15%), n (%)	Chi square p value
<b>Participant age, mean (SD), in years</b>	41.35 (0.07)	48.64 (0.10)	< 0.001
<b>Comorbidities</b>			
No	17770 (56.52)	13494 (43.48)	< 0.001
Yes	5989 (53.98)	5052 (46.02)	
Cardiovascular	653 (46.21)	760 (53.79)	< 0.001
Diabetes	858 (41.96)	1187 (58.04)	< 0.001
Hypertension	1505 (46.94)	1701 (53.06)	< 0.001
Autoimmune	400 (60.42)	262 (39.58)	0.001
Musculoskeletal	230 (53.24)	202 (46.76)	0.809
Pulmonary	381 (61.85)	235 (38.15)	< 0.001
Allergies	389 (68.73)	177 (31.27)	< 0.001
Skin disorders	171 (66.54)	86 (33.46)	< 0.001
Urogenital	192 (63.37)	111 (36.63)	0.001
Nephrology	125 (53.42)	109 (46.58)	0.903
Liver disorders	132 (65.35)	70 (34.65)	0.001
Thyroid disorders	1421 (61.86)	886 (38.14)	< 0.001
Cerebral disorders	348 (64.68)	190 (35.32)	< 0.001
Mental disorders	100 (63.69)	57 (36.31)	0.013
Cancer	165 (43.88)	211 (56.12)	< 0.001
Digestive system	321 (63.82)	182 (36.18)	< 0.001
Lipid disorder	323 (52.18)	296 (47.82)	0.407
Others	433 (61.16)	275 (38.84)	< 0.001
<b>History of COVID-19</b>			
No	20009 (54.95)	16402 (45.05)	< 0.001
Yes	3459 (61.67)	2148 (38.33)	
<b>Vaccine type</b>			
Sputnik	9194 (43.97)	11713 (56.03)	< 0.001
AstraZeneca	12685 (72.72)	4756 (27.28)	
Sinopharm	1589 (43.27)	2081 (56.73)	
<b>Gender</b>			
Female	15750 (60.93)	10099 (39.07)	< 0.001
Male	7718 (47.72)	8451 (52.28)	
<b>Age group (year)</b>			
< 30	4698 (70.42)	1973 (29.58)	< 0.001
30-39	7121 (67.96)	3356 (32.04)	
40-49	4769 (59.49)	3246 (40.51)	
50-59	5309 (45.14)	6451 (54.86)	
60-69	1161 (33.83)	2268 (66.17)	
≥ 70	412 (24.69)	1256 (75.31)	
<b>Education</b>			
Bachelors degree	6284 (60.03)	4183 (39.97)	< 0.001
Masters degree	1857 (65.65)	970 (34.35)	
Doctorate	11106 (55.31)	8973 (44.69)	
Specialist	2886 (51.16)	2754 (48.84)	
Unknown	13337 (44.45)	1670 (55.55)	
<b>Occupational field</b>			< 0.001
Dentist	3674 (51.12)	3513 (48.88)	
Pathologist	549 (50.09)	547 (49.91)	
Gynecologist	331 (43.96)	422 (56.04)	
Dermatologist	98 (44.95)	120 (55.05)	
Specialist in internal medicine	120 (42.70)	161 (57.30)	
Infectious disease specialist	30 (48.39)	32 (51.61)	
Cardiologist	107 (49.08)	111 (50.92)	
Pediatrician	238 (41.75)	332 (58.25)	
Neurologist	204 (50.87)	197 (49.13)	
Anesthesiologist	144 (47.21)	161 (52.79)	
Radiotherapist	231 (47.24)	258 (52.76)	
Social medicine	61 (57.55)	45 (42.45)	
Physiotherapist	2418 (62.85)	1429 (37.15)	
Surgeon	278 (38.45)	445 (61.55)	
Ophthalmologist, Audiometer	549 (55.07)	448 (44.93)	
Pharmacist	3103 (63.42)	1790 (36.58)	
Intensive Care Specialist	37 (56.92)	28 (43.08)	
ENT	98 (40.83)	142 (59.17)	
Specialist in nutrition	1372 (65.71)	716 (34.29)	
Physician	5086 (55.25)	4120 (44.75)	
Pulmonologist	1 (9.09)	10 (90.91)	
Gastroenterologist	16 (38.10)	26 (61.90)	
Midwife	4161 (57.39)	3089 (42.61)	
Audiologists	432 (63.16)	252 (36.84)	
Others	128 (44.76)	158 (55.24)	

COVID-19: coronavirus disease 2019; ENT: ear nose throat.

vaccination program for healthcare workers in Iran. Data on the severity of side effects and hospitalization, if it happened, were also collected.

*Study variables*

The questionnaire was used to collect general and clinical information. The general information section included demographic variables such as age, gender, and education level. The clinical information section included the following variables:

1. Vaccine-related variables included the type of vaccine and the date of vaccination, personal medical information such as underlying disease, and the history of COVID-19 infection.

2. Variables related to vaccine side effects such as general side effects (fever, sweating, chills, injection site pain, injection site swelling, lethargy, and swollen lymph nodes), cardiovascular side effects (palpitations, arrhythmias, chest pain, abnormal vascular bleeding), respiratory side effects (cough, hypoxemia, dyspnea, tachypnea, chest pressure), neurological side effects (headache, restlessness and anxiety, irritability and anger, sleep disorder, seizures, delirium, blurred vision, confusion and speech disorder), skin and mucosal side

effects (any allergic symptoms and their locations, skin rash and its location, urticaria, bruising under the skin, mucous bruising, itchy skin), musculoskeletal side effects (new muscle pain, exacerbation of previous muscle pain, joint pain, swelling and redness, leg or hand swelling), genitourinary side effects (urinary incontinence, anemia, urinary irritation, urinary retention, hematuria, menstrual irregularities) and other reported side effects such as hair loss; feeling pain in eye, ear, sinus, lymph node and jaw; nasal congestion; cold hands; thirst; dry nasal mucosa; eye irritation; eyelid swelling; burning soles of the feet; oral plaque; herpes; runny nose; and hearing loss.

*Follow-up and outcome*

This study's primary outcome was assessing the side effects and serious adverse events (SAEs) of COVID-19 vaccination. The participants were contacted through short message service (SMS) to complete the questionnaire within 48 to 72 hours, in the first and second weeks, and again, one month after receiving the first dose of the vaccine.

*Statistical analysis*

The continuous variables were described using mean ± standard deviation (SD), and the categorical variables were reported as frequency and percentage. The mean of continuous variables in the two groups was compared using Student's t-test. Differences in distributions were assessed by Chi-square or Fisher's exact test for dichotomous and categorical variables. Predictors of the incidence and severity of side effects were evaluated in univariate level, followed by multivariable logistic regression. Variables with a *p* value ≤ 0.2 in univariate analysis were used in the multivariable logistic regression model. Age, gender, education, vaccine type, underlying disease, and the history of COVID-19 were treated as potential confounding factors. In this study, the analysis was based on the information regarding the side effect after the first dose of the vaccines. The results were reported as odds ratio (OR) with 95% confidence interval (95% CI). A *p* value < 0.05 was considered statistically significant. Data analysis was performed using STATA-16 (StataCorp LLC, College Station, TX 77845, USA).

**Results**

Forty-two thousand and eighteen members of the Medical Council of the Islamic Republic of Iran received the first dose of the COVID-19 vaccines. They completed the online questionnaire based on the first

**Table 2.** Medical attendance of adverse events following COVID-19 vaccination.

Participants status	Frequency (%)
Having any reaction/adverse events	
No	18550 (44.15)
Yes	23468 (55.85)
<b>Reaction requiring any treatment</b>	
No	6286 (26.79)
Yes	17182 (73.21)
<b>Reaction requiring any diagnostic/treatment center</b>	
No	21842 (95.41)
Yes	1077 (4.59)
<b>Reaction requiring hospitalization</b>	
No	22946 (99.98)
Yes	3 (0.02)
<b>Reaction requiring any special tests</b>	
No	21935 (93.49)
Yes	1529 (6.51)
<b>Medication type used</b>	
Pain killers and anti-inflammatories	17211 (64.03)
Antihistamines	571 (2.48)
Aspirin and anticoagulants	241 (1.05)
Sedatives	142 (0.62)
Beta-blockers and heart medications	177 (0.77)
Antibiotics	202 (0.88)
Gastrointestinal antacids medications	479 (2.08)
Cortone	170 (0.74)
Antitussives and bronchodilators	106 (0.46)
Serum therapy	349 (1.52)
Vitamins	429 (1.86)
Epinephrine, interferons, and oxygen therapy	71 (0.31)
Other	18 (0.08)
<b>Was the medication effective</b>	
No	1724 (10.03)
Yes	15456 (89.97)

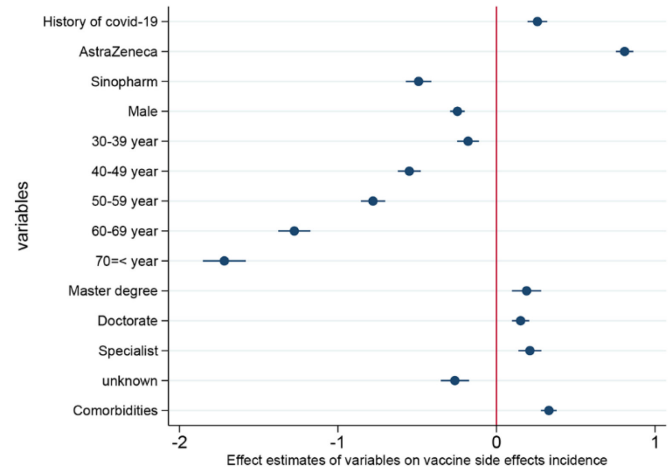
COVID-19: coronavirus disease 2019.

dose of the vaccine. The incidence rate of side effects after the first dose was 558.5 out of 1,000 participants. The incidence rates (per 1000 individuals) were 478.28 for general side effects, 54.47 for cardiovascular, 114.59 for respiratory, 123.58 for gastrointestinal, 32.86 for skin and mucosal, 150.40 for musculoskeletal, 53.58 for genital, 158.40 for neurological, and 121.37 for other side effects. Table 1 shows the characteristics of study participants from groups with and without side effects. The mean age of participants with and without side effects group was 41.35 (± 0.07) years and 48.64 (± 0.10) years, respectively. Women, younger individuals, people with a history of COVID-19, and individuals with comorbidities were more likely to experience side effects.

Of the 23,468 participants who reported at least one side effect after the first dose, 17,180 (73.21%) sought medical treatment; 10.03% of them reported that the medications were not effective in relieving the side effects. The most commonly used medications, in order of frequency, were analgesics, anti-inflammatories, antihistamines, gastrointestinal drugs, and antacids. 1077 (4.59%) of the group with side effects were referred to diagnostic/treatment centers by medical practitioners (Table 2).

The results of multivariable logistic regression showed that the risk of developing at least one side effect was higher among women, people with higher

**Figure 1.** Coefficient of logistic regression along with 95% confidence intervals for COVID-19 vaccine side effects.



education, those with a history of COVID-19, and those with comorbidities. The AstraZeneca vaccine was associated with a significantly higher risk of developing side effects than the Sputnik vaccine, while the Sinopharm vaccine was associated with a lower risk of side effects. The results showed that the risk of developing side effects decreased with age (Table 3, Figure 1).

Table 4 shows the association between the severity of vaccine side effects and the study variables based on multivariable logistic regression.

**Table 3.** Results of univariate and multivariable logistic regression of COVID-19 vaccine side effects.

Characteristics	Complication (Total n = 23468), N (%)	Odds ratio (95% CI)	Adjusted odds ratio (95%CI)	p value
<b>Comorbidities</b>				
No	17541 (56.52)	1	1	
Yes	5927 (53.98)	0.90 (0.86, 0.94)	1.38 (1.32, 1.45)	< 0.001
<b>History of COVID-19</b>				
No	20009 (54.95)	1	1	
Yes	3459 (61.67)	1.31 (1.24, 1.39)	1.29 (1.21, 1.37)	< 0.001
<b>Type of vaccine</b>				
Sputnik	9194 (43.97)	1	1	
AstraZeneca	12685 (72.72)	3.39 (3.25, 3.54)	2.19 (2.07, 2.32)	< 0.001
Sinopharm	1589 (43.27)	0.97 (0.90, 1.04)	0.59 (0.55, 0.65)	< 0.001
<b>Gender</b>				
Female	15750 (60.93)	1	1	
Male	7718 (47.72)	0.58 (0.56, 0.60)	0.76 (0.72, 0.80)	< 0.001
<b>Age group (year)</b>				
< 30	4698 (70.42)	1	1	
30-39	7120 (67.96)	0.89 (0.83, 0.95)	0.84 (0.78, 0.88)	< 0.001
40-49	4769 (59.49)	0.61 (0.57, 0.66)	0.59 (0.54, 0.63)	< 0.001
50-59	5309 (45.14)	0.34 (0.32, 0.36)	0.46 (0.43, 0.50)	< 0.001
60-69	1160 (33.83)	0.21 (0.19, 0.23)	0.28 (0.25, 0.31)	< 0.001
≥ 70	412 (24.69)	0.13 (0.12, 0.15)	0.18 (0.15, 0.21)	< 0.001
<b>Education</b>				
Bachelors degree	6283 (60.03)	1	1	
Masters degree	1856 (65.65)	1.27 (1.16, 1.38)	1.13 (1.03, 1.24)	0.010
Doctorate	11106 (55.31)	0.82 (0.78, 0.86)	1.02 (0.91, 1.13)	0.708
Specialist	2886 (51.16)	0.69 (0.65, 0.74)	1.16 (1.03, 1.32)	0.013
Unknown	1337 (44.45)	0.53 (0.49, 0.57)	0.70 (0.62, 0.78)	< 0.001

COVID-19: coronavirus disease 2019.

**Table 4.** Results of univariate and multivariable logistic regression of COVID-19 vaccine side effects severity.

Characteristics	Moderate and severe complication (Total n = 1077), N (%)	Odds ratio (95%CI)	Adjusted odds ratio (95% CI)	p value
<b>Comorbidities</b>				
No	770 (4.37)	1	1	
Yes	307 (5.14)	1.18 (1.03,1.36)	1.42 (1.22,1.64)	< 0.001
<b>History of COVID-19</b>				
No	801 (3.98)	1	1	
Yes	276 (7.88)	2.06 (1.78,2.37)	2.06 (1.79,2.39)	< 0.001
<b>Type of vaccine</b>				
Sputnik	353 (3.82)	1	1	
AstraZeneca	686 (5.37)	1.43 (1.25,1.63)	1.11 (0.94,1.30)	0.193
Sinopharm	38 (1.39)	0.61 (0.43,0.86)	0.42 (0.29,0.60)	< 0.001
<b>Gender</b>				
Female	878 (5.53)	1	1	
Male	199 (2.57)	0.45 (0.38,0.53)	0.57 (0.48,0.68)	< 0.001
<b>Age group(year)</b>				
< 30	329 (6.94)	1	1	
30-39	331 (4.62)	0.65 (0.55,0.76)	0.68 (0.58,0.80)	< 0.001
40-49	204 (4.26)	0.59 (0.49,0.71)	0.64 (0.53,0.78)	< 0.001
50-59	162 (3.04)	0.42 (0.34,0.50)	0.48 (0.38,0.60)	< 0.001
60-69	36 (3.08)	0.42 (0.30,0.60)	0.52 (0.36,0.77)	0.001
≥ 70	15 (3.61)	0.50 (0.29,0.85)	0.73 (0.41,1.29)	0.293
<b>Education</b>				
Bachelors degree	441 (6.95)	1	1	
Masters degree	93 (4.98)	0.70 (0.55,0.88)	0.83 (0.65,1.06)	0.146
Doctorate	404 (3.62)	0.50 (0.43,0.57)	0.88 (0.64,1.20)	0.428
Specialist	84 (2.90)	0.40 (0.31,0.50)	0.76 (0.50,1.17)	0.222
Unknown	55 (4.10)	0.57 (0.42,0.76)	0.77 (0.63,1.24)	0.494

COVID-19: coronavirus disease 2019.

**Table 5.** Results of multivariable logistic regression of COVID-19 vaccine and different types of adverse effects.

Characteristics	General side effects adjusted OR (95%CI)	Cardiovascular adjusted OR (95% CI)	Respiratory adjusted OR (95% CI)	Nervous Adjusted OR (95% CI)
<b>Comorbidities</b>				
No	1	1	1	1
Yes	0.86 (0.79, 0.94)**	1.32 (1.19, 1.46)***	1.30 (1.21, 1.41)***	1.29 (1.20, 1.38)***
<b>History of COVID-19</b>				
No	1	1	1	1
Yes	1.11 (0.99, 1.23)	1.22 (1.08, 1.37)**	1.26 (1.15, 1.37)***	1.04 (0.96, 1.13)
<b>Type of vaccine</b>				
Sputnik	1	1	1	1
AstraZeneca	1.48 (1.34, 1.64)***	1.54 (1.36, 1.74)***	1.12 (1.03, 1.22)**	1.33 (1.23, 1.44)***
Sinopharm	0.43 (0.37, 0.49)***	0.72 (0.57, 0.90)**	0.72 (0.62, 0.84)***	0.75 (0.66, 0.87)***
<b>Gender</b>				
Female	1	1	1	1
Male	1.38 (1.26, 1.51)***	0.59 (0.53, 0.66)***	0.76 (0.70, 0.82)***	0.76 (0.71, 0.81)***
<b>Age group(year)</b>				
< 30	1	1	1	1
30-39	0.67 (0.59, 0.77)***	1.06 (0.94, 1.19)	0.92 (0.84, 1.01)	1.02 (0.94, 1.10)
40-49	0.51 (0.45, 0.59)***	0.90 (0.78, 1.03)	0.77 (0.70, 0.86)***	0.87 (0.80, 0.95)**
50-59	0.34 (0.30, 0.40)***	0.79 (0.67, 0.94)**	0.73 (0.65, 0.83)***	0.77 (0.69, 0.86)***
60-69	0.28 (0.23, 0.34)**	0.76 (0.58, 0.99)*	0.70 (0.58, 0.85)***	0.58 (0.49, 0.70)***
≥ 70	0.18 (0.13, 0.23)***	1.09 (0.76, 1.60)	0.95 (0.73, 1.25)	0.51 (0.38, 0.68)***
<b>Education</b>				
Bachelors degree	1	1	1	1
Masters degree	0.91 (0.77, 1.06)	0.94 (0.79, 1.12)	1.05 (0.92, 1.19)	1.05 (0.93, 1.8)
Doctorate	1.04 (0.86, 1.27)	0.94 (0.74, 1.17)	0.87 (0.73, 1.02)	0.92 (0.79, 1.06)
Specialist	1.04 (0.83, 1.33)	1.00 (0.76, 1.32)	0.85 (0.70, 1.04)	0.96 (0.80, 1.15)
Unknown	0.92 (0.74, 1.13)	1.06 (0.83, 1.37)	0.89 (0.74, 1.07)	0.95 (0.80, 1.12)

COVID-19: coronavirus disease 2019; OR: odds ratio; CI: confidence interval; \*p value < 0.05; \*\*p value < 0.01; \*\*\*p value < 0.001.

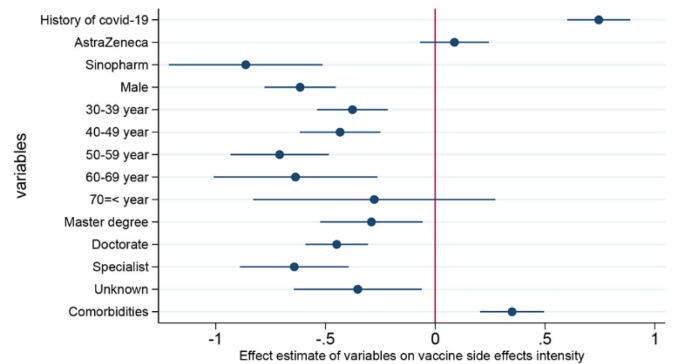
The risk of moderate and severe side effects was significantly associated with gender (women), comorbidities, and a previous history of COVID-19. The people who received the Sinopharm vaccine reported fewer, moderate and severe side effects. The moderate and severe side effects were more common among younger individuals, after adjusting for the effects of other variables (Figure 2).

Tables 5 and 6 show the results for multivariable logistic regression analysis of the association between the study variables and the groups with significant COVID-19 vaccine side effects, including general side effects, cardiovascular, respiratory, neurological, gastrointestinal, skin and mucosal, musculoskeletal, genital, and other side effects.

**Discussion**

Vaccination is an essential tool for controlling the COVID-19 pandemic. However, vaccines are associated with unwanted side effects [18,19]. The present study showed that out of 42,018 Iranian healthcare workers, 55.85% experienced side effects after the first dose of the vaccine. Although most of the consequences of vaccination were mild to moderate, 0.02% of the recipients were hospitalized. In this study, the side effects of administering the first dose of AstraZeneca/Oxford, Sputnik, and Sinopharm vaccines were estimated as 72.72%, 43.97%, and 43.27%, respectively. Previous studies from around the world

**Figure 2.** Coefficient of logistic regression along with 95% confidence intervals for intensity of COVID-19 vaccine side effects.



have reported the incidence of complications due to the COVID-19 vaccine and the AstraZeneca vaccine accounted for the highest percentage of the mild to moderate adverse events after the first dose [20-23]. Xiong et al. reported that 7% of the people who received the COVID-19 vaccine were referred to hospitals due to side effects [24].

Generally, after the administration of the first dose of the vaccine, the immune system is stimulated and the body produces antibodies against the targeted antigen. As a result, there is a more robust immune response and reactogenicity after the first dose compared with second and third doses. Accordingly, experiencing mild to moderate side effects is more common and remarkable after the first course of vaccination. We must consider

**Table 6.** Results of multivariable logistic regression of COVID-19 vaccine and different types of adverse effects (continued).

Characteristics	Digestive adjusted OR (95% CI)	Mucosal and skin adjusted OR(95%CI)	Musculoskeletal adjusted OR (95% CI)	Genitourinary adjusted OR(95% CI)	Others adjusted OR (95% CI)
<b>Comorbidities</b>					
No	1	1	1	1	1
Yes	1.27 (1.18, 1.38)***	1.48 (1.30, 1.68)***	1.16 (1.06, 1.25)***	1.28 (1.15, 1.43)***	1.49 (1.38, 1.60)***
<b>History of COVID-19</b>					
No	1	1	1	1	1
Yes	1.11 (1.02, 1.22)*	1.16 (1.00, 1.35)*	1.16 (1.08, 1.25)***	1.07 (0.95, 1.22)	0.97 (0.89, 1.06)
<b>Type of vaccine</b>					
Sputnik	1	1	1	1	1
AstraZeneca	1.43 (1.31, 1.55)***	1.22 (1.04, 1.41)**	1.14 (1.05, 1.23)**	1.36 (1.20, 1.54)***	1.07 (0.98, 1.17)
Sinopharm	0.68 (0.58, 0.79)***	1.20 (0.94, 1.52)	0.45 (0.38, 0.52)***	0.77 (0.62, 0.95)***	1.42 (1.24, 1.62)***
<b>Gender</b>					
Female	1	1	1	1	1
Male	0.59 (0.54, 0.64)***	0.67 (0.59, 0.77)***	0.82 (0.76, 0.88)***	0.39 (0.35, 0.44)***	0.48 (0.45, 0.53)***
<b>Age group(year)</b>					
< 30	1	1	1	1	1
30-39	0.81 (0.74, 0.88)***	1.11 (0.95, 1.31)	0.96 (0.88, 1.04)	1.06 (0.94, 1.19)	1.08 (0.98, 1.18)
40-49	0.65 (0.59, 0.72)***	0.99 (0.82, 1.19)	0.87 (0.79, 0.95)**	0.94 (0.58, 1.07)	1.17 (1.06, 1.30)**
50-59	0.50 (0.44, 0.56)***	1.16 (0.94, 1.43)	0.72 (0.65, 0.81)***	0.58 (0.48, 0.69)***	1.30 (1.16, 1.46)***
60-69	0.39 (0.32, 0.48)***	1.50 (1.12, 2.00)**	0.55 (0.46, 0.65)***	0.59 (0.44, 0.80)**	1.09 (0.91, 1.31)
≥ 70	0.45 (0.32, 0.62)***	1.88 (1.25, 2.83)**	0.49 (0.37, 0.65)***	1.10 (0.73, 1.65)	1.42 (1.08, 1.84)*
<b>Education</b>					
Bachelor	1	1	1	1	1
Master degree	0.95 (0.84, 1.08)	1.19 (0.96, 1.48)	1.12 (0.99, 1.26)	1.10 (0.94, 1.30)	1.14 (1.01, 1.30)*
Doctorate	1.04 (0.89, 1.23)	1.44 (1.10, 1.89)**	1.11 (0.96, 1.30)	1.04 (0.81, 1.28)	1.07 (0.91, 1.26)
Specialist	1.19 (0.98, 1.44)	1.59 (1.14, 2.22)**	1.17 (0.98, 1.41)	0.89 (0.64, 1.10)	0.97 (0.80, 1.19)
Unknown	1.02 (0.86, 1.22)	1.23 (0.91, 1.66)	0.93 (0.79, 1.10)	0.89 (0.67, 1.12)	0.93 (0.78, 1.12)

COVID-19: coronavirus disease 2019; OR: odds ratio, CI: confidence interval, \*p value < 0.05, \*\*p value < 0.01, \*\*\*p value < 0.001.

that the type and severity of the side effects may vary between individuals [25].

The present study concluded that gender, age, level of education, comorbidities, history of COVID-19 infection, and the type of vaccine are directly associated with the incidence and severity of the side effects after the first dose of vaccine.

Earlier studies have shown that a more significant fraction of women experienced at least one side effect than men. Moreover, the incidence and severity of the events were higher in women than men. This can be due to the production of estrogen in women, which may result in a more robust immune response than in men [20,24,26]. Alternatively, it could be that women pay more attention to their health, seek medical assistance quicker than men, and are usually better at self-reporting than men.

We found that younger participants were more prone to develop post-vaccination side effects than the older ones, and the severity of the complications was higher among younger people. This may be due to a more robust immune system in young adults, or, a weaker immune system in older people. In this regard, our results were consistent with other studies [24,26].

As reported by other investigators, our results showed that the incidence of side effects among recipients of vaccines and their severity was higher among people with comorbidities [20]. However, two studies that investigated the factors related to the adverse effects of the first dose of the AstraZeneca/Oxford vaccine reported results contrary to the results of the present study [22,27]. This discrepancy can be related to the difference between study populations, sample size, type of vaccinations, and research methodologies. We suppose that the underlying diseases and related medications may weaken the immune system and produce a generalized weakness that causes a more exaggerated demonstration of the side effects in people with comorbidities [24]. More studies are required to understand the side effects of COVID-19 vaccines in groups of people with different genetic, medical and medication backgrounds.

Interestingly, the level of education was associated with a higher incidence of the side effects of the vaccines in our study. The medical staff with higher education reported more side effects. The higher education of healthcare workers has been associated with a higher level of awareness and reporting of side effects. Other studies claimed the same that higher education was associated with higher reporting rate of side effects. [26,28].

In agreement with the current literature, this study showed that having a history of COVID-19 infection was associated with higher incidence and severity of side effects [29]. One of the assumptions related to this observation is that previous infection with COVID-19 alerted the sensitivity of the immune system against any form of future SARS-CoV-2 infection, including vaccines, which in turn led to a stronger immune response to the vaccines and higher incidence and severity of the vaccine side effects.

Regarding the type of vaccines and their association with the incidence and severity of post-vaccination events, our observations are in agreement with other reports from different countries. The incidence and severity of side effects, after adjustment for other related factors, were more significant in people who had received the AstraZeneca vaccine, compared to other vaccines [20,23]. Sinopharm is an inactivated type of SARS-CoV2 vaccine which stimulates the immune system to create antibodies. Systemic reactions such as fever, fatigue, and pain have been reported as its prevalent side effects. However, AstraZeneca and Sputnik vaccines contain adenovirus vectors, which are genetically built to carry a targeted piece of the viral genome into the hosts' cells. Vector-based vaccines may be associated with immune responses against the target virus and the vector base; as a result, they can cause more severe side effects [30]. The difference in the type of vaccines may be the reason behind different side effects. In addition, we observed different incidence and severity rates of adverse events such as general, cardiovascular, nervous, respiratory, gastrointestinal, muscular, skin, and genital side effects. However, we were not able to make any conclusions about the relative efficacy of the vaccines.

In our findings, severe adverse events were not reported after the first dose of the COVID-19 vaccine, and the reported side effects may not be directly due to the vaccine [30]. Sahraian *et al.* reported a higher incidence of gastrointestinal side effects after the first dose of the Sinopharm vaccine among patients in Iran with multiple sclerosis [31]. Therefore, further consideration of the specific clinical events along with the type of vaccines is required.

Finally, as genes, proteins, metabolites, extracellular RNAs, and gender (genes related to sex hormones) may affect the severity and prognosis of the COVID-19 disease [32,33], these may also play an essential role in reactogenicity to the COVID-19 vaccines. It can be assumed that vaccine recipients' reactions may differ based on the vaccines' technologies. This needs further studied to clarify the



exact relationship between the vaccine recipients' genotype and the type of vaccine.

Apart from reversible side effects, using COVID-19 vaccines is safe in most individuals with comorbidities and those in high-risk groups. Our results also showed that the side effects were tolerable, and only a few participants, some with underlying diseases, sought specific medical treatments.

### Limitations

Our study had some limitations. First, response and recall bias are some of the most critical constraints in questionnaire-based studies; so, the results may be underestimated. Second, the study was conducted only on Iranian healthcare workers who had received one dose of the COVID-19 vaccines. Therefore, it may affect the generalizability of the study. Additionally, there was no information on concomitant COVID-19 infection at the time of administering the vaccine, which may affect the incidence and severity of the reported side effects.

### Conclusions

Clinical complications after COVID-19 vaccination, directly or indirectly caused by the vaccines, are common. However, the benefits of COVID-19 vaccines greatly outweigh the risk of reversible side effects, especially among the high-risk population. Monitoring vaccine side effects provides vital information that leads to evaluating vaccine safety. The results of the current study can contribute to evaluating the success of COVID-19 vaccination programs. An active and precise surveillance and monitoring system is required to register vaccination side effects, to manage these side effects, and improve vaccine safety at a national level.

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### Corresponding author

Seyed Saeed Hashemi Nazari, MD, MPH, PhD.  
 School of Public Health and Safety, Shahid Beheshti University of Medical Sciences,  
 Daneshjoo Blvd, Evin Ave, Tehran, Iran.  
 Tel: +98 (21) 22431993  
 Fax: +98 (21) 22 43 97 84  
 Email: saeedh\_1999@yahoo.com

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