




# Comparison of Time to Report the Side Effects after AstraZeneca and Sinopharm Vaccinations in Users of the COVID-19 Symptom Study App: A Survey in South Iran

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## Abstract

**Background:** Concerns about the side effects of SARS-CoV-2 vaccines have been raised nationwide. We aimed to compare the time to report the side effects of the Oxford-AstraZeneca and Sinopharm COVID-19 vaccines.

**Methods:** Information on side effects of AstraZeneca and Sinopharm COVID-19 vaccines was obtained from the COVID-19 Symptom Study App affiliated with Shiraz University of Medical Science during 2021. A COX regression model with an adjusted Hazard Ratio and 95% Confidence Interval; HR (95% C.I) was reported at the significance level of  $< 0.05$ .

**Results:** 4478 and 5555 participants received the AstraZeneca and Sinopharm vaccines, respectively; more age, history of SARS-CoV-2 infection, first vaccine dose, hypertension, and hypertension with cardiovascular disease were seen in the AstraZeneca group ( $P < 0.05$  for all). However, the AstraZeneca group had lower immune deficiency and time to report the side effects ( $P < 0.05$  for both). There was significantly less time to pain HR(95% C.I.); 0.50 (0.47-0.52), vertigo 0.65 (0.61-0.69), weakness 0.41 (0.38-0.44), headache 0.43 (0.39-0.74), anorexia 0.31 (0.28-0.34), nausea 0.56 (0.51-0.62), severer allergy 0.71 (0.63-0.81), general inflammation 0.27 (0.23-0.31), fever  $> 38^{\circ}\text{C}$  0.12 (0.1-0.15), eye inflammation 0.45 (0.39-0.52), diarrhea 0.85 (0.73-0.99), blurred vision 0.73 (0.61-0.86), injection site redness 0.32 (0.26-0.39), fatigue/paleness 0.53 (0.50-0.57), joint pain 0.55 (0.41-0.73), auxiliary gland inflation 0.59 (0.43-0.80), convulsions 0.30 (0.17-0.52), and severe side effects 0.3 (0.27-0.33) in the AstraZeneca group; However, skin rash 0.77 (0.57-1.05) and hospitalization 0.72 (0.21-2.55) were the same.

**Conclusion:** Sinopharm COVID-19 vaccine recipients reported longer times to report vaccine-related side effects than AstraZeneca; due to the lack of adverse effects like hospitalization, vaccination should continue to control the pandemic; more real-population studies are needed on the long-term effects of vaccination against COVID-19.

**Keywords:** Oxford-AstraZeneca COVID-19 Vaccine, Sinopharm BIBP COVID-19 Vaccine, Side Effects, Cumulative Survival Rate

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## Introduction

Vaccination seemed the only way to eliminate COVID-19 (1). The Oxford-AstraZeneca (ChAdOx1 nCoV-19, Se-

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### ↑What is “already known” in this topic:

Due to the high infectivity of SARS-CoV-2, besides sanitation, vaccination was the only way to eliminate COVID-19. The Oxford-AstraZeneca and Sinopharm COVID-19 vaccines were the most widely used vaccines; however, concerns about the safety and side effects of SARS-CoV-2 vaccines have been raised among communities nationwide.

### →What this article adds:

Sinopharm COVID-19 vaccine recipients reported significantly longer times to report vaccine-related side effects than AstraZeneca COVID-19 vaccine recipients did; due to the lack of adverse effects, such as hospitalization, vaccination should not be halted as an urgent tool controlling the pandemic.

rum Institute of India) and Sinopharm BIBP (Beijing Institute of Biological Products) COVID-19 vaccines were the most widely used vaccines with effectiveness rates of 70% and 79.43%; in addition, the most common side effects of COVID-19 vaccines are mild/moderate (2, 3) with no serious complications (4, 5). It showed that recipients of the AstraZeneca vaccine reported significantly more side effects than the Sinopharm vaccine (79% vs. 32%) (4). People showed vaccine uncertainty for COVID-19 for producing in a rush, vaccine incompetence due to the mild nature of COVID-19, hesitation about the vaccine's effectiveness, and belief that they were already immune from former infection (6, 7). In attracting the public's attention to the importance of vaccination, the current survey aimed to compare the time to report the side effects of AstraZeneca and Sinopharm vaccines in a population in southern Iran.

## Methods

### Study population/design

In this survey, information about the side effects of vaccines against SARS-CoV-2 was obtained for 15901 vaccine takers from the COVID-19 Symptom Study App (cts.sums.ac.ir/vse) affiliated with Shiraz University of Medical Science; the cases were recorded from 26 cities in Fars Province, Iran, during 2021. Among these cases, 10033 cases received AstraZeneca and Sinopharm vaccines. The features included age of the participant, vaccine dose, history of SARS-CoV-2 infection, comorbidity, vaccination date, date of using the COVID-19 Symptom Study App, date of side effect onset, time to report the side effects (interval between vaccination date and date of side effect onset), remedy type, vaccine type, and vaccine side effect.

### Variable definition

Features included age (year), vaccine dose (first and second), history of SARS-CoV-2 infection (SARS-CoV-2 infection before vaccination; yes/no), comorbidity (presence of any chronic diseases including diabetes mellitus (DM), chronic respiratory disease (CRD), cardiovascular disease (CVD), high blood pressure (HBP), and immune deficiency (ID); yes/no), time to report the side effects (day), and remedy alleviating the side effects (rest/water, acetaminophen (paracetamol) (5), naproxen (6), coldax (7), and cetirizine (8); yes/no). These remedies were taken after reporting the side effects.

Reported side effects were pain, vertigo, weakness, headache, skin rash, anorexia, nausea, severe allergy, general inflammation, fever >38°C, eye inflammation, diarrhea, blurred vision, injection site redness, fatigue/paleness, joint pain, auxiliary gland inflammation, convulsions, severe side effects, and hospitalization; yes/no). Sinopharm COVID-19 vaccine was an inactivated virus vaccine developed by Beijing Bio-Institute of Biological Products (BBIBP); AstraZeneca COVID-19 vaccine is a viral vector vaccine made by the Serum Institute of India (SII) (3).

### Ethical statement

All the study stages, including data collection and analysis and reporting the results, were in accordance with the

standards approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1401.267). The data were analyzed anonymously, and the results were reported to the study participants.

### Statistical analysis

(Min-max) and median (IQR; Inter Quartile Range (Q<sub>3</sub>-Q<sub>1</sub>)) were used to describe quantitative variables; frequency (relative frequency) was used to describe qualitative variables. To test the normality distribution of a variable, the Kolmogorov-Smirnov normality test was used, the Chi-square test was used to identify the relationship between categorical variables, and the exact-Fisher test was used to test the relationship between categorical variables using hyper-geometric distribution in a small sample size. Furthermore, the median test, Log-Rank test, and COX regression investigating the effects of several variables on the time it takes for a specified event to occur with the cumulative survival rate (the probability of surviving this day multiplied by the probability of surviving the previous period) were applied, and the adjusted Hazard Ratio (HR) with 95% confidence interval; HR (95% C.I) was reported, HR is a measure of how frequently a particular event occurred in one group versus another, a HR=1 demonstrates lack of association, HR<1 demonstrates a smaller risk, and HR>1 demonstrate an increased risk. IBM SPSS v.22 software was used at a significance level of < 0.05.

## Results

From the 10033 participants, 45% (4478/10033) and 55% (5555/10033) received AstraZeneca and Sinopharm vaccines, respectively. Background features of 10033 vaccine takers by vaccine type have been compared in Table 1.

More age, history of SARS-CoV-2 infection, and first vaccine dose were seen in the AstraZeneca group compared with Sinopharm (p-value<0.05 for all). Although no significant difference was seen in terms of comorbidity ( $P > 0.05$ ), HPD and CVD+HPD were significantly higher in AstraZeneca ( $P < 0.05$  for both), but ID was lower ( $P < 0.05$ ). A lower time to report the side effects was seen in the AstraZeneca group ( $P < 0.05$ ), and there were more rest, water, acetaminophen, Coldax, and naproxen in the AstraZeneca group ( $P < 0.05$  for all); however, cetirizine was taken less ( $P < 0.05$ ). The median time to report side effects of 10033 vaccine takers by vaccine type has been compared in Table 2.

The median of time to report pain, vertigo, weakness, headache, anorexia, nausea, severe allergy, general inflammation, fever > 38°C, eye inflammation, blurred vision, injection site redness, fatigue/paleness, joint pain, auxiliary gland inflammation, convulsion, and severe side effect degree were significantly higher in Sinopharm compared with AstraZeneca vaccine takers ( $P < 0.05$  for all). However, skin rash, diarrhea, and hospitalization did not differ ( $P > 0.05$  for all).

The reported side effects frequency and time to report side effects (adjusted for age, vaccine dose, history of SARS-CoV-2 infection, HPB, ID, and CVD+HPD) have been compared between 4478 AstraZeneca and 5555 Sinopharm vaccine takers in Table 3 and Figure 1.

**Table 1.** Comparison of background features among 10033 vaccine takers by AstraZeneca and Sinopharm vaccines

Background Feature		Total, n=10033	AstraZeneca, n=4478	Sinopharm, n=5555	P-value	
Age (year), (min-max), median(IQR)		(12-94), 39 (20)	(18-94), 40 (21)	(12-93), 38 (20)	<0.001 <sup>#</sup>	
Vaccine dose, n (%)	1	9658 (96.3%)	4373 (97.7%)	5285 (95.1%)	<0.001	
	2	375 (3.7%)	105 (2.3%)	270 (4.9%)		
History of SARS-CoV-2 infection, n (%)	Yes	1345 (13.4%)	654 (14.6%)	691 (12.4%)	0.002	
Comorbidity, n (%)	Yes	1510 (15.1%)	659 (14.7%)	851 (15.3%)	0.400	
Comorbidity type, n (%)	HBP	409 (27.1%)	197 (29.9%)	212 (24.9%)	0.030	
	DM	202 (13.4%)	82 (12.4%)	120 (14.1%)	0.350	
	CVD	168 (11.1%)	78 (11.8%)	90 (10.6%)	0.440	
	ID	149 (9.8%)	36 (5.5%)	113 (13.2%)	<0.001	
	CVD+HBP	119 (7.9%)	69 (10.5%)	50 (6%)	0.001	
	DM+HPD	116 (7.7%)	55 (8.3%)	61 (7.2%)	0.400	
	CRD	94 (6.2%)	35 (5.2%)	59 (6.9%)	0.150	
	CVD+DM+HPD	75 (5%)	35 (5.5%)	40 (4.7%)	0.550	
	CVD+DM	39 (2.6%)	20 (3%)	19 (2.2%)	0.330	
	ID+HPD	21 (1.4%)	8 (1.2%)	13 (1.5%)	0.610	
	CRD+HPD	17 (1.1%)	7 (1.1%)	10 (1.2%)	0.840	
	others	101 (6.7%)	41 (6.2%)	60 (7%)	*	
Time to report the side effects (day), (min-max), median (IQR)		(0-28), 1 (2)	(0-28), 1 (1)	(0-28), 2 (3)	<0.001	
Remedy type	Rest/ water, n (%)	Yes	1578 (15.7%)	860 (19.2%)	718 (12.9%)	<0.001
	Acetaminophen, n (%)	Yes	1579 (15.7%)	1005 (22.4%)	574 (10.3%)	<0.001
	Naproxen, n (%)	Yes	58 (0.6%)	45 (1%)	13 (0.2%)	<0.001
	Coldax, n (%)	Yes	13 (0.1%)	10 (0.2%)	3 (0.1%)	0.020
	Cetirizine, n (%)	Yes	6 (0.1%)	0 (0%)	6 (0.1%)	0.040

IQR; Inter quartile range, SARS-CoV-2; severe acute respiratory syndrome coronavirus type 2, HBP; high blood pressure, DM; diabetes mellitus, CVD; cardio vascular disease, CRD; chronic respiratory disease, ID; Immune deficiency, \*no statistics are computed because other is constant, # Median test

**Table 2.** Comparison of median time to report side effects among 4478 AstraZeneca vaccine recipients and 5555 Sinopharm vaccine recipients

Feature (day)	Vaccine type		P-value*
	AstraZeneca, n=4478 median of time to report	Sinopharm, n=5555 median of time to report	
Pain	2.13	4.14	<0.001
Vertigo	2.16	4.42	<0.001
Weakness	1.91	4.20	<0.001
Headache	1.83	4.38	<0.001
Anorexia	1.92	4.58	<0.001
Skin rash	3.77	4.35	0.13
Nausea	1.97	3.92	<0.001
Severe allergy	2.03	4.32	<0.001
General inflammation	2.2	4.25	<0.001
Fever>38°C	1.91	6.00	<0.001
Eye inflammation	1.52	3.68	<0.001
Diarrhea	2.24	3.72	0.19
Blurred vision	2.14	3.86	<0.001
Injection site redness	2.63	4.35	<0.001
Fatigue/paleness	2.02	4.51	<0.001
Joint pain	1.83	5.26	<0.001
Auxiliary gland inflation	1.75	4.29	0.002
Convulsion	1.85	6.43	<0.001
Hospitalization	2.00	5.12	0.57
Severe side effect degree	1.96	5.16	0.002

\*Log- Rank test

Pain, vertigo, weakness, headache, anorexia, skin rash, nausea, severe allergy, general inflammation, fever > 38°C, eye inflammation, diarrhea, blurred vision, injection site redness, fatigue/paleness, joint pain, auxiliary gland inflammation, convulsions, and hospitalization were the most commonly reported symptoms in the 10033 participants, and nearly 21% (2126/100033) reported severe side effects.

After adjusting for age, vaccine dose, history of SARS-CoV-2 infection, HBP, ID, and CVD+HBP, the AstraZeneca group had significantly less time to pain, vertigo, weakness, headache, anorexia, nausea, severe allergy, general inflammation, fever > 38°C, eye inflammation, diarrhea, blurred vision, injection site redness, fatigue/paleness,

joint pain, auxiliary inflation, convulsions, and severe side effects compared with those in the Sinopharm group ( $P < 0.05$  for all), HR= 0.5 for time to pain demonstrated that on average, there was a 50% lower risk of reporting time to pain in Sinopharm vaccine takers compared with AstraZeneca vaccine takers; however, no differences were seen in terms of skin rash and hospitalization ( $P > 0.05$  for both), HR= 0.72 for time to hospitalization demonstrated that on average, there was the same risk of reporting time to hospitalization in AstraZeneca vaccine takers compared with Sinopharm vaccine takers.

Table 3. Comparison of reported side effects frequency and time to report side effects among 4478 AstraZeneca vaccine recipients and 5555 Sinopharm vaccine recipients

Feature		Total, n=10033	Astra-Zeneca, n=4478	Sinopharm, n=5555	P-value <sup>□</sup>	HR* (95% C.I)
Pain, n (%)	Yes	5895 (58.8%)	3129(69.9%)	2766(49.8%)	<0.001	0.50(0.47-0.52)
Vertigo, n (%)	Yes	4130 (41.2%)	1908(42.6%)	2222(40%)	0.008	0.65(0.61-0.69)
Weakness, n (%)	Yes	3141 (31.3%)	1841(41.1%)	1300(23.4%)	<0.001	0.41(0.38-0.44)
Headache, n (%)	Yes	2432 (24.2%)	1382(30.9%)	1050(18.9%)	<0.001	0.43(0.39-0.74)
Anorexia, n (%)	Yes	2018 (20.1%)	1291(28.8%)	727(13.1%)	<0.001	0.31(0.28-0.34)
Skin rash, n (%)	Yes	186 (1.9%)	72(1.6%)	114(2.1%)	0.100	0.77(0.57-1.05)
Nausea, n (%)	Yes	1601 (16%)	823(18.4%)	778(14%)	<0.001	0.56(0.51-0.62)
Severer allergy, n (%)	Yes	1031 (10.3%)	451(10.1%)	580(10.4%)	0.540	0.71(0.63-0.81)
General inflammation, n (%)	Yes	906 (9%)	611(13.6%)	295(5.3%)	<0.001	0.27(0.23-0.31)
Fever>38°C, n (%)	Yes	867 (8.6%)	708(15.8%)	159(2.9%)	<0.001	0.12(0.1-0.15)
Eye inflammation, n (%)	Yes	837 (8.3%)	480(10.7%)	357(6.4%)	<0.001	0.45(0.39-0.52)
Diarrhea, n (%)	Yes	711 (7.1%)	275(6.1%)	436(7.8%)	0.001	0.85(0.73-0.99)
Blurred vision, n (%)	Yes	590 (5.9%)	261(5.8%)	329(5.9%)	0.840	0.73(0.61-0.86)
Injection site redness, n (%)	Yes	433 (4.3%)	268(6%)	165(3%)	<0.001	0.32(0.26-0.39)
Fatigue/paleness, n (%)	Yes	5034 (50.2%)	2589(57.8%)	2445(44%)	<0.001	0.53(0.50-0.57)
Joint pain, n (%)	Yes	202 (2%)	101(2.3%)	101(1.8%)	0.120	0.55(0.41-0.73)
Auxiliary gland inflation, n (%)	Yes	173 (1.7%)	84(1.9%)	89(1.6%)	0.300	0.59(0.43-0.80)
Convulsion, n (%)	Yes	61 (0.6%)	40(0.9%)	21(0.4%)	0.001	0.30(0.17-0.52)
Hospitalization, n (%)	Yes	11 (0.1%)	5(0.1%)	6(0.1%)	0.960	0.72(0.21-2.55)
Side effect degree, n (%)	Mild & moderate (ref category)	7907 (78.8%)	3110(69.5%)	4797(86.4%)	<0.001	.-.
	Severe	2126 (21.2%)	1368(30.5%)	758(13.6%)		0.3(0.27-0.33)

HR; Hazard ratio, \* adjusted on age, vaccine dose, history of SARS-CoV-2 infection, high blood pressure, immune deficiency, and cardiovascular disease + high blood pressure, □ Chi-square test, Note; the exact p-value for HR were depicted on the related survival curves on Figure 1.

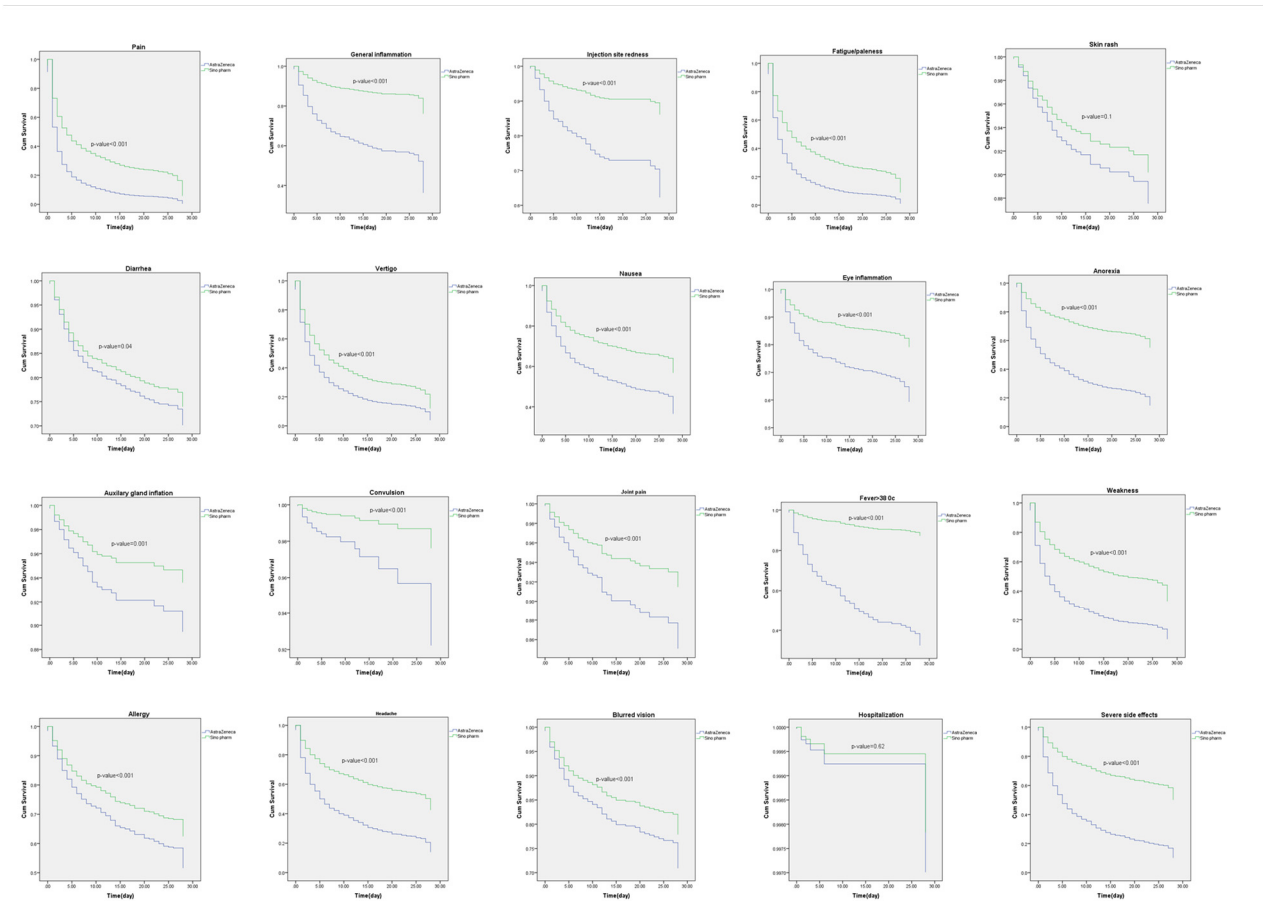


Figure 1. Comparison of times to report the side effects of 4478 AstraZeneca and 5555 Sinopharm vaccine takers based on Cox regression model adjusted on age, vaccine dose, history of SARS-CoV-2 infection, high blood pressure, immune deficiency, and cardiovascular disease + high blood pressure.

Discussion

Although most symptoms were not life-threatening such

as hospitalization, severe side effects, and death (9, 10), the major side effects after taking AstraZeneca and Sinopharm



vaccines were pain, fatigue, headache, nausea, and diarrhea in different orders (11, 12). In the current survey, similar side effects were reported that were also consistent with those reported in phase III clinical trials (13, 14). In addition, several studies have reported higher side effects and symptoms for the AstraZeneca vaccine than those for the Sinopharm vaccine which were parallel to the current findings (11, 15). Though not statistically significant, both AstraZeneca and Sinopharm groups experienced more severe side effects than previously reported (5).

It seems that vaccine dose affects the prevalence of vaccination side effects in different ways; in one study, more side effects were reported after taking the first dose of the Sinopharm vaccine (11); however, in another study, the second dose of vaccination was related to more side effects (16).

There are controversies regarding the positive and negative effects of a history of SARS-CoV-2 infection on vaccination side effects; studies have reported more side effects with a history of infection (16, 17); however, another study reported fewer side effects with a history of infection (18).

In a trial, more adverse effects have been associated with older age (19); however, another study reported that this association could be confounded by the first and second doses of vaccination so that the side effects decreased with age after the first dose and increased after the second dose of vaccination (18); and other studies reported that the prevalence of side effects were inversely related to older age (16, 20).

The increased number of side effects in people with comorbidities, particularly people with a history of CVD, HPD, and ID, was a prominent finding of COVID-19 studies (1, 21, 22). Despite no discrimination regarding first and second doses of vaccines in the current work, the analyses were adjusted on vaccine dose, age, history of SARS-CoV-2 infection, and comorbidity to reach more reliable estimations on time to report the side effects comparing AstraZeneca and Sinopharm vaccines.

One study reported that the most prevalent symptoms of AstraZeneca and Sinopharm vaccines occurred 72 hours after the first dose; However, the symptoms were the same for the first and second doses after 72 hours of vaccination (18). These findings could point to links between vaccination type and the time for side effects to occur. In the current study, it was demonstrated that there was an association between time to report the side effects and vaccine types; AstraZeneca vaccination was associated with a shorter time to report the side effects compared with Sinopharm vaccine during the 28 days after vaccination.

### Strengths and limitations

Females have reported more side effects than males regardless of the vaccine dose (10, 16, 18); however, as a limitation of the work, no sex was recorded in the current work, resulting in no comparison for gender categories; it was the same for other influential variables such as participants' level of COVID-19 awareness and society culture; in addition, due to the self-reporting nature of the work, not all vaccine side effects were recorded and the evaluation was

limited to the side effects reported in COVID-19 Symptom Study App. Other limitations are: i) not all vaccine takers participated in the study, and the information was limited to the COVID-19 Symptom Study App users, so the participation rate could not be estimated, and the estimated effect sizes might be prone to underestimation; ii) the majority of vaccine takers received only the first dose by the time of applying the COVID-19 Symptom Study App. As a result, a comparison of the side effects between the first and second dose takers was not possible; however, to manage it, the effect sizes were reported adjusting on vaccination dose; iii) due to the low sample sizes of other vaccines (Sputnik V, Bharat Biotech, COVIran Barekat, and Sinovac), the comparison was limited to Sinopharm and AstraZeneca vaccine takers; and iv) although this study relies on the self-reported COVID-19 vaccination side effects, it targeted a large-scale survey with a well-defined population; in addition, the many potential confounders were controlled, enhancing the generalizability of the results. Finally, to be more concise in arbitrating COVID-19 vaccination side effects, information is needed during the hospitalization period of the patients.

### Conclusion

Significantly more age, first vaccine dose, history of SARS-CoV-2 infection, HPD, and CVD+HPD were seen in the AstraZeneca group compared with Sinopharm; ID and time to report the side effects were significantly lower, however. The median of time to report pain, vertigo, weakness, headache, anorexia, nausea, severe allergy, general inflammation, fever>38°C, eye inflammation, blurred vision, injection site redness, fatigue/paleness, joint pain, auxiliary gland inflation, convulsion, and severe side effect degree were significantly higher in Sinopharm compared with AstraZeneca vaccine takers. However, skin rash, diarrhea, and hospitalization did not differ. After adjustment on age, vaccine dose, history of SARS-CoV-2 infection, HBP, ID, and CVD + HBP, there was significantly less time in the AstraZeneca group to report pain, vertigo, weakness, headache, anorexia, nausea, severe allergy, general inflammation, fever>38°C, eye inflammation, diarrhea, blurred vision, injection site redness, fatigue/paleness, joint pain, auxiliary gland inflation, convulsions, and severe side effects compared with the Sinopharm group which could result in more rest/water, acetaminophen, coldax, and naproxen remedies. Due to the lack of adverse effects such as hospitalization, vaccination as an urgent tool for controlling the pandemic should not be halted. In addition, more real-population studies are needed on the long-term effects of vaccination against COVID-19 in the area. Also, a comparison time to report the side effects of non-vaccinated COVID-19 infected participants as another control group with vaccinated groups is recommended.

### Abbreviation list

Severe Acute Respiratory Syndrome-Corona Virus Type 2; SARS-CoV-2

Corona Virus Disease 2019; COVID 19

World Health Organization; WHO

Diabetes mellitus; DM  
 Chronic respiratory disease; CRD  
 Cardiovascular disease; CVD  
 High blood pressure; HBP  
 Immune deficiency; ID  
 IQR; Inter Quartile Range  
 Hazard Ratio; HR  
 Beijing Bio-Institute of Biological Products; BBIBP

#### Availability of Data and Materials

Due to the confidentiality of the work, the datasets generated during the current study are available in the corresponding author contact.

#### Authors' contributions

Zare. M conducted the analysis, interpreted the data, wrote and revised the manuscript, and approved the final version of the manuscript. Mirahmadizadeh. A conducted the study design revised the draft of the manuscript and approved the final version of the work. Karimi. M conducted the study concept, revised the draft of the manuscript, and approved the final version of the work. Khosravi. M prepared the data, revised the draft of the manuscript, and approved the final version of the work. Dehghani. L conducted the analysis, interpreted the data, wrote and revised the manuscript, and approved the final version of the manuscript. All authors are responsible for the accuracy of data (table, figures, etc.)

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#### Conflict of Interests

The authors declare that they have no competing interests.

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