



# Clinical Challenges of the COVID-19 Vaccines: Frequency of Serious Adverse Events After Immunization in Hospitalized Patients

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## Abstract

**Background and aims:** Today, the role of coronavirus disease 19 (COVID-19) vaccines in preventing the disease and reducing the severity of the disease is undeniable; however, there is a possibility of serious adverse events following immunization (sAEFI) that might be life-threatening. The present study was designed to identify the frequency of the most common sAEFI in hospitalized people after receiving the COVID-19 vaccine in the south of Iran.

**Methods:** This cross-sectional study was conducted in 2022. In total, since the start of the COVID-19 vaccination program in the city of Larestan, in the south of Iran, a total of 68 sick people have been hospitalized due to complications caused by the vaccine. The research tool of the present study was a standard checklist called the sAEFI of the COVID-19 vaccine.

**Results:** A total of 68 hospital cases were reviewed. The mean age of the individuals with sAEFI was  $59.78 \pm 12.70$  years, and 21 (56.8%) of them were females. Acute respiratory distress syndrome (ARDS) was the most common 24 (64.9%) sAEFI. Based on the results, 2 (5.4%) had acute coronary syndrome (ACS), 2 (5.4%) had Guillain-Barré syndrome, and 2 (5.4%) had a stroke.

**Conclusion:** It can be mentioned that there is always a possibility of sAEFI, but its frequency in the general population is extremely rare. However, the most common sAEFIs included *adverse drug reactions*, stroke, and Guillain-Barré syndrome. The readiness of health care staff for early detection of possible sAEFI can be effective in reducing the severity of the sAEFI.

**Keywords:** COVID-19, COVID-19 vaccines, Drug-related side effects and adverse reactions, Immunization

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## Introduction

In January 2020, the World Health Organization (WHO) announced the outbreak of COVID-19 as the sixth public health emergency of international concern.<sup>1</sup> There were no effective methods to control the disease before the discovery of the COVID-19 vaccine, and no vaccine against the disease had been globally injected by December 2020; thus, people around the world faced major health challenges, anxiety, and stress during the COVID-19 pandemic.<sup>2</sup> Vaccines are generally the most effective tools for controlling and stopping the COVID-19 pandemic and achieving herd immunity.<sup>3</sup> As of January 2022, approximately 212 vaccines for the prevention of COVID-19 are in various stages of development worldwide, of which about 50 are under clinical evaluation and 162 are in the preclinical development phase.<sup>3</sup> The Pfizer-BioNTech vaccine was the first COVID-19 vaccine to receive emergency use; the second vaccine approved by the United States Food and Drug Administration was

the Moderna-1273 vaccine, which was introduced a week later.<sup>2,4</sup> Both vaccines are mRNA-based and are estimated to be more than 94% effective.<sup>2</sup> The next vaccine is the Sinopharm vaccine from the Wuhan Institute of Biological Products, which is the first COVID-19 inactivated vaccine in the world to receive clinical trial approval; Sinopharm and Sinovac are two inactivated vaccines made in China that are used today.<sup>3</sup> The third phase of clinical trials of the Sinopharm vaccine was shown to be about 79% effective, while its effectiveness in the United Arab Emirates was about 86%.<sup>5</sup> Examination of previous research has demonstrated that the most common side effects following the injection of COVID-19 vaccines include pain, swelling, and redness at the injection site, fever and chills, fatigue, headache, muscle ache, gastrointestinal complications, and pruritus.<sup>6</sup> Another COVID-19 vaccine that has been used worldwide is the Astra-Zeneca vaccine, which has been reported to be up to 90% effective.<sup>7</sup> The Sputnik vaccine, made in Russia, is

another vaccine utilized in some countries of the world.<sup>8</sup> The inactivated COVIran Barekat vaccine made in Iran is also employed in Iran today.<sup>9</sup>

Technological advances and the continuous increase in knowledge about vaccines have led to research focusing on the safety of existing vaccines, which sometimes raises concerns.<sup>10</sup> Any adverse medical event after immunization is called an adverse event following immunization (AEFI). An adverse event may be any unfavorable or unintended disease, sign, or symptom (including an abnormal laboratory finding).<sup>11</sup> According to the form prepared by the WHO (13 April 2021) for standard reporting for AEFI, a sAEFI is an event resulting in hospitalization or prolongation of a hospital stay, persistent or significant disability, congenital malformation/congenital defect or it is either life-threatening or a significant medical event or reaction. The types and characteristics of serious AEFI, especially the rare and extremely rare side effects that may occur following the injection of the COVID-19 vaccine, are currently unknown.<sup>12,13</sup> So far, limited studies have been performed in this field in Iran. Accordingly, the present study was designed to identify the frequency of the most common sAEFI in hospitalized people after getting the COVID-19 vaccine in the cities of Larestan, Evaz, Khonj, and Juyom in the south of Iran in 2022.

## Materials and Methods

### Study Design

The present research was a cross-sectional study designed in 2022.

### Sampling Location

All individuals with sAEFI of COVID-19 vaccines are referred to Imam Reza hospital in Larestan. Imam Reza Hospital, as an educational medical centre, covers 4 cities, including Larestan, Evaz, Khonj, and Juyom. According to the latest census in Iran in 2016, these four cities have a population of about 273,000. These four cities are located in the south of Fars Province in the south of Iran.

### Research Tools

The research tool of the present study was a standard checklist called the sAEFI of the COVID-19 vaccine. The individuals' information, including age, gender, history of underlying disease, vital signs, brand of injected vaccine, injection dose, the time interval between vaccination and hospitalization, duration of hospitalization, initial diagnosis, final diagnosis, PCR test, adverse event outcome, and final opinion of the scientific committee, was recorded in this form.

### Sampling Method

After obtaining the necessary legal and ethical clearance, the researcher referred to Imam Reza Hospital in Lar, examining all the cases of persons who were hospitalized due to sAEFI of the COVID-19 vaccine. From the beginning of the COVID-19 vaccination program in Iran (February

2021) until January 2022, a total of 68 cases were filed in this regard. The individuals' files were analyzed by the hospital scientific committee, and the final opinion on the sAEFI was approved or rejected by this committee. The criteria for inclusion in the study included patients who were admitted to the hospital for the injection of COVID-19 vaccines and for whom a medical record was prepared, the availability of the patients' medical records, and the availability of the required information in the patient's file.

### Committee Considerations

The checklist of sAEFI for the COVID-19 vaccination was prepared by the Center for Infectious Disease Management of the Ministry of Health and Medical Education of Iran and reviewed by the scientific committee of the university. The members of the scientific committee included an anesthesiologist, neurologist, surgeon, head of the hospital, cardiologist, infectious disease specialist, and two internists (one of whom was considered the focal point of vaccine side effects). The classification of people into the sAEFI group was also according to the guidelines and checklist provided by the WHO.<sup>13</sup>

### Statistical Analysis

First, the collected data were entered into Excel 2013 software and then SPSS software (version 19) for analysis. Frequencies (%) and means (standard deviations) were used to report descriptive statistics. An independent t-test was utilized to compare quantitative variables in the group of confirmed and unconfirmed sAEFI. In addition, the Chi-square test was employed to compare qualitative variables in confirmed and unconfirmed groups. The significance level was considered to be 0.05.

### Results

Since the beginning of the COVID-19 vaccination program in the areas covered by Larestan University of Medical Sciences until January 2022, a total of 68 patients have been hospitalized after vaccination. The sAEFI was confirmed for 37 (54.42%) of these people. The mean age of the individuals with sAEFI was  $59.78 \pm 12.70$  years, and females included 21 (56.8%) of them. More than 81% of individuals with sAEFI reported one or more histories of underlying diseases. The mean interval between vaccination and the onset of adverse events was about 8 days. Further, the comparison of the characteristics of the two groups of sAEFI (confirmed and unconfirmed) showed that there was no significant difference between the two groups in terms of the investigated characteristics ( $P < 0.05$ , Table 1). From a total of 185 000 vaccine doses, 37 cases of sAEFI were observed, and the overall incidence was estimated at 20 per 100 000 population (95% CI: 17–32 per 100 000 population).

The data related to the frequency (%) of the most common sAEFIs caused by the injection of COVID-19 vaccines are provided in Table 2. Acute respiratory distress syndrome (ARDS) was the most common 24

**Table 1.** Comparison of Demographic, Clinical, and Vaccine-related Information in the Confirmed Group of Serious AEFI and the Unconfirmed Group

Variables	Confirmed Group of Serious AEFI (n=37)	Unconfirmed Group (n=31)	P Value
Age (Year), Mean±SD*	59.78±12.70	65.80±16.68	0.103**
Gender, n (%)			
Male	16 (43.2)	11 (35.5)	0.515***
Female	21 (56.8)	20 (64.5)	
Underlying disease, n (%)			
Have	30 (81.08)	26 (83.87)	0.742***
Haven't	7 (18.92)	5 (16.13)	
Injection time interval to referral (Day), Mean±SD	8.10±8.00	16.58±22.83	0.057**
Vaccine Brand, n (%)			
Astra-Zeneca	4 (10.8)	5 (16.1)	0.227***
Sinopharm	26 (70.3)	25 (80.6)	
COVIran Barekat	5 (13.5)	0 (0.0)	
Sputnik V	1 (2.7)	0 (0.0)	
AstraZeneca - South Korea	1 (2.7)	1 (3.2)	
Vaccine dose, n (%)			
Dose 1	26 (70.3)	17 (54.8)	0.121***
Dose 2	7 (18.9)	14 (45.2)	
Dose 3	4 (10.8)	0 (0.0)	
Duration of hospitalization (Day), Mean±SD	6.18±4.92	5.06±3.50	0.277**
PCR test, n (%)			
Have	29 (78.4)	21 (67.7)	0.322***
Haven't	8 (21.6)	10 (32.3)	

Note. \* Standard deviation; \*\* Based on the independent t-test results; \*\*\* Based on the chi-square test results; PCR: Polymerase chain reaction; AEFI: Adverse events following immunization.

(64.9%) sAEFI. Overall, 2 (5.4%) had acute coronary syndrome (ACS), 2 (5.4%) had Guillain-Barré syndrome, and 2 (5.4%) had a stroke. Atrial fibrillation [1 (2.7%)], cardiac arrest [1 (2.7%)], encephalomyelitis [1 (2.7%)], hypertension [1 (2.7%)], seizure [1 (2.7%)], sinus arrest [1 (2.7%)], transient ischemic attack (TIA) [1 (2.7%)] were also the other reported sAEFI. In people with unconfirmed sAEFI, the most common diagnoses based on the individual's condition were ARDS, cardiac arrest, and stroke, respectively. Two cases of pneumonia were also diagnosed in this group of people (Table 2).

Of the 37 cases of sAEFI, 26 (70.28%) were caused by the Sinopharm vaccine. In addition, 17 (70.84%) and 5 (20.82%) of ARDS occurred with Sinopharm and COVIran Barekat vaccines, respectively. Of the two cases of Guillain-Barre syndrome diagnosed, 1 (50%) was caused by the Sinopharm vaccine, and 1 (50%) was caused by the AstraZeneca vaccine (Table 3).

## Discussion

The results of the present study showed that there was a possibility of sAEFI in COVID-19 vaccines. ARDS, cardiovascular problems, Guillain-Barré syndrome, and

**Table 2.** Frequency (%) of the Most Common Adverse Effects Based on the Final Decision

Final Diagnosis	Final Decision			
	Confirmed		Rejected	
	No.	%	No.	%
ACS	2	5.40	0	0.00
ARDS	24	64.90	14	45.16
Atrial fibrillation	1	2.70	0	0.00
Cardiac arrest	1	2.70	5	16.13
Encephalomyelitis	1	2.70	0	0.00
Guillain-Barré syndrome	2	5.40	0	0.00
Hypertension	1	2.70	1	3.23
Seizure	1	2.70	0	0.00
Sinus arrest	1	2.70	0	0.00
Stroke	2	5.40	3	9.66
TIA	1	2.70	0	0.00
Cerebral hemorrhage	0	0.00	1	3.23
CHF	0	0.00	1	3.23
Fever	0	0.00	1	3.23
Gastrointestinal problems	0	0.00	1	3.23
Kidney failure	0	0.00	1	3.23
Pneumonia	0	0.00	2	6.44
Sepsis	0	0.00	1	3.23

Note. ACS: Acute coronary syndrome; ARDS: Acute respiratory distress syndrome; TIA: Transient ischemic attack; CHF: Congestive heart failure.

encephalomyelitis were the most common sAEFI.

A study by Sefiani et al in Morocco demonstrated that among more than 8 million vaccinations, 15,187 cases of adverse events following immunization (AEFI) were reported, of which at least 181 (1.2%) were sAEFI. The incidence was higher in this study<sup>14</sup> than in the present study. The incidence of sAEFI was higher in women, the elderly, and individuals with a history of underlying disease. Today, various studies have shown that all types of injectable vaccines in the world are safe and effective in reducing the risk of severe COVID-19 infection. However, all approved vaccines, in addition to the common AEFI such as injection site pain and fever, also cause sAEFI such as anaphylaxis, thrombocytopenia, myocarditis/pericarditis, Guillain-Barré syndrome, acute transverse myelitis, acute disseminated encephalomyelitis, and rhabdomyolysis.<sup>15</sup> The results of this study revealed that 17 cases of ARDS and 2 cases of stroke occurred after the injection of the Sinopharm vaccine. Furthermore, other sAEFIs included atrial fibrillation, cardiac arrest, encephalomyelitis, Guillain-Barré syndrome, hypertension, stroke, and TIA. A study conducted by Xia et al on 320 healthy participants aged 18–59 years reported that fever and pain at the injection site were the most common adverse reactions associated with the Sinopharm vaccine. There was also a transient change in laboratory parameters, such as total lymphocyte count and bilirubin. All these altered laboratory parameters resolved spontaneously without any treatment.<sup>16</sup> According to a

**Table 3.** Frequency (%) of Final Diagnosis of sAEFI Based on Vaccine Brand Name and Outcome

Final Diagnosis	Vaccine Brand Name				
	Sinopharm	Astra-Zeneca	Sputnik V	COVIran Barekat	AstraZeneca - South Korea
ACS	1 (50.00)	1 (50.00)	0 (0)	0 (0)	0 (0)
ARDS	17 (70.84)	0 (0)	1 (4.17)	5 (20.82)	1 (4.17)
Atrial fibrillation	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Cardiac arrest	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Encephalomyelitis	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Guillain-Barré syndrome	1 (50.00)	1 (50.00)	0 (0)	0 (0)	0 (0)
Hypertension	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Seizure	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)
Sinus arrest	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)
Stroke	2 (100)	0 (0)	0 (0)	0 (0)	0 (0)
TIA	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)

Note. ACS: Acute Coronary Syndrome; ARDS: Acute respiratory distress syndrome; TIA: Transient Ischemic Attack; sAEFI: Serious adverse events following immunization; COV: Coronavirus.

study conducted by Aksu and Öztürk in Turkey in 2021, a rare case of shingles was observed after the injection of the covid-19 vaccine.<sup>17</sup> Another study in Italy reported that 4 patients with COVID-19 developed herpes zoster about 5 days after the onset of the disease.<sup>18</sup> Similarly, cases diagnosed with herpes zoster have been detected after recovery from COVID-19.<sup>19,20</sup> Although the cause is not yet known, immunosuppression of live vaccines, which are weakened and reduce reactivity to inactivated vaccines, might account for mechanisms that reactivate herpes zoster.<sup>21</sup> In our study, it was found that the most common sAEFIs that occur after the AstraZeneca vaccine include ACS, Guillain-Barré syndrome, seizures, and sinus arrest.

According to the information reported in this study, this is the first case of an adverse reaction to the AstraZeneca vaccine that has been investigated in detail for skin and systemic autoimmune reactions; however, it appears that there is no evidence of autoimmunity after vaccination. The results indicated that vaccination in susceptible individuals could induce an autoimmune reaction as a natural infection.<sup>22</sup>

So far, limited studies have been conducted in Iran. According to a study by Sahraian et al on 583 patients with multiple sclerosis, the most common AEFI of the Sinopharm vaccine included lethargy, fatigue, fever and chills, general body aches, headaches, and injection site reactions. In this study, no serious adverse events were reported,<sup>23</sup> while in our study, the Sinopharm vaccine was one of the main causes of sAEFI. Another study in Iran that examined the AEFI of the Sputnik vaccine in healthcare workers showed that injection site pain, fatigue, body aches, headaches, fever and chills, and muscle and joint pain were the most common AEFI, and these adverse events were significantly higher in women and young people. These side effects often started within 24 hours of vaccination and resolved in less than three days. sAEFI such as anaphylactic shock in this study were about 0.1%.<sup>24</sup> The only sAEFI reported from this vaccine

in our study was ARDS. All sAEFIs recorded for the COVIran Barekat vaccine in our study were ARDS. Based on the findings of another study in Iran that compared the AEFI of three vaccines, AstraZeneca, Sputnik v, and Covaxin, about 85% of participants reported at least one adverse reaction, with injection site pain, fatigue, muscle aches, headache, fever, and chills being the most common ones. There was AEFI in all three vaccines, which were more common in women than men. The frequency of systemic AEFI was higher in the AstraZeneca vaccine than the other two vaccines, and the incidence of adverse events was higher in people with a body mass index of above 25 in the AstraZeneca and Covaxin vaccines. The frequency of AEFI was higher in the age group less than 40 years than the age group over 40 years, while in our study, the mean age of people with sAEFI was about 60 years.<sup>25</sup>

### Conclusion

ARDS, Guillain-Barré syndrome, cardiovascular problems, and encephalomyelitis were the most common sAEFIs diagnosed in these subjects. Although there is a possibility of sAEFI occurring for COVID-19 vaccines, its incidence is highly rare (20 per 100 000 population), so encouraging the community to inject the vaccine should still be taken into consideration. Necessary education about the possibility of sAEFI and its associated symptoms is important for all people. The readiness of health care staff for early detection of possible sAEFI can be effective in reducing the severity of the sAEFI. It is recommended that other researchers in the world design more research to clarify the possibility of the occurrence of sAEFI for COVID-19 vaccines.

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**Authors' Contribution****Conceptualization:** Hamed Delam.**Data curation:** Sahar Akbarpoor.**Formal analysis:** Hamed Delam.**Investigation:** Atefeh Ghadri.**Methodology:** Hamed Delam.**Project administration:** Behzad Rezaei, Zahra Keshtkaran.**Writing—original draft:** Hamed Delam, Atefeh Ghadri, Zahra Keshtkaran, Behzad Rezaei.**Writing—review & editing:** Hamed Delam, Atefeh Ghadri.**Competing Interests**

The authors declare that there is no conflict of interests.

**Data Availability Statement**

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

**Ethical Approval**

The present study, with the code of IR.LARUMS.REC.1400.026, was approved by the Ethics Committee of Larestan University of Medical Sciences. Patient information remained confidential throughout the study.

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**Informed Consent**

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