# Comparison of severe acute respiratory syndrome coronavirus 2 (COVID-19) vaccine side effects by age groups

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# **SUMMARY**

**OBJECTIVE:** This online survey aims to compare the side effects that may occur after inactivated severe acute respiratory syndrome coronavirus 2 (COVID-19) vaccination by age groups.

METHODS: A total of 411 participants aged 18-100 who received inactivated coronavirus disease 2019 vaccine were included in the study.

**RESULTS:** Participants were divided into four groups according to their ages (i.e., 20–35, 36–50, 51–65, and over 65 years old). Vaccine-related side effects were primarily seen in the 20–35 age group and at least in the >65 age group (p<0.001). The most common side effects were pain, redness, swelling, and numbness at the injection site. Fatigue and headache were other common side effects. After vaccination, 3 (0.73%) participants had hypertension, and 1 (0.24%) had an asthma attack and was admitted to the hospital. No severe side effects were observed in any of the patients. The most critical factors determining the development of side effects were female gender and young age.

**CONCLUSION:** According to the results of this study, different types and rates of side effects are seen in all age groups after the inactivated coronavirus disease 2019 vaccine. Since the 20–35 age group and female gender are at risk of side effects, it would be more appropriate to follow up the side effects after vaccination according to gender and age.

KEYWORDS: Age groups. SARS-CoV-2. Inactivated vaccine. Adverse effects.

# INTRODUCTION

The coronavirus disease 2019 (COVID-19) outbreak caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), which was declared a pandemic by the World Health Organization on March 11, 2020, is the most important health problem of the 21st century<sup>1</sup>. The high contagiousness of the virus and the absence of treatments that can improve the prognosis of the disease increase the importance of effective and safe vaccines against this disease. For this reason, different types of vaccines have been developed against COVID-19 around the world.

Inactivated COVID-19 vaccine is a non-living virus vaccine that can create an immune response in the body, obtained by eliminating the disease-causing feature of the SARS-CoV-2 virus that causes COVID-19 through chemical and physical applications<sup>2</sup>. In our country, mass vaccination was initiated for the COVID-19 pandemic with this inactivated COVID-19 vaccine as of January 14, 2021, with a total of two doses at 4-week intervals for people aged 18 years and above<sup>3</sup>. A phase 3 study conducted in our country with this vaccine shows that it can be used effectively and reliably against COVID-19<sup>4</sup>. Despite the fact that there are sufficient scientific studies on the side effects, risks, and efficacy of this new vaccine, there are some hesitations in the society for vaccine-related side effects. This study aimed to compare the side effects that may occur after vaccination according to age groups by analyzing the safety and more detailed side-effect profile of the inactivated COVID-19 vaccine using an online questionnaire to respond to these hesitations.

#### **METHODS**

Ethics committee approval was received for our study from both the Ministry of Health (approval number: 2021-02-26T10\_33\_23) and Adiyaman University Clinical Research Ethics Committee (date: March 16, 2021, protocol number: 2021/03-11). A total of 411 participants who were given the COVID-19 vaccine (CoronaVac, Sinovac Life Sciences, Beijing, China) and lived in Adiyaman between the ages of 18 and 100 years participated in the study. Participants were divided into

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four groups (i.e., 20–35, 36–50, 51–65, and above 65 years) according to age.

In our study, an online questionnaire was used as the data source. The consent of the volunteers who filled out and approved the online questionnaire was accepted. The researchers shared the online questionnaire form on the web for about 1 month (March 17, 2021, to April 10, 2021). During this period, 614 people who were previously vaccinated were reached via telephone, email, and WhatsApp. The participation rate in the study was 67%.

Online survey forms the age, gender, systemic diseases, medications used, allergic conditions, profession of people who have received COVID-19 vaccine, whether the COVID-19 test was performed during the epidemic, or whether there was contact with someone who had a positive COVID-19 test, it was composed of a total of 16 questions, including the absence of the disease, thoughts about the vaccine and the side effects after the vaccination, and whether he/she had COVID-19 disease after vaccination.

#### **Statistical analysis**

SPSS program (Statistical Package for Social Science version 21, IBM Corp., Chicago, IL, USA) was used to analyze the data. The chi-square test was used to compare categorical data by groups. Kruskal-Wallis test and Mann-Whitney U test were used to compare the continuous data. Continuous data were given as mean±standard deviation or median (range), and categorical data were presented as n (%). Logistic regression analysis was performed to predict vaccine-related side effects. 95% of confidence intervals (CIs) were used; p<0.05 was considered statistically significant.

## RESULTS

Detailed sociodemographic characteristics of the participants by age groups are given in Table 1. Accordingly, gender distribution, allergic disease history, COVID-19 disease history in the past 6 months, post-vaccination COVID-19 infection status, and the number of vaccine-related side effects were similar in all four age groups (p>0.05). However, vaccine-related side effects were most common in the 20–35 age group (118, 68.2%), while they were least common in the >65 age group (31, 38.8%) (p<0.001). During the pandemic period, the status and results of the COVID-19 test differed between the groups (p<0.001). As expected, when the groups were compared in terms of occupations, most of the >65 age group were retired or housewives. In addition, there was an increase in systemic disease rates with age (p<0.001). The incidence of vaccine-related side effects according to age groups is shown in Table 2. Accordingly, the most common side effects are pain in the vaccinated area, redness, swelling and numbness, fatigue, headache, a tendency to sleep, and muscle joint pain. When the vaccine-related side effects were compared according to the groups, pain, redness, swelling and numbness complaints, fatigue, and tendency to sleep were primarily seen in the 20–35 age group; headache was mostly seen in the 36–50 age group and fever was primarily seen in the 51–65 age group (p<0.05). There was no statistically significant difference between the groups in terms of other vaccine-related side effects (p>0.05).

In Table 3, the parameters (i.e., age, gender, systemic diseases, and allergic conditions) of the participants in the study that may affect the occurrence of side effects against the vaccine were compared. Accordingly, lower mean age (p<0.001), more female gender (p<0.001), and more allergic diseases (p=0.037) were detected in the group with side effects. In the binary logistic regression analysis conducted to evaluate whether age, gender, systemic disease, and allergic condition can be used to predict vaccine-related side effects, it was found that only age and gender could be used in prediction (p<0.001, Nagelkerke R<sup>2</sup>: 0.181). The odds ratio was 1.04 (95%CI 1.02–1.05, p<0.001) for age and 3.2 (95%CI 2.1–4.9, p<0.001) for gender.

#### DISCUSSION

The COVID-19 pandemic is a serious public health emergency due to the high contagiousness of the virus and the lack of effective treatment<sup>5</sup>. For this reason, vaccines in different categories have been developed in many countries and started to be applied in our country and all over the world. With the onset of vaccination, there have been some hesitations in society since there are not enough scientific studies on the side effects, allergy risks, and efficacy of these new vaccines. In this study conducted to respond to these hesitations, the distribution of the detailed side-effect profile of the inactivated COVID-19 vaccine applied in our country according to age groups was evaluated. In the literature, the incidence of mild and moderate side effects is between 17% and 47% in studies conducted with inactivated COVID-19 vaccine<sup>6-10</sup>. In only one of these studies, serious side effects such as hypersensitivity reaction have been reported. None of the participants had severe vaccine-related side effects in our study, and approximately 60% of the participants had mild or moderate side effects. The high rate of mild side effects in our study may be due to the heterogeneity of the participant population. The incidence of moderate side effects was similar to the studies in the literature.

Of the 4 (0.9%) participants who developed mild side effects, 3 (0.7%) had to apply to the hospital because hypertension developed, and 1 (0.2%) had an asthma attack. However, it is necessary to investigate whether these disease exacerbations are related to vaccination in the literature, primarily as side effects attributed to vaccination, but not proven<sup>11</sup>. Post-vaccination fatigue, headache, fever, tremor, muscle/joint pain, vomiting, diarrhea, and systemic and local side effects such as pain, redness, and swelling in the vaccinated area can be seen in patients who received inactivated COVID-19 vaccine<sup>12</sup>. The frequency of side effects may vary according to the demographic characteristics of the study population. In a phase I study conducted with a total of 192 people with BBIBP-CorV, an inactivated COVID-19 vaccine, 42% of side effects were observed in the

18-59 age group and 17% in the >60 age group in the first 7 days after vaccination<sup>10</sup>. Unlike this study, although the incidence of side effects was higher in all age groups (59.9%), the highest was found in the 25-35 age group (68.2%) and the lowest in the >65 age group (38.8%), similar to the literature.

Although there are different results in the literature about the most common types of vaccine-related side effects, local side effects are more common than systemic side effects. In phase I and phase II studies conducted with inactivated COVID-19 vaccines, injection site pain, the most common local side effect in the young age group (<60 years), varies between 5% and 35.0%<sup>6,7,10,13</sup>. Similarly, the most common side effect in the >60 age group is injection site pain $^{9,10}$ . However, this side effect is seen at lower rates in the >60 age group compared to

Table 1. Characteristics of	patients by age groups.
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·	Age	20-35 years	36–50 years	51–65 years	>65 years	
	n	173	119	39	80	р
Gender (n, %)	Female	84 (48.6)	48 (40.3)	19 (48.7)	36 (45.0)	0.552
	Male	89 (51.4)	71 (59.7)	20 (51.3)	44 (55.0)	
Professions (n, %)	Retired	0 (0.0)	0 (0.0)	6 (15.4)	42 (52.5)	< 0.001
	Housewife	0 (0.0)	0 (0.0)	13 (33.3)	34 (42.5)	
	Health professions	76 (43.9)	88 (73.9)	18 (46.2)	0 (0.0)	
	Others	97 (56.1)	31 (26.1)	2 (5.1)	4 (5.0)	
	None	151 (87.3)	93 (78.2)	10 (25.6)	16 (20.0)	<0.001
	Hypertension	2 (1.2)	4 (3.4)	14 (35.9)	22 (27.5)	
	Cardiovascular disease	2 (1.2)	2 (1.7)	4 (10.3)	16 (20.0)	
Systemic diseases (n, %)	Asthma	6 (3.5)	4 (3.4)	2 (5.1)	7 (8.8)	
	Diabetes	1 (0.6)	5 (4.2)	3 (7.7)	9(11.3)	
	Goiter	4 (2.3)	4 (3.4)	4 (10.3)	7 (8.8)	
	Others	7 (4.0)	7 (5.9)	2 (5.1)	3 (3.8)	
Continuous drug use (n, %)		26 (15.0)	19 (16.0)	26 (66.7)	56 (70.0)	<0.001
Allergic disease (n, %)		36 (20.8)	27 (22.7)	9 (23.1)	11 (13.8)	0.430
Has the COVID test been	None	91 (52.6)	43 (36.1)	19 (48.7)	60 (75.0)	<0.001
done in the pandemic? (n, %)	Positive	29 (16.8)	20 (16.8)	6 (15.4)	7 (8.8)	
	Negative	53 (30.6)	56 (47.1)	14 (35.9)	13 (16.3)	
Have you had COVID in the last 6 months? (n, %)	No	131 (75.7)	89 (74.8)	33 (84.6)	71 (88.8)	0.067
	Unknown	6 (3.5)	8 (6.7)	0 (0.0)	1 (1.3)	
	Treatment in home	26 (15.0)	20 (16.8)	6 (15.4)	7 (8.8)	
	Treatment in hospital	1 (0.6)	1 (0.8)	0 (0.0)	1 (1.3)	
	Other*	9 (5.2)	1 (0.8)	0 (0.0)	0 (0.0)	
Side effect (n, %)		118 (68.2)	75 (63.5)	22 (56.4)	31 (38.8)	<0.001
How many side effects were there? (Median, range)		2 (1-15)	2 (1-9)	2 (1-8)	1 (1-5)	0.575
Have you had COVID-19 post-vaccination? (n, %)		2 (1.2)	4 (3.4)	0 (0.0)	1 (1.3)	0.882

\*I think I have the infection, but I have not been tested.

the younger age group (9–13% vs. 5–35.0%). Similar to the literature, in our study, the most common side effect in all age groups was redness and pain at the vaccine site. According to our results, the incidence of this side effect decreases with age. This finding is consistent with the literature. However, we think the possible reason for the higher incidence of local side effects than the literature is that we expressed all the side effects (e.g., complaints of pain, redness, swelling, and numbness in the vaccine area) developing at the vaccine site in a single question.

There are different results in the literature regarding the incidence of systemic side effects due to the inactivated COVID-19 vaccine. In the study conducted by Xia et al.<sup>10</sup>, it was found

Table 3. Factors that may affect the development of side effects.

		With side effects	No side effects	р	
		246	165		
Age (mean±SD)		39.4+16.5	48.4+19.9	<0.001	
Gender (n, %)	Female	139 (56.5)	48 (29.1)	<0.001	
	Male	107 (43.5)	117 (70.9)		
Systemic diseases (n, %)		79 (32.1)	62 (37.6)	0.253	
Allergic disease (n, %)		58 (23.6)	25 (15.2)	0.037	

SD: standard deviation.

	Age	20-35 years	36-50 years	51–65 years	>65 years	
	n	173	119	39	80	р
Local side effects	Complaints of pain, redness, swelling, and numbness in the vaccine area (n, %)	116 (67.1)	62 (52.1)	13 (33.3)	23 (28.7)	<0.001
	Fatigue (n, %)	55 (31.8)	24 (20.2)	6 (15.4)	8 (10.0)	0.001
	Headache (n, %)	35 (20.2)	29 (24.4)	8 (20.5)	6 (7.5)	0.025
	Somnolence (n, %)	26 (15.0)	15 (12.6)	4 (10.3)	2 (2.5)	0.033
	Muscle-joint pain (n, %)	20 (11.6)	15 (12.6)	5 (12.8)	3 (3.8)	0.180
	Dizziness (n, %)	9 (5.2)	6 (5.0)	3 (7.7)	5 (6.3)	0.917
	Fever (n, %)	6 (3.5)	0 (0.0)	4 (10.3)	2 (2.5)	0.011
	Back pain (n, %)	9 (5.2)	3 (2.5)	2 (5.1)	0 (0.0)	0.054
	Lumbago (n, %)	8 (4.6)	5 (4.2)	1 (2.6)	0 (0.0)	0.088
	Throat ache (n, %)	6 (3.5)	1 (0.8)	0 (0.0)	3 (3.8)	0.186
	Sweating (n, %)	4 (2.3)	3 (2.5)	1 (2.6)	1 (1.3)	0.934
	Abdominal pain (n, %)	5 (2.9)	2 (1.7)	0 (0.0)	2 (2.5)	0.517
	Dryness of throat (n, %)	7 (4.0)	1 (0.8)	1 (2.6)	0 (0.0)	0.068
	Tremor (n, %)	8 (4.6)	2 (1.7)	3 (7.7)	1 (1.3)	0.163
Systemic side	Difficulty breathing (n, %)	3 (1.7)	1 (0.8)	2 (5.1)	1(1.3)	0.468
0110000	Loss of taste (n, %)	4 (2.3)	1 (0.8)	1 (2.6)	0 (0.0)	0.291
	Hypertension (n, %)	0 (0.0)	2 (1.7)	2 (5.1)	2 (2.5)	0.077
- - - - - - - - - - - - - - - - - - -	Palpitation (n, %)	2 (1.2)	2 (1.7)	0 (0.0)	1 (1.3)	0.765
	Itching (n, %)	1 (0.6)	0 (0.0)	0 (0.0)	1(1.3)	0.524
	Vomiting (n, %)	4 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	0.073
	Nasal Discharge (n, %)	1 (0.6)	3 (2.5)	0 (0.0)	0 (0.0)	0.194
	Cough (n, %)	3 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0.156
	Diarrhea (n, %)	2 (1.2)	1 (0.8)	0 (0.0)	0 (0.0)	0.546
	Hallucination (n, %)	2 (1.2)	0 (0.0)	1 (2.6)	0 (0.0)	0.223
	Fainting (n, %)	1 (0.6)	0 (0.0)	1 (2.6)	2 (2.5)	0.098
	Skin rash (n, %)	1 (0.6)	1 (0.8)	0 (0.0)	2 (2.5)	0.623
	Speech disorder (n, %)	1 (0.6)	0 (0.0)	1 (2.6)	0 (0.0)	0.297
	Anosmia (n. %)	3(17)	0(00)	0(00)	0(00)	0.156

#### Table 2. Distribution of side effects by age groups.

that the incidence of fever, which is the most common systemic side effect, was 6% in the <60 age group and 1% in the 60-age group and above. In the phase II study of the same vaccine, fever was detected in 2% of the participants in all age groups. In other inactivated COVID-19 vaccine studies, it has been shown that the incidence of fatigue, which is seen as the most common systemic side effect, varies between 6% and 10%<sup>7,13,14</sup>. In another inactivated COVID-19 vaccine study conducted with healthy people over the age of 60, the most common systemic side effect was fever (3%)8. Since the comparison of COVID-19 vaccine side effects by age groups in the literature was not made in detail as in our study, sufficient comparison could not be made. In our study, fatigue was the most common systemic side effect in the 20–35 age group and >65 age group, while headache was more common in the 36-50 age group and 51-65 age group, and fever was more common in the 51-65 age group. Somnolence, muscle joint pain, and dizziness were less common systemic side effects. The fact that systemic side effects are seen at different rates according to age groups fits the purpose of our study.

The development of post-vaccination anaphylaxis is one of the most severe side effects of vaccines<sup>15,16</sup>. Current reports from the Centers for Disease Control and Prevention (CDC) show that anaphylactic reactions to the BNT162b2 mRNA vaccine may occur more frequently than other vaccines<sup>17</sup>. On December 14–23, 2020, 21 cases of anaphylaxis were identified after the administration of the reported 1,893,360 first doses of Pfizer-BioNTech COVID-19 vaccine (11.1 cases per million doses). Similarly, in a review of COVID-19 vaccines by Kaur et al.<sup>18</sup>, serious vaccine side effects were not associated with inactivated vaccines. In our study, none of the participants developed severe side effects such as anaphylaxis supports this information.

The most important limitation of our study was due to involuntary errors that may occur due to the way the data were collected. In addition, the selection of cases from a single region, the time of onset of symptoms after vaccination, and the inability to provide specific data on the duration of symptoms were among our other limitations. However, it was the

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superiority of our study to investigate the factors affecting the side effect against inactivated COVID-19 vaccines. Another advantage of our study was that side effects were examined in detail according to age groups, unlike other studies. The most important factors determining the development of side effects were found to be female gender and young age.

#### **CONCLUSIONS**

According to our study, side effects after inactivated COVID-19 vaccine were most common in female gender and 20–35 age group, while vaccine-related side effects were least common in >65 age group. The most common vaccine-related side effects were pain, redness, swelling, and numbness in the vaccinated area, while the most common systemic side effect was fatigue. Most of the reported side effects were mild, and no severe side effects such as anaphylaxis were observed. According to these findings, it may be necessary to be more careful about side effects, especially in women and young people, after inactivated COVID-19 vaccine administration.

## ETHICAL ASPECTS

Approval for this study was obtained from the Ministry of Health (decision no: 2021-02-26T10\_33\_23) and Adıyaman University Clinical Research Ethics Committee (date: March 16, 2021, decision no: 2021/03-11).

## **AUTHORS' CONTRIBUTIONS**

**FT:** Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. **MB:** Conceptualization, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **İT:** Conceptualization, Data curation, Project administration, Resources, Software, Validation, Visualization.

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