ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

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# Local and Systemic Adverse Effects of CoronaVac Vaccine in Risk Groups: Prospective, Cross-Sectional Study

## CoronaVac Aşısının Risk Gruplarında Lokal ve Sistemik İstenmeyen Etkilerinin Değerlendirilmesi: Prospektif, Kesitsel Çalışma

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**ABSTRACT Objective:** Coronavirus disease-2019 (COVID-19) infection progresses as an asymptomatic disease in some cases, whereas as a symptomatic disease and fatal in other cases. Due to its high spread, vaccines have been produced in many countries to control the infection. We aimed to evaluate local and allergic adverse effects of the CoronaVac vaccine in the risk group such as healthcare workers, individuals over 65 years of age, individuals who had COVID-19 infection. **Material and Methods:** A total of 189 healthcare workers and 122 individuals over the age of 65 who received the 2nd dose of CoronaVac vaccine 20 days ago were included in the study. Allergic, systemic and local symptoms were evaluted through a questionnaire which included 50 questions. **Results:** The most common local symptom was pain at the injection site (48.6%) and the most common systemic skin symptom after vaccination is pruritus outside the injection site (2.3%). There was a significant increase in symptoms of pruritus outside the injection site, rash outside the injection site, maculopapular rash, swelling around the eyelids, lips, or mouth, pale, sweaty, cold skin (vasovagal reflex) fever, chills, shortness of breath in participants who had COVID-19 infection ($p<0.05$). Symptoms of swelling around the eyelids, lips, and mouth, urticarial lesions outside the injection site were found to be significantly increase in indivuduals with a positive allergy history ($p<0.05$). **Conclusion:** Our study determined that the inactivated CoronaVac vaccine is safe in terms of serious adverse reactions in risk group. Therefore, CoronaVac vaccine has also adverse effect profile like other vaccines.

**Keywords:** Local adverse effects; systemic adverse effects; CoronaVac vaccine

**ÖZET Amaç:** Koronavirüs hastalığı-2019 [coronavirus disease-2019 (COVID-19)] enfeksiyonu, bazı durumlarda asemptomatik bir hastalık olarak ilerlerken, bazı durumlarda semptomatik ve ölümcül olabilmektedir. Yüksek yayılımı nedeniyle birçok ülkede bu enfeksiyonu kontrol altına almak için aşılar üretilmiştir. Çalışmamızda; sağlık çalışanları, COVID-19 enfeksiyonu geçiren ve 65 yaş üstü gibi risk grubunda olan bireylerin, CoronaVac aşısının lokal ve sistemik istenmeyen ve alerjik etkilerini değerlendirmeyi amaçladık. **Gereç ve Yöntemler:** Çalışmaya 20 gün önce 2. doz CoronaVac aşısı olan 189 sağlık çalışanı ve 65 yaş üstü 122 birey dâhil edildi. Sistemik, lokal istenmeyen ve alerjik semptomlar 50 soruluk bir anket ile değerlendirildi. **Bulgular:** Aşı sonrası gelişen en sık gözlenen lokal semptom enjeksiyon yerinde ağrı (%48,6) ve en sık gözlenen sistemik deri semptomu ise enjeksiyon bölgesi dışında kaşıntı (%2,3) idi. COVID-19 enfeksiyonu geçiren katılımcılarda bu enfeksiyonu geçirmeyenlere göre enjeksiyon bölgesi dışında kaşıntı, enjeksiyon bölgesi dışında döküntü, makülopapüler döküntü, göz kapakları, dudaklar veya ağız çevresinde şişlik, soluk, terli, soğuk cilt (vazovagal refleks), ateş, titreme, nefes darlığı semptomlarında önemli bir artış vardı ($p<0,05$). Alerjik hastalık öyküsü pozitif olanlar ve olmayanlar kıyaslandığında, alerjik hastalık öyküsü pozitif olanlar da göz kapakları, dudaklar ve ağız çevresinde şişlik, enjeksiyon bölgesi dışındaki ürtiker gözlenen birey sayısında belirgin artış saptandı ($p<0,05$). **Sonuç:** Çalışmamız, inaktif CoronaVac aşısının risk grubunda bulunan bireylerde ciddi yan etkiler açısından güvenli olduğunu göstermiştir. CoronaVac aşısının, daha önce kullanılan diğer aşılarla benzer oranda yan etki profiline sahip olduğu kanaatine varılmıştır.

**Anahtar Kelimeler:** Lokal yan etkiler; sistemik yan etkiler; CoronaVac aşısı

Coronavirus disease-2019 (COVID-19) is a respiratory disease caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) that emerged in China in December 2019 and has spread to many countries of the world since then.[1] COVID-19 has spread worldwide, becoming a global pandemic affecting more than 156 million people as of May 2021 and caused more than 3,200,000 deaths.[2] COVID-19

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infection progresses as an asymptomatic disease in some cases, whereas as a symptomatic disease and fatal in other cases. Measures such as social distance, hygiene and masks have been implemented in the world to prevent COVID-19 infection.[1,2] However, the use of an effective vaccine against COVID-19 has been very important in protecting from infection and maintaining normal life. Currently, many vaccines have been approved for various countries. In our country, inactivated SARS-CoV-2 vaccine with aluminum hydroxide originating from China and a vaccine known as CoronaVac, of which phase-3 studies have been completed, is applied.

The SARS-CoV-2 virus was grown and produced in Vero cells in CoronaVac (Sinovac, China) vaccine. The virus produced was inactivated using-propiolactone and further purified. The bulk vaccine material obtained from this step was then adsorbed in aluminum hydroxide, formulated with sodium chloride as the final product and inactivated with phosphate buffered saline (PBS).[3]

Vaccination is the most effective public health practice in preventing infectious diseases with high morbidity and mortality. In the past, infectious diseases have decreased significantly with the increase in vaccination rate. The most important adverse effects of these are severe allergic reactions. However, severe allergic responses to the vaccine is rare and difficult to predict, they can occur in any individual.[4]

Confirmed allergic reactions to vaccines are often thought to be due not to active ingredients but rather to inactive ingredients or excipients including egg protein, gelatin, formaldehyde, aluminum hydroxide, thimerosal, or neomycin.[5] It has been shown in studies that there are various skin reactions such as urticaria and angioedema after vaccinations.[6-8] In addition, almost all vaccines have the potential to trigger anaphylaxis and all ingredients of the vaccine can cause anaphylaxis.

Allergic reactions are commonly immunoglobulin (Ig) E-mediated. Symptoms range from relatively mild skin signs and symptoms (erythema and pruritus) to multisystem involvement (anaphylaxis). With this classification, IgE-mediated reactions (Type I immunological reaction) (e.g., anaphylaxis) that are life-threatening and must be evaluated urgently and they are distinguished from other types.[9,10]

Local reactions are the most common adverse event after vaccination and have a significant impact in clinical practice.[8]

The fastest period for a vaccine to be developed and approved is for the mumps vaccine, which takes about 5 years.[4] Therefore, developing a vaccine against COVID-19 over 12-24 month period is clearly a challenge. Therefore, many clinical follow-up and studies are needed to investigate the adverse effects of vaccines against COVID-19. In our study, based on this requirement, we aimed to evaluate local and systemic allergic adverse effects of the CoronaVac vaccine, which is currently applied in our country, in individuals who are considered to be in the risk group, such as healthcare workers (HCWs), individuals who have history of COVID-19 infection and individuals over age of 65.

## MATERIAL AND METHODS

### COLLECTION OF DATA

This study was approved by Adıyaman University Ethics Committee for Non-interventional Procedures (Date: 16.03.2021, No: 2021/03-10). Each participants gave written informed consent. This study, a cross-sectional questionnaire study, was conducted at a tertiary healthcare institution that served as a pandemic Adıyaman University Faculty of Medicine Hospital between 01 March-15 April 2021. A total of 189 volunteer HCWs, 122 volunteers over the age of 65 who received the 2nd dose of CoronaVac vaccine 20 days ago were included in the study.

An online questionnaire consisting of 50 questions was applied to the participants. Inclusion criteria in the study were having administered the 2nd dose of CoronaVac vaccine 20 days ago, being over 18 years old, having the education level to understand and answer the questions.

### DESIGN OF QUESTIONNAIRE

Sociodemographic characteristics such as gender, age, profession (healthcare professional, physician,

nurse/midwife, or others), history of any allergic disease (asthma, allergic rhinitis, allergic conjunctivitis, atopic dermatitis), history of comorbid diseases (hypertension, diabetes mellitus, coronary artery disease, hyperlipidemia...), the history of reaction to any previous vaccine, history of allergy to drugs, vaccines, foods, and other substances, the presence of previous COVID infection [polymerase chain reaction (PCR) positivity] were questioned.

Allergic symptoms (urticarial lesion outside the injection site, swelling around the lips, eyelid, and mouth, anaphylaxis, rash outside the injection site, maculopapular eruption, pruritus outside the injection site, shortness of breath) and local symptoms (pain, redness, swelling, fever, rash, acne, nodule, abscess, inflammation at the injection site) and undesirable symptoms (fever, nausea-vomiting, muscle and joint pain, headache, shortness of breath, pale, sweaty, cold skin) that could occur after the 1st dose and 2nd dose CoronaVac vaccine were also questioned.

### STATISTICAL METHODS

This is a prospective cross-sectional descriptive study. All data were evaluated using a statistical package program. Descriptive statistics were expressed in numbers and percentages. McNemar test was used to compare systemic reactions that occurred after the 1st dose and the 2nd dose, which are among the categorical variables. Again, the chi-square or the Fischer exact chi-square test was used in the evaluation of systemic and local reactions that occurred after the first and second dose of CoronaVac vaccine.

## RESULTS

### DEMOGRAPHIC DATA

A total of 311 individuals (female; n=177 56.9%, male; n=134 43.1%) were included in the study. The mean age of the participants was 44.12±16.30 years. The age range was between 21-89. While 189 (60.8%) of the participants were HCWs, 122 (39.2%) were not HCWs. When we look at the allergy histories, 15 of the participants (4.8%) had history of allergic asthma, 16 (5.1%) of them had history of atopic dermatitis, 20 (6.5%) of them had history of allergic rhinitis, 17 (5.5%) of them had history of allergic conjunctivitis, 10 (3.2%) of them had history of urticaria, 4 (1.3%) of them had history of angioedema.

While 16 participants (5.1%) had a reaction against any vaccine before, 295 (94.9%) of them had no vaccine reaction. Again, 51 (16.3%) of the participants had COVID-19 infection, which was confirmed with PCR positivity 6 months ago, while 260 (83.6%) individuals did not have COVID-19 infection. The chronic disease distribution of the participants is shown in Table 1.

### DISTRIBUTION OF LOCAL AND SYSTEMIC SYMPTOMS OCCURRING AFTER THE 1st DOSE AND THE 2nd DOSE OF THE VACCINE

Local reactions occurring after the 1st dose and the 2nd dose of the vaccine are shown in Table 2. The

**TABLE 1:** Demographic characteristic of the participants.

| Characteristic of the participants | n (%) |
|---|---|
| Demographic characteristic | |
| Age | 44.12 (±16.3) |
| Female | 177 (56.9) |
| Male | 134 (43.1) |
| History of allergic disease | |
| Allergic asthma | 15 (4.8) |
| Atopic dermatit | 16 (5.1) |
| Allergic rhinitis | 20 (6.5) |
| Allergic conjunctivitis | 17 (5.5) |
| Urticaria | 10 (3.2) |
| Angioedema | 4 (1.3) |
| Other | |
| History of allergic symptoms after a vaccination | 16 (5.1) |
| Number of healthcare workers | 189 (60.8) |
| Those who had COVID-19 | 51 (16.3) |
| Hypertension | 23 (7.3) |
| Diabetes mellitus | 15 (4.8) |
| Coronary artery disease | 17 (5.4) |
| Hyperlipidemia | 19 (6.1) |
| Hypothyroidism | 12 (3.8) |
| Multinodular goiter | 8 (2.5) |
| Gastric ulcer | 21 (6.7) |
| Asthma | 15 (4.8) |
| Anxiety | 24 (7.7) |

most common symptom was pain at the injection site after 1st and 2nd doses. It was detected in 125 (48.6%) participants after the 1st dose and 100 (38.9%) participants after the 2nd dose. Abscess and inflammation at the injection site and rash and peeling at the injection site were least described local reactions with 3 participants (1.0%) after the 1st dose and 1 person (0.3%) after the 2nd dose. Erythema and edema were reported in 3 of the participants, acne in 7 (2.3%), and pruritus in 18 (5.8%) of the participants after the 1st dose of the vaccine. There was no difference between the 1st dose and the 2nd dose in all local symptoms (p>0.05).

Systemic reactions occurring after the 1st dose and the 2nd dose of the vaccine are shown in Table 3. The most common systemic skin symptom was pruritus outside the injection site. There was a significant difference between the 1st and 2nd doses in symptoms such as pruritus outside the injection site and rash outside the injection site swelling around eyelids, lips and mouths, muscle and joint pain (p<0.05). No difference was observed between the two doses in other systemic symptoms (p>0.05).

## DISTRIBUTION OF LOCAL AND SYSTEMIC SYMPTOMS OCCURRING AFTER VACCINATION IN RISK GROUPS

There was no difference between the HCWs and non-HCWs in terms of symptoms of local reaction (redness, swelling, abscess, nodule, rash) and systemic symptoms such as pruritus outside the injection site, rash outside the injection site, milimetric red rashes all over the body, urticarial lesion outside the injection site, swelling around the eyelids, lips, or mouth, pale, sweaty, cold skin (vasovagal reflex), fever, chills, and shaking, and shortness of breath (p>0.05) (Table 4). There was a significant increase in the participants who had COVID-19 infection in terms of symptoms such as pruritus outside the injection site, rash outside the injection site, maculopapular eruption (milimetric red rashes all over the body), swelling around the eyelids, lips, or mouth, pale, sweaty, cold skin (vasovagal reflex) fever, chills, and shaking, shortness of breath (p<0.05) (Table 4). In local reactions and urticarial lesions outside the injection site, there was no difference between the participants who had COVID-19 infection and who did not (p>0.05).

When participants who had a vaccine reaction before and who did not have were compared, a difference was found between them in terms of symptoms such as pruritus outside the injection site, rash outside the injection site, urticarial lesion outside the injection site, swelling around the eyelids, lips, or mouth (p<0.05). These symptoms were significantly increased in individuals who had a previous reaction to any vaccine. However, there was no significant difference between these 2 groups in local symptoms (redness, swelling, abscess, nodule, rash), macu-

**TABLE 2:** Comparison of local symptoms and reactions at injection site after first dose and second dose vaccine.

| | First dose n=311 | Second dose n=311 | p value |
|---|---|---|---|
| Tenderness | 90 (35%) | 73 (28.4%) | 0.051 |
| Pain | 125 (48.6%) | 100 (38.9%) | 0.054 |
| Erythema | 17 (5.5%) | 14 (4.5%) | 0.67 |
| Edema and swelling | 17 (5.5%) | 12 (3.9%) | 0.38 |
| Pruritus | 18 (5.8%) | 11 (5.8%) | 0.24 |
| Numbness. tingling | 24 (7.7%) | 19 (6.1%) | 0.48 |
| Rash and peeling | 3 (1%) | 5 (1.6%) | 0.68 |
| Acne | 7 (2.3%) | 5 (1.6%) | 0.72 |
| Nodule | 6 (1.9%) | 8 (2.6%) | 0.77 |
| Abscess and inflammation | 3 (1.0%) | 5 (1.6%) | 0.68 |

Analyzed by McNemar test; p<0.05 is significant.

**TABLE 3:** Comparison of systemic reactions after first dose and second dose vaccine.

| | First dose n=311 | Second dose n=311 | p value |
|---|---|---|---|
| Pruritus outside the injection site | 6 (1.9%) | 15 (4.8%) | **0.03** |
| Millimetric red rashes all over the body (maculopapuler rash) | 2 (0.6%) | 4 (1.2%) | 0.68 |
| Urticaria lesion outside the injection site | 4 (1.2%) | 7 (2.3%) | 0.45 |
| Swelling around the eyelids, lips and mouth | 2 (0.6%) | 9 (2.9%) | **0.03** |
| Pale, sweaty, cold skin (vasovagal reflex) | 19 (6.1%) | 10 (3.2%) | 0.12 |
| Rash outside the injection site | 3 (1%) | 7 (2.3%) | **0.004** |
| Fever, chills | 33 (8.2%) | 21 (12.8%) | 0.067 |
| Headache | 76 (24.43%) | 88 (28.29%) | 0.097 |
| Muscle and joint pain | 95 (30.54%) | 73 (23.47%) | **0.004** |

Analyzed by McNemar test; p<0.05 is significant.

**TABLE 4:** Distrubition of local and systemic symptoms occurring in healthcare professionals and with a history of COVID-19 disease.

| | Non-healthcare worker n=122 (39.2%) | Healthcare worker n=189 (60.8%) | p[1] value | No-history of COVID-19 infection n=260 (83.6%) | History of COVID-19 infection n=51 (16.4%) | p value |
|---|---|---|---|---|---|---|
| Local reaction (redness, swelling. abscess, nodule, rash) | 20 (37.0%) | 34 (63.0%) | 0.43 | 42 (77.8%) | 12 (22.2%) | 0.23 |
| Pruritus outside the injection site | 6 (40%) | 9 (60%) | 0.51 | 8 (53.3%) | 7 (46.7%) | 0.01 |
| Rash outside the injection site | 2 (28%) | 5 (72%) | 0.35 | 3 (42.8%) | 4 (57.2%) | 0.02 |
| Millimetric red rashes all over the body (maculopapuler rash) | 1 (25.0%) | 3 (75.0%) | 0.42 | 1 (25%) | 3 (75%) | 0.01 |
| Urticaria lesion outside the injection site | 1 (14%) | 6 (86%) | 0.11 | 6 (%) | 1 (%) | 0.23 |
| Swelling around the eyelids, lips and mouth | 1 (11%) | 8 (89%) | 0.57 | 3 (85.7%) | 6 (14.3%) | <0.01 |
| Pale, sweaty, cold skin (vasovagal reflex) | 2 (20%) | 8 (80%) | 0.11 | 5 (50.0%) | 5 (50.0%) | 0.01 |
| Fever, chills | 5 (23.8%) | 16 (76.2%) | 0.065 | 14 (66.7%) | 7 (33.3%) | 0.03 |
| Shortness of breath, respiratory distress | 4 (26.6%) | 11 (73.4%) | 0.18 | 9 (60%) | 6 (40%) | 0.02 |

Analyzed by chi square test; p<0.05 is significant; p1 value: Comparison of local and systemic symptoms occurring in participants between healthcare worker and non-healthcare worker; p value: Comparison of local and systemic symptoms occurring in participants between history of COVID-19 infection and no-history of COVID-19 infection.

lopapular eruption, pale, sweaty, cold skin (vasovagal reflex), fever chills and shortness of breath (p>0.05) (Table 5).

When participants with a positive history of allergic disease and negative history of allergic disease were compared, no significant difference was found between them in terms of systemic symptoms such as pruritus outside the injection site, rash outside the injection site, maculopapular rash, pale, sweaty, cold skin (vasovagal reflex), and shortness of breath (p>0.05). Symptoms of swelling around the eyelids, lips, and mouth, urticarial lesions outside the injection site, fever, chills, and shaking were found to be significantly increased in participants with positive allergy history (p<0.05) (Table 5).

## DISCUSSION

Countries have entered into a rapid vaccination process to ensure herd immunity, which is the most important way to protect against COVID-19 infection. This rapid vaccination process has raised concerns about vaccines in societies. Due to the current conditions, the rapid approval of the use of the COVID-19 vaccine and the short completion of phase studies compared to other vaccines have raised questions among people.

**TABLE 5:** Distrubition of local and systemic symptoms occurring in participants with a history of allergic disease and a history of vaccine reaction.

| | History of symptoms after vaccination n=16 (5.1%) | No-history of symptoms after vaccination n=295 (94.9%) | $p^1$ value | No-history of allergic disease n=229 (73.7%) | History of allergic disease n=82 (26.3%) | $p^2$ value |
|---|---|---|---|---|---|---|
| Local reaction (redness, swelling, abscess, nodule, rash) | 4 (7.3%) | 50 (92.6%) | 0.43 | 37 (68.5%) | 17 (31.5%) | 0.396 |
| Pruritus outside the injection site | 3 (20.0%) | 12 (80.0%) | **0.03** | 9 (60.0%) | 6 (40.0%) | 0.17 |
| Rash outside the injection site | 2 (28.5%) | 5 (71.5%) | **0.04** | 5 (71.4%) | 2 (28.6%) | 0.59 |
| Millimetric red rashes all over the body (maculopapuler eruption) | 1 (25.0%) | 3 (75.0%) | 0.19 | 2 (50.0%) | 2 (50.0%) | 0.28 |
| Urticaria lesion outside the injection site | 2 (28.5%) | 5 (71.5%) | **0.04** | 5 (71.4%) | 2 (28.6%) | **0.01** |
| Swelling around the eyelids, lips and mouth | 1 (11.1%) | 8 (88.9%) | 0.41 | 7 (77.7%) | 2 (22.3%) | **0.002** |
| Pale, sweaty, cold skin (vasovagal reflex) | 8 (80%) | 2 (20%) | 0.08 | 6 (60.0%) | 4 (40.0%) | 0.25 |
| Fever, chills | 2 (10.5%) | 19 (89.5%) | 0.29 | 10 (47.6%) | 11 (52.4%) | 0.02 |
| Shortness of breath | 1 (6.6%) | 14 (8.3%) | 0.55 | 9 (60%) | 6 (40%) | 0.23 |

Analyzed by chi-square test; $p<0.05$ is significant; $p^1$ value: Comparison of local and systemic symptoms occurring in participants between a history of vaccine reaction and no history of vaccine reaction; $p^2$ value: Comparison of local and systemic symptoms occurring in participants between a history of allergic reaction and no history of allergic reaction.

Although numerically rare, vaccine reactions can cause significant fear and anxiety in the general population and may contribute to a reduced desire to get COVID-19 vaccine. In addition, not all immediate reactions associated with vaccines are true allergic reactions (e.g., redness, transient dyspnea).[11] This is evident in the recent Centers for Disease Control and Prevention report, which showed that 86 (49%) out of 175 possible severe allergic reactions were non-serious allergic reactions.[12,13]

Serious allergic reactions to vaccines, such as anaphylaxis, are much less common, with an estimated incidence of one to three per million vaccine doses.[14] In our study, no serious systemic allergic reactions such as anaphylaxis and anaphylaxis-like allergic reactions were observed.

Different types of systemic reactions can be distinguished depending on the clinical features and timing of the reaction. Delayed urticaria and/or angioedema occurring several hours after vaccine administration and maculopapular or other nonspecific rash that occurs days after vaccination is relatively common. The patho-mechanisms of these reactions are not clearly understood; however, it is thought that there may be nonspecific activation of the immune system and nonspecific degranulation of mastocytes.[8]

There are few studies so far regarding the frequency of local and systemic adverse symptoms that may be related to the CoronaVac vaccine. As far as we know, our study is the first study on this subject in our country.

In our study, no significant difference was found in local and systemic reactions between the 1st dose and the 2nd dose of CoronaVac vaccine. However, when the 1st dose and the 2nd dose were compared, symptoms such as pruritus outside the injection site, rash outside the injection site, and swelling around the eyelids, lips, and mouth were significantly increased after the 2nd dose. The reason for this situation is the development of angioedema after the type 1 hypersensitivity reaction at the 2nd dose, providing the sensitization with the formation of specific IgE antibodies produced after the 1st dose of vaccine. Eczema and pruritus outside the injection site are caused by type 4 hypersensitivity reaction.

In the study conducted by Zhu et al. in CoronaVac vaccine, as in our study, soreness and pain at injection region was the most common symptom [39 (9%) of 421 participants] and no serious adverse events such as anaphylactoid reactions related to vaccination were recorded.[15]

Again, in the report where the Phase 1 and Phase 2 studies of the CoronaVac vaccine made by Xia et al.

were evaluated, as in our study, the most common side effect was mild and self-limiting pain at the injection site. In the Phase 1 trial, where 96 participants aged 18 to 59 were evaluated, adverse reactions were 20.8% in the low-dose group, 16.7% in the medium-dose group, 25% (6 out of 24) in the high-dose group and 12.5% in the aluminum adjuvant placebo group.[16] The incidence rate of adverse reactions (15.0% among all participants) was lower compared to the results of other candidate vaccines.[15,16] However, the reason why symptom rates were lower than ours in this study was that one participant was counted only once in a particular (local or systemic) reaction category, even if a participant had more than 1 adverse reaction.

In Phase 1 and 2 studies in adults aged 18 to 55 years, dose-dependent mild or moderate systemic or local reactions were noted for the BNT162 vaccine (Biontech, Pfizer, Germany). The severity of these symptoms increased depending on the dose.[17] As in our study, no serious adverse events were reported.[17]

A randomized, single-blind study was conducted using AstraZeneca vaccine ChAdOx1 nCoV-19 (Astrazeneca, England) on 1,077 healthy participants aged 18 to 55 years enrolled in the UK study. 328 (67%) of 543 participants in the ChAdOxl nCoV-19 vaccine group and 180 (38%) of 534 participants in the MenACWY group, a meningitis vaccine, reported mostly mild to moderate pain after vaccination.[18] Fatigue and headache were the most frequently reported systemic reactions. Local and systemic reactions were examined in 2 groups, with and without paracetamol treatment. In the group who did not receive paracetamol treatment, redness, itching, and edema at the injection site were found mild at a rate of less than 5%.[18] In our study, the symptoms were also mild.

Adjuvants are substances that are not immunogen in themselves, do not form antibodies, but increase the immunogenicity of the antigen. Aluminum hydroxide and aluminum phosphate are the most commonly used excipients in vaccines. Since the excipient used in CoronaVac vaccine is aluminum hydroxide, sudden hypersensitivity to these adjuvants has been reported, however; contact allergy, urticaria, small granulomas or nodules may occur after vaccines containing aluminum.[19,20] In our study, the rate of nodules at the injection site was found to be higher than other adjuvant-containing vaccines.[20,21] In another study, aluminum was reported to cause local itchy granuloma in approximately 1% of cases in pediatric vaccines.[22]

Nakayama et al. reported 366 clinical reactions cases to mumps, measles, rubella, including 34 anaphylaxis, 76 urticaria, and 215 non-urticarial generalized rash, 41 had only local reactions.[23]

Significant local inflammatory reactions are encountered especially after the injection of vaccines containing toxoids, but may also occur after the administration of vaccines, particularly HBV, pneumococcal and Hemophilus influenzae vaccines.[8,21,22] These reactions may represent an Arthus reaction in patients with IgG antibodies obtained from previous vaccinations.[23]

Based on these data, it is likely that most of these accelerated large local reactions in the CoronaVac vaccine are caused by a non-specific inflammation and various factors including aluminum hydroxide and/or substances of microbial origin.[8]

Local eczema lesions have been reported mainly in adults vaccinated with vaccines containing aluminum hydroxide, thimerosal, and formaldehyde.[8,24,25] Studies have reported that non-immediate hypersensitivity reactions can be detected with positive patch tests to these ingredients.[26]

In our study, unlike other studies, these symptoms occurring after vaccination were compared between the group of HCWs and non-HCWs, but no difference was found. The reason for this is the comparison of the HCW group, who is in the high-risk group and have intensive working conditions due to the pandemic and have a high level of anxiety, and the non-HCW group, who is the priority group in our country, with a high rate of comorbid diseases over the age of 65. Again, compared to the group that had COVID-19 infection mean 6 months ago, we found that many systemic symptoms were significantly higher in participants who had history of COVID-19 infection. We think that specific antibodies and sensitization in participants who had history of COVID-19 may facilitate the formation of systemic symptoms.

Rash outside the injection site, pruritus outside the injection site, and urticarial lesion outside the injection site were significantly increased in participants with a history of vaccine allergy. The number of urticarial lesions outside the injection site, swelling around the eyelids, lips, and mouth was significantly increased in induviduals with history of positive allergic diseases. Therefore, we came to the conclusion that in COVID-19 vaccines, as in other vaccines, we should apply vaccines under appropriate conditions in individuals with a history of allergic disease and allergic reactions.

In our study, the frequency of local and systemic adverse symptoms is higher than other studies. The reasons for these are that vaccination was first initiated in HCWs and over 65 years of age in our country, the majority of the participants were advanced age and the rates of comorbid diseases were high, the participants had a high ratio of allergic diseases, the study was carried out in HCWs with a high level of anxiety due to the intense work pace in the COVID-19 pandemic, and some of the participants have had a previous COVID-19 infection.

The limitations of our study are that it is not multi-centric, the symptoms were evaluated by a questionnaire, the number of cases is insufficient and the participants were in the risk group who were over the age of 65, HCWs and had previous COVID-19 infection.

## CONCLUSION

In conclusion, our study determined that the inactivated CoronaVac vaccine is a very safe vaccine in terms of serious adverse reactions. Local and systemic adverse effects are seen at the same rate as in other vaccines. However, multi-centric, controlled studies in all age groups are needed to evaluate the results more clearly.

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### *Conflict of Interest*

*No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.*

### *Authorship Contributions*

***Idea/Concept:*** *Esra İnan Doğan;* ***Design:*** *Akın Aktaş;* ***Control/Supervision:*** *Akın Aktaş;* ***Data Collection and/or Processing:*** *Esra İnan Doğan;* ***Analysis and/or Interpretation:*** *Akın Aktaş;* ***Literature Review:*** *Esra İnan Doğan;* ***Writing the Article:*** *Esra İnan Doğan;* ***Critical Review:*** *Akın Aktaş;* ***References and Fundings:*** *Esra İnan Doğan;* ***Materials:*** *Esra İnan Doğan.*

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