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Are Allergic Diseases a Risk Factor for Systemic Side Effects After COVID-19 Vaccines?

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Abstract

Background: This study aims to evaluate local and systemic adverse reactions following COVID-19 vaccines in patients with a history of allergic diseases and to determine potential risk factors for emerging adverse events.

Methods: During the period from April 1, 2021, to September 30, 2021, a total of 648 adult patients who had been exposed to COVID-19 vaccines were enrolled in this retrospective case-control study. All vaccinated patients were asked to answer a detailed retrospective questionnaire, including systemic and local side effects.

Results: Six hundred forty-eight adult patients [Female: 446 (68.8%), Male: 202 (32.2%)] were enrolled in the study. After the 1st dose of COVID-19 vaccine, 24.1% of patients, and after the 2nd dose of COVID-19 vaccines, 67 patients (12.3%) developed side effects. Female gender, history of previous COVID-19 infection, and COVID-19 vaccine type administered were found to be independent risk factors for systemic side effects after COVID-19 vaccines. Premedication was found to be a protective factor for systemic side effects developing after COVID-19 vaccines.

Conclusion: Systemic side effects against COVID-19 vaccines are very low. Patients with allergic disease do not have an increased risk for systemic side effects that may develop after COVID-19 vaccines. Moreover, doubts or fears about possible side effects in the allergic patient group should not be an obstacle to COVID-19 vaccination.

Keywords: COVID-19, CoronaVac, Pfizer-BioNTech, vaccine side effects, allergies

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (Sars-CoV-2) was first reported in December 2019 and then spread all over the world in a short time and was accepted as a pandemic by the World Health Organization (WHO) in March 2020. In the 2 years following its identification, coronavirus disease 2019 (COVID-19) has killed more than 5 million people (1). There is still no effective treatment for the disease. Thus, herd immunity (mass vaccination and herd immunity) for virus protection seems to be the most effective way to turn back to the pre-pandemic period and end of pandemic. However, due to sociodemographic inequalities, vaccine supply problems and vaccine hesitancy, unfortunately, COVID-19 vaccination does not have the desired level and effect.

In Turkey, the first COVID-19 vaccination was started on January 13, 2021, with CoronaVac (Sinovac Biotech, China) to healthcare workers, and then the Pfizer-BioNTech COVID-19 vaccine was added to the vaccination calendar. After April 2021, individuals aged ≥ 60 started to be vaccinated. In December 2021, the total number of COVID-19 vaccines administered in Turkey was 125 million doses (2).

Unfortunately, Covid-19 vaccines also have many side effects and metabolic effects (3). Although the side effects reported with COVID-19 vaccines are usually minor and can be easily controlled with necessary interventions, these side effects lead to doubts about COVID-19 vaccines in patients during the periods when COVID-19 vaccination should be done most rapidly and intensively (4). Additionally, the rapid development and production phases of COVID-19 vaccines and the limited data of the post-vaccination period increase

these doubts.

In phase 2 and 3 of currently approved COVID-19 vaccines, patients with a known allergy or a history of anaphylaxis were excluded from the study (5). After the first Pfizer-BioNTech COVID-19 vaccine was administered, 2 anaphylaxis cases were reported in the media before 24 hours had passed (6). Also, during December 14–23 2020, 175 severe allergic reactions were reported after approximately 2 million Pfizer-BioNTech COVID-19 vaccine administrations, and 21 of these cases were reported to be anaphylaxis (7). This situation created doubts and unanswered questions about the risk of side effects of COVID-19 vaccines in patients with allergic diseases, as well well in patients and clinicians dealing with this patient group (8). Although there are studies on the efficacy and safety of COVID-19 vaccines, however, studies on the course of COVID-19 vaccines in allergic patients are limited. Therefore, our aim with this study was to evaluate local (LSE) and systemic (SSE) side effects after COVID-19 vaccines in patients with allergic diseases, especially allergic rhinitis, asthma, and chronic urticaria, and to determine possible risk factors for these side effects.

METHODS

Among the patients who applied to the allergy and immunology clinic in Konya City Hospital between April 1, 2021 and September 30, 2021, 648 adult patients who received any COVID-19 vaccine and agreed to participate were included in this retrospective case-control study.

An anonymous self-reporting based on a questionnaire related to safety and tolerance of vaccine was applied to the patients included in the study. This questionnaire included demographic data of patients and questions about LSE and SSE developed after vaccination. Age, gender, history of previous COVID-19 infection, COVID-19 vaccine type and number of doses, atopy status of patients, use of a drug that may affect the COVID-19 vaccine side effects, such as antihistamine, steroid and omalizumab before the COVID-19 vaccine, and demographic characteristics such as the presence of a doctor-diagnosed allergic disease were questioned in this survey. The local and systemic side effects developed after vaccination, the time elapsed between immunization and side effects, and the need for treatment for the side effects were also questioned. Information on atopy status, allergen sensitivity and allergic diseases of the patients were obtained from their files.

Patients with a diagnosis/history of asthma, urticaria/angioedema, rhinitis, drug allergy, venom allergy, and contact dermatitis were considered atopic. Pain, redness, swelling at the vaccination site were considered as LSE, and symptoms such as weakness, fatigue, myalgia, arthralgia, fever, headache were diagnosed as SSE. Patients with symptoms indicating that at least two of the skin, respiratory, cardiovascular, and gastrointestinal systems are affected after the COVID-19 vaccine (urticaria/angioedema, dyspnea, syncope, presyncope, hypotension, shock..) were considered anaphylaxis.

Patients who were treated with drugs that have the potential to affect local and systemic side effects such as antihistamine, oral steroid or omalizumab, and patients who were treated with antihistamine and/or steroid therapy to avoid the development of side effects before the COVID-19 vaccine were considered as the patient group who received premedication.

Ethics committee approval of the study was granted by University of Health Sciences Konya City Hospital Ethics Committee (Date: 15.10.2021, decision 2021/012). Written informed consent was obtained from all patients participating in the study.

STATISTICAL ANALYSIS

IBM SPSS 20.0 (Chicago, IL, USA) statistics software was used for the analysis of all data obtained during the study and recorded in the study form. Kolmogorov Smirnov test was used to determine whether or not the distribution of discrete and continuous numerical variables was in accordance with the normal distribution. Descriptive statistics were demonstrated as mean±standard deviation (SD) or median (minimum-maximum) for discrete and continuous numerical variables, and as number of cases and (%) for categorical variables. Chi-square was used to evaluate categorical variables, and t test or Mann Whitney U test was used to evaluate continuous variables. Independent risk factors for LSE and SSE were determined by univariant and multivariant binominal regression analysis. Parameters with $p < 0.2$, which are independent risk factors for LSE and SSE, were included in the univariant regression analysis. Parameters that were found to be significant in the univariant regression analysis were included in the multivariate regression analysis. For $p<0.05$, the results were considered statistically significant.

RESULTS

Six hundred and forty-eight adult patients [Female (F): 446 (68.8%), Male (M): 202 (32.2%)] participated in the study. Detailed clinical and laboratory characteristics of the patients are listed in Table 1. Pfizer-BioNTech vaccine was administered to 68.5% of the patients (648 patients), and double-dose COVID-19 vaccine was administered to 84% (544 patients). Ninety-six patients (14.8%) were premedicated with anti-allergic drugs before the administration of the COVID-19 vaccine. Among the patients, 35.2%, 22.8% and 26.5% were followed up for allergic rhinitis, asthma and chronic urticaria respectively.

Two hundred ninety-three patients (45.2% of the patients) reported side effects after the 1st dose of COVID-19 vaccine. The most frequently reported LSE was pain at the injection site (34.7 %) occurring within the first 4 hours (26.9%). The most frequently reported SSE was fatigue (14.5%) occurring within 24-72 hours (13.9%) after immunization. Among the patients who reported SSE, 44 (6.8%) needed treatment with antipyretic and anti-inflammatory drugs. Anaphylaxis requiring adrenaline injections developed in two patients (0.3%).

Five-hundred and forty-four patients received a 2nd dose of COVID-19 vaccine. One hundred and four of them (19.1%) developed LSE, and LSE most frequently developed after the 4th hour of the vaccine injection. Sixty-seven (12.3%) of the 544 patients who were administered the 2nd dose of the vaccine developed SSE. SSE occurred most frequently at 24-72 hours after the injection. Twelve patients needed treatment with antipyretic and anti-inflammatory drugs, but no case of anaphylaxis and adrenaline injection was reported. Thirteen patients (2%) developed COVID-19 infection despite being vaccinated. Data on all local and systemic side effects are summarized in **Table 1**.

Comparison of patient groups reporting or not reporting LSE after the 1st dose of COVID-19 vaccine, showed a significant difference was found between the two groups in terms of age, of the proportion of patients aged less than 50 years of the applied COVID-19 vaccines (CoronaVac vaccine vs Pfizer-BioNTech vaccine), the rate of premedicated patients, and the presence of allergic rhinitis ($p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$ and p: 0.002), respectively. On the other hand, there was a significant difference between patients who reported SSE after the 1st of COVID-19 vaccine and those who did not, in terms of gender, the proportion of patients aged less than 50 years, history of previous COVID-19 infection, applied COVID-19 vaccines, and premedication status (respectively p: 0.021, p: 0.012, p: 0.021, $p<0.001$, $p<0.001$, $p< 0.001$) (**Table 2a**).

Comparison of the patients that did and did not develop LSE after the 2nd dose of vaccine showed significant differences in terms of the rate of patients aged less than 50 years, the administered COVID-19 vaccines, the rate of premedicated patients, and the presence of allergic rhinitis (respectively p: 0.031, $p< 0.001$, $p< 0.001$, $p< 0.001$, p: 0.006). On the other hand, a significant difference was found between patients who reported SSE after the 2nd dose of vaccine and those who did not in terms of the ratio of patients aged less than 50 years, history of previous COVID-19 infection, the number

Table 1. Demographic, clinical and laboratory parameters of the study population and characteristics of LSE and SSE developing after COVID-19 vaccines

Parameters	Results	After 1st dose of COVID-19 vaccine n: 648	Results	After 2nd dose of COVID-19 vaccine n: 544	Results
Gender, Female n (%)	446 (68.8)	LSE	227 (35)	LSE	104 (19.1)
Age, year (mean,min-max)	41 (18-86)	SSE	156 (24.1)	SSE	67 (12.3)
Atopy n (%)	378 (58.3)	**Type of LSE, n (%)**		**Type of LSE, n (%)**	
Previous COVID-19 infection n (%)	96 (14.8)	Redness	6 (0.9)	Redness	2 (0.4)
COVID-19 vaccines n (%)		Local pain at injection site	225 (34.7)	Local pain at injection site	103 (18.9)
Pfizer-BioNTech n (%)	444 (68.5)	Swelling at injection site	19 (2.9)	Swelling at injection site	7 (1.3)
CoronaVac n (%)	204 (31.5)	**Time of LSE, n (%)**		**Time of LSE, n (%)**	
COVID-19 vaccine doses n (%)		Hyper acute (in 30 minutes):	3 (0.5)	Hyper acute (in 30 minutes):	2 (1.9)
Single dose n (%)	104 (16)	Acute (in 4 hours):	50 (7.7	Acute (in 4 hours):	16 (15.4)
Double dose n (%)	544 (84)	Late (After 4 hours):	174 (26.9)	Late (After 4 hours):	86 (82.7)
Premedications, n (%)	96 (14.8)	SSE after 1st dose of COVID-19 vaccine	156 (24.1)	SSE after 2nd dose of COVID-19 vaccine	67 (12.3)
Comorbidity n (%)		**Type of SSE, n (%)**		**Type of SSE, n (%)**	
Asthma	148 (22.8)	Fatique	94 (14.5)	Fatique	49 (9.1)
Chronic urticaria	171 (26.5)	Arthralgia	62 (9.6)	Arthralgia	43 (7.9)
Allergic rhinitis	227 (35.2)	Myalgia	51 (7.9)	Myalgia	33 (6.1)
Contact dermatitis	9 (1.4)	Headache	60 (9.3)	Headache	28 (5.1)
Pruritus	62 (9.6)	Fever	45 (6.9)	Fever	21 (3.9)
Venom allergy	13 (2.0)	38 °C>	39 (6)	38 °C>	17 (3.2)
Drug allergy	18 (2.8)	38 °C <	6 (0.9)	38 °C <	4 (0.7)
		Urticaria/ Angioedema	11 (1.7)	Urticaria/ Angioedema	5 (0.9)
COVID-19 infection after vaccinacion (n)	13 (2)	Dyspnea/ Wheezing	12 (1.9)	Dyspnea/ Wheezing	2 (0.4)
After 2 dose of Pfizer-BioNTech (n)	6	Nausea/ Vomiting	14 (2.2)	Nausea/ Vomiting	4 (0.7)
After 2 dose of CoronaVac (n)	6	Hypotension/ tachcardia/ syncope/ presyncope	13 (2)	Hypotension/ tachcardia/ syncope/ presyncope	3 (0.6)
After single dose of BioNTech (n)	1	**Time of SSE, n (%)**		**Time of SSE, n (%)**	
		In 24 hours	63 (9.7)	In 24 hours	13 (2.4)
Anapyhlaxis n (%)		24-72 hours	90 (13.9)	24-72 hours	53 (9.7)
After 1. dose	2 (0.3)	72h-7 days	2 (0.3)	72h-7 days	1 (0.2)
After 2. dose	-	After 7 days	1 (0.2)	After 7 days	-
		Treatment	44 (6.8)	Treatment	12 (2.2)

LSE: local side effects, SSE: systemic side effects, COVID-19: Coronavirus disease 2019

Table 2a. Comparison of LSE and SSE reported after 1st dose COVID-19 vaccines with demographic and clinical characteristics of patients

	After 1st dose of COVID-19 vaccines					
Parameters	LSE (+) n: 227	LSE (-), n: 421	p	SSE (+), n: 156	SSE (-), n: 492	p
Gender, female, n (%)	167 (73.6)	279 (66.3)	0.056	119 (76.3)	327 (66.5)	0.021
Age, year (mean,min-max)	38(17-71)	43(17-86)	<0.001	40.50(18-70)	41(18-86)	0.463
Age (<50 year),n (%)	181 (79.7)	260 (61.8)	<0.001	119 (76.3)	322 (65.4)	0.012
Presence of atopy, n (%)	146 (64.3)	232 (55.1)	0.230	101 (64.7)	277 (56.3)	0.062
History of previous COVID-19 infection n (%)	40 (17.6)	56 (13.3)	0.140	32 (20.5)	64 (13.0)	0.021
Pfizer-BioNTech vaccine, n (%)	202 (89)	242 (57.5)	<0.001	137 (87.8)	307 (62.4)	<0.001
Premedication n (%)	55 (24.2)	41 (9.7)	<0.001	38 (24.4)	58 (11.8)	<0.001
History of Asthma n (%)	42 (18.5)	106 (25.2)	0.053	37 (23.7)	111 (22.6)	0.764
History of Urticaria n (%)	52 (22.9)	120 (28.5)	0.124	43 (27.6)	129 (26.2)	0.740
History of Rhinitis n (%)	98 (43.2)	130 (30.9)	0.002	56 (35.9)	172 (35.0)	0.831
History of Pruritus n (%)	27 (11.9)	35 (8.3)	0.139	16 (10.3)	46 (9.3)	0.737
History of Drug allergy n (%)	3 (1.3)	15 (3.6)	0.132	2 (1.3)	16 (3.3)	0.267
History of Venom allergy n (%)	4 (1.8)	9 (2.1)	0.745	3 (1.9)	10 (2.0)	0.932
History of Contact dermatitis n (%)	3 (1.3)	6 (1.4)	0.914	1 (0.6)	8 (1.6)	0.360

LSE: local side effects, SSE: systemic side effects, COVID-19: Coronavirus disease 2019, ºPremedication before vaccination

of administered doses of COVID-19 vaccines, and the rate of premedicated patients (respectively p: 0.032, p< 0.001, p< 0.001, p< 0.001, and p< 0.001) (**Table 2b**).

As a result of the univariate and multivariate analysis, female gender, (Odds ratio (OR): 1.757, 95%Cl: 1.143-2.702, p: 0.010), history of previous COVID-19 infection, (OR: 1.762, 95%Cl: 1.068-2.906, p: 0.026), and COVID-19 vaccine type administered (Pfizer-BioNTech vaccine vs CoronaVac vaccine, OR: 4.443, 95% CI: 2.640-7.476, p<0.001) were found to be independent risk factors for SSE after the 1st dose of COVID-19 vaccine. Conversely, premedication (OR: 0.454, 95% Cl: 0.281-0.733, p<0.001), on the other hand, was found to be a protective factor for SSE developing after 1st dose of COVID-19 vaccines (**Table 3a** and **Table 3b**).

As a result of univariate and multivariate analysis, female gender gender (OR: 1.919, 95%Cl: 1.017-3.621, p: 0.044), history of previous COVID-19 infection (OR: 4.715, 95%Cl: 2.526-8.802, p<0.001), and the type of COVID-19 vaccine administered (Pfizer-BioNTech vaccine vs CoronaVac vaccine, OR: 4.486, 95% CI: 2.043-9.850) were found to be independent risk factors for SSE after the 2nd dose of COVID-19 vaccine. Conversely again, premedication (OR: 0.280, 95% CI: 0.141-0.560), on the other hand, was found to be a protective factor for SSE developing after 1st dose of CoVid-19 vaccines (Table 3a and Table 3b).

DISCUSSION

To our knowledge, our study is among the rare studies evaluating the impact of allergic diseases on tolerance of COVID-19 vaccines. The study showed three main and important results. Firstly, the most common LSE reported after COVID-19 vaccines is injection site pain, and the most common SSE is fatigue. Secondly, female gender, history of previous COVID-19 infection and Pfizer-BioNTech vaccine were found to be risk factors for SSE, but conversely, premedication was found to be protective. Lastly, the presence of allergic disease and atopy, especially allergic rhinitis, asthma and chronic urticaria, was not a risk factor for SSE developing after COVID-19 vaccine.

It has been reported in many studies examining the side

Table 2b. Comparison of LSE and SSE reported after 2nd dose of COVID-19 vaccines with demographic and clinical characteristics of patients

	After 2nd dose of COVID-19 vaccines					
Parameters	LSE (+), n: 104	LSE (-), n: 440	p	SSE (+), n: 67	SSE (-), n: 477	p
Gender, female, n (%)	74 (71.2)	294 (66.8)	0.395	51 (76.1)	317 (66.5)	0.113
Age, year (mean,min-max)	40.5(17-71)	42(17-86)	0.264	40(18-70)	42(17-86)	0.487
Age (<50 year),n (%)	78 (75.0)	281 (63.9)	0.031	52 (77.6)	307 (64.4)	0.032
Presence of atopy, n (%)	67 (64.4)	251 (57.0)	0.170	43 (64.2)	275 (57.7)	0.310
History of previous COVID-19 infection n (%)	20 (19.2)	56 (12.7)	0.085	23 (34.2)	53 (11.1)	<0.001
Pfizer-BioNTech vaccine, n (%)	92 (88.5)	270 (61.4)	<0.001	59 (88.1)	303 (63.5)	<0.001
Premedication n (%)	31 (29.8)	24 (5.5)	<0.001	17 (25.4)	38 (8.0)	<0.001
History of Asthma n (%)	19 (18.3)	114 (25.9)	0.103	16 (23.9)	117 (24.5)	0.908
History of Urticaria n (%)	31 (29.8)	127 (28.9)	0.849	18 (26.9)	140 (29.4)	0.675
History of Rhinitis n (%)	46 (44.2)	133 (30.2)	0.006	25 (37.3)	154 (32.3)	0.412
History of Pruritus n (%)	6 (5.8)	34 (7.7)	0.491	7 (10.4)	33 (6.9)	0.300
History of Drug allergy n (%)	2 (1.9)	16 (3.6)	0.380	2 (3.0)	16 (3.4)	0.874
History of Venom allergy n (%)	1 (1.0)	9 (2.0)	0.459	1 (1.5)	9 (1.9)	0.822
History of Contact dermatitis n (%)	1 (1.0)	7 (1.6)	0.632	0	8 (1.7)	0.604

LSE: local side effects, SSE: systemic side effects, COVID-19: Coronavirus disease 2019

Table 3a. Univariate and multivariate binomial regression analyses demonstrating the relationship between baseline characteristics and SSEs after 1st dose COVID-19 vaccines

	SSE After 1st dose of COVID-19 vaccines			
	Univariate Analysis		Multivariate Analysis	
Parameters	OR (95% CI)	P value	OR (95% CI)	P-value
Gender, female, n (%)	1.62 (1.073-2.454)	0.022	1.757 (1.143-2.702)	0.010
Age, year	0.993 (0.981-1.009)	0.264	0.999 (0.985-1.014)	0.917
Age (<50 year)	1.698 (1.123-2.566)	0.012	1.294 0(0.826-2.029)	0.261
Presence of atopy, n (%)	1.425 (0.981-2.071)	0.063	0.821 (0.552-1.221)	0.329
History of previous COVID-19 infection, n (%) *	1.726 (1.080-2.759)	0.023	1.762 (1.068-2.906)	0.026
Pfizer-BioNTech, vaccine, n (%)	4.345 (2.601-7.260)	<0.001	4.443 (2.640-7.476)	<0.001
Premedication, n (%) º	2.410 (1.526-3.805)	<0.001	2.203 (1.323-3.32)	<0.001
History of asthma, n (%)	1.067 (0.698-1.633)	0.764	1.210 (0.772-1.897)	0.405
History of urticaria, n (%)	1.071 (0.714-1.605)	0.740	1.196 (0.744-1.922)	0.461
History of rhinitis, n (%)	1.042 (0.715-1.517)	0.831	2.207 (0.729-6.683)	0.161
History of pruritus, n (%)	1.108 (0.608-2.018)	0.737	1.254 (0.656-2.398)	0.493
History of drug allergy, n (%)	0.386 (0.088-1.699)	0.208		
History of venom allergy, n (%)	0.945 (0.257-3.478)	0.932		
History of contact dermatitis, n (%)	0.390 (0.048-3.145)	0.377		

COVID: 2019 novel coronavirus, SSE: systemic side effects, *: COVID-19 infection status before vaccination, ºPremedication before vaccination

effects developed after COVID-19 vaccines that the most common LSE caused by COVID-19 is pain at the injection site, and the most common SSE is weakness/fatigue (9-13). Pain at the injection site was reported as the most common adverse event in the CoronaVac, phase 1 and 2 studies (14). The most frequently reported side effect after another inactive COVID-19 vaccine (BBV152) is pain at the injection site (15). Menni et al. reported a 71.9% incidence of LSE after the 1st dose of Pfizer-BioNTech vaccine and a 68.5% after the 2nd dose (16). In this study, the incidence of SSE was 13.5% after the 1st dose and 22.0% after the 2nd dose. Thomas et al reported that the most common LSE after Pfizer-BioNTech vaccine was mild-moderate pain at the injection site, and that fatigue was the most common SSE (17). In another cohort, side effects were reported in 64.9% of 8682 patients who received the 1st dose of Pfizer-BioNTech or Moderna vaccine, and 80.3% of patients who received the 2nd dose of these vaccines. In this cohort, the most common side effects after COVID-19 vaccines were fatigue and pain at the injection site (18). We think that both LSE and SSE rates are lower than in other studies because some of our patient group received various premedications that could prevent the development of LSE and SSE. However, the most common LSE and SSE symptoms support similar data in the literature.

Anaphylaxis after vaccination is rare and typically emerges within minutes of vaccination (19). The CDC COVID-19 Response Team reported that the rate of anaphylaxis after Pfizer-BioNTech vaccine was 11.1 per million (20). This rate is approximately 8 times the risk of anaphylaxis developing due to commonly used vaccines (1.31 per million) (21). In our study, after Pfizer-BioNTech and CoronaVac, anaphylaxis developed in a total of two patients, one different patient each. The rate of anaphylaxis was higher than previously reported (0.3% after the 1st dose of COVID-19 vaccine). This

Table 3b. Univariate and multivariate binomial regression analyses demonstrating the relationship between baseline characteristics and SSEs after 2nd dose COVID-19 vaccines

	SSE After 2nd dose of COVID-19 vaccines			
Parameters	Univariate Analysis		Multivariate Analysis	
Variables	OR (95% CI)	P value	OR (95% CI)	P-value
Gender, female, n (%)	1.609(0.889-2.911)	0.116	1.919(1.017-3.621)	0.044
Age, year	0.993(0.977-1.010)	0.410	-	-
Age (<50 year)	1.920(1.049-3.513)	0.034	1.753 (0.895-3.434)	0.102
Presence of atopy, n (%)	1.316(0.774-2.239)	0.311	-	-
History of previous COVID-19 infection, n (%) *	4.182(2.342-7.465)	<0.001	4.715(2.526-8.802)	<0.001
Pfizer-BioNTech, vaccine, n (%)	4.235(1.977-9.077)	<0.001	4.486(2.043-9.850)	<0.001
Premedication, n (%) º	3.922(1.356-4.239)	<0.001	3.571(1.243-3.968)	<0.001
History of asthma, n (%)	0.965(0.530-1.757)	0.908	1.297(0.669-2.515)	0.441
History of urticaria, n (%)	0.884(0.498-1.571)	0.675	2.987 (0.366-24.377)	0.307
History of rhinitis, n (%)	1.248(0.734-2.123)	0.413	1.243(0.615-2.511)	0.544
History of pruritus, n (%)	1.570(0.665-3.706)	0.304	1.886(0.734-4.847)	0.188
History of drug allergy, n (%)	0.788(0.098-6.319)	0.874	-	-
History of venom allergy, n (%)	-	-	-	-
History of contact dermatitis, n (%)	-	-	-	-

COVID: 2019 novel coronavirus, SSE: systemic side effects, *: COVID-19 infection status before vaccination, ºPremedication before vaccination

may be because our patient group consists of patients with a high tendency to anaphylaxis.

Women generally have stronger immune functions and higher antibody levels, but also develop more frequent side effects to vaccines including COVID-19 vaccines (22,23). In the study by Menni et al. women reported more side effects after COVID-19 vaccines (16). In their meta-analysis, Alhumaid et al. found female gender as a risk factor for anaphylaxis and non-anaphylactic reactions (24). In a cohort evaluating side effects of Pfizer-BioNTech and Moderna vaccines, it was reported that female gender was associated with higher odds in terms of both side effects and severe adverse effects (18). In our study also, the rate of SSE was higher in women after both 1st and 2nd dose of COVID-19 vaccines, although significance was attained only for SSE developing after the first dose. Additionally, the risk of developing SSE in women after COVID-19 vaccines was 1.9 times higher than in men. The difference in terms of SSE between genders may be caused by genetic, hormonal and immunological differences or the combination of these differences (25,26).

Previous COVID-19 infection is an important parameter that affects post-COVID-19 vaccine side effects, and, in many studies, this relationship has been investigated. Bandolli et al. reported that the rates of LSE after Pfizer-BioNTech vaccine were similar, but that SSE developed more frequently in patients with a history of previous COVID-19 infection compared to patients without previous infection (27). In the study by Mathioudakis et al. that previous COVID-19 infection is a risk factor for side effects, fever, breathlessness, flu-like illness and fatigue after COVID-19 vaccines (28). Another study stated that previous COVID-19 infection increased the risk of SSE by 2.9 times after Pfizer-BioNTech and a similar relationship was found for LSE (16). Beatty et al. reported that history of previous COVID-19 infection was associated with higher odds of adverse effects to COVID-19 vaccines (18). They suggested that the reason for this situation is that vaccines increase immunogenicity in infected individuals, thus inducing stronger humoral and T-cell responses in patients with previous COVID-19 infection, and increasing vaccine reactogenicity after COVID-19 vaccines (29,30). Although we did not reach a similar conclusion in our study, reporting more frequent side effects after the 2nd dose of COVID-19 vaccines may support these hypotheses. There are many studies in the literature reporting that more frequent side effects are observed after the 2nd dose of COVID-19 vaccines (10, 16,18,28,31), probably due to the boosting effect of the second injection on sensitized T cells and neutralizing antibodies formed after the 1st (immunizing) dose of the vaccines, similar to patients who have had a previous COVID-19 infection.

CoronaVac is an alum adjuvanted inactivated COVID-19 vaccine. Pfizer-BioNTech COVID-19 vaccine is an mRNA-lipid nanoparticle-based vaccine. It contains polyethylene glycol (PEG) derivatives as an adjuvant, affects both humoral and cellular steps of the adaptive immune system, and the incidence of side effects to this vaccine is relatively higher (32-34). In many studies, it has been reported that less LSE and SSE develop after inactivated COVID-19 vaccines administration than with protein subunit vaccines, RNA based vaccines and viral vector vaccines (9,11,14). Wu et al. reported that both local and systemic side effects are rarer after inactivated COVID-19 vaccines than after mRNA vaccines administration (23.7%-89.4% for LSE, 21%-83.3% for SSE) (9). In another meta-analysis, 31.75% of side effects were reported in patients immunized with inactivated virus vaccines and 81.76% in patients immunized with RNA-based COVID-19 vaccines (11). Likewise, in our study, both LSE and SSE were observed more frequently after Pfizer-BioNTech COVID-19 vaccine, and Pfizer-BioNTech vaccine, and this vaccine was found to be a risk factor for SSE.

Antihistamines, corticosteroids and omalizumab are the most frequently used treatments in allergic patients. Premedication with corticosteroids and antihistamines may theoretically suppress the immune response and reduce post-COVID-19 side effects, but premedication with these drugs before vaccination is not recommended (5,35). Some studies suggested that antihistamines protect against post-COVID-19 side effects, that these drugs have anti-viral effects, can bind to ACE2 and prevent the entry of Sars-CoV-2 virus into the cell (36,37). Similarly, in a study in 79.083 Spanish patients, Vila-Corcoles et al. found that antihistamines were protective for COVID-19 (38). In another study, 70 patients out of 80 who reported allergic(-like) complaints after the 1st dose of Pfizer-BioNTech vaccine received the 2nd dose of vaccine after allergic evaluation, and 89% of these patients developed no reaction or mildly reaction only after antihistamine premedication (39). Conversely, in a Turkish study conducted on healthcare workers who received CoronaVac, post-vaccine rashes, fever, chills, and headache were reported more frequently in patients receiving antihistamines (40). Unfortunately, our study was insufficient to comment on this issue because the ratio of the number of premedication patients to the general population was low. Hence, the potential relationship between antihistamine drugs and adverse effects of COVID-19 vaccines needs further research.

Another finding in our study was that allergic diseases, especially asthma, allergic rhinitis and chronic urticaria, or the presence of atopy are not risk factors for SSE developing after COVID-19 vaccines. Studies on the side effects of allergic diseases after COVID-19 vaccines are very limited. In a meta-analysis, Alhumaid et al. found

that history of atopy was a risk factor of anaphylactic and non-anaphylactic reactions to SARS-CoV-2 vaccines (Pfizer-BioNTech and Moderna vaccines). Inoue et al. reported that, although no cases of anaphylaxis were reported, the frequency of adverse events after COVID-19 vaccination was higher in allergic patients and that the duration of adverse events was longer (41). Nittner et al. reported that local side effects such as swelling and redness develop more frequently in allergic patients after Pfizer-BioNTech vaccine, that these side effects last longer, and that allergic individuals need medical intervention due to the side effects more frequently (x2) than non-allergic individuals (31). On the other hand, Beatty et al. reported that asthma was associated with lower odds in terms of both side effects and severe adverse effects after Pfizer-BioNTech and Moderna vaccines (18). EACCI (European Academy of Allergy and Clinical Immunology) declared that there is no contraindication for allergic patients to receive COVID-19 vaccines, except for patients with sensitivity to components of these vaccines, and that allergy to drugs, food, insect venom, or inhalant allergens (house dust mites, pollens, animal dander, molds) generally does not constitute a contraindication for any vaccine, including SARS-CoV-2 vaccines (42). Moreover, the American College of Allergy Asthma and Immunology (ACAAI) has stated that "Individuals with common allergies (foods, inhalants, latex, insects) are not more likely than the general population to develop allergic reactions to the Pfizer-BioNTech vaccine" (43). The results of our study, showing that neither the presence of atopy nor the presence of allergic disease was a risk factor for SSE after COVID-19 vaccines, agree with these recommendations.

The strength of our study is that the allergic diseases of the patients were diagnosed by a physician, self-reported allergy being typically much higher than confirmed allergy, and that the size of the population studied is important and includes numerous allergic patients. Our study also has some limitations. First, the data on side effects, and drug uses considered as premedication was obtained through personal notification. This makes possible a bias linked to social desirability. It is well known that reporting of side effects may vary among patients. Also, our study classified patients according to the allergic disease for which they were primarily followed. Other concomitant allergic diseases (diagnosed or undiagnosed) may have affected the results in some patients. Additionally, the number of patients diagnosed with venom allergy, drug allergy, and contact dermatitis was relatively low. The fact that the study was retrospective and included patients from only one ethnic background makes it difficult to generalize the results. These limitations may have impacted the power of statistical analyses in the patient groups.

CONCLUSION

In our study, CoronaVac and Pfizer-BioNTech COVID-19 vaccines were well-tolerated, and SSE against both vaccines was very low. Patients with allergic or atopic diseases do not have an increased risk for SSE that may develop after COVID-19 vaccines, so this should not have doubts in the minds of either clinicians or patients and prevent vaccination.

ETHICAL DECLARATIONS

Conflict of Interest Statement: The author declares no conflicts of interest related to this research.

Informed consent: Informed consent was taken from the patients.

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Ethical Issues: This study was conducted in agreement with the Declaration of Helsinki-Ethical principle for medical research involving human subjects.

Author Contributions: The authors declared that they all participated in the design, execution, and analysis of the study and that they approved the final version of the paper.

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