Evaluation of the Autoimmunity and Preexisting Risky Conditions for Hypersensitivity Reactions to COVID-19 Vaccines

Can Tuzer[a]   Kadriye Terzioglu[b]

[a]Adult Immunology and Allergy Clinic, Batman Research and Education Hospital, Batman, Turkey;
[b]Adult Immunology and Allergy Clinic, Kartal Dr. Lütfi Kırdar City Hospital, İstanbul, Turkey

Abstract

Introduction: The role of autoimmunity and other preexisting risky conditions in hypersensitivity reactions (HSRs) to COVID-19 vaccines seems unclear. The aim of the study was to investigate the autoimmunity and preexisting risky conditions in HSRs to COVID-19 vaccines. *Methods:* The patients aged ≥18 years with a history of HSR to CoronaVac or Pfizer-BioNTech COVID-19 vaccines within 24 h in 2 tertiary centers were assessed. The patients were divided according to the type of vaccine which they showed immediate-type (<4 h) HSR to (group A1 for CoronaVac and group B1 for Pfizer-BioNTech). Equal number of subjects who did not show HSR to two doses of either CoronaVac or Pfizer-BioNTech was recruited into the study as control groups (group A2 for CoronaVac and group B2 for Pfizer-BioNTech). The autologous serum skin test (ASST) was performed on patient and control groups. Later, the demographic, clinical, and laboratory features were compared between groups. *Results:* A total number of 27 patients were included in the study. Subjects with chronic spontaneous urticaria (CSU) were more frequent in group B1 than in group B2 (*p*:0.041). In addition to CSU, the presence of HSRs to drugs was higher in group A1 than in A2 (both *p*:0.007). The presence of autoimmunity and autoimmune diseases, positivity of antithyroid peroxidase antibody, and ASST were less in group A2 than in A1 (*p*:0.015, *p*:0.048, *p*:0.048, and *p*:0.037). Additionally, COVID-19 infection history was less in group A2 than in A1 (*p*:0.037). *Discussion/Conclusion:* Type IIb autoimmunity seems to play a role in immediate type HSRs to the CoronaVac vaccine as previously shown in autoimmune CSU and multidrug hypersensitivity.

© 2022 S. Karger AG, Basel

Introduction

Mortality and morbidity from COVID-19 are very important [1], and limited treatment options are available [2]. Thus, vaccination against COVID-19 seems to be the only preferable option [2]. However, allergic reac-

Edited by: H.-U. Simon, Bern.

Correspondence to:
Can Tuzer, cancantuzer@gmail.com

tions occur in a range from 1 in 50,000 to 1 in 100,000 doses with most commonly administered vaccines [3]. Hypersensitivity reactions (HSRs) to the Pfizer-BioNTech and Moderna vaccines have been reported in 5.0 and 2.8 cases per million doses, respectively [4]. In phase 1/2 clinical trial of CoronaVac (a COVID-19 vaccine developed by Sinovac Life Sciences), only 1 case (4%) of 24 subjects experienced a HSR (urticaria) 48 h after the first dose [5]. In phase 3 trial of the same vaccine from Turkey, only one of 6,646 participants had a grade-3 systemic allergic reaction [6]. In general, primary series and additional doses should be completed with the same vaccine [7]. In addition to IgE-mediated allergy, complement-activation-related pseudo-allergy, which involves anaphylatoxins (C3a and C5a), anti-PEG IgM and IgG activation, mast cell activation, and direct degranulation of mast cells are mentioned for HSRs to mRNA-based vaccines [8]. It has been mentioned by a recent consensus statement that it should be highlighted who are at risk of a severe HSR to COVID-19 vaccines and what the underlying immune mechanism is [9]. Herein, the important issue is the growing interest in allergic reactions to COVID-19 vaccines and the growing anxiety in general population.

The autologous skin serum test (ASST) and functional autoantibodies should be searched in chronic spontaneous urticaria (CSU) [10]. Autoimmune CSU is a subtype of CSU having more frequent positive ASST results [11]. Also, the positivity of antithyroid, antinuclear antibodies and the presence of autoimmune comorbidities exist more frequently [12]. Circulating functional IgG autoantibodies to IgE or its receptor FcεRI are supposed to cause mast cell degranulation. Therefore, the term of type IIb autoimmunity was postulated [11]. Another important issue was that higher positivity rates of ASST were found in patients with multidrug hypersensitivity (MDH) and multiple nonsteroidal anti-inflammatory drugs intolerance, and this was explained by the presence of circulating histamine-releasing factors [13, 14]. Besides, the patients with multiple or single hypersensitivity to nonsteroidal anti-inflammatory drugs tend to develop CSU [15]. As a mechanism, serum histamine-releasing factors and an activated coagulation cascade are suggested to play a role in MDH as well as in CSU [16]. Based on these observations, the present study aimed to assess the role of autoimmunity, which is evaluated by the presence of autoimmune diseases, circulating autoantibodies, and ASST and other preexisting risky conditions in HSRs to CoronaVac and Pfizer-BioNTech COVID-19 vaccines.

Materials and Methods

Study Design

The patients aged ≥18 years with a history of HSR to CoronaVac or Pfizer-BioNTech COVID-19 vaccines and referred to adult allergy outpatient clinics in two tertiary centers (the adult immunology and allergy clinics in Batman Training and Research Hospital and Kartal Dr. Lütfi Kırdar City Hospital) were retrospectively assessed in the present study. All the referred cases were handled carefully to exclude other conditions that mimic anaphylaxis (vasovagal reaction, panic, or anxiety) by two experienced allergists using the relevant literature [17] and underwent comprehensive assessment to search for any potential cause of HSR (infection, use of other medication, venom, and food) in their histories before the reaction time. Subjects with a history of HSR that occurred 24 h later following the vaccination [18] and nonallergic adverse reactions (fever, thrill, vomit, diarrhea, and headache) were excluded. The interval from the vaccine receipt to the symptom onset and the severity of the reactions were considered according to the hospital documents. The HSRs were divided into immediate (within 4 h) or delayed type (after 4 h) HSRs [19]. The severity of the reaction was determined as severe (anaphylaxis) or nonsevere (nonanaphylaxis) using the relevant literature [20]. In addition, the cases with anaphylaxis were designated as severe or nonsevere according to the presence of hypoxemia (oxygen saturations by pulse oximetry <90 mm Hg), collapse, altered consciousness, or incontinence [21].

The patients were allocated into two groups according to the type of vaccine they showed HSR to. The demographic features of all patients and clinical characteristics of HSRs were assessed. Later, the patients who had a history of immediate type HSR to CoronaVac and Pfizer-BioNTech COVID-19 vaccines were selected and formed group A1 and B1, respectively. As control groups, subjects who had no HSR to two doses of either the CoronaVac or Pfizer-BioNTech COVID-19 vaccine were randomly selected and formed group A2 (for CoronaVac) and B2 (for Pfizer-BioNTech), respectively. Equal number of subjects to those in the patient groups was selected for control groups.

Allergological and Laboratory Workup

All patients were further investigated for systemic mastocytosis with basal serum tryptase levels and latex hypersensitivity with specific IgE measurement and skin prick testing (SPT). Laboratory parameters comprising peripheral leukocyte counts, peripheral platelet counts, absolute peripheral eosinophil and basophil counts, basal serum tryptase, total IgE, and high-sensitive C-reactive protein levels were assessed in all patients. The same laboratory levels and the positivity rates of antithyroid peroxidase antibody (anti-TPO ab), anti-thyroglobulin antibody, and autologous serum skin test (ASST) were also evaluated between patient and control groups.

Patients who had chronic rhinitis symptoms were categorized as allergic rhinitis (AR) when the clinically relevant sensitization to a common aeroallergen was confirmed with SPT and/or serum-specific IgE measurements [22] and as non-AR when the diagnostic workup produced a negative result. In all chronic rhinitis patients, the Visual Analog Scale (VAS) and in AR patients, Total Symptom Score-6 was evaluated [23, 24]. Evaluations below 5 cm of VAS were defined as mild rhinitis and equal to or above 5 cm of it as moderate/severe rhinitis in AR patients [23]. In patients with

Table 1. The demographic features of patients and the clinical characteristics of HSRs

	CoronaVac (n:13)	Pfizer/Biontech (n:14)	p value OR (CI%)
Age, year	34.38±7.8	37.28±11.97	>0.05
Sex, n (%)			
Females	12 (92.3)	6 (42.9)	**0.009 16 (1.607–159.310)[a]**
Males	1 (7.7)	8 (57.1)	
Body mass index	22.1 (21.1–24.7)	26.6 (23.5–31.4)	>0.05
Smokers, n (%)	6 (50)	6 (42.9)	>0.05
Alcohol users, n (%)	0 (0)	0 (0)	>0.05
Median reaction time after vaccination, min	10 (1.5–30)	180 (8.75–510)	>0.05
Reaction to which dose, n (%)			
First dose	10 (77)	12 (85.7)	>0.05
Second dose	3 (23)	2 (14.3)	>0.05
History of the reaction type, n (%)			
Urticaria	1 (15.4)	7 (50)	**0.021 12 (1.211–118.889)[a]**
Angioedema	2 (15.4)	0 (0)	>0.05
Urticaria/angioedema	1 (7.7)	1 (7.1)	>0.05
Anaphylaxis	9 (69.2)	6 (42.9)	>0.05
Patients according to the reaction time, n (%)			
0–4 h	13 (100)	9 (64.3)	**0.025 1.556 (1.053–2.299)[a]**
4–24 h	0 (0)	5 (35.7)	
Patients according to the severity of the reaction, n (%)			
Nonsevere reaction	4 (30.8)	8 (57.1)	>0.05
Severe reaction (anaphylaxis)	9 (69.2)	6 (42.9)	>0.05
After vaccination, patients showing anaphylaxis (n of N), n (%)			
Nonsevere	1 (11.2)	2 (33.3)	>0.05
Severe	8 (88.9)	4 (66.7)	>0.05
Patients with a history of reactions to other vaccines, n (%)	1 (7.7)	0 (0)	>0.05
Patients with latex sensitivity,* n (%)	0 (0)	0 (0)	–

Parametric values given as mean ± SD and nonparametric values given as median (IQR 25–75). IQR, interquartile range. [a] Fischer's exact test used. * Those with a clinically relevant hypersensitivity determined by the skin prick test or specific IgE.

asthma, the duration and severity of the disease and the scores of the asthma control test were noted. The scores of 20–25 in the asthma control test were defined as well-controlled, 16–19 not well-controlled, and 5–15 poorly controlled asthma. The severity of asthma was classified as mild, moderate, and severe according to the step of the controller treatment [25]. In patients with CSU, the duration of the disease and the urticaria activity score-7 were recorded. The autoimmunity was defined as having at least one of the following criteria: (a) anti-TPO ab positivity, (b) anti-thyroglobulin antibody positivity, (c) ASST positivity, and (d) the presence of an autoimmune disease. All the demographic, clinical features, medical histories, and previous laboratory values were compared between groups (group A1 vs. A2 and B1 vs. B2).

Statistics Statement
Categorical variables were summarized as frequencies and percentages, and continuous variables were defined as median with interquartile range values or mean with standard deviation when appropriate. To compare the continuous variables for the data of 2 groups, two-tailed t and Mann-Whitney U tests were used where appropriate. The frequencies of categorical variables were compared using the χ^2 and Fischer's exact tests. When more than 20%

of cells have expected frequencies <5, Fischer's exact test or otherwise the χ^2 test was used. p values <0.05 were considered significant. All statistical analyses were done by Statistical Package for the Social Sciences version 24.0 (SPSS Inc., Chicago, IL, USA), and graphs were generated using GraphPad Prism version 8.4.3 software (GraphPad Software Inc., San Diego, CA, USA).

Results

The Demographic and Clinical Characteristics of Patients

Twenty-seven patients were included in the study. Thirteen out of them had a history of HSR to CoronaVac and 14 subjects to Pfizer-BioNTech. The mean ages for them were 34.38 ± 7.8 and 37.28 ± 11.97, respectively. The number of female subjects and history of immediate type HSRs were higher in HSRs to CoronaVac (p:0.009 and p:0.025), whereas urticarial HSR history was more preva-

Fig. 1. a, b Skin prick test results in the patient and one of the 5 control subjects.

Table 2. CoronaVac desensitization protocol

Steps	Doses	Cumulative doses	Interval
First step	0.02 mL	0.02 mL	30 min
Second step	0.03 mL	0.05 mL	30 min
Third step	0.05 mL	0.1 mL	30 min
Fourth step	0.1 mL	0.2 mL	30 min
Fifth step	0.15 mL	0.35 mL	30 min
Sixth step	0.15 mL	0.5 mL	180 min

lent in HSRs to Pfizer-BioNTech (*p*:0.021). The most common type of HSR to CoronaVac was anaphylaxis (*n*:9, 69.2%), while it was urticaria (*n*:7, 50%) in the HSRs to Pfizer-BioNTech. All of the delayed type HSRs to Pfizer-BioNTech were urticarial reaction (*n*:5, 35.7%). The demographic features of patients and the clinical characteristics of HSRs are given in Table 1.

Two patients were desensitized to the second dose of CoronaVac. One patient had a history of nonsevere anaphylaxis and was desensitized with a six-step protocol (Table 2) despite having negative results of SPT (by neat vaccine) and intradermal testing (IDT) (with 1/1,000, 1/100 dilutions). Bronchospasm without hypoxemia (>90%) within a min following the last step occurred, but it relieved with inhaler salbutamol (4 puffs) and methylprednisolone (40 mg) treatment, and no HSR reoccurred later. The other subject had a history of urticaria/angioedema at the 15th min and was desensitized to Coro-

naVac with the same protocol (Table 2). However, SPT with a neat vaccine resulted positive in this patient and comparably negative in 5 healthy subjects (Fig. 1). One min after the last step, the patient had a severe itching on her legs. However, it resolved with 45.5 mg pheniramine, and no HSR reoccurred later.

One subject had a history of syncope (without hypotension and hypoxemia) within a min and urticaria 20 h later following the first dose of Pfizer-BioNTech. SPT by a neat vaccine and an IDT with 1/100 dilution were performed, and they all resulted negative on the assessment of immediate (20 min) and late readings (24 h). Afterward, the vaccine was administrated with split doses (one-tenth and then nine-tenths with a 30-min interval). No immediate type HSR happened, but urticaria occurred 16 h later. Another subject having a history of urticaria and angioedema at the 30th min following the first dose of Pfizer-BioNTech did not want to continue allergological workup and underwent the second dose administration without split doses in another center. Urticaria/angioedema with bronchospasm (without hypoxemia) immediately occurred, and 45.5 mg pheniramine and 40 mg methylprednisolone were administered. Two hours after the relief of the symptoms, he was discharged. However, urticaria developed 16 h later again and lasted 3 days despite full doses (four times a day) of antihistamine therapy. Another case with a history of urticaria at the 4th h following the first dose of Pfizer-BioNTech developed dyspnea and generalized urticaria 5 min after the first split dose (1/10) of the second vaccination despite having
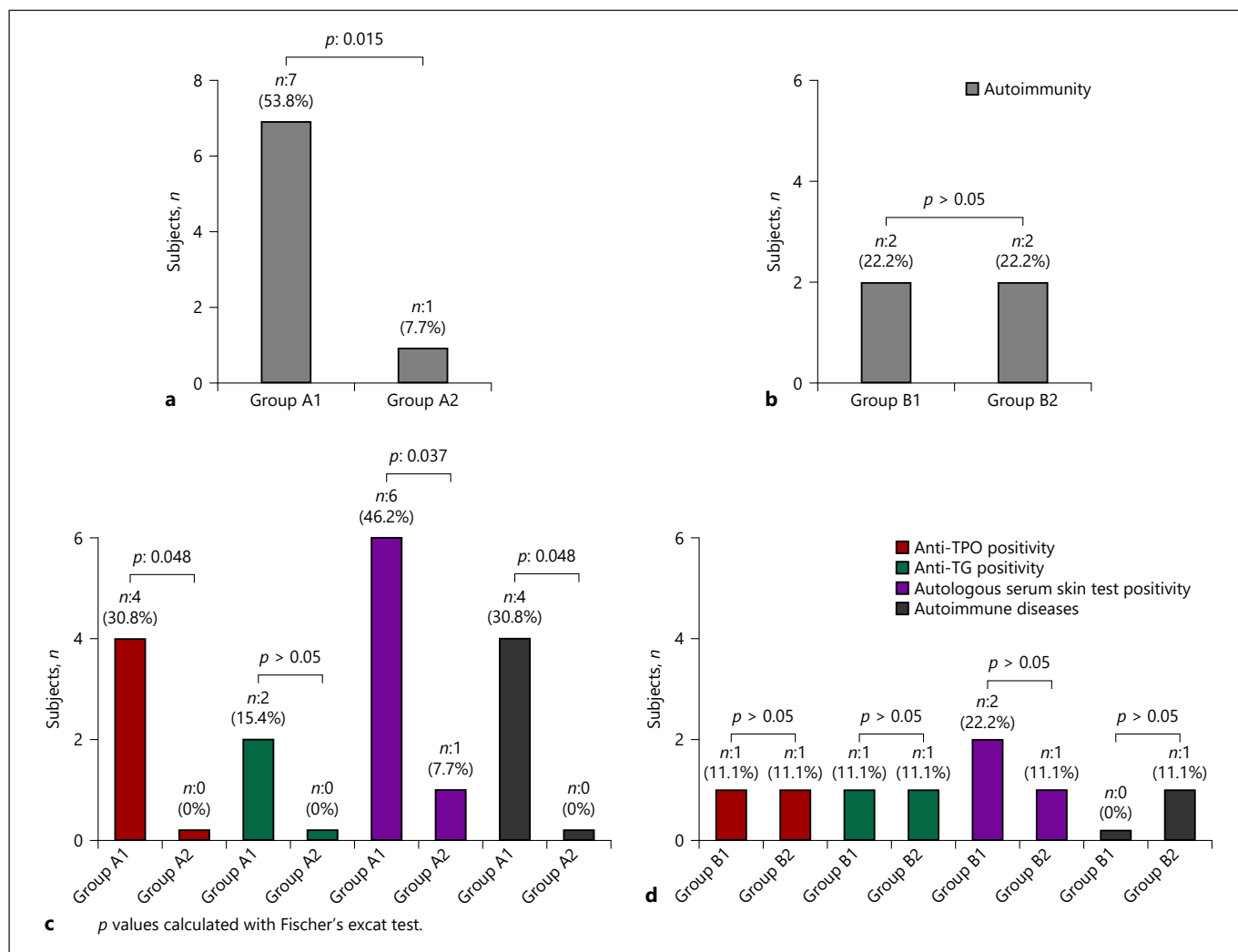
Fig. 2. a–d Comparison of autoimmunity including preexisting autoimmune diseases, positivity rates of ASST, antithyroid peroxidase, and anti-thyroglobulin antibodies between patient and control groups.

negative SPT (neat vaccine) and IDT (1/100 dilution) results. The detailed demographic and clinical characteristics of all patients are given in online supplementary Table S1 (for all online suppl. material, see www.karger. com/doi/10.1159/000521709).

The Evaluation of Patient and Control Groups

The mean ages for group A1 and A2 were 34.38 ± 7.8 and 38.38 ± 12.88, respectively. Most of the patients were female in both groups (n:12 vs. n:10, $p > 0.05$). A higher number of patients had allergic comorbidities in group A1 than in group A2 (n:11 vs. n:4, p:0.005). Also, the presence of CSU and drug HSRs were more common in group A1 than in A2 (both p:0.007). Most importantly, the pres-

ence of autoimmunity and autoimmune hallmarks such as anti-TPO ab positivity, ASST positivity, and the presence of autoimmune diseases were significantly higher in group A1 than in A2 (p:0.015, p:0.048, p:0.037, and p:0.048, respectively) (Fig. 2). Nearly half of the patients (n:6, 46.2%) in group A1 had a COVID-19 infection history, while only 1 patient had it in group A2 (p:0.037). The demographic, clinical, and laboratory features of group A1 and A2 are given in Table 3.

A total number of 9 patients had a history of immediate type HSR to Pfizer-BioNTech and formed group B1. Four (44.4%) and 6 (66.7%) subjects were female, and the mean ages were 38 ± 8.48 and 34.33 ± 13.58 years in group B1 and B2, respectively. The only more common allergic

Table 3. Comparison of the demographic, clinical, and laboratory data between the subjects who showed an immediate HSR to CoronaVac and control groups

	Group A1 (*n*:13)	Group A2 (*n*:13)	*p* value OR (CI%)
Age, year	34.38±7.8	38.38±12.88	>0.05
Sex, *n* (%)			
Females	12 (92.3)	10 (76.9)	>0.05
Males	1 (7.7)	3 (23.1)	>0.05
Body mass index	22.1 (21.1–24.7)	25.53 (22.18–26)	>0.05
Smokers, *n* (%)	2 (15.4)	4 (30.8)	>0.05
Alcohol users, *n* (%)	0 (0)	0 (0)	–
Patients with allergic comorbidity, *n* (%)	11 (84.6)	4 (30.8)	**0.005 0.081 (0.012–0.547)[a]**
AR*	8 (61.5)	4 (30.8)	>0.05
Allergic asthma	4 (30.8)	1 (7.7)	>0.05
HSR to food	2 (15.4)	0 (0)	>0.05
HSR to drug	6 (46.2)	0 (0)	**0.007 0.350 (0.193–0.636)[b]**
Allergic contact dermatitis	1 (7.7)	0 (0)	>0.05
CSU	6 (46.2)	0 (0)	**0.007 0.350 (0.193–0.636)[b]**
Bee venom allergy	1 (7.7)	0 (0)	>0.05
Patients with latex sensitivity,* *n* (%)	0 (0)	1 (7.7)	>0.05
Patients with inhalant allergen sensitization,* *n* (%)	8 (61.5)	4 (30.8)	>0.05
House dust mite	4 (50)	3 (75)	>0.05
Pollen	4 (50)	1 (25)	>0.05
Mold	1 (12.5)	0 (0)	>0.05
Animal dander	4 (50)	1 (25)	>0.05
Patients with nonallergic comorbidities, *n* (%)	8 (61.5)	4 (30.8)	>0.05
Non-AR	2 (15.4)	0 (0)	>0.05
Hypertension	0 (0)	1 (7.7)	>0.05
Hypothyroidism	2 (15.4)	0 (0)	>0.05
Hyperthyroidism	1 (7.7)	0 (0)	>0.05
Malignancy**	1 (7.7)	0 (0)	>0.05
Cardiac arrhythmia	1 (7.7)	0 (0)	>0.05
Primary immunodeficiency	1 (7.7)	0 (0)	>0.05
Chronic hepatitis B	2 (15.4)	0 (0)	>0.05
Hyperlipidemia	0 (0)	2 (15.4)	>0.05
Familial Mediterranean fever	0 (0)	1 (7.7)	>0.05
Autoimmune diseases	4 (30.8)	0 (0)	**0.048 0.409 (0.248–0.676)[b]**
Hashimoto thyroiditis	1 (7.7)	0 (0)	>0.05
Rheumatoid arthritis	1 (7.7)	0 (0)	>0.05
Psoriasis vulgaris	1 (7.7)	0 (0)	>0.05
Graves's disease	1 (7.7)	0 (0)	>0.05
Patients with a family history of allergic diseases, *n* (%)	8 (61.5)	8 (61.5)	>0.05
AR	6 (46.2)	5 (38.5)	>0.05
Allergic asthma	3 (23.1)	3 (23.1)	>0.05
HSR to food	2 (15.4)	1 (7.7)	>0.05
HSR to drug	1 (7.7)	0 (0)	>0.05
Allergic contact dermatitis	1 (7.7)	0 (0)	>0.05
CSU	1 (7.7)	2 (15.4)	>0.05
Bee venom allergy	0 (0)	0 (0)	–
COVID-19 infection history, *n* (%)	6 (46.2)	1 (7.7)	**0.037 0.097 (0.010–0.983)[b]**
Asthma duration, months	246.5±333.4	120±0	>0.05
Patients by asthma control categories (*n* of *N*), *n* (%)	4 (30.8)	1 (7.7)	>0.05
Well-controlled	1 (25)	1 (100)	>0.05
Not well-controlled	2 (50)	–	–
Poorly controlled	1 (25)	–	–
Asthma severity (*n* of *N*), *n* (%)	4 (30.8)	1 (7.7)	>0.05
Mild	1 (25)	1 (100)	>0.05
Moderate	2 (50)	–	–
Severe	1 (25)	–	–

Tuzer/Terzioglu

Table 3 (continued)

	Group A1 (*n*:13)	Group A2 (*n*:13)	*p* value OR (CI%)
Asthma control test score	17.75±5.5	22±0	>0.05
Rhinitis duration, months			
AR	108.25±91.95	141±92.1	>0.05
Non-AR	38±48.08	–	–
Rhinitis persistence (for AR) (*n* of *N*), *n* (%)			
Persistent	4 (50)	1 (25)	>0.05
Intermittent	4 (50)	3 (75)	>0.05
Rhinitis severity (for AR) (*n* of *N*), *n* (%)			
Mild	5 (62.5)	3 (75)	>0.05
Moderate/severe	3 (37.5)	1 (25)	>0.05
Total Symptom Score-6 (for AR)	8.87±2.58	6.75±4.99	>0.05
VAS Symptom Score (for all rhinitis)	5.25±1.82	3.87±2.78	>0.05
Chronic urticaria duration, months	54 (9.75–201)	–	–
Chronic urticaria 7-day activity score	3.5±3.01	–	–
Leukocyte count, *n*/μL	7,163±1,281	7,248±1,577	>0.05
Absolute neutrophil count, *n*/μL	4,262±848	4,423±1,075	>0.05
Absolute lymphocyte count, *n*/μL	2,159±754	2,178±629	>0.05
Absolute eosinophil count, *n*/μL	167±108	114±55.9	>0.05
Absolute basophil count, *n*/μL	44.6±25	36.9±14.4	>0.05
Platelet count, $n \times 10^3$/μL	274±55	274±50.5	>0.05
hs-CRP level, mg/L	1.8 (1.42–5.17)	1.6 (1.35–2.6)	>0.05
Total IgE, IU/mL	31.6 (14.55–133.7)	24 (4–47.8)	>0.05

Parametric values are given as mean ± SD and nonparametric values as median (IQR). hs-CRP, high-sensitive C-reactive protein; IQR, interquartile range. [a] Chi-square test. [b] Fischer's exact test used. * Those with a history of hypersensitivity determined by the skin prick test and/or specific IgE. ** Papillary thyroid carcinoma.

Discussion/Conclusion

disease in group B1 than in B2 was CSU (*n*:4 vs. *n*:0, *p*:0.023). The presence of autoimmunity was not different between group B1 and B2 (*p* > 0.05) (Fig. 2). The demographic, clinical, and laboratory features of group B1 and B2 are given in Table 4. Other parameters involving the presence of asthma, AR, HSRs to food, nonallergic comorbidities, inhalant allergen sensitization, family histories of allergic diseases, and laboratory values were similar between either group A1 and A2 or group B1 and B2.

The type IIb autoimmunity seems important in HSRs to the CoronaVac vaccine, which was the first time evaluated in the HSRs to COVID-19 vaccines in the present study. Additionally, it seems essential to investigate CSU in HSRs to Pfizer-BioNTech and HRSs to drugs as well as CSU in HSRs to CoronaVac.

HSRs to drugs are explained by immune or nonimmune mechanisms, and even on the first exposure to a drug, an immune reaction can occur because of being sensitized to the active ingredient or excipient [26]. Some components such as polyethylene glycol (PEG) 2000, N-ditetradecyl acetamide, 1,2-distearoyl-sn-glycero-3-phosphocholine, polysorbate 80, PEG 2000 dimyristoyl glycerol, tromethamine, tromethamine hydrochloride, and SM-102 have been supposed to be potential allergens [26, 27]. In addition to IgE-mediated allergy, one possible mechanism that is the interaction of RNA in the vaccine with mast cells causes to produce type I interferons and TNF-alpha as well as antiviral proteins by mast cells [4]. Another one is that nucleic acids in the vaccine may activate factor XII in the contact system, and it leads to the generation of bradykinin, which causes angioedema and/or anaphylactoid reactions. Also, the development of anti-PEG IgM and IgG antibodies seems to be a potential route, and as it is known, IgG binds to Fc gamma receptors on granulocytes and/or platelets and leads secretion of serotonin and cytokines [28]. Nonetheless, the development of IgE-mediated HSRs, especially against PEGs with different molecular weights, is the most emphasized mechanism [29–31]. On the other side, CoronaVac is an inactivated SARS-CoV2 vaccine absorbed onto alumi-

Table 4. Comparison of demographic, clinical, and laboratory data between the subjects who showed an immediate HSR to Pfizer-BioNTech and control groups

	Group B1 (n:9)	Group B2 (n:9)	p value OR (CI%)
Age, year	38±8.48	34.33±13.58	>0.05
Sex, n (%)			
Females	4 (44.4)	6 (66.7)	>0.05
Males	5 (55.6)	3 (33.3)	>0.05
Body mass index	25.81±4.03	30.30±13.06	>0.05
Smokers, n (%)	4 (44.4)	1 (11.1)	>0.05
Alcohol users, n (%)	0 (0)	0 (0)	>0.05
Patients with allergic comorbidity, n (%)	8 (88.9)	4 (44.4)	>0.05
AR*	4 (44.4)	3 (33.3)	>0.05
Allergic asthma	2 (22.2)	0 (0)	>0.05
HSR to food	2 (22.2)	1 (11.1)	>0.05
HSR to drug	1 (11.1)	0 (0)	>0.05
Allergic contact dermatitis	0 (0)	1 (11.1)	>0.05
CSU	4 (44.4)	0 (0)	**0.041 0.357 (0.177–0.721)[a]**
Bee venom allergy	1 (11.1)	0 (0)	>0.05
Patients with latex sensitivity,* n (%)	0 (0)	0 (0)	>0.05
Patients with inhalant allergen sensitization* (n of N), n (%)	4 (44.4)	3 (33.3)	>0.05
House dust mite	1 (12.5)	1 (33.3)	>0.05
Pollen	1 (12.5)	2 (66.7)	>0.05
Mold	0 (0)	0 (0)	>0.05
Animal dander	2 (50)	1 (33.3)	>0.05
Patients with nonallergic comorbidities, n (%)	4 (44.4)	1 (11.1)	>0.05
Non-AR	3 (33.3)	0 (0)	>0.05
Hypertension	1 (11.1)	0 (0)	>0.05
Diabetes mellitus	0 (0)	1 (11.1)	>0.05
Patients with a family history of allergic diseases, n (%)	4 (44.4)	3 (33.3)	>0.05
AR	2 (22.2)	3 (33.3)	>0.05
Allergic asthma	1 (11.1)	3 (33.3)	>0.05
HSR to food	1 (11.1)	0 (0)	>0.05
HSR to drug	0 (0)	0 (0)	–
CSU	1 (11.1)	0 (0)	>0.05
COVID-19 infection history, n (%)	1 (11.1)	2 (22.2)	>0.05
Asthma duration, months	84±50.91	–	–
Patients by asthma control categories (n of N), n (%)			
Well-controlled	2 (100)	–	–
Not well-controlled	0 (0)	–	–
Poorly controlled	0 (0)	–	–
Asthma severity (n of N), n (%)			
Mild	2 (100)	–	–
Moderate	0 (0)	–	–
Severe	0 (0)	–	–
Asthma control test score	22.5±2.12		–
Rhinitis duration, months			
AR	47.5±49.48	48.66±62.74	>0.05
Non-AR	108±78.68	–	–
Rhinitis persistence (for AR) (n of N), n (%)			
Persistent	2 (50)	1 (33.3)	>0.05
Intermittent	2 (50)	2 (66.7)	>0.05
Rhinitis severity (for AR) (n of N), n (%)			
Mild	1 (25)	2 (66.7)	>0.05
Moderate/severe	3 (75)	1 (33.3)	>0.05
Total Symptom Score-6 (for AR)	9.25±4.11	8.33±4.93	>0.05
VAS Symptom Score (for all rhinitis)	5.42±2.71	4.83±3.01	>0.05
Chronic urticaria duration, months	46±74.48	–	–
Chronic urticaria 7-day activity score	11.66±7.76	–	–

Table 4 (continued)

	Group B1 (n:9)	Group B2 (n:9)	p value OR (CI%)
Leukocyte count, n/µL	8,594±2,378	8,774±3,227	>0.05
Absolute neutrophil count, n/µL	5,357±1,859	5,818±3,090	>0.05
Absolute lymphocyte count, n/µL	2,558±922	2,285±718	>0.05
Absolute eosinophil count, n/µL	203.33±169.41	135.55±116.63	>0.05
Absolute basophil count, n/µL	28.88±16.15	30±18.02	>0.05
Platelet count, $n \times 10^3$/µL	277.55±70.74	258.22±60.53	>0.05
hs-CRP level, mg/L	2.6 (1.95–5.29)	2.80 (1.55–4.95)	>0.05
Total IgE, IU/mL	49.1 (7.55–116.45)	27.6 (15–564.55)	>0.05

Parametric values are given as mean ± SD and nonparametric values as median (IQR). hs-CRP, high-sensitive C-reactive protein; IQR, interquartile range. [a] Fischer's exact test used. * Those with a history of sensitivity determined by the skin prick test and/or specific IgE.

num hydroxide. Later, the absorbed material is diluted in a sodium chloride, phosphate-buffered saline, and water solution [5]. Any component in this vaccine does not seem potentially immunogenic. Aluminum hydroxide has not been reported to be a typical allergen for an immediate type of HSRs so far, but several adverse effects were determined [32]. In addition, 6 cases had a HSR history with various drugs in group A1. Considering the additive components in CoronaVac, it does not contain the ones (except sodium chloride) similar in the drugs which the patients had a HSR history with. However, there are some reports demonstrating HSRs to CoronaVac [33–35]. Urticaria was detected as the most common cutaneous reaction in healthcare workers vaccinated with CoronaVac [33]. Most of the HSRs in a latter study were mild except 1 case of anaphylaxis. However, there is a report of 12 cases with CoronaVac induced anaphylaxis from Thailand [36]. Another issue, delayed reactions were reported to be common and self-limited in a study from Turkey [34]. Delayed HSRs that occurred 24 h later following the vaccination were not included and that would be probably why the most common HSR type with CoronaVac is anaphylaxis in the present study. Although HSRs within 4 h were accepted to be immediate type of HSR to COVID-19 vaccines according to a review [19], we included the cases showed HSRs to COVID-19 vaccines within 24 h to demonstrate their clinical findings as in previous studies [37, 38]. However, we later compared the subjects who had immediate type HSRs with their control groups.

One of the risky groups, patients with systemic mastocytosis were recommended to be vaccinated in the hospital with longer observation [9]. However, the early reports demonstrate that COVID-19 vaccines were safely applied, even in subjects with history of anaphylaxis [39, 40]. In this study, there was no patient diagnosed with

systemic mastocytosis. Two patients had an elevated basal serum tryptase value (>11.4 µg/L) [41], but they refused to undergo bone marrow biopsy. Uncontrolled asthma and a severe allergic reaction history were also considered as risk factors [9]. In our findings, the presence and severity of asthma was not different between controls and patients. In the Vaccine Adverse Event Reporting System dataset of the USA, the vaccine recipients with preexisting allergic comorbidities were twice likely to develop anaphylaxis after vaccination when compared to those without [42]. In a retrospective cohort study, atopy was not suggested to be a risk factor because none of the AR patients on subcutaneous immunotherapy showed HSR to mRNA COVID-19 vaccines [43]. In this study, the presence of CSU was found more common in patients when compared to controls. In addition to CSU, HSRs to drugs were also higher in group A1 than A2. Thus, we recommend searching these two allergic comorbidities.

IgG antibodies targeting the viral nucleocapsid, spike, and the S receptor-binding domain of spike proteins have been shown to be produced in recovered SARS-CoV2-infected patients. Even more, a long-lasting survival of these IgG antibodies was detected in some cases following the infection [44, 45]. Comparing to controls, the positivity rate of anti-TPO abs was higher in group A1 of the present study, as shown previously in CSU [12]. For example, the patient who was desensitized to CoronaVac with a history of anaphylaxis revealed anti-TPO ab and ASST positivity, and she had negative SPT and IDT results. A non-IgE-mediated HSR to CoronaVac should be considered in this female patient. Another important finding is that the higher incidence of COVID-19 infection history in group A1 raises the possibility of the presence of circulating antibodies against SARS-CoV2. These preexisting antibodies may act as autoantibodies to IgE-

and FcεRI-like anti-TPO abs and might play role in the activation of HSRs to CoronaVac similar to the mechanism in autoimmune CSU and MDH [11].

Some desensitization protocols have been identified for COVID-19 vaccines. One is for patients having suspected history of HSR to Pfizer-BioNTech [38]. Another one was administered in 2 patients with a HSR to Moderna COVID-19 vaccine [46]. Similar to this protocol, a graded administration was also applied to a patient with a history of HSR to CoronaVac in Turkey [47]. In the present study, the positivity of SPT was clear in a patient, and a new protocol was safely administered in 2 patients with a HSR to CoronaVac.

A few limitations can be identified. First, we could not perform SPT and IDT with COVID-19 vaccines in all patients because of the reluctance of patients for allergological workup and limited number of vaccines. Second, anti-SARS-Cov2 IgG antibody and basophil histamine release assays would have been supportive if they had been analyzed. Third, the number of subjects was relatively small. However, HSRs to COVID-19 vaccines are rare, and the urgency to identify the underlying mechanisms of HSRs to COVID-19 vaccines stirred us to show our findings.

In conclusion, the findings in the present study emphasize that type IIb autoimmunity is quite important for HSRs to CoronaVac, and autoimmune markers should be evaluated in patients with HSRs to CoronaVac. Moreover, the new desensitization protocol in this study can be applied safely for HSRs to CoronaVac.

References

1 Rossen LM, Branum AM, Ahmad FB, Sutton P, Anderson RN. Excess deaths associated with COVID-19, by age and race and ethnicity: United States, January 26–October 3, 2020. MMWR Morb Mortal Wkly Rep. 2020; 69(42):1522–7.

2 CDC COVID-19 Response Team; Food and Drug Administration. Allergic reactions including anaphylaxis after receipt of the first dose of Pfizer-BioNTech COVID-19 vaccine: United States, December 14–23, 2020. MMWR Morb Mortal Wkly Rep. 2021;70(2):46–51.

3 Dreskin SC, Halsey NA, Kelso JM, Wood RA, Hummell DS, Edwards KM, et al. International consensus (ICON): allergic reactions to vaccines. World Allergy Organ J. 2016;9(1): 32.

4 Cabanillas B, Akdis CA, Novak N. COVID-19 vaccine anaphylaxis: IgE, complement or what else? A reply to – COVID-19 vaccine anaphylaxis – PEG or not? Allergy. 2021; 76(6):1938–40.

5 Zhang Y, Zeng G, Pan H, Li C, Hu Y, Chu K, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet Infect Dis. 2021;21(2):181–92.

6 Tanriover MD, Doğanay HL, Akova M, Güner HR, Azap A, Akhan S, et al. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. Lancet. 2021;398(10296):213–22.

7 CDC; Centers for Disease Control and Prevent. Interim clinical considerations for use of COVID-19 vaccines currently approved and authorized in the United States [updated 2021 Oct 25]. Available from: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html?CDC_AA_refVal=https%3A%2F%2F Accessed 2021 Oct 27.

8 Pfaar O, Mahler V. Allergic reactions to COVID-19 vaccinations-unveiling the secret(s). Allergy. 2021;76(6):1621–3.

9 Sokolowska M, Eiwegger T, Ollert M, Torres MJ, Barber D, Del Giacco S, et al. EAACI statement on the diagnosis, management and prevention of severe allergic reactions to COVID-19 vaccines. Allergy. 2021;76(6):1629–39.

10 Zuberbier T, Abdul Latiff AH, Abuzakouk M, Aquilina S, Asero R, Baker D, et al. The international EAACI/GA2LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. Allergy. 2021.

11 Schoepke N, Asero R, Ellrich A, Ferrer M, Gimenez-Arnau A, Grattan EHC, et al. Biomarkers and clinical characteristics of autoimmune chronic spontaneous urticaria: results of the PURIST Study. Allergy. 2019; 74(12):2427–36.

12 Confino-Cohen R, Chodick G, Shalev V, Leshno M, Kimhi O, Goldberg A. Chronic urticaria and autoimmunity: associations found in a large population study. J Allergy Clin Immunol. 2012;129(5):1307–13.

13 Colombo G, Yacoub MR, Burastero SE, Garattini E, Girlanda S, Saporiti N, et al. Multiple drug hypersensitivity: insight into the underlying mechanism and correlation with autoimmune diseases. Eur Ann Allergy Clin Immunol. 2009;41(2):50–5.

14 Asero R, Tedeschi A, Lorini M. Autoreactivity is highly prevalent in patients with multiple intolerances to NSAIDs. Ann Allergy Asthma Immunol. 2002;88(5):468–72.

15 Asero R. Intolerance to nonsteroidal anti-inflammatory drugs might precede by years the onset of chronic urticaria. J Allergy Clin Immunol. 2003;111(5):1095–8.

16 Asero R, Tedeschi A, Riboldi P, Griffini S, Bonanni E, Cugno M. Coagulation cascade and fibrinolysis in patients with multiple-drug allergy syndrome. Ann Allergy Asthma Immunol. 2008;100(1):44–8.

17 Department for Health and Wellbeing, Government of South Australia. Vasovagal episode or anaphylaxis; 2019. Available from: https://www.sahealth.sa.gov.au/wps/wcm/connect/7bf436004f0c7c268dc7af791a12b24c/Vasovagal+episode+or+anaphylaxi s+Chart+-+201907+%28v1.0%29.pdf?MOD=AJPERES&CACHEID=ROOTWORKSPACE-7bf436004f0c7c268dc7af791a12b24c-niQpYNW Accessed 2021 Jan 14.

18 CDC; COVID-19 Response Team; Food and Drug Administration. Allergic reactions including anaphylaxis after receipt of the first dose of Pfizer-BioNTech COVID-19 vaccine – United States, December 14–23, 2020. MMWR Morb Mortal Wkly Rep. 2021;70(2):46–51.

19 Nilsson L, Csuth Á, Storsaeter J, Garvey LH, Jenmalm MC. Vaccine allergy: evidence to consider for COVID-19 vaccines. Curr Opin Allergy Clin Immunol. 2021;21(4):401–9.

20 Cardona V, Ansotegui IJ, Ebisawa M, El-Gamal Y, Fernandez Rivas M, Fineman S, et al. World allergy organization anaphylaxis guidance 2020. World Allergy Organ J. 2020;13(10):100472.

21 Brown SG, Stone SF, Fatovich DM, Burrows SA, Holdgate A, Celenza A, et al. Anaphylaxis: clinical patterns, mediator release, and severity. J Allergy Clin Immunol. 2013;132(5):1141–9.

22 Greiner AN, Hellings PW, Rotiroti G, Scadding GK. Allergic rhinitis. Lancet. 2011;378(9809):2112.

23 Bousquet PJ, Combescure C, Neukirch F, Klossek JM, Méchin H, Daures JP, et al. Visual analog scales can assess the severity of rhinitis graded according to ARIA guidelines. Allergy. 2007;62(4):367–72.

24 Demoly P, Bousquet PJ, Mesbah K, Bousquet J, Devillier P. Visual analogue scale in patients treated for allergic rhinitis: an observational prospective study in primary care: asthma and rhinitis. Clin Exp Allergy. 2013;43(8):881–8.

25 Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention (update 2021). Avaliable from: https://ginasthma.org/reports/https: //ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf Accessed 2021 Sep 30.

26 Rutkowski K, Mirakian R, Till S, Rutkowski R, Wagner A. Adverse reactions to COVID-19 vaccines: a practical approach. Clin Exp Allergy. 2021;51(6):770–7.

27 Cabanillas B, Novak N. Allergy to COVID-19 vaccines: a current update. Allergol Int. 2021;70(3):313–8.

28 Risma KA, Edwards KM, Hummell DS, Little FF, Norton AE, Stallings A, et al. Potential mechanisms of anaphylaxis to COVID-19 mRNA vaccines. J Allergy Clin Immunol. 2021;147(6):2075–82.

29 Sellaturay P, Nasser S, Ewan P. Polyethylene glycol-induced systemic allergic reactions (Anaphylaxis). J Allergy Clin Immunol Pract. 2021;9(2):670–5.

30 Lu IN, Rutkowski K, Kennard L, Nakonechna A, Mirakian R, Wagner A. Polyethylene glycol may be the major allergen in depot medroxy-progesterone acetate. J Allergy Clin Immunol Pract. 2020;8(9):3194–7.

31 Krantz MS, Liu Y, Phillips EJ, Stone CA Jr. Anaphylaxis to PEGylated liposomal echocardiogram contrast in a patient with IgE-mediated macrogol allergy. J Allergy Clin Immunol Pract. 2020;8(4):1416–3.

32 Goullé JP, Grangeot-Keros L. Aluminum and vaccines: current state of knowledge. Med Mal Infect. 2020;50(1):16–21.

33 Durmaz K, Aykut Temiz S, Metin Z, Dursun R, Abdelmaksoud A. Allergic and cutaneous reactions following inactivated SARS-CoV-2 vaccine (CoronaVac®) in healthcare workers. Clin Exp Dermatol. 2021.

34 Akdaş E, Öğüt B, Erdem Ö, Öztaş MO, İlter N. Cutaneous reactions following CoronaVac COVID-19 vaccination: a case series of six healthcare workers from a single centre. J Eur Acad Dermatol Venereol. 2021.

35 Cebeci F, Kartal İ. Petechial skin rash associated with CoronaVac vaccination: first cutaneous side effect report before phase 3 results. Eur J Hosp Pharm. 2021:ejhpharm. ejhpharm-2021-002794.

36 Laisuan W, Wongsa C, Chiewchalermsri C, Thongngarm T, Rerkpattanapipat T, Iamrahong P, et al. CoronaVac COVID-19 vaccine-induced anaphylaxis: clinical characteristics and revaccination outcomes. J Asthma Allergy. 2021;14:1209–15.

37 Paoletti G, Racca F, Piona A, Melone G, Merigo M, Puggioni F, et al. Successful SARS-CoV-2 vaccine allergy risk-management: the experience of a large Italian University hospital. World Allergy Organ J. 2021;14(5):100541.

38 Shimabukuro T, Nair N. Allergic reactions including anaphylaxis after receipt of the first dose of Pfizer-BioNTech COVID-19 vaccine. JAMA. 2021;325(8):780–1.

39 Kaakati R, Khokhar D, Akin C. Safety of COVID-19 vaccination in patients with mastocytosis and monoclonal mast cell activation syndrome. J Allergy Clin Immunol Pract. 2021;9(8):3198–9.

40 Rama TA, Moreira A, Castells M. mRNA COVID-19 vaccine is well tolerated in patients with cutaneous and systemic mastocytosis with mast cell activation symptoms and anaphylaxis. J Allergy Clin Immunol. 2021;147(3):877–8.

41 Fellinger C, Hemmer W, Wöhrl S, Sesztak-Greinecker G, Jarisch R, Wantke F. Clinical characteristics and risk profile of patients with elevated baseline serum tryptase. Allergol Immunopathol. 2014;42(6):544–52.

42 Desai AP, Desai AP, Loomis GJ. Relationship between pre-existing allergies and anaphylactic reactions post mRNA COVID-19 vaccine administration. Vaccine. 2021;39(32):4407–9.

43 Dages KN, Pitlick MM, Joshi AY, Park MA. Risk of allergic reaction in patients with atopic disease and recent coronavirus disease 2019 vaccination. Ann Allergy Asthma Immunol. 2021;127(2):257–8.

44 Premkumar L, Segovia-Chumbez B, Jadi R, Martinez DR, Raut R, Markmann A, et al. The receptor binding domain of the viral spike protein is an immunodominant and highly specific target of antibodies in SARS-CoV-2 patients. Sci Immunol. 2020;5(48):eabc8413.

45 Chen Y, Zuiani A, Fischinger S, Mullur J, Atyeo C, Travers M, et al. Quick COVID-19 healers sustain anti-SARS-CoV-2 antibody production. Cell. 2020;183(6):1496–507.

46 Mustafa SS, Ramsey A, Staicu ML. Administration of a second dose of the Moderna COVID-19 vaccine after an immediate hypersensitivity reaction with the first dose: two case reports. Ann Intern Med. 2021;174(8):1177–8.

47 Cerci P, Ucan A. Immediate-type systemic hypersensitivity reactions after the inactivated Sars-Cov-2 vaccine in healthcare workers. Osmangazi J Med. 2021.