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

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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 COVID-19 vaccines). 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.

Introduction
Mortality and morbidity from COVID-19 are very important [1], and limited treatment options are available. Thus, vaccination against COVID-19 seems to be the only preferable option [2]. However, allergic reac-
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 Ib 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 Kirdar 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
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 χ² and Fischer’s exact tests. When more than 20% of cells have expected frequencies <5, Fischer’s exact test or otherwise the χ² 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-
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 CoronaVac 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 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

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  |

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

Table 2. CoronaVac desensitization protocol
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 presence 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

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.
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 (%) |                 |                 |                 |
| 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)           | >0.05           |
| Allergic contact dermatitis     | 1 (7.7)         | 0 (0)           | >0.05           |
| 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)           | >0.05           |
| Allergic contact dermatitis     | 1 (7.7)         | 0 (0)           | >0.05           |
| CSU                             | 6 (46.2)        | 0 (0)           | >0.05           |
| 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 (%) |                 |                 |                 |
| 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 (%) |                 |                 |                 |
| 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)           | >0.05           |
| 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 (%) |                 |                 |                 |
| 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)         | >0.05           |
| Asthma duration, months         | 246.5±333.4     | 120±0           | >0.05           |
| Patients by asthma control categories (n of N), n (%) |                 |                 | >0.05           |
| Well-controlled                 | 4 (30.8)        | 1 (7.7)         | >0.05           |
| Not well-controlled             | 2 (50)          | –               | –               |
| Poorly controlled               | 1 (25)          | –               | –               |
| Asthma severity (n of N), n (%) |                 |                 | >0.05           |
| Mild                            | 4 (30.8)        | 1 (7.7)         | >0.05           |
| Moderate                        | 2 (50)          | –               | –               |
| Severe                          | 1 (25)          | –               | –               |
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 co-morbidities, inhalant allergen sensitization, family histories of allergic diseases, and laboratory values were similar between either group A1 and A2 or group B1 and B2.

**Discussion/Conclusion**

The type IIb autoimmunity seems important in HSRs to the CoronaVac vaccine, which was the first time evaluated in 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                | 25.8±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)* |
| 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 | –             | –               |
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 basaI 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 in group A1 raises the possibility of the presence of circulating antibodies against SARS-CoV2. These preexisting antibodies may act as autoantibodies to IgE-

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**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 | 203.3±169.41 | 135.5±116.63 | >0.05           |
| Absolute basophil count, n/μL | 28.8±16.15   | 30±18.02     | >0.05           |
| Platelet count, n × 10³/μL | 277.5±70.74  | 258.2±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. *Fischer’s exact test used. *Those with a history of sensitivity determined by the skin prick test and/or specific 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.

Statement of Ethics

This study was approved by the Turkish Ministry of Health, and the ethical approval was obtained from the Ethics Committee of Kartal Dr. Lütfi Kirdar City Hospital (approval no. 2021/514/203/4, date: June 9, 2021). All patients gave written informed consent.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All the authors have made substantial contributions to conception and design or acquisition of data or analysis and interpretation of data, have been involved in drafting the manuscript, or revising it critically for important intellectual content.

Data Availability Statement

The data that support the findings of this study are not publicly available due to the fact that their containing information could compromise the privacy of research participants but are available from the corresponding author upon a reasonable request (email address: cancantuzer@gmail.com).

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