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Impact of Co-morbidities on Hypersensitivity Reactions to COVID-19 Vaccines

Pelin KORKMAZ, Deniz EYICE KARABACAK, Ilkim Deniz TOPRAK, Osman Ozan YEGIT, Derya UNAL, Semra DEMIR, Asli AKKOR

Istanbul University, Faculty of Medicine, Department of Internal Medicine, Division of Allergy and Clinical Immunology, Istanbul, Türkiye

Corresponding Author: Pelin Korkmaz ✉ dr.korkmazpelin@gmail.com

ABSTRACT

Background and Aim: Coronavirus disease of 2019 (COVID-19), also known as SARS Coronavirus-2, is an infectious disease caused by a single-stranded RNA (ssRNA) virus that emerged in Wuhan, China, in December 2019, leading to a global pandemic. Among the vaccines developed for COVID-19, BioNTech, CoronaVac, and TURKOVAC™ have been administered in Türkiye. While they were the best way to control the pandemic, allergic reactions associated with these vaccines have been reported. We aimed to evaluate the possible risk factors by examining the demographic and clinical characteristics of patients who showed hypersensitivity reactions to BioNTech and CoronaVac vaccines, and especially any concomitant diseases. TURKOVAC™ was not administered to any of the patients who presented to our clinic.

Materials and Methods: This retrospective study included 45 patients who presented with hypersensitivity reactions to COVID-19 vaccines at the Istanbul Faculty of Medicine's adult allergy clinic. Demographic and clinical characteristics were assessed, as well as whether patients who experienced hypersensitivity reactions subsequently continued vaccination. A control group (CG) of 50 age- and sex-matched individuals without hypersensitivity reactions to COVID-19 vaccines was established for comparison. The severity of hypersensitivity reactions was assessed using the World Allergy Organization (WAO) criteria.

Results: Of the 45 patients, 26 had hypersensitivity reactions to the BioNTech and 19 to CoronaVac vaccines, with 55.6% reporting reactions within the first hour of administration. Compared to the CG, patients with a history of drug allergy, allergic asthma, or allergic rhinitis were more likely to develop hypersensitivity reactions to the vaccines. Drug allergies were identified as a significant risk factor, with an odds ratio (OR) of 8.939 (95% confidence interval [CI]: 3–31, p=0.001). Additionally, allergic asthma (OR: 4.325, 95% CI: 1–18, p=0.042) was associated with an increased risk for hypersensitivity reactions to COVID-19 vaccines.

Conclusion: A history of drug allergy and allergic asthma significantly increased the risk of hypersensitivity reactions to COVID-19 vaccines. However, no significant association was found between clinical features and the severity of the reaction.

Keywords: COVID-19, Hypersensitivity Reactions, Vaccine

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a viral respiratory illness caused by SARS-CoV-2. First detected in Wuhan, China, in December 2019, it rapidly escalated into a global pandemic, impacting public health, economies, and social structures. In response, several COVID-19 vaccines received emergency use authorization, including mRNA, viral vector, and inactivated formulations (1,2). Türkiye also developed an inactivated vaccine, TURKOVAC™ (3). However, TURKOVAC™ was utilized less frequently compared to CoronaVac and BNT162b2.

Although COVID-19 vaccines, particularly mRNA-based formulations, represent a major advancement, vaccine hesitancy remains a concern due to potential side

ORCID Pelin Korkmaz / 0000-0002-0225-2485, Deniz Eyice Karabacak / 0000-0001-7627-8621, İlkim Deniz Toprak / 0000-0002-9320-1252, Osman Ozan Yegit / 0000-0003-4256-6048, Derya Unal / 0000-0001-9741-5939, Semra Demir / 0000-0003-3449-5868, Asli Akkor / 0000-0002-3524-9952

effects (4). Allergic reactions have been reported at rates ranging from 1 in 1,000,000 to 30 in 100,000 vaccinations (5-7). Furthermore, rare adverse events, including allergic and anaphylactic reactions following mRNA vaccination, as well as thrombosis and thrombocytopenia associated with non-replicating viral vector vaccines, have also been documented (8,9). These findings underscore the importance of addressing public fears and misconceptions surrounding vaccination. The "Allergy and Its Impact on Asthma" (ARIA) group and EAACI have emphasized that allergic patients should be observed for at least 15 minutes after vaccination and that healthcare staff involved in vaccination should be trained to recognize anaphylaxis (10).

Several mechanisms have been described to explain the adverse reactions associated with vaccines. Among these mechanisms, IgE-mediated reactions can occur when allergen-specific IgE antibodies bind to FcεRI receptors on mast cells and basophils, leading to mast cell activation and degranulation (11-13). The mRNA vaccines, in particular, have been associated with allergic reactions. Reports indicate a prevalence of anaphylaxis at 11.1 cases per million for the BNT162b2 vaccine and 2.5 cases per million for the mRNA-1273 vaccine (14). Although the causes of reported HSRs to COVID-19 vaccines have not yet been determined, adjuvants have been suggested as the leading causes (15,16). The approved mRNA vaccines contain polyethylene glycol (PEG), while AstraZeneca's and Johnson & Johnson's vaccines contain polysorbate 80 (11,17). Given that the molecular weight (MW) of PEG ranges between 300 and 10,000 g/mol, it has the potential to induce hypersensitivity reactions (18). Specifically, the PEG 2000 in Pfizer-BioNTech's BNT162b2 and Moderna's mRNA-1273 vaccines may trigger hypersensitivity in previously sensitized individuals (19,20).

Based on the available evidence, certain factors have been identified as increasing the risk of severe COVID-19 in adults. These include demographic factors such as older age, male gender, and ethnicity, as well as underlying health conditions such as cardiovascular diseases, hypertension, and chronic obstructive pulmonary disease (COPD) (21). Considering the limited data, individuals with a history of allergic reactions may have a slightly higher risk of developing hypersensitivity reactions to COVID-19 vaccines, though this risk remains generally low (22). However, the extent to which pre-existing comorbidities influence vaccine-related hypersensitivity reactions remains unclear. In this study, we aimed to investigate the relationship between comorbidities and hypersensitivity reactions to COVID-19 vaccines. By identifying potential risk factors, we seek to contribute to a better understanding of vaccine-related hypersensitivity and its clinical implications.

MATERIAL AND METHODS

Study Design

We analyzed patients who presented to the Adult Allergy and Immunology Outpatient Clinic of Istanbul University Faculty of Medicine between January 2021 and June 2023, having been identified in emergency departments as experiencing hypersensitivity reactions to COVID-19 vaccines and referred with notes from emergency rooms.

The study group included 95 patients consisting of 45 patients who had hypersensitivity reactions to the COVID-19 vaccines and 50 control group patients who did not have any reactions to these vaccines. The control group was selected to represent a similar population in terms of age and gender to the patient group, ensuring comparability.

The vaccines administered included BioNTech and CoronaVac, the two vaccines widely used in Turkey. Patients who received at least one dose of either vaccine were eligible for inclusion. Skin testing for hypersensitivity to PEG and polysorbate 80 was performed on patients who consented to the procedure (23-25). Testing for PEG was conducted using methylprednisolone acetate (containing PEG-3350) via both prick and intradermal (ID) methods at serial dilutions of 1/1000, 1/100, and 1/10. Similarly, skin testing for polysorbate 80 was performed using triamcinolone acetonide (containing polysorbate 80), following the same dilutions for ID testing. For each test, adequate positive (histamine) and negative (saline) controls were included to ensure validity. The choice of methylprednisolone acetate and triamcinolone acetonide as testing agents was guided by the established literature and their known content of PEG-3350 and polysorbate 80, respectively (26). Concomitant diseases were recorded for each patient. The presence of these concomitant diseases was analyzed and compared between the patients and the control group.

Definitions of Allergic Conditions

Allergic conditions including allergic asthma, allergic rhinitis, atopic dermatitis, and allergies to foods, drugs, and venom were defined. The diagnosis of asthma was based on the Global Initiative for Asthma (GINA) guide-

lines (27), while the rhinitis diagnosis followed the Allergic Rhinitis and its Impact on Asthma (ARIA) criteria (28). Atopic dermatitis was diagnosed according to the Hanifin and Rajka criteria (29). Diagnoses of food, drug, and venom allergies were confirmed based on patient medical histories and allergen-specific IgE testing.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS), and visual figures were generated using Microsoft PowerPoint. The Kolmogorov-Smirnov test was applied to assess the distribution of quantitative data. Baseline characteristics were evaluated using descriptive analysis, with the interquartile range presented as median percentages (IQR 25-75) based on data distribution. Continuous variables were compared between groups using either the independent t-test or the Mann-Whitney U test, with statistical significance set at $p < 0.05$.

Ethical Considerations

The study received approval from the local ethics committee (approval number: 27.03.2024-2499600) and was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants in both the patient and control groups prior to their inclusion in the study.

RESULTS

A total of 95 patients received at least one dose of the COVID-19 vaccine, and 45 had hypersensitivity reactions. Among those with reactions, 80% were female, with a mean age of 38.98 years (min-max: 18–59), while in the control group, 56% were female, with a mean age of 45.82 years (min-max: 24–71). Reactions were observed in 26 individuals vaccinated with BioNTech and 19 individuals vaccinated with CoronaVac.

Most reactions (84.4%) occurred after the first dose, with lower rates following the second (13.3%) and third (2.2%) doses. When vaccinated with BioNTech, 84.6% had a reaction with the first dose, while 80% of those vaccinated with CoronaVac reported reactions with the first dose. Additionally, 53.9% of patients who reacted to BioNTech and 57.9% of those who reacted to CoronaVac experienced the reaction within the first-hour post-vaccination. Skin testing was not performed on all participants because the patient did not give consent.

Skin testing with PEG and polysorbate 80 was performed in 57.7% of the patients who reacted to BioNTech and all were negative. Among CoronaVac-reactive patients, only four underwent testing, with one patient (5.3%) showing a positive reaction to PEG. The frequency of anaphylaxis was 73.1% for the BioNTech and 68.4% for the CoronaVac vaccine. Reaction severity was assessed per World Allergy Organization (WAO) criteria, with 42.2% experiencing grade 4 reactions (Table I). The most frequent symptoms were dyspnea (62.2%), urticaria and angioedema (60.0%), and syncope (37.8%).

When analyzing the presence of additional co-morbidities between the groups, the overall co-morbidity rate was 37.8% in the vaccine-reaction group, compared to 54% in the control group. Hypertension and coronary artery disease were present in 15.8% and 10.5% of the patient and control groups, respectively, and the most common concomitant disease was hypertension (15.8%). Other prevalent diseases included hypothyroidism (12.6%), diabetes mellitus (11.6%), and malignancies (5.3%) (Table II). The comorbidities observed in the patient group showed no significant differences between those with and without anaphylaxis.

Allergic manifestations were more common in the patient group with hypersensitivity to COVID-19 vaccines.

Table I. Distribution of the severity of the hypersensitivity reactions to COVID-19

	Immediate reaction <1 hour n=25 (56%)	Immediate reaction 1-6 hours n=20 (44%)
Grade 1, n (%)	2 (4.44)	11 (24.44)
Grade 2, n (%)	0 (0.0)	0 (0.0)
Grade 3, n (%)	8 (17.77)	3 (6.66)
Grade 4, n (%)	14 (31.11)	5 (11.11)
Grade 5, n (%)	1 (2.22)	1 (2.22)

Allergic rhinitis was the most prevalent allergic manifestation in the patient group (71.1%) (Table III). Drug allergies (60%) were identified as a significant risk factor, with an odds ratio (OR) of 8.939 (95% confidence interval: 3–31, p=0.001). Upon reviewing the available medication data, most of the formulations did not contain PEG. In all cases, more than six months had passed since the drug reactions occurred. Skin testing was performed with available and known culprit drugs and only ampicillin and amoxicillin among these yielded positive skin test results, while all NSAID-related skin tests were negative. Additionally, allergic asthma (OR: 4.325, 95% CI: 1–18, p=0.042) was associated with an increased risk for hypersensitivity reactions to COVID-19 vaccines (Table IV).

Table II. Co-morbidities of patients who experienced hypersensitivity reactions with COVID-19 vaccines

	Patients n=45
Hypertension, n (%)	8 (17.8)
Diabetes mellitus, n (%)	8 (17.8)
Coronary artery disease, n (%)	5 (11.1)
Hypothyroidism, n (%)	5 (11.1)
Malignancies, n (%)	2 (4.4)
Bechet's disease, n (%)	2 (4.4)
Chronic obstructive pulmonary disease, n (%)	1 (2.2)
Rheumatoid arthritis, n (%)	1 (2.2)
Gout disease, n (%)	1 (2.2)
Hashimoto's thyroiditis, n (%)	1 (2.2)
Systemic lupus erythematosus, n (%)	1 (2.2)
Factor 5 Leiden mutation, n (%)	1 (2.2)

Table III. Allergic manifestations in the patient and control groups

	Patients n=45	Control groups n=50
Drug allergy, n (%)	27 (60)	4 (8)
Asthma, n (%)	21 (46.7)	4 (8)
Allergic Rhinitis, n (%)	32 (71.1)	12 (24)
Food allergy, n (%)	3 (6.7)	1 (2)
Venom allergy, n (%)	6 (13.3)	1 (2)
Atopic dermatitis, n (%)	4 (8.9)	2 (4)
Chronic urticaria, n (%)	9 (20.0)	4 (8)

In our clinic, an alternative vaccine was recommended to all patients who had hypersensitivity reactions following any dose of a COVID-19 vaccine. However, during the pandemic period, some patients chose to receive the same vaccine—particularly BNT162b2 (BioNTech)—based on their belief in its higher efficacy and proceeded with re-vaccination by their own preference. We did not perform these re-vaccinations ourselves; rather, we recommended that they be carried out in hospitals with appropriate emergency and intensive care facilities. Re-vaccinations were conducted in appropriate medical settings using a graded protocol (1/10, 1/4, 1/2, and the remaining dose), administered at 30-minute intervals under close observation. No premedication was given, as its efficacy remains controversial and it may potentially mask early signs of anaphylaxis during subsequent doses (30). Therefore, premedication was not recommended for patients receiving alternative vaccines. Patients who opted to receive the same vaccine again did so on their own initiative, and it was later reported that the graded challenge protocol (1/10, 1/4, 1/2, and the remaining dose) was applied without premedication. In our clinic, no patients were re-vaccinated in outpatient clinics or inpatient wards, nor was this approach recommended. All patients requiring re-vaccination were advised to undergo the procedure in hospitals equipped to provide immediate emergency intervention and access to intensive care if necessary. Although no patients ultimately required intensive care, this precautionary recommendation was made to ensure patient safety and effective management of potential adverse reactions. Among the patients who had a hypersensitivity reaction to any COVID-19 vaccine, 55.6% declined to receive fur-

Table IV. Predictors of hypersensitivity reactions to COVID-19 vaccines (Logistic regression analysis)

	p-value	Odds ratio	95% Confidence interval
Drug allergy	0.001	8.939	2.540-31.464
Allergic Asthma	0.042	4.325	1.055-17.730
Allergic Rhinitis	NS	0.858	0.265-2.773

Abbreviations: NS – Not significant.

ther vaccination. Seven patients were administered an alternative vaccine, while 13 received the same vaccine. Among these, only one patient had a hypersensitivity reaction again (Table V). Additionally, 10 patients developed chronic urticaria after vaccination and are being followed up at our clinic. In one patient, recurrent idiopathic anaphylaxis occurred following BioNTech vaccination, and was refractory to prophylactic high-dose antihistamines and corticosteroids. Serum tryptase levels measured 2 h and 1 day after anaphylaxis were 8.17 and 4.89 ng/mL, respectively. This difference was 2.30, more than 20% of the baseline value, verifying the anaphylaxis diagnosis. The

Table V. Clinical Profiles and Outcomes in Patients Evaluated for COVID-19 Vaccine Allergy

Patient	Allergic comorbidity	Clinical findings	Vaccine type	PEG skin test result	Subsequent dose	Reaction During Re-Vaccination	Baseline Tryptase
Patient 1	Asthma Allergic rhinitis Food allergy (unknown trigger)	Dyspnea, urticaria, and angioedema	BioNTech	Not performed (patient refusal)	CoronaVac	No allergic reaction	Not performed (patient refusal)
Patient 2	Asthma Allergic rhinitis Drug allergy (unknown antibiotic; uvular edema and dyspnea)	Dyspnea, urticaria, angioedema, and syncope	BioNTech	Not performed (patient refusal)	No further vaccination (patient preference)		5.85
Patient 3	None	Pruritus, urticaria, and angioedema	BioNTech	Negative	No further vaccination (patient preference)		Not performed (patient refusal)
Patient 4	Asthma Allergic rhinitis Drug allergy (anaphylaxis with ampicillin; radiocontrast media)	Dyspnea, syncope, vomiting, and nausea	BioNTech	Not performed (patient refusal)	No further vaccination (patient preference)		1.01
Patient 5	Asthma Allergic rhinitis Drug allergy (dyspnea with NSAID)	Dyspnea, urticaria, angioedema, and syncope	BioNTech	Not performed (patient refusal)	No further vaccination (patient preference)		4.58
Patient 6	Asthma Allergic rhinitis Drug allergy (unknown antibiotic; lip edema and dyspnea) Atopic dermatitis	Dyspnea, urticaria, angioedema, and syncope	CoronaVac	Not performed (patient refusal)	No further vaccination (patient preference)		Not performed (patient refusal)
Patient 7	Asthma Allergic rhinitis Drug allergy (reaction to vitamin B complex)	Dyspnea and syncope	CoronaVac	Not performed (patient refusal)	Patient received the same vaccine (alternative was recommended)	No allergic reaction	6.03
Patient 8	Allergic rhinitis Food allergy (unknown trigger)	Dyspnea, urticaria, angioedema	BioNTech	Negative	No further vaccination (patient preference)		5.81

Table V. Continue

Patient	Allergic comorbidity	Clinical findings	Vaccine type	PEG skin test result	Subsequent dose	Reaction During Re-Vaccination	Baseline Tryptase
Patient 9	Allergic rhinitis Drug allergy (dyspnea and throat tightness with unknown antibiotic and NSAID)	Angioedema and pruritus	BioNTech	Negative	No further vaccination (patient preference)		Not performed (patient refusal)
Patient 10	None	Dyspnea, urticaria, and angioedema	BioNTech	Negative	Patient received the same vaccine (alternative was recommended)	Syncope	5.88
Patient 11	Allergic rhinitis	Urticaria	BioNTech	Negative	Patient received the same vaccine (alternative was recommended)	No allergic reaction	Not performed (patient refusal)
Patient 12	Asthma Allergic rhinitis	Dyspnea	BioNTech	Negative	No further vaccination (patient preference)		Not performed (patient refusal)
Patient 13	Allergic rhinitis	Dyspnea, urticaria, angioedema, and syncope	BioNTech	Negative	No further vaccination (patient preference)		7.10
Patient 14	Asthma Allergic rhinitis Drug allergy (dyspnea and urticaria with unknown antibiotic and NSAID)	Dyspnea and syncope	CoronaVac	Negative	No further vaccination (patient preference)		Not performed (patient refusal)
Patient 15	None	Syncope	BioNTech	Negative	Patient received the same vaccine (alternative was recommended)	No allergic reaction	6.39
Patient 16	Asthma Allergic rhinitis	Dyspnea	BioNTech	Negative	Patient received the same vaccine (alternative was recommended)	No allergic reaction	Not performed (patient refusal)
Patient 17	Asthma Allergic rhinitis Drug allergy (urticaria with ciprofloxacin, metronidazole, and NSAIDs)	Urticaria and pruritus	BioNTech	Not performed (patient refusal)	Patient received the same vaccine (alternative was recommended)	No allergic reaction	4.56
Patient 18	Asthma Atopic dermatitis	Urticaria and pruritus	BioNTech	Not performed (patient refusal)	No further vaccination (patient preference)		Not performed (patient refusal)
Patient 19	Allergic rhinitis Venom-induced anaphylaxis Drug allergy (urticaria with NSAIDs)	Urticaria and pruritus	BioNTech	Negative	No further vaccination (patient preference)		8.98

Table V. Continue

Patient	Allergic comorbidity	Clinical findings	Vaccine type	PEG skin test result	Subsequent dose	Reaction During Re-Vaccination	Baseline Tryptase
Patient 20	Asthma Allergic rhinitis Chronic urticaria	Dyspnea, urticaria, angioedema, syncope, and pruritus	CoronaVac	Not performed (patient refusal)	Patient received the same vaccine (alternative was recommended)	No allergic reaction	3.29
Patient 21	Atopic dermatitis	Dyspnea, angioedema, and pruritus	CoronaVac	Not performed (patient refusal)	BioNTech	No allergic reaction	2.90
Patient 22	Allergic rhinitis	Dyspnea, urticaria–angioedema, and syncope	CoronaVac	Not performed (patient refusal)	No further vaccination (patient preference)		3.64
Patient 23	Drug allergy (penicillin-induced anaphylaxis)	Dyspnea and syncope	CoronaVac	Not performed (patient refusal)	No further vaccination (patient preference)		3.39
Patient 24	Allergic rhinitis Drug allergy (urticaria with antibiotics; angioedema with NSAIDs)	Dyspnea and vomiting	CoronaVac	Positive	Patient received the same vaccine (alternative was recommended)	No allergic reaction	5.15
Patient 25	Asthma Allergic rhinitis Chronic urticaria	Dyspnea, urticaria, angioedema, pruritus, and syncope	CoronaVac	Not performed (patient refusal)	Patient received the same vaccine (alternative was recommended)	No allergic reaction	3.29
Patient 26	Venom-induced anaphylaxis Atopic dermatitis	Urticaria	CoronaVac	Not performed (patient refusal)	Patient received the same vaccine (alternative was recommended)	No allergic reaction	Not performed (patient refusal)
Patient 27	Allergic rhinitis Drug allergy (urticaria; unknown drug)	Syncope and vomiting	CoronaVac	Not performed (patient refusal)	BioNTech	No allergic reaction	3.24
Patient 28	Allergic rhinitis	Syncope	BioNTech	Negative	No further vaccination (patient preference)		7.85
Patient 29	Allergic rhinitis Chronic urticaria Drug allergy (urticaria with NSAIDs)	Dyspnea, urticaria, angioedema, and hypotension	CoronaVac	Negative	No further vaccination (patient preference)		Not performed (patient refusal)
Patient 30	Drug allergy (urticaria with NSAID) Asthma Allergic rhinitis Food allergy (anaphylaxis with shrimp)	Urticaria	CoronaVac	Not performed (patient refusal)	Patient received the same vaccine (alternative was recommended)	No allergic reaction	Not performed (patient refusal)

Table V. Continue

Patient	Allergic comorbidity	Clinical findings	Vaccine type	PEG skin test result	Subsequent dose	Reaction During Re-Vaccination	Baseline Tryptase
Patient 31	Asthma Allergic rhinitis Drug allergy (dyspnea and lip angioedema with unknown drug)	Dyspnea, urticaria, angioedema, syncope, and pruritus	BioNTech	Negative	CoronaVac	No allergic reaction	4.60
Patient 32	Drug allergy (dyspnea with unknown antibiotic)	Dyspnea, tongue swelling, and syncope	CoronaVac	Not performed (patient refusal)	No further vaccination (patient preference)		4.35
Patient 33	Venom-induced anaphylaxis Drug allergy (dyspnea with NSAID)	Uvula edema and dyspnea	BioNTech	Not performed (patient refusal)	No further vaccination (patient preference)		7.90
Patient 34	Asthma Allergic rhinitis Chronic urticaria Drug allergy (radiocontrast media–induced anaphylaxis)	Dyspnea, urticaria, angioedema, syncope, diarrhea, and vomiting	CoronaVac	Not performed (patient refusal)	BioNTech	No allergic reaction	4.27
Patient 35	Chronic urticaria Drug allergy (urticaria-angioedema with NSAIDs)	Urticaria and angioedema	BioNTech	Not performed (patient refusal)	Patient received the same vaccine (alternative was recommended)	No allergic reaction	3.09
Patient 36	Asthma Allergic rhinitis Drug allergy (dyspnea with unknown NSAID)	Urticaria	CoronaVac	Not performed (patient refusal)	No further vaccination (patient preference)		6.19
Patient 37	Chronic urticaria Drug allergy (urticaria-angioedema with NSAIDs)	Dyspnea, urticaria, angioedema, and pruritus	BioNTech	Not performed (patient refusal)	No further vaccination (patient preference)		2.31
Patient 38	Asthma Allergic rhinitis	Syncope, dyspnea, and hypotension	BioNTech	Negative	No further vaccination (patient preference)		8.76
Patient 39	Allergic rhinitis Venom-induced anaphylaxis Chronic urticaria Drug allergy (urticaria-angioedema with NSAIDs)	Dyspnea, urticaria, angioedema, and pruritus	BioNTech	Not performed (patient refusal)	CoronaVac	No allergic reaction	6.19
Patient 40	Allergic rhinitis Chronic urticaria Drug allergy (Urticaria with unknown drug)	Urticaria	CoronaVac	Not performed (patient refusal)	No further vaccination (patient preference)		9

Table V. Continue

Patient	Allergic comorbidity	Clinical findings	Vaccine type	PEG skin test result	Subsequent dose	Reaction During Re-Vaccination	Baseline Tryptase
Patient 41	Chronic urticaria Asthma	Urticaria	CoronaVac	Negative	BioNTech	No allergic reaction	4.92
Patient 42	Asthma Allergic rhinitis Food allergy (anaphylaxis with shrimp) Drug allergy (radiocontrast media–induced anaphylaxis)	Dyspnea, urticaria, laryngeal edema, syncope	BioNTech	Not performed (patient refusal)	No further vaccination (patient preference)		4.98
Patient 43	Asthma Allergic rhinitis Venom-induced anaphylaxis Drug allergy (dyspnea and urticaria with unknown antibiotic)	Urticaria and angioedema	CoronaVac	Not performed (patient refusal)	No further vaccination (patient preference)		Not performed (patient refusal)
Patient 44	Allergic rhinitis Drug allergy (dyspnea and urticaria with unknown antibiotic)	Urticaria and angioedema	BioNTech	Negative	No further vaccination (patient preference)		4.89
Patient 45	Venom-induced anaphylaxis Drug allergy (dyspnea and throat tightness with unknown antibiotic)	Dyspnea	BioNTech	Negative	Patient received the same vaccine (alternative was recommended)	No allergic reaction	Not performed (patient refusal)

NSAIDs: Nonsteroidal anti-inflammatory drugs

treatment regimen included cetirizine 10 mg/day, fexofenadine 180 mg twice a day, ketotifen 2 mg/day, and methylprednisolone 16 mg/day. However, after the cessation of methylprednisolone, anaphylaxis attacks and chronic urticaria continued under high-dose antihistamines. Therefore, omalizumab 300 mg per month was initiated, and the patient's attacks were successfully brought under control with this treatment. The patient continues to be monitored at our clinic. Additionally, food-dependent exercise-induced anaphylaxis (FDEIA) was excluded, as the patient's anaphylactic episodes were unrelated to food intake or physical exertion. Furthermore, no evidence of food-specific IgE sensitization was detected. However, tryptase levels were not routinely assessed in the emergency departments where other patients were initially managed. For cases in which we were able to measure baseline tryptase levels in our clinic, these values are presented in Table V.

DISCUSSION

In our study, drug allergies and asthma were identified as significant contributors to hypersensitivity reactions to COVID-19 vaccines. These findings highlight the importance of thorough medical history evaluations to identify individuals at higher risk. While not a universal rule for all vaccines, our results are particularly valuable for understanding reactions to COVID-19 vaccines and may also offer insights for vaccines with mechanisms that are not yet fully understood.

The predominance of hypersensitivity reactions after the first dose of the COVID-19 vaccine in our study (84.4%) is consistent with previous reports, including data from the United States, where anaphylaxis occurred at a rate of 11.1 per million doses following the first dose of the

Pfizer-BioNTech vaccine (31). One potential explanation for this phenomenon is pre-existing sensitization to PEG, an excipient found in mRNA vaccines. However, skin testing for PEG and polysorbate 80 was negative in most patients in our study, except for one case. This suggests that mechanisms other than IgE-mediated hypersensitivity, such as direct mast cell activation or non-IgE-mediated immune responses, may also contribute to these reactions. Additionally, the psychological stress and fear associated with an emerging disease during the pandemic may have contributed to heightened sensitivity or misattribution of symptoms as allergic reactions. Given the challenges of diagnosing anaphylaxis under pandemic conditions, laboratory markers such as tryptase levels were not systematically recorded in all cases. This limitation further complicates the ability to differentiate true anaphylactic reactions from anxiety-related or vasovagal responses. Interestingly, hypersensitivity reactions did not recur in most patients upon re-vaccination. This may be explained by the resolution of transient cofactors (e.g., infections, stress, or concurrent medications) that may have contributed to the initial reactions. Additionally, differences in vaccine storage, handling, or administration conditions during the initial dose may also have played a role in altering the clinical response upon re-vaccination. These observations highlight the need for further research into the underlying immunological mechanisms of vaccine-induced hypersensitivity.

While asthma has been established as a risk factor for a severe COVID-19 clinical picture due to its impact on lung function (32-34), its role in predicting hypersensitivity reactions to COVID-19 vaccines remains uncertain. A systematic review and meta-analysis based on 119 studies including 403,392 cases have shown that the prevalence of asthma in COVID-19 patients was similar to the general population (8.3% vs. 4.3-8.6%) and did not indicate an increased risk for adverse COVID-19 outcomes (35). However, we found an association between asthma and the development of hypersensitivity reactions to the COVID-19 vaccine in this study (p=0.042). This finding, although noteworthy, may become clearer with studies including a larger number of patients. On the other hand, it highlights the importance of closer monitoring and longer observation periods for asthmatic patients during vaccination, suggesting the need for more careful management before vaccination in this group.

Studies on the link between prior drug allergy history and the risk of allergic reactions to COVID-19 vaccines are limited. Some evidence suggests an elevated risk in such individuals (36,37). In our study, drug allergy (OR: 8.939, p=0.001) was determined as significant risk factor for anaphylaxis. Luxi et al. found that individuals with a history of drug allergy may have a heightened sensitivity to COVID-19 mRNA vaccines, especially to components like PEG and polysorbate 80, underscoring the importance of thorough pre-vaccination screening (38). In alignment with these findings, carefully assessing the patients' drug allergy history before vaccination is advisable.

PEG has been clearly implicated in the reported hypersensitivity reactions against COVID-19 vaccines in some publications (15,16,39). However, managing patients with suspected hypersensitivity reactions requires individualized decisions, considering the risk-benefit ratio. Notably, hypersensitivity reactions to PEG depend on its molecular weight, and patients with PEG allergy have been reported to tolerate COVID-19 vaccines in most cases (16). The role of other excipients, such as polysorbate 80 (PS80), in allergic reactions remains controversial (40,41). In a study conducted by Nappi et al., a skin test positivity rate of 12.7% for PEG and polysorbate 80 was reported among patients evaluated for hypersensitivity reactions to mRNA COVID-19 vaccines, yet no severe reactions occurred in those who were re-vaccinated (42). Although CoronaVac does not contain PEG, skin testing for PEG was performed in some patients due to the necessity of subsequent vaccination with mRNA vaccines containing PEG and patient safety concerns. Given the urgency of mass vaccination efforts, ensuring a safer alternative was essential. Additionally, one patient who experienced a reaction to CoronaVac tested positive for PEG, despite having no prior reactions to PEG-containing medications. This finding raises the possibility of previously unrecognized sensitization mechanisms or non-specific immune activation pathways contributing to hypersensitivity reactions, emphasizing the need for further research. Furthermore, as newly introduced and upcoming vaccines may contain unknown excipients or altered formulations, this approach was chosen to ensure safe vaccination strategies in the evolving landscape of COVID-19 immunization.

In our study, a significant proportion of patients developed CU following mRNA COVID-19 vaccination. While PEG hypersensitivity has been suggested as a potential trigger for vaccine-related reactions, most of our patients tested negative for PEG-specific reactivity. Instead, we considered alternative immunological mechanisms, par-

ticularly vaccine-induced autoreactivity. Previous studies have demonstrated that SARS-CoV-2 infection is associated with elevated autoantibody production through molecular mimicry involving the viral spike protein (43-45). Given that CU is well recognized as an autoimmune-mediated condition (46), it is plausible that immune dysregulation triggered by mRNA vaccination may contribute to its development. Indeed, some reports have documented CU onset within a few months of mRNA vaccine administration (47-49). These findings suggest that vaccine-induced immune responses, rather than PEG exposure, may play a more significant role in CU development in this patient group.

A recent study by Gümüşburun et al. demonstrated the successful administration of the second dose of the same COVID-19 vaccine in patients with prior hypersensitivity reactions through a graded dose escalation protocol that included premedication (50). This aligns with our findings, where we recommended graded dose administration—using an alternative vaccine—in settings equipped for emergency intervention. In contrast, some patients in our cohort independently chose to receive the same vaccine at external centers. Interestingly, only one of these patients experienced a recurrent reaction. The key difference between our approach and that of Gümüşburun et al. lies in the absence of premedication in our patients. Despite this, outcomes were largely favorable, suggesting that dose fractionation alone—without the need for premedication—may be sufficient to reduce the risk of hypersensitivity reactions. This observation warrants further investigation and may support the safe use of a graded challenge protocol as a standalone strategy in select cases.

One patient in the current study developed recurrent idiopathic anaphylaxis following BioNTech mRNA COVID-19 vaccination, and was unresponsive to prophylactic treatment. Despite high-dose antihistamines, the symptoms persisted after corticosteroid cessation, necessitating omalizumab 300 mg/month to successfully control the condition (51). This suggested that autoreactivity triggered by mRNA vaccination may contribute to anaphylaxis, similar to mechanisms observed in chronic urticaria. To our knowledge, this is the only reported case of recurrent idiopathic anaphylaxis following mRNA vaccination, highlighting the need for further studies to explore the underlying immunological pathways.

Our study is limited by the inability to test all participants and by the fact that only patients who applied to our outpatient clinic could be evaluated. Despite this limitation, the results suggest that additional factors may play a role in vaccine-induced hypersensitivity reactions. Our study is further limited by the fact that patients were referred to our clinic from emergency rooms, and this referral process was accepted as the basis for inclusion. However, this approach has its challenges, as not all physicians may accurately recognize anaphylaxis. In Türkiye, over 152 million COVID-19 vaccine doses have been administered, with nearly 58 million individuals receiving at least one dose. However, national data on the frequency of vaccine-related allergic reactions remain scarce, limiting the ability to compare our findings with population-wide statistics. The absence of tryptase testing in many emergency departments, which could serve as a confirmatory diagnostic tool, is an additional limitation. Moreover, we cannot account for patients who may have been referred to us with misdiagnosed cases, such as vasovagal reactions, which represents another limitation of our study. Expanding diagnostic capabilities and ensuring systematic adherence to guidelines could help mitigate these challenges and improve the accuracy of identifying true anaphylactic cases.

CONCLUSION

We indicated that the presence of drug allergy and allergic asthma was associated with an 8.9 and 4.3-fold increased risk for the development of hypersensitivity reactions to COVID-19 vaccines, respectively. However, we did not detect any impact of clinical features on the severity of a reaction. This study has strengths in predicting vaccine-induced hypersensitivity reactions. To our knowledge, this is the largest study in the field of allergy and immunology, based on patients who applied to allergy and immunology outpatient clinics in Türkiye and experienced hypersensitivity reactions with COVID-19 vaccines, and examined the individual demographic characteristics of patients experiencing these reactions by cause. Perhaps the presence of a history of allergic asthma and drug allergy can be used to predict hypersensitivity reactions that may occur for other vaccines to be administered and may reduce vaccine-related complications by encouraging longer observation of these patients in hospitals after vaccination.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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Author Contributions

Concept: **Pelin Korkmaz, Deniz Eyice Karabacak, Semra Demir,** Design: **Pelin Korkmaz, Semra Demir,** Data collection or processing: **Pelin Korkmaz, İlkim Deniz Toprak, Osman Ozan Yegit, Derya Unal,** Analysis or Interpretation: **Pelin Korkmaz, Deniz Eyice Karabacak, Asli Akkor,** Literature search: **Pelin Korkmaz, Deniz Eyice Karabacak,** Writing: **Pelin Korkmaz, Deniz Eyice Karabacak,** Approval: **Pelin Korkmaz, Deniz Eyice Karabacak, İlkim Deniz Toprak, Osman Ozan Yegit, Derya Unal, Semra Demir, Asli Akkor.**

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