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ORIGINAL RESEARCH

Adverse Cutaneous Reactions Following COVID-19 Vaccination Among Patients with Pre-Existing Urticaria: A Cross-Sectional Study at a Tertiary Care Center in Saudi Arabia

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Purpose: To investigate the incidence, characteristics, and associated factors of cutaneous adverse reactions to COVID-19 vaccines among adult patients with pre-existing urticaria in Saudi Arabia.

Patients and Methods: A cross-sectional study enrolled 190 adult patients (≥18 years) with urticaria attending allergy/dermatology clinics at King Khalid University Hospital, Riyadh (November 2021–April 2022). Data on demographics, urticaria characteristics, vaccination status, cutaneous reactions, and comorbidities were collected via questionnaire. Statistical analyses included descriptive statistics, Chi-square/Fisher exact tests, Cochran's test, and binary logistic regression.

Results: Participants were predominantly female (87.4%), with chronic spontaneous urticaria (97.9%); 78.9% used regular antihistamines. Reactions occurred after dose 1 (22.7%), dose 2 (26.2%), and dose 3 (31.0%). Among symptomatic individuals, onset was typically <24h, resolving in 1–3 days for ~50%. Common reactions included injection site reactions (13.1–16.3%), pruritus (7.8–-10.5%), and urticaria exacerbation (3.9–9.1%). Urticaria exacerbation decreased significantly after dose 3 (p=0.030). Regular antihistamine use was associated with fewer reactions after dose 1 (adjusted OR 0.4, p=0.028). Female gender, asthma/atopy, and autoimmune disease were associated with specific reactions. Adjusted vaccine type showed no significant association.

Conclusion: Cutaneous reactions post-COVID-19 vaccination in urticaria patients are relatively common but generally mild and transient. Decreasing urticaria exacerbations after dose 3 is reassuring. Regular antihistamine use may offer some protection, particularly after the first dose. Findings support vaccine safety and aid patient counseling.

Plain Language Summary: Understanding how COVID-19 vaccines affect people with existing skin allergies is 41 crucial for public health. Our study focused on patients with urticaria (chronic hives) 42 who received COVID-19 vaccines. We found that while many patients experienced 43 mild skin reactions after vaccination, these reactions were generally temporary and 44 manageable. Most reactions occurred within 24 hours of vaccination and resolved within 45 a few days. Importantly, patients who regularly took antihistamine medications were 46 less likely to develop reactions. This research provides reassurance that COVID-19 47 vaccines can be safely administered to people with pre-existing urticaria, although some 48 may experience temporary symptoms. These findings help both healthcare providers 49 and patients make informed decisions about vaccination.

Keywords: COVID-19, vaccine, urticaria, cutaneous adverse reaction, antihistamine, Saudi Arabia, cross-sectional study

Introduction

The COVID-19 pandemic, identified in late 2019, rapidly escalated into a global health crisis, presenting unprecedented social, political, economic, and health challenges.[1] This was met by a swift scientific response, leading to the development and

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dissemination of diagnostics, therapeutics, and vaccines in record time.[2,3] While these vaccines have been crucial in mitigating the pandemic's impact, their rapid rollout was accompanied by considerable public apprehension regarding safety and potential adverse effects from the outset,[4] despite extensive vaccine surveillance programs indicating that the vast majority (approximately 90%) of reported adverse effects were non-serious.[5]

Commonly reported adverse effects of COVID-19 vaccines include self-limiting local injection site reactions such as pain, heat, swelling, redness, and occasionally urticarial rashes or morbilliform eruptions. Systemic events like fever, fatigue, arthralgias, myalgias, and headache, typically developing within the first 1–2 days post-vaccination, are also frequent.[5–7] Beyond these, new onset or exacerbation of other cutaneous reactions, including exanthematous rashes, vesicular eruptions, chilblain-like lesions, erythromelalgia, angioedema, erythema multiforme-like lesions, and herpes zoster reactivation, have been documented following COVID-19 vaccination.[8–12]

The frequent occurrence of cutaneous adverse effects associated with COVID-19 vaccines raises specific concerns for individuals with pre-existing dermatological conditions. These patients may theoretically have an increased susceptibility to more severe reactions or an exacerbation of their underlying skin disease. Indeed, reports have described the worsening of pre-existing psoriasis,[13,14] eczema,[13] bullous pemphigoid,[15] pemphigus vulgaris,[16] and lichen planus[16] after COVID-19 vaccination.

Urticaria, characterized by the development of short-lived, intensely itchy wheals (hives), angioedema, or both, is a common clinical condition affecting a significant portion of the population, with a point prevalence estimated between 0.5% and 1%.[17,18] It affects women approximately twice as often as men.[19] Although rarely life-threatening, chronic urticaria can persist for years or even decades, leading to a substantial impairment in an individual's quality of life.[20,21] In addition to new-onset urticaria, the exacerbation of pre-existing urticaria after receiving COVID-19 vaccines, predominantly with mRNA-based vaccines, has been reported in the literature.[12,22–24] However, the proportion of patients experiencing such exacerbations has been inconsistent across studies. For instance, a study from Qatar reported that 16.4% of patients experienced COVID-19 vaccination-induced exacerbation of underlying chronic urticaria,[24] whereas a more recent report from the multinational Urticaria Centers of Reference and Excellence (UCARE) network indicated this occurred in only 9% of their extensive patient cohort.[23]

Given these variable findings and the significant concern among patients with urticaria regarding vaccine safety, the current study was designed to contribute robust, region-specific evidence. Our primary aim was to determine the incidence, clinical characteristics (type, onset, duration), and associated factors of cutaneous adverse reactions following COVID-19 vaccination among adult patients with a history of urticaria who were managed at a large tertiary care medical center in Riyadh, Saudi Arabia. This research seeks to enhance the understanding of COVID-19 vaccine safety within this specific patient demographic, providing valuable data to inform clinical practice and patient counseling.

Patients and Methods

Study Design and Setting

This quantitative, cross-sectional study was conducted within the Allergy and Dermatology clinics of King Khalid University Hospital (KKUH), a major tertiary care referral center and university teaching hospital in Riyadh, Saudi Arabia. Patient recruitment took place between November 2021 and April 2022. KKUH serves a diverse patient population, including university affiliates and referrals from other healthcare facilities.

Participants

Adult patients (aged ≥18 years) with a physician-confirmed diagnosis of urticaria (either acute or chronic) attending the clinics for routine follow-up appointments for their pre-existing urticaria were invited to participate. Inclusion criteria were: 1) age 18 years or older, and 2) a documented physician diagnosis of urticaria. Exclusion criteria were: 1) age <18 years (as the clinics primarily serve adults and initial vaccine rollouts targeted this demographic), and 2) inability or unwillingness to provide informed consent. Eligible patients were recruited consecutively as they presented during the study period, resulting in a sample of 190 participants. This approach aimed to capture a representative sample of urticaria patients attending these specialist clinics within the defined timeframe, rather than all dermatology attendees or a population-based sample.

Data Collection Instrument and Procedure

Data were collected using a structured, self-administered questionnaire, developed by the research team and available in both Arabic and English to ensure comprehensibility and accessibility for all participants in the diverse hospital setting. The questionnaire was pilot-tested on 20 dermatology patients for clarity and revised accordingly. It was administered electronically (accessible via patient devices), allowing for convenient and efficient data collection, often while patients were awaiting their consultation, a method particularly practical during the COVID-19 pandemic.

The instrument comprised four main sections:

Demographic Information: Age, gender, marital status, educational level, and employment status.

Urticaria Characteristics: Diagnosed type of urticaria, current medications for urticaria (regular or PRN antihistamines, omalizumab, montelukast), and associated allergies.

COVID-19 Vaccination and Reactions: Number of doses and type(s) of COVID-19 vaccine received; occurrence, type, onset, duration of cutaneous symptoms after each dose; and any medications taken for reactions.

Medical and Allergy History: Previous adverse drug reactions (including to other vaccines or contrast media) and relevant comorbidities (asthma, atopy, autoimmune diseases, hypothyroidism, multiple sclerosis).

Information on clinical diagnoses and reactions was self-reported. While direct physician verification of each acute reaction was not part of this study's protocol, all participants were established patients under regular specialist care, implying familiarity with their skin condition and that baseline diagnoses were physician-confirmed. The validity of self-reported adverse event data is a common aspect of clinical history gathering and pharmacovigilance.

Ethical Considerations

The study protocol received full ethical approval from the Institutional Review Board (IRB) of King Saud University. The research was conducted in strict adherence to the ethical principles outlined in the Declaration of Helsinki. Written informed consent was obtained from every participant prior to their enrollment. Participants were informed of the voluntary and anonymous nature of their participation and their right to withdraw at any time without impact on their medical care.

Statistical Analysis

Data were analyzed using SPSS Statistics for Mac, version 27.0 (SPSS Inc., Chicago, Ill., USA). Descriptive statistics (frequencies, percentages) summarized participant characteristics and reaction profiles. The primary outcome was the self-reported presence of any cutaneous reaction after each vaccine dose.

The Chi-square test or Fisher's exact test assessed associations between categorical variables (reactions vs demographics, urticaria type, medications, comorbidities). Cochran's Q test compared the frequency of common symptoms (urticaria exacerbation, pruritus, injection site reactions) across the three doses for participants who received all three.

Binary logistic regression analysis identified factors independently associated with cutaneous reactions, with a specific model evaluating vaccine type adjusted for regular daily antihistamine use. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. A two-sided p-value < 0.05 was considered statistically significant. An *a priori* sample size calculation was not performed for this descriptive, observational study; the sample size was determined by eligible, consenting patients during the study period.

Results

Participant Characteristics

A total of 190 adult patients with urticaria were enrolled in the study. The sociodemographic characteristics of the participants are detailed in Table 1. Females constituted the majority of the sample (166/190, 87.4%). Most participants were married (134/190, 70.5%), and a significant proportion held a Bachelor's degree or higher (98/190, 51.6% for Bachelor; 15/190, 7.9% for Master/PhD).

Chronic spontaneous urticaria (CSU) was the predominant type of urticaria, reported by 186 participants (97.9%). Other forms of physical urticaria were less common: dermatographism was noted in 12 (6.3%) patients, delayed-pressure

Table 1 Sociodemographic Characteristics of Participants (N=190)

Characteristic	Category	n	%
Age Group (years)	18–25	21	11.1%
	26–35	46	24.2%
	36–45	35	18.4%
	46–55	46	24.2%
	> 55	42	22.1%
Gender	Male	24	12.6%
	Female	166	87.4%
Marital Status	Married	134	70.5%
	Single	46	24.2%
	Divorced	5	2.6%
	Widowed	5	2.6%
Educational Level	Elementary	21	11.1%
	Middle	7	3.7%
	High school	36	18.9%
	Diploma	13	6.8%
	Bachelor	98	51.6%
	Master	9	4.7%
	PhD	6	3.2%
Job Status	Student	13	6.8%
	Employee	81	42.6%
	Housewife	50	26.3%
	Retired	16	8.4%
	Unemployed	30	15.8%
Total		190	100.0%

urticaria in 10 (5.3%), heat urticaria in 5 (2.6%), solar urticaria in 4 (2.1%), contact urticaria in 4 (2.1%), and cold urticaria in 3 (1.6%) (Table 2). It was possible for patients to report more than one type of urticaria.

Regarding the management of their underlying urticaria, 150 (78.9%) participants were on regular daily antihistamine therapy. Twenty-nine (15.3%) used antihistamines on an as-needed (PRN) basis. More specialized treatments were less common, with omalizumab being used by 10 (5.3%) patients and montelukast by 14 (7.4%). Thirty-eight (20.0%) participants reported not using any regular medication for their urticaria at the time of the survey (Table 3).

COVID-19 Vaccination Status and Reasons for Non-Vaccination

Out of the 190 participants, 176 (92.6%) had received at least one dose of a COVID-19 vaccine. The distribution of doses was as follows: 129 (67.9% of total sample) had received three doses, 43 (22.6%) had received two doses, and 4 (2.1%) had received only one dose. Fourteen participants (7.4%) had not received any COVID-19 vaccine dose.

Table 2 Types of Urticaria Reported by Participants (N=190)

Type of Urticaria	Reported (Yes) n (%)	Not Reported (No) n (%)
Chronic spontaneous urticaria	186 (97.9%)	4 (2.1%)
Dermatographism	12 (6.3%)	178 (93.7%)
Cold urticaria	3 (1.6%)	187 (98.4%)
Delayed-pressure urticaria	10 (5.3%)	180 (94.7%)
Solar urticaria	4 (2.1%)	186 (97.9%)
Heat urticaria	5 (2.6%)	185 (97.4%)
Contact urticaria	4 (2.1%)	186 (97.9%)

Notes: Participants could report more than one type of urticaria.

Table 3 Medications and Strategies Used for Urticaria by Participants (N=190)

Medication Strategy	Used (Yes) n (%)	Not Used (No) n (%)
None (Regularly)	38 (20.0%)	152 (80.0%)
Antihistamine (Regular Daily)	150 (78.9%)	40 (21.1%)
Antihistamine PRN*	29 (15.3%)	161 (84.7%)
Omalizumab	10 (5.3%)	180 (94.7%)
Montelukast	14 (7.4%)	176 (92.6%)

Notes: *PRN: Pro re nata (as needed). Participants could report using multiple medication types/strategies.

Among the 14 participants who had not received the first dose, 9 (64.3%) cited fear of urticaria exacerbation as the primary reason. Among the 46 participants who had received two doses but not the third (at the time of survey), 12 (26.1%) expressed fear of urticaria exacerbation.

Characteristics of Post-Vaccination Cutaneous Reactions

Cutaneous reactions were reported by 40 out of 176 (22.7%) participants after the first vaccine dose, by 45 out of 172 (26.2%) after the second dose, and by 40 out of 129 (31.0%) after the third dose.

Among those who experienced symptoms, the onset was typically rapid. Symptoms appeared within 24 hours for 23 (57.5%) of the 40 symptomatic individuals after the first dose, for 29 (64.4%) of the 45 symptomatic after the second dose, and for 31 (77.5%) of the 40 symptomatic after the third dose. The duration of these cutaneous symptoms was generally short-lived; for approximately half of the symptomatic participants, reactions resolved within 1–3 days (18/40, 45.0% after dose 1; 23/45, 51.1% after dose 2; 20/40, 50.0% after dose 3). Detailed information on the onset and duration of symptoms among those affected is provided in Table 4.

The most common specific cutaneous reactions reported by participants after any dose were injection site reactions, pruritus (itching), and exacerbation of their pre-existing urticaria. Less frequently reported reactions included angioedema, maculopapular rash, and a single case of rosacea flare and anaphylaxis (Table 5).

Table 4 Onset and Duration of Cutaneous Symptoms Following COVID-19 Vaccination (Among Symptomatic Participants)

Variable	Time Frame	Dose 1 (N=40*) n (%)	Dose 2 (N=45*) n (%)	Dose 3 (N=40*) n (%)
Onset of Cutaneous Symptoms	< 24 hours	23 (57.5%)	29 (64.4%)	31 (77.5%)
	2 days - 1 week	12 (30.0%)	12 (26.7%)	7 (17.5%)
	1 week - 1 month	4 (10.0%)	2 (4.4%)	0 (0.0%)
	> 1 month	1 (2.5%)	2 (4.4%)	2 (5.0%)
Duration of Cutaneous Symptoms	1–3 days	18 (45.0%)	23 (51.1%)	20 (50.0%)
	4–7 days	10 (25.0%)	12 (26.7%)	14 (35.0%)
	1–6 weeks	10 (25.0%)	4 (8.9%)	3 (7.5%)
	> 6 weeks	2 (5.0%)	6 (13.3%)	3 (7.5%)

Notes: *N represents the number of participants who reported experiencing cutaneous symptoms after the respective dose.

Table 5 Frequency of Specific Cutaneous Reactions Reported After Each COVID-19 Vaccine Dose

Specific Cutaneous Reaction	Dose 1 (N=176) n (%)	Dose 2 (N=172) n (%)	Dose 3 (N=129) n (%)
Injection site reaction	23 (13.1%)	28 (16.3%)	20 (15.5%)
Pruritus (Itching)	18 (10.2%)	18 (10.5%)	10 (7.8%)
Urticaria Exacerbation	16 (9.1%)	15 (8.7%)	5 (3.9%)
Angioedema	2 (1.1%)	1 (0.6%)	1 (0.8%)
Maculopapular rash	1 (0.6%)	1 (0.6%)	0 (0.0%)
Rosacea flare	0 (0.0%)	1 (0.6%)	0 (0.0%)
Wheals (other than exacerbation)	0 (0.0%)	0 (0.0%)	1 (0.8%)
Anaphylaxis	1 (0.6%)	0 (0.0%)	0 (0.0%)

Notes: Denominator (N) is the number of participants who received the respective dose. Participants could report more than one reaction type.

Previous Cutaneous Reactions and Comorbidities

Regarding history of previous cutaneous reactions to substances other than COVID-19 vaccines, 146 (76.8%) participants reported no such history. However, 35 (18.4%) had previously developed cutaneous reactions from medications, 11 (5.8%) from X-ray contrast media, and 4 (2.1%) from previous non-COVID-19 vaccinations.

Common comorbidities included asthma or any atopy, reported by 53 (27.9%) participants. Autoimmune diseases were reported by 33 (17.4%) participants, and hypothyroidism by 7 (3.7%). Over half of the sample (108/190, 56.8%) indicated having an allergy, with food allergies being the most common (67/190, 35.3%).

Comparison of Common Symptoms Across Doses (Paired Analysis)

A paired sample analysis using Cochran's Q test (for participants receiving all three doses) revealed that urticaria exacerbation showed a statistically significant association across the three doses (p=0.030), with a notably lower number of patients developing urticaria after the third dose (6.2% based on N=129) compared to the first (9.1% based on N=176)

and second doses (8.7% based on N=172). However, pruritus (p=0.343) and injection site reactions (p=0.452) did not show a statistically significant difference in frequency across the three doses in this paired analysis.

Factors Associated with Cutaneous Reactions (Unadjusted Analysis)

Female gender was significantly associated with higher rates of injection site reactions after all three doses ($p<0.05$ for each). A history of asthma or atopy was associated with higher odds of injection site reaction after the first dose (OR=2.8, 95% CI [1.1–7.1], p=0.029). Patients with autoimmune diseases showed significantly higher odds of developing pruritus after the second dose (OR=14.8, 95% CI [1.9–117.3], p=0.009).

Taking regular daily antihistamines prior to the first dose was associated with statistically significant lower odds of developing any cutaneous reaction (OR=0.4, 95% CI [0.2–1.0], p=0.042). The type of vaccine was significantly associated with cutaneous manifestations only after the second dose in the unadjusted analysis (p=0.040) (Table 6).

Adjusted Analysis of Vaccine Type and Reactions

After adjusting for the use of regular daily antihistamines, the type of COVID-19 vaccine received (Pfizer-BioNTech, Oxford-AstraZeneca, or Moderna) did not demonstrate a statistically significant association with the likelihood of developing cutaneous reactions for any of the three doses ($p > 0.05$ for all comparisons) (Table 7). The adjusted

Table 6 Unadjusted Association of Any Cutaneous Reaction with Vaccine Type and Baseline Medication Use, Stratified by Dose

Variable Group	Dose	Reaction Yes n (%)	Reaction No n (%)	Unadjusted OR (95% CI)	P-value*
Type of Vaccine	Dose 1				>0.999
Pfizer-BioNTech (N=146)		34 (23.3%)	112 (76.7%)	Ref	
Oxford-AstraZeneca (N=29)		6 (20.7%)	23 (79.3%)	0.8 (0.3–2.2)	
Moderna (N=1)		0 (0.0%)	1 (100.0%)	NE†	
Type of Vaccine	Dose 2				0.040
Pfizer-BioNTech (N=149)		40 (26.8%)	109 (73.2%)	Ref	
Oxford-AstraZeneca (N=16)		3 (18.8%)	13 (81.3%)	0.6 (0.2–2.2)	
Moderna (N=7)		2 (28.6%)	5 (71.4%)	1.1 (0.2–5.9)	
Type of Vaccine	Dose 3				0.638
Pfizer-BioNTech (N=112)		35 (31.3%)	77 (68.8%)	Ref	
Oxford-AstraZeneca (N=1)		0 (0.0%)	1 (100.0%)	NE†	
Moderna (N=16)		8 (50.0%)	8 (50.0%)	2.2 (0.8–6.0)	
No Regular Meds (vs Yes)	Dose 1	30 (26.3%)	84 (73.7%)	0.8 (0.4–1.5)	0.512
(N=114 No vs 76 Yes)		24 (31.6%)	52 (68.4%)	Ref	
No Regular Meds (vs Yes)	Dose 2	23 (23.0%)	77 (77.0%)	0.4 (0.2–0.7)	0.002
(N=100 No vs 90 Yes)		40 (44.4%)	50 (55.6%)	Ref	
No Regular Meds (vs Yes)	Dose 3	20 (28.2%)	51 (71.8%)	0.2 (0.1–0.4)	<0.001
(N=71 No vs 119 Yes)		83 (69.7%)	36 (30.3%)	Ref	

(*Continued*)

Table 6 (Continued).

Variable Group	Dose	Reaction Yes n (%)	Reaction No n (%)	Unadjusted OR (95% CI)	P-value*
Regular Antihistamine (vs No)	Dose 1	8 (16.3%)	41 (83.7%)	0.4 (0.2–1.0)	0.042
(N=49 Yes vs 141 No)		46 (32.6%)	95 (67.4%)	Ref	
Regular Antihistamine (vs No)	Dose 2	16 (30.8%)	36 (69.2%)	0.9 (0.5–1.7)	0.732
(N=52 Yes vs 138 No)		47 (34.1%)	91 (65.9%)	Ref	
Regular Antihistamine (vs No)	Dose 3	18 (41.9%)	25 (58.1%)	0.5 (0.3–1.0)	0.082
(N=43 Yes vs 147 No)		85 (57.8%)	62 (42.2%)	Ref	

Notes: *P-value calculated using Chi-square or Fisher exact test. † NE: Not estimable due to zero events in one group. Denominators (N) represent participants with available data for the specific comparison.

Table 7 Logistic Regression Analysis of the Association Between Vaccine Type and Cutaneous Reactions, Adjusted for Regular Antihistamine Use

Dose	Vaccine Type	N	Crude OR (95% CI)	Adjusted OR* (95% CI)	P-value (Adjusted)
Dose 1	Pfizer-BioNTech	176	Ref	Ref	-
	Oxford-AstraZeneca	176	1.2 (0.4–3.1)	1.1 (0.4–2.9)	0.285
	Moderna	176	0 (0 -.)†	0 (0 -.)†	0.214
Dose 2	Pfizer-BioNTech	172	Ref	Ref	-
	Oxford-AstraZeneca	172	1.6 (0.4–5.9)	1.7 (0.5–6.4)	0.381
	Moderna	172	0.9 (0.2–4.7)	0.8 (0.2–4.5)	0.529
Dose 3	Pfizer-BioNTech	129	Ref	Ref	-
	Oxford-AstraZeneca	129	0 (0 -.)†	0 (0 -.)†	0.251
	Moderna	129	0.5 (0.2–1.3)	0.5 (0.2–1.4)	0.139

Notes: *Adjusted for regular daily antihistamine use at the time of vaccination. † 0 (0 -.): Indicates odds ratio could not be calculated due to zero events in one group.

model for the first dose confirmed that regular antihistamine use was independently associated with a reduced likelihood of cutaneous reactions (aOR 0.4, 95% CI [0.2–0.9], p=0.028).

Discussion

This cross-sectional study provides a detailed examination of cutaneous adverse reactions following COVID-19 vaccination among adult patients with pre-existing urticaria in Saudi Arabia. Our findings demonstrate that while cutaneous reactions are relatively common in this specific patient population, they are predominantly mild, self-limiting, and occur shortly after vaccine administration. The most frequently reported reactions were localized injection site events, generalized pruritus, and exacerbations of their underlying urticaria. A key reassuring observation was the significant decrease in the frequency of urticaria exacerbations after the third vaccine dose. Furthermore, the regular use of antihistamines by patients showed an association with a reduced likelihood of developing post-vaccination cutaneous reactions, particularly after the first dose.

The overall pattern and types of cutaneous reactions observed in our cohort are largely consistent with those described in broader international literature on COVID-19 vaccine adverse events.[6,7,25] The notable female predominance (87.4% of our sample) among those reporting reactions, especially for injection site reactions, mirrors findings from numerous large-scale

studies.[7,9,16,26] This trend is also seen in studies specifically focusing on urticaria patients receiving COVID-19 vaccines.[23,24] Differences in immune reactivity, potentially influenced by hormonal factors, are considered plausible contributors.[27]

The incidence of urticaria exacerbation in our study (ranging from 3.9% to 9.1% across doses) is comparable to the 9% rate reported in the UCARE COVAC-CU study.[23] However, it differs from other reports,[7,24] highlighting potential variations due to study design, population characteristics, or vaccine types. The significant decrease in urticaria exacerbations after the third dose is an important finding, possibly suggesting immune adaptation or a desensitization-like phenomenon with repeated antigenic exposure, warranting further investigation.

The rapid onset (typically <24 hours) and relatively short duration (resolution within 1–3 days for ~50%) of reactions suggest immediate-type hypersensitivity mechanisms or transient inflammatory responses for most events.[23] Potential mechanisms could involve IgE-mediated responses to vaccine components, non-specific mast cell activation, or generalized inflammatory responses.[28]

A clinically relevant finding is the association between regular daily antihistamine use and a reduced likelihood of cutaneous reactions, which was statistically significant after the first dose in both unadjusted (OR 0.4) and adjusted analyses (aOR 0.4). This supports clinical experience and other studies suggesting a beneficial role for antihistamines.[23,29–31] The higher odds of reactions in PRN antihistamine users might reflect poorer baseline urticaria control or increased symptom awareness when not on continuous therapy. These interpretations require caution due to the observational design and potential for confounding by indication.

This study contributes important regional data on COVID-19 vaccine safety in patients with urticaria. The findings can aid healthcare providers in counseling patients, managing expectations, and potentially advising the continuation of regular antihistamine therapy around vaccination, which may improve vaccine acceptance and adherence.

Limitations

This study has several limitations that should be considered when interpreting the findings. Firstly, the cross-sectional design relies on patient recall, which may introduce bias regarding the specifics of reactions to earlier vaccine doses, and it cannot establish causality between vaccination and reported reactions. Secondly, being a single-center study conducted in a tertiary care hospital, the findings may not be fully generalizable to patients managed in primary care settings or to the broader population of individuals with urticaria in Saudi Arabia or other countries. Thirdly, data on reaction severity were self-reported and not assessed using a standardized grading scale, although all participants were under specialist care. Fourthly, the exclusion of pediatric patients means the findings are not applicable to this age group. Fifthly, an *a priori* sample size calculation was not performed for this observational study, which might affect the statistical power for some subgroup analyses. Lastly, despite statistical adjustments for antihistamine use, the potential for residual confounding by unmeasured variables, such as the baseline severity or activity of urticaria or the use of other intermittent medications, cannot be entirely dismissed.

Future Directions

Prospective, multi-center studies are needed to confirm these findings, minimize recall bias, and enhance generalizability, including to pediatric populations. Future research should incorporate standardized severity scoring for reactions (eg, Urticaria Activity Score) and objective dermatological assessments. Investigating immunological mechanisms underlying vaccine-related cutaneous reactions in urticaria patients (eg, through specific IgE testing, measurement of mast cell mediators) and long-term follow-up would also be valuable. Further studies on the role of different antihistamine strategies in mitigating reactions in this population are warranted.

Conclusion

In this cohort of adult Saudi patients with pre-existing urticaria, COVID-19 vaccination was associated with cutaneous adverse reactions that were generally mild and transient. Urticaria exacerbations decreased significantly after the third vaccine dose. Regular antihistamine use appeared to offer some protection, particularly after the first dose. These findings support the overall safety of COVID-19 vaccination in this patient population and provide useful information for patient counseling and management strategies.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and received ethical approval from the Institutional Review Board of King Khalid University Hospital (IRB approval reference number available upon request). Written informed consent was obtained from all individual participants included in the study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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The authors report no conflicts of interest in this work.

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