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Post-COVID-19 Vaccination Trimester Evaluation in Mastocytosis: A Single-Center Real-Life Experience

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ABSTRACT

Objective: The aim of this study was to evaluate the long-term impact of Coronavirus Disease 2019 (COVID-19) vaccination on mastocytosis.

Materials and Methods: Patients with mastocytosis were divided into two groups as those who received COVID-19 vaccination (Group 1) and those who did not (Group 2). In group 1, the history of symptoms related to mast cell activation was obtained for the three-month periods before and after vaccination. Psychological status of both groups was assessed using the Depression, Anxiety, and Stress Scale (DASS-21). A modified Fear of COVID-19 Scale was employed to evaluate the fear of COVID-19 vaccination.

Results: Fifty-three patients were included in the study, with six patients not receiving vaccination. The Fear of COVID-19 vaccination score was higher in group 2 (p=0.031). Among the vaccinated patients, 70.2% experienced non-allergic adverse reactions. Only one patient experienced anaphylaxis within 20 minutes after the first dose. None of the vaccinated patients reported any change in the frequency of anaphylaxis episodes after vaccination.

Conclusion: To conclude, this study suggested that the COVID-19 vaccine can be safe for patients with mastocytosis in both early and late stages. While, further detailed studies on long-term outcomes are necessary, it is recommended to administer the COVID-19 vaccine to patients with mastocytosis while taking the necessary precautions in accordance with the provided recommendations.

Keywords: Mastocytosis, COVID-19 vaccination, urticarial, fear of vaccination

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a significant global issue that can lead to mortality, especially among patients with comorbidities. Following the identification of the first case, people worldwide underwent quarantine measures to protect themselves from the disease. The world has since had the opportunity to restore normal social life through natural immunization or vaccination against COVID-19. Vaccination has also been observed to have a positive effect on the clinical course of individuals who with the disease who require treatment in the intensive care unit (1). While vaccination is crucial during the pandemic, it initially created hesitancy within the society. Concerns were also raised regarding the effect of vaccination on disease progression in specific patient groups, including those with mastocytosis.

Mastocytosis is a condition characterized by the abnormal proliferation of mast cells. Certain triggers, such as Hymenoptera venom, drug, or food can activate mast cells and lead to systemic hypersensitivity reactions (HRs) in patients with mastocytosis. These reactions may include symptoms like urticaria, flushing, or even anaphylaxis (2-4). In 2017, a retrospective study examining various vaccines (such as influenza, hepatitis b, pneumococcal etc.) in patients diagnosed with mastocytosis has reported that vaccination is safe for individuals with mastocytosis

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(5). However, in the context of the COVID-19 pandemic, vaccination has gained increased attention among adult mastocytosis patients, as vaccination is widely recognized as the most effective method of protection. Hesitancy regarding vaccination is frequently encountered by physicians in clinical practice, posing an additional challenge.

There were early reports of anaphylaxis associated with COVID-19 vaccines, particularly the Pfizer/ BioNTech mRNA vaccine (6-8). Although data on vaccine safety during the initial period were later presented (9), it is known that COVID-19 vaccination can result in anaphylaxis 5-10 times more frequently compared to other types of vaccines (10,11). As a result, both patients and physicians expressed concerns about potential negative effects of COVID-19 vaccination, such as an increased risk of anaphylaxis or worsening of mastocytosis, leading to more frequent or severe attacks. Studies conducted thus far have indicated that the frequency of immediate systemic HRs caused by COVID-19 vaccination was similar between patients with mastocytosis and the general population (12-15). Consequently, it has been concluded the Pfizer-BioNTech mRNA vaccine is safe and well tolerated (14). Furthermore, the management of vaccine reactions occurring within a timeframe of less than 4 hours has become a topic of discussion in the literature (16).

However, it should be noted that certain authors have reported cases where chronic spontaneous urticaria showed a progression with relapses after COVID-19 vaccination, suggesting a potential impact of vaccination on the long term course of the disease (17-19). Considering that mastocytosis is a mast cell-related disorder similar to chronic urticaria, it is reasonable to speculate that COVID-19 vaccination could potentially increase mast cell-mediated reactions in patients with mastocytosis.

Nevertheless, the long-term effects of the vaccine, particularly on the course of mastocytosis, still remain unknown. Patients with mastocytosis are particularly concerned as they are more susceptible to potential reactions. Therefore, our objective was to assess the impact of the COVID-19 vaccination on patients with mastocytosis over the relatively long term – 3 months following vaccination.

MATERIAL and METHODS

Patient Selection and Study Design

Fifty-three adult patients diagnosed with mastocytosis and classified according to the latest World Health Organization (WHO) diagnosis and classification criteria (20) were selected. These patients were being monitored at the outpatient allergy clinic, which serves as a tertiary reference center for mastocytosis. We excluded patients under the age of 18 and patients who did not consent to participate in the study. The study collected demographic information, clinical characteristics, and basal tryptase levels of the patients from their medical records.

The patients were divided into two groups: those who received the COVID-19 vaccination and those who did not. In the vaccinated group, the study obtained the patients' medical records and diaries to collect information on any history of anaphylaxis or other types of attacks related to mast cell activation within the three months prior to vaccination. Additionally, the specific brands of vaccines administered and the number of doses received by each patient were noted.

Furthermore, the vaccinated patients were specifically queried about any side effects they may have experienced post-vaccination. Those who reported side effects were further questioned about the specific nature of these side effects. Additionally, the vaccinated patients were also asked about any history of anaphylaxis or other symptoms related to mast cell activation within the three months following vaccination. The questionnaire we used to evaluate all these information is listed in supplementary Table I. Participants were asked to complete the Depression, Anxiety, and Stress Scale (DASS-21) and the scores obtained from the DASS-21 were then used to calculate the current levels of depression, anxiety, and stress in the participants (21-24).

Additionally, a questionnaire consisting of seven questions related to the fear of vaccination was administered to the patients. This questionnaire was adapted from the validated Turkish version of the Fear of COVID-19 Score (Suppl Table II) (25,26). A total score ranging from 7 to 35 was determined, with higher scores indicating a greater fear of COVID-19 vaccines. The study also compared the demographic and clinical characteristics of the patients who received vaccination versus those who did not, as well as their Fear of COVID-19 vaccination (FoCV) scores and the scores obtained from the DASS-21.

Clinical features in vaccinated patients, including the frequency of mast cell activation-related symptoms, were compared between the 3-month periods before and after receiving the COVID-19 vaccination. Furthermore, the features of vaccinated patients with and without side effects were compared.

Table Suppl I: Questionnaire on vaccination.

1. Have you received all your childhood vaccinations?
2. Have you received the COVID 19 vaccine?
If yes:
i. How many doses of vaccine have you received?
ii. Did you take any medication prior to vaccination?
iii. Did your treatment change prior to vaccination?
iv. Last 3 months before vaccination:
a. How frequently did you experience attacks?
b. What symptoms did you experience during an attack?
c. Did you identify any specific triggers that caused anaphylaxis?
d. How many times have you required the use of adrenaline in the last 3 months prior to vaccination?
v. Did you experience an increase in the number of attacks after vaccination?
a. If yes, after which doses did you experience more attacks?
vi. 3 months after vaccination:
a. What has been the frequency of your attacks?
b. What were your experiences during an attack?
c. Have you been able to identify any specific agent that caused anaphylaxis?
d. How many times have you needed adrenaline in the 3 months after vaccination?
e. Have you experienced any attacks related to mastocytosis within 1 week after vaccination?
f. Have you noticed an increase in the number of attacks triggered by drug usage after vaccination?
g. Do you believe that the number of attacks has increased after vaccination?
h. Did you experience any side effect(s) from the vaccine?
i. If yes, please specify which side effect(s) you experienced?
ii. If you had a reaction, at what dose did you experience it?
iii. If you experienced any side effect from the vaccine, when did they start?
iv. If there was a reaction to the vaccine, how long did it last?

Table Suppl II: Fear of COVID-19 vaccination scale, adapted from the validated Turkish version of the Fear of COVID-19 Scale.

Fear of COVID-19 vaccination scale	1: strongly disagree 2: disagree 3: neither agree or disagree 4: agree 5: strongly agree				
Before I got the vaccine, I was terrified of the COVID-19 vaccine.	1	2	3	4	5
Before I got vaccinated, it bothered me to think about the COVID-19 vaccine.	1	2	3	4	5
Before I got the vaccine, my hands became clammy when I thought about the COVID-19 vaccine.	1	2	3	4	5
Before I got vaccinated, I was afraid of losing my life because of COVID-19 vaccine.	1	2	3	4	5
Before I got the vaccine, I used to be nervous or anxious when I watched news and stories about COVID-19 vaccine on social media.	1	2	3	4	5
Before I got vaccinated, I couldn't sleep when I thought I was going to get the COVID-19 vaccine.	1	2	3	4	5
Before I got vaccinated, my heart was beating strongly when I thought I was going to get the COVID-19 vaccine.	1	2	3	4	5

The current study received approval from the local ethics committee (approval number: 847937).

Statistical Analysis

The data were analyzed using the Statistical Package for Social Sciences, and the GraphPad Prism Software 8 (San Diego, CA, USA) was used generate the figures. Demographic and clinical features were assessed using descriptive analysis and presented as percentages, mean ± standard deviation, or median with interquartile range percentile 25-75 (IQR 25-75), depending on the data distribution. The Kolmogorov-Smirnov test was employed to evaluate the distribution pattern of the quantitative data. Continuous variables were compared using the independent t Test or the Mann-Whitney U test between the two groups. The Wilcoxon rank test and Paired Sample T Test were used to compare dependent means, and correlation analysis was performed using Pearson's or Spearman's correlation tests, depending on the data distribution. p-values less than 0.05 were considered as statistically significant.

RESULTS

Demographics and Clinical Characteristics of the Patients

The study included fifty-three patients with mastocytosis. The mean age of the patients was 46.39±10.99 years, and 56.6% of them were female. In terms of education, 30.18% of the patients had completed primary school, 20.75% had graduated from high school, 41.50% had a university degree, and 7.54% held a master's degree. Among the patients, 29 (54.71%) were smokers. The majority of the patients had indolent mastocytosis (n=46), while 3 patients had advanced mastocytosis, and 4 patients had cutaneous mastocytosis. Additionally, 35.84% of the patients had a comorbid disease, with hypertension (18.9%) being the most common, followed by diabetes mellitus (11.3%). Among the patient population, 45.28% had a history of anaphylaxis. The most common trigger for anaphylaxis was venom, accounting for 26.41% of cases, while 13.2% of patients had experienced drug-induced anaphylaxis. The median basal tryptase level was 26 mg/L (IQR: 13.3-60.2). In terms of mental health, the median scores on the Depression, Anxiety, and Stress Scale-21 (DASS-21) were 2 for depression, 3 for anxiety, and 2 for stress. Concerning COVID-19 vaccination, 11.32% of patients chose not to be vaccinated due to worries about potential side effects and its impact on their existing condition. Two adults received only 1 dose of the vaccine. Among those who were vaccinated, 34% received CoronaVac® (SinoVac®), 71.7% received the Pfizer/BioNTech® vaccine, and 1.9% received the TURKOVAC® vaccine. The features of the patients are shown in Table I in detail.

DASS-21 anxiety and stress scores showed a correlation with the fear score (for anxiety: p=0.05 r=0.284; for stress p=0.01 r=0.363) (Figure 1,2). However, there was no significant difference in the median DASS-21 and FoCV scores between patients with a history of previous anaphylaxis and those without (p>0.05).

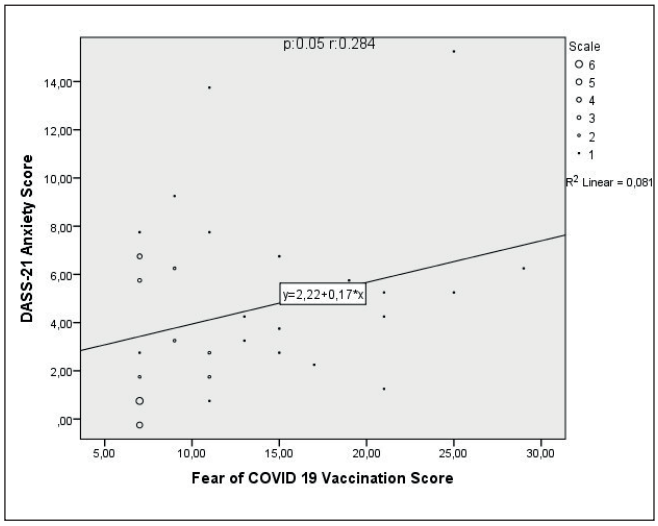

Figure 1. Correlation analyses between DASS-21 Anxiety score and Fear of COVID 19 Vaccination Score.

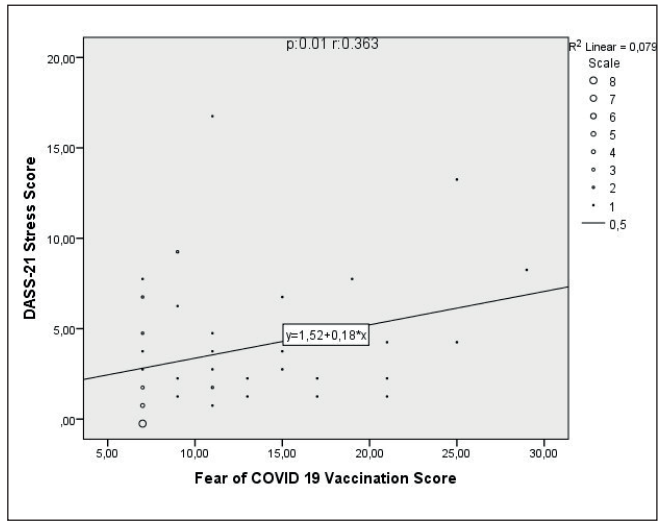

Figure 2. Correlation analyses between DASS-21 Stress Score and Fear of COVID 19 Vaccination Score.

Table I: The comparison of demographic and clinical characteristics of patients who were or were not vaccinated with the COVID-19 vaccine.

Variables, n (%)	Total	Vaccinated	Unvaccinated	p
	53 (100)	47 (88.7)	6 (11.3)	
Sex, n (%)				0.385
Female	30 (56.6)	28 (59.57)	2 (33.33)	
Male	23 (43.4)	19 (40.42)	4 (66.66)	
Age, years, mean ± SD	46.39 ± 10.99	46.40 ± 10.79	46.33 ± 13.60	0.988
Education status, n (%)				0.857
Primary school	16 (30.18)	14 (29.78)	2 (33.33)	
High school	11 (20.75)	11 (23.40)	0 (0)	
University	22 (41.50)	18 (38.29)	4 (66.66)	
Master's degree	4 (7.54)	4 (8.51)	0 (0)	
Body mass index kg/m² mean ± SD	27.06 ± 5.85	27.21 ± 5.52	25.95 ± 8.44	0.626
Smoking, n (%)	29 (54.71)	24 (51.06)	5 (83.33)	0.204
Alcohol use, n (%)	1 (1.88)	1 (2.12)	0 (0)	1
Comorbid disease, n (%)				
Diabetes mellitus	6 (11.3)	5 (10.63)	1 (16.66)	0.532
Hypertension	10 (18.9)	9 (19.14)	1 (16.66)	1
Cardiac disease	1 (1.9)	1 (2.12)	0 (0)	1
Thyroid disease	5 (9.4)	4 (8.51)	1 (16.66)	0.465
Malignancy	1 (1.9)	1 (2.12)	0 (0)	1
Mastocytosis type, n (%)				0.914
Advanced	3 (5.66)	3 (6.38)	0 (0)	
Indolent	46 (86.79)	41 (87.23)	5 (83.33)	
Cutaneous	4 (7.54)	3 (6.38)	1 (16.66)	
History of anaphylaxis, n (%)				0.518
Food	3 (5.66)	3 (6.4)	0	0.564
Venom	14 (26.41)	12 (25.5)	2 (33.3)	0.492
Drug	7 (13.20)	5 (10.6)	2 (33.3)	0.070
Idiopathic	8 (15.09)	7 (14.9)	1 (16.7)	0.766
Basal tryptase, mg/L, median (IQR)	26 (13.3-60.2)	26 (11.72-68.72)	22.40 (19.35-2.95)	0.528
Depression, Anxiety, and Stress Scale Score, Median(IQR)				
Depression	2 (0.25-6)	2 (0-6)	1.5 (1-6.5)	0.928
Anxiety	3 (1-6)	3 (1-6)	4 (1.75-12.25)	0.627
Stress	2 (1-5)	2 (1-5)	2 (1-10.5)	0.928
Brand of vaccine, n (%)				
Coronavac (SinoVac)®	18 (34)	18 (38.29)		
Pfizer-BioNTech®	38 (71.7)	38 (80.85)		
Turkovac®	1 (1.9)	1 (2.12)		

n: Number, **SD:** Standard deviation, **IQR:** Interquartile range

Comparison of the Features of the Vaccinated and Unvaccinated Patients

There was no significant difference in terms of gender, age, education status, body mass index, smoking or alcohol use, concomitant disease, mastocytosis subtype, and basal tryptase levels between vaccinated and unvaccinated patients. Furthermore, the histories of previous anaphylaxis and childhood vaccination were similar between the groups (p>0.05). The frequency of anaphylaxis history triggered by drug-, venom- and food- or idiopathic anaphylaxis, median scores for total DASS-21, as well as depression, anxiety, and stress scores, were similar between the vaccinated and unvaccinated patients (p>0.05) (Table I). However, there was a significant difference in the median FoCV scores, with vaccinated patients having a median score of 7.5 (IQR: 7-10.75) and unvaccinated patients having a median score of 14 (IQR: 11.5-22.5) (p=0.031) (Figure 3).

Evaluation of the Vaccinated Patients and Side Effects

Out of the total patient population, 33 individuals reported experiencing side effects after vaccination. Among these, 10 patients experienced side effects after the first dose, 4 after the second dose, 3 after the third dose, 2 after the fourth dose, 1 after the fifth dose, and 13 patients experienced side effects after each dose. The majority of these side effects were non-allergic adverse reactions, including local reactions, myalgia (muscle pain), fever, and arthralgia (joint pain), accounting for 70.2% of the reported side effects among our patients.

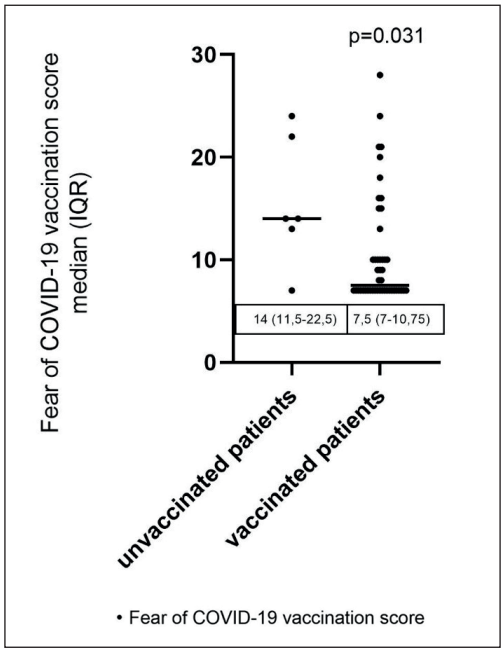

Figure 3. The comparison of fear of COVID-19 vaccination score in vaccinated and unvaccinated patients.

There were no significant differences between patients who experienced side effects after vaccination and those who did not, in terms of age, gender, education status, body mass index, smoking or alcohol use, presence of comorbid disease, mastocytosis subtype, routine antihistamine, montelukast and/or omalizumab usage, premedication before vaccination, and the FoCV and DASS-21 scores (Table II).

A 52-year-old female patient diagnosed with indolent mastocytosis experienced anaphylaxis approximately 20 minutes after receiving the first dose of SinoVac injection. Prior to the incident, the patient had been using a beta-blocker and angiotensin receptor blocker, and had a history of both drug- and food-induced anaphylaxis. According to the patient, she developed symptoms such as a sensation of throat obstruction, shortness of breath, dizziness, hypotension, and syncope shortly after receiving the SinoVac injection. Immediate medical intervention was administered, including intravenous pheniramine, methylprednisolone, and intramuscular adrenaline. Despite the administration of adrenaline, the patient's hypotension persisted, leading to the decision to transfer her to the intensive care unit for further treatment. Approximately 24 hours later, the patient experienced a recurrence of hypotension, indicative of biphasic anaphylaxis. However, with appropriate medical care, the patient ultimately made a full recovery and was discharged from the hospital.

The Impact of Vaccination on the Course of Mastocytosis

None of the patients included in the study had required adrenaline in the last 3 months preceding the COVID-19 vaccination. Among the vaccinated patients, including the individual who experienced anaphylaxis following vaccine injection, there were no reported differences in the frequency of anaphylaxis episodes between the three-month periods before and after receiving the COVID-19 vaccine. However, two patients, one female and one male patient, both diagnosed with indolent mastocytosis, described an increase in urticaria and flushing attacks in the 3-month period following vaccination compared to the 3-month

Table II: Demographic and clinical characteristics of the vaccinated patients who experienced side effects or who did not

Variables	Patients who experienced side effects n=33, 71.73%	Patients who did not experience side effects n=13, 28.26%	P
Age, years, mean ± SD	44.54 ± 9.97	49.92 ± 11.75	0.125
Sex, n (%)			0.466
Female	19 (57.6)	9 (69.2)	
Male	14 (42.4)	4 (30.8)	
Education status, n (%)			0.719
Primary school	10 (30.3)	4 (30.8)	
High school	7 (21.2)	4 (30.8)	
University	13 (39.4)	4 (30.8)	
Master's degree	3 (9.1)	1 (7.7)	
Body mass index kg/m^2 mean ± SD	27.85 ± 5.41	25.45 ± 5.94	0.224
Smoking, n (%)	18	6	0.608
Alcohol use, n (%)	0	1 (7.7)	0.289
Comorbid disease, n (%)			
Diabetes mellitus	4 (12.1)	1 (7.7)	1
Hypertension	5 (15.2)	3 (23.1)	0.669
Cardiac disease	0	1 (7.7)	0.283
Thyroid disease	3 (9.1)	1 (7.7)	1
Malignancy	0	1 (7.7)	0.283
Mastocytosis subtype, n (%)			0.058
Advanced	2 (6.1)	1 (7.7)	
Indolent	28 (84.8)	12 (92.3)	
Cutaneous	3 (9.1)	0	
Medication, n (%)			
Antihistamines	28 (84.8)	12 (92.3)	0.659
Montelukast	9 (27.3)	2 (15.4)	0.473
Omalizumab	3 (9.1)	2 (15.4)	0.612
Premedication, n (%)	2 (6.1)	1 (7.7)	1
Fear of COVID-19 vaccination score median (IQR)	8 (7-10)	7 (7-14)	0.529
Depression, Anxiety, and Stress Scale Score, median (IQR)			
Depression	2 (0.5-6)	3 (0-8)	0.810
Anxiety	3 (1.5-6)	3 (0-7)	0.650
Stress	2 (1-5.5)	2 (0-5)	0.504

n: Number, **SD:** Standard deviation, **IQR:** Interquartile range

period prior to vaccination. The male patient, aged 34, reported experiencing flushing and pruritus an average of six times per month before receiving the vaccine. He received 2 doses of SinoVac, followed by a dose of BioNTech. After receiving the 2 doses of SinoVac, there was no noticeable difference, but after a single dose of BioNTech, the frequency of flushing numbers increased to 12 times per month. These attacks began to increase within the first week after the BioNTech injection. The 39-year-old female patient received 2 doses of SinoVac followed by 2 doses of

BioNTech. Prior to vaccination, she experienced an average of three urticaria attacks per month, which increased to an average of six attacks per month after vaccination. It is important to indicate that this patient used antihistamine treatment irregularly, especially after receiving the vaccination.

No significant relationships were observed between the use of antihistamines, omalizumab, and montelukast, the brand of the vaccine, the number of vaccination doses, DASS-21 scores, basal median tryptase levels or premedication usage before vaccine injections, and no relation with the vaccination was observed.

DISCUSSION

The current study has provided valuable information for both patients and physicians, shedding light on an important issue by demonstrating the relatively long-term safety of COVID-19 vaccination in mastocytosis within a real-life setting for the first time.

It is known that COVID-19 vaccination carries a higher risk of anaphylaxis compared to other vaccines, with a reported risk that is 5-10 times higher (10,11). However, it is crucial to emphasize that vaccination is essential in preventing a life-threatening COVID-19 infection. This reality has raised concerns among both patients with mastocytosis, which is associated with anaphylaxis, and the physicians who care for them. According to the data published by the Ministry of Health, vaccination rates in Türkiye range from 85.68% to 93.35% (27). Despite a high vaccination rate (88.7%) among our mastocytosis patients, we found that the main reason for non-vaccination was the fear of adverse events related to the vaccination. To assess this fear, we created an adapted scale from the validated Turkish version of the Fear of COVID-19 Score since there was no validated scale available specifically for evaluating this state (25,26). Our findings indicated that unvaccinated patients had higher FoCV scores than vaccinated patients. Furthermore, the FoCV scores were correlated with the DASS-21 anxiety and stress score. Therefore, real-life clinical studies play a crucial role in informing, addressing fears and concerns, and increasing vaccination rates. Psychological counseling may also be beneficial for these patients. Previous studies have only reported that the vaccination was not associated with the immediate type of HRs such as anaphylaxis, in mastocytosis, which is consistent with our findings (12-15). Another main concern of both patients and physicians was the relatively long-term potential negative impact of the vaccination on the frequency of the anaphylaxis attacks. This aspect has not been assessed so far as previous reports mainly focused on COVID-19-induced exacerbations in conditions such as chronic urticaria (28,29). A systemic review involving autoimmune diseases and allergic and atopic diseases has reported no flare-up in the disease course in 2 patients with mastocytosis (30). Given the limited evidence on this issue, we conducted this study to address these concerns.

In the current study, we found no evidence of anaphylactic reactions in patients with mastocytosis following COVID-19 vaccination in the 3-month period after vaccination. However, two patients reported that the frequency of urticarial and flushing episodes increased in the 3-month period after vaccination. When reviewing the existing data regarding urticaria, there are various publications suggesting that certain autoimmune events may be triggered after receiving the COVID-19 vaccine (31,32). Additionally, some authors have proposed that upregulation of the Mas-related G-protein coupled receptor-X2 (MRGPRX2) may play a role in chronic spontaneous urticaria (33). Therefore, it is possible that a potential MRGPRX2-mediated pathway triggered by the COVID-19 vaccine in patients with mastocytosis could also contribute to the urticaria and flushing episodes. It is evident that further studies are required to investigate this subject in more detail.

Recent recommendations for vaccination in patients with mast cell-mediated symptoms suggest postponing the vaccination until symptoms are well under control (34-36). The European Competence Network on Mastocytosis (ECNM) and the American Initiative in Mast Cell Diseases (AIM) published recommendations in 2021 stating that unstable patients with mastocytosis should receive treatment until their symptoms are clearly managed before receiving the vaccination (36). Studies have demonstrated that patients with a history of allergy may experience more local or systemic symptoms following vaccination (37,38). Similarly, in our study, we observed an increase in urticaria and flushing attacks in two of our patients after vaccination. The male patient, who was regularly using antihistamines, experienced an increase in attacks from 6 to 12 per month after vaccination. The female patient, who was irregularly using her medication after the vaccination, reported 3 and 6 attacks per month before and after vaccination, respectively. It is unclear whether these changes are directly attributable to the vaccine or to the irregular use of medication. Therefore, we agree that patients with

mast cell-mediated symptoms should continue their medication during vaccination to achieve symptom control.

In our study group, 45.3% of the patients had a history of anaphylaxis. Among the triggers, venom accounted for the highest percentage at 13.2%, while seven patients had a history of drug-induced anaphylaxis. However, we did not observe any significant relationship between the presence of a history of anaphylaxis or drug-induced anaphylaxis and vaccination status in our patients. Furthermore, the presence of anaphylaxis history did not show any significant correlation with the DASS-21 and FoCV scores, indicating that it did not have a significant impact on anxiety and fear related to COVID-19 vaccination in our study population.

In a retrospective analysis of 119 patients with mastocytosis, 26 patients reported adverse reactions following COVID-19 vaccination, including local injection site reaction, fever, and lymphadenopathy (15). Lazarinis et al. reported immediate mild reactions in 73 patients with mastocytosis who received a total of 146 COVID-19 vaccine injections (14). They also noted that non-allergic adverse reactions such as pain or tenderness at the injection site, myalgia, malaise, or chills were more common (14). In the same article, it is worth noting that all patients in that study received premedication with antihistamine (10 mg desloratadine) 30 to 60 minutes prior to the vaccination (14). In our study, we also observed common non-allergic adverse reactions such as local reactions, myalgia, fever and arthralgia in 70.2% of the vaccinated patients, which is consistent with the findings of the previous study. However, unlike the previous study, routine premedication was not administered to our patients. Furthermore, the occurrence of adverse reactions in our study group was not dependent on whether the patients were receiving regular antihistamines, omalizumab, or montelukast treatment. This suggests that the development of adverse reactions in our patients was not influenced by these specific medications.

In a published study, it was noted that patients with a history of allergies (including inhaled allergens, food allergens, drugs, insect venom, and other factors), experienced side effects more commonly with the second dose of the COVID-19 vaccine compared to the first dose (38). However, in our study, we observed that side effects were predominantly seen with the first dose (30.30%) and remained consistent across subsequent doses (39.39%) of the COVID-19 vaccination in patients with mastocytosis. The underlying differences in the patient populations may contribute to the contrasting observations regarding the frequency and timing of side effects following COVID-19 vaccination.

In a recently published study by Giannetti et al., a higher rate of anaphylaxis was reported in patients with mastocytosis compared to the general population (39). Hovewer, it was stated that there were no deaths, intubations, or admissions to the intensive care unit (39). In contrast, in our study, the patient who experienced anaphylaxis required hospitalization in the intensive care unit. These findings highlight the importance of evaluating security measures based on individual risk for patients with mastocytosis. The recommendations provided by the European Competence Network on Mastocytosis (ECNM) and the American Initiative in Mast Cell Diseases (AIM) are based on data, observations, and expert opinions (36). Considering that vaccination can potentially lead to serious adverse reactions, it is significant that our study identified a case of anaphylaxis requiring intensive care treatment. Therefore, in line with the recommendations, it is advised that patients with mastocytosis carry an epinephrine autoinjector during vaccination and receive their vaccination in a center equipped to respond to anaphylaxis and other severe adverse reactions (36). Close observation after vaccination is also recommended to promptly identify and manage any potential complications (36). These measures aim to ensure the safety of patients with mastocytosis during the vaccination process.

In the study conducted by Sriskandarajah et al., two female patients out of 227 patients with mastocytosis experienced anaphylaxis after receiving the Pfizer/BioNTech and Oxford/AstraZeneca vaccines (40). The patient who experienced anaphylaxis after the Pfizer/BioNTech vaccination had not experienced any anaphylaxis episode requiring adrenaline in the 12 months prior to the injection. The other patient who experienced anaphylaxis after Oxford/AstraZeneca vaccine injection had the history of anaphylaxis episodes in the 12 months prior to the dose (40). In our study, the patient who had anaphylaxis after receiving the SinoVac vaccine was also a woman with indolent mastocytosis. This patient did not experience anaphylaxis requiring adrenaline treatment in the 3 months leading up to the vaccination. Based on these observations, it can be inferred that the development of anaphylaxis following vaccination in patients with masto-

cytosis is not necessarily associated with the specific vaccine type or a history of anaphylaxis episodes prior to the vaccination.

Although the current real-life study provided important findings for the clinical practice, it had some limitations. The side effects of the vaccine and the history of anaphylaxis, urticaria and flushing attacks before and after vaccination were evaluated subjectively by relying on self-reports from patients. This approach introduced a potential recall bias, as relying solely on patients' self-reported symptoms can be constraining and less reliable than medically confirmed diagnoses and observable symptoms. Secondly, the number of cases was limited, especially the number of unvaccinated patients diagnosed with mastocytosis, which was significantly low for a meaningful comparison. Therefore, it was obvious that there was a need for more comprehensive studies involving a larger number of patients. The third limitation was the assessment of the FoCV using an unvalidated scale since there was no published and validated scoring system specifically designed for this purpose. However, we adapted this scale from the validated fear of the COVID-19 infection scoring system, and thus believed that it provided a reasonably accurate reflection of the patients' fear states. Another limitation was the duration of the evaluation period. Considering the duration of the evaluation period, three months may not represent exactly the long-term period. In this regard, three months may not be enough. Large-scale studies over longer periods of time are needed.

In conclusion, this study suggests that the COVID-19 vaccine can be safe for patients with mastocytosis, regardless of whether they are in the early or late stages of the condition. While further in-depth studies on long-term outcomes are necessary, we consider our study to be pioneering in this aspect. Therefore, it is advisable to administer the COVID-19 vaccine to patients with mastocytosis while adhering to the recommended precautions.

Conflict of Interest

No conflict of interest.

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Authorship Contributions

Concept: **İlkim Deniz Toprak, Nida Oztop,** Design: **İlkim Deniz Toprak, Semra Demir, Nida Oztop, Ayşe Feyza Aslan,** Data collection or processing: **İlkim Deniz Toprak, Ayşe Feyza Aslan,** Analysis or Interpretation: **İlkim Deniz Toprak, Semra Demir, Aslı Gelincik,** Literature search: **İlkim Deniz Toprak,** Writing: **İlkim Deniz Toprak, Semra Demir, Nida Oztop, Ayşe Feyza Aslan, Derya Unal, Aslı Gelincik,** Approval: **Semra Demir, Derya Unal, Aslı Gelincik.**

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