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## Original Article

## Impact of mental health on disease activity in mastocytosis during COVID-19 pandemic

Nida Öztop<sup>a</sup>, Semra Demir<sup>a</sup>, Şengül Beyaz<sup>a</sup>, Derya Ünal<sup>b</sup>, Bahauddin Çolakoğlu<sup>a</sup>, Suna Büyükoztürk<sup>a</sup>, Aslı Gelincik<sup>a,\*</sup><sup>a</sup> Division of Immunology and Allergic Diseases, Department of Internal Medicine, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey<sup>b</sup> Division of Immunology and Allergic Diseases, Department of Internal Medicine, Yedikule Education and Training Hospital, Istanbul, Turkey

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AdvSM, Advanced systemic mastocytosis; AS, Anxiety subscale; CM, Cutaneous mastocytosis; COVID-19, Coronavirus Disease-19; CRH, Corticotrophin releasing hormone; CRHR-1, Corticotrophin releasing hormone receptor-1; DS, Depression subscale; FCV-19S, Fear of COVID-19 Scale; ISM, Indolent systemic mastocytosis; IQR, Interquartile range; LP, Lockdown Period; MCs, Mast cells; RTNP, Return to Normal Period; SARS-COV2, Severe Acute Respiratory Syndrome Coronavirus2; SCORMA, Scoring Mastocytosis Index; SS, Stress subscale; tDASS-21, total Depression-Anxiety-Stress Scale; NS, Not significant

## ABSTRACT

**Background:** Mast cell-related symptoms might be influenced by mental health status in mastocytosis. In this study, we aimed to investigate the influence of mental health problems developed during the COVID-19 pandemic on the course of mastocytosis.

**Methods:** Mental health status in 60 adult patients with mastocytosis was prospectively evaluated with the total Depression-Anxiety-Stress Scale (tDASS-21) and Fear of COVID-19 Scale (FCV-19S) in the lockdown period (LP) and the return to normal period (RTNP) during the pandemic. The disease course was assessed from emergency and outpatient medical reports, including Scoring Mastocytosis (SCORMA) index and serum baseline tryptase levels, by telephone interviews and clinical visits.

**Results:** The mean FCV-19S and median tDASS-21 scores were significantly higher in LP than RTNP ( $p < 0.001$ ) and there was a positive correlation between FCV-19S and tDASS-21 in LP ( $r = 0.820$ ,  $p < 0.001$ ) and in RTNP ( $r = 0.572$ ,  $p < 0.001$ ). Disease-related symptoms including skin lesions, flushing and anaphylaxis attacks increased in 22 patients in LP, and in this group, mean FCV-19S and median tDASS-21 were higher than those without symptom exacerbation ( $p < 0.001$ ). During the study period, four (6.7%) patients who experienced COVID-19 recovered without any requirement for hospitalization and had not experienced symptom exacerbation.

**Conclusions:** Fear of COVID-19 can be a reason for mental health changes, including depression, anxiety and stress which may further increase mast cell-related symptoms. Therefore, psychological support is important to control the severity of mast cell-related symptoms in mastocytosis during a pandemic.

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## Introduction

The coronavirus disease 19 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-COV2),<sup>1–3</sup>

is considered the major global health crisis of our century.<sup>4</sup> After the declaration of the first case on March 11, 2020 by the Turkish Ministry of Health, the first restrictions on transportation were imposed on March 13, 2020, and a national lockdown in Turkey was declared on April 11, 2020 similar to other countries.<sup>4</sup> Turkish Ministry of Health announced that 163,942 people were infected with COVID-19 and 4540 people died due to COVID-19 in Turkey from March 2020 to the end of May 2020.<sup>5</sup> Social restrictions together with the fear of the disease itself, have affected mental health by increasing depression, anxiety, fear, insomnia and stress

\* Corresponding author. Division of Immunology and Allergic Diseases, Department of Internal Medicine, Istanbul University Faculty of Medicine, Turgut Özal Millet Cd, 34093, Fatih, Istanbul, Turkey.

E-mail address: [gelincikasli@hotmail.com](mailto:gelincikasli@hotmail.com) (A. Gelincik).

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in the general population.<sup>6,7</sup> Fear of being infected or dying, unemployment and thoughts of an uncertain future are some consequent results of this pandemic-related social life.<sup>6–9</sup> It is a matter of concern that patients with chronic diseases can be more affected by this situation. In recent studies, the impact of COVID-19 on patients with chronic diseases has been reported,<sup>6–8</sup> however, there is no data about the psychological effects of the pandemic on symptoms of mastocytosis.

Mastocytosis is a rare heterogeneous disease characterized by abnormal proliferation and accumulation of mast cells in different organs.<sup>10</sup> Depending on the mediators released from mast cells (MCs),<sup>11</sup> clinical symptoms can vary from flushing to severe anaphylaxis.<sup>12</sup> Although most MC-related symptoms can occur spontaneously in mastocytosis, insects can be a common etiologic factor of anaphylaxis.<sup>13</sup> Furthermore, it has been reported in mice and human studies that psychological and environmental stress can cause an increase in MC-related symptoms.<sup>14</sup> Interestingly, in a study, stress by stimulating coronary MCs has been shown to induce or worsen coronary artery diseases.<sup>15</sup> However, there is limited data that show the impact of mental health problems on MC mediator-related symptoms in patients with mastocytosis.<sup>14,16,17</sup>

By the onset of the COVID-19 pandemic, many people with chronic diseases have been declared as risky groups for a more severe COVID-19<sup>18</sup> course which increased the concerns for other candidate chronic diseases like mastocytosis resulting in fear of getting infected in such patients. In this current study, we aimed to investigate the effects of mental health problems developed in relation to COVID-19 pandemic on symptoms of mastocytosis.

## Methods

### *Patient recruitment and study design*

Sixty adult mastocytosis patients, diagnosed and classified according to the recent World Health Organization diagnosis and classification criteria,<sup>11</sup> were included in the study. Patients who had psychiatric diseases and/or those who were receiving psychiatric medication were excluded from the study. According to the level of social restrictions applied by the government, the study included two periods. The first period, defined as the lockdown period (LP), was in March–May 2020, when strict restrictions were announced with the detection of the first case in the country, and the second period, called the return to normal period (RTNP), was in June–August 2020, when the previous restrictions were lessened with the permission of the controlled social life.<sup>19</sup>

Patient assessments, including disease-related symptoms and mental health status, were completed by telephone interviews and face-to-face visits in late May 2020 and late September 2020 at the end of the LP and RTNP, respectively. During the assessment calls, sociodemographic and clinical features including age, education, employment status, smoking habits, alcohol consumption, comorbid diseases, disease-related symptoms, hospital admissions for treatment or follow-up, treatment changes and diagnosis of COVID-19 during the pandemic were evaluated. Disease-related symptoms defined as anaphylaxis, flushing and increased skin lesions which are caused by mast cell activation. For the evaluation of disease-related symptoms, patients were questioned in terms of flushing attacks, skin lesions and anaphylaxis attacks. In LP or RTNP, the patients who described skin lesions were invited to the outpatient clinic and examined for skin lesions by the same physician. The scoring mastocytosis SCORMA index,<sup>20</sup> for evaluation of skin lesions in mastocytosis,

was used and compared to baseline measures that had been applied before the pandemic. The patients who declared anaphylaxis attacks were also invited to the clinic and questioned in terms of triggers, attack numbers, intervention and emergent medications. Also, medical records of emergency room applications were reviewed. Those only experiencing a sensation of flushing were asked to take photographs when they felt flushing to be evaluated by the physicians in the clinic afterwards. In addition, if patients had COVID-19 during the study period, they were evaluated in terms of suspicious contact history, the course of the infection, treatment of COVID-19, hospital or intensive care unit admissions and possible drug reactions. Serum baseline tryptase levels were measured during the LP and compared with pre-pandemic values found in the patients' files.

### *Evaluation of mental health*

During the LP and RTNP, mental health status including depression, anxiety and stress were evaluated with the validated Turkish version of Depression-Anxiety-Stress Scale 21 (DASS-21),<sup>21,22</sup> a four-point Likert scale, consisting of seven items for three subscales with a rating system (0: never, 1: sometimes, 2: often, 3: almost always) (Table 1).<sup>21</sup>

The fear of COVID-19 was determined during the LP and RTNPs with the validated Turkish version of the Fear of COVID-19 Scale (FCV-19S),<sup>23,24</sup> a self-reported seven-item, five-point Likert scale. A total score ranging from seven to 35 meant that the higher the score, the greater the fear of COVID-19 (Table 1).<sup>23,24</sup> DASS-21 and FCV-19S were eligible for self-administration and did not require psychiatrist evaluation.

This study was approved by the local institution's ethics committee (Approval number: 2020–86348) and received permission from the Turkish Ministry of Health (Approval number: 2020-06-03T12\_43\_29). Written informed consent was received from all study participants.

### *Statistical analysis*

The data were analysed using the Statistical Package for Social Sciences (SPSS Inc. Armonk, NY, USA) v22.0, and GraphPad Prism Software 8 (San Diego, CA, USA) was used for figures. Demographic and clinical features were assessed by descriptive analysis and shown as percentages and mean  $\pm$  standard deviation or median with interquartile range percentile 25–75 (IQR 25–75) according to the distribution of the data. The Kolmogorov–Smirnov test was used to assess the distribution pattern of the quantitative data. Continuous variables were compared by Independent t Test or Mann Whitney-U test between the two groups. Wilcoxon rank test and Paired Sample T Test were used to compare dependent means, and correlation analysis was performed by Pearson's or Spearman's correlation tests depending on the distribution of the data. Binary regression analysis was used to determine the association between mental health status and increased disease symptoms. In all analyses, p values less than <0.05 were considered as statistically significant.

## Results

### *Results of demographic and clinical characteristics of the patients*

The demographic and clinical features of the patients are demonstrated in detail in Table 2. The mean age of the patients was  $43.60 \pm 9.90$  years and 56.7% of the patients (n = 34) were female.

**Table 1**  
The psychological scales used in the evaluation of the patients.

DASS-21 Scale <sup>20</sup>	0	1	2	3	
Did not apply to me at all					
Applied to me to some degree, or some of the time					
Applied to me to a considerable degree, or a good part of time					
Applied to me very much or most of the time					
I found it hard to wind down	0	1	2	3	
I was aware of dryness of my mouth	0	1	2	3	
I couldn't seem to experience any positive feeling at all	0	1	2	3	
I experienced breathing difficulty (e.g., excessively rapid breathing, breathlessness in the absence of physical exertion)	0	1	2	3	
I found it difficult to work up the initiative to do things	0	1	2	3	
I tended to over-react to situations	0	1	2	3	
I experienced trembling (e.g. in the hands)	0	1	2	3	
I feel that I was using a lot of nervous energy	0	1	2	3	
I was worried about situations in which I might panic and make a fool of myself	0	1	2	3	
I felt that I had nothing to look forward to	0	1	2	3	
I found myself getting agitated	0	1	2	3	
I found it difficult to relax	0	1	2	3	
I felt down-hearted	0	1	2	3	
I was intolerant of anything that kept me from getting on with what I was doing	0	1	2	3	
I felt I was close to panic	0	1	2	3	
I was unable to become enthusiastic about anything	0	1	2	3	
I felt I wasn't worth much as a person	0	1	2	3	
I felt that I was rather touchy	0	1	2	3	
I was aware of the action of my heart in the absence of physical exertion (e.g. sense of heart rate increase, heart missing a beat)	0	1	2	3	
I felt scared without any good reason	0	1	2	3	
I felt that life was meaningless	0	1	2	3	
FCV-19 Scale <sup>23</sup>	1	2	3	4	5
1 strongly disagree					
2 disagree					
3 neither agree or disagree					
4 agree					
5 strongly agree					
I am most afraid of coronavirus-19	1	2	3	4	5
It makes me uncomfortable to think about coronavirus-19	1	2	3	4	5

**Table 1 (continued)**

FCV-19 Scale <sup>23</sup>	1	2	3	4	5
My hands become clammy when I think about coronavirus-19	1	2	3	4	5
I am afraid of losing my life because of coronavirus-19	1	2	3	4	5
When watching news and stories about coronavirus-19 on social media, I become nervous or anxious	1	2	3	4	5
I can not sleep because I'm worrying about getting coronavirus-19	1	2	3	4	5
My heart races or palpitates when I think about getting coronavirus-19	1	2	3	4	5

While 35 patients (58.3%) were living in Istanbul, the others were living in neighbouring cities. Fifty-four (90%) and 26 (43.3%) patients could not come to the hospital for follow-up visits in LP and RTNP, respectively. Eight patients (13.3%) with mastocytosis continued receiving venom immunotherapy either every four or eight weeks. Five (8.33%) with uncontrolled recurrent anaphylaxis attacks and two patients (3.33%) with increased skin lesions were on omalizumab treatment and continued their treatment without any interruption during the pandemic. All patients had c-KIT D816V gene mutation.

*Comparison of mental health status measures in LP and RTNP*

The median (IQR 25–75) values of tDASS-21 were 8.5 (0–20) and 0 (0–3), and the mean values of FCV-19S were 21.07 ± 7.52 and 15.63 ± 5.56 in LP and RTNP, respectively. The median tDASS-21 and the mean FCV-19S significantly decreased in RTNP compared to LP (p < 0.001). In addition, the median (IQR 25–75) values of depression (DS), anxiety (AS) and stress (SS) subscale scores were lower in RTNP than those in LP (p < 0.001, for each comparison). In [Figure 1](#), comparison of FCV-19S, tDASS-21, DS, AS, SS and median, mean and p values in LP and RTNP were shown.

The distribution of the patients according to the severity of their mental health findings is shown in [Table 3](#). While more patients had normal mental health status or mild mental health findings in the RTNP, the number of patients with moderate to severe mental health findings was higher in the LP ([Table 3](#)).

In the correlation analysis, FCV-19S was positively correlated with tDASS-21 (LP; r = 0.826, p < 0.001, RTNP; r = 0.572 p = <0.001) and with DASS-21 three subscales in both LP and RTNP [(with DASS-21 DS scores: in LP: r = 0.746, p < 0.001; in RTNP: r = 0.372, p = 0.003) (with DASS-21 AS scores: in LP; r = 0.893, p < 0.001; in RTNP: r = 0.399, p = 0.002) (with DASS-21 SS scores: in LP; r = 0.702, p < 0.001, in RTNP; r = 0.621, p < 0.001)]. In [Figure 2](#), correlations of FCV-19S, tDASS-21, DS, AS, SS with each other and p values and r correlation coefficients in LP and RTNP were shown.

*Frequency of disease-related symptoms and their correlation with mental health status in the LP and RTNP*

The patients were further allocated into two groups: those with and without an increased number of disease-related symptoms.

Disease-related symptoms were more common among younger patients ( $p = 0.036$ , Table 4). During the LP, anaphylaxis, flushing attacks and skin rash increased in number in three, 12 and seven patients, corresponding to 36.7% ( $n = 22$ ) of the patients when compared to the frequency of symptoms during the pre-pandemic period, respectively ( $p < 0.001$ ). Anaphylaxis was seen in two patients with indolent systemic mastocytosis (ISM) and in one patient with advanced systemic mastocytosis (AdvSm) in LP. No triggers for anaphylaxis were detected in these patients. The mean SCORMA index in seven patients significantly increased in the LP when compared to their baseline mean SCORMA index ( $34.95 \pm 5.98$  vs  $26.15 \pm 5.09$ ,  $p < 0.001$ ). Skin lesions increased in two patients with cutaneous mastocytosis (CM) and in five patients with ISM, however, in AdvSM, no skin lesion increases were seen. Flushing attacks were seen 11 patients with ISM and one patients with AdvSM in LP. During the RTNP, 13.3% ( $n = 8$ ) of the patients had only an increased number of flushing attacks in the RTNP when compared to the number of attacks during the pre-pandemic period, there were not detected any increases in anaphylaxis attack or skin lesions in RTNP.

The mean value of FCV-19S and the median values of tDASS-21, DS, AS and SS scores were significantly higher in patients with increased disease-related symptoms than in others in both the LP and RTNP (please refer to Table 4 for  $p$  values).

Median (IQR 25–75) serum baseline tryptase levels before the pandemic and during LP were 26 (13.3–60) kU/L and 26 (12.1–61) kU/L, respectively ( $p = 0.161$ ). When comparing the serum baseline tryptase levels measured before the pandemic and during the LP among the patients with increased symptoms in LP, the median (IQR 25–75) serum baseline tryptase levels were significantly higher during LP than before the pandemic [30.71 (13.5–38) kU/L vs 42.25 (17.17–52.2) kU/L,  $p < 0.001$ ].

In correlation analysis between mental health scales in the group with increased disease-related symptoms, FCV-19S was positively correlated with tDASS-21 ( $r = 0.764$ ,  $p < 0.001$ ), DASS-21 DS ( $r = 0.544$ ,  $p = 0.009$ ), DASS-21 AS ( $r = 0.786$ ,  $p < 0.001$ ) and DASS-21 SS ( $r = 0.412$ ,  $p = 0.03$ ) in LP. When correlation analysis was done in the RTNP, FCV-19S was positively correlated with tDASS-21 ( $r = 0.522$ ,  $p = 0.013$ ) and DASS-21 SS ( $r = 0.588$ ,  $p = 0.004$ ), but there was no correlation with DASS-21 AS ( $r = 0.379$ ,  $p = 0.08$ ) and DASS-21 DS scores ( $r = 0.350$ ,  $p = 0.111$ ).

According to the binary regression analysis, there were no relationships between FCV-19S, DASS-21 AS scores and increased number of disease-related symptoms, while DASS-21 DS and DASS-21 SS were related to the presence of an increased number of disease-related symptoms (Table 5). There were no association between FCV-19S, tDASS-21, DASS-21 DS, DASS-21 AS, DASS-21 SS and working or education status.

#### Demographic and clinical features of the patients who were diagnosed with COVID-19

Four patients (6.7%), mean age  $38.75 \pm 21.48$  years, had COVID-19 in the LP. All patients had positive polymerase chain reaction for COVID-19, and two patients' thoracic computerized tomography findings were compatible with COVID-19. None of them needed to stay at the hospital, and all of them well tolerated the medications for COVID-19. During COVID-19 infection, increased MC-related symptoms weren't seen in any of the patients. The demographic and clinical characteristics of these patients are summarized in Table 6.

## Discussion

The current study evaluates the effects of psychological factors related to the COVID-19 pandemic on the course of mastocytosis for

the first time and reports a mastocytosis patient series having COVID-19. It reveals that mental health deterioration due to the pandemic can negatively influence mastocytosis symptoms even though the patients are not infected, especially during the strict social restriction measures applied during the pandemic.

In the current study, we determined that depression, anxiety and stress levels are higher in patients with mastocytosis in the LP and can decrease when the restriction measures are lessened. In the past, during similar pandemics, serious concerns such as the fear of death arose; furthermore, during lockdown, anxiety and anger developed in people due to loneliness and uncertainty about the future.<sup>25</sup> Additionally, during the COVID-19 pandemic, the study scale, DASS-21, revealed rises in depression, anxiety and stress levels in the general population in India,<sup>26</sup> Mexico<sup>25</sup> and Philippines.<sup>27</sup> Karabacak *et al.* have recently reported the pandemic effect on hereditary angioedema attacks by using the same psychiatric scales and have found that the restriction measures during COVID-19 outbreak can cause an increase in the number of HAE attacks in relation to anxiety, depression, stress and fear of COVID-19.<sup>28</sup> Up to now, no studies evaluating the influence of mental health problems developed during the COVID-19 pandemic on the course of mastocytosis have been published, and our findings are important in this sense. Due to the rapid spread and pandemic announcement of COVID-19, worldwide fear of infection has increased.<sup>23,24</sup> Interestingly, it was assumed that fear-induced stigma in a pandemic can hide clinically relevant early symptoms and increase the transmission of the virus in a community.<sup>29</sup> Reducing fear and stigma between individuals during pandemics can be important in controlling transmission and mental health.<sup>29</sup> Consequently, a validated tool assessing the level of fear

**Table 2**  
Demographic and clinical features of the patients with mastocytosis.

Demographic and clinical features of patients (n = 60)	
Age (years, mean $\pm$ SD)	43.60 $\pm$ 9.90
Gender	
Female (n,%)	34 (56.7%)
Male (n,%)	26 (43.3%)
Smokers (n,%)	38 (63.3%)
Alcohol consumption (n,%)	10 (16.7%)
Education	
Not going to school (n,%)	4 (6.7%)
Primary school (n,%)	14 (23.3%)
High school (n,%)	21 (35%)
University (n,%)	21 (35%)
Working status (n,%)	
Active work (n,%)	7 (11.7%)
Flexible work (n,%)	23 (38.3%)
Housewife (n,%)	19 (31.7%)
Salary without work (n,%)	6 (10%)
Retired (n,%)	3 (5%)
Fired (n,%)	2 (2%)
Comorbid diseases	
Diabetes mellitus (n,%)	9 (15%)
Hypertension (n,%)	13 (21.7%)
Hyperlipidemia (n,%)	4 (6.7%)
Hypothyroidism (n,%)	3 (5%)
Malignancy (n,%)	2 (3.3%)
Type of mastocytosis	
CM (n,%)	5 (8.3%)
ISM (n,%)	50 (83.3%)
AdvSM (n,%)	5 (8.3%)
Duration of disease (years, mean $\pm$ SD)	6.27 $\pm$ 4.91
Serum baseline tryptase level (kU/L), (median, IQR25–75)	25.7 (12.65–38.55)
Regular visit to hospital for follow-up in LP (n,%)	6 (10%)
Regular visit to hospital for follow-up in RTNP (n,%)	34 (56.7%)

AdvSM, Advanced systemic mastocytosis; CM, Cutaneous mastocytosis; FCV-19S, Fear of COVID-19 scale; ISM, Indolent systemic mastocytosis; LP, Lockdown period; RTNP, Return to Normal period; SD, Standart deviation.



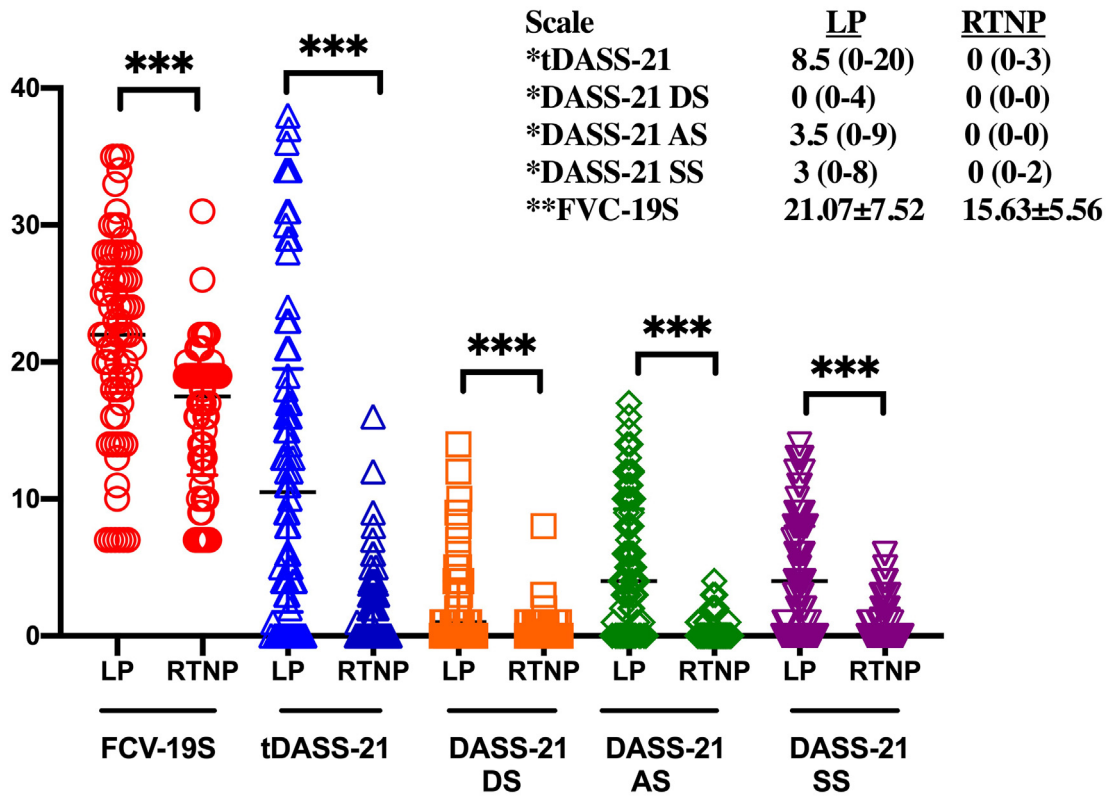


Fig. 1. Comparison of FCV-19S, tDASS-21, DS, AS and SS in LP and RTNP. \*Scale value was given as median (IQR 25–75) \*\* Scale value was given as mean ± SD \*\*\*p < 0.001.

**Table 3**  
Distribution of patients according to the severity of depression, anxiety and stress in LP and RTNP.

	LP	RTNP
<b>Depression</b>		
Normal (n,%)	49 (81.7%)	59 (98.3%)
Mild (n,%)	4 (6.7%)	0 (0%)
Moderate (n,%)	5 (8.3%)	1 (1.7%)
Severe (n,%)	1 (1.7%)	0 (0%)
Extremely severe (n,%)	1 (1.7%)	0 (0%)
<b>Anxiety</b>		
Normal (n,%)	30 (50%)	59 (98.3%)
Mild (n,%)	7 (11.7%)	1 (1.7%)
Moderate (n,%)	6 (10%)	0 (0%)
Severe (n,%)	4 (6.7%)	0 (0%)
Extremely severe (n,%)	13 (21.7%)	0 (0%)
<b>Stress</b>		
Normal (n,%)	41 (68.3%)	60 (100%)
Mild (n,%)	10 (16.7%)	0 (0%)
Moderate (n,%)	4 (6.7%)	0 (0%)
Severe (n,%)	5 (8.3%)	0 (0%)
Extremely severe (n,%)	0 (0%)	0 (0%)

LP, Lockdown period; RTNP, Return to normal period.

associated with COVID-19, FCV-19S, to reduce the mental health problems that may develop during the pandemic has been developed and used in many countries.<sup>23,24</sup> In our study, the mean FCV-19S was significantly higher in the LP than in the RTNP in strong correlation with tDASS-21 and DASS-21 subscale scores. It has been reported that factors about pandemic could have negative effects on mental health in healthy population in general<sup>30</sup> also anxiety,

depression, fear and stress were seen not only in patients with COVID-19, it has also seen in healthy individuals.<sup>30</sup> In Turkey, it has been reported that increased depression and anxiety frequencies were detected in healthy population during the pandemic.<sup>31</sup> Although we have no data about the mental health status of our mastocytosis patients before the pandemic, according to these findings, we can speculate that anxiety, depression and stress developed during the pandemic are related to the fear of COVID-19 in mastocytosis. However, since we did not have a healthy control group, we could not know how much the effect of COVID-19 on mental health in mastocytosis compared to the normal population.

There are several clinical clues showing the role of psychological stress in inducing MC-related diseases, including mastocytosis. Psychological stress, by stimulating the release of corticotrophin releasing hormone (CRH) into the serum, can induce MC degranulation.<sup>17</sup> In case of acute stress, increased serum CRH can lead to a rise in skin vascular permeability by stimulating MCs.<sup>15</sup> Additionally, MCs can synthesize CRH and express CRH receptor-1 (CRHR-1).<sup>32,33</sup> Both environmental and psychological stress can worsen symptoms of anxiety, flushing and angioedema in patients with MC-associated diseases like anaphylaxis, asthma, CM and angioedema.<sup>17,32</sup> An increase in skin lesions after an acute anxiety attack in a female patient with urticaria pigmentosa was found to be associated with high serum CRH levels and skin CRH-R1 expression.<sup>33</sup> In another case report, anaphylaxis induced by psychological stress was detected in a 33-year-old female patient.<sup>34</sup> In line with these reports, in our study, an increase in disease related symptoms in correlation with mental health status findings was observed in 22 patients during the LP and in eight patients during the RTNP. In patients with increased symptoms in LP, serum baseline tryptase

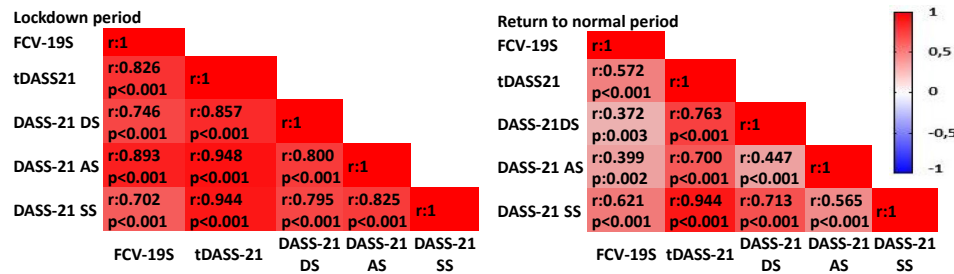


Fig. 2. P values and r correlation coefficients between all scales in lockdown period and return to normal period according to the correlation analysis.

**Table 4**  
Demographic and clinical features and mental health scale results in patients with or without increased disease related symptoms in LP.

Features	Patients with increased symptoms (n = 22)	Patients without increased symptoms (n = 38)	p
Age (years) (mean ± SD)	40.09 ± 7.99	45.63 ± 10.42	<b>0.036</b>
Gender			
Female (n,%)	15 (68.2%)	19 (50%)	0.171
Male (n,%)	7 (31.8%)	19 (50%)	
Body mass index (kg/m <sup>2</sup> ) (mean ± SD)	27.72 ± 4.90	26.46 ± 4.82	0.336
Smoking habits (n,%)	13 (59.1%)	25 (65.8%)	0.604
Type of mastocytosis			
CM (n,%)	2 (9.1%)	3 (7.9%)	0.872
ISM (n,%)	18 (81.8%)	32 (84.2%)	0.811
AdvSM (n,%)	2 (9.1%)	3 (7.9%)	0.872
Comorbid diseases			
Diabetes mellitus (n,%)	2 (9.1%)	7 (18.4%)	0.329
Hypertension (n,%)	3 (13.6%)	10 (26.3)	0.251
Hyperlipidemia (n,%)	2 (9.1%)	2 (5.3%)	0.567
Hypothyroidism (n,%)	1 (4.5%)	2 (5.3%)	0.902
Malignancy (n, %)	1 (4.5%)	1 (2.6%)	0.691
Duration of diseases (years) (median, IQR 25–75)	6 (3–9.5)	4.5 (3–6.25)	0.479
Serum baseline tryptase level (kU/L) (median, IQR 25–75)	26 (14.2–38)	22.7 (11.7–60)	0.948
FCV-19S (mean ± SD)			
LP	26.36 ± 4.59	18.00 ± 7.20	<b>&lt;0.001</b>
RTNP	18.23 ± 3.93	14.13 ± 5.85	<b>0.005</b>
tDASS-21 (median, IQR 25–75)			
LP	21 (13.75–31.75)	3 (0–6.5)	<b>&lt;0.001</b>
RTNP	2.5 (2.5–5.25)	0 (0–0)	<b>&lt;0.001</b>
DASS-21 DS (median, IQR 25–75)			
LP	3.5 (1–7.5)	0 (0–1)	<b>0.001</b>
RTNP	0 (0–1)	0 (0–0)	<b>0.003</b>
DASS-21 AS (median, IQR 25–75)			
LP	9.5 (5.75–12.25)	1 (0–4)	<b>&lt;0.001</b>
RTNP	0 (0–1.25)	0 (0–0)	<b>0.013</b>
DASS-21 SS (median, IQR 25–75)			
LP	9 (7.75–11.25)	0.5 (0–3)	<b>&lt;0.001</b>
RTNP	1.5 (0–4)	0 (0–0)	<b>&lt;0.001</b>

AdvSM, Advanced Systemic Mastocytosis; AS, Anxiety subscale; CM, Cutaneous mastocytosis; DS, Depression subscale; FCV-19S, Fear of COVID-19 scale; IQR, Interquartile range; ISM, Indolent Systemic Mastocytosis; LP, Lockdown period; SD, Standard deviation; SS, Stress subscale; RTNP, Return to Normal period; tDASS-21, Total depression, anxiety, stress scale with 21 questions. P values <0.05 in bold is considered significant.

levels were significantly higher during LP than before the pandemic period. Since serum tryptase level is a marker of mast cell degranulation, this finding can show us that psychological stress and other mental health problems induced during the pandemic are strongly associated with disease activity of mastocytosis and are higher when strict social restriction measures are applied. Although we have no previous data about the mental health status of our patients prior to the pandemic, our findings indicated that fear of COVID-19 during the LP can lead to an increase in MC-related

symptoms by causing an increase in the level of stress and depression in patients with mastocytosis.

Due to the rapid spread of COVID-19, many physicians were concerned about the course of COVID-19 in mastocytosis and, however, assumed it to be the same as seen in general population.<sup>3</sup> In our study, all of whom were receiving famotidine and fexofenadine for mastocytosis, were reported as having experienced COVID-19. All these patients well tolerated medications for COVID-19 and did not possess severe COVID-19 symptoms. Also same as

**Table 5**  
Factors in association with increased symptoms in LP according to the binary regression analysis.

	Increased symptoms		
	OR	95% CI for OR (Lower-Upper)	p
LP			
FCV-19S	1.131	0.751–1.703	0.556
DASS-21 DS	0.805	1.183–3.357	<b>0.010</b>
DASS-21 AS	0.646	0.346–1.208	0.171
DASS-21 SS	0.372	0.207–0.667	<b>0.001</b>

AS, Anxiety subscale; CI, Confidence Interval; DASS-21, depression, anxiety, stress scale with 21 questions; DS, Depression subscale; FCV-19S, Fear of COVID-19 scale; LP, Lockdown Period; SS, Stress subscale.  
P values <0.05 in bold is considered significant.

the literature, none of the mastocytosis patients had increased disease related symptoms during COVID-19 infection.<sup>35</sup> It is hard to make definite conclusions regarding the small number of patients infected during our study; however, we may speculate that being at a younger age, having no comorbidities and taking no immunosuppressive agents during the COVID-19 pandemic might have reduced the mortality and hospitalization rates due to COVID-19 in patients with mastocytosis. In the literature, it has been reported that using high dose famotidine could be effective on improvement COVID-19 symptoms.<sup>36,37</sup> Since the evidence is very low, we can only speculate that using famotidine could have a positive effect on the improvement of COVID-19 symptoms in our study population. However, further studies with a higher number of patients are needed to confirm these findings.

Our study has several limitations. First, we could not evaluate the mental health status of our patients with the same scales in the pre-pandemic period, which restricted us from reaching more accurate conclusions. However, by excluding those taking psychiatric medications and those having psychiatric diagnoses, we believe that we have increased the strength of our findings. Furthermore, all the patients recovered during the RTNP without applying to a psychiatrist or consuming psychiatric medications during strict social restrictions so that we can assume that the deterioration in mental health status was possibly related to the pandemic rather than the disease itself. A second limitation is that we could not have confirmed the presence of anaphylaxis by measuring serum tryptase levels during anaphylaxis episodes since such tests are not available in most emergency rooms. However, the presence of medical records taken during the attacks and the fact that none of the patients' attacks were their first attacks have supported the anaphylaxis diagnosis of our patients. As a third limitation of our study, we could not compare our findings with a healthy control group since pandemic related social restrictions did not lead healthy subjects' admissions to a hospital for a clinical study. However, by comparing the data of mastocytosis patients without having any psychiatric comorbidities in two different social restriction periods, our findings can suggest that patients can experience an increase in neuropsychiatric findings influenced by the pandemic that may further cause an increase in mast-related symptoms. Furthermore, the SCORMA index may be argued as not being a precise objective scale in mastocytosis. However, in our clinic, patients with mastocytosis are regularly followed up by the same physicians from their initial visits and are evaluated with this index since it is a determinant for skin lesions.

In conclusion, the fear of COVID-19 occurred as a result of the COVID-9 pandemic, and social restriction measures can deteriorate mental health status and thereby the course of mastocytosis.

**Table 6**  
Demographic and clinical characteristic of patients infected by SARS-COV-2.

Case No	Age (year)	Gender	Smoker	Job	Comorbidity	Type of mastocytosis	Suspicious mastocytosis contact	Biologic agent	Treatment for mastocytosis	COVID-19 PCR	Lung Involvement	Symptoms of COVID-19	Stay at hospital ICU	Stay at Treatment of COVID-19	Drug reaction to anti-COVID-19 agents	Drug reaction in history
1	37	F	No	Nurse	Absent	ISM	Yes	Absent	Famotidine, Fexofenadine	Positive	Positive	Myalgia and diarrhea	No	HCQ + AZ + FP + EP	No	No
2	69	F	No	Retired	Absent	ISM	Yes	Omalizumab	Famotidine, Fexofenadine	Positive	Positive	Fever, cough, myalgia	No	HCQ + FP + EP	No	No
3	30	F	Yes	Fashion designer	Absent	ISM	Unknown	Absent	Famotidine, Fexofenadine	Positive	Negative	Fever, sore throat, myalgia	No	HCQ + AZ	No	No
4	19	F	Yes	Student	Absent	ISM	Yes	Absent	Famotidine, Fexofenadine	Positive	Negative	Anosmia, headache, myalgia	No	FP	No	No

AZ, Azithromycin; EP, Enoxaparin; F, Female; FP, Favipiravir; HCQ, Hydroxychloroquine; HT, Hypertension; ISM, Indolent systemic mastocytosis; M, Male.



Therefore, psychological support seems to be important to control the symptoms of mastocytosis in conditions like a pandemic that can affect the patient's mental health status.

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## Conflict of interest

The authors have no conflict of interest to declare.

## Authors' contributions

NÖ, SD, ŞB, DÜ and AG designed the study, contributed to data collection, performed the statistical analysis and wrote the manuscript. SBü and BÇ performed interpretation of the results. All authors read and approved the final manuscript.

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